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New Advances in Pharmacologic and Non-pharmacologic Therapy in Heart Failure and Heart Transplant

Edited by
Daniele Masarone and Carlo Lombardi

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Editorial

Recent Advances across the Spectrum of Heart Failure and Heart Transplant

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1. Introduction

In recent years, remarkable progress has been accomplished in the heart failure (HF) landscape, with novel drugs and groundbreaking device approaches. Nevertheless, the prognosis is still severe, and patients' quality of life (QoL) is undermined by the HF-related hospitalizations that follow from the progressive nature of the disease. Indeed, despite a variable clinical trajectory, HF relentlessly reaches the end-stage phase, for which only heart transplantation (HTx) or durable mechanical circulatory support (MCS) are viable therapeutic options. In this Special Issue, "New Advances in Pharmacologic and Non-Pharmacologic Therapy in Heart Failure and Heart Transplant", experts in the field contributed through in-depth reviews, original research, and a network meta-analysis (NMA). We are excited to introduce 17 papers that address several topics across the HF spectrum: from pharmacological and device therapy for both chronic and advanced HF to acute HF (AHF) and its most severe form, i.e., cardiogenic shock (CS).

2. Chronic Heart Failure: Focus on Pharmacological Therapy

For a long time, HF therapy was limited to relieving congestion with diuretics and improving the cardiac output, reducing the afterload, and increasing contractility with vasodilators and inotropes, respectively. Subsequently, triple neurohormonal blockade and then quadruple therapy have become the standard of care (SoC). To date, several different pathways are successfully targeted with novel drugs [1,2]. Thus, HF specialists went from an era in which disease-modifying therapies were lacking to a new era, where they needed to tailor pharmacologic treatment according to patients' phenotype. However, now physicians struggle to reach target doses and choose the proper sequence in which to introduce all recommended therapies. Indeed, when novel drugs reach phase III randomized controlled trials (RCTs), they are usually compared to a placebo on top of the SoC. Since plenty of therapies have proved effective, and head-to-head comparisons are unlikely, their respective efficacy is uncertain. In this regard, Pagnesi et al. (Contribution 1) conducted an NMA including 12 RCTs. Most of them compared Sodium Glucose Transporter 2 inhibitors (SGLT2is) to placebo, whereas two RCTs evaluated Vericiguat, and two studies randomized patients to omecamtiv mecarbil in the experimental group. SGLT2is were found to be superior to Vericiguat and omecamtiv mecarbil on the primary endpoint (a composite of cardiovascular death and HF-related hospitalizations). However, authors correctly identified differences in baseline characteristics (background use of angiotensin receptor neprylisin (ARNI), percentage of New York Heart Association (NYHA) III/IV class patients, N-Terminal Pro-B-Type Natriuretic Peptide (proBNP-NT) levels) as relevant limitations.

With concerns for proper titration, a historical barrier is chronic kidney disease (CKD), which not only worsens the prognosis for HF and limits titration but also contraindicates

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the most effective therapies in advanced stages. Beltrami et al. (Contribution 2) extensively reviewed this topic and suggested a promising approach to optimize treatment in patients with a low estimated glomerular filtration rate (eGFR). In this regard, SGLT2is have demonstrated renal protection, blunting the decline of the eGFR slope, and they can even be used in stage IV CKD [3]. Sacubitril/valsartan has shown a similar effect on the eGFR slope, and in this Special Issue, Gioia et al. (Contribution 3) reported direct protective renal effects of sacubitril/valsartan, which are independent from cardiac beneficial effects.

Another obstacle to achieving guideline-directed medical therapy (GDMT) is the progression of HF to an advanced stage. The fact that patients may gradually become intolerant to disease-modifying therapies has been extensively reported; indeed, it is included in the "I NEED HELP" criteria. In a small and selected cohort of advanced HF patients, Masarone et al. (Contribution 4) reported Levosimendan periodic ambulatory infusions as a potential enabler of the up-titration of GDMT.

3. Chronic Heart Failure: Focus on Device Therapy

Despite the triumphs of translational research, HF mortality is still high, comparable to many cancers. In this context, dedicated devices have become crucial to improving clinical outcomes. Besides implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT), several new devices targeting structural abnormalities or modulating autonomic, electrophysiological, and respiratory systems are under investigation. An extensive review of valvular devices is provided by Cammalleri et al. (Contribution 5). As for autonomic modulation, growing evidence supports fluid redistribution as a critical process in the worsening of HF. Indeed, many patients do not experiment with fluid retention and weight gain before decompensation. Preclinical investigations demonstrated that the adrenergic system heavily supplies splanchnic circulation and, when stimulated, shifts a large amount of blood to the thoracic compartment. On the one hand, in healthy subjects, this is an essential mechanism to support increases in cardiac output.

On the other hand, its dysregulation in HF may contribute to a further increase in filling pressure and exercise intolerance. These concepts lead investigators to assess different approaches towards a common target: the greater splanchnic nerve (GSN) [4]. In this Special Issue, we present a pre-specified retrospective analysis of a single-arm, two-center, open-label prospective study evaluating permanent surgical ablation of the right GSN via thoracoscopic surgery in hemodynamic-adjudicated HF with preserved ejection fraction (HFpEF) patients (Surgical Resection of the Greater Splanchnic Nerve in Subjects Having Heart Failure With Preserved Ejection Fraction, NCT03715543). In this study, Gajewski et al. (Contribution 6) demonstrated that hemodynamic effects are appreciable 24 h after the procedure. As with ICD and CRT, cardiac contractility modulation (CCM) therapy is provided by leads positioned in the right ventricle. Recently, the interplay between cardiac implantable electronic devices (CIEDs) and tricuspid regurgitation (TR) has been reviewed and recognized as a distinct clinical entity that increased the risk of death [5]. Herein, a unique prospective study aimed to assess TR after CCM implantation was published by Masarone et al. (Contribution 7). Nearly half of the cohort had moderate TR, whereas patients with severe regurgitation were excluded.

Furthermore, all patients underwent CIED implantation before CCM. After six months, their TR remained stable, regardless of previous device and lead burden. The authors speculated that biventricular reverse remodeling, ventricular–arterial coupling restoration, and lowered filling pressure account for the neutral effect on TR, with possible improvements in the long term. Despite being fascinating and accurate from a pathophysiological standpoint, further studies are needed to confirm these short-term findings. In addition, CCM's safety and efficacy were assessed, evaluating its impact on the global longitudinal strain (GLS) and mechano-energetic efficiency (MEE) for the first time.

Finally, the AMY-CCM registry (NCT05167799) is presented. It aims to provide further insights into CCM therapy in a specific HF etiology, i.e., transthyretin amyloidosis.

4. Acute Heart Failure

Current guidelines identify four distinct phenotypes of AHF: acutely decompensated heart failure, acute pulmonary edema, isolated right ventricular failure, and cardiogenic shock (CS) [6]. This latter represents the most severe form of AHF, often requiring MCS. Abiragi et al. (Contribution 8) published an observational study on patients with CS who are treated by advanced HF/transplant cardiologists in a high-volume tertiary center. Unlike in most RCTs evaluating the percutaneous axial pump Impella, few patients had acute myocardial infarction (AMI). In this highly selected cohort, clinicians favored Impella in less stable patients who were post-AMI and had higher inotrope scores and body mass indexes.

Consequently, death after admission was slightly lower, albeit significant, in the Impella group. However, the overall death rates were not statistically different, and the majority of patients were successfully stabilized and even bridged to heart transplantation (HTx), highlighting the crucial role of clinicians in the selection of the more suitable MCS. Finally, a practical review summarizing recent findings on AHF management is provided by Mauro et al. (Contribution 9).

5. Advanced Heart Failure: Focus on Inotropes and Heart Transplantation

Although inotropes improve short-term hemodynamics, this has not translated into consistent survival benefits [7]; indeed, historical adrenergic inotropes have critical drawbacks: an increase in myocardial oxygen consumption, the trigger of arrhythmias, and stimulation of deleterious signaling pathways. Therefore, new mechanistic pathways have been explored, highlighting the pivotal role of calcium and enzymes modulating their cytoplasmatic concentration, i.e., sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a). Two comprehensive reviews summarized recent evidence on Levosimendan and Istaroxime in this Special Issue. Despite being the gold standard for advanced HF, the long-term management of HTx recipients remains complex [8]. This population has an increased thrombotic risk, and therefore, antithrombotic management is of the utmost importance. Despite direct oral anticoagulants (DOACs) becoming the first choice in several clinical scenarios due to a comparable efficacy and lower bleeding risk compared to historical anticoagulants, their use in HTx recipients is still debatable [9]. Darche et al. (Contribution 10) sought to assess the frequency, indications, and complications of DOACs and Vitamin K Antagonists (VKAs) in recipients who underwent HTx in the past 20 years. Nearly 50% of the selected cohort received a DOAC in this single-center retrospective analysis. Most patients were prescribed Apixaban or Rivaroxaban, whereas the use of Dabigatran was an exclusion criterion due to its pharmacokinetic interactions with immunosuppression agents. The VKA and DOAC groups were comparable for demographics and surgical and clinical variables. The occurrence of ischemic stroke and thromboembolic events was not statistically different between the two groups.

Conversely, the use of DOACs was linked to significantly fewer bleedings (both overall and gastrointestinal). Advances in immunosuppression regimens have improved outcomes and reduced rejection rates. However, recipients are exposed to a high infection risk. Thus, antimicrobial prophylaxis is a milestone in their comprehensive management [10]. Pneumocystis Jiroveci is an increasingly diagnosed opportunistic pathogen, especially within the first six months post HTx. Trimethoprim-sulfamethoxazole (TMP-SMX) is the first choice. Allergic or intolerant patients are usually switched to Dapsone. This latter option, however, has a less favorable safety profile than TMP-SMX. Indeed, documented glucose-6-phosphate dehydrogenase (G6PD) deficiencies may trigger hemolytic anemia. In this Special Issue, Lor et al. (Contribution 11) present a retrospective study of HTx patients who received prophylaxis with Dapsone after normal G6PD activity was documented.

Interestingly, 22% of patients developed significant anemia, and nearly 10% required hospitalization or blood transfusion. On the other hand, Dapsone withdrawal resulted in the rapid recovery of baseline hemoglobin levels. Therefore, periodic laboratory monitoring with a blood count is advisable. Besides long-term management, the main issue remains

donor shortage. Hence, it is crucial to broaden the pool of potential donors to decrease the death rates among patients on the waiting list. AB0 compatibility is an essential prerequisite to HTx. Indeed, ABH antigens are expressed both on red blood cells and endothelial cells. Thus, ABO antibodies are responsible for hyperacute rejection [11]. Historically, zero patients had longer wait times, since recipients with high titers of antibodies received no organs. AB0-independent approaches were successfully implemented in kidney and liver transplantation to overcome this barrier, leading to higher transplantation rates and reduced wait times without significant safety drawbacks [12]. Limited data, however, exist for this approach in HTx. Cao et al. (Contribution 12) compared the outcomes between match and mismatch groups of patients with blood type A. The mismatch group was further divided based on donor and recipient subtypes. Due to reduced antigen expression, this has potentially critical implications, since non-A1 donors may have reduced immunogenicity, allowing for safe HTx. Although the investigators did not analyze each mismatch subgroup distinctly (i.e., non-A1 donors and A1 recipients; 44% vs. non-A1 recipients and A1 donors; 56%), the fact that significant differences in outcomes between match and mismatch groups were lacking makes it unlikely that worse outcomes among non-A1 recipients will be found.

Conflicts of Interest: The authors declare no conflict of interest.

List of Contributions

1. Pagnesi, M.; Baldetti, L.; Aimo, A.; Inciardi, R.M.; Tomasoni, D.; Vizzardi, E.; Vergaro, G.; Emdin, M.; Lombardi, C.M. Prognostic Benefit of New Drugs for HFrEF: A Systematic Review and Network Meta-Analysis. *J. Clin. Med.* **2022**, *11*, 348. https://doi.org/10.3390/jcm11020348.
2. Beltrami, M.; Milli, M.; Dei, L.L.; Palazzuoli, A. The Treatment of Heart Failure in Patients with Chronic Kidney Disease: Doubts and New Developments from the Last ESC Guidelines. *J. Clin. Med.* **2022**, *11*, 2243. https://doi.org/10.3390/jcm11082243.
3. Gioia, M.I.; Parisi, G.; Grande, D.; Albanese, M.; Alcidi, G.; Correale, M.; Brunetti, N.D.; Ciccone, M.M.; Iacoviello, M. Effects of Sacubitril/Valsartan on the Renal Resistance Index. *J. Clin. Med.* **2022**, *11*, 3683. https://doi.org/10.3390/jcm11133683.
4. Masarone, D.; Kittleson, M.M.; Martucci, M.L.; Valente, F.; Gravino, R.; Verrengia, M.; Ammendola, E.; Contaldi, C.; Di Palma, V.; Caiazzo, A.; et al. Levosimendan as a "Bridge to Optimization" in Patients with Advanced Heart Failure with Reduced Ejection-A Single-Center Study. *J. Clin. Med.* **2022**, *11*, 4227. https://doi.org/10.3390/jcm11144227.
5. Cammalleri, V.; Antonelli, G.; De Luca, V.M.; Carpenito, M.; Nusca, A.; Bono, M.C.; Mega, S.; Ussia, G.P.; Grigioni, F. Functional Mitral and Tricuspid Regurgitation across the Whole Spectrum of Left Ventricular Ejection Fraction: Recognizing the Elephant in the Room of Heart Failure. *J. Clin. Med.* **2023**, *12*, 3316. https://doi.org/10.3390/jcm12093316.
6. Gajewski, P.; Fudim, M.; Kittipibul, V.; Engelman, Z.J.; Biegus, J.; Zymliński, R.; Ponikowski, P. Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction. *J. Clin. Med.* **2022**, *11*, 1063. https://doi.org/10.3390/jcm11041063.
7. Masarone, D.; Kittleson, M.M.; De Vivo, S.; D'Onofrio, A.; Rao, I.; Ammendola, E.; Errigo, V.; Martucci, M.L.; Nigro, G.; Pacileo, G. Effects of Cardiac Contractility Modulation Electrodes on Tricuspid Regurgitation in Patients with Heart Failure with Reduced Ejection Fraction: A Pilot Study. *J. Clin. Med.* **2022**, *11*, 7442. https://doi.org/10.3390/jcm11247442.
8. Abiragi, M.; Singer-Englar, T.; Cole, R.M.; Emerson, D.; Esmailian, F.; Megna, D.; Moriguchi, J.; Kobashigawa, J.A.; Kittleson, M.M. Temporary Mechanical Circulatory Support in Patients with Cardiogenic Shock: Clinical Characteristics and Outcomes. *J. Clin. Med.* **2023**, *12*, 1622. https://doi.org/10.3390/jcm12041622.
9. Mauro, C.; Chianese, S.; Cocchia, R.; Arcopinto, M.; Auciello, S.; Capone, V.; Carafa, M.; Carbone, A.; Caruso, G.; Castaldo, R.; et al. Acute Heart Failure: Diagnostic–Therapeutic Pathways and Preventive Strategies—A Real-World Clinician's Guide. *J. Clin. Med.* **2023**, *12*, 846. https://doi.org/10.3390/jcm12030846.
10. Darche, F.F.; Fabricius, L.C.; Helmschrott, M.; Rahm, A.-K.; Ehlermann, P.; Bruckner, T.; Sommer, W.; Warnecke, G.; Frey, N.; Rivinius, R. Oral Anticoagulants after Heart Transplantation—Comparison between Vitamin K Antagonists and Direct Oral Anticoagulants. *J. Clin. Med.* **2023**, *12*, 4334. https://doi.org/10.3390/jcm12134334.

11. Lor, K.W.; Kransdorf, E.P.; Patel, J.K.; Chang, D.H.; Kobashigawa, J.A.; Kittleson, M.M. Dapsone-Associated Anemia in Heart Transplant Recipients with Normal Glucose-6-Phosphate Dehydrogenase Activity. *J. Clin. Med.* **2022**, *11*, 6378. https://doi.org/10.3390/jcm11216378.
12. Cao, L.; Kim, S.; Klapper, E.; Kobashigawa, J.A.; Kittleson, M.M. Blood Type A1 Mismatch Does Not Affect Heart Transplant Outcomes at One Year. *J. Clin. Med.* **2023**, *12*, 1337. https://doi.org/10.3390/jcm12041337.

References

1. Planelles-Herrero, V.J.; Hartman, J.J.; Robert-Paganin, J.; Malik, F.I.; Houdusse, A. Mechanistic and structural basis for activation of cardiac myosin force production by omecamtiv mecarbil. *Nat. Commun.* **2017**, *8*, 190. [CrossRef] [PubMed]
2. Falco, L.; Brescia, B.; Catapano, D.; Martucci, M.L.; Valente, F.; Gravino, R.; Contaldi, C.; Pacileo, G.; Masarone, D. Vericiguat: The Fifth Harmony of Heart Failure with Reduced Ejection Fraction. *J. Cardiovasc. Dev. Dis.* **2023**, *10*, 388. [CrossRef] [PubMed]
3. Zannad, F.; Ferreira, J.P.; Pocock, S.J.; Anker, S.D.; Butler, J.; Filippatos, G.; Brueckmann, M.; Ofstad, A.P.; Pfarr, E.; Jamal, W.; et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: A meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* **2020**, *396*, 819–829. [CrossRef] [PubMed]
4. Fudim, M.; Khan, M.S.; Paracha, A.A.; Sunagawa, K.; Burkhoff, D. Targeting Preload in Heart Failure: Splanchnic Nerve Blockade and Beyond. *Circ. Heart Fail.* **2022**, *15*, e009340. [CrossRef] [PubMed]
5. Andreas, M.; Burri, H.; Praz, F.; Soliman, O.; Badano, L.; Barreiro, M.; Cavalcante, J.L.; de Potter, T.; Doenst, T.; Friedrichs, K.; et al. Tricuspid valve disease and cardiac implantable electronic devices. *Eur. Heart J.* **2023**, *45*, 346–365. [CrossRef] [PubMed]
6. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef]
7. Nandkeolyar, S.; Ryu, R.; Mohammad, A.; Cordero-Caban, K.; Abramov, D.; Tran, H.; Hauschild, C.; Stoletniy, L.; Hilliard, A.; Sakr, A. A Review of Inotropes and Inopressors for Effective Utilization in Patients with Acute Decompensated Heart Failure. *J. Cardiovasc. Pharmacol.* **2021**, *78*, 336–345. [CrossRef] [PubMed]
8. Kim, I.-C.; Youn, J.-C.; Kobashigawa, J.A. The Past, Present and Future of Heart Transplantation. *Korean Circ. J.* **2018**, *48*, 565–590. [CrossRef] [PubMed]
9. Zakko, J.; Ganapathi, A.M.; Whitson, B.A.; Mokadam, N.A.; Henn, M.C.; Lampert, B.; Kahwash, R.; Franco, V.; Haas, G.; Emani, S.; et al. Safety of direct oral anticoagulants in solid organ transplant recipients: A meta-analysis. *Clin. Transplant.* **2022**, *36*, e14513. [CrossRef] [PubMed]
10. Enzler, M.J.; Berbari, E.; Osmon, D.R. Antimicrobial Prophylaxis in Adults. *Mayo Clin. Proc.* **2011**, *86*, 686–701. [CrossRef] [PubMed]
11. Chang, A.T.; Platt, J.L. The role of antibodies in transplantation. *Transplant. Rev.* **2009**, *23*, 191–198. [CrossRef]
12. Salvadori, M.; Tsalouchos, A. Current protocols and outcomes of ABO-incompatible kidney transplantation. *World J. Transplant.* **2020**, *10*, 191–205. [CrossRef]

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Article

Oral Anticoagulants after Heart Transplantation—Comparison between Vitamin K Antagonists and Direct Oral Anticoagulants

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Abstract: Aims: Patients after heart transplantation (HTX) often require oral anticoagulants (OACs) due to atrial arrhythmias or thromboembolic events but little is known about the post-transplant use of direct oral anticoagulants (DOACs). We investigated the frequency, indications, and complications of DOACs and vitamin K antagonists (VKAs) after HTX. Methods: We screened all adult patients for the use of post-transplant OACs who underwent HTX at Heidelberg Heart Center between 2000 and 2021. Patients were stratified by type of OAC (DOAC or VKA) and by DOAC agents (apixaban, dabigatran, edoxaban, or rivaroxaban). Indications for OACs comprised atrial fibrillation, atrial flutter, pulmonary embolism, upper and lower extremity deep vein thrombosis, as well as intracardiac thrombus. Results: A total of 115 of 459 HTX recipients (25.1%) required OACs, including 60 patients with DOACs (52.2%) and 55 patients with VKAs (47.8%). Concerning DOACs, 28 patients were treated with rivaroxaban (46.7%), 27 patients with apixaban (45.0%), and 5 patients with edoxaban (8.3%). We found no significant differences between both groups concerning demographics, immunosuppressive drugs, concomitant medications, indications for OACs, ischemic stroke, thromboembolic events, or OAC-related death. Patients with DOACs after HTX had a significantly lower one-year rate of overall bleeding complications ($p = 0.002$) and a significantly lower one-year rate of gastrointestinal hemorrhage ($p = 0.011$) compared to patients with VKAs after HTX in the Kaplan–Meier estimator. Conclusions: DOACs were comparable to VKAs concerning the risk of ischemic stroke, thromboembolic events, or OAC-related death but were associated with significantly fewer bleeding complications in HTX recipients.

Keywords: atrial fibrillation; bleeding; direct oral anticoagulant; heart transplantation; oral anticoagulant; stroke; vitamin K antagonist

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1. Introduction

Although heart transplantation (HTX) has been an established treatment for patients with end-stage heart failure for several decades, the clinical management of HTX recipients remains very challenging [1,2]. Various risk factors and complications can impair survival and quality of life after HTX including graft failure, acute rejection, infections, type 2 diabetes mellitus, heart rhythm disorders, and thromboembolic complications [3–12]. Particularly atrial fibrillation (AF), stroke, and venous thromboembolism (VTE) represent common causes of morbidity and mortality after HTX with reported overall incidences of 10.1% for AF, 10.7% for stroke, and 8.5% for VTE after HTX [10–12]. Given these numbers,

oral anticoagulants (OACs) play an important role in the aftercare of HTX recipients but comprehensive guidelines for the use of OACs in HTX recipients are missing [1,13,14].

In terms of OACs, vitamin K antagonists (VKAs) were the primary OACs for several decades due to the absence of alternatives [13–18]. The disadvantages of VKAs are a long half-life, a narrow therapeutic window which requires constant laboratory monitoring, multiple drug-drug interactions, and prolonged re–establishment of the therapeutic window after a periprocedural pause [13–19]. During the last two decades, direct oral anticoagulants (DOACs) have been approved and clinically introduced which show a number of advantages over VKAs including a shorter half-life, no need for routine laboratory monitoring, fewer drug-drug interactions, and shorter periprocedural drug offset and onset effects [13–19]. In addition, several studies showed similar or even better efficacy and safety of DOACs over VKAs for the treatment of AF and VTE in the general population [20–27]. However, data on the efficacy and safety of DOACs in HTX recipients are very limited as they are often derived from small sample-size studies [17–19,28–35].

Given the little knowledge about the clinical management of HTX recipients requiring OACs, we decided to analyze HTX recipients with DOACs and VKAs focusing on indications and complications. In addition, we performed a sub-analysis of HTX recipients on DOACs comparing apixaban and rivaroxaban.

2. Patients and Methods

2.1. Patients

Our study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The institutional review board (IRB) of Heidelberg University, Heidelberg, Germany, gave approval (ethics approval number: S-286/2015, Version 1.2, 28 July 2020). We obtained written informed consent from patients for their inclusion in the Heidelberg HTX Registry and the clinical and scientific use of their data. The ethics approval does not require additional consent for this observational study as only routine clinical data were utilized [4–9].

We screened all patients ($\geq$18 years) for post-transplant use of OACs who underwent HTX at Heidelberg Heart Center, Heidelberg, Germany, between 2000 and 2021. Patients who had undergone repeat HTX were excluded. We also excluded patients with mechanical heart valves after HTX for comparison purposes as the use of DOACs is contraindicated in patients with mechanical heart valves [36]. All other adult patients with post-transplant use of OACs were included and stratified by OAC types (DOAC or VKA) and DOAC agents. Due to potential drug interactions with calcineurin inhibitors resulting in bleeding complications [13,14,34], the DOAC agent dabigatran was not used for HTX recipients at Heidelberg Heart Center. Besides this limitation, there was neither a preselection nor randomization of HTX recipients concerning the application of DOACs or VKAs during the study period as both agents were considered comparable, nor regarding the use of a specific DOAC agent (apixaban, edoxaban, or rivaroxaban). Factors influencing the prescription of DOACs or VKAs were individual physician's practice and patient's preference including pre-transplant use of DOACs or VKAs.

Indications for OACs in our study comprised AF, atrial flutter, pulmonary embolism, upper and lower extremity deep vein thrombosis (DVT), as well as intracardiac thrombus. There was no preselection or randomization of HTX recipients concerning the application of DOACs or VKAs during the study period as both agents were considered comparable.

2.2. Follow-Up

Follow-up of HTX recipients was performed in accordance with Heidelberg Heart Center's routine clinical protocol. After hospital discharge following HTX, patients were seen monthly as outpatients in the HTX clinic during the first six post-transplant months, then bimonthly until the end of the first year after HTX, and approximately three to four times per year thereafter (with additional visits on demand) [4–9].

Post-transplant routine follow-up included medical history, physical examination, systolic and diastolic blood pressure measurement, blood and laboratory tests including immunosuppressive drug monitoring, resting 12-lead ECG, echocardiography, endomyocardial biopsy, annual chest X-ray as well as annual 24-h Holter monitor. We were able to obtain complete follow-up data after HTX from all patients as no patient was lost to follow-up [4–9].

2.3. Post-Transplant Medications

Medications after HTX including immunosuppressive drugs were administered as per Heidelberg Heart Center's standard of care. Patients were perioperatively treated with an anti-thymocyte globulin-based immunosuppression induction therapy. The majority of patients in this study received an immunosuppressive drug therapy consisting of tacrolimus and mycophenolic acid as mycophenolic acid consequently replaced azathioprine from 2001 onward, and tacrolimus subsequently replaced cyclosporine A since 2006. In addition, everolimus was used depending on the clinical course of HTX recipients. Steroids were tapered incrementally during the initial post-transplant months and were routinely discontinued six months after HTX (unless clinically needed) [4–9].

2.4. Statistical Analysis

The primary outcome of this study was to compare overall bleeding complications between patients with DOACs or VKAs as oral anticoagulation after HTX. Causes of OAC-related bleeding complications after HTX were further assessed by stratification into the following categories: intracranial hemorrhage, severe epistaxis, gastrointestinal hemorrhage, and hemorrhagic shock. In addition, we analyzed the need for transfusion of FFP and PRBCs. Secondary outcomes included analysis of frequency and indications of OACs after HTX as well as ischemic stroke, thromboembolic events, and OAC-related death. We performed multiple univariate analyses in order to investigate potential intergroup differences between patients with DOACs or VKAs as oral anticoagulation after HTX as well as between patients with apixaban or rivaroxaban as oral anticoagulation after HTX. Analyzed variables comprised recipient data, recipient's previous open-heart surgery, recipient principal diagnosis for HTX, donor data, transplant sex mismatch, perioperative data, immunosuppressive drug therapy, and post-transplant concomitant medications [4–9].

Data were analyzed using SAS (Version 9.4, SAS Institute, Cary, NC, USA) and shown as mean ± standard deviation (SD), median with quartiles (Q), or as count (n) with percentage (%). For measures of association, a difference of mean with a 95% confidence interval (CI) was applied. Depending on the variable type and question, we used Student's t-test, Mann–Whitney U-test, analysis of variance (ANOVA), Kruskal–Wallis test, chi-squared test, or Fisher's exact test, as appropriate. The Kaplan–Meier estimator using log-rank test was applied to graphically compare 1-year freedom from overall bleeding complications between patients with DOACs or VKAs as oral anticoagulation after HTX as well as to analyze 1-year freedom from gastrointestinal hemorrhage between patients with DOACs or VKAs as oral anticoagulation after HTX. A p-value of < 0.050 was considered statistically significant [4–9].

3. Results

3.1. Demographics of Heart Transplant Recipients with Oral Anticoagulants

After applying exclusion criteria, a total of 115 of 459 HTX recipients (25.1%) required the use of post-transplant oral anticoagulation, including 55 patients with VKAs (55 of 115 (47.8%)) and 60 patients with DOACs (60 of 115 (52.2%)). Concerning the 60 HTX recipients with DOACs, 27 patients were treated with apixaban (27 of 60 (45.0%)), 5 patients were treated with edoxaban (5 of 60 (8.3%)), and 28 patients were treated with rivaroxaban (28 of 60 (46.7%)). No patient received dabigatran (0 of 60 (0.0%)) due to potential interactions.

The median interval from HTX to the start of oral anticoagulation was 3.3 years (Q1: 0.3 years; Q3: 8.4 years) and the median interval from the start of oral anticoagulation until the end of oral anticoagulation was 0.8 years (Q1: 0.3 years; Q3: 2.3 years). There was neither a statistically significant difference between the median interval from HTX to the start of oral anticoagulation between patients with DOACs after HTX (3.5 years (Q1: 0.2 years; Q3: 9.3 years)) and patients with VKAs after HTX (3.3 years (Q1: 0.3 years; Q3: 8.1 years; $p = 0.373$)), nor a statistically significant difference between the median interval from the start of oral anticoagulation until the end of oral anticoagulation between patients with DOACs after HTX (0.8 years (Q1: 0.4 years; Q3: 2.4 years)) and patients with VKAs after HTX (0.7 years (Q1: 0.3 years; Q3: 2.3 years; $p = 0.204$)).

Concerning demographics, we found no statistically significant differences between patients with DOACs or VKAs after HTX with regard to recipient data, recipient previous open-heart surgery, recipient principal diagnosis for HTX, donor data, transplant sex mismatch, or perioperative data (all $p \geq 0.050$). Demographics stratified by DOACs and VKAs after HTX are shown in Table 1.

Table 1. Demographics—stratified by DOACs and VKAs after HTX.

Parameter	All OACs after HTX (*n* = 115)	DOACs after HTX (*n* = 60)	VKAs after HTX (*n* = 55)	Difference	95% CI	*p*-Value
Recipient data						
Age (years), mean ± SD	52.4 ± 10.4	52.0 ± 10.8	52.9 ± 9.9	0.9	−2.9–4.7	0.652
Male sex, *n* (%)	84 (73.0%)	44 (73.3%)	40 (72.7%)	0.6%	−15.6–16.8%	0.942
BMI (kg/m^2), mean ± SD	25.2 ± 4.1	25.1 ± 4.2	25.4 ± 4.0	0.3	−1.2–1.8	0.678
Arterial hypertension, *n* (%)	61 (53.0%)	28 (46.7%)	33 (60.0%)	13.3%	−4.8–31.4%	0.152
Dyslipidemia, *n* (%)	69 (60.0%)	32 (53.3%)	37 (67.3%)	14.0%	−3.7–31.7%	0.127
Diabetes mellitus, *n* (%)	26 (22.6%)	11 (18.3%)	15 (27.3%)	9.0%	−6.3–24.3%	0.252
Peripheral artery disease, *n* (%)	4 (3.5%)	2 (3.3%)	2 (3.6%)	0.3%	−6.4–7.0%	0.929
COPD, *n* (%)	14 (12.2%)	7 (11.7%)	7 (12.7%)	1.0%	−11.0–13.0%	0.862
History of smoking, *n* (%)	56 (48.7%)	32 (53.3%)	24 (43.6%)	9.7%	−8.5–27.9%	0.299
Renal insufficiency ^, *n* (%)	62 (53.9%)	28 (46.7%)	34 (61.8%)	15.1%	−2.9–33.1%	0.103
eGFR (ml/min/1.73 m^2), mean ± SD	60.7 ± 23.8	63.7 ± 20.7	57.4 ± 26.6	6.3	−2.5–15.1	0.159
Previous open-heart surgery						
Overall open-heart surgery, *n* (%)	41 (35.7%)	24 (40.0%)	17 (30.9%)	9.1%	−8.3–26.5%	0.309
CABG surgery, *n* (%)	13 (11.3%)	5 (8.3%)	8 (14.5%)	6.2%	−5.5–17.9%	0.293
Other surgery °, *n* (%)	8 (7.0%)	6 (10.0%)	2 (3.6%)	6.4%	−2.7–15.5%	0.180
VAD surgery, *n* (%)	22 (19.1%)	15 (25.0%)	7 (12.7%)	12.3%	−1.8–26.4%	0.095
Principal diagnosis for HTX						
Ischemic CMP, *n* (%)	32 (27.8%)	17 (28.3%)	15 (27.3%)	1.0%	−15.4–17.4%	0.899
Non-ischemic CMP, *n* (%)	63 (54.8%)	31 (51.7%)	32 (58.2%)	6.5%	−11.7–24.7%	0.483
Valvular heart disease, *n* (%)	3 (2.6%)	2 (3.3%)	1 (1.8%)	1.5%	−4.3–7.3%	0.611
Cardiac amyloidosis, *n* (%)	17 (14.8%)	10 (16.7%)	7 (12.7%)	4.0%	−8.9–16.9%	0.552
Donor data						
Age (years), mean ± SD	46.0 ± 11.8	46.4 ± 12.6	45.5 ± 11.0	0.9	−3.4– 5.2	0.663
Male sex, *n* (%)	44 (38.3%)	24 (40.0%)	20 (36.4%)	3.6%	−14.2–21.4%	0.689
BMI (kg/m^2), mean ± SD	25.2 ± 4.3	25.6 ± 5.1	24.7 ± 3.1	0.9	−0.6–2.4	0.256
Transplant sex mismatch						
Mismatch, *n* (%)	47 (40.9%)	25 (41.7%)	22 (40.0%)	1.7%	−16.3–19.7%	0.856
Donor (m) to recipient (f), *n* (%)	3 (2.6%)	2 (3.3%)	1 (1.8%)	1.5%	−4.3–7.3%	0.611
Donor (f) to recipient (m), *n* (%)	44 (38.3%)	23 (38.3%)	21 (38.2%)	0.1%	−17.7–17.9%	0.987
Perioperative data						
Ischemic time (min), mean ± SD	253.9 ± 54.0	253.1 ± 57.5	254.9 ± 50.4	1.8	−17.9–21.5	0.858
Biatrial anastomosis, *n* (%)	1 (0.9%)	1 (1.7%)	0 (0.0%)	1.7%	−1.6–5.0%	0.336
Bicaval anastomosis, *n* (%)	114 (99.1%)	59 (98.3%)	55 (100.0%)	1.7%	−1.6–5.0%	0.336

BMI = body mass index; CABG = coronary artery bypass graft; CI = confidence interval; CMP = cardiomyopathy; COPD = chronic obstructive pulmonary disease; DOAC = direct oral anticoagulant; f = female; eGFR = estimated glomerular filtration rate; HTX = heart transplantation; m = male; *n* = number; OAC = oral anticoagulant; SD = standard deviation; VAD = ventricular assist device; VKA = vitamin K antagonist; ^ = eGFR < 60 mL/min/1.73 m^2; ° = congenital, valvular, or ventricular surgery.

Similarly, we observed no statistically significant differences between patients with apixaban or rivaroxaban after HTX relating to demographics (all $p \geq 0.050$). Demographics stratified by apixaban and rivaroxaban after HTX are presented in Table 2.

Table 2. Demographics—stratified by apixaban and rivaroxaban after HTX.

Parameter	Both DOACs after HTX (*n* = 55)	Apixaban after HTX (*n* = 27)	Rivaroxaban after HTX (*n* = 28)	Difference	95% CI	*p*-Value
Recipient data						
Age (years), mean ± SD	51.7 ± 11.1	52.6 ± 8.8	50.8 ± 13.1	1.8	−4.1–7.7	0.549
Male sex, *n* (%)	41 (74.5%)	20 (74.1%)	21 (75.0%)	0.9%	−22.1–23.9%	0.937
BMI (kg/m^2), mean ± SD	25.2 ± 4.4	25.0 ± 4.3	25.4 ± 4.5	0.4	−1.9–2.7	0.736
Arterial hypertension, *n* (%)	27 (49.1%)	13 (48.1%)	14 (50.0%)	1.9%	−24.5–28.3%	0.891
Dyslipidemia, *n* (%)	30 (54.5%)	16 (59.3%)	14 (50.0%)	9.3%	−16.9–35.5%	0.491
Diabetes mellitus, *n* (%)	10 (18.2%)	6 (22.2%)	4 (14.3%)	7.9%	−12.4–28.2%	0.446
Peripheral artery disease, *n* (%)	2 (3.6%)	1 (3.7%)	1 (3.6%)	0.1%	−9.8–10.0%	0.979
COPD, *n* (%)	6 (10.9%)	3 (11.1%)	3 (10.7%)	0.4%	−16.1–16.9%	0.962
History of smoking, *n* (%)	29 (52.7%)	14 (51.9%)	15 (53.6%)	1.7%	−24.7–28.1%	0.898
Renal insufficiency ^, *n* (%)	26 (47.3%)	15 (55.6%)	11 (39.3%)	16.3%	−9.8–42.4%	0.227
eGFR (ml/min/1.73 m^2), mean ± SD	63.8 ± 20.7	59.0 ± 21.3	68.3 ± 19.4	9.3	−1.5–20.1	0.097
Previous open-heart surgery						
Overall open-heart surgery, *n* (%)	21 (38.2%)	8 (29.6%)	13 (46.4%)	16.8%	−8.5–42.1%	0.200
CABG surgery, *n* (%)	5 (9.1%)	2 (7.4%)	3 (10.7%)	3.3%	−11.8–18.4%	0.670
Other surgery °, *n* (%)	5 (9.1%)	2 (7.4%)	3 (10.7%)	3.3%	−11.8–18.4%	0.670
VAD surgery, *n* (%)	13 (23.6%)	5 (18.5%)	8 (28.6%)	10.1%	−12.1–32.3%	0.380
Principal diagnosis for HTX						
Ischemic CMP, *n* (%)	17 (30.9%)	8 (29.6%)	9 (32.1%)	2.5%	−21.9–26.9%	0.840
Non-ischemic CMP, *n* (%)	28 (50.9%)	13 (48.1%)	15 (53.6%)	5.5%	−20.9–31.9%	0.688
Valvular heart disease, *n* (%)	1 (1.8%)	0 (0.0%)	1 (3.6%)	3.6%	−3.3–10.5%	0.322
Cardiac amyloidosis, *n* (%)	9 (16.4%)	6 (22.2%)	3 (10.7%)	11.5%	−7.9–30.9%	0.249
Donor data						
Age (years), mean ± SD	46.4 ± 12.0	47.6 ± 11.2	45.3 ± 12.8	2.3	−4.0–8.6	0.486
Male sex, *n* (%)	21 (38.2%)	8 (29.6%)	13 (46.4%)	16.8%	−8.5–42.1%	0.200
BMI (kg/m^2), mean ± SD	25.7 ± 5.2	25.1 ± 4.6	26.3 ± 5.8	1.2	−1.5–3.9	0.384
Transplant sex mismatch						
Mismatch, *n* (%)	25 (45.5%)	12 (44.4%)	13 (46.4%)	2.0%	−24.3– 28.3%	0.883
Donor (m) to recipient (f), *n* (%)	2 (3.6%)	0 (0.0%)	2 (7.1%)	7.1%	−2.4–16.6%	0.157
Donor (f) to recipient (m), *n* (%)	23 (41.8%)	12 (44.4%)	11 (39.3%)	5.1%	−21.0–31.2%	0.698
Perioperative data						
Ischemic time (min), mean ± SD	251.4 ± 59.4	249.4 ± 53.2	253.3 ± 65.7	3.9	−27.7–35.5	0.812
Biatrial anastomosis, *n* (%)	1 (1.8%)	0 (0.0%)	1 (3.6%)	3.6%	−3.3–10.5%	0.322
Bicaval anastomosis, *n* (%)	54 (98.2%)	27 (100.0%)	27 (96.4%)	3.6%	−3.3–10.5%	0.322

BMI = body mass index; CABG = coronary artery bypass graft; CI = confidence interval; CMP = cardiomyopathy; COPD = chronic obstructive pulmonary disease; DOAC = direct oral anticoagulant; f = female; eGFR = estimated glomerular filtration rate; HTX = heart transplantation; m = male; *n* = number; SD = standard deviation; VAD = ventricular assist device; ^ = eGFR < 60 mL/min/1.73 m^2; ° = congenital, valvular, or ventricular surgery.

3.2. Medications of Heart Transplant Recipients with Oral Anticoagulants

In terms of the immunosuppressive drug therapy, we discovered no statistically significant differences between patients with DOACs or VKAs after HTX regarding the use of cyclosporine A, tacrolimus, everolimus, azathioprine, mycophenolic acid, or steroids (all $p \geq 0.050$).

We also observed no statistically significant differences between patients with DOACs or VKAs after HTX concerning the administration of oral antiplatelet drugs, beta-blockers, ivabradine, calcium channel blockers, angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers, diuretics, statins, or gastric protection drugs (all $p \geq 0.050$). Medications stratified by DOACs and VKAs after HTX are provided in Table 3.

Likewise, there were no statistically significant differences between patients with apixaban or rivaroxaban after HTX concerning immunosuppressive drugs or concomitant medications (all $p \geq 0.050$). Medications stratified by apixaban and rivaroxaban after HTX are given in Table 4.

Table 3. Medications—stratified by DOACs and VKAs after HTX.

Parameter	All OACs after HTX (*n* = 115)	DOACs after HTX (*n* = 60)	VKAs after HTX (*n* = 55)	Difference	95% CI	*p*-Value
Immunosuppressive drug therapy						
Cyclosporine A, *n* (%)	22 (19.1%)	11 (18.3%)	11 (20.0%)	1.7%	−12.7–16.1%	0.820
Tacrolimus, *n* (%)	73 (63.5%)	38 (63.3%)	35 (63.6%)	0.3%	−17.3–17.9%	0.973
Everolimus, *n* (%)	54 (47.0%)	28 (46.7%)	26 (47.3%)	0.6%	−17.7–18.9%	0.948
Azathioprine, *n* (%)	1 (0.9%)	0 (0.0%)	1 (1.8%)	1.8%	−1.7–5.3%	0.294
Mycophenolic acid, *n* (%)	80 (69.6%)	43 (71.7%)	37 (67.3%)	4.4%	−12.4–21.2%	0.609
Steroids, *n* (%)	55 (47.8%)	28 (46.7%)	27 (49.1%)	2.4%	−15.9–20.7%	0.795
Concomitant medications						
Oral antiplatelet drug, *n* (%)	18 (15.7%)	10 (16.7%)	8 (14.5%)	2.2%	−11.1–15.5%	0.754
Beta blocker, *n* (%)	76 (66.1%)	40 (66.7%)	36 (65.5%)	1.2%	−16.1–18.5%	0.891
Ivabradine, *n* (%)	30 (26.1%)	16 (26.7%)	14 (25.5%)	1.2%	−14.9–17.3%	0.882
Calcium channel blocker, *n* (%)	32 (27.8%)	17 (28.3%)	15 (27.3%)	1.0%	−15.4–17.4%	0.899
ACE inhibitor/ARB, *n* (%)	81 (70.4%)	43 (71.7%)	38 (69.1%)	2.6%	−14.1–19.3%	0.762
Diuretic, *n* (%)	82 (71.3%)	42 (70.0%)	40 (72.7%)	2.7%	−13.8–19.2%	0.747
Statin, *n* (%)	100 (87.0%)	53 (88.3%)	47 (85.5%)	2.8%	−9.6–15.2%	0.647
Gastric protection †, *n* (%)	86 (74.8%)	44 (73.3%)	42 (76.4%)	3.1%	−12.8–19.0%	0.709

ACE inhibitor = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; CI = confidence interval; DOAC = direct oral anticoagulant; HTX = heart transplantation; *n* = number; OAC = oral anticoagulant; VKA = vitamin K antagonist; † = gastric protection drug defined as proton pump inhibitor (PPI) or histamine receptor (H2) blocker.

Table 4. Medications—stratified by apixaban and rivaroxaban after HTX.

Parameter	Both DOACs after HTX (*n* = 55)	Apixaban after HTX (*n* = 27)	Rivaroxaban after HTX (*n* = 28)	Difference	95% CI	*p*-Value
Immunosuppressive drug therapy						
Cyclosporine A, *n* (%)	8 (14.5%)	3 (11.1%)	5 (17.9%)	6.8%	−11.7–25.3%	0.478
Tacrolimus, *n* (%)	36 (65.5%)	19 (70.4%)	17 (60.7%)	9.7%	−15.3–34.7%	0.452
Everolimus, *n* (%)	28 (50.9%)	12 (44.4%)	16 (57.1%)	12.7%	−13.5–38.9%	0.346
Azathioprine, *n* (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0%	n. a.	n. a.
Mycophenolic acid, *n* (%)	38 (69.1%)	20 (74.1%)	18 (64.3%)	9.8%	−14.5–34.1%	0.432
Steroids, *n* (%)	25 (45.5%)	11 (40.7%)	14 (50.0%)	9.3%	−16.9–35.5%	0.491
Concomitant medications						
Oral antiplatelet drug, *n* (%)	10 (18.2%)	5 (18.5%)	5 (17.9%)	0.6%	−19.8–21.0%	0.949
Beta blocker, *n* (%)	37 (67.3%)	16 (59.3%)	21 (75.0%)	15.7%	−8.8–40.2%	0.214
Ivabradine, *n* (%)	15 (27.3%)	6 (22.2%)	9 (32.1%)	9.9%	−13.4–33.2%	0.409
Calcium channel blocker, *n* (%)	15 (27.3%)	8 (29.6%)	7 (25.0%)	4.6%	−18.9–28.1%	0.700
ACE inhibitor/ARB, *n* (%)	39 (70.9%)	18 (66.7%)	21 (75.0%)	8.3%	−15.6–32.2%	0.496
Diuretic, *n* (%)	38 (69.1%)	17 (63.0%)	21 (75.0%)	12.0%	−12.3–36.3%	0.334
Statin, *n* (%)	49 (89.1%)	24 (88.9%)	25 (89.3%)	0.4%	−16.1–16.9%	0.962
Gastric protection †, *n* (%)	39 (70.9%)	18 (66.7%)	21 (75.0%)	8.3%	−15.6–32.2%	0.496

ACE inhibitor = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; CI = confidence interval; DOAC = direct oral anticoagulant; HTX = heart transplantation; *n* = number; n. a. = not applicable; † = gastric protection drug defined as proton pump inhibitor (PPI) or histamine receptor (H2) blocker.

3.3. Indications and Complications of Heart Transplant Recipients with Oral Anticoagulants

Indications for the use of OACs included 33 HTX recipients with post-transplant AF (28.7%), 27 HTX recipients with post-transplant atrial flutter (23.5%), 8 HTX recipients with post-transplant pulmonary embolism (7.0%), 12 HTX recipients with post-transplant upper extremity DVT (10.4%), 28 HTX recipients with post-transplant lower extremity DVT (24.3%), and 7 HTX recipients with post-transplant intracardiac thrombus (6.1%).

We observed no statistically significant differences between HTX recipients with DOACs and VKAs regarding the indication of AF ($p = 0.462$), atrial flutter ($p = 0.399$),

pulmonary embolism ($p = 0.898$), upper extremity DVT ($p = 0.873$), lower extremity DVT ($p = 0.257$), or intracardiac thrombus ($p = 0.611$).

Assessment of OAC-related complications showed no statistically significant differences between HTX recipients with DOACs and VKAs concerning ischemic stroke ($p = 0.929$), thromboembolic events ($p = 0.611$), or OAC-related death ($p = 0.508$) but HTX recipients with VKAs had a significantly higher percentage of overall bleedings (18 of 55 (32.7%)) in comparison to HTX recipients with DOACs (6 of 60 (10.0%); difference: 22.7%; 95% CI: 8.2–37.2%; $p = 0.003$). Indications and complications split by DOACs and VKAs after HTX are shown in Table 5.

Table 5. Indications and complications—split by DOACs and VKAs after HTX.

Parameter	All OACs after HTX (*n* = 115)	DOACs after HTX (*n* = 60)	VKAs after HTX (*n* = 55)	Difference	95% CI	*p*-Value
Indications						
Atrial fibrillation, *n* (%)	33 (28.7%)	19 (31.7%)	14 (25.5%)	6.2%	−10.3–22.7%	0.462
Atrial flutter, *n* (%)	27 (23.5%)	16 (26.7%)	11 (20.0%)	6.7%	−8.7–22.1%	0.399
Pulmonary embolism, *n* (%)	8 (7.0%)	4 (6.7%)	4 (7.3%)	0.6%	−8.7–9.9%	0.898
Upper extremity DVT, *n* (%)	12 (10.4%)	6 (10.0%)	6 (10.9%)	0.9%	−10.3–12.1%	0.873
Lower extremity DVT, *n* (%)	28 (24.3%)	12 (20.0%)	16 (29.1%)	9.1%	−6.6–24.8%	0.257
Intracardiac thrombus, *n* (%)	7 (6.1%)	3 (5.0%)	4 (7.3%)	2.3%	−6.5–11.1%	0.611
OAC-related complications						
Overall bleedings, *n* (%)	24 (20.9%)	6 (10.0%)	18 (32.7%)	22.7%	8.2–37.2%	0.003 *
Ischemic stroke, *n* (%)	4 (3.5%)	2 (3.3%)	2 (3.6%)	0.3%	−6.4–7.0%	0.929
Thromboembolic event, *n* (%)	3 (2.6%)	2 (3.3%)	1 (1.8%)	1.5%	−4.2–7.2%	0.611
OAC-related death, *n* (%)	3 (2.6%)	1 (1.7%)	2 (3.6%)	1.9%	−4.0–7.8%	0.508
OAC-related bleedings						
Intracranial hemorrhage, *n* (%)	2 (1.7%)	0 (0.0%)	2 (3.6%)	3.6%	−1.3–8.5%	0.136
Severe epistaxis, *n* (%)	4 (3.5%)	1 (1.7%)	3 (5.5%)	3.8%	−3.1–10.7%	0.268
Gastrointestinal hemorrhage, *n* (%)	16 (13.9%)	4 (6.7%)	12 (21.8%)	15.1%	2.5–27.7%	0.019 *
Hemorrhagic shock, *n* (%)	2 (1.7%)	1 (1.7%)	1 (1.8%)	0.1%	−4.7–4.9%	0.950
Transfusion of FFP, *n* (%)	2 (1.7%)	1 (1.7%)	1 (1.8%)	0.1%	−4.7–4.9%	0.950
Transfusion of PRBCs, *n* (%)	22 (19.1%)	6 (10.0%)	16 (29.1%)	19.1%	4.9–33.3%	0.009 *

CI = confidence interval; DVT = deep vein thrombosis; DOAC = direct oral anticoagulant; FFP = fresh frozen plasma; HTX = heart transplantation; *n* = number; OAC = oral anticoagulant; PRBCs = packed red blood cells; VKA = vitamin K antagonist; * = statistically significant ($p < 0.050$).

In addition, Kaplan–Meier estimator displayed a significantly higher one-year rate of overall bleeding complications in patients with VKAs after HTX ($p = 0.002$).

Further investigations revealed that HTX recipients with VKAs showed a significantly higher percentage of gastrointestinal hemorrhage (12 of 55 (21.8%) vs. 4 of 60 (6.7%); difference: 15.1%; 95% CI: 2.5–27.7%; $p = 0.019$) and required more frequent transfusion of PRBCs (16 of 55 (29.1%) vs. 6 of 60 (10.0%); difference: 19.1%; 95% CI: 4.9–33.3%; $p = 0.009$). Patients with VKAs after HTX also had a higher one-year rate of gastrointestinal hemorrhage in the Kaplan–Meier estimator ($p = 0.011$). Kaplan–Meier estimators are displayed in Figures 1 and 2.

At the time of bleeding complications, two-thirds of HTX recipients with VKAs (12 of 18 (66.7%)) had an international normalized ratio (INR) level above the therapeutic range which is associated with a higher risk of bleeding. In contrast, we could not observe a relationship between DOAC dosing and bleeding complications of those six HTX recipients on DOACs who suffered from bleeding complications, only two patients were on full dose DOACs (2 of 6 (33.3%)), while four patients were on reduced dose DOACs (4 of 6 (66.7%)).

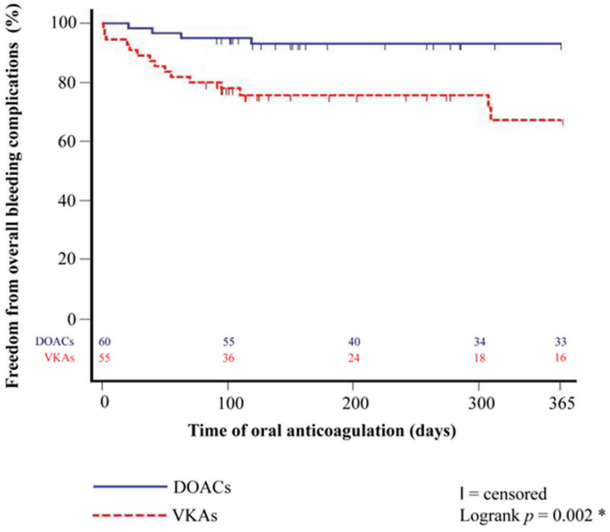

Figure 1. One-year freedom from overall bleeding complications between patients with DOACs and VKAs after HTX (Kaplan–Meier estimator). Patients with DOACs after HTX had a significantly lower one-year rate of overall bleeding complications than patients with VKAs after HTX ($p = 0.002$). DOAC = direct oral anticoagulant; HTX = heart transplantation; VKA = vitamin K antagonist; * = statistically significant ($p < 0.050$).

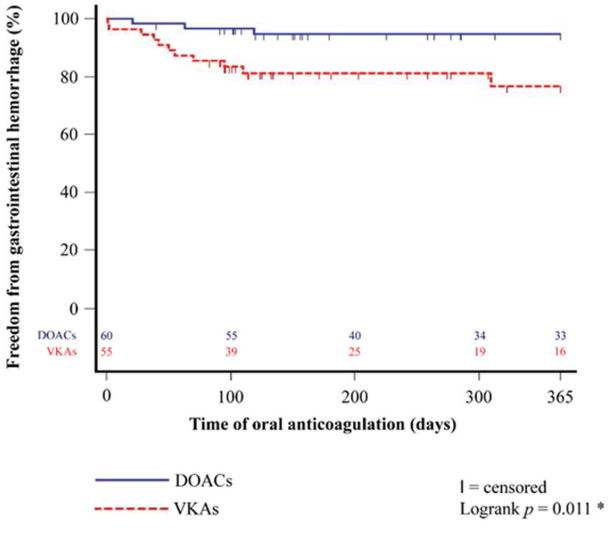

Figure 2. One-year freedom from gastrointestinal hemorrhage between patients with DOACs and VKAs after HTX (Kaplan–Meier estimator). Patients with DOACs after HTX had a significantly lower one-year rate of gastrointestinal hemorrhage than patients with VKAs after HTX ($p = 0.011$). DOAC = direct oral anticoagulant; HTX = heart transplantation; VKA = vitamin K antagonist; * = statistically significant ($p < 0.050$).

In terms of dosing of DOACs in general, 30 of 60 HTX recipients (50.0%) received a reduced dose of DOAC. Reasons for dose adjustment included reduced renal function in 20 of 30 HTX recipients (66.7%) and concomitant anti-platelet use in 10 of 30 HTX recipients (33.3%). Comparison of HTX recipients with apixaban or rivaroxaban showed

no statistically significant difference in overall reduced dose of DOAC (13 of 27 (48.1%) vs. 12 of 28 (42.9%); difference: 5.2%; 95% CI: −21.1–31.5%; $p = 0.694$), dose adjustment of DOAC due to reduced renal function (8 of 27 (29.6%) vs. 7 of 28 (25.0%); difference: 4.6%; 95% CI: −18.9–28.1%; $p = 0.700$), or a dose of DOAC adjustment due to concomitant anti-platelet use (5 of 27 (18.5%) vs. 5 of 28 (17.9%); difference: 0.6%; 95% CI: −19.8–21.0%; $p = 0.949$). We also observed no statistically significant differences between HTX recipients with apixaban or rivaroxaban in terms of indications, OAC-related complications, and OAC-related bleeding (all $p \geq 0.050$). Indications and complications split by apixaban and rivaroxaban after HTX are given in Table 6.

Table 6. Indications and complications—split by apixaban and rivaroxaban after HTX.

Parameter	Both DOACs after HTX (*n* = 55)	Apixaban after HTX (*n* = 27)	Rivaroxaban after HTX (*n* = 28)	Difference	95% CI	*p*-Value
Indications						
Atrial fibrillation, *n* (%)	16 (29.1%)	10 (37.0%)	6 (21.4%)	15.6%	−8.1–39.3%	0.203
Atrial flutter, *n* (%)	16 (29.1%)	6 (22.2%)	10 (35.7%)	13.5%	−10.2–37.2%	0.271
Pulmonary embolism, *n* (%)	4 (7.3%)	3 (11.1%)	1 (3.6%)	7.5%	−6.2–21.2%	0.282
Upper extremity DVT, *n* (%)	5 (9.1%)	3 (11.1%)	2 (7.1%)	4.0%	−11.2–19.2%	0.609
Lower extremity DVT, *n* (%)	11 (20.0%)	4 (14.8%)	7 (25.0%)	10.2%	−10.7–31.1%	0.345
Intracardiac thrombus, *n* (%)	3 (5.5%)	1 (3.7%)	2 (7.1%)	3.4%	−8.5–15.3%	0.574
OAC-related complications						
Overall bleedings, *n* (%)	5 (9.1%)	3 (11.1%)	2 (7.1%)	4.0%	−11.2–19.2%	0.609
Ischemic stroke, *n* (%)	2 (3.6%)	1 (3.7%)	1 (3.6%)	0.1%	−9.8–10.0%	0.979
Thromboembolic event, *n* (%)	2 (3.6%)	1 (3.7%)	1 (3.6%)	0.1%	−9.8–10.0%	0.979
OAC-related death, *n* (%)	1 (1.8%)	1 (3.7%)	0 (0.0%)	3.7%	−3.4–10.8%	0.304
OAC-related bleedings						
Intracranial hemorrhage, *n* (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0%	n.a.	n.a.
Severe epistaxis, *n* (%)	1 (1.8%)	1 (3.7%)	0 (0.0%)	3.7%	−3.4–10.8%	0.304
Gastrointestinal hemorrhage, *n* (%)	3 (5.5%)	1 (3.7%)	2 (7.1%)	3.4%	−8.5–15.3%	0.574
Hemorrhagic shock, *n* (%)	1 (1.8%)	1 (3.7%)	0 (0.0%)	3.7%	−3.4–10.8%	0.304
Transfusion of FFP, *n* (%)	1 (1.8%)	1 (3.7%)	0 (0.0%)	3.7%	−3.4–10.8%	0.304
Transfusion of PRBCs, *n* (%)	5 (9.1%)	3 (11.1%)	2 (7.1%)	4.0%	−11.2–19.2%	0.609

CI = confidence interval; DVT = deep vein thrombosis; DOAC = direct oral anticoagulant; FFP = fresh frozen plasma; HTX = heart transplantation; *n* = number; n.a. = not applicable; OAC = oral anticoagulant; PRBCs = packed red blood cells.

3.4. Sensitivity Analysis

Due to the long study period (2000–2021), we investigated a possible era effect by dividing all 115 HTX recipients with OACs into two different time periods (48 patients with the date of HTX between 2000 and 2009 vs. 67 patients with the date of HTX between 2010 and 2021). There was no statistically significant difference regarding the use of OACs between patients who received HTX between 2000 and 2009 (27 of 48 HTX recipients with VKA (56.2%) vs. 21 of 48 HTX recipients with DOACs (43.8%)) and patients who received HTX between 2010 and 2021 (28 of 67 HTX recipients with VKA (41.8%) vs. 39 of 67 HTX recipients with DOACs (58.2%); $p = 0.126$). Further analysis showed comparable results for both subgroups supporting the robustness of our findings and reducing the likelihood of a potential era effect.

4. Discussion

4.1. Frequency and Indications of Oral Anticoagulants after Heart Transplantation

Clinical management of HTX recipients frequently involves the treatment of atrial arrhythmias or thromboembolic events implying the need for OACs [10–16]. However, data about OACs in HTX recipients, especially about the efficacy and safety of DOACs, are scarce and mainly based on case series or small sample size studies [17–19,28–35]. We, therefore, performed the largest known study about the frequency, indications, and complications of

DOACs after HTX. A total of 115 of 459 HTX recipients (25.1%) required OACs, including 60 patients with DOACs (52.2%) and 55 patients with VKAs (47.8%). This frequency of OACs after HTX is in line with findings by Tremblay-Gravel and colleagues [35] who reported 80 of 426 HTX recipients (18.8%) on OACs, including 57 patients with DOACs (71.3%), as well as with findings by Kim and colleagues [33] who reported 18 of 55 HTX recipients (32.7%) on OACs, including 7 patients with DOACs (38.9%).

Among HTX recipients with DOACs, most patients in our study received either apixaban (45.0%) or rivaroxaban (46.7%), while only a minority received edoxaban (8.3%). Given the potential interactions with calcineurin inhibitors resulting in bleeding complications [13,14,34], no patient in our study received dabigatran. A similar distribution of DOACs after HTX was reported by Bellam and colleagues [32] with apixaban (73.9%) and rivaroxaban (26.1%) as the two most used DOACs, while also no patient received dabigatran.

As DOACs can be used for several indications [13,14], we compared the different indications of DOACs and VKAs after HTX. We found no significant differences between HTX recipients with DOACs or VKAs concerning the indications of AF, atrial flutter, pulmonary embolism, upper extremity DVT, lower extremity DVT, and intracardiac thrombus. We would like to emphasize that we excluded patients with mechanical heart valves after HTX for comparison purposes as the use of DOACs is contraindicated in patients with mechanical heart valves [36].

Altogether, about one-quarter of HTX recipients in our study required OACs for several indications, highlighting the clinical importance of DOACs as an alternative to VKAs.

4.2. Efficacy of Oral Anticoagulants after Heart Transplantation

The primary goal of OACs is the prevention of thromboembolic stroke in patients with AF and the prevention of the progression or recurrence of thromboembolic events in patients with VTE [13–16]. Several studies have shown a comparable efficacy of DOACs in comparison to VKAs in the general population [20–27] but data about the efficacy of DOACs after HTX are limited [17–19,28–35].

In terms of efficacy, we observed no statistically significant differences between HTX recipients with DOACs and VKAs concerning ischemic stroke (3.3% vs. 3.6%), thromboembolic events (3.3% vs. 1.8%), or OAC-related death (1.7% vs. 3.6%). Similar results were reported by Henricksen and colleagues [19] who reported VTE recurrence in 2 of 51 HTX recipients with DOACs (3.9%), while they observed no recurrence of VTE in 22 HTX recipients with VKAs (0.0%). Likewise, Lichvar and colleagues [28] reported two VTE (5.4%) during DOAC therapy in 37 cardiothoracic transplant recipients including five patients with HTX, one single lung transplant recipient with lower extremity VTE, and one HTX recipient with a left ventricular apical thrombus. In addition, no strokes or transient ischemic attacks were reported [28].

Regarding the efficacy of apixaban and rivaroxaban in HTX recipients, we detected no statistically significant differences concerning ischemic stroke, thromboembolic events, or OAC-related death which is in accordance with results by Pasley and colleagues [29] who also reported no statistically significant differences between 26 cardiothoracic transplant recipients with apixaban and 12 cardiothoracic transplant recipients with non-apixaban DOACs (10 patients with rivaroxaban and 2 patients with dabigatran) regarding thromboembolic events ($p = 0.23$) or death while on DOAC ($p = 1.0$).

In this light, the above-mentioned data suggest that DOACs are as effective as VKAs in HTX recipients regarding the prevention of ischemic stroke and VTE after HTX. In addition, the efficacy of apixaban and rivaroxaban in HTX recipients appears to be comparable.

4.3. Safety of Oral Anticoagulants after Heart Transplantation

Besides efficacy, safety plays an important role in HTX recipients requiring OACs [13,14]. The safe use of VKAs necessitates a stable therapeutic INR level within a narrow therapeutic window including close laboratory monitoring [13,14,37–39]. Lower INR levels can increase the risk of thromboembolic events, while INR levels above the therapeutic

range are associated with a higher risk of bleeding complications [13,14,37–43]. A time in the therapeutic range (TTR) > 70% is regarded as INR stability [40]. However, this target TTR is rarely achieved or sustained for long [41]. In terms of patients after HTX, there are no available data about the percentage of time in which HTX recipients with VKAs are in the therapeutic range but Pokorney and colleagues [42] reported that patients in community-based clinical practice with AF and VKAs had INR levels between 2.0 and 3.0 only in 59% of the time. Likewise, Rose and colleagues [43] reported a rate of only 58% of INR levels in the therapeutic range. The causes for INR instability are multifactorial including age, heart failure, diabetes mellitus, alimentation, adherence to therapy, drug interactions, and genetic polymorphisms which makes it difficult to predict future changes in INR levels [37–43]. Thus, clinical prediction tools can only explain less than 10% of INR fluctuations and more than 40% of all hemorrhagic events occur at INR levels > 3.0 [41].

In our study, HTX recipients with VKAs had a significantly higher percentage of overall bleeding complications, gastrointestinal hemorrhage, and transfusion of PRBCs in comparison to HTX recipients with DOACs. Of notice, two-thirds of HTX recipients with VKAs who suffered from overall bleeding complications had an INR level above the therapeutic range (12 of 18 (66.7%)). Similar results were reported by Henricksen and colleagues [19] who observed a trend toward a lower rate of overall bleeding complications in HTX recipients with DOACs (5 of 51 (9.8%)) compared to HTX recipients with VKAs (5 of 22 (22.7%); $p = 0.08$). Furthermore, they found a significantly lower rate of bleeding requiring transfusion in HTX recipients with DOACs ($p = 0.04$) compared to HTX recipients with VKAs [19].

Concerning the safety of apixaban and rivaroxaban in HTX recipients, we observed no statistically significant differences regarding overall bleeding complications, gastrointestinal hemorrhage, or transfusion of PRBCs which is in line with findings by Pasley and colleagues [29] who also found no statistically significant differences between 26 cardiothoracic transplant recipients with apixaban and 12 cardiothoracic transplant recipients with non-apixaban DOACs (ten patients with rivaroxaban and two patients with dabigatran) regarding overall bleeding complications ($p = 0.35$).

Hence, based on our data and the findings from other studies, the use of DOACs after HTX appears safe and effective. Given the lack of data about the use of edoxaban after HTX and the potential interactions between dabigatran and calcineurin inhibitors, apixaban or rivaroxaban seem to be the first choice for the treatment of atrial arrhythmias or thromboembolic events after HTX.

4.4. Study Limitations

Our findings were derived from a large single-center registry (Heidelberg HTX Registry). Given the known limitations of this retrospective analysis of data, our findings should be interpreted carefully and within the context of the existing literature. However, we would like to emphasize that our analysis is the largest known study so far about the use of OACs in HTX recipients comparing DOACs and VKAs. Furthermore, we obtained highly detailed data from all 115 HTX recipients with OACs, as our patients received standardized treatment and follow-up, reducing the likelihood of selection bias and potential confounders [4–9].

In order to acquire a reasonable number of HTX recipients with post-transplant use of OACs, we decided to analyze patients who received HTX at the Heidelberg Heart Center between 2000 and 2021. Given the long study period, a possible era effect due to changes in surgical and medical care may have influenced our results. We, therefore, investigated a possible era effect by dividing HTX recipients with OACs into two different time periods. We found no statistically significant difference regarding the use of OACs between patients who received HTX between 2000 and 2009 vs. 2010 and 2021. In addition, a sensitivity analysis of both groups showed similar findings supporting the robustness of our results and reducing the likelihood of a potential era effect [4–9].

Given the lack of routine assessment of DOAC-specific anti-Xa activity, we could not perform further investigations to explore the use of DOAC-specific anti-Xa monitoring. However, data about the benefits of DOAC-specific anti-Xa monitoring in HTX recipients are rare and its clinical use is still the subject of debate [19,30,31].

Finally, our findings should be interpreted as hypothesis-generating, particularly in the context of bleeding complications after HTX as several factors can cause an increased risk for hemorrhage. We can therefore neither prove nor disprove a causal relationship but merely indicate an association. Additionally, long-term differences between DOACs and VKAs in HTX recipients remain unknown and require further investigation, preferably in the form of large multicenter trials.

5. Conclusions

In summary, based on our results, DOACs were comparable to VKAs concerning the risk of ischemic stroke, thromboembolic events, or OAC-related death but were associated with significantly fewer bleeding complications in HTX recipients. In addition, subgroup analysis of HTX recipients with apixaban and rivaroxaban indicated comparable effects of both agents regarding clinical efficacy and safety after HTX.

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Institutional Review Board Statement: This study was performed in accordance with the ethical standards of the Declaration of Helsinki. Approval was granted by the institutional review board (IRB) of Heidelberg University (ethics approval number: S-286/2015, Version 1.2, 28 July 2020).

Informed Consent Statement: We obtained written informed consent from patients for their inclusion in the Heidelberg HTX Registry and the clinical and scientific use of their data. The ethics approval does not require additional consent for this observational study as only routine clinical data were used.

Data Availability Statement: The original contributions presented in this study are included in the article, further inquiries can be directed to the corresponding author.

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References

1. Costanzo, M.R.; Dipchand, A.; Starling, R.; Anderson, A.; Chan, M.; Desai, S.; Fedson, S.; Fisher, P.; Gonzales-Stawinski, G.; Martinelli, L.; et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J. Heart Lung Transplant.* **2010**, *29*, 914–956. [CrossRef]
2. Mehra, M.R.; Canter, C.E.; Hannan, M.M.; Semigran, M.J.; Uber, P.A.; Baran, D.A.; Danziger-Isakov, L.; Kirklin, J.K.; Kirk, R.; Kushwaha, S.S.; et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. *J. Heart Lung Transplant.* **2016**, *35*, 1–23. [CrossRef] [PubMed]
3. Kirklin, J.K.; Naftel, D.C.; Bourge, R.C.; McGiffin, D.C.; Hill, J.A.; Rodeheffer, R.J.; Jaski, B.E.; Hauptman, P.J.; Weston, M.; White-Williams, C. Evolving trends in risk profiles and causes of death after heart transplantation: A ten-year multi-institutional study. *J. Thorac. Cardiovasc. Surg.* **2003**, *125*, 881–890. [CrossRef] [PubMed]

4. Heil, K.M.; Helmschrott, M.; Darche, F.F.; Bruckner, T.; Ehlermann, P.; Kreusser, M.M.; Doesch, A.O.; Sommer, W.; Warnecke, G.; Frey, N.; et al. Risk Factors, Treatment and Prognosis of Patients with Lung Cancer after Heart Transplantation. *Life* **2021**, *11*, 1344. [CrossRef]
5. Rivinius, R.; Helmschrott, M.; Ruhparwar, A.; Schmack, B.; Darche, F.F.; Thomas, D.; Bruckner, T.; Katus, H.A.; Ehlermann, P.; Doesch, A.O. COPD in patients after heart transplantation is associated with a prolonged hospital stay, early posttransplant atrial fibrillation, and impaired posttransplant survival. *Clin. Epidemiol.* **2018**, *10*, 1359–1369. [CrossRef]
6. Rivinius, R.; Gralla, C.; Helmschrott, M.; Darche, F.F.; Ehlermann, P.; Bruckner, T.; Sommer, W.; Warnecke, G.; Kopf, S.; Szendroedi, J.; et al. Pre-transplant Type 2 Diabetes Mellitus Is Associated with Higher Graft Failure and Increased 5-Year Mortality After Heart Transplantation. *Front. Cardiovasc. Med.* **2022**, *9*, 890359. [CrossRef]
7. Rivinius, R.; Helmschrott, M.; Rahm, A.K.; Darche, F.F.; Thomas, D.; Bruckner, T.; Doesch, A.O.; Ehlermann, P.; Katus, H.A.; Zitron, E. Risk factors and survival of patients with permanent pacemaker implantation after heart transplantation. *J. Thorac. Dis.* **2019**, *11*, 5440–5452. [CrossRef]
8. Darche, F.F.; Helmschrott, M.; Rahm, A.K.; Thomas, D.; Schweizer, P.A.; Bruckner, T.; Ehlermann, P.; Kreusser, M.M.; Warnecke, G.; Frey, N.; et al. Atrial fibrillation before heart transplantation is a risk factor for post-transplant atrial fibrillation and mortality. *ESC Heart Fail.* **2021**, *8*, 4265–4277. [CrossRef]
9. Rahm, A.K.; Reinhardt, S.; Helmschrott, M.; Darche, F.F.; Bruckner, T.; Lugenbiel, P.; Thomas, D.; Ehlermann, P.; Sommer, W.; Warnecke, G.; et al. Frequency, Risk Factors, and Clinical Outcomes of Late-Onset Atrial Flutter in Patients after Heart Transplantation. *J. Cardiovasc. Dev. Dis.* **2022**, *9*, 337. [CrossRef] [PubMed]
10. Chokesuwattanaskul, R.; Bathini, T.; Thongprayoon, C.; Preechawat, S.; O'Corragain, O.A.; Pachariyanon, P.; Ungprasert, P.; Cheungpasitporn, W. Atrial fibrillation following heart transplantation: A systematic review and meta-analysis of observational studies. *J. Evid. Based Med.* **2018**, *11*, 261–271. [CrossRef]
11. Alnsasra, H.; Asleh, R.; Kumar, N.; Lopez, C.; Toya, T.; Kremers, W.K.; Edwards, B.; Daly, R.C.; Kushwaha, S.S. Incidence, Risk Factors, and Outcomes of Stroke Following Cardiac Transplantation. *Stroke* **2021**, *52*, e720–e724. [CrossRef]
12. Alvarez-Alvarez, R.J.; Barge-Caballero, E.; Chavez-Leal, S.A.; Paniagua-Martin, M.J.; Marzoa-Rivas, R.; Caamaño, C.B.; López-Sainz, Á.; Grille-Cancela, Z.; Blanco-Canosa, P.; Herrera-Noreña, J.M.; et al. Venous thromboembolism in heart transplant recipients: Incidence, recurrence and predisposing factors. *J. Heart Lung Transplant.* **2015**, *34*, 167–174. [CrossRef] [PubMed]
13. Boswell, R.; Pearson, G.J. A review of the use of direct oral anticoagulant use in orthotopic heart transplantation recipients. *Transplant. Rev.* **2018**, *32*, 151–156. [CrossRef]
14. Rizk, J.; Mehra, M.R. Anticoagulation management strategies in heart transplantation. *Prog. Cardiovasc. Dis.* **2020**, *63*, 210–218. [CrossRef] [PubMed]
15. Bixby, A.L.; Lichvar, A.B.; Salerno, D.; Park, J.M. Use of direct-acting oral anticoagulants in solid organ transplantation: A systematic review. *Pharmacotherapy* **2021**, *41*, 28–43. [CrossRef] [PubMed]
16. Zakko, J.; Ganapathi, A.M.; Whitson, B.A.; Mokadam, N.A.; Henn, M.C.; Lampert, B.; Kahwash, R.; Franco, V.; Haas, G.; Emani, S.; et al. Safety of direct oral anticoagulants in solid organ transplant recipients: A meta-analysis. *Clin. Transplant.* **2022**, *36*, e14513. [CrossRef] [PubMed]
17. Lindauer, K.E.; Ingemi, A.I.; McMahon, M.R.; Lichvar, A.; Baran, D.A.; Cameron, C.; Badiye, A.; Sawey, E.J.; Old, W.; Yao, A.; et al. The utilization and safety of apixaban for therapeutic anticoagulation in heart transplant population requiring routine endomyocardial biopsies. *Clin. Transplant.* **2022**, *36*, e14828. [CrossRef]
18. McMahon, M.; Lichvar, A.; Baran, D.A.; Herre, J.M.; Yehya, A.; Sawey, E.J.; Badiye, A.; Cameron, C.; Yao, A.; Ingemi, A.I. Use of Apixaban in Heart Transplant Patients Receiving Biopsies: A Case Series. *J. Heart Lung Transplant.* **2021**, *40*, S283. [CrossRef]
19. Henricksen, E.J.; Tremblay-Gravel, M.; Moayedi, Y.; Yang, W.; Lee, R.; Ross, H.J.; Hiesinger, W.; Teuteberg, J.J.; Khush, K.K. Use of direct oral anticoagulants after heart transplantation. *J. Heart Lung Transplant.* **2020**, *39*, 399–401. [CrossRef]
20. Granger, C.B.; Alexander, J.H.; McMurray, J.J.; Lopes, R.D.; Hylek, E.M.; Hanna, M.; Al-Khalidi, H.R.; Ansell, J.; Atar, D.; Avezum, A.; et al. Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **2011**, *365*, 981–992. [CrossRef]
21. Connolly, S.J.; Ezekowitz, M.D.; Yusuf, S.; Eikelboom, J.; Oldgren, J.; Parekh, A.; Pogue, J.; Reilly, P.A.; Themeles, E.; Varrone, J.; et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **2009**, *361*, 1139–1151. [CrossRef]
22. Giugliano, R.P.; Ruff, C.T.; Braunwald, E.; Murphy, S.A.; Wiviott, S.D.; Halperin, J.L.; Waldo, A.L.; Ezekowitz, M.D.; Weitz, J.I.; Špinar, J.; et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* **2013**, *369*, 2093–2104. [CrossRef]
23. Patel, M.R.; Mahaffey, K.W.; Garg, J.; Pan, G.; Singer, D.E.; Hacke, W.; Breithardt, G.; Halperin, J.L.; Hankey, G.J.; Piccini, J.P.; et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N. Engl. J. Med.* **2011**, *365*, 883–891. [CrossRef]
24. Agnelli, G.; Buller, H.R.; Cohen, A.; Curto, M.; Gallus, A.S.; Johnson, M.; Masiukiewicz, U.; Pak, R.; Thompson, J.; Raskob, G.E.; et al. Oral apixaban for the treatment of acute venous thromboembolism. *N. Engl. J. Med.* **2013**, *369*, 799–808. [CrossRef]
25. Schulman, S.; Kearon, C.; Kakkar, A.K.; Mismetti, P.; Schellong, S.; Eriksson, H.; Baanstra, D.; Schnee, J.; Goldhaber, S.Z.; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N. Engl. J. Med.* **2009**, *361*, 2342–2352. [CrossRef]
26. Hokusai-VTE Investigators; Büller, H.R.; Décousus, H.; Grosso, M.A.; Mercuri, M.; Middeldorp, S.; Prins, M.H.; Raskob, G.E.; Schellong, S.M.; Schwocho, L.; et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N. Engl. J. Med.* **2013**, *369*, 1406–1415. [PubMed]

27. EINSTEIN Investigators; Bauersachs, R.; Berkowitz, S.D.; Brenner, B.; Buller, H.R.; Decousus, H.; Gallus, A.S.; Lensing, A.W.; Misselwitz, F.; Prins, M.H.; et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N. Engl. J. Med.* **2010**, *363*, 2499–2510. [PubMed]
28. Lichvar, A.B.; Moore, C.A.; Ensor, C.R.; McDyer, J.F.; Teuteberg, J.J.; Shullo, M.A. Evaluation of Direct Oral Anticoagulation Therapy in Heart and Lung Transplant Recipients. *Prog. Transplant.* **2016**, *26*, 263–269. [CrossRef] [PubMed]
29. Pasley, T.; Logan, A.; Brueckner, A.; Bowman-Anger, L.; Silverman, A.; Rumore, A. Direct Oral Anticoagulants: An Evaluation of the Safety and Efficacy in Cardiothoracic Transplant Recipients. *J. Heart Lung Transplant.* **2019**, *38*, S304. [CrossRef]
30. Rubido, E.D.; Cooper, M.H.; Donahue, K.R.; Krisl, J. Descriptive analysis evaluating the use of direct oral anticoagulation therapy in heart and lung transplant recipients. *Clin. Transplant.* **2023**, *37*, e14897. [CrossRef]
31. Ambrosi, P.; Kreitmann, B.; Cohen, W.; Habib, G.; Morange, P. Anticoagulation with a new oral anticoagulant in heart transplant recipients. *Int. J. Cardiol.* **2013**, *168*, 4452–4453. [CrossRef] [PubMed]
32. Bellam, N.; Kamath, M.; DePasquale, E.C.; Smith, J.G.; Fuentes, J.; Ardehali, R.; Baas, A.S.; Cadeiras, M.; Deng, M.; Kwon, M.H.; et al. Direct Acting Oral Anticoagulant Utilization, Safety and Efficacy in Heart Transplant (HT). *J. Heart Lung Transplant.* **2018**, *37*, S112–S113. [CrossRef]
33. Kim, M.; Gabardi, S.; Townsend, K.R.; Page, D.S.; Woodcome, E.L.; Givertz, M.M. Post Transplant Thrombosis and Atrial Arrhythmia May Be Safely Managed by Direct Oral Anticoagulants in Cardiac Transplant Patients. *J. Heart Lung Transplant.* **2016**, *35*, S123. [CrossRef]
34. Shuster, J.E.; LaRue, S.J.; Vader, J.M. Dabigatran May Have More Significant Drug Interactions with Calcineurin Inhibitors Than Oral Anti-Xa Inhibitors. *J. Heart Lung Transplant.* **2016**, *35*, S417. [CrossRef]
35. Tremblay-Gravel, M.; Alexander, K.M.; Czobor, P.; Lee, R.; Foroutan, F.; Yang, W.A.; Hayes, A.; Hiesinger, W.; Ross, H.J.; Khush, K.K.; et al. Directly to a DOAC? Safety of Alternatives to Warfarin for Anticoagulation in Heart Transplantation. *J. Heart Lung Transplant.* **2019**, *38*, S389. [CrossRef]
36. Writing Committee Members; Otto, C.M.; Nishimura, R.A.; Bonow, R.O.; Carabello, B.A.; Erwin, J.P., 3rd; Gentile, F.; Jneid, H.; Krieger, E.V.; Mack, M.; et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2021**, *77*, e25–e197. [CrossRef] [PubMed]
37. Salerno, D.M.; Tsapepas, D.; Papachristos, A.; Chang, J.H.; Martin, S.; Hardy, M.A.; McKeen, J. Direct oral anticoagulant considerations in solid organ transplantation: A review. *Clin. Transplant.* **2017**, *31*, e12873. [CrossRef] [PubMed]
38. Ruff, C.T.; Giugliano, R.P.; Braunwald, E.; Hoffman, E.B.; Deenadayalu, N.; Ezekowitz, M.D.; Camm, A.J.; Weitz, J.I.; Lewis, B.S.; Parkhomenko, A.; et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet* **2014**, *383*, 955–962. [CrossRef]
39. Pastori, D.; Pignatelli, P.; Cribari, F.; Carnevale, R.; Saliola, M.; Violi, F.; Lip, G.Y. Time to therapeutic range (TtTR), anticoagulation control, and cardiovascular events in vitamin K antagonists-naive patients with atrial fibrillation. *Am. Heart J.* **2018**, *200*, 32–36. [CrossRef]
40. Scridon, A.; Balan, A.I. Challenges of Anticoagulant Therapy in Atrial Fibrillation-Focus on Gastrointestinal Bleeding. *Int. J. Mol. Sci.* **2023**, *24*, 6879. [CrossRef]
41. Schein, J.R.; White, C.M.; Nelson, W.W.; Kluger, J.; Mearns, E.S.; Coleman, C.I. Vitamin K antagonist use: Evidence of the difficulty of achieving and maintaining target INR range and subsequent consequences. *Thromb. J.* **2016**, *14*, 14. [CrossRef] [PubMed]
42. Pokorney, S.D.; Simon, D.N.; Thomas, L.; Fonarow, G.C.; Kowey, P.R.; Chang, P.; Singer, D.E.; Ansell, J.; Blanco, R.G.; Gersh, B.; et al. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry. *Am. Heart J.* **2015**, *170*, 141–148. [CrossRef] [PubMed]
43. Rose, A.J.; Hylek, E.M.; Ozonoff, A.; Ash, A.S.; Reisman, J.I.; Berlowitz, D.R. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation: Results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). *Circ. Cardiovasc. Qual. Outcomes* **2011**, *4*, 22–29. [CrossRef] [PubMed]

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Temporary Mechanical Circulatory Support in Patients with Cardiogenic Shock: Clinical Characteristics and Outcomes

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Abstract: Patients with cardiogenic shock may require stabilization with temporary mechanical circulatory support (tMCS) to assess candidacy for definitive therapy, including heart transplantation (HTx) or durable MCS, and/or maintain stability while on the HTx waiting list. We describe the clinical characteristics and outcomes of patients with cardiogenic shock who underwent intra-aortic balloon pump (IABP) vs. Impella [Abiomed, Danvers, MA, USA] placement at a high-volume advanced heart failure center. We assessed patients $\geq$ 18 years who received IABP or Impella support for cardiogenic shock from 1 January 2020 to 31 December 2021. Ninety patients were included, 59 (65.6%) with IABP and 31 (34.4%) with Impella. Impella was used more frequently in less stable patients, as evidenced by higher inotrope scores, greater ventilator support, and worse renal function. While patients on Impella support had higher in-hospital mortality, despite the worse cardiogenic shock in patients for whom clinicians chose Impella support, over 75% were successfully stabilized to recovery or transplantation. Clinicians elect Impella support over IABP for less stable patients, though a high proportion are successfully stabilized. These findings demonstrate the heterogeneity of the cardiogenic shock patient population and may inform future trials to assess the role of different tMCS devices.

Keywords: heart failure; cardiogenic shock; cardiac transplantation; mechanical circulatory support

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1. Introduction

Heart transplantation (HTx) remains the definitive therapy for patients with end-stage heart disease. However, some patients with cardiogenic shock require stabilization with temporary mechanical circulatory support (tMCS) to improve end-organ function, assess candidacy for definitive therapy, and/or maintain stability while on the HTx waiting list. Options for stabilization include an intra-aortic balloon pump (IABP) or catheter-based microaxial temporary ventricular assist device (Impella device, Abiomed, Danvers, MA). Randomized trials of IABP vs. Impella support show comparable outcomes [1–3], though these trials are limited by small sample size, a narrow focus on cardiogenic shock after acute myocardial infarction, and the use of Impella 2.5 [1] or Impella CP [2,3] devices as opposed to the Impella 5.5 which offers greater circulatory support.

Observational analyses of Impella vs. IABP in cardiogenic shock offer variable conclusions. In cardiogenic shock post-acute myocardial infarction, there was higher mortality in patients receiving Impella support [4], but in heart transplant recipients supported with Impella vs. IABP, post-transplant survival was comparable [5].

The optimal strategy in patients with cardiogenic shock who may be considered candidates for heart transplantation or durable MCS remains unclear. With the increased use of tMCS as a bridge to transplantation following the 2018 revised UNOS allocation policy [6], a better understanding of clinicians' choices in the management of cardiogenic

shock with tMCS is essential. The purpose of this study was to describe the clinical characteristics and outcomes of patients with cardiogenic shock who undergo IABP vs. Impella placement at the discretion of the treating clinicians at a high-volume advanced heart failure center.

2. Materials and Methods

The patient population inclusion criteria comprised patients ≥ 18 years of age who were initiated on IABP or Impella support for cardiogenic shock from 1 January 2020 to 31 December 2021, at a large center, identified by procedure charge codes, who were cared for during admission by an advanced heart failure/transplant cardiologist. Patients were excluded if Impella CP was utilized, tMCS was placed for high-risk percutaneous coronary intervention, unplanned deterioration in the cardiac catheterization laboratory, or for left ventricular venting in a patient on extracorporeal membrane oxygenation.

Demographic and clinical information was obtained via chart review of a prospectively maintained database utilizing the hospital-based electronic medical record. Baseline demographic and clinical characteristics were collected at the time of tMCS initiation.

Outcomes assessed include tMCS complications and longer-term outcomes of morbidity as well as mortality. Complications assessed include any bleeding, limb ischemia, vascular complications (pseudoaneurysm, AV fistula, vessel thrombosis/distal embolization, vessel dissection, perforation or rupture, vessel stenosis, cannulation site bleeding, and vascular access site infection), major hemolysis, minor hemolysis, infection adverse event, stage 3 acute kidney injury (AKI), need for renal replacement therapy (RRT) due to stage 3 AKI, need for RRT due to chronic renal dysfunction, type 1 neurologic dysfunction adverse event (acutely symptomatic central nervous system injury), and major device malfunction. All complications were defined by the criteria outlined in the MCS academic research consortium consensus statement [7]. Minor hemolysis is defined as laboratory evidence of hemolysis without clinical signs, symptoms, or pump malfunction, whereas major hemolysis is laboratory evidence of hemolysis plus at least one of these features [7]. Outcomes included duration of support, recovery, transition to durable MCS, heart transplantation, in-hospital mortality, and all-cause mortality.

Clinical characteristics and outcomes were compared between patients supported with IABP and patients supported with Impella. Categorical variables were reported as percentages and compared using Fisher's exact test. Continuous variables were reported as median (25th–75th percentile) and compared with the Mann–Whitney test. Adverse events were reported as the number of incidences per 100 person-years and compared via Poisson distribution.

Kaplan–Meier survival analysis was performed for freedom from mortality estimates and a Fine–Gray competing risk model was generated to assess for risk of mortality with transplantation and LVAD as a competing event. Competing risks analysis was performed to compare time to the first outcome of death, transplant, or LVAD between groups. Statistical analysis was performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient Population

Between January 2020 and December 2021, 343 patients had an IABP or Impella placed (Figure 1).

Of those, a total of 253 were excluded due to tMCS placement: (a) pre-emptively for high-risk percutaneous coronary intervention, coronary artery bypass grafting (CABG), or VT ablation (n = 40); (b) tMCS placement for unplanned deterioration in the cardiac catheterization laboratory, during CABG or OHT (n = 7); (c) left ventricular venting for patients receiving extracorporeal membrane oxygenation support (n = 27); (d) not being followed by an advanced heart failure-transplant cardiologist (n = 173); or (e) utilization of the Impella CP (n = 6).

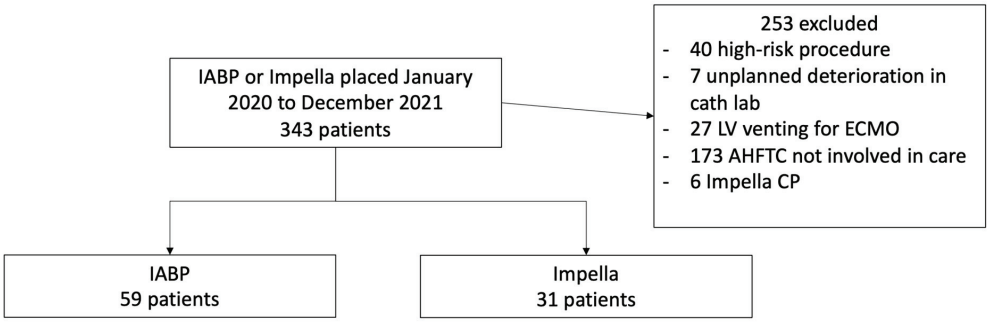

Figure 1. Cohort derivation flow chart. AHFTC, advanced heart failure and transplant cardiologist; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; LV, left ventricular; PCI, percutaneous coronary intervention.

The cohort for subsequent analysis included 90 patients, 59 (65.6%) with IABP and 31 (34.4%) with Impella support. Impella support included 1 (3.2%) Impella 5.0, and 30 (96.8%) Impella 5.5. Table 1 describes the clinical characteristics of patients at the time of tMCS placement.

Table 1. Clinical characteristics.

	IABP Group (*n* = 59)	**Impella Group (*n* = 31)**	***p*-Value**
Age (years)	60 (51.5–67)	56 (48–64.5)	0.140
Female	14 (23.7%)	2 (6.5%)	0.047
Height (cm)	173 (165–180)	178 (174–183)	0.022
Weight (kg)	71 (61–88)	94 (79–105)	<0.001
BMI (kg/m^2)	24.2 (22.1–27.4)	30.2 (24.8–32.6)	<0.001
Blood Type			
A	21 (35.6%)	7 (22.6%)	0.239
B	10 (17.0%)	9 (29.0%)	0.276
AB	1 (1.7%)	2 (6.5%)	0.272
O	27 (45.8%)	13 (42.0%)	0.825
Race/Ethnicity			
Caucasian	25 (42.4%)	12 (38.7%)	0.823
African American	8 (13.6%)	7 (22.6%)	0.373
Hispanic	12 (20.3%)	2 (6.5%)	0.126
Asian	7 (11.9%)	3 (9.7%)	1.000
Other	7 (11.9%)	7 (22.6%)	0.225
Diabetes Mellitus	31 (52.5%)	14 (45.2%)	0.658
Type of Cardiomyopathy			
Nonischemic dilated	35 (59.3%)	22 (71.0%)	0.359
Ischemic	22 (37.3%)	9 (29.0%)	0.490
Restrictive/infiltrative	0	0	1.000

Table 1. *Cont.*

	IABP Group (n = 59)	Impella Group (n = 31)	p-Value
Congenital	1 (1.7%)	0	1.000
Other	1 (1.7%)	0	1.000
Prior transplant evaluation	6 (10.2%)	4 (12.9%)	0.732
Prior transplant listing	3 (5.1%)	1 (3.2%)	1.000
Primary etiology of cardiogenic shock			
Acute decompensated HF	58 (98.3%)	26 (83.9%)	0.017
Acute myocardial infarction	1 (1.7%)	5 (16.1%)	0.017
Postcardiotomy shock	0	0	1.000
Myocarditis	0	0	1.000
Transplant rejection	0	0	1.000
Systolic blood pressure, mm Hg	88 (83–95)	91 (83–101)	0.368
Hemodynamics			
RA, mm Hg	13 (9–19)	17 (15–19)	0.360
PA mean, mm Hg	34 (28–40)	35 (28–39)	0.885
PCWP, mm Hg	23 (17–27)	25 (20–29)	0.297
CI, L/min/m^2	1.9 (1.6–2.5)	2.1 (1.8–2.5)	0.188
INTERMACS Profile			
Profile 1	4 (6.8%)	3 (9.7%)	0.688
Profile 2	33 (55.9%)	21 (67.7%)	0.366
Profile 3	22 (37.3%)	7 (22.6%)	0.235
Inotrope use			
Inotrope score *	6.0 (2.0–7.6)	6.9 (5.9–10.8)	0.005
Dobutamine, mcg/kg/min	3 (3–4.9)	3 (2.8–5.0)	0.243
Milrinone, mcg/kg/min	0.25 (0.25–0.38)	0.25 (0.25–0.25)	0.186
Epinephrine, mcg/min	10 (8–12.5)	5 (2.8–7)	0.221
Dopamine, mcg/kg/min	3 (3–3.5)	5 (3.5–6)	0.155
Norepinephrine, mcg/min	9 (5.5–24.5)	7 (6–7)	0.089
Cardiopulmonary resuscitation	1 (1.7%)	0	1.000
Ventilator support	0	5 (16.1%)	0.004
Continuous renal replacement therapy	2 (3.4%)	3 (9.7%)	0.335
Ejection fraction (%)	15 (12–19)	16 (10–20)	0.765
Creatinine if not on dialysis (mg/dL)	1.2 (0.9–1.6)	1.9 (1.2–2.7)	0.005
Total bilirubin (mg/dL)	1.4 (0.8–1.9)	1.7 (1.2–2.9)	0.173
Axillary access (vs. femoral)	4 (6.8%)	31 (100%)	<0.001
Lactate (mmol/L)	1.2 (0.9–1.7)	1.2 (0.9–1.7)	0.795
Surgical cut-down (vs. percutaneous)	4 (6.8%)	31 (100%)	<0.001

* Inotrope score was compared only for those on inotropes. The inotrope score was calculated as follows: dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) with each drug dosed in µg/kg/min. BMI, body mass index; CI, cardiac index; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrial.

There were no differences in age or race/ethnicity between groups. Patients with IABP were more likely to be female (23.7% vs. 6.5%, $p = 0.047$). Clinicians elected for Impella support in patients who had higher body mass index (30.2 kg/m^2 vs. 24.2 kg/m^2, $p < 0.001$). The underlying etiology of cardiomyopathy was similar between groups, though clinicians chose Impella to support more often for patients in cardiogenic shock post-myocardial infarction (16.1% vs. 1.7%, $p = 0.03$) and less often in patients with shock from acute decompensated heart failure (83.9% vs. 98.3%. $p = 0.017$). There were no significant differences in the proportion of patients with diabetes mellitus or renal replacement therapy.

There were no significant differences in ejection fraction, systolic blood pressure, right atrial pressure, pulmonary artery pressures, pulmonary capillary wedge pressure, or cardiac index. However, patients for whom clinicians chose Impella support had a higher inotrope score (6.9 vs. 6.0, $p = 0.005$), though it is not clear whether this is a clinically relevant difference given the lack of significant differences in dosages of individual inotropic agents. The lack of observed elevation in lactate levels may reflect the fact that these patients were already stabilized with inotropic support prior to tMCS placement. While there was no difference in the use of CPR at the time of tMCS initiation between groups, patients in the Impella group were more likely to be on ventilator support (16.1% vs. 0%, p< 0.001) at the time of tMCS and had higher creatinine levels (1.7 mg/dL vs. 1.2, $p = 0.004$). There was no difference in the INTERMACS profile at the time of tMCS initiation.

3.2. Temporary MCS Complications

Table 2 describes MCS complications among patients in both groups.

Table 2. Temporary MCS complications.

All Events Per 100 Person-Years	IABP Group ($n = 59$)	Impella Group ($n = 31$)	p-Value
Bleeding adverse events	582.4	1568.6	0.035
Limb ischemia	79.4	0.0	<0.001
Pseudoaneurysm	0.0	0.0	1.000
AV * fistula	0.0	0.0	1.000
Vessel thrombosis/distal embolization	0.0	0.0	1.000
Vessel dissection, perforation, or rupture	0.0	0.0	1.000
Vessel stenosis	0.0	0.0	1.000
Cannulation site bleeding	493.6	1404.8	0.060
Vascular access site infection	0.0	0.0	1.000
Major hemolysis	80.3	1776.3	<0.001
Minor hemolysis	250.7	772.2	0.058
Infection adverse event	797.9	1400.7	0.173
Stage 3 AKI	162.7	756.4	0.008
Need for RRT due to stage 3 AKI	159.5	617.6	0.028
Need for RRT due to chronic renal dysfunction	281.0	60.8	<0.001
Type 1 neurologic dysfunction adverse event (acutely symptomatic CNS injury)	0.0	0.0	1.000
Major device malfunction	161.3	327.3	0.189

* AV, arteriovenous; AKI, acute kidney injury; CNS, central nervous system; RRT, renal replacement therapy.

There was no difference in the event rates of the majority of temporary MCS complications between patients with Impella versus IABP support, including no difference

in cannulation site bleeding, minor hemolysis, infections, neurologic events, or major device malfunction.

Patients for whom clinicians chose Impella support experienced lower rates of limb ischemia (expected as an axillary approach was used) but higher rates of major hemolysis and acute kidney injury. Both complications would be expected given the larger cannula size, mechanism of action, and less stable patient population who received Impella support.

3.3. Outcomes

Table 3 describes the acceptable clinical outcomes of the two groups of patients.

Table 3. Outcomes.

	IABP Group (n = 59)	Impella Group (n = 31)	p-Value
Duration of support (d)	7 (4–10)	15 (10–26.5)	<0.001
Recovery	10 (17.0%)	3 (9.7%)	0.530
Durable MCS	2 (3.4%)	1 (3.2%)	1.000
HeartWare LVAD	0	0	1.000
HeartMate 3 LVAD	2 (3.4%)	1 (3.2%)	1.000
Total Artificial Heart	0	0	1.000
Heart transplantation	45 (76.3%)	21 (67.7%)	0.455
Death during admission	2 (3.4%)	6 (19.4%)	0.018
Death	6 (10.2%)	8 (25.8%)	0.068

Compared with patients supported with IABP, patients with Impella support had a longer median duration of support (15 vs. 7 days, $p < 0.001$). Patients with Impella support also had a higher in-hospital mortality (19.4% vs. 3.4%, $p = 0.018$); however, there was no significant difference in all-cause mortality over the course of follow-up. Figure 2 depicts a survival analysis for patients in the two groups.

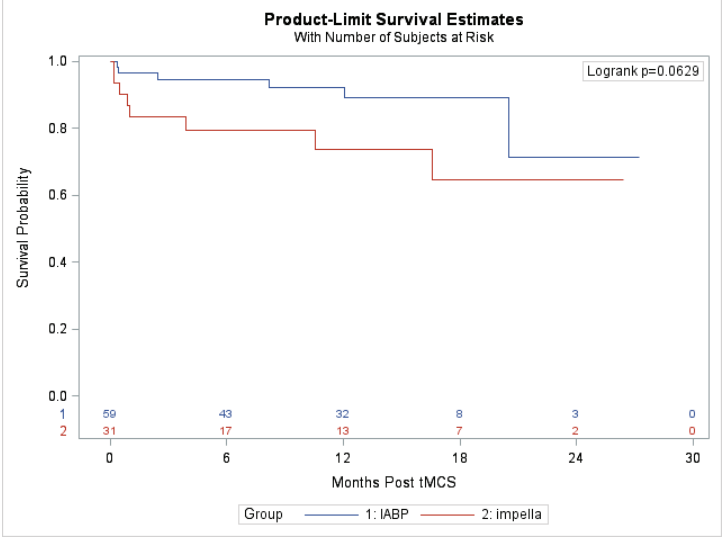

Figure 2. Survival analysis for patients with Impella vs. IABP placed for cardiogenic shock.

There was no significant difference in the proportion of patients that experienced recovery (17% vs. 9.7%; $p = 0.53$) transitioned to durable MCS (3.4% vs. 3.2%; $p = 1.0$; Figure 3), or underwent heart transplantation (67.7% vs. 76.3%, $p = 0.455$).

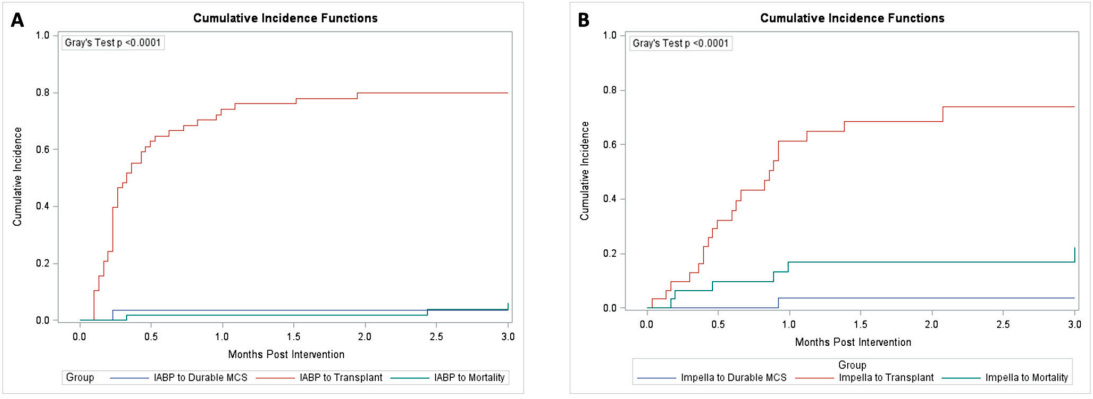

Figure 3. (**A**) Competing event model of outcomes for IABP for mortality, transplant, and durable MCS; (**B**) Competing event model of outcomes for Impella for mortality, transplant, and durable MCS.

4. Discussion

In patients with cardiogenic shock at a high-volume advanced heart failure center, clinicians were more likely to choose IABP support for patients not on ventilatory support, with a lower inotrope score, and without myocardial infarction as the cause of cardiogenic shock. These patients were successfully stabilized with low in-hospital mortality. Impella support, on the other hand, was chosen for patients in cardiogenic shock who were less stable, had a higher inotrope score, required greater ventilatory support, and had worse renal function. Patients in the Impella group had a longer median duration of support but comparable complications to patients on IABP support. While patients on Impella support had higher in-hospital mortality, despite the worse cardiogenic shock in patients for whom clinicians chose Impella support, over 75% were successfully stabilized to recovery or transplantation.

Randomized controlled trials of IABP vs. Impella support in cardiogenic shock have resulted in statistically similar clinical outcomes between the two devices [1–3] but it is not clear whether these findings are generalizable to all patients with cardiogenic shock due to several limitations. First, these trials comprised a limited number of patients, 26 [1] and 48 [2,3] patients, respectively. Second, these trials enrolled only patients with post-myocardial infarction cardiogenic shock and utilized the Impella 2.5 [1] and Impella CP [2,3] which offer inferior circulatory support compared to the contemporary Impella 5.5. With the noted caveats, while one trial found that patients randomized to Impella support had a higher cardiac index after 30 min compared to those randomized to IABP, 30-day mortality was no different [1]. Similarly, the other randomized trial observed comparable mortality between patients randomized to Impella and IABP at 30 days, 6 months [2], and 5 years [3].

On the other hand, a retrospective cohort study also focusing only on patients with post-myocardial infarction cardiogenic shock noted that patients with Impella support had higher rates of major bleeding and in-hospital mortality [4], which may reflect confounding by indication: patients who receive Impella versus IABP support at the clinician's discretion are more unstable.

When assessing the impact of Impella versus IABP support in all patients with cardiogenic shock awaiting HTx, not restricted to just those with post-myocardial infarction, only observational data are available. In an analysis of the United Network of Organ Sharing (UNOS) registry, Impella versus IABP support did not impact post-transplant survival.

However, patients who received Impella support were sicker with higher use of preoperative ventilation and higher risk of waitlist delisting compared with IABP-supported candidates, though there were no differences in post-transplant survival [5]. While randomized controlled trials are the gold standard for the assessment of causation, and large registry analyses offer the benefit of a large sample size with the power to detect differences and widespread applicability, a single-center analysis offers the distinct advantage of a detailed and granular assessment. In this case, we can provide a unique perspective: (1) highlighting the role of the clinician's choice in selecting contemporary Impella 5.5 for patients with worse cardiogenic shock; and (2) describing the overall trajectory of patients with advanced heart disease who require tMCS, rather than focusing only on those who are waitlisted for HTx, as in the UNOS registry analysis, thereby reducing survival bias.

The triage of patients with cardiogenic shock to Impella versus IABP support is a complex decision that is based on the patient's stability and clinical course. The improved outcomes in patients with IABP support were undoubtedly related to their greater relative stability at the time of tMCS implantation. The importance of clinician discretion in the triage of patients with cardiogenic shock to tMCS indicates the difficulty of factoring heterogeneity of patient presentations in randomized controlled trials of tMCS devices. Based on this study design, the criteria by which clinicians chose Impella vs. IABP remains unclear and based on individualized judgment and experience rather than a set clinical algorithm.

The limitations of our study include a single-center design in which patients were cared for by a select cohort of clinicians, which may limit generalizability. The patient population was highly selected to be cared for by advanced heart failure specialists and comprised very few patients with acute myocardial infarction as the cause of cardiogenic shock and ventilatory support prior to tMCS placement. Another limitation is that without randomization, the results are subject to confounding by indication as those factors that led clinicians to choose Impella support for their patients may have also influenced outcomes. However, the purpose of this study was not to determine the impact of Impella vs. IABP on outcomes but to provide an evaluation of clinician-guided therapy to survey the practices of real-world clinicians as they care for patients with cardiogenic shock and inform future shared decision making as patients are stabilized and the candidacy for advanced heart failure therapies is assessed.

5. Conclusions

In patients with cardiogenic shock at a high-volume advanced heart failure center, patients for whom their clinicians chose Impella versus IABP support for cardiogenic shock were more unstable at the time of tMCS implantation. Nonetheless, the majority were successfully stabilized and either recovered or survived to heart transplantation, indicating that clinicians perform important triage decisions on an individualized basis. This study offers preliminary insight from a highly selected sample into the real-world clinical characteristics, complications, and outcomes to guide clinicians in this complex decision-making process.

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References

1. Seyfarth, M.; Sibbing, D.; Bauer, I.; Fröhlich, G.; Bott-Flügel, L.; Byrne, R.; Dirschinger, J.; Kastrati, A.; Schömig, A. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. *J. Am. Coll. Cardiol.* **2008**, *52*, 1584–1588. [CrossRef] [PubMed]
2. Ouweneel, D.M.; Eriksen, E.; Sjauw, K.D.; van Dongen, I.M.; Hirsch, A.; Packer, E.J.; Vis, M.M.; Wykrzykowska, J.J.; Koch, K.T.; Baan, J.; et al. Percutaneous Mechanical Circulatory Support Versus Intra-Aortic Balloon Pump in Cardiogenic Shock After Acute Myocardial Infarction. *J. Am. Coll. Cardiol.* **2017**, *69*, 278–287. [CrossRef] [PubMed]
3. Karami, M.; Eriksen, E.; Ouweneel, D.M.; Claessen, B.E.; Vis, M.M.; Baan, J.; Beijk, M.; Packer, E.J.S.; Sjauw, K.D.; Engstrom, A.; et al. Long-term 5-year outcome of the randomized IMPRESS in severe shock trial: Percutaneous mechanical circulatory support vs. intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction. *Eur. Heart J. Acute Cardiovasc. Care* **2021**, *10*, 1009–1015. [CrossRef] [PubMed]
4. Dhruva, S.S.; Ross, J.S.; Mortazavi, B.J.; Hurley, N.C.; Krumholz, H.M.; Curtis, J.P.; Berkowitz, A.; Masoudi, F.A.; Messenger, J.C.; Parzynski, C.S.; et al. Association of Use of an Intravascular Microaxial Left Ventricular Assist Device vs Intra-aortic Balloon Pump With In-Hospital Mortality and Major Bleeding Among Patients With Acute Myocardial Infarction Complicated by Cardiogenic Shock. *JAMA* **2020**, *323*, 734–745. [CrossRef] [PubMed]
5. Nordan, T.; Critsinelis, A.C.; Mahrokhian, S.H.; Kapur, N.K.; Vest, A.; DeNofrio, D.; Chen, F.Y.; Couper, G.S.; Kawabori, M. Microaxial Left Ventricular Assist Device Versus Intraaortic Balloon Pump as a Bridge to Transplant. *Ann. Thorac. Surg.* **2021**, *114*, 160–166. [CrossRef] [PubMed]
6. Jawitz, O.K.; Fudim, M.; Raman, V.; Bryner, B.S.; DeVore, A.D.; Mentz, R.J.; Milano, C.; Patel, C.B.; Schroder, J.N.; Rogers, J.G. Reassessing Recipient Mortality Under the New Heart Allocation System: An Updated UNOS Registry Analysis. *JACC Heart Fail.* **2020**, *8*, 548–556. [CrossRef] [PubMed]
7. Kormos, R.L.; Antonides, C.F.J.; Goldstein, D.J.; Cowger, J.A.; Starling, R.C.; Kirklin, J.K.; Rame, J.E.; Rosenthal, D.; Mooney, M.L.; Caliskan, K.; et al. Updated definitions of adverse events for trials and registries of mechanical circulatory support: A consensus statement of the mechanical circulatory support academic research consortium. *J. Heart Lung Transplant.* **2020**, *39*, 735–750. [CrossRef] [PubMed]

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Review

Functional Mitral and Tricuspid Regurgitation across the Whole Spectrum of Left Ventricular Ejection Fraction: Recognizing the Elephant in the Room of Heart Failure

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Abstract: Functional mitral regurgitation (FMR) and tricuspid regurgitation (FTR) occur due to cardiac remodeling in the presence of structurally normal valve apparatus. Two main mechanisms are involved, distinguishing an atrial functional form (when annulus dilatation is predominant) and a ventricular form (when ventricular remodeling and dysfunction predominate). Both affect the prognosis of patients with heart failure (HF) across the entire spectrum of left ventricle ejection fraction (LVEF), including preserved (HFpEF), mildly reduced (HFmrEF), or reduced (HFrEF). Currently, data on the management of functional valve regurgitation in the various HF phenotypes are limited. This review summarizes the epidemiology, pathophysiology, and treatment of FMR and FTR within the different patterns of HF, as defined by LVEF.

Keywords: heart failure; mitral regurgitation; tricuspid regurgitation; atrial functional mitral regurgitation; atrial functional tricuspid regurgitation; transcatheter tricuspid valve intervention

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1. Introduction

Functional (secondary) mitral (FMR) and tricuspid (FTR) valve regurgitation are shared across the entire spectrum of heart failure (HF) and negatively affect symptoms and prognosis [1,2]. They may occur isolated or concomitantly (bivalvular functional regurgitation), independent of the HF subgroup [3]. By definition, any functional regurgitation occurs due to cardiac remodeling and dysfunction and appears in a structurally normal valve apparatus [3–7]. Annular dilatation and impaired contraction cause atrial functional regurgitation. Restricted motion of the leaflets due to ventricular remodeling and dysfunction produces ventricular functional regurgitation. We can diagnose FMR and FTR in any HF phenotype as defined by left ventricular ejection fraction (LVEF): preserved (HFpEF), mildly reduced (HFmrEF), or reduced (HFrEF). Proper and simultaneous recognition of the specific mechanism of regurgitation on the one hand (functional atrial, ventricular, or mixed) and the phenotype of HF on the other (HfrEF, HFmrEF, and HFpEF) is crucial for prognosis and therapy. In the present review, we aim to focus on the epidemiology, pathophysiology, prognosis, and therapy of atrial and ventricular FMR and FTR within the different HF phenotypes defined by LVEF.

2. Epidemiology

In HF, moderate or severe FMR affects up to 30% of patients, and it seems more frequent in HFrEF, followed by HFmrEF and HFpEF [2]. The prospective analysis of the European Society of Cardiology (ESC) Heart Failure Long-Term Registry shows a prevalence of moderate-to-severe FMR approaching 35% in the HFrEF group, 30% in the HFmrEF group, and 20% in the HFpEF group ($p < 0.001$) (Figure 1) [8]. In advanced HFrEF (stage C–D), the prevalence of severe FMR can reach 45% [9–12]. There are no dedicated

studies linking the prevalence of the specific mechanism causing FMR (atrial vs. ventricular) to the single HF phenotypes (HFrEF, HFmrEF, and HFpEF). However, we can hypothesize that in HFrEF, ventricular mechanisms are likely to prevail, but atrial mechanisms can coexist and are proportional to the disease severity. Moving from HFrEF to HFmrEF and HFpEF, the ventricular mechanisms become less relevant, leaving atrial mechanisms the primary determinants of FMR.

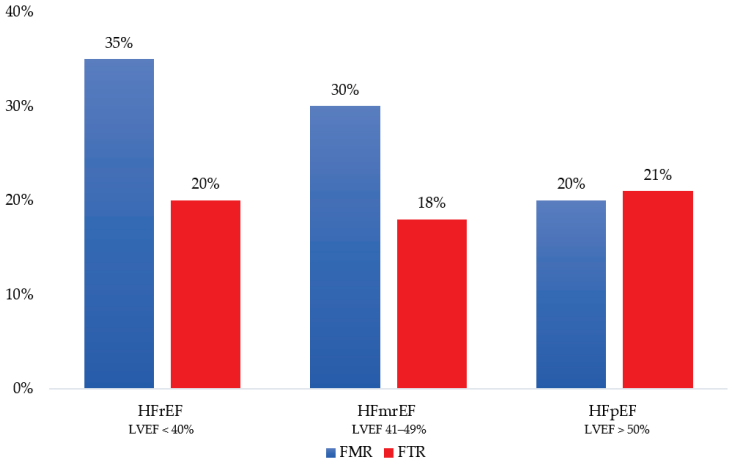

Figure 1. Distribution of functional mitral regurgitation (FMR) and functional tricuspid regurgitation (FTR) across the heart failure phenotype as defined by left ventricular ejection fraction (LVEF): reduced (HFrEF), mildly reduced (HFmrEF) and preserved (HFpEF).

Most studies on FTR focus on the community and not specifically on HF [13–15]. An incidental finding of moderate and severe FTR occurs in 7% of the general population and 12% of patients hospitalized for HF [15–17]. The ESC Heart Failure Long-Term Registry reports a prevalence for moderate-to-severe FTR equally distributed among HF phenotypes, ranging from 18% in HFmrEF to 20% in HFrEF and 21% in HFpEF ($p = 0.164$) (Figure 1) [8,18]. Since no data on right atrial and ventricular remodeling are available in this study, it is impossible to establish the role of the atrial and ventricular mechanisms of FTR across HF phenotypes. The significantly older age of HFpEF patients does not allow for excluding a coexisting organic etiology in these patients [14].

In the entire spectrum of HF, FMR and FTR often coexist. Moderate or severe bivalvular functional regurgitation has been observed in about 35% of patients suffering from HFrEF [1,18]. In the same way, biatrial dilatation is commonly present in patients with HFpEF, resulting in concomitant aFMR and aFTR [19]. Significant bivalvular functional regurgitation is rarely observed in patients with sinus rhythm or atrial fibrillation (AFib) $\leq$1 year. In contrast, 25% of patients with AFib >10 years have significant bivalvular regurgitation, adding complexity to diagnosis and management [19].

3. Pathophysiology and Prognosis

Two main mechanisms are responsible for functional mitral and tricuspid regurgitation: (1) the annular dilation and/or loss of annular contraction, through a condition of atrial remodeling (atrial functional); (2) restricted leaflets motion due to ventricular remodeling, which implies papillary muscle displacement, causing chordal tethering (ventricular functional). These geometrical alterations and functional impairments occur in the presence of a structurally normal valve apparatus.

Ventricular FMR typically occurs in HFrEF due to ischemic or non-ischemic ventricular disease. According to the general classification, the presence of coronary artery disease

affecting LV geometry and function allows for differentiation between ischemic and non-ischemic FMR. Dilated cardiomyopathy (DCM), regardless of its etiology, often leads to secondary MR, due to the changes in LV shape (increase in LV sphericity and enlargement in LV diameters). DCM recognizes genetic, but also acquired causes. Monogenic diseases, syndromic forms, and neuromuscular diseases are described among genetic forms. Drugs, toxins, and nutritional deficiencies can lead to acquired forms of DCM with FMR.

The mechanism of FMR is valve tenting (a more apical position of the leaflets and their coaptation point during the systolic phase) (Figure 2). Specifically, valve tenting results from an imbalance between tethering and closing forces. In ventricular FMR, tethering forces increase (due to LV remodeling), and closing forces decrease (due to reduced contractility and dyssynchrony) [20,21]. Valve tenting can be symmetric or asymmetric. While symmetric tenting occurs more often in global ventricular remodeling, asymmetric tenting usually occurs if the tethering forces predominate on the posterior mitral valve leaflet. FMR negatively impacts survival, either in HFpEF [adjusted hazard ratio (adj. HR) 1.40, 95% confidence interval (CI) 1.09–1.81; $p = 0.009$] [22], HFmrEF (adj. HR 1.72, 95% CI 1.24–2.39; $p = 0.0012$) [8] and HFrEF (adj. HR 1.61, 95% CI 1.22–2.12; $p = 0.001$] [2]. In HFrEF, small amounts of FMR increase short- and long-term mortality. Particularly, there is an exponential mortality increase for any effective regurgitant orifice area (EROA) increment above a threshold of 0.10 cm^2 when compared with degenerative MR [23].

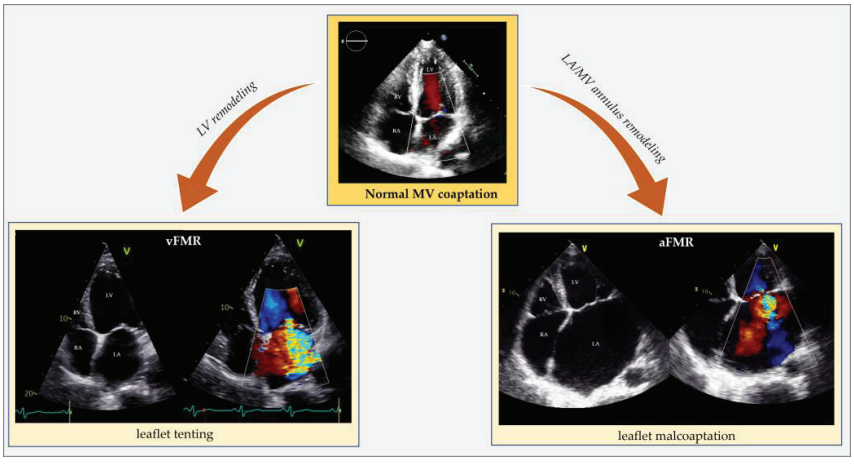

Figure 2. Echocardiographic comparison of normal mitral valve coaptation and functional mitral regurgitation in the context of left ventricle remodeling and dysfunction (vFMR) opposed to left atrial and annular dilatation (aFMR). aFMR: atrial functional mitral regurgitation; LA: left atrium; LV: left ventricle; MV: mitral valve; RA: right atrium; RV: right ventricle; vFMR: ventricular functional mitral regurgitation.

Atrial FMR is common in AFib but also occurs in sinus rhythm. HFpEF can generate atrial FMR by causing an increase in left atrium (LA) pressure and, eventually, LA remodeling without needing AFib to develop (Figure 2) [6,7,19,24,25].

Previously published data showed that not all patients with significant aFMR had known atrial arrhythmias. Dziadzko V. et al. found that 46% of patients with aFMR do not have atrial arrhythmias [24]. More recently, Mesi O. et al. demonstrated that 23% of the aFMR population had sinus rhythm [26]. This suggests that diastolic dysfunction with resultant atrial dilation and annular remodeling could be sufficient in promoting the genesis of mitral regurgitation. Nevertheless, AFib, HFpEF, and atrial FMR often coexist and negatively interact since they share most pathophysiological mechanisms [26–31]. AFib, causing LA remodeling, impaired atrial function, and atrial fibrosis, may negatively

contribute to HFpEF and atrial FMR [28–32]. HFpEF, through diastolic dysfunction and increased LA pressures, systemic inflammation, and endothelial dysfunction, plays a crucial role in causing LA anatomical, mechanical and electrical remodeling favoring AFib and, consequently, atrial FMR. Once established, FMR negatively contributes to AFib and HFpEF progression.

Figure 3 resumes the complex pathophysiological relationship between AFib, LA enlargement, and MR.

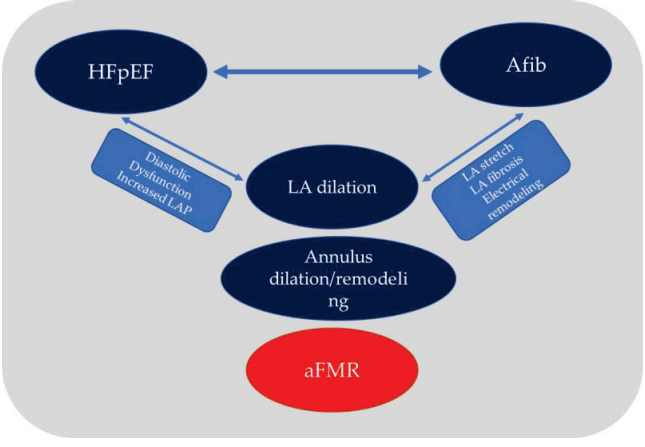

Figure 3. Pathophysiology of aFMR resulting from a sequential relationship between HFpEF (sinus rhythm) and atrial fibrillation. Adapted with permission from Deferm S. et al. [19].

In a Dziadzko V et al. study, patients with aFMR were significantly older than those with vFMR (80 ± 10 vs. 73 ± 14 years), translating into a different distribution of causes by age group [24]. The aFMR patients suffered mainly from atrial fibrillation/flutter (54% vs. 28%) and hypertension (81% vs. 69%). In contrast, vFMR patients were predominantly male (59% vs. 33%) with a prevalent history of myocardial infarction (17% vs. 9%) [24]. In addition, patients with ventricular FMR had the most significant LV remodeling, highest pulmonary pressure and lowest LVEF, stroke volume, and E/e'. Patients with atrial FMR presented smaller LV size, generally normal LVEF and stroke volume, with a modest MR volume and orifice, while E/e' and pulmonary pressure were elevated [24]. In advanced LA and LV remodeling, a net distinction between the atrial and ventricular mechanism is no longer possible because these entities usually coexist. In HFmrEF, the volume overload caused by atrial FMR promotes the transition to HFrEF (and eventually to ventricular FMR) [18].

Even if current guidelines do not emphasize the need to discriminate the atrial from the ventricular mechanism in FMR, an early distinction is crucial to establish prognostic and therapeutic decisions [19]. The prognosis of ventricular FMR is significantly worse than atrial FMR, and each etiology leads to different treatments [24,33]. Though, the question remains whether the relationship between vFMR and mortality is direct or indirect, assuming that FMR is independently responsible for the outcomes and in all circumstances. On the one hand, a direct relationship between the degree of FMR and mortality has been widely described; on the other hand, several cohort publications stated that FMR was not independently responsible for the poor outcomes observed, suggesting that FMR is a surrogate for another cause of reduced survival [24,33,34]. In very advanced HFrEF, the underlying myocardial impairment and severity of LV dysfunction have a more negative impact on prognosis than FMR [18].

Similar to the left side of the heart, right ventricular remodeling, causing leaflet tethering and systolic restricted motion, is typical of vFTR. This can occur in case of left heart

diseases (left ventricular dysfunction or left heart valve diseases) resulting in pulmonary hypertension, primary pulmonary hypertension, secondary pulmonary hypertension and right ventricular dysfunction from any cause (e.g., myocardial diseases, ischemic heart disease, chronic right ventricular pacing). Atrial FTR develops due to tricuspid annular dilatation following right atrium (RA) remodeling, with the concomitant valve leaflets, right ventricle (RV), pulmonary circulation, and left side of the heart being macroscopically normal (Figure 4) [35–38]. In HFpEF, due to cardiac amyloidosis complicated by atrial FTR, an organic component usually coexists because of amyloid deposit infiltration in the leaflets [39,40].

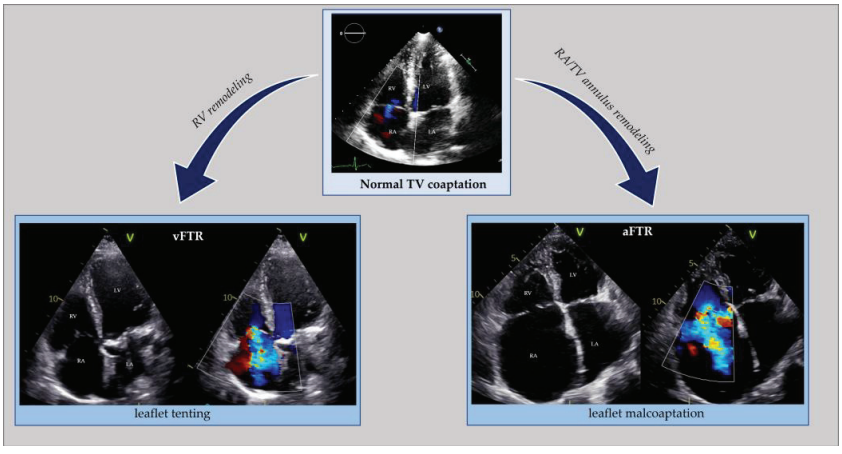

Figure 4. Echocardiographic comparison of normal tricuspid valve coaptation and functional tricuspid regurgitation in the context of right ventricle remodeling (vFTR) opposed to right atrial and annular dilatation (aFTR). aFTR: atrial functional tricuspid regurgitation; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle; vFTR: ventricular functional mitral regurgitation; TV: tricuspid valve.

A remarkable past medical history for AFib is widespread in atrial FTR. Atrial and ventricular FTR can coexist in simultaneous RA and RV remodeling. The same happens in FTR due to cardiovascular implantable electronic devices [37].

A stand-alone diagnosis of atrial FTR should make us search for HFpEF [41]. The high prevalence of atrial FTR in HFpEF is consistent with shared risk factors such as renal dysfunction, aging, and AFib. AFib is also a primary determinant of atrial FTR. In HFrEF, the role of AFib in determining FTR diminishes. Compared to HFpEF, a lower percentage of patients with HFrEF have AFib [16,42,43]. In HFrEF, right ventricular remodeling and dysfunction are the main determinants of ventricular FTR.

Distinguishing between the atrial and ventricular FTR has prognostic and therapeutic implications [44–46]. The presence of FTR in the HF population significantly impairs prognosis, functional capacity, and quality of life and increases the risk of hospital admission. A strong association between FTR and mortality exists both in HFrEF (adj. HR 1.30, 95% CI 1.06–1.60; $p = 0.014$) [47] and HFpEF (adj. HR 2.87, 95% CI 1.61–5.09; $p < 0.001$) [48]. To our knowledge, dedicated studies on HFmrEF are missing, but the presence of FTR is proven to be an independent risk predictor of mortality in mixed cohorts of HFrEF and HFmrEF patients (adj. HR 1.57, 95% CI 1.39–1.78; $p < 0.0001$) [16,49]. Atrial FTR progresses rapidly but has a better outcome than ventricular FTR [37,50]. Additionally, while regurgitation severity is the only independent prognostic predictor in atrial FTR, RV function also predicts outcomes in ventricular FTR [16,50–52].

4. Therapeutic Implications

A multidisciplinary approach is a cornerstone for adequately managing HF complicated by FMR or FTR. The team should include HF specialists, imaging experts, cardiac surgeons, interventional cardiologists, and electrophysiologists. Proper management of comorbidities, such as hypertension, diabetes, renal dysfunction, and depression, is also essential and improves outcomes [53–56].

The first therapeutic approach includes guideline-directed drug therapy (GDMT), followed by surgical valve correction when indicated. Transcatheter repair and replacement for FMR and FTR are emerging as complementary and promising therapeutic options across all HF phenotypes. These techniques can significantly reduce the harmful effects of regurgitant volume overload and interrupt the vicious circle of valvular-driven HF progression.

4.1. Functional Mitral Regurgitation

GDMT is the first mandatory therapeutic step in FMR complicating HFrEF (and likely HFmrEF and HFpEF). Treatment with beta-blockers, renin–angiotensin–aldosterone system antagonists, angiotensin receptor neprilysin inhibitors, and most recently, sodium-glucose co-transporter inhibitors, which may result in LV unloading and reverse remodeling and pleiotropic drug effects, secondarily reducing FMR [18,38,57]. Following GDMT, appropriately selected patients can take advantage of cardiac resynchronization therapy (CRT) [38,57]. Medical therapy and CRT can improve atrial and ventricular FMR by favorably acting on leaflet tethering and closing forces and ventricular performance and decreasing LA pressure. Bartko et al. found that the interpapillary longitudinal dyssynchrony was markedly increased in patients with severe FMR than moderate or less FMR. Restoration of longitudinal papillary muscle synchronicity by CRT was correlated with FMR regression. Similarly, the improvement of FMR was associated with improved interpapillary radial and longitudinal dyssynchrony [58]. Unfortunately, the positive effects of CRT are not immediate, and only about half of the patients implanted take advantage of it [18,54]. A positive response to CRT implantation is expected in the presence of an anteroseptal to posterior wall radial strain dyssynchrony > 200 milliseconds and an end-systolic LV dimension indexed < 29 mm/m^2, and in the absence of a scar at lead insertion [59]. In addition, FMR improvement after CRT is less common in patients with AFib than sinus rhythm despite a comparable extent of LV reverse remodeling [58–60]. Herein, restoring sinus rhythm before CRT implantation may positively affect the time course of FMR severity [25,53]. Reestablishing sinus rhythm, regardless of the LV function, has a therapeutic effect by reversing LA anatomical and mechanical remodeling, particularly on atrial FMR. Dell'Era et al. observed a significant improvement in the LA deformation index (peak atrial longitudinal strain), LA volume, and FMR grade shortly after cardioversion [61]. Gertz et al. reported that successful catheter ablation for AFib results in a significant reduction in LA size and annular dimension and lower rates of important atrial FMR [25]. Taken together, these data, on the one hand, highlight the role of AFib (and LA and annular remodeling) in causing atrial FMR, and on the other, they provide therapeutic indications for its treatment [38,57,62].

Surgical or transcatheter treatment is an option in patients with persistent FMR despite GDMT and, when applicable, CRT [38,57]. Nowadays, an isolated surgical approach to ventricular FMR is rare because of the considerable risk of surgery and the remarkable recurrence rates after mitral repair in the presence of LV remodeling [56,57]. On the contrary, when the primary mechanism of FMR is annular dilation (atrial FMR), a surgical approach targeting the mitral annulus only is a valuable option. The results of surgical annuloplasty for atrial FMR are encouraging [62,63], although this approach, when isolated, is not always sufficient [24,25,48]. In this scenario, transcatheter therapies for FMR, thanks to their potentially low procedural risks and long-lasting results, are the focus of intense clinical research in atrial and ventricular FMR settings.

Table 1 summarizes the most applied transcatheter techniques currently commercialized for managing MR.

Table 1. Overview of transcatheter mitral valve repair and replacement devices, with CE approval, for treating mitral regurgitation (Adapted with permission from [64,65]).

Type of Intervention	Target Structure	Device	Description	Eligibility Criteria
Edge-to-edge	Mitral leaflets	MitraClip (Abbott Vascular, Abbott Park, IL, USA) PASCAL (Edwards Lifesciences, Irvine, CA, USA)	Based on edge-to-edge technique Transfemoral transeptal approach Approved for FMR and DMR	Central A2-P2 (ideal) No calcification Mean gradient < 4 mmHg MVA > 3 cm^2 Sufficient leaflet tissue for grasping
Direct Annuloplasty	Mitral annulus	Cardioband (Edwards Lifesciences, Irvine, CA, USA)	Implantation of a flexible ring into the posterior annulus Ideal for annular dilatation mainly due to LA enlargement (atrial FMR) Anchoring on the hinge of the annulus Transfemoral transeptal approach	Annular dilatation with functional (or mixed, functional-dominant) etiology
Indirect Annuloplasty	Coronary sinus	Carillon (Cardiac Dimensions, Kirkland, WA, USA)	Nitinol anchors placed in the distal and proximal coronary sinus Reduction of MV annulus diameter upon deployment of the device Transjugular approach	Annular dilatation with functional (or mixed, functional-dominant) etiology Coronary sinus proximity and coplanarity
Chordal replacement	Papillary muscles	NeoChord (NeoChord, St Louis Park, MN, USA)	Surgical off-pump procedure Implantation of artificial chords Transapical access	Prolapse or flail Leaflet-to-annulus index $\geq$ 1.25
MV replacement	MV apparatus	Tendyne (Abbott Vascular, Abbott Park, IL, USA)	Self-expanding valve Indicated in suboptimal anatomy for transcatheter repair Transapical approach	MVA 1.0–3.0 cm^2 Multisegment disease Commissural disease, perforations, clefts Mean gradients 5–10 mmHg Unlikely LVOT obstruction LVEF $\geq$ 30% Suboptimal MR reduction expected with transcatheter repair No scar or remodeled LV (transapical access)

DMR: degenerative mitral regurgitation; FMR: functional mitral regurgitation; LA: left atrium; LV: left ventricle; LVEF: left ventricle ejection fraction; LVOT: left ventricle outflow tract; MR: mitral regurgitation; MV: mitral valve; MVA: mitral valve area.

European guidelines recommend transcatheter edge-to-edge repair (TEER) in high-risk symptomatic MR not eligible for surgery and satisfying a set of anatomic criteria. This recommendation applies both to functional (Class IIa, level of evidence B) and degenerative (Class IIb, level of evidence B) etiology [57]. American guidelines recommend TEER in chronic severe FMR and persistent symptoms despite GDMT in patients fulfilling specific anatomical criteria: LVEF 20–50%, left ventricular end-systolic dimension $\leq$ 70 mm, and pulmonary artery systolic pressure $\leq$ 70 mmHg (Class IIa, level of evidence B). The same

evidence of recommendation is applicable for degenerative MR in patients with high or prohibitive surgical risk if mitral valve anatomy is favorable [38].

The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) and Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trials compared the TEER with the MitraClip device vs. GDMT in patients with FMR [66,67]. In the COAPT trial, MitraClip was superior to medical therapy alone at two years in reducing mortality and rehospitalization [66]. In the MITRA-FR trial, the mortality and the rehospitalization rate at one year were similar in the two arms of treatment [67]. A comprehensive analysis of the discrepancies between these two studies led to a complete knowledge of the patients enrolled and their echocardiographic characteristics (Table 2). Grayburn et al. proposed a new conceptional framework reconciling the results of the MITRA-FR and COAPT, based on the concordance between the grade of FMR and the amount of LV dilatation ("proportional" MITRA-FR-like) [68]. The authors concluded that, in "proportional" patients, MR correction would bring little or no improvement to a diseased ventricle affected by a nonsignificant amount of FMR-induced volume overload. Conversely, the benefit might be higher with a relatively large EROA associated with only a moderately dilated ventricle ("disproportionate" COAPT-like). Although this concept is attractive and elegant from an intellectual point of view, it seems to be mainly a theoretical assumption, because the echocardiographic characterization of MR and the hemodynamics of the patients in both studies are not convincing [69]. In order to assess the FMR proportionality, some authors suggest focusing on the ratio of regurgitant volume to ventricular end-diastolic volume. This ratio could anticipate the extent of reverse remodeling occurring after FMR correction. Similarly, regurgitant fraction, by including FMR severity, ventricular volumes and function may also provide prognostic information [69]. Interestingly the rate of AFib and/or atrial flutter was 34.5% in the MITRA-FR trial vs. 57.3% in the COAPT trial, suggesting also different MR etiologies among enrolled patients. Most recently, the single-arm Transcatheter Mitral Valve Repair System Study (CLASP) assessed the PASCAL edge-to-edge device (Edwards Lifesciences, Irvine, CA, USA) in patients with degenerative and functional MR [70]. In the FMR cohort, the two-year mortality and freedom from HF hospitalizations were comparable with that obtained from the MitraClip in the COAPT trial (CLASP: 28% and 78%, respectively; COAPT: 30% and 65%, respectively). In addition, two years after treatment, the prevalence of significant MR decreased and symptoms improved, as confirmed by 95% of patients with MR $\leq$ moderate and 88% of patients in New York Heart Association (NYHA) functional class I–II after the procedure as compared to 36% at baseline [70]. Table 2 summarizes the main difference between COAPT, MITRA-FR and CLASP studies.

Table 2. Similarities and differences among COAPT, MITRA-FR, and CLASP trials with respect to study design and endpoints (Adapted with permission from [68,70]).

	COAPT	MITRA-FR	CLASP	CLASP (FMR)
Patients enrolled	614	304	124	85 (single arm)
Technical implantation success	98%	96%	96%	96%
Atrial fibrillation/Flutter	57.3%	34.5%	53.4%	45%
LVEF	31 ± 9%	33 ± 7%	44 ± 14%	37 ± 10%
EROA	41 ± 15 mm^2	31 ± 10 mm^2	38 ± 15 mm^2	34 ± 11 mm^2
LVEDV	101 ± 34 mL/m^2	135 ± 35 mL/m^2	181 ± 61 mL	199 ± 59 mL
Mortality at 1 y and 2 y	19% and 29%	23% and 34%	9% and 20%	12% and 28%
MR $\geq$ 3+ at discharge $\rightarrow$ 12 mo $\rightarrow$ 24 mo	7.4% $\rightarrow$ 5% $\rightarrow$ 0.9%	8% $\rightarrow$ 17% $\rightarrow$ not recorded	4% * $\rightarrow$ 0% $\rightarrow$ 3%	4% * $\rightarrow$ 0% $\rightarrow$ 5%

FMR: functional mitral regurgitation; LVEF: left ventricle ejection fraction; EROA: effective regurgitant orifice area; LVEDV: left ventricle end-diastolic volume. * Data at 30 days.

A recent study by Gertz ZM et al. analyzed patients in the COAPT trial with a history of AFib, assuming they were most likely to have a mixed atrial and ventricular FMR [71]. Patients with a history of AFib had larger LA, higher LVEF, smaller LV volumes, and similar FMR severity. Patients with a history of AFib had a worse prognosis but benefited from the MitraClip [71]. Other studies investigating TEER in atrial FMR confirmed that this approach could provide sustained FMR reduction over two years and improved clinical outcomes [72–74]. In particular, LA volume index and leaflet-to-annulus index may predict the extent of improvement of atrial FMR provided by TEER [75].

Transcatheter approaches mimicking surgical annuloplasty could also be helpful, particularly in atrial FMR [75–77].

Although preliminary data from multiple transcatheter techniques are encouraging, further studies are warranted to determine the most appropriate strategy for the different phenotypes of FMR across the entire LVEF spectrum.

4.2. Functional Tricuspid Regurgitation

FTR in HFrEF, by increasing the risk of overt right-sided HF and end-organ dysfunction, negatively impacts symptoms and prognosis. Although consistent data on the direct effect of GDMT on the reduction of TR are missing, diuretics, sodium, and water restriction by acting on volume overload remain the cornerstone of medical treatment [78].

Scientific guidelines recommend surgery for severe FTR only in the presence of associated left-sided lesions deserving simultaneous treatment. In these patients, surgery for FTR is also an option when the degree is not severe but the annulus is dilated [38,57].

Depending on the predominant etiology, surgical corrective measures should restore valve competence by addressing the underlying specific mechanisms. When annular dilatation is the primary mechanism of FTR (atrial FTR), surgical annuloplasty is the preferred approach to reduce annular dimensions, remodel annular shape, and improve leaflets coaptation [38,57]. On the contrary, surgical annuloplasty carries a high risk of recurrence in the case of ventricular FTR because of the significant leaflet tethering and RV dysfunction/remodeling [79,80]. In routine practice, isolated tricuspid valve surgery, particularly valve replacement, is rare because of the significant operative risk, mainly linked to the high prevalence of severe comorbidities in these patients [81]. Accordingly, the scientific community now perceives transcatheter tricuspid valve interventions as a potential tool to improve symptoms and perhaps the prognosis of patients with HF complicated by FTR.

Table 3 summarizes the most applied transcatheter techniques currently used to manage FTR.

The TriValve Registry showed a procedural success rate of 73%, periprocedural mortality of 0%, and a 30-days adverse event rate of 11% [84]. A sub-optimal result of the procedure, defined as residual regurgitation $\geq$ grade 2+, was a predictor of future adverse outcomes [84]. Specifically, predictors of suboptimal procedural results were baseline TR grade (defined by EROA), gap of coaptation, tenting area, and TR jet localization (no central or anteroseptal). Additionally, clinical predictors of one-year mortality included procedural failure, worsening renal function, and absence of sinus rhythm [84]. A successive propensity-matched analysis compared the transcatheter valve therapy of the TRiValve population to medical treatment alone. The results suggest that transcatheter intervention is associated with more favorable one-year survival and freedom from HF hospitalizations even after the adjustment for confounders at baseline [85]. In the transcatheter plus medical therapy group, 22% of patients had LVEF $\leq$ 35% (21% in the medical therapy alone group). This figure indicates that most patients enrolled in the registry were likely affected by HFmrEF and HFpEF complicated by atrial FTR. Nevertheless, the transcatheter treatment improved the outcome in all subsets of LVEF [85].

Table 3. Overview of transcatheter tricuspid valve repair and replacement devices, with CE approval, for treating functional tricuspid regurgitation (Adapted with permission from [82,83]).

Type of Intervention	Target Structure	Device	Description	Eligibility Criteria
Edge-to-edge	Tricuspid leaflets	TriClip (Abbott Vascular, Abbott Park, IL, USA) PASCAL (Edwards Lifesciences, Irvine, CA, USA)	Based on edge-to-edge technique Approximation of the septal and anterior leaflets or septal and posterior leaflets	Small septolateral gap $\leq$ 7 mm Anteroseptal jet location Trileaflet morphology Diffusely degenerated leaflets and pacemaker lead impingement are unfavorable anatomic conditions
Direct Annuloplasty	Tricuspid annulus	Cardioband (Edwards Lifesciences, Irvine, CA, USA)	Implantation of a flexible ring with multiple anchors on the hinge of the annulus Challenging procedure Distance between RCA and annulus may be a limitation	Annular dilatation as primary mechanism of TR Mild tethering (tenting height <0.76 cm, tenting area < 1.63 cm^2, tenting volume < 2.3 mL) Central jet location Sufficient landing zone for anchoring
Heterotopic replacement	Superior and inferior caval veins	TricValve (Orbus Vienna AU, Wien, Austria)	Self-expanding valves Indicated in patients with significant backflow in the IVC and/or SVC Palliative care in unfavorable anatomy for transcatheter repair Irrespective of the TR etiology	Appropriate caval diameters (and intercaval distance) Contraindicated in severe RV dysfunction and pulmonary hypertension

FTR: functional tricuspid regurgitation; IVC: inferior vena cava; RA: right atrium; RCA: right coronary artery; RV: right ventricle; SVC: superior vena cava; TR: tricuspid regurgitation.

Recent data from the randomized TRILUMIATE trial showed that TEER with the TriClip system (Abbott Vascular, Abbott Park, IL, USA) was safe for patients with severe TR, reducing the grade of regurgitation, and improving the quality of life [86]. Into details, the primary end point (including death from any cause or tricuspid-valve surgery; hospitalization for HF; and an improvement in quality of life) favored the transcatheter group over medical controls (win ratio, 1.48; 95% confidence interval, 1.06 to 2.13; $p = 0.02$). At 30 days, 87.0% of the TriClip patients and 4.8% of medical therapy patients had TR of no greater than moderate severity ($p < 0.001$). In addition, the quality-of-life score changed by a mean ($\pm$SD) of 12.3 $\pm$ 1.8 points in the TriClip group, as compared with 0.6 $\pm$ 1.8 points in the control group ($p < 0.001$) [86]. As regards the echocardiographic characteristics of the patients enrolled, 94.8% of the TEER group and 92.9% of the control group had FTR; the mean LVEF was 59.3 $\pm$ 9.3% in the TEER group and 58.7 $\pm$ 10.5% in the control group, with 14% of patients with LVEF < 50% in both groups. In the TriClip group, 87.4% and 11.4% suffered from AFib and atrial flutter, respectively; in the medical therapy group, 92.6% and 12.6% had AFib and atrial flutter, respectively. These data suggest that most patients enrolled in the trial were likely affected by aFTR, associated with a preserved or mildly reduced LVEF.

Although surgery can effectively address atrial FTR, most patients with HFmrEF and HFpEF remain untreated because they are considered higher-risk surgical candidates. However, data from relatively small experiences and registries suggest that a transcatheter approach is valuable even for these patients [40,86–88]. The correction of atrial FTR while

reducing right atrial pressure, backward signs, and symptoms of right HF driven by congestion could increase forward stroke volume [40]. The increase in cardiac output could have a clinical and prognostic impact, particularly in patients with restrictive pathophysiology, such as HFpEF [40]. Therefore, transcatheter annuloplasty could be effective when leaflet tethering is less pronounced, and TR is mainly due to RA and tricuspid annulus dilatation (atrial FTR) [82,86,89]. In patients with advanced geometrical remodeling, TV replacement could be a promising option that is still in its infancy, but no transcatheter devices are currently available for commercial use [37,89].

Prospective randomized studies addressing these unmet clinical needs across all HF stages must confirm these hypotheses generated from exploratory studies.

5. Conclusions

Functional MR and TR are common findings in HFrEF, HFmrEF, and HFpEF. The proper and simultaneous recognition of the specific mechanism of regurgitation on the one hand and the phenotype of HF on the other is crucial for defining prognosis and therapy. GMDT is the first-line treatment for functional regurgitation across all HF phenotypes, followed by CRT in appropriately selected patients. Behind GDMT and CRT, surgical or transcatheter valve therapy is a valuable option for patients remaining symptomatic. Pharmacological and non-pharmacological treatments are complementary and can interrupt valvular-driven HF progression in appropriately selected patients.

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References

1. Kadri, A.N.; Gajulapalli, R.D.; Sammour, Y.M.; Chahine, J.; Nusairat, L.; Gad, M.M.; Al-Khadra, Y.; Hernandez, A.V.; Rader, F.; Harb, S.C.; et al. Impact of Tricuspid Regurgitation in Patients with Heart Failure and Mitral Valve Disease from a Nationwide Cohort Study. *Am. J. Cardiol.* **2019**, *124*, 926–931. [CrossRef] [PubMed]
2. Goliasch, G.; Bartko, P.E.; Pavo, N.; Neuhold, S.; Wurm, R.; Mascherbauer, J.; Lang, I.M.; Strunk, G.; Hülsmann, M. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur. Heart J.* **2018**, *39*, 39–46. [CrossRef] [PubMed]
3. Bartko, P.E.; Arfsten, H.; Heitzinger, G.; Pavo, N.; Winter, M.-P.; Toma, A.; Strunk, G.; Hengstenberg, C.; Hülsmann, M.; Goliasch, G. Natural history of bivalvular functional regurgitation. *Eur. Heart J.—Cardiovasc. Imaging* **2018**, *20*, 565–573. [CrossRef] [PubMed]
4. Schlotter, F.; Dietz, M.F.; Stolz, L.; Kresoja, K.-P.; Besler, C.; Sannino, A.; Rommel, K.-P.; Unterhuber, M.; von Roeder, M.; Delgado, V.; et al. Atrial Functional Tricuspid Regurgitation: Novel Definition and Impact on Prognosis. *Circ. Cardiovasc. Interv.* **2022**, *15*, 011958. [CrossRef] [PubMed]
5. Badano, L.P.; Muraru, D.; Enriquez-Sarano, M. Assessment of functional tricuspid regurgitation. *Eur. Heart J.* **2013**, *34*, 1875–1885. [CrossRef]
6. Ennezat, P.V.; Maréchaux, S.; Pibarot, P.; Le Jemtel, T.H. Secondary Mitral Regurgitation in Heart Failure with Reduced or Preserved Left Ventricular Ejection Fraction. *Cardiology* **2013**, *125*, 110–117. [CrossRef]
7. Hoit, B.D. Atrial Functional Mitral Regurgitation: The Left Atrium Gets its Due Respect. *J. Am. Coll. Cardiol.* **2011**, *58*, 1482–1484. [CrossRef]
8. Chioncel, O.; Lainscak, M.; Seferovic, P.M.; Anker, S.D.; Crespo-Leiro, M.G.; Harjola, V.-P.; Parissis, J.; Laroche, C.; Piepoli, M.F.; Fonseca, C.; et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: An analysis of the ESC Heart Failure Long-Term Registry. *Eur. J. Heart Fail.* **2017**, *19*, 1574–1585. [CrossRef]

9. Bursi, F.; Barbieri, A.; Grigioni, F.; Reggianini, L.; Zanasi, V.; Leuzzi, C.; Ricci, C.; Piovaccari, G.; Branzi, A.; Modena, M.G. Prognostic implications of functional mitral regurgitation according to the severity of the underlying chronic heart failure: A long-term outcome study. *Eur. J. Heart Fail.* **2010**, *12*, 382–388. [CrossRef]
10. Patel, J.B.; Borgeson, D.D.; E Barnes, M.; Rihal, C.S.; Daly, R.C.; Redfield, M.M. Mitral regurgitation in patients with advanced systolic heart failure. *J. Card. Fail.* **2004**, *10*, 285–291. [CrossRef]
11. Grigioni, F.; Enriquez-Sarano, M.; Zehr, K.; Bailey, K.; Tajik, A. Ischemic mitral regurgitation. Long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* **2001**, *103*, 1759–1764. [CrossRef] [PubMed]
12. Rossi, A.; Dini, F.L.; Faggiano, P.; Agricola, E.; Cicoira, M.; Frattini, S.; Simioniuc, A.; Gullace, M.; Ghio, S.; Enriquez-Sarano, M.; et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart* **2011**, *97*, 1675–1680. [CrossRef] [PubMed]
13. D'Arcy, J.L.; Coffey, S.; Loudon, M.A.; Kennedy, A.; Pearson-Stuttard, J.; Birks, J.; Frangou, E.; Farmer, A.J.; Mant, D.; Wilson, J.; et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: The OxVALVE Population Cohort Study. *Eur. Heart J.* **2016**, *37*, 3515–3522. [CrossRef] [PubMed]
14. Singh, J.P.; Evans, J.C.; Levy, D.; Larson, M.G.; A Freed, L.; Fuller, D.L.; Lehman, B.; Benjamin, E.J. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am. J. Cardiol.* **1999**, *83*, 897–902. [CrossRef]
15. Topilsky, Y.; Maltais, S.; Medina-Inojosa, J.; Oguz, D.; Michelena, H.; Maalouf, J.; Mahoney, D.W.; Enriquez-Sarano, M. Burden of Tricuspid Regurgitation in Patients Diagnosed in the Community Setting. *JACC Cardiovasc. Imaging* **2019**, *12*, 433–442. [CrossRef] [PubMed]
16. Benfari, G.; Antoine, C.; Miller, W.L.; Thapa, P.; Topilsky, Y.; Rossi, A.; Michelena, H.I.; Pislaru, S.; Enriquez-Sarano, M. Excess Mortality Associated with Functional Tricuspid Regurgitation Complicating Heart Failure with Reduced Ejection Fraction. *Circulation* **2019**, *140*, 196–206. [CrossRef]
17. Chorin, E.; Rozenbaum, Z.; Topilsky, Y.; Konigstein, M.; Ziv-Baran, T.; Richert, E.; Keren, G.; Banai, S. Tricuspid regurgitation and long-term clinical outcomes. *Eur. Heart J. Cardiovasc. Imaging* **2020**, *21*, 157–165. [CrossRef]
18. E Bartko, P.; Hülsmann, M.; Hung, J.; Pavo, N.; A Levine, R.; Pibarot, P.; Vahanian, A.; Stone, G.W.; Goliasch, G. Secondary valve regurgitation in patients with heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction. *Eur. Heart J.* **2020**, *41*, 2799–2810. [CrossRef]
19. Deferm, S.; Bertrand, P.B.; Verbrugge, F.H.; Verhaert, D.; Rega, F.; Thomas, J.D.; Vandervoort, P.M. Atrial Functional Mitral Regurgitation: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* **2019**, *73*, 2465–2476. [CrossRef]
20. Magne, J.; Sénéchal, M.; Dumesnil, J.G.; Pibarot, P. Ischemic Mitral Regurgitation: A Complex Multifaceted Disease. *Cardiology* **2009**, *112*, 244–259. [CrossRef]
21. Lancellotti, P.; Moura, L.; Pierard, L.A.; Agricola, E.; Popescu, B.A.; Tribouilloy, C.; Hagendorff, A.; Monin, J.-L.; Badano, L.; Zamorano, J.L.; et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: Mitral and tricuspid regurgitation (native valve disease). *Eur. Heart J.—Cardiovasc. Imaging* **2010**, *11*, 307–332. [CrossRef] [PubMed]
22. Kajimoto, K.; Sato, N.; Takano, T.; on behalf of the investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry. Functional mitral regurgitation at discharge and outcomes in patients hospitalized for acute decompensated heart failure with a preserved or reduced ejection fraction. *Eur. J. Heart Fail.* **2016**, *18*, 1051–1059. [CrossRef] [PubMed]
23. Benfari, G.; Antoine, C.; Essayagh, B.; Batista, R.; Maalouf, J.; Rossi, A.; Grigioni, F.; Thapa, P.; Michelena, H.I.; Enriquez-Sarano, M. Functional Mitral Regurgitation Outcome and Grading in Heart Failure With Reduced Ejection Fraction. *JACC Cardiovasc. Imaging* **2021**, *14*, 2303–2315. [CrossRef] [PubMed]
24. Dziadzko, V.; Dziadzko, M.; Medina-Inojosa, J.R.; Benfari, G.; Michelena, H.I.; Crestanello, J.A.; Maalouf, J.; Thapa, P.; Enriquez-Sarano, M. Causes and Mechanisms of Isolated Mitral Regurgitation in the Community: Clinical Context and Outcome. *Eur. Heart J.* **2019**, *40*, 2194–2202. [CrossRef]
25. Gertz, Z.M.; Raina, A.; Saghy, L.; Zado, E.S.; Callans, D.J.; Marchlinski, F.E.; Keane, M.G.; Silvestry, F.E. Evidence of Atrial Functional Mitral Regurgitation Due to Atrial Fibrillation: Reversal With Arrhythmia Control. *J. Am. Coll. Cardiol.* **2011**, *58*, 1474–1481. [CrossRef]
26. Mesi, O.; Gad, M.M.; Crane, A.D.; Ramchand, J.; Puri, R.; Layoun, H.; Miyasaka, R.; Gillinov, M.A.; Wierup, P.; Griffin, B.P.; et al. Severe Atrial Functional Mitral Regurgitation: Clinical and Echocardiographic Characteristics, Management and Outcomes. *JACC Cardiovasc. Imaging* **2021**, *14*, 797–808. [CrossRef]
27. Redfield, M.M.; Jacobsen, S.J.; Borlaug, B.A.; Rodeheffer, R.J.; Kass, D.A. Age- and Gender-Related Ventricular-Vascular Stiffening: A Community-Based Study. *Circulation* **2005**, *112*, 2254–2262. [CrossRef]
28. Lam, C.S.P.; Roger, V.L.; Rodeheffer, R.J.; Bursi, F.; Borlaug, B.A.; Ommen, S.R.; Kass, D.A.; Redfield, M.M. Cardiac Structure and Ventricular–Vascular Function in Persons with Heart Failure and Preserved Ejection Fraction From Olmsted County, Minnesota. *Circulation* **2007**, *115*, 1982–1990. [CrossRef]
29. Kawaguchi, M.; Hay, I.; Fetics, B.; Kass, D.A. Combined Ventricular Systolic and Arterial Stiffening in Patients with Heart Failure and Preserved Ejection Fraction: Implications for Systolic and Diastolic Reserve Limitations. *Circulation* **2003**, *107*, 714–720. [CrossRef]

30. January, C.T.; Wann, L.S.; Calkins, H.; Chen, L.Y.; Cigarroa, J.E.; Cleveland, J.C., Jr.; Ellinor, P.T., Jr.; Ezekowitz, M.D.; Field, M.E.; Furie, K.L.; et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeons. *Circulation* **2019**, *140*, E28. [CrossRef]
31. Hindricks, G.; Potpara, T.; Dagres, N.; Arbelo, E.; Bax, J.J.; Blomström-Lundqvist, C.; Boriani, G.; Castella, M.; Dan, G.A.; Dilaveris, P.E.; et al. 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation Developed in Collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the Diagnosis and Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Developed with the Special Contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur. Heart J.* **2021**, *42*, 4194. [PubMed]
32. Manning, W.J.; Silverman, D.I.; Katz, S.E.; Riley, M.F.; Come, P.C.; Doherty, R.M.; Munson, J.T.; Douglas, P.S. Impaired left atrial mechanical function after cardioversion: Relation to the duration of atrial fibrillation. *J. Am. Coll. Cardiol.* **1994**, *23*, 1535–1540. [CrossRef] [PubMed]
33. Okamoto, C.; Okada, A.; Nishimura, K.; Moriuchi, K.; Amano, M.; Takahama, H.; Amaki, M.; Hasegawa, T.; Kanzaki, H.; Fujita, T.; et al. Prognostic comparison of atrial and ventricular functional mitral regurgitation. *Open Heart* **2021**, *8*, e001574. [CrossRef] [PubMed]
34. Enriquez-Sarano, M.; Benfari, G.; Messika-Zeitoun, D.; Grigioni, F.; Michelena, H.I. Functional mitral regurgitation: A proportionate or disproportionate focus of attention? *Eur. J. Heart Fail.* **2021**, *23*, 1759–1762. [CrossRef]
35. Guta, A.C.; Badano, L.P.; Tomaselli, M.; Mihalcea, D.; Bartos, D.; Parati, G.; Muraru, D. The Pathophysiological Link between Right Atrial Remodeling and Functional Tricuspid Regurgitation in Patients with Atrial Fibrillation: A Three-Dimensional Echocardiography Study. *J. Am. Soc. Echocardiogr.* **2021**, *34*, 585–594.e1. [CrossRef]
36. Muraru, D.; Addetia, K.; Guta, A.C.; Ochoa-Jimenez, R.C.; Genovese, D.; Veronesi, F.; Basso, C.; Iliceto, S.; Badano, L.P.; Lang, R.M. Right atrial volume is a major determinant of tricuspid annulus area in functional tricuspid regurgitation: A three-dimensional echocardiographic study. *Eur. Heart J.—Cardiovasc. Imaging* **2020**, *22*, 660–669. [CrossRef]
37. Hahn, R.T.; Badano, L.P.; Bartko, P.E.; Muraru, D.; Maisano, F.; Zamorano, J.L.; Donal, E. Tricuspid regurgitation: Recent advances in understanding pathophysiology, severity grading and outcome. *Eur. Heart J.—Cardiovasc. Imaging* **2022**, *23*, 913–929. [CrossRef]
38. Otto, C.M.; Nishimura, R.A.; Bonow, R.O.; Carabello, B.A.; Erwin, J.P., 3rd; Gentile, F.; Jneid, H.; Krieger, E.V.; Mack, M.; McLeod, C.; et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **2021**, *77*, 450–500. [CrossRef]
39. Fagot, J.; Lavie-Badie, Y.; Blanchard, V.; Fournier, P.; Galinier, M.; Carrié, D.; Lairez, O.; Cariou, E.; Alric, L.; Bureau, C.; et al. Impact of tricuspid regurgitation on survival in patients with cardiac amyloidosis. *ESC Heart Fail.* **2021**, *8*, 438–446. [CrossRef]
40. Nusca, A.; Cammalleri, V.; Carpenito, M.; Bono, M.C.; Mega, S.; Grigioni, F.; Ussia, G.P. Percutaneous Repair of Atrial Functional Tricuspid Regurgitation in Cardiac Amyloidosis: Combining Linear with Lateral Thinking. *JACC Case Rep.* **2023**, *5*, 101685. [CrossRef]
41. Mascherbauer, J.; Kammerlander, A.A.; Zotter-Tufaro, C.; Aschauer, S.; Duca, F.; Dalos, D.; Winkler, S.; Schneider, M.; Bergler-Klein, J.; Bonderman, D. Presence of ´isolated´ tricuspid regurgitation should prompt the suspicion of heart failure with preserved ejection fraction. *PLoS ONE* **2017**, *12*, e0171542. [CrossRef]
42. Fender, E.A.; Petrescu, I.; Ionescu, F.; Zack, C.J.; Pislaru, S.V.; Nkomo, V.T.; Cochuyt, J.J.; Hodge, D.O.; Nishimura, R.A. Prognostic Importance and Predictors of Survival in Isolated Tricuspid Regurgitation: A Growing Problem. *Mayo Clin. Proc.* **2019**, *94*, 2032–2039. [CrossRef] [PubMed]
43. Ren, Q.; Li, X.; Fang, J.; Chen, Y.; Wu, M.; Yu, Y.; Liao, S.; Tse, H.; Yiu, K. The prevalence, predictors, and prognosis of tricuspid regurgitation in stage B and C heart failure with preserved ejection fraction. *ESC Heart Fail.* **2020**, *7*, 4051–4060. [CrossRef] [PubMed]
44. Topilsky, Y.; Nkomo, V.T.; Vatury, O.; Michelena, H.I.; Letourneau, T.; Suri, R.M.; Pislaru, S.; Park, S.; Mahoney, D.W.; Biner, S.; et al. Clinical Outcome of Isolated Tricuspid Regurgitation. *JACC: Cardiovasc. Imaging* **2014**, *7*, 1185–1194. [CrossRef] [PubMed]
45. Chen, E.; L'official, G.; Guérin, A.; Dreyfus, J.; Lavie-Badie, Y.; Sportouch, C.; Eicher, J.-C.; Maréchaux, S.; Le Tourneau, T.; Oger, E.; et al. Natural history of functional tricuspid regurgitation: Impact of cardiac output. *Eur. Heart J.—Cardiovasc. Imaging* **2021**, *22*, 878–885. [CrossRef]
46. Hell, M.M.; Emrich, T.; Kreidel, F.; Kreitner, K.-F.; Schoepf, U.J.; Münzel, T.; von Bardeleben, R.S. Computed tomography imaging needs for novel transcatheter tricuspid valve repair and replacement therapies. *Eur. Heart J.—Cardiovasc. Imaging* **2020**, *22*, 601–610. [CrossRef]
47. Bartko, P.E.; Arfsten, H.; Frey, M.; Heitzinger, G.; Pavo, N.; Cho, A.N.N.A.; Neuhold, S.; Tan, T.; Strunk, G.; Hengstenberg, C.; et al. 5937Natural history of functional tricuspid regurgitation: Implications of quantitative doppler assessment. *JACC Cardiovasc. Imaging* **2019**, *12*, 389–397. [CrossRef]
48. Santas, E.; Chorro, F.J.; Miñana, G.; Méndez, J.; Muñoz, J.; Escribano, D.; García-Blas, S.; Valero, E.; Bodí, V.; Núñez, E.; et al. Tricuspid Regurgitation and Mortality Risk Across Left Ventricular Systolic Function in Acute Heart Failure. *Circ. J.* **2015**, *79*, 1526–1533. [CrossRef]

49. Topilsky, Y.; Inojosa, J.M.; Benfari, G.; Vaturi, O.; Maltais, S.; Michelena, H.; Mankad, S.; Enriquez-Sarano, M. Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction. *Eur. Heart J.* **2018**, *39*, 3584–3592. [CrossRef]
50. Gavazzoni, M.; Heilbron, F.; Badano, L.P.; Radu, N.; Cascella, A.; Tomaselli, M.; Perelli, F.; Caravita, S.; Baratto, C.; Parati, G.; et al. The atrial secondary tricuspid regurgitation is associated to more favorable outcome than the ventricular phenotype. *Front. Cardiovasc. Med.* **2022**, *9*, 1022755. [CrossRef]
51. Dietz, M.F.; Prihadi, E.A.; van der Bijl, P.; Goedemans, L.; Mertens, B.J.; Gursoy, E.; van Genderen, O.S.; Marsan, N.A.; Delgado, V.; Bax, J.J. Prognostic Implications of Right Ventricular Remodeling and Function in Patients with Significant Secondary Tricuspid Regurgitation. *Circulation* **2019**, *140*, 836–845. [CrossRef] [PubMed]
52. Itelman, E.; Vatury, O.; Kuperstein, R.; Ben-Zekry, S.; Hay, I.; Fefer, P.; Barbash, I.; Klempfner, R.; Segev, A.; Feinberg, M.; et al. The Association of Severe Tricuspid Regurgitation with Poor Survival Is Modified by Right Ventricular Pressure and Function: Insights from SHEBAHEART Big Data. *J. Am. Soc. Echocardiogr.* **2022**, *35*, 1028–1036. [CrossRef] [PubMed]
53. Masuda, M.; Sekiya, K.; Asai, M.; Iida, O.; Okamoto, S.; Ishihara, T.; Nanto, K.; Kanda, T.; Tsujimura, T.; Matsuda, Y.; et al. Influence of catheter ablation for atrial fibrillation on atrial and ventricular functional mitral regurgitation. *ESC Heart Fail.* **2022**, *9*, 1901–1913. [CrossRef] [PubMed]
54. Coats, A.J.S.; Anker, S.D.; Baumbach, A.; Alfieri, O.; von Bardeleben, R.S.; Bauersachs, J.; Bax, J.J.; Boveda, S.; Čelutkienė, J.; Cleland, J.G.; et al. The management of secondary mitral regurgitation in patients with heart failure: A joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC. *Eur. Heart J.* **2021**, *42*, 1254–1269. [CrossRef] [PubMed]
55. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; Deswal, A.; Drazner, M.H.; Dunlay, S.M.; Evers, L.R.; et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* **2022**, *146*, E185. [CrossRef] [PubMed]
56. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. Corrigendum to: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **2021**, *42*, 4901. [CrossRef]
57. Vahanian, A.; Beyersdorf, F.; Praz, F.; Milojevic, M.; Baldus, S.; Bauersachs, J.; Capodanno, D.; Conradi, L.; De Bonis, M.; De Paulis, R.; et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur. Heart J.* **2022**, *43*, 561–632. [CrossRef]
58. Bartko, P.E.; Arfsten, H.; Heitzinger, G.; Pavo, N.; Strunk, G.; Gwechenberger, M.; Hengstenberg, C.; Binder, T.; Hulsmann, M.; Goliasch, G. Papillary Muscle Dyssynchrony-Mediated Functional Mitral Regurgitation: Mechanistic Insights and Modulation by Cardiac Resynchronization. *JACC Cardiovasc. Imaging* **2019**, *12*, 1728–1737. [CrossRef]
59. Onishi, T.; Onishi, T.; Marek, J.J.; Ahmed, M.; Haberman, S.C.; Oyenuga, O.; Adelstein, E.; Schwartzman, D.; Saba, S.; Gorcsan, J. 3rd. Mechanistic features associated with improvement in mitral regurgitation after cardiac resynchronization therapy and their relation to long-term patient outcome. *Circ. Heart Fail.* **2013**, *6*, 685–693. [CrossRef]
60. Van Der Bijl, P.; Vo, N.M.; Leung, M.; Ajmone Marsan, N.; Delgado, V.; Stone, G.W.; Bax, J.J. Impact of Atrial Fibrillation on Improvement of Functional Mitral Regurgitation in Cardiac Resynchronization Therapy. *Heart Rhythm.* **2018**, *15*, 1816–1822. [CrossRef]
61. Dell'Era, G.; Rondano, E.; Franchi, E.; Marino, P. Atrial asynchrony and function before and after electrical cardioversion for persistent atrial fibrillation. *Eur. J. Echocardiogr.* **2010**, *11*, 577–583. [CrossRef] [PubMed]
62. Kihara, T.; Gillinov, A.M.; Takasaki, K.; Fukuda, S.; Song, J.-M.; Shiota, M.; Shiota, T. Mitral Regurgitation Associated with Mitral Annular Dilation in Patients with Lone Atrial Fibrillation: An Echocardiographic Study. *Echocardiography* **2009**, *26*, 885–889. [CrossRef] [PubMed]
63. Takahashi, Y.; Abe, Y.; Sasaki, Y.; Bito, Y.; Morisaki, A.; Nishimura, S.; Shibata, T. Mitral valve repair for atrial functional mitral regurgitation in patients with chronic atrial fibrillation. *Interact. Cardiovasc. Thorac. Surg.* **2015**, *21*, 163–168. [CrossRef] [PubMed]
64. Yousef, S.; Arnaoutakis, G.J.; Gada, H.; Smith, A.J.C.; Sanon, S.; Sultan, I. Transcatheter mitral valve therapies: State of the art. *J. Card. Surg.* **2021**, *37*, 225–233. [CrossRef] [PubMed]
65. Cammalleri, V.; Mega, S.; Ussia, G.P.; Grigioni, F. Mitral and Tricuspid Valves Percutaneous Repair in Patients with Advanced Heart Failure: Panacea, or Pandora's Box? *Heart Fail. Clin.* **2021**, *17*, 607–618. [CrossRef]
66. Stone, G.W.; Lindenfeld, J.; Abraham, W.T.; Kar, S.; Lim, D.S.; Mishell, J.M.; Whisenant, B.; Grayburn, P.A.; Rinaldi, M.; Kapadia, S.R.; et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N. Engl. J. Med.* **2018**, *379*, 2307–2318. [CrossRef]
67. Obadia, J.-F.; Messika-Zeitoun, D.; Leurent, G.; Iung, B.; Bonnet, G.; Piriou, N.; Lefèvre, T.; Piot, C.; Rouleau, F.; Carrié, D.; et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N. Engl. J. Med.* **2018**, *379*, 2297–2306. [CrossRef]
68. Grayburn, P.A.; Sannino, A.; Packer, M. Proportionate and disproportionate functional mitral regurgitation: A new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc. Imaging* **2019**, *12*, 353–362. [CrossRef]
69. Hagendorff, A.; Doenst, T.; Falk, V. Echocardiographic assessment of functional mitral regurgitation: Opening Pandora's box? *ESC Heart Fail.* **2019**, *6*, 678–685. [CrossRef]

70. Szerlip, M.; Spargias, K.S.; Makkar, R.; Kar, S.; Kipperman, R.M.; O'neill, W.W.; Ng, M.K.; Smith, R.L.; Fam, N.P.; Rinaldi, M.J.; et al. 2-Year Outcomes for Transcatheter Repair in Patients with Mitral Regurgitation From the CLASP Study. *JACC Cardiovasc. Interv.* **2021**, *14*, 1538–1548. [CrossRef]
71. Gertz, Z.M.; Herrmann, H.C.; Lim, D.S.; Kar, S.; Kapadia, S.R.; Reed, G.W.; Puri, R.; Krishnaswamy, A.; Gersh, B.J.; Weissman, N.J.; et al. Implications of Atrial Fibrillation on the Mechanisms of Mitral Regurgitation and Response to MitraClip in the COAPT Trial. *Circ. Cardiovasc. Interv.* **2021**, *14*, E010300. [CrossRef] [PubMed]
72. Tanaka, T.; Sugiura, A.; Öztürk, C.; Vogelhuber, J.; Tabata, N.; Wilde, N.; Zimmer, S.; Nickenig, G.; Weber, M. Transcatheter Edge-to-Edge Repair for Atrial Secondary Mitral Regurgitation. *JACC Cardiovasc. Interv.* **2022**, *15*, 1731–1740. [CrossRef] [PubMed]
73. Yoon, S.-H.; Makar, M.; Kar, S.; Chakravarty, T.; Oakley, L.; Sekhon, N.; Koseki, K.; Nakamura, M.; Hamilton, M.; Patel, J.K.; et al. Outcomes After Transcatheter Edge-to-Edge Mitral Valve Repair According to Mitral Regurgitation Etiology and Cardiac Remodeling. *J. Am. Coll. Cardiol. Interv.* **2022**, *15*, 1711–1722. [CrossRef]
74. Sodhi, N.; Asch, F.M.; Ruf, T.; Petrescu, A.; von Bardeleben, S.; Lim, D.S.; Maisano, F.; Kar, S.; Price, M.J. Clinical Outcomes with Transcatheter Edge-to-Edge Repair in Atrial Functional MR From the EXPAND Study. *JACC Cardiovasc. Interv.* **2022**, *15*, 1723–1730. [CrossRef] [PubMed]
75. Schofer, J.; Siminiak, T.; Haude, M.; Herrman, J.P.; Vainer, J.; Wu, J.C.; Levy, W.C.; Mauri, L.; Feldman, T.; Kwong, R.Y.; et al. Percutaneous Mitral Annuloplasty for Functional Mitral Regurgitation: Results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation* **2009**, *120*, 326–333. [CrossRef]
76. Nickenig, G.; Hammerstingl, C.; Schueler, R.; Topilsky, Y.; Grayburn, P.A.; Vahanian, A.; Messika-Zeitoun, D.; Urena Alcazar, M.; Baldus, S.; Volker, R.; et al. Transcatheter Mitral Annuloplasty in Chronic Functional Mitral Regurgitation: 6-Month Results with the Cardioband Percutaneous Mitral Repair System. *JACC Cardiovasc. Interv.* **2016**, *9*, 2039–2047. [CrossRef]
77. Gooley, R.P.; Meredith, I.T. The Accucinch transcatheter direct mitral valve annuloplasty system. *Eurointervention* **2015**, *11*, W60–W61. [CrossRef]
78. Houston, B.A.; Brittain, E.L.; Tedford, R.J. Right Ventricular Failure. *N. Engl. J. Med.* **2023**, *388*, 1111–1125. [CrossRef]
79. McCarthy, P.M.; Bhudia, S.K.; Rajeswaran, J.; Hoercher, K.J.; Lytle, B.W.; Cosgrove, D.M.; Blackstone, E.H. Tricuspid valve repair: Durability and risk factors for failure. *J. Thorac. Cardiovasc. Surg.* **2004**, *127*, 674–685. [CrossRef]
80. Fukuda, S.; Song, J.-M.; Gillinov, A.M.; McCarthy, P.M.; Daimon, M.; Kongsaerepong, V.; Thomas, J.D.; Shiota, T. Tricuspid Valve Tethering Predicts Residual Tricuspid Regurgitation after Tricuspid Annuloplasty. *Circulation* **2005**, *111*, 975–979. [CrossRef]
81. Zack, C.J.; Fender, E.A.; Chandrashekar, P.; Reddy, Y.N.; Bennett, C.E.; Stulak, J.M.; Miller, V.M.; Nishimura, R.A. National Trends and Outcomes in Isolated Tricuspid Valve Surgery. *J. Am. Coll. Cardiol.* **2017**, *70*, 2953–2960. [CrossRef] [PubMed]
82. Cammalleri, V.; Carpenito, M.; Bono, M.C.; Mega, S.; Ussia, G.P.; Grigioni, F. Transcatheter Tricuspid Valve Therapy: From Anatomy to Intervention. *Front. Cardiovasc. Med.* **2021**, *8*, 778445. [CrossRef] [PubMed]
83. Praz, F.; Muraru, D.; Kreidel, F.; Lurz, P.; Hahn, R.T.; Delgado, V.; Senni, M.; von Bardeleben, R.S.; Nickenig, G.; Hausleiter, J.; et al. Transcatheter treatment for tricuspid valve disease. *Eurointervention* **2021**, *17*, 791–808. [CrossRef] [PubMed]
84. Taramasso, M.; Alessandrini, H.; Latib, A.; Asami, M.; Attinger-Toller, A.; Biasco, L.; Braun, D.; Brochet, E.; Connelly, K.A.; Denti, P.; et al. Outcomes after Current Transcatheter Tricuspid Valve Intervention: Mid-Term Results from the International Trivalve Registry. *JACC Cardiovasc. Interv.* **2019**, *12*, 155–165. [CrossRef] [PubMed]
85. Taramasso, M.; Benfari, G.; van Der Bijl, P.; Alessandrini, H.; Attinger-Toller, A.; Biasco, L.; Lurz, P.; Braun, D.; Brochet, E.; Connelly, K.A.; et al. Transcatheter versus Medical Treatment of Symptomatic Severe Tricuspid Regurgitation. *J. Am. Coll. Cardiol.* **2019**, *74*, 2998–3008. [CrossRef] [PubMed]
86. Nickenig, G.; Weber, M.; Schüler, R.; Hausleiter, J.; Nabauer, M.; von Bardeleben, R.S.; Sotiriou, E.; Schäfer, U.; Deuschl, F.; Alessandrini, H.; et al. Tricuspid valve repair with the Cardioband system: Two-year outcomes of the multicentre, prospective TRI-REPAIR study. *Eurointervention* **2021**, *16*, e1264–e1271. [CrossRef]
87. Tanaka, T.; Sugiura, A.; Kavsur, R.; Vogelhuber, J.; Öztürk, C.; Becher, M.U.; Zimmer, S.; Nickenig, G.; Weber, M. Leaflet-to-annulus index and residual tricuspid regurgitation following tricuspid transcatheter edge-to-edge repair. *Eurointervention* **2022**, *18*, e169–e178. [CrossRef]
88. Carpenito, M.; Cammalleri, V.; Vitez, L.; De Filippis, A.; Nobile, E.; Bono, M.C.; Mega, S.; Bunc, M.; Grigioni, F.; Ussia, G.P. Edge-to-Edge Repair for Tricuspid Valve Regurgitation. Preliminary Echo-Data and Clinical Implications from the Tricuspid Regurgitation IMAging (TRIMA) Study. *J. Clin. Med.* **2022**, *11*, 5609. [CrossRef]
89. Webb, J.G.; Chuang, A.M.; Meier, D.; von Bardeleben, R.S.; Kodali, S.K.; Smith, R.L.; Hausleiter, J.; Ong, G.; Boone, R.; Ruf, T.; et al. Transcatheter Tricuspid Valve Replacement with the EVOQUE System: 1-Year Outcomes of a Multicenter, First-in-Human Experience. *JACC Cardiovasc. Interv.* **2022**, *15*, 481–491. [CrossRef]

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Opinion

Cardiac Contractility Modulation Therapy in Patients with Amyloid Cardiomyopathy and Heart Failure, Case Report, Review of the Biophysics of CCM Function, and AMY-CCM Registry Presentation

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Abstract: Cardiac amyloidosis may result in an aggressive form of heart failure (HF). Cardiac contractility modulation (CCM) has been shown to be a concrete therapeutic option in patients with symptomatic HF, but there is no evidence of its application in patients with cardiac amyloidosis. We present the case of TTR amyloidosis, where CCM therapy proved to be effective. The patient had a history of multiple HF hospitalizations due to an established diagnosis of wild type TTR-Amyloidosis with significant cardiac involvement. Since he was highly symptomatic, except during continuous dobutamine and diuretic infusion, it was opted to pursue CCM therapy device implantation. At follow up, a significant improvement in clinical status was reported with an increase of EF, functional status (6 min walk test improved from zero meters at baseline, to 270 m at 1 month and to 460 m at 12 months), and a reduction in pulmonary pressures. One year after device implantation, no other HF hospital admission was needed. CCM therapy may be effective in this difficult clinical setting. The AMY-CCM Registry, which has just begun, will evaluate the efficacy of CCM in patients with HF and diagnosed TTR amyloidosis to bring new evidence on its potential impact as a therapeutic option.

Keywords: cardiac contractility modulation; heart failure; amyloidosis

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1. Background

Cardiac amyloidosis is primarily associated with aggregates of amyloidogenic proteins, which may be immunoglobulin light chain proteins (AL) or transthyretin proteins (TTR), in many cardiac structures causing different types of amyloidosis. It may result in an aggressive form of heart failure (HF) [1]. In addition to the studies currently ongoing, other therapeutic options that can work synergistically in this clinical setting should be tested. Randomized clinical trials showed that cardiac contractility modulation (CCM) therapy may be considered in patients with symptomatic HF despite optimal medical therapy (OMT), with Ejection Fraction (EF) between 25% and 45%, and without an indication for cardiac resynchronization therapy (CRT) [2–4]. We present the case of a patient with TTR amyloidosis, where CCM therapy proved to be effective. We reviewed the biophysics and molecular biology mechanisms underlying CCM function which led to the idea of designing a registry to further explore the efficacy of CCM in cardiac amyloidosis.

2. Case Report: Wild Type TTR

The patient is a 67 year old male with a history of multiple HF hospitalizations due to an established diagnosis of wild type TTR-Amyloidosis for at least 6 years, with significant cardiac involvement requiring dobutamine and diuretic infusions. His baseline EF was 38%, with a restrictive diastolic pattern. After informed consent, the patient

underwent CCM therapy device implantation in September 2020. Of note, two days after CCM implantation, the patient's clinical status improved. Three months post-implant, the patient's 6 min walk test (6MWT) was 320 m, and the EF was 43%. It was also possible to start therapy with beta-blockers and a low dose of sacubitril/valsartan, which were not tolerated before CCM. At the 6 month follow up, the EF was 48% and there was improvement in the echocardiographic diastolic pattern (pseudo-normal) and a reduction in pulmonary pressures (Figure 1).

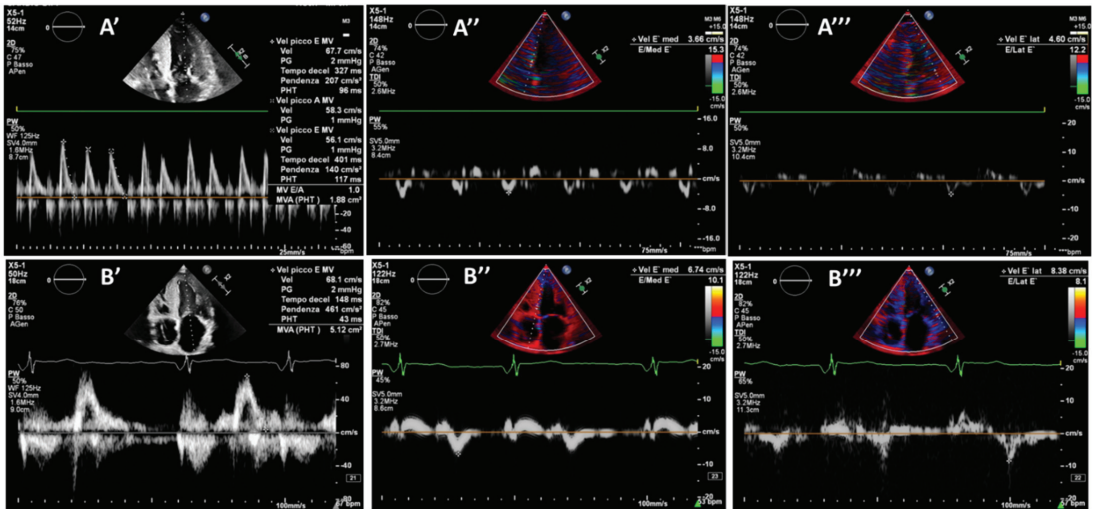

Figure 1. Diastolic function improvement. Baseline diastolic function E/A (**A′**), E/E′ septal (**A″**), E/E′ lateral (**A‴**); 12-month diastolic function E/A (**B′**), E/E′ septal (**B″**), E/E′ lateral (**B‴**).

At the 12 month follow up, for the 6MWT he walked 460 m. Furthermore, at that time point, the Kansas City Cardiomyopathy score improved from 11.1 at baseline to 82.8. At this point in time, the improvements allowed us to start Tafamidis. Echo and functional parameters have been stable, and no other HF hospital admission occurred during the 26 months of follow ups.

To the best of our knowledge, this is the first published case of cardiac amyloidosis successfully treated with CCM therapy. In other clinical settings it has been proven that the short- and long-term use of CCM therapy improves both the strength of the ventricular contraction and the pumping capacity of the heart by modulating myocardial contraction, thus improving the reported symptoms, and reducing HF hospitalizations [2–4].

3. Discussion and Review of CCM Function

In heart failure, mortality is still high despite the advances in medical and device therapy. Most patients receiving optimal medical therapy (OMT) have limited possibility possibly for up-titration and this is far more difficult in the clinical setting of cardiac amyloid because of intolerance to several HF drugs.

ICD is not HF therapy and unfortunately only one-third of patients with HF have a QRS complex wider than 120 msec and would thus be suitable for CRT. Moreover, one-third of patients receiving CRT are non-responders, thus they remain symptomatic, despite OMT [5].

CCM therapy is a proper HF therapy and delivers high amplitude non-excitatory biphasic electrical signals during the myocardial refractory period. It is applicable for patients with NYHA class II or III status, an LVEF < 50% (per CE Mark), peak VO2 $\geq$ 10 mL/kg/min, and PVCs less than 10,000 per day. CCM is also suitable for patients with atrial fibrillation and non-responders to CRT.

The CCM implant procedure does not differ from pacemaker implantation, with the exception of the placement of two leads in the RV rather than one. It is performed using cephalic or subclavian vein access (often right sided because often there is already an ICD in place on the left side). Two active fixation leads are secured to the right ventricular septum at least 2–3 cm apart from each other and at least 3 cm from the defibrillation RV lead. The leads are used for sensing ventricular activity and for bipolar delivery of CCM signals. Electrical testing of the leads includes the standard testing for pacemaker leads with a higher focus on the sensing function. Active CCM treatment is generally programmed to be delivered daily for at least 7 h, in equally spaced one hour intervals throughout the day, targeting a minimum of 90% CCM therapy delivery [3–8].

4. CCM "Pharmacodynamic": Are We Dealing with Quantum Medicine?

Prior studies have shown that when applied to isolated papillary muscles in vitro, CCM signals increase myocardial contractility [9]. The mechanism has been shown to fundamentally relate to an increase in action potential duration by CCM signals, which enhances trans-sarcolemmal calcium entry. This in turn causes calcium loading of the sarcoplasmic reticulum and increased calcium release to the myofilaments. Though the acute impact of CCM signals on contractile strength was shown to be limited to only the region of signal application, at three months, changes are documented to extend to regions remote from signal delivery.

CCM action could be possibly due to production of a specific electromagnetic field (EMF) that modulates the quantum mechanics aspects of biological process of the HF [10].

Richard Friedman (1965 Nobel Prize in Physics "for their fundamental work in quantum electrodynamics, with deep-ploughing consequences for the physics of elementary particles") used to say, "I think I can safely say that nobody understands quantum mechanics". Based on this prestigious assumption, we felt emboldened in trying to theorize the biophysical background of CCM "pharmacodynamics".

In quantum theory, according to the Born-Oppenheimer Approximation assumption, EMFs interact more strongly with electrons because of their unusually high charge to mass ratio. Electrons are assumed to respond instantaneously compared to protons and heavier atomic nuclei because of their much smaller mass. In biological systems, therefore, it is reasonable to expect EMFs to interact initially with small subatomic particles and with whole molecules by specific electrical charged regions, leading to early-onset effects which are more likely due to enzymes function modulation and late-onset effects which are related with DNA interaction via specific electromagnetic response elements (EMREs).

5. CCM Early-Onset Effects: Enzymes Modulation

Enzymes are large biological molecules, usually proteins, that speed up chemical reactions. Molecules that speed up chemical reactions, but are unchanged afterwards, are known as catalysts. The substances that enzymes act on with a remarkable specificity are known as substrates [11].

The focus of the last 50 years' experiences is known as transition state theory (TST), aiming to understand how enzymes facilitate passage of the reaction over a static potential-energy barrier to proceed from reactants to products [12] (Figure 2A). However, recent studies have revealed that passage through, rather than over, the barrier can occur, and that quantum mechanical phenomena can play a crucial role in enzyme action [13–15]. Matter has particle-like properties but can also be considered as having wave-like properties (especially those with smaller mass): this is known as the wave-particle duality of matter. Specifically, according to quantum mechanics, particles do not have defined positions in space, but their position is instead defined by a diffuse wave function. This is known as an aspect of Heisenberg's uncertainty principle, which implies the possibility that the edges of particle waves leak through classical barriers, a process known as quantum tunnelling.

Electrons can travel large distances (up to 3 nm) through proteins despite the latter being electrical insulators. This paradox can be explained in terms of the wave-like properties

of the electron that allow it to pass via quantum tunnelling through regions from which it would be excluded by its particle-like nature [16].

Quantum tunnelling may also play an important role in driving enzyme-catalysed reactions, especially for the transfer of small nuclei, such as hydrogen. The pathway from reactants to products in an enzyme-catalysed reaction may not need to pass over the barrier, as in TST with particle-like behaviour, but could pass through the barrier [17] (Figure 2B). The wider the barrier and the higher its energy, the lower the probability of tunnelling. It has been also demonstrated that when an external EMF is applied, the potential barrier outside the conductor becomes steeper and its width decreases for an electron with a given kinetic energy. In turn, the probability that an electron will tunnel across the barrier becomes exponentially larger [14,15] (Figure 2C).

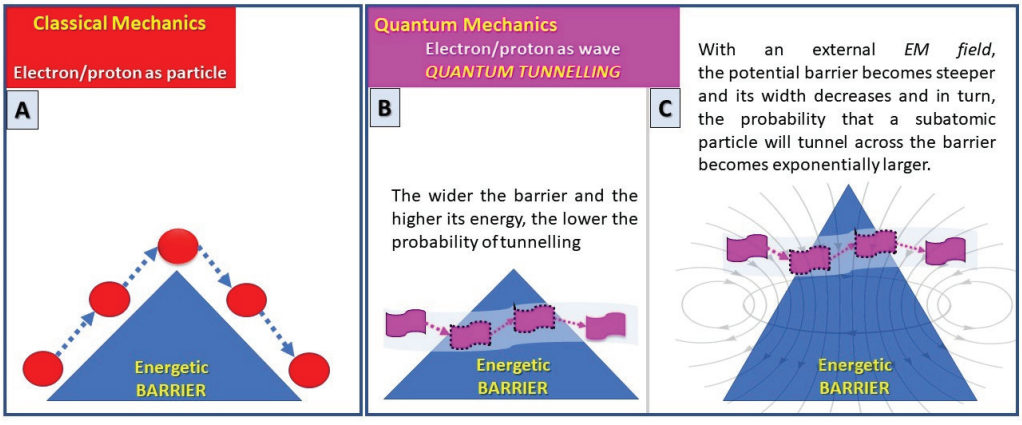

Figure 2. ***Schematic representation of quantum tunnelling.*** (**A**) Old Transition state theory, aiming to understand how enzymes facilitate passage of the reaction over a static potential-energy barrier to proceed from reactants to products. (**B**) In quantum mechanics, particles don't have defined positions in space, but their position is instead defined by a diffuse wave function. This is known as an aspect of Heisenberg's uncertainty principle which implies the possibility that the edges of particle waves leak through classical barriers, a process known as quantum tunnelling. (**C**) Effect of external EMF could enhance the probability that a particle will tunnel across the barrier.

Accordingly, low frequency electric and magnetic fields were shown to affect enzyme function. Notably, both fields accelerated the reaction only when the intrinsic chemical forces are relatively weak and when enzyme activity was low [10]. However, the exact mechanism of EMF action on enzymes at atomic level is not fully understood. It might be due to creation of additional active sites or positive modification of existing active sites/overall globular structure. EMF impact may also increase the probability of quantum tunnelling by inducing proper orientation of substrates and enzymes toward each other (Figure 3A). In addition, EMF can induce refolding of denatured enzymes, which can further enhance the activity [18–21] (Figure 3B).

Remarkably, this is an early-onset effect. Sun et al. demonstrated that EMFs could induce the phosphorylation of stress-activated protein kinase (SAPK) extracted from Chinese hamster lung cells within 15 min in a time- and intensity-dependent manner [22].

Consistently, it has been proven that CCM EMF acts early on specific phosphorylation enzymes, such as the one that enhanced the phosphorylation state of phospholamban (PPL) [23] within just 2 h of signal application. The PPL phosphorylation increases sarcoplasmic reticulum calcium sequestration by enhancing the activity and/or affinity of SERCA-2a for Ca^{2+}. This in turn enhances intracellular calcium-cycling capacity and, hence, contractility (Figure 4).

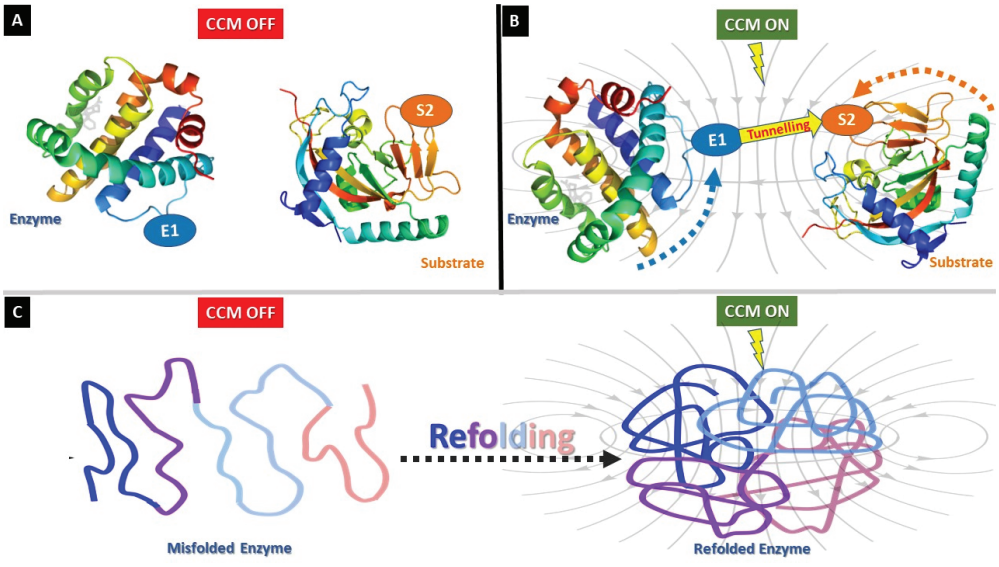

Figure 3. *Schematic representation of CCM induced EM field mechanism of action on enzymes.* EMFs impact may also increase the probability of quantum tunnelling by inducing proper orientation of substrates and enzymes toward each other (**A**,**B**). In addition, EMF can induce refolding of denatured enzymes which can further enhance the activity (**C**).

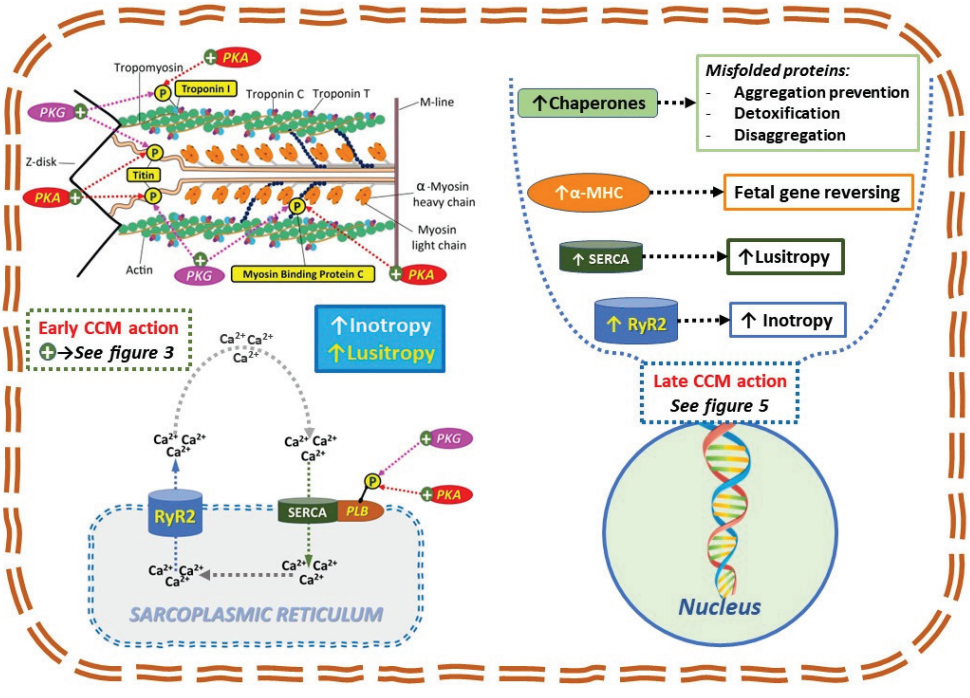

Figure 4. Schematic representation of early and late onset effects on CCM function (see explanation in the text. The left panel refers to early onset effect which are related to enzyme modulation by CCM

induced EMF (green positive circle refers to mechanism depicted in Figure 3). An increase in the phosphorylation state of troponin and myosin binding protein C leads to positive inotropy. An increase in the phosphorylation state of PLB and titin leads to positive lusitropy. PKA = phosphokinase A; PKB = phosphokinase B. The right panel refers to late onset effects which are related to DNA transcription modulation by CCM induces EMF (see Figure 5 for detailed mechanism on DNA strands). There is a substantial fetal gene reverse remodelling by increasing the down regulated RyR2, SERCA, and α-MHC. Moreover, the increase in Chaperones transcription (such as HSP70) has several positive effects such as aggregation prevention, detoxification, and disaggregation of misfolded proteins.

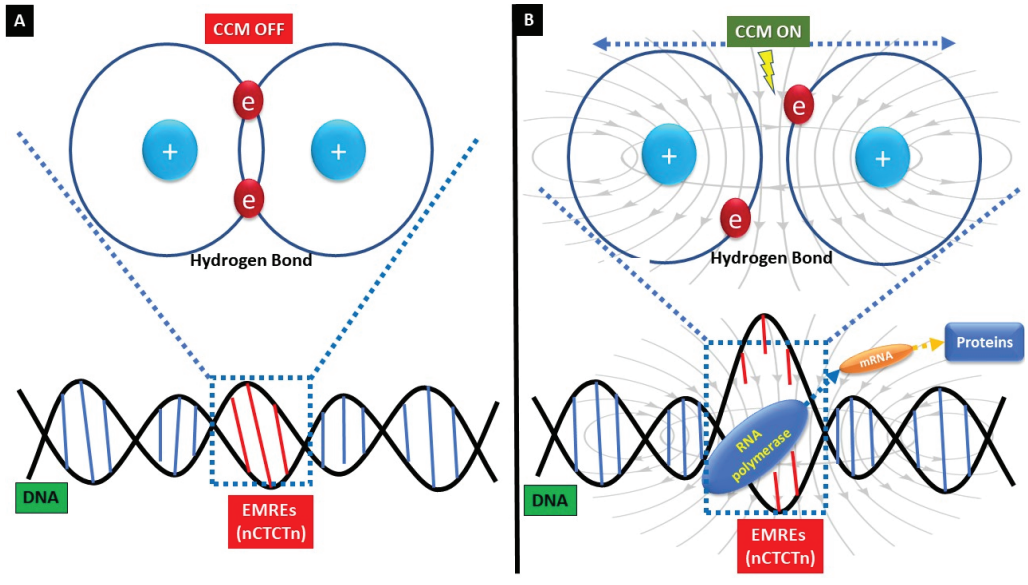

Figure 5. Schematic representation on CCM action on DNA and protein synthesis. CCM improves myocardial gene expression by EM field action on specific DNA sequences (nCTCTn, (**A**)). EM fields displace electrons, and this causes transient charging of small groups of DNA base pairs. At the charged sites, disaggregation forces overcome H-bonds. Disaggregation of the two chains at those sites enables transcription (**B**).

Additionally, in HFrEF patients, CCM increases phosphokinase G and A related phosphorylation state of TnI, and of myosin-binding protein C in LV and RV, as soon as 30 min after signal delivery and was sustained after 3 months of CCM therapy [24]. Since the sensitivity of the cardiac myofilaments to Ca^{2+} is primarily positively regulated by the phosphorylation state of TnI and of myosin-binding protein, this leads to CCM mediated increased contractility (Figure 4).

Moreover, the hypo-phosphorylation of titin leads to an increase in stiffness of the myocyte. It has been proven that an increase in both right and left ventricle, with a 21% and 36% rise in total titin phosphorylation (PKA and PKG mediated) observed at 30 min and 3 months post CCM therapy, respectively (positive lusitropy, Figure 4) [7].

6. CCM Late-Onset Effects: Maladaptive Fetal Gene Remodeling

In pathophysiologic conditions including hypoxia, ischemia, hypertrophy, and atrophy, stressed myocytes return to fetal metabolism which uses carbohydrates as substrates for energy provision in hypoxic environment instead of oxidation of fatty acids. Common features of all of these conditions are extensive protein remodelling, a decrease in the rate of aerobic metabolism in the cardiomyocyte, and a temporary increase in cardiac efficiency.

Nonetheless, in failing heart muscle, at a certain point, the fetal gene program is no longer sufficient to support cardiac structure and function [25].

CCM improves myocardial gene expression by EM field action on specific DNA sequences (nCTCTn, Figure 5A). EM fields displace electrons, and this causes transient charging of small groups of DNA base pairs. At the charged sites, disaggregation forces overcome H-bonds. Disaggregation of the two chains at those sites enables transcription (Figure 5B). Inserting these EMREs into a promoter of a reporter gene that is unresponsive to EM fields makes that gene EM field-responsive. Removing or mutating these EMREs eliminates the EM field response [10].

CCM reverses the cardiac maladaptive fetal gene program and normalizes expression of key sarcoplasmic reticulum genes (Figure 4). Preclinical studies demonstrated that CCM signal treatment reverses the cardiac maladaptive fetal gene program and normalizes expression of key sarcoplasmic reticulum Ca^{2+} cycling and stretch response genes. Specifically, 3 months on CCM therapy resulted in decreased expression of A- and B-type natriuretic peptides, and p21 Ras, and increased the expression of α-MHC, SERCA-2a, phospholamban, and ryanodine receptors [9]. CCM also attenuated interstitial fibrosis by reducing collagen production and fibroblast differentiation by inhibiting TGF-β1 signaling [26].

CCM also acts on several processes which are involved in amyloid cardiomyopathy (Figure 6). CCM-driven normalization of elevated diastolic Ca^{2+} levels in the failing heart might be associated with ROS reductions and activation of CaMKII [8]. CCM decreased the expression of p38 mitogen activated protein kinase (p38MAPK), which is involved in the direct toxic amyloidogenic-mediated oxidative stress, dysfunction, and cell death of cardiomyocytes [27].

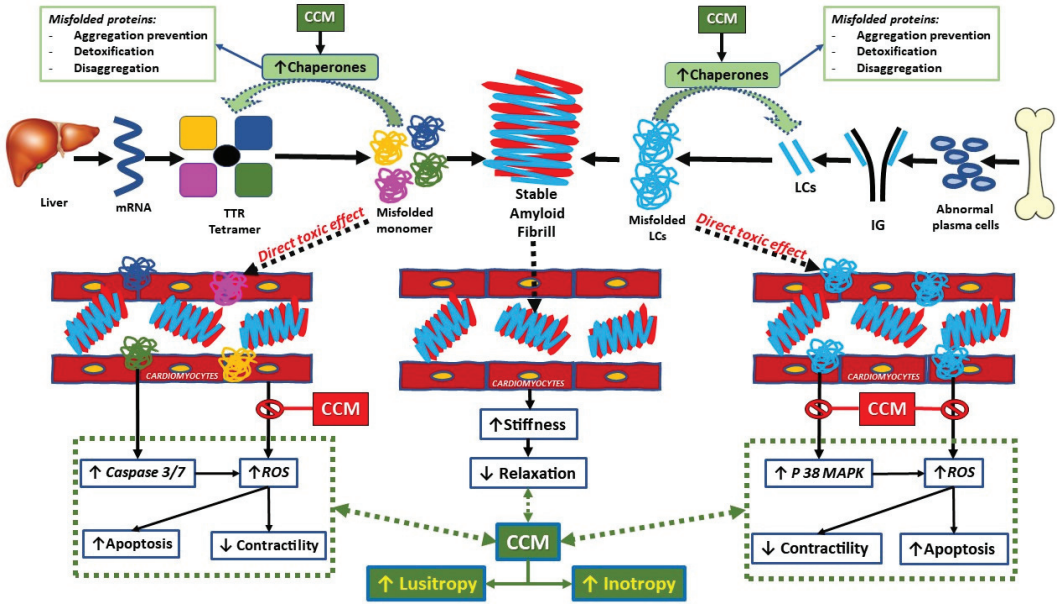

Figure 6. ***Cardiac Amyloid phatophysiology and CCM therapeutic effect.*** See explanation in the text. TTR: transtiretin. CCM: cardiac contractility modulation; LC: light chains; IG: immune globulin; ROS: reactive oxygen species; P 38 MAPK: p38 mitogen activated protein kinase.

Remarkably, CCM enhances the transcription of chaperones (such as HSP70), which regulate the balance of protein synthesis and degradation, assist with refolding misfolded proteins, and can protect against cell death in stressful/pathological conditions such as amyloid [28,29].

7. Cardiac Contractility Modulation Therapy in Amyloid Cardiomyopathy Patients with Heart Failure (AMY-CCM: ClinicalTrials.gov Identifier: NCT05167799)

CCM's mechanism of action could be beneficial in cardiac amyloidosis but there are no data in this specific clinical setting. To fill this gap in knowledge, we promoted an observational registry whose primary aim is to evaluate the efficacy of CCM in patients with HF and diagnosed TTR amyloidosis. We will focus on TTR, as AL could have different confounding factors, such as more systemic involvement compared to TTR forms, and thus a different prognosis according to specific hematologic treatment.

The Registry has already been approved by competent Ethics Committees and registered on clinicaltrials.gov as the AMY-CCM Registry. The results could bring new evidence on the potential impact of CCM therapy in cardiac amyloidosis as a synergistic therapeutic option.

Author Contributions: Conceptualization, methodology, writing—original draft preparation, P.M.; writing—review and editing, visualization, supervision, all the authors. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from the patient.

Data Availability Statement: No new data were created.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Liao, R.; Ward, J. Amyloid Cardiomyopathy: Disease on the Rise. *Circ. Res.* **2017**, *120*, 1865–1867. [CrossRef]
2. Abraham, W.T.; Kuck, K.-H.; Goldsmith, R.L.; Lindenfeld, J.; Reddy, V.Y.; Carson, P.E.; Mann, D.L.; Saville, B.; Parise, H.; Chan, R.; et al. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation. *JACC Heart Fail.* **2018**, *6*, 874–883. [CrossRef] [PubMed]
3. Cappannoli, L.; Scacciavillani, R.; Rocco, E.; Perna, F.; Narducci, M.L.; Vaccarella, M.; D'Amario, D.; Pelargonio, G.; Massetti, M.; Crea, F.; et al. Cardiac contractility modulation for patient with refractory heart failure: An updated evidence-based review. *Heart Fail. Rev.* **2021**, *26*, 227–235. [CrossRef]
4. Kuschyk, J.; Nägele, H.; Heinz-Kuck, K.; Butter, C.; Lawo, T.; Wietholt, D.; Roeger, S.; Gutterman, D.; Burkhoff, D.; Rousso, B.; et al. Cardiac contractility modulation treatment in patients with symptomatic heart failure despite optimal medical therapy and cardiac resynchronization therapy (CRT). *Int. J. Cardiol.* **2019**, *277*, 173–177. [CrossRef] [PubMed]
5. Tint, D.; Florea, R.; Micu, S. New Generation Cardiac Contractility Modulation Device—Filling the Gap in Heart Failure Treatment. *J. Clin. Med.* **2019**, *8*, 588. [CrossRef] [PubMed]
6. Anker, S.D.; Borggrefe, M.; Neuser, H.; Ohlow, M.-A.; Röger, S.; Goette, A.; Remppis, B.A.; Kuck, K.; Najarian, K.B.; Gutterman, D.D.; et al. Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction. *Eur. J. Heart Fail.* **2019**, *21*, 1103–1113. [CrossRef]
7. Tschöpe, C.; Van Linthout, S.; Spillmann, F.; Klein, O.; Biewener, S.; Remppis, A.; Gutterman, D.; Linke, W.A.; Pieske, B.; Hamdani, N.; et al. Cardiac contractility modulation signals improve exercise intolerance and maladaptive regulation of cardiac key proteins for systolic and diastolic function in HFpEF. *Int. J. Cardiol.* **2016**, *203*, 1061–1066. [CrossRef]
8. Lyon, A.R.; Samara, M.A.; Feldman, D.S. Cardiac contractility modulation therapy in advanced systolic heart failure. *Nat. Rev. Cardiol.* **2013**, *10*, 584–598. [CrossRef]
9. Butter, C.; Rastogi, S.; Minden, H.-H.; Meyhöfer, J.; Burkhoff, D.; Sabbah, H.N. Cardiac Contractility Modulation Electrical Signals Improve Myocardial Gene Expression in Patients with Heart Failure. *J. Am. Coll. Cardiol.* **2008**, *51*, 1784–1789. [CrossRef]
10. Blank, M.; Goodman, R. A mechanism for stimulation of biosynthesis by electromagnetic fields: Charge transfer in DNA and base pair separation. *J. Cell. Physiol.* **2008**, *214*, 20–26. [CrossRef]
11. Albery, W.J.; Knowles, J.R. Evolution of enzyme function and the development of catalytic efficiency. *Biochemistry* **1976**, *15*, 5631–5640. [CrossRef]
12. Kraut, J. How Do Enzymes Work? *Science* **1988**, *242*, 533–540. [CrossRef] [PubMed]
13. Sutcliffe, M.J.; Scrutton, N.S. Enzymology takes a quantum leap forward. *Philos. Trans. Ser. A Math. Phys. Eng. Sci.* **2000**, *358*, 367–386. [CrossRef] [PubMed]
14. Johannissen, L.O.; Hay, S.; Scrutton, N.S. Nuclear quantum tunnelling in enzymatic reactions—An enzymologist's perspective. *Phys. Chem. Chem. Phys.* **2015**, *17*, 30775–30782. [CrossRef] [PubMed]

15. Klinman, J.P.; Kohen, A. Hydrogen Tunneling Links Protein Dynamics to Enzyme Catalysis. *Annu. Rev. Biochem.* **2013**, *82*, 471–496. [CrossRef]
16. Marcus, R.; Sutin, N. Electron transfers in chemistry and biology. *Biochim. Et Biophys. Acta BBA Rev. Bioenerg.* **1985**, *811*, 265–322. [CrossRef]
17. Devault, D. Quantum mechanical tunnelling in biological systems. *Q. Rev. Biophys.* **1980**, *13*, 387–564. [CrossRef]
18. Miklavčič, D. *Handbook of Electroporation*, 1st ed.; Springer International Publishing: Cham, Switzerland, 2017.
19. Li, Y.; Zhang, S.; Bao, Z.; Sun, N.; Lin, S. Exploring the activation mechanism of alcalase activity with pulsed electric field treatment: Effects on enzyme activity, spatial conformation, molecular dynamics simulation and molecular docking parameters. *Innov. Food Sci. Emerg. Technol.* **2022**, *76*, 102918. [CrossRef]
20. Masgrau, L.; Roujeinikova, A.; Johannissen, L.O.; Hothi, P.; Basran, J.; Ranaghan, K.E.; Mulholland, A.J.; Sutcliffe, M.J.; Scrutton, N.S.; Leys, D. Atomic Description of an Enzyme Reaction Dominated by Proton Tunneling. *Science* **2006**, *312*, 237–241. [CrossRef]
21. Moser, C.C.; Anderson, R.; Dutton, P.L. Guidelines for tunneling in enzymes. *Biochim. Et Biophys. Acta BBA Bioenerg.* **2010**, *1797*, 1573–1586. [CrossRef]
22. Sun, W.J.; Chiang, H.; Fu, Y.T.; Yu, Y.N.; Xie, H.Y.; Lu, D.Q. Exposure to 50 Hz Electromagnetic Fields Induces the Phosphorylation and Activity of Stress-Activated Protein Kinase in Cultured Cells. *Electromagn. Biol. Med.* **2001**, *20*, 415–423. [CrossRef]
23. Imai, M.; Rastogi, S.; Gupta, R.C.; Mishra, S.; Sharov, V.G.; Stanley, W.C.; Mika, Y.; Rousso, B.; Burkhoff, D.; Ben-Haim, S.; et al. Therapy with Cardiac Contractility Modulation Electrical Signals Improves Left Ventricular Function and Remodeling in Dogs with Chronic Heart Failure. *J. Am. Coll. Cardiol.* **2007**, *49*, 2120–2128. [CrossRef] [PubMed]
24. Tschöpe, C.; Kherad, B.; Klein, O.; Lipp, A.; Blaschke, F.; Gutterman, D.; Burkhoff, D.; Hamdani, N.; Spillmann, F.; Van Linthout, S. Cardiac contractility modulation: Mechanisms of action in heart failure with reduced ejection fraction and beyond. *Eur. J. Heart Fail.* **2019**, *21*, 14–22. [CrossRef]
25. Rajabi, M.; Kassiotis, C.; Razeghi, P.; Taegtmeyer, H. Return to the fetal gene program protects the stressed heart: A strong hypothesis. *Heart Fail. Rev.* **2007**, *12*, 331–343. [CrossRef] [PubMed]
26. Zhang, F.; Dang, Y.; Li, Y.; Hao, Q.; Li, R.; Qi, X. Cardiac Contractility Modulation Attenuate Myocardial Fibrosis by Inhibiting TGF-β1/Smad3 Signaling Pathway in a Rabbit Model of Chronic Heart Failure. *Cell. Physiol. Biochem.* **2016**, *39*, 294–302. [CrossRef] [PubMed]
27. Shi, J.; Guan, J.; Jiang, B.; Brenner, D.A.; del Monte, F.; Ward, J.E.; Connors, L.H.; Sawyer, D.B.; Semigran, M.J.; Macgillivray, T.E.; et al. Amyloidogenic light chains induce cardiomyocyte contractile dysfunction and apoptosis via a non-canonical p38α MAPK pathway. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 4188–4193. [CrossRef]
28. Wentink, A.; Nussbaum-Krammer, C.; Bukau, B. Modulation of Amyloid States by Molecular Chaperones. *Cold Spring Harb. Perspect. Biol.* **2019**, *11*, a033969. [CrossRef]
29. Wentink, A.S.; Nillegoda, N.B.; Feufel, J.; Ubartaitė, G.; Schneider, C.P.; Rios, P.D.L.; Hennig, J.; Barducci, A.; Bukau, B. Molecular dissection of amyloid disaggregation by human HSP70. *Nature* **2020**, *587*, 483–488. [CrossRef]

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Blood Type A1 Mismatch Does Not Affect Heart Transplant Outcomes at One Year

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Abstract: There are subtypes within blood type A, termed non-A1, that have reduced expression of A antigen on cell surfaces. This can result in the development of anti-A1 antibodies. There is limited information regarding the impact of this in heart transplant (HTx) recipients. We conducted a single-center cohort study of 142 Type A HTx recipients in which we compared outcomes of a match group (an A1/O heart into an A1 recipient or a non-A1/O heart into a non-A1 recipient) with a mismatch group (an A1 heart into a non-A1 recipient or a non-A1 heart into an A1 recipient). At one year post-transplant, there were no differences between the groups in survival, freedom from non-fatal major adverse cardiovascular events, freedom from any treated rejection, or freedom from cardiac allograft vasculopathy. There was an increased hospital length of stay in the mismatch group (13.5 vs. 17.1 days, $p = 0.04$). Our study showed that A1 mismatch was not associated with worse outcomes at one year post-HTx.

Keywords: heart transplant; ABO subtype; rejection

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1. Introduction

ABO blood type compatibility is a prerequisite for heart transplantation (HTx) due to the risk of hyperacute rejection mediated by ABO antibodies [1]. These antibodies bind specific carbohydrate moieties defining the A and B antigens. However, conventional ABO grouping does not capture inter-individual variation in antigen expression.

Within blood type A there are subtypes, termed non-A1, which have reduced antigen expression and density because of variation in transferase specificity and efficiency. For example, the A2 subgroup, which makes up 20% of group A individuals, expresses fewer A antigen epitopes per red blood cell and is considered less immunogenic [2]. When considering transplantation of an A1 organ to a non-A1 recipient, there is a theoretical risk for adverse outcomes given the potential for interaction of recipient anti-A1 antibodies, if present, with the A1 donor organ. In 2013, an update to the Organ Procurement and Transplantation Network policy stipulated that two ABO results from donors and recipients must be documented, and that confirmation of the A or AB subtype must occur prior to proceeding with transplantation [3].

Research into the safety of organ transplantation across the A1 barrier has been very limited. There are a few case reports of non-A1 recipients with anti-A1 titers of $\leq$ 1:8 receiving A1 kidneys that did not result in allograft rejection [4–6]. A review of the heart transplantation (HTx) literature revealed only one small single-center study with eight non-A1 recipients, none of whom developed anti-A1 antibodies even though five donor hearts were A1. There was no difference in freedom from rejection, graft dysfunction, cardiac allograft vasculopathy (CAV), or re-transplantation at 6 months compared to A1 recipients [7]. We sought to gather further data on the effect of A1-mismatched HTx at our high-volume transplant center. We hypothesized that these would have worse outcomes

when compared to A1-matched HTx due to anti-A1 antibodies driving immunologically-mediated phenomena, such as rejection and CAV. However, we found that A1 mismatch did not result in adverse outcomes at one year post-HTx.

2. Materials and Methods

This was a single-center cohort study conducted at Cedars-Sinai Medical Center in Los Angeles, California. Adults aged 18 years or older with blood type A who received a HTx between 2013 and 2020 were eligible for inclusion in the study. Subjects were excluded if they had a previous HTx or if they were younger than 18 years old. Subjects' blood samples were collected and tested for the A1 subtype if there was a discrepancy in blood type testing. Anti-A1 antibody titer testing was performed once, at the time of enrollment, on all subjects who were identified as non-A1. Donor blood types (A versus O) and A subtypes (A1 versus non-A1) were collected from the United Network of Organ Sharing (UNOS).

Desensitization therapy was performed if calculated panel reactive antibodies (cPRA) were greater than 50–70%. All subjects received a standard post-HTx immunosuppression regimen of prednisone, mycophenolate mofetil, and tacrolimus. Blood subtype and the presence/absence of anti-A1 antibodies did not influence desensitization or immunosuppression strategy. Surveillance for rejection via endomyocardial biopsy was performed at protocolized intervals for all subjects regardless of A1 matching. Acute cellular rejection was defined according to the International Society for Heart and Lung Transplantation (ISHLT) 2004 grading system [8]. Antibody-mediated rejection was defined according to the ISHLT 2013 grading system [9]. Cardiac allograft vasculopathy was defined as any angiographic stenosis greater than 30% on a routine surveillance angiogram.

All other demographic and clinical information was collected from chart review utilizing the Cedars-Sinai Electronic Medical Record (EPIC™). To account for the 2018 change in status listings, we defined "urgent status at transplant" as status 1A in the previous scheme and statuses 1, 2, and 3 in the current scheme. Predicted heart mass (PHM) was calculated using a UNOS calculator [10].

Our outcomes of interest were survival, freedom from CAV, freedom from non-fatal major adverse cardiac events (NF-MACE: myocardial infarction, heart failure (HF), percutaneous coronary intervention (PCI), defibrillator/pacemaker implant (ICD/PM), or stroke), and freedom from any treated rejection (ATR), acute cellular rejection (ACR), and antibody-mediated rejection (AMR) at one year post-HTx. We assessed subclinical markers, including ejection fraction (EF) and donor-specific antibodies (DSA), at one year. We also collected immediate post-HTx data including primary graft dysfunction (PGD), vasoplegia, and length of stay (LOS) in the intensive care unit (ICU) and hospital.

Results were compared between a "match" group (an A1/O donor into an A1 recipient or a non-A1/O donor into a non-A1 recipient) and a "mismatch" group (an A1 donor into a non-A1 recipient or a non-A1 donor into an A1 recipient). Continuous variables were reported as mean ± standard deviation and compared using the independent samples t-test. Categorical variables were reported as percentages and compared using Fischer's exact test. Survival was calculated using the Kaplan–Meier method. All comparisons were two-tailed, and p-values < 0.05 were considered significant. Statistical analysis was performed using the data analysis program, SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

The study protocol was approved by the Cedars-Sinai institutional review board (ethical approval code Pro00057683).

3. Results

We identified 150 patients with blood type A who were transplanted between 2013 and 2020. Of 142 enrolled subjects, 8 were excluded because they had a previous HTx. Subjects were enrolled between 10 days and 6.5 years after HTx. with an average of 2.4 years between HTx and enrollment. Fifty-five (39%) subjects were enrolled within one year post-transplant. Allocation into study groups is depicted in Figure 1; 121 (85%) subjects

were identified as A1, and 21 (15%) were identified as non-A1. Of 142 subjects, 110 (77%) were included in the match group as follows: 107 A1/O hearts into A1 recipients and 3 non-A1/O hearts into non-A1 recipients. Of 142 subjects, 32 (23%) were included in the mismatch group: 18 A1 hearts into non-A1 recipients and 14 non-A1 hearts into A1 recipients. None of the non-A1 recipients were found to have anti-A1 antibodies when tested at the time of study enrollment.

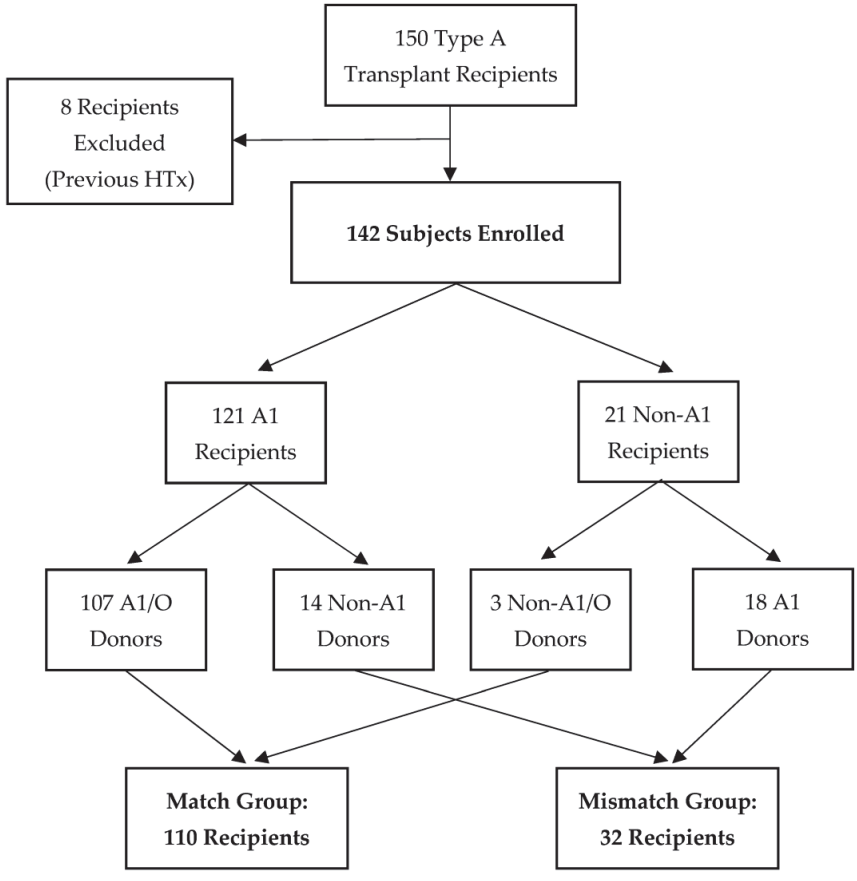

Figure 1. Allocation of Subjects into Match and Mismatch Groups.

3.1. Pre-Transplant Clinical Characteristics

Pre-transplant clinical characteristics are shown in Table 1. Between the match and mismatch groups, there was a difference in racial composition, which was driven by a large proportion of patients identifying as "other" (2.7% vs. 18.8%, respectively, $p = 0.02$). All other baseline demographics, including recipient age, donor age, sex, body mass index, and predicted heart mass, were similar between groups. There were no differences in comorbidities such as diabetes, hypertension, or prior cardiac surgery. Both groups had similar types of underlying cardiomyopathy. The two groups had similar risks for pre-transplant sensitization, as indicated by rates of previous pregnancy, previous blood transfusions, PRA with mean fluorescence intensity (MFI) > 5000, pre-transplant desensitization, and induction with anti-thymocyte globulin (ATG). Subjects in the match and mismatch groups had similar waitlist trajectories with no significant difference in time spent on the waitlist. Each group had similar proportions of subjects who were seriously ill, as represented by an urgent transplant status, and had similar kidney function, as measured

via creatinine immediately prior to transplant. Ischemic time in the donor heart was similar between groups.

Table 1. Pre-Transplant Clinical Characteristics [1].

	A1 Donor-Recipient Match (n = 110)	A1 Donor-Recipient Mismatch (n = 32)	p-Value
Recipient Age (Years)	57.4 ± 12.9	55.2 ± 12.1	0.40
Donor Age (Years)	37.3 ± 12.8	34.9 ± 13.2	0.35
Race			0.02
White	80.9% (n = 89)	62.5% (n = 20)	-
African-American	12.7% (n = 14)	12.5% (n = 4)	-
Asian	3.6% (n = 4)	6.3% (n = 2)	-
Other	2.7% (n = 3)	18.8% (n = 6)	-
BMI (kg/m^2)	25.1 ± 4.8	25.9 ± 4.2	0.41
PHM	1.08 ± 0.230	1.01 ± 0.163	0.10
Female	29.0% (n = 32)	25.0% (n = 8)	0.65
Type of Cardiomyopathy			0.63
Nonischemic	61.8% (n = 68)	65.6% (n = 21)	-
Ischemic	26.4% (n = 29)	21.9% (n = 7)	-
Congenital	0.9% (n = 1)	3.1% (n = 1)	-
Restrictive/Infiltrative	10.9% (n = 12)	9.4% (n = 3)	-
Previous Diabetes	33.6% (n = 37)	31.3% (n = 10)	0.80
Previous Hypertension	59.0% (n = 65)	53.1% (n = 17)	0.55
Prior Cardiac Surgery	41.8% (n = 46)	34.4% (n = 11)	0.45
Cytomegalovirus Mismatch	46.4% (n = 51)	59.4% (n = 19)	0.20
Previous Pregnancy in Females	65.6% (n = 21)	50.0% (n = 4)	0.44
Prior Blood Transfusion	30.9% (n = 34)	31.3% (n = 10)	0.97
Pre-transplant PRA with MFI > 5000	15.5% (n = 17)	6.3% (n = 2)	0.24
Pre-transplant Desensitization	9.1% (n = 10)	9.4% (n = 3)	1.00
Induction with ATG	58.2% (n = 64)	50.0% (n = 16)	0.41
Time on Waitlist (days)	149.7 ± 269.8	153.8 ± 254.4	0.94
Urgent Status at Transplant [2]	66.4% (n = 73)	65.6% (n = 21)	0.94
Mechanical Circulatory Support	41.8% (n = 46)	43.8% (n = 14)	0.85
Pre-transplant Creatinine (mg/dL)	1.5 ± 0.9	1.6 ± 1.8	0.69
Ischemic Time (min)	181.7 ± 52.7	195.4 ± 44.0	0.18

[1] Values listed as mean ± SD or as %. [2] Status 1A pre-2018 scheme change; Status 1, 2, 3 post-change.

3.2. Post-Transplant Outcomes

Post-transplant outcomes are shown in Table 2 and Figure 2. There was no difference in outcomes at one year post-transplant, including survival (99.1% in the match group vs. 100% in the mismatch group, p = 0.58), freedom from CAV (98.2% vs. 96.9%, p = 0.67), and freedom from NF-MACE (93.6% vs. 90.6%, p = 0.52). There were seven NF-MACE events in the match group: one HF, one PCI, one ICD/PM, and four strokes. There

were three NF-MACE events in the mismatch group: two ICD/PMs and one stroke. The mismatch group did not have an increased incidence of immune-mediated adverse events, with similar rates of freedom from ATR (76.4% vs. 81.3%, $p = 0.61$), freedom from ACR (87.3% vs. 90.6%, $p = 0.62$), and freedom from AMR (91.8% vs. 90.6%, $p = 0.80$) between groups. At a subclinical level, there was no difference in ejection fraction (62.6% vs. 60.9%, $p = 0.11$) or the incidence of donor-specific antibodies (17.3% vs. 9.4%, $p = 0.41$) at one year.

Table 2. Post-Transplant Outcomes [1].

	A1 Donor-Recipient Match ($n = 110$)	A1 Donor-Recipient Mismatch ($n = 32$)	p-Value
Primary Graft Dysfunction	12.7% ($n = 14$)	18.8% ($n = 6$)	0.40
Vasoplegia	11.8% ($n = 13$)	15.6% ($n = 5$)	0.56
Intensive Care Unit Length of Stay (Days)	6.5 ± 3.6	8.0 ± 5.8	0.08
Hospital Length of Stay (Days)	13.5 ± 8.4	17.1 ± 10.2	0.04
Ejection Fraction (%) [2]	62.6 ± 5.2	60.9 ± 4.7	0.11
Donor-Specific Antibodies [2]	17.3% ($n = 19$)	9.4% ($n = 3$)	0.41
Survival [2]	99.1%	100.0%	0.58
Freedom from CAV[2]	98.2%	96.9%	0.67
Freedom from NF-MACE [2]	93.6%	90.6%	0.52
Freedom from ATR [2]	76.4%	81.3%	0.61
Freedom from ACR [2]	87.3%	90.6%	0.62
Freedom from AMR [2]	91.8%	90.6%	0.80

[1] Values listed as mean ± SD or as %. [2] Outcomes at one year post-transplant.

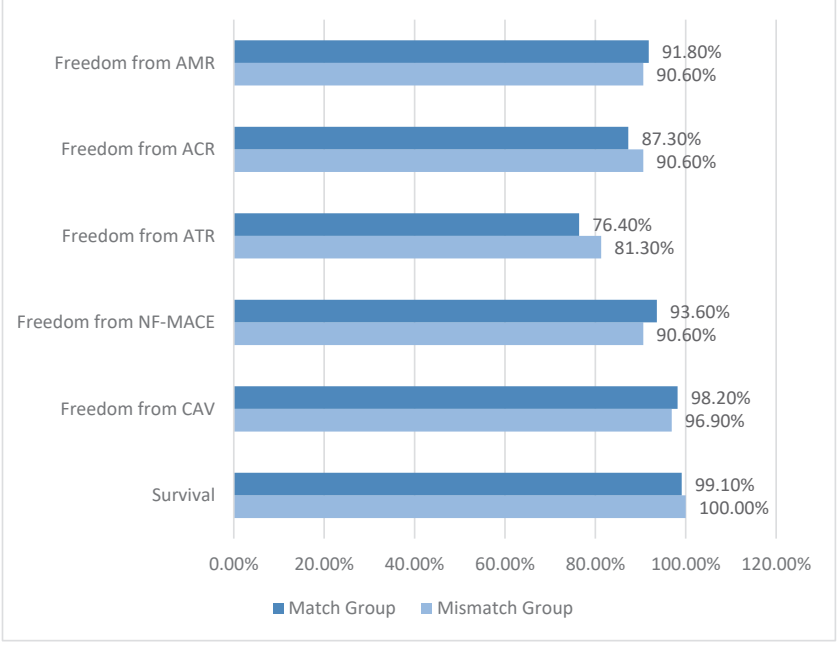

Figure 2. Post-Transplant Outcomes at One Year Post-HTx.

The mismatch group did have a higher post-transplant LOS in the hospital overall (13.5 vs. 17.1 days, $p = 0.04$), but not in the ICU (6.5 vs. 8.0 days, $p = 0.08$). This may have been driven by numerically higher rates of PGD (12.7% vs. 18.8%, $p = 0.40$) and vasoplegia (11.8% vs. 15.6%, $p = 0.56$), although these differences were not statistically significant.

4. Discussion

In this study, we divided HTx recipients with blood type A into match and mismatch groups based on the donor and recipient subtypes. These two groups were very similar in terms of demographics, comorbidities, severity of illness while on the transplant waitlist, and risk for sensitization. We did not observe any significant difference in one-year outcomes between these two groups.

The mismatch group was further broken down into two subgroups. For A1 recipients who received non-A1 hearts, we expected comparable outcomes with the match group given there were no foreign antigens to sensitize the recipient. However, for non-A1 recipients, the presence of A1 antigen on the donor heart may have resulted in the development of antibodies and subsequent adverse outcomes. We also expected subclinical evidence of an immune response in the form of DSA, which is a major risk factor for the development of AMR and CAV and a poor prognostic factor for mortality [11]. Although our study did not analyze this specific subgroup, the essentially equivalent outcomes of the match and mismatch groups make it very unlikely that they fared worse at one year post-HTx. Future studies should focus on A1 into non-A1 HTx and compare these with non-A1 into A1 and ABO-matched HTx.

We did find that the mismatch group had a higher hospital LOS after their HTx. This may have been driven by a higher incidence of PGD and vasoplegia. The mechanisms underlying PGD and vasoplegia are poorly defined; extensive research has revealed various donor, recipient, and intraoperative risk factors, although none of these are related to blood type mismatch [12,13]. It is unclear what would have caused an increase in these complications in our cohort given their similar pre-transplant characteristics. Further study is required to confirm our findings and determine their underlying mechanism.

Even though they had a higher hospital LOS, the mismatch group had similar one-year outcomes compared to the match group. Our study offers preliminary evidence that suggests A1-mismatched HTx can be performed safely. If future studies confirm our results, donor hearts can be more efficiently allocated. Currently, non-A1 recipients with anti-A1 antibodies often receive O organs [5]; this can prolong wait times for O recipients, which are already up to three times longer than for patients with other blood types [14]. Eliminating the requirement for A1 matching would decrease time on the transplant waitlist, especially for non-A1 and O recipients.

Another way to take advantage of the reduced immunogenicity of non-A1 subtypes is transplanting these organs across the ABO barrier [15]. This practice has already been established in kidney and liver transplantation. Group O and B recipients with low (<1:8) anti-A titers who received A2 kidneys have rates of transplant success similar to ABO-compatible transplants [16]. In 2014, the kidney allocation system expanded to allow transplantation of A2 and A2B kidneys into group B recipients resulting in a subsequent > 9% increase in kidney transplants among these patients [17]. Similar experiences have been reported in liver transplantation, with one registry analysis of O recipients showing no difference in retransplantation, rejection, graft survival, or overall survival when using A2 livers versus O livers [18]. As such, A2 to O liver transplantation has been promoted as a strategy to decrease long waitlist times for these patients [19]. Study on this topic in HTx is much more limited, with one case of an A2 heart transplanted into an O recipient reported in 1993. The patient was hemodynamically stable but retransplanted after only four days. Pathology did not reveal any cellular infiltrate or antibody deposition [20]. This strategy's success in kidney and liver transplantation suggests that it would be viable in HTx as well; further study is needed to determine its benefits and risks.

An important caveat is that no study of A1-mismatched organ transplantation has found recipient anti-A1 antibody titers >1:8, including ours. Anti-A1 antibodies are rare, with a prevalence of 1% in A2 individuals. When they do exist, they are often non-reactive at body temperature and considered clinically insignificant [5]. Our study only measured anti-A1 antibody titer once. As the titer was measured at time of enrollment, there was a variable amount of time between HTx and titer monitoring between each subject. We were also unable to confirm or refute any possible association between anti-A1 antibody titers and HTx complications, such as PGD, vasoplegia, and rejection.

Given the increased LOS in the mismatch group, further study is needed to determine whether these associations exist. Such a study should include daily titer monitoring in the peri-HTx period as well as during episodes of suspected rejection. This would provide valuable information on the trajectory of anti-A1 antibody titers in response to HTx and its associated immunosuppression. Previous studies lacked consistency in checking titers before and/or after transplant and have not been able to provide this level of detail. Additional information regarding early post-transplant biomarkers, such as troponin and B-type natriuretic peptide, would also be useful. Rather than emphasizing A subtyping, more frequent titer monitoring may allow for its use in the prognostication of HTx outcomes, and potentially influence decisions on whether to perform HTx or modify immunosuppression.

A limitation of this study is that with an average of 2.3 years between HTx and enrollment, only 39% of our subjects were enrolled prior to the one-year mark. Subjects who had short-term post-HTx morbidity and mortality were therefore likely under-represented, resulting in reported outcomes that are better than expected. Although this effect would have had an equal impact on the match and mismatch groups, our study likely minimizes any possible effect that A1 mismatch may have had on adverse outcomes in the early post-HTx period. The increased LOS in the mismatch group already suggests higher short-term risk in these transplants. A fully prospective study with enrollment of all subjects prior to HTx is required to provide more data regarding early adverse events.

As we did not collect data beyond one year post-HTx, we were unable to fully assess the incidence of CAV, which increases with time and affects up to 50% of recipients at ten years post-HTx [21]. It is conceivable that non-A1 recipients may eventually develop antibodies against A antigen expressed by the allograft endothelium, resulting in the development of CAV. Studies with longer follow-up times and larger sample sizes are necessary prior to establishing A1-mismatched HTx as safe.

5. Conclusions

Our study is the largest analysis of A1-mismatched HTx to date. Although it was limited by delayed enrollment of subjects and short follow-up time, our results provide an encouraging initial sign that A1-mismatched HTx does not result in worse outcomes at one year. Future study focused specifically on A1 into non-A1 HTx with a large cohort entirely enrolled prior to HTx and a longer follow-up interval is required to confirm the safety of A1-mismatched HTx. Emphasis should be placed on examining the increased hospital LOS that was found in our mismatch group. If future studies establish the safety of A1-mismatched HTx, elimination of the A1 barrier would reduce waitlist time, especially for non-A1 and O recipients.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available to protect patient privacy.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Bergenfeldt, H.; Andersson, B.; Bućin, D.; Stehlik, J.; Edwards, L.; Rådegran, G.; Nilsson, J. Outcomes after ABO-incompatible heart transplantation in adults: A registry study. *J. Heart Lung Transplant.* **2015**, *34*, 892–898. [PubMed]
2. Breimer, M.E.; Samuelsson, B.E. The specific distribution of glycolipid-based blood group A antigens in human kidney related to A1/A2, Lewis, and secretor status of single individuals. A possible molecular explanation for the successful transplantation of A2 kidneys into O recipients. *Transplantation* **1986**, *42*, 88–91. [PubMed]
3. Public Comment Archive. Available online: https://optn.transplant.hrsa.gov/governance/public-comment/public-comment-archive/ (accessed on 22 August 2022).
4. Ueda, N.; Nishimura, K.; Yoshida, Y.; Hirai, T.; Kishikawa, H.; Ichikawa, Y. Living-donor kidney transplant from a type a donor to a type a subgroup recipient. *Exp. Clin. Transplant.* **2015**, *13*, 193–195. [PubMed]
5. Fadeyi, E.A.; Stratta, R.J.; Farney, A.C.; Pomper, G.J. Successful ABO-Incompatible Renal Transplantation: Blood Group A1B Donor into A2B Recipient with Anti-A1 Isoagglutinins. *Am. J. Clin. Pathol.* **2016**, *146*, 268–271. [PubMed]
6. Fadeyi, E.A.; Stratta, R.J.; Farney, A.C.; Pomper, G.J. Successful unintentional ABO-incompatible renal transplantation: Blood group A1B donor into an A2B recipient. *Am. J. Clin. Pathol.* **2014**, *141*, 724–726. [CrossRef] [PubMed]
7. Basha, H.I.; Hussain, S.; Raichlin, E.; Gudipati, S.; Liebo, M.; McGee, E.; De Christopher, P.; Heroux, A. Impact of Blood Group A Subtyping on Heart Transplantation: A Single Center Experience. *J. Heart Lung Transplant.* **2019**, *38*, S394. [CrossRef]
8. Stewart, S.; Winters, G.L.; Fishbein, M.C.; Tazelaar, H.D.; Kobashigawa, J.; Abrams, J.; Andersen, C.B.; Angelini, A.; Berry, G.J.; Burke, M.M.; et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J. Heart Lung Transplant.* **2005**, *24*, 1710–1720. [CrossRef] [PubMed]
9. Berry, G.J.; Burke, M.M.; Andersen, C.; Bruneval, P.; Fedrigo, M.; Fishbein, M.C.; Goddard, M.; Hammond, E.H.; Leone, O.; Marboe, C.; et al. The 2013 International Society for Heart and Lung Transplantation Working Formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. *J. Heart Lung Transplant.* **2013**, *32*, 1147–1162. [CrossRef] [PubMed]
10. Predicted Heart Mass (PHM) Match Calculator. Available online: https://insights.unos.org/phm-calculator (accessed on 16 August 2022).
11. Barten, M.J.; Schulz, U.; Beiras-Fernandez, A.; Berchtold-Herz, M.; Boeken, U.; Garbade, J.; Hirt, S.; Richter, M.; Ruhpawar, A.; Sandhaus, T.; et al. The clinical impact of donor-specific antibodies in heart transplantation. *Transplant. Rev.* **2018**, *32*, 207–217.
12. Chan, J.; Kobashigawa, J.; Aintablian, T.L.; Dimbil, S.J.; Perry, P.A.; Patel, J.K.; Kittleson, M.M.; Czer, L.S.; Zarrini, P.; Velleca, A.; et al. Characterizing Predictors and Severity of Vasoplegia Syndrome After Heart Transplantation. *Ann. Thorac. Surg.* **2018**, *105*, 770–777. [CrossRef] [PubMed]
13. Smith, N.F.; Omran, S.S.; Genuardi, M.V.; Horn, E.T.; Kilic, A.; Sciortino, C.M.; Keebler, M.E.; Kormos, R.L.; Hickey, G.W. Primary Graft Dysfunction in Heart Transplant Recipients-Risk Factors and Longitudinal Outcomes. *ASAIO J.* **2021**, *68*, 394–401. [CrossRef] [PubMed]
14. Patients with Certain Blood Groups Wait Much Longer for Heart Transplants. 2018. Available online: https://www.organdonation.nhs.uk/get-involved/news/patients-with-certain-blood-groups-wait-longer-for-heart-transplants/ (accessed on 12 September 2022).
15. Montgomery, J.R.; Berger, J.C.; Warren, D.S.; James, N.T.; Montgomery, R.A.; Segev, D.L. Outcomes of ABO-incompatible kidney transplantation in the United States. *Transplantation* **2012**, *93*, 603–609.
16. Rydberg, L. ABO-incompatibility in solid organ transplantation. *Transfus. Med.* **2001**, *11*, 325–342.
17. Bryan, C.F.; Cherikh, W.S.; Sesok-Pizzini, D.A. A2/A2 B to B Renal Transplantation: Past, Present, and Future Directions. *Am. J. Transplant.* **2016**, *16*, 11–20. [PubMed]
18. Kluger, M.D.; Guarrera, J.V.; Olsen, S.K.; Brown, R.S., Jr.; Emond, J.C.; Cherqui, D. Safety of blood group A2-to-O liver transplantation: An analysis of the United Network of Organ Sharing database. *Transplantation* **2012**, *94*, 526–531. [PubMed]
19. Ge, J.; Roberts, J.P.; Lai, J.C. A2 liver transplantation across the ABO barrier: Increasing options in the donor pool? *Clin. Liver Dis.* **2017**, *10*, 135–138.
20. Ott, G.Y.; Norman, D.; Ratkovec, R.R.; Hershberger, R.; Hosenpud, J.D.; Cobanoglu, A. ABO-incompatible heart transplantation: A special case for the A2 donor. *J. Heart Lung Transplant.* **1993**, *12*, 504–507. [PubMed]
21. Pober, J.S.; Chih, S.; Kobashigawa, J.; Madsen, J.C.; Tellides, G. Cardiac allograft vasculopathy: Current review and future research directions. *Cardiovasc. Res.* **2021**, *117*, 2624–2638. [CrossRef] [PubMed]

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Review

Acute Heart Failure: Diagnostic–Therapeutic Pathways and Preventive Strategies—A Real-World Clinician's Guide

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Abstract: Acute heart failure (AHF) is the most frequent cause of unplanned hospital admission in patients of >65 years of age and it is associated with significantly increased morbidity, mortality, and healthcare costs. Different AHF classification criteria have been proposed, mainly reflecting the clinical heterogeneity of the syndrome. Regardless of the underlying mechanism, peripheral and/or pulmonary congestion is present in the vast majority of cases. Furthermore, a marked reduction in cardiac output with peripheral hypoperfusion may occur in most severe cases. Diagnosis is made on the basis of signs and symptoms, laboratory, and non-invasive tests. After exclusion of reversible causes, AHF therapeutic interventions mainly consist of intravenous (IV) diuretics and/or vasodilators, tailored according to the initial hemodynamic status with the addition of inotropes/vasopressors and mechanical circulatory support if needed. The aim of this review is to discuss current concepts on the diagnosis and management of AHF in order to guide daily clinical practice and to underline the unmet needs. Preventive strategies are also discussed.

Keywords: acute heart failure; biomarkers; cardiac ultrasound; computer tomography; therapeutic interventions; preventive strategies

1. Introduction

AHF is defined as a new onset or recurrence of HF symptoms and signs requiring emergency therapeutic interventions [1,2]. It may occur as the first manifestation of HF, or more frequently as an acute decompensation of chronic HF [3].

Different AHF classification criteria have been proposed, mainly reflecting the clinical heterogeneity of the syndrome [e.g., hemodynamic status (wet/dry–warm/cold) or according to clinical scenario (decompensated heart failure, acute right heart failure, acute pulmonary edema, cardiogenic shock)] [3] (Table 1).

Table 1. Classification of AHF.

	Acutely Decompensated Heart Failure	Acute Pulmonary Oedema	Isolated Right Ventricular Failure	Cardiogenic Shock
Description	Progressive fluid retention in patients with history of HF	Lung congestion and acute respiratory failure	RV dysfunction and/or pre-capillary pulmonary hypertension	Severe cardiac dysfunction with marked hypotension (SBP < 90 mmHg) despite adequate LV filling pressure
Onset	Gradual (days)	Rapid (hours)	Gradual/rapid	Gradual/rapid
Main clinical presentation	Wet and warm (rarely wet and cold)	Wet and warm (rarely wet and cold)	Wet and cold	Wet and cold
Heart rate	↑	↑	Usually ↓	↑
SBP	Variable	Variable	↓	↓
Cardiac index	Variable	Variable	↓	↓
Hypoperfusion	+/−	+/−	+	+
PCWP	↑↑	↑↑↑	↓	↑↑
Main treatment	Diuretics Inotropic agents/vasopressors (If peripheral hypoperfusion/hypotension) Short-term MCS or RRT if needed	O_2 (CPAP/NIV) Diuretics Vasodilators Inotropic agents/vasopressors (If peripheral hypoperfusion/hypotension) Short-term MCS or RRT if needed	Diuretics for congestion Inotropic agents/vasopressors (If peripheral hypoperfusion/hypotension) Short-term MCS or RRT if needed	Inotropic agents/vasopressors Short-term MCS or RRT if needed

Abbreviations: CPAP: continuous positive airway pressure; HF: heart failure; LV: left ventricle; MCS: mechanical circulatory support; NIV: non-invasive ventilation; PCWP: pulmonary capillary wedge pressure; RRT: renal replacement therapy; RV: right ventricle; SBP: systolic blood pressure; ↑: increase; ↓: decrease. Modified from "McDonagh T.A.; et al.; 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure" [3].

AHF is the most frequent cause of unplanned hospital admissions in patients >65 years of age and is associated with poor outcomes, with in-hospital and 1-year mortality rates of ~10% and ~30%, respectively, with 90-day readmission rates ~20–30% [4]. Moreover, it imposes a significant financial burden to health systems, with the total medical cost of annual median hospitalizations estimated at USD ~16,000 per patient [5,6].

2. Epidemiology

The mean age of patients presenting with AHF ranges between 70 and 73 years. About half of patients are male. The majority (65–75%) have a known history of HF. At presentation, most of them have normal or increased blood pressure, while patients presenting with hypotension are generally less than $\leq$8%, including patients with cardiogenic shock (CS) that represent less than $\leq$1–2% of cases [7].

Patients presenting with AHF often suffer from several other conditions besides HF. Comorbid states are roughly divided into cardiovascular and non-cardiovascular states. The

cardiovascular history usually comprises arterial hypertension (HTN) (~70% of patients), coronary artery disease (CAD) (~50–60%), and atrial fibrillation (AF) (~30–40%) [8,9].

Non-cardiovascular comorbidities include diabetes mellitus (DM) (~40%), renal dysfunction (~20–30%), chronic obstructive pulmonary disease (COPD) (~20–30%), and anemia (~15–30%) [7,10,11].

A significant number of AHF patients (~35–40%) do not have reduced left ventricle ejection fraction (LVEF) [5,12]. In this regard, patients with preserved LVEF are usually older (mean age of 75 years) and more frequently female (~60% of patients). Furthermore, they are less affected by CAD but suffer HTN and DM more frequently [13].

3. Management

3.1. Pre-Hospital

AHF patients should immediately ('time-to-treatment' concept) receive appropriate therapy and be rapidly transferred to the nearest hospital, preferably to a site with an intensive cardiology unit (CCU/ICU) [3,14].

In the pre-hospital setting, AHF patients benefit from non-invasive monitoring, including heart and respiratory rate (HR and RR), BP, pulse oximetry (SpO_2), and continuous electrocardiogram (ECG) [3,15].

Oxygen therapy should be administered if $SpO_2 < 90\%$. In patients with respiratory distress, non-invasive ventilation (NIV) should be implemented [3,16].

3.2. In Hospital

3.2.1. Triage

AHF patients admitted to the emergency department (ED) with mild symptoms and signs of congestion, no renal dysfunction, negative troponin values, and very low neuropeptide (NP) levels can be discharged directly home after a small dose of diuretics and adjustments of oral therapy as needed. They should be referred to their physician with the advice to be clinically followed by the HF multidisciplinary outpatient clinic [17].

On the other hand, hemodynamically unstable patients should be admitted to the cardiology ward or ICU. In this regard, admission ICU criteria include RR > 25, $SpO_2 < 90\%$, use of accessory muscles for breathing, SBP < 90 mmHg, need for intubation (or already intubated), or signs of hypoperfusion [oliguria, cold peripheries, altered mental status, lactate > 2 mmol/L, metabolic acidosis, and venous oxygen saturation (SvO_2) < 65%] [17,18] (Figure 1).

3.2.2. Diagnostic Workup (Figure 2)

Step 1

a. Search for reversible causes (Table 2)

Management starts with the search for specific causes of AHF. These include acute coronary syndromes (ACS), hypertensive emergency, rapid arrhythmias or severe bradycardia/conduction disturbances, acute mechanical causes (i.e., acute valve regurgitation), acute pulmonary embolism (PE), infections, and tamponade (CHAMPIT). Dietary and fluid restriction and medication noncompliance should also be ascertained at this time.

After exclusion of these conditions, which need to be treated/corrected urgently, management of AHF differs according to clinical presentation [3,17].

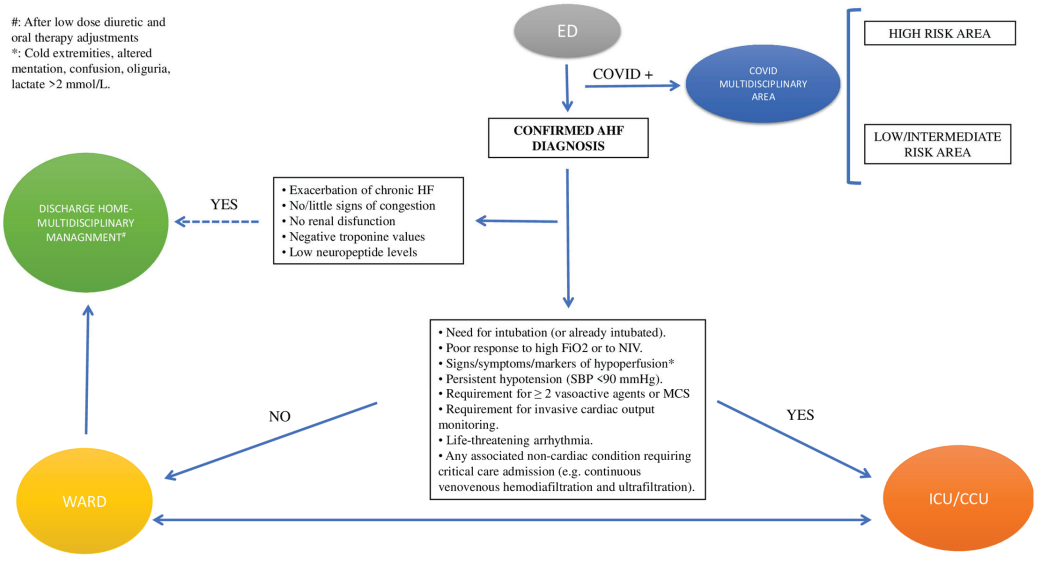

Figure 1. Triage. Abbreviations: AHF: acute heart failure; ED: emergency department; ICU/CCU: intensive cardiology unit/critical care unit; MCS: mechanical circulatory support; NIV: non-invasive ventilation; SBP: systolic blood pressure.

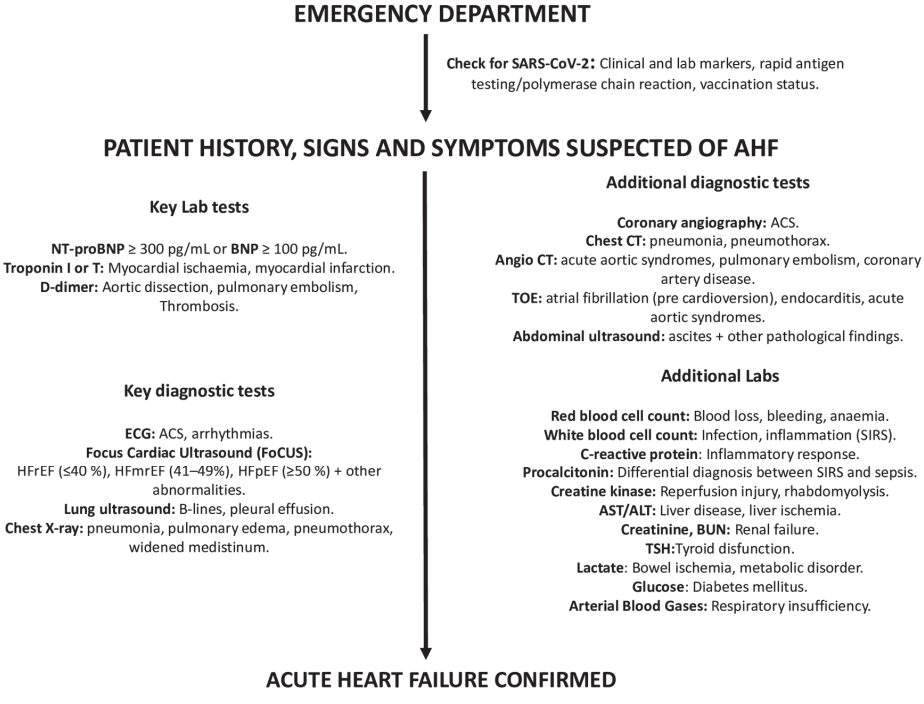

Figure 2. Diagnostic workup of AHF. Abbreviations: ACS: acute coronary syndrome; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen, BNP: brain natriuretic peptide; CT: computed tomography; ECG: electrocardiogram; TOE: transesophageal echocardiogram; TSH: thyroid-stimulating hormone.

Table 2. Triggers of AHF.

Triggers	Lab Test	Invasive/Non-Invasive Test	Notes
ACS [19,20]	hs-cTn (I or T)	1. ECG 2. TTE 3. Coronary angiography	- Immediate primary PCI (or CABG in selected cases) is recommended. - Centers without 24/7 PCI availability must transfer the patient immediately.
Arrhythmias [21–23]	Electrolytes, TFTs	1. ECG 2. TTE 3. Interrogation of ICD (in selected patients)	- Electrical cardioversion is recommended in patients hemodynamically compromised by AF/SMVT and in whom urgent restoration of sinus rhythm is required to improve the patient's clinical condition rapidly. - ALS/defibrillation in VF/VT without pulse. - Pacing is recommended in patients hemodynamically compromised by severe bradycardia or heart block to improve the patient's clinical condition.
Acute Myocarditis [24]	hs-cTn (I or T), PCR, ESR, WBC count	1. ECG + TTE 2. CCT/coronary angiography 3. Endomyocardial biopsy in patients presenting with severe heart failure or cardiogenic shock	- Patients presenting with severe heart failure or cardiogenic shock should immediately be referred to hub centers. - CMRI should be performed within 2/3 weeks from the onset of symptoms when the patient is hemodynamically stable.
Endocarditis [25]	ESR, CRP, blood culture, autoimmunity testing in selected cases	1. TTE + TOE 2. CCT/total-body CT scan	Patients presenting with severe heart failure or cardiogenic shock should be referred early and managed in a reference center with immediate surgical facilities.
Acute aortic syndromes [26]	D-dimer	1. TTE + CTA (1st choice) 2. TTE + TOE (2nd choice)	D-dimer is highly sensitive to rule out classical AAD within the first 6 h of symptom onset in low–moderate-risk patients.
Mechanical cause (free wall rupture, ventricular septal defect, acute mitral regurgitation, cardiac tamponade) [19,20]	hs-cTn (I or T), D-dimer	TTE	Prompt intervention/surgery is needed; transfer to Hub center.
Pulmonary embolism [27]	D-dimer, hs-cTn, ABG	1. ECG + TTE 2. CTPA 3. Compression ultrasonography	If hemodynamically unstable, transfer to ICU.
Hypertension emergency [28]	FBC, creatinine, electrolytes, LDH, haptoglobin, hs-cTn, pregnancy test in women of child-bearing age	1. Chest X-ray 2. TTE 3. CT or MRI brain in suspected nervous system involvement 4. CTA in suspected acute aortic disease	Patients with severe hypertension associated with AHF require an urgent reduction of BP with IV drug administration.

Table 2. *Cont.*

Triggers	Lab Test	Invasive/Non-Invasive Test	Notes
Pneumonia [29]	FBC, ESR, CRP, PCT	1. Chest X-ray 2. Chest CT	Admission to an ICU for patients with hypotension requiring vasopressors or respiratory failure requiring mechanical ventilation.
COPD exacerbation or asthma [30]	ABG, PCR, PCT	1. Chest X-ray 2. Chest CT	Admission to an ICU for patients with hypotension requiring vasopressors or respiratory failure requiring mechanical ventilation.
Thyroid dysfunction [31]	TFTs	1. ECG 2. TTE	Management of myxedema coma and thyroid storm requires both medical and supportive therapies and should be treated in an ICU setting.
Anemia [32]	FBC	-	Urgent RBC transfusion needed.

Abbreviations: ABG: arterial blood gases; ALS: advanced life support; CABG: coronary artery bypass graft surgery; CCT: cardiac computer tomography; CRP: C-reactive protein; CT: computer tomography; CTA: computed tomography angiography; CTPA: CT pulmonary angiogram; ECG: electrocardiogram; ESR: erythrocyte sedimentation rate; FBC: full blood count; hs-Tn: high-sensitive troponins; ICD: implantable cardioverter defibrillator; ICU: intensive care unit; MRI: magnetic resonance imaging; PCI: percutaneous coronary intervention; PCT: procalcitonin; RBC: red blood cells; TFTs: thyroid function tests; TOE: transesophageal echocardiogram; TTE: transthoracic echocardiogram, SMVT: sustained monomorphic ventricular tachycardia.

b. Check for SARS-CoV-2 infection [33,34]

At the time of hospital admission, it is advisable to:

- Search for clinical and laboratory clues suggesting COVID-19 infection;
- Perform SARS-CoV-2 rapid antigen testing/polymerase chain reaction;
- Check for COVID-19 vaccination status.

c. Assess presenting symptoms and signs

The most common symptoms (reflecting pulmonary and/or systemic congestion) include dyspnea during exercise or at rest, orthopnea, fatigue, and reduced exercise tolerance. Clinical signs usually include peripheral oedema, jugular vein distension, the presence of a third heart sound and pulmonary rales [2].

Symptoms and signs such as cold and clammy skin, altered mental status, and oliguria indicate peripheral hypoperfusion—impending CS [2].

Step 2

a. Lab tests

Neuropeptides

Cardiovascular biomarkers play a crucial role in the diagnostic–prognostic process of AHF. Upon presentation to the ED, plasma NP levels (BNP, NT-proBNP, or MR-proANP) should be measured (point-of-care assay) in all patients with acute dyspnea. Due to the strong link with hemodynamic intracardiac stress, they may help to differentiate between cardiac and non-cardiac causes of acute dyspnea [35,36].

Cut-offs for AHF are BNP < 100 pg/mL, NT-proBNP < 300 pg/mL, and MR-proANP < 120 pg/mL, with normal NP concentrations making the diagnosis of AHF extremely unlikely.

However, there are many causes of elevated NP levels—both cardiovascular (CV) and non-CV—that might reduce their diagnostic accuracy. These causes include AF, increasing age, and acute or chronic kidney disease. Conversely, NP concentrations may be disproportionately low in obese patients, in patients with pre-left ventricle causes of HF (i.e., mitral stenosis and acute mitral regurgitation), or pericardial diseases.

As a note, NT-pro BNP instead of BNP should be tested in patients taking sacubitril-valsartan [37].

It should also be highlighted that NP levels are strong predictors of readmissions and death [38].

Troponin

In addition to ACS, elevated high-sensitivity troponin I/T (hsTn I/T) levels may be observed in most non-ACS AHF patients and are associated with worse in-hospital and post-discharge outcomes [39].

Others

Further lab tests (i.e., BUN (or urea), creatinine, electrolytes, glucose, complete blood count, procalcitonin, PCR, and D-dimer) may be useful to detect and/or to confirm clinically suspected comorbidities and/or end-organ damage [15].

SpO_2/arterial blood gas (ABG)

SpO_2 should be measured routinely at the time of AHF patient presentation and continuous monitoring may be needed in the first hours or days.

Routine ABG is not needed. Specific indications for ABG are: respiratory distress [defined as acute increase in the work of breathing or significant tachypnea (RR > 25 breaths/min)], documented hypoxemia (SpO_2 < 90%) not responsive to supplemental oxygen, and evidence of acidosis or elevated lactate levels. In the case of respiratory failure, ABG may show PaO_2 < 60 mmHg, $PaCO_2$ > 45 mmHg or PaO_2/FiO_2 < 300 mmHg. Of note, venous sample might acceptably indicate pH and CO_2 [15].

b. ECG

Routine admission ECG is recommended since it can exclude ACS and arrhythmias. In this regard, careful attention should be paid to ECG changes suggestive of myocardial ischemia. Tachyarrhythmias [i.e., AF (present in 20% to 30% patients), ventricular tachycardia] or bradyarrhythmias (i.e., advanced atrio-ventricular blocks) are also a common trigger for AHF [3,21,22].

c. Chest X-ray

Chest X-ray may reveal lung congestion and/or pleural effusion. Furthermore, it may identify non-cardiac-disease causes of the patient's symptoms (i.e., pneumonia, pneumothorax, widened mediastinum).

d. Transthoracic echocardiography (TTE)

TTE represents the single most useful imaging technique to investigate AHF etiology and to guide related therapeutic interventions.

A "Focus Cardiac Ultrasound" (FoCUS), followed by comprehensive TTE exam, is recommended in all patients to assess LV global systolic (reduced vs. preserved EF) and diastolic function, regional wall abnormalities, valvular heart (stenosis and/or regurgitations) and pericardial disease. In addition, it is of paramount importance to evaluate right heart structure and function, as well as pulmonary pressures, as these are major prognostic determinants [40].

As a note, an E:E' ratio greater than 15 predicts a pulmonary arterial wedge pressure (PAWP) greater than 15 mm Hg, and has been demonstrated to be accurate in the ED and intensive care settings [2,41] (Figure 3).

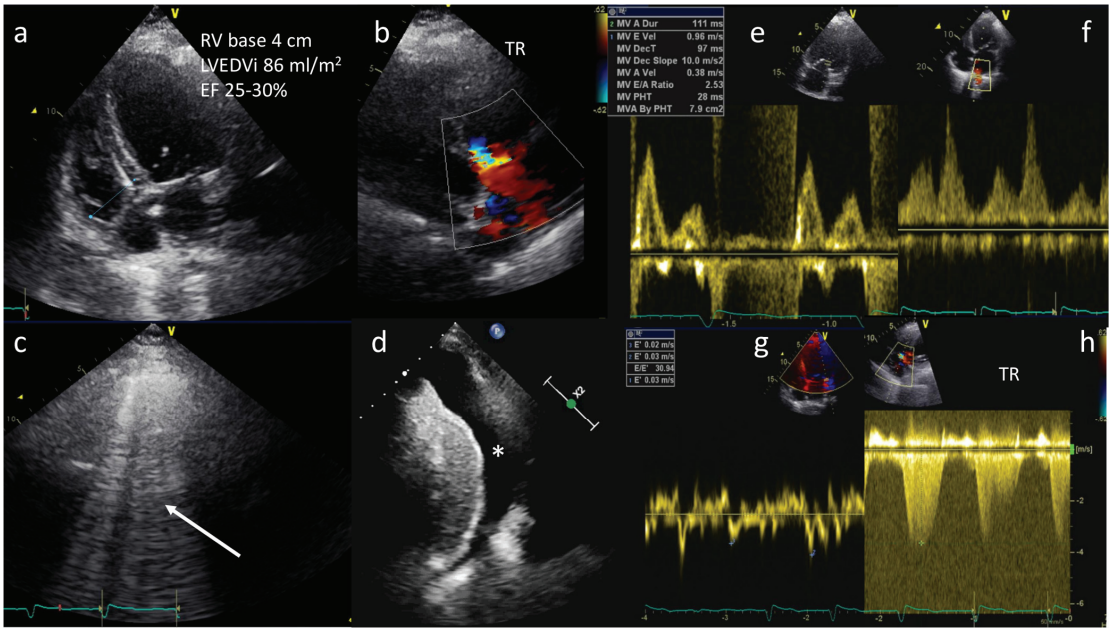

Figure 3. A 68-year-old female with history of dilated cardiomyopathy was admitted for shortness of breath, fatigue, and low-extremity edema. A diagnosis of acute pulmonary edema was made. TTE showed severe LV dilation (LVEDVi 86 mL/m^2), severe reduction in ejection fraction (EF 25–30%), mildly dilated right ventricle (basal diameter 4 cm) (**a**), and moderate tricuspid regurgitation (TR) (**b**). Lung ultrasound showing B-lines in all sites explored (arrow) and pleural effusion (*) (**c**,**d**). Diastolic dysfunction with increased left ventricular end-diastolic pressures (LVEDP) and PAWP (E/A: 2.5, E/E': 30 and S < D on pulmonary veins) (**e**–**g**) and estimated pulmonary artery pressure of 70 mmHg (**h**).

e. Lung ultrasound (LUS)

LUS has emerged as a valuable modality to detect and monitor pulmonary congestion in patients with AHF in a low-cost, portable, real-time, and radiation-free manner.

It outperforms the diagnostic accuracy of the chest radiograph in the detection of pleural water (pleural effusion) and lung water (pulmonary congestion as multiple B-lines) [42].

B-lines are well defined (laser-like), hyperechoic, vertical comet-tail artifacts that arise strictly from the pleural line, move in sync with lung sliding and spread to the edge of the screen without fading and erasing A lines. The number of lines is proportional to the severity of congestion and identifies the cardiogenic origin of dyspnea with 85% sensitivity and 92% specificity [43].

The B profile is useful to track dynamic changes in pulmonary congestion in responses to treatment, and its persistence at pre-discharge or in clinically stable outpatients with heart failure is predictive of heart failure hospitalization or death [44].

The amount of pleural effusion can be scored as trivial (<2 mm), small (2 to 15 mm), moderate (15 to 25 mm), or large (>25 mm). Furthermore, LUS represents a guide to thoracentesis in patients with AHF and at least moderate pleural effusion [45].

As a note, the evaluation of "lung sliding" (a horizontal, to-and-fro movement, beginning at the pleural line and synchronous with respiration) is helpful in the differential diagnosis of several parenchymal lung diseases that are present as comorbidities in HF or as causes of dyspnea suspected to be cardiac in origin. For instance, "lung sliding"

disappears in pneumothorax and it is reduced or abolished in the case of pneumonia, acute respiratory distress syndrome (ARDS), or pleural adhesions [43].

f. Abdominal ultrasound (AUS)

AUS can be useful for measurement of the inferior vena cava (IVC) diameter as an indirect measure of right atrial pressures (IVC < 21 mm that collapses >50% suggests normal right atrial pressure) [46].

In HF patients, an increased IVC diameter might detect abnormal intravascular volume even prior to any change in symptoms or body weight, and in turn monitor the response to diuretics. AUS can also detect ascites and abdominal aortic aneurysm [46].

Recently, ultrasound techniques have also been implemented to assess renal blood flow [47].

g. Transesophageal echocardiogram (TEE)

TEE may be performed in suspected endocarditis and acute aortic syndromes (AAS). Furthermore, it may be useful to better define heart valve abnormalities and to detect intracardiac shunt and thrombi. Absolute contraindications include: unrepaired tracheoesophageal fistula, esophageal obstruction/stricture, perforated hollow viscus, active gastric/esophageal bleeding, poor airway control, severe respiratory depression, and uncooperative, unsedated patient [48].

Step 3. Additional Non-Invasive and Invasive Tests

a. High-resolution chest computed tomography (Chest HR-CT)

Chest HR-CT should be considered when pulmonary parenchymal component is suspected among patients presenting with AHF.

CT can also identify signs of pulmonary edema, such as interlobular septal thickening, fissural thickening, peribronchovascular thickening, perihilar or bat-wing appearance of oedema, increased artery-to-bronchus ratio, pleural effusion, and cardiac enlargement in more advanced HF [49,50].

Furthermore, high-resolution CT provides an effective modality to evaluate patients with suspected COVID-19.

b. Chest CT angiography (CTA)

CTA can be used as a one-step imaging modality (dual rule-out strategy) to exclude PE or AAS. It can be performed with most CT equipment. Furthermore, with state-of-the-art CT equipment, synchronizing image acquisition with the cardiac cycle, it is possible to perform the so-called Triple Rule-Out strategy (TRO). This protocol allows the heart and the coronary arteries to be imaged, allowing the exclusion of ACS in a clinical context where this diagnosis might not be straightforward. The main drawbacks of CTA are the administration of iodinated contrast agent, which may cause acute kidney injury or allergic reactions, even though the amount of contrast material currently required to perform the scan is quite low compared to in the past (i.e., using state-of-the-art CT technology, 50 mL). Furthermore, the use of ionizing radiation should be avoided in younger patients, especially women [51].

Recent CT technology also allows the performance of a full anatomical and functional assessment of cardiac and thoracic structures. Hence, a patient undergoing this kind of assessment will have all heart chamber volumes and functionality assessed, the presence of thrombosis within the cardiac chambers ruled out, the superior and inferior vena cava assessed for patency and distention, the pulmonary artery evaluated for dilatation, and so forth. When COVID-19 is assessed in the context of a TRO protocol, it is referred to as Quadruple Rule-Out [52]. When other causes for the acute settings are included in the evaluation, it can be referred to as Quintuple Rule-Out. Because of this flexibility and wide range of rule-in/rule-out capabilities and its relatively easy access, CT is already, and will become, an increasingly central tool in all acute clinical settings (Figures 4 and 5).

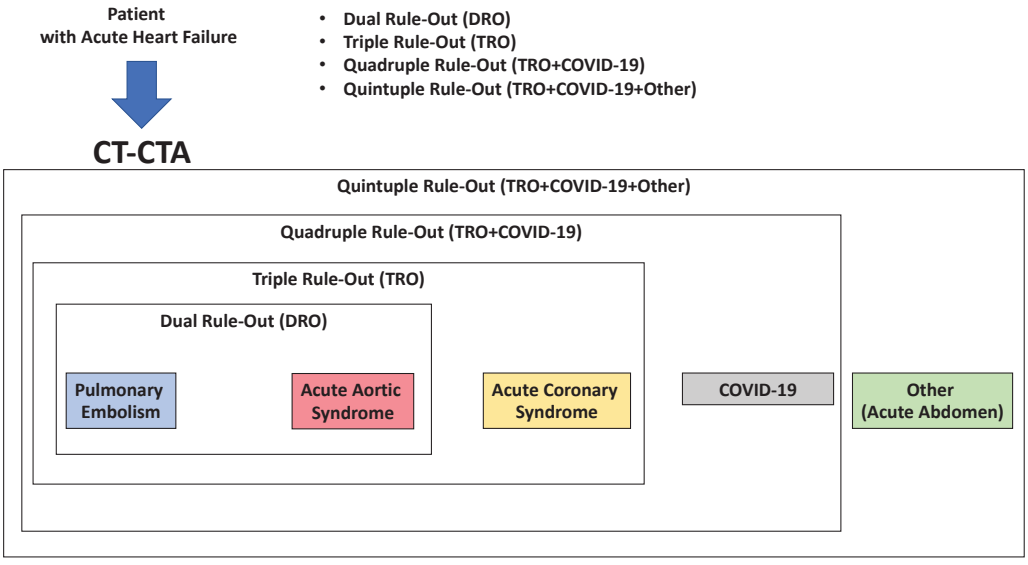

Figure 4. Use of CT in acute heart failure.

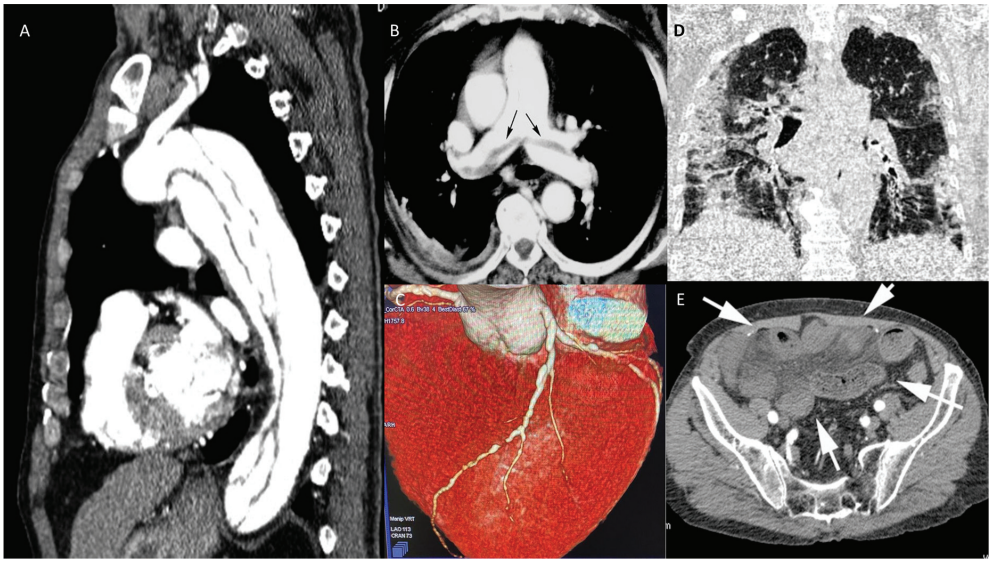

Figure 5. CT in different scenarios. Type B thoracic aortic dissection: post-contrast sagittal CT reconstruction of the aorta demonstrates a medio-intimal flap that begins below left subclavian arterial origin and extends up to diaphragmatic hiatus (**A**). Pulmonary thromboembolism: post-contrast axial CT reconstruction depicts linear contrast defects inside the lumen of main pulmonary arteries (arrows) due to thromboembolism (**B**). Volume rendering post-contrast CT of the left descending coronary artery depicts a brief stenosis of the medium segment (**C**). Coronal unenhanced chest CT shows ground glass opacities of the lungs, especially on the left side, due to interstitial COVID pneumonia (**D**). Post-contrast axial CT image of the pelvis demonstrates ileal loops ischemia with a stratified appearance of the ileal loop's wall (arrows) due to intramural edema and low submucosal enhancement associated with mesenterial free fluid. (**E**).

CIN (contrast induced nephropathy) remains one of the most serious complications of iodinated contrast medium (CM). It is defined as a ≥25% increase in serum creatinine from the baseline value, or an absolute increase of at least 0.5 mg/dL (44.2 μmol/L), 48–72 h after the administration of radiographic contrast media that is not attributable to other causes [53].

Pre-existing renal impairment represents the most important risk factor for CIN. The baseline renal function of patients undergoing contrast studies is best assessed with calculations of glomerular filtration rate (GFR), such as the MDRD or Cockcroft–Gault formulae in adults [53].

Patients at high risk of developing CIN should be identified early and prophylactic measures implemented before the procedure (Table 3).

Table 3. Prevention of contrast-induced nephropathy.

GFR ≥ 60 mL/min
Extremely low risk for CIN: specific prophylaxis or follow up not required
GFR < 60 mL/min (Moderate–Severe Kidney Disease)
• Avoid iodinated CM whenever possible. • Use iso-osmolar or low-osmolar CM at minimum possible volume. • Pre- and post-hydration with isotonic saline should be considered if the expected contrast volume is > 100 mL (1 mL/kg/h 12 h before and continued for 24 h after the procedure (0.5 mL/kg/h if LVEF ≤ 35% or NYHA > 2). • In statin-naive patients, pre-treatment with high-dose statins should be considered (Rosuvastatin 40/20 mg or atorvastatin 80 mg).

Abbreviations: CIN: contrast-induced nephropathy; CM: contrast medium; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association. Modified from "Neumann FJ; et al. 2018 ESC/EACTS Guidelines on myocardial revascularization" [53].

The frequency of allergic-like adverse events related to the intravascular administration of iodinated CM is low and has decreased considerably since the use of nonionic low-osmolality contrast media. However, the majority of adverse side effects to CM are mild non-life-threatening events that usually require only observation, reassurance, and/or supportive measures [54]. Severe reactions (i.e., bronchospasm, laryngeal edema, anaphylaxis) occur rarely and are unpredictable. A frequently recommended premedication oral regimen for elective examinations is shown in Table 4.

Table 4. Premedication protocols to avoid allergic reactions.

Reaction Severity	Symptoms	Recommendation
Mild	Limited urticaria, pruritus, or skin edema; mild nasopharyngeal symptoms such as sneezing, rhinorrhea, or nasal congestion	Do not require premedication
Moderate	Generalized erythema, urticaria, pruritus, or edema Hoarseness or throat tightness with or without mild hypoxia; wheezing with mild hypoxia	Premedication is recommended Prednisone—50 mg by mouth at 13 h, 7 h, and 1 h before contrast media injection OR Methylprednisolone—32 mg by mouth 12 h and 2 h before contrast media injection PLUS Diphenhydramine—50 mg intravenously, intramuscularly, or by mouth 1 h before contrast medium

Table 4. *Cont.*

Reaction Severity	Symptoms	Recommendation
Severe	Severe edema, including facial and laryngeal edema, anaphylaxis, hypoxia	Consider alternative tests. If the test is necessary premedication is recommended Prednisone—50 mg by mouth at 13 h, 7 h, and 1 h before contrast media injection OR Methylprednisolone—32 mg by mouth 12 h and 2 h before contrast media injection PLUS Diphenhydramine—50 mg intravenously, intramuscularly, or by mouth 1 h before contrast medium

c. Coronary angiography

In AHF patients with a clinical picture related to ACS, an immediate coronary angiography, along with revascularization (if needed), should be performed [19,20].

4. In-Hospital Therapeutic Interventions

The main goals of treatment in AHF consist of alleviating symptoms, improving congestion and organ perfusion, restoring oxygenation, and preventing thromboembolism.

4.1. Pharmacologic

4.1.1. Diuretics (Table 5)

The cornerstone of AHF treatment is represented by diuretics with IV loop diuretics (e.g., furosemide, bumetanide or torasemide) used as first-line therapy in patients with AHF and congestion [3].

Table 5. Diuretics [2,55].

Drug	Mechanism of Action	Dose	Adverse Reactions	Notes
Diuretics				
Used in hypervolemia to relief symptoms of congestion				
Loop diuretics				
Furosemide *, Torsemide *, Bumetanide.	Sulfonamide loop diuretics. Inhibit cotransport system ($Na^+/K^+/2Cl^-$) of thick ascending limb of loop of Henle. Abolish hypertonicity of medulla, preventing concentration of urine. Associated with increased PGE (vasodilatory effect on afferent arteriole). Increase Ca^{2+} excretion.	Initial dose, diuretic-naive: - furosemide: 20–40 mg IV - torsemide: 10–20 mg IV - bumetanide: 0.5–1 mg IV Initial dose, for those on chronic diuretics: 1–2 times the daily oral chronic dose as intermittent IV boluses or continuous IV infusion. Adjust dose to relieve symptoms, reduce volume excess, and avoid hypotension.	Ototoxicity, hypokalemia, hypomagnesemia, dehydration, allergy, metabolic alkalosis, nephritis, gout.	Monitor symptoms, urine output, renal function, and serum electrolytes regularly during therapy. Consider continuous infusion in diuretic-resistant patients. A satisfactory diuretic response can be defined as a urine sodium content >50–70 mEq/L at 2 h and/or by a urine output >100–150 mL/h during the first 6 h.

Table 5. *Cont.*

Drug	Mechanism of Action	Dose	Adverse Reactions	Notes
Thiazide diuretics				
Hydrochlorothiazide *, chlorthalidone, metolazone.	Inhibit NaCl reabsorption in early distal convolute tubule. Decrease Ca^{2+} excretion.	- Hydrochrothiazide: start with 25 mg PO once or twice daily (dose range: 12.5–200 mg/day) - Chlorthalidone: start with 25 mg PO once daily (dose range: 12.5–200 mg/day) - Metolazone: start with 1.25–5 mg PO 1–7 times/week (dose range: 1.25–20 mg/day)	Hypokalemic metabolic alkalosis, hyponatremia, hyperglycemia, hyperlipidemia, hyperuricemia, hypercalcemia. Sulfa allergy.	Use with caution in patients with severe renal disease, hepatic impairment, or progressive liver disease.
Potassium-sparing diuretics				
Spironolactone *, Eplerenone *, Amiloride, Triamterene.	Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Amiloride blocks Na+ channels at the same part of the tubule.	- Spironolactone: start with 12.5–25 mg PO daily (target dose: 25–50 mg PO daily) - Eplerenone: start with 25 mg PO once daily (target dose: 50 mg PO once daily) - Amiloride: start with 5 mg PO once daily (dose range: 1.25–20 mg/day).	Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (e.g., gynecomastia, antiandrogen effects).	Monitor serum potassium.

*: Principal drugs. Abbreviations: IV: intravenous; PGE: prostaglandin E; PO: per os.

The use of an IV dose of diuretics at least equal to the pre-existing oral dose is recommended in those already receiving oral diuretics, and 20–40 mg IV furosemide (or equivalent) in those who are not on regular oral diuretics [3,56].

Furosemide can be given as 2–3 daily boluses or as a continuous infusion. Daily single bolus administrations are discouraged for the possibility of post-dosing sodium retention [3,56].

The diuretic response is evaluated by measuring the urinary volume output and/or spot urinary sodium content, with a satisfactory diuretic response defined as a urine sodium content >50–70 mEq/L at 2 h and/or by a urine output >100–150 mL/h during the first 6 h [56].

If there is an insufficient diuretic response, the loop diuretic IV dose can be doubled. Transition to oral treatment should be started when the patient's clinical condition is stable.

In patients with resistant oedema, dual treatment with a loop diuretic and a thiazide or a thiazide-like diuretic (e.g., metolazone) may be considered to achieve adequate diuresis (so-called "sequential nephron blockade") [56].

4.1.2. Vasodilators (Table 6)

Intravenous vasodilators may be considered to relieve AHF symptoms when SBP is >110 mmHg [3].

They may be started at low doses and up-titrated to achieve clinical improvement and BP control. Nitrates are generally administered with an initial bolus followed by continuous infusion. However, these agents should be avoided in patients with concurrent obstructive valvular disease (i.e., severe aortic stenosis) or restrictive physiology (i.e., hypertrophic cardiomyopathy) [57].

Table 6. Vasodilators [2,57].

Drug	Mechanism of action	Dose	Adverse reactions	Notes
Vasodilators				
Used for relief of dyspnea in patients without hypotension (SBP > 110 mmHg), potentially useful in severely congested patients with hypertension or severe mitral valve regurgitation complicating LV dysfunction.				
Nitroglycerine Isosorbide dinitrate	Vasodilate by increasing NO in vascular smooth muscle that leads to increase of cGMP and smooth muscle relaxation (veins > arteries).	Nitroglycerine: start with 10–20 μg/min, increase up to 200 μg/min IV. Isosorbide dinitrate: start with 1 mg/h, increase up to 10 mg/h IV.	Hypotension, reflex tachycardia, headache. Tolerance in continuous use.	Contraindicated in right ventricular infarction, hypertrophic cardiomyopathy, severe aortic stenosis and with concurrent PDE-5 inhibitor use.
Nitroprusside	Short acting vasodilator (arteries = veins). Increases cGMP via direct release of NO.	Start with 0.3 μg/kg/min and increase up to 5 μg/kg/min IV.	Hypotension, isocyanate toxicity, light sensitivity.	Contraindicated in right ventricular infarction, hypertrophic cardiomyopathy, severe aortic stenosis, and with concurrent PDE-5 inhibitor use.

Abbreviations: cGMP: cyclic guanosine monophosphate; IV: intravenous; NO: nitric oxide; PDE: phosphodiesterase; SBP: systolic blood pressure.

4.1.3. Opiates

Although the routine use of opiates (i.e., morphine) in AHF is not recommended, they may be considered in selected patients, particularly in case of severe pain, anxiety or in the setting of palliation [58,59].

4.1.4. Digoxin

Digoxin is mostly indicated (boluses of 0.25–0.5 mg IV if not used previously, followed by an oral or IV dose of 0.25 mg at least 12 h after the initial dose) in patients with AF and rapid ventricular rate (>110 bpm) despite beta-blockers [3,60].

Caution should be taken in the elderly or in patients with factors affecting digoxin metabolism (i.e., renal failure, drug interaction) [3].

Furthermore, unless the risk of toxicity outweighs the benefit, discontinuation of digoxin is generally discouraged. In this regard, an association between withdrawal of therapy and worsening HF has been well documented [60].

4.1.5. Anticoagulants

AHF patients are at high risk of deep venous thrombosis (DVT) and PE as a direct consequence of higher venous pressures and lower cardiac output. In this regard, current guidelines support the use of thromboprophylaxis [e.g., low-molecular-weight heparin (LMWH) given at 4000 to 5000 units daily, or 2500 to 3000 units twice daily subcutaneously] in all appropriate hospitalized AHF patients, unless contraindicated [61].

In addition, oral anticoagulation [preferring new oral anticoagulants (NOACs) to vitamin K antagonists (VKAs), except in patients with mechanical heart valves or moderate–severe mitral stenosis] is recommended in AHF patients with paroxysmal, persistent, or permanent AF with a CHA2DS2-VASc score $\geq$ 2 in men and $\geq$ 3 in women. The HAS-BLED score should be considered to identify patients at high risk of bleeding (HAS-BLED score $\geq$ 3) for early and more frequent clinical assessments and follow-up [22].

4.1.6. Inotropes/Vasopressors (Table 7)

Inotropes [including sympathomimetics/synthetic catecholamines (e.g., dobutamine, adrenaline), phosphodiesterase inhibitors (e.g., milrinone, enoximone), and, more recently, Ca^{2+} sensitizers (e.g., levosimendan)] should be reserved for patients with LV systolic dysfunction, low cardiac output and low SBP (e.g., <90 mmHg), resulting in poor vital organ perfusion [2].

Inotropes improve myocardial contractility, but, especially in the case of the sympathomimetics, also increase myocardial O_2 consumption. As a direct consequence they may trigger supraventricular and ventricular tachyarrhythmias. In this regard, it should be underlined that all patients under inotrope treatment require close monitoring of cardiac rhythm and hemodynamic parameters [62,63].

Table 7. Inotropes/vasopressors [2,63].

Drug	Mechanism of Action	Dose	Adverse Reactions	Notes
Inotropes/Vasopressors				
Used for maintenance of systemic perfusion and preservation of end organ function in patients with severe systolic dysfunction presenting with hypotension (<90 mmHg) or low cardiac output in the presence of congestion and organ hypoperfusion.				
Dobutamine	Agonist of both beta1- and beta2-adrenergic receptors with variable effects on the alpha receptors	Continuous IV infusion rate of 2–20 mcg/kg/minute	Hypotension, increased myocardial oxygen demand, phlebitis	Continuously monitor ECG and blood pressure. Dobutamine is preferred over milrinone in patients who are acutely unstable or hypotensive, or those with renal insufficiency.
Dopamine	Agonist of both adrenergic and dopaminergic receptors	Infusion rate of 3–5 μg/kg/min; inotropic (beta+); >5 μg/kg/min: (beta+), vasopressor (alpha+)	Arrhythmias, tachycardia	Continuously monitor ECG and blood pressure. Clinical effects are dose-related; low doses increase renal blood flow/urine output, intermediate doses also increase cardiac contractility and chronotropy, and high doses result in vasoconstriction.
Milrinone	PDE inhibitor (increases cAMP)	Bolus: 25–75 μg/kg over 10–20 min then infusion rate of 0.375–0.75 μg/kg/min continuous IV infusion.	Tachycardia, ventricular arrhythmias, hypotension	Continuously monitor ECG and blood pressure. Not recommended in acutely worsened ischemic heart failure.
Levosimendan	Cardiac Ca^{2+} channels sensitizer. Activator of K^+ channels of vascular smooth muscle cells.	Optional bolus: 2 μg/kg over 10 min, infusion rate of 0.1 μg/kg/min, which can be decreased to 0.05 or increased to 0.2 μg/kg/min.	Tachycardia, ventricular arrhythmias, hypotension.	Continuously monitor ECG and blood pressure. Bolus not recommended in hypotensive patients.
Norepinephrine	Potent agonist of the beta1 and the alpha 1 receptors	Infusion rate of 0.2–1.0 μg/kg/min.	End-organ hypoperfusion and tissue necrosis, arrhythmias.	Continuously monitor ECG and blood pressure.
Epinephrine	Full beta receptor agonist	Infusion rate of 0.05–0.5 μg/kg/min. A bolus of 1 mg can be given IV during resuscitation, repeated every 3–5 min.	End-organ hypoperfusion and tissue necrosis, arrhythmias.	Continuously monitor ECG and blood pressure. Use should be restricted to patients with persistent hypotension despite adequate cardiac filling pressures and the use of other vasoactive agents, as well as for resuscitation protocols.

Abbreviations: cAMP: cyclic adenosine monophosphate; ECG: electrocardiogram; IV: intravenous; PDE: phosphodiesterase.

Of note, while inotropes have been shown to improve symptoms and signs of congestion, these agents have failed to reveal any improvement in mortality in patients with AHF [64].

4.1.7. Future Directions

In the EMPULSE trial, early initiation of SGLT-2 inhibitor empagliflozin in patients hospitalized for AHF led to a statistically significant clinical benefit at 90 days with fewer deaths, improvement in quality of life, lower NT-pro BNP levels, and weight loss [65,66].

The ADVOR trial has reported that, when used in combination with loop diuretic, acetazolamide (a carbonic anhydrase inhibitor) can lead to a greater incidence of successful decongestion [67].

Istaroxime, a novel compound with inotropic and lusitropic positive properties and a dual mechanism of action (activation of the sarcoplasmic reticulum Ca^{2+}/ATPase 2a (SERCA2a) and inhibition of the Na^+/K^+-ATPase), has been shown to increase SBP without activating the adrenergic system, and to improve pulmonary capillary wedge pressure and diastolic cardiac function [68–71].

Furthermore, in AHF patients, early administration (within 16 h) of serelaxin, a peptide involved in cardiovascular adaptations during pregnancy, has been shown to be associated with a reduction in 5-day worsening HF and markers of renal dysfunction [72].

4.1.8. Management of Chronic HF Therapy

Temporary discontinuation of angiotensin-converting enzyme (ACE), inhibitor/angiotensin receptor blockers (ARB), or beta-blockers may be necessary in the settings of CS or symptomatic hypotension. ACE-I/ARB and mineralocorticoid receptor antagonists (MRAs) may also need to be temporarily held in case of renal dysfunction, oliguria, and/or hyperkalemia [73].

The Initiation of beta-blocker therapy during AHF is contraindicated due to acute negative inotropic effects. However, initiation of beta-blocker in euvolemic patients prior to discharge is safe and associated with increased long-term survival [74].

4.2. Non-Pharmacologic

4.2.1. Mechanical Ventilation

NIV consists of applying positive intrathoracic pressure (PIP) to conscious patients through different interfaces, and can be either continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) [75].

It should be highlighted that NIV has to be started as soon as possible in patients with respiratory distress (respiratory rate >25 breaths/minute, SpO_2 < 90%) to improve gas exchange and reduce the rate of endotracheal intubation [3].

Absolute contraindications to NIV include [75]:

- Cardiac or respiratory arrest;
- Anatomical abnormality (unable to fit the interface);
- Inability to keep patent airway (uncontrolled agitation, coma or obtunded mental status);
- Refractory hypotension.

If there is only hypoxemia, CPAP is the treatment of choice. In cases of hypoxemia and hypercapnia, BiPAP is preferred. CPAP is generally started at a pressure of 5 cm H_2O, which is increased in a stepwise manner to up to 10 cm H_2O. In BiPAP, it is reasonable to start with an EPAP of 5 cm H_2O and an IPAP of 10–14 cm H_2O. EPAP and IPAP can be adjusted further according to the effect on oxygenation and ventilation, respectively [75].

The response to NIV should be assessed after 60 min, and thereafter on a continuous basis. Signs of NIV failure are patient fatigue, progressive worsening of level of consciousness, hemodynamic instability, persistent tachypnoea (>35 breaths/minute), and progressive worsening of respiratory failure with acidosis, hypoxemia, or hypercapnia [75].

Endotracheal intubation and mechanical ventilation are only required in a minority of AHF patients, as most of them will respond to NIV.

Criteria for endotracheal intubation are the following [75]:

- Cardiac or respiratory arrest;
- Progressive worsening of altered mental status;
- Progressive worsening of pH, $PaCO_2$, or PaO_2 despite NIV;
- Progressive signs of fatigue during NIV;
- Need to protect the airway;
- Persistent hemodynamic instability;
- Agitation or intolerance to NIV with progressive respiratory failure.

4.2.2. Electric Cardioversion

AF patients presenting with a rapid ventricular rate and acute hemodynamic instability (i.e., acute pulmonary oedema, ongoing myocardial ischemia, symptomatic hypotension or CS) require prompt intervention, and emergency electrical cardioversion should be attempted without delay. In this setting, amiodarone may also be considered in order to control heart rate response [3,22].

4.2.3. Mechanical Circulatory Support (MCS)

Short-term MCS (which increases cardiac output and supports end organ damage) may be implemented as a bridge to recovery (BTR), bridge to decision (BTD) or bridge to transplant (BTT) (Table 8). Intra-aortic balloon pump (IABP) is not routinely recommended [76].

Table 8. Mechanical circulatory support.

	IABP	Impella (2.5, CP, 5.0)	TandemHeart	VA-ECMO
Mechanism	Diastolic augmentation of aortic pressure and improved LV performance via systolic balloon deflation (decrease in afterload)	Expels blood from LV to AO	Aspirates oxygenated blood from LA and returns to iliac artery	Drainage of deoxygenated venous blood via an extracorporeal centrifugal pump over a membrane oxygenator, and pumping back oxygenated blood to iliac artery
Indications	Consider in patients with cardiogenic shock refractory to medical therapy	Consider in patients with cardiogenic shock refractory to medical therapy	Consider in patients with cardiogenic shock refractory to medical therapy	Consider in patients with cardiogenic shock coupled with respiratory failure refractory to medical therapy
Insertion	Femoral or axillary artery to aorta	Access through femoral artery placed from LV to aorta	- Venous cannula: femoral vein to LA (requires transeptal puncture) - Arterial cannula: iliac artery	- Venous cannula: RA - Arterial cannula: iliac artery
Sheath size	7–8 Fr	13–14 Fr (2.5, CP)21 Fr (Impella 5)	15–17 Fr Arterial 21 Fr Venous	14–16 Fr Arterial 18–21 Fr Venous
Cardiac Flow	0.3–0.5 L/min	1–5 L/min	2.5–5 L/min	3–7 L/min
Duration	Weeks	7 days	14 days	Weeks
Cardiac synchrony/stable rhythm	Yes	No	No	No

Table 8. *Cont.*

	IABP	Impella (2.5, CP, 5.0)	TandemHeart	VA-ECMO
Preload	—	↓↓	↓↓	↓
Afterload	↓	↓	↑	↑↑↑
MAP	↑	↑↑	↑↑	↑↑
PCWP/LVEDP	↓	↓↓	↓↓	—
Coronary perfusion	↑	↑	—	—
Complications	- Limb ischemia - Hemolysis - Thrombocytopenia - Bleeding - Infection	- Limb ischemia - Hemolysis - Bleeding - Infection	- Limb ischemia - Bleeding - Infection	- Hemolysis - Thromboembolic complications (large artificial surface) - Renal failure - Limb ischemia/amputation - Infection - Bleeding - LV overloading (may require LV decompression strategies such as septostomy, IABP, Impella, etc.) - Harlequin syndrome (upper body hypoxia from incomplete retrograde filling and oxygenation)
Contraindications	- Moderate-to-severe aortic regurgitation - Severe aortic disease	- Severe aortic stenosis - Prosthetic aortic valve - LV thrombus - VSD - Peripheral vascular disease	- Severe aortic insufficiency - Aortic dissection - Peripheral vascular disease - RV failure - VSD - Inability to tolerate systemic anticoagulation	- Severe aortic insufficiency - Aortic dissection - Inability to tolerate systemic anticoagulation

Abbreviations: AO: aorta; IABP: intra-aortic balloon pump; LA: left atrium; LV: left ventricle; LVEDP: left ventricular end diastolic pressure; MAP: mean arterial pressure; PCWP: pulmonary capillary wedge pressure; RA: right atrium; VA-ECMO: venoarterial extracorporeal membrane oxygenation; ↑: increase; ↓: decrease. Modified from "Atkinson T.M. et al.; A Practical Approach to Mechanical Circulatory Support in Patients Undergoing Percutaneous Coronary Intervention" [76].

4.2.4. Renal Replacement Therapy

Ultrafiltration (i.e., hemodialysis) may be indicated in case of refractory congestion non-responsive to diuretics [17]. It may be considered if the following criteria are met:

- Oliguria unresponsive to fluid resuscitation measures;
- Severe hyperkalemia ($K^+ > 6.5$ mmol/L);
- Severe acidemia (pH < 7.2);
- Serum urea level > 25 mmol/L (> 150 mg/dL);
- Serum creatinine > 300 mmol/L (> 3.4 mg/dL) that is worsening.

5. Daily Patient Monitoring

Daily patient monitoring includes:

- Weight check along with completion of an accurate fluid balance chart;
- Standard non-invasive monitoring of HR, RR, BP;
- Renal function and electrolyte measurement.

Invasive monitoring with pulmonary artery catheter failed to show any positive influence on inpatient or follow-up outcomes of patients admitted with AHF, and should be carefully used for selected patients [77].

6. Pre-Discharge and Post-Discharge Planning

6.1. Pre-Discharge

Once hemodynamic stabilization is achieved with IV therapy, treatment should be optimized before discharge according to current HF guidelines in order to (a) relieve congestion, (b) treat comorbidities, and (c) initiate or restart oral optical medical treatment (OMT) [3,78–82].

Indicators of good response to initial therapy that might be considered in discharge include [15]:

- Patient-reported subjective improvement;
- Resting HR < 100 bpm
- Lack of orthostatic changes in BP;
- Adequate urine output;
- SpO_2 > 95% in room air;
- Decreased body weight.

6.2. Post-Discharge (Figure 6)

In order to reduce hospitalizations and mortality, enrollment in a HF multidisciplinary management program is recommended as it has been shown to improve outcomes based on three main aspects [3,14]:

1. Patient self-monitoring (i.e., regular weight checks, adherence to therapy, structured exercise program, and dietary sodium and fluid restriction).
2. Periodic follow-up visits, including monitoring of signs and symptoms of HF, assessment of volume status, BP, HR, and laboratory tests primarily of renal function, electrolytes, iron status, hepatic function, and NP. In patients with minimal symptoms of HF, comparison of NP level with predischarge values should be considered to detect worsening subclinical congestion. At the visit, the physician should also verify that the patient is receiving all guideline-directed chronic HF therapies for which they are eligible. Likewise, laboratory monitoring for corresponding drug adverse effects (i.e., renal insufficiency, electrolyte disturbances) should be considered [3]. Furthermore, planning for additional diagnostic and interventional procedures can be undertaken, including device therapy. It should be highlighted that the 2021 European Society of Cardiology (ESC) HF guidelines recommend the first follow-up outpatient visit within 1 to 2 weeks after discharge [83].
3. Remote monitoring via telemedicine/teleconsulting evaluations. Home telemonitoring can help maintain quality of care, facilitate rapid access to care when needed, reduce patient travel costs, and minimize the frequency of clinic visits [84]. Remote pulmonary arterial pressure monitoring with implantable pressure sensors, with adjustment of diuretic therapy according to pulmonary arterial pressure measurements, substantially reduced HF hospitalizations and improved outcomes in both patients with HFpEF and HFrEF [85].

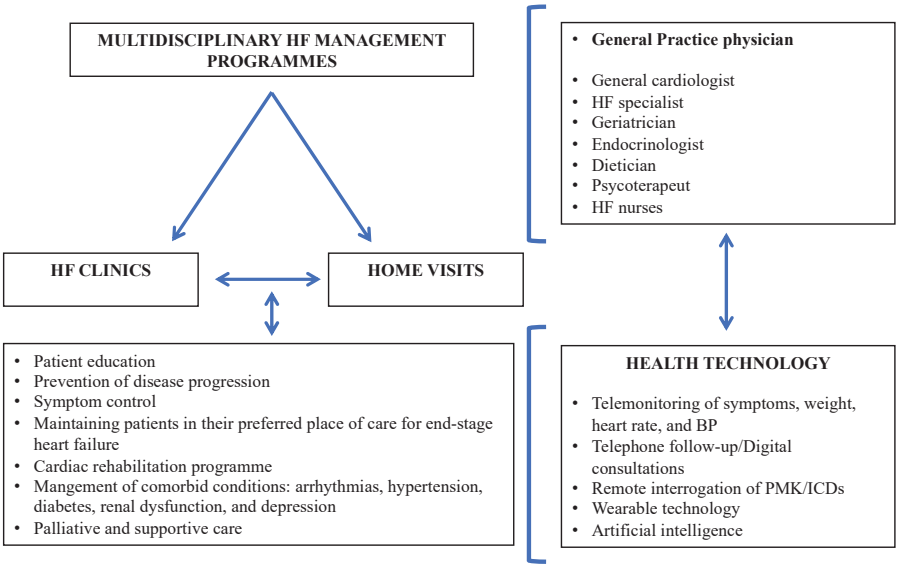

Figure 6. Outpatient management. Abbreviations: BP: blood pressure; HF: heart failure; ICD: implantable cardiac defibrillator; PMK: pacemaker.

7. In-Hospital and Long-Term Outcomes

7.1. In-Hospital Outcomes

AHF is characterized by relatively low in-hospital mortality but a high rate of recurrent post-discharge events. AHF inpatient mortality ranges between 3% and 7%, with the exception of patients with CS, who have an in-hospital mortality of approximately 40% [5].

At hospital admission, specific predictors of poor prognosis consist of advanced age, HF hospitalization history, decreased kidney function, high NP concentrations, and low BP.

Furthermore, higher degrees of congestion are associated with longer hospital stay [38].

Persistent congestion and high NP levels at discharge are predictors of worse quality of life, recurrent rehospitalization, and higher mortality [86].

7.2. Long-Term Outcomes

Approximately 25% of patients hospitalized with HF are readmitted within 30 days of discharge, and mortality during this period can approach 10%. Rates of rehospitalization within 6 months approach 50% in many cohorts, particularly the elderly [83].

In the EVEREST trial, careful adjudication of post-discharge hospitalizations showed that 46% were for HF, 15% for other CV causes, and 39% for non-CV causes.

Of note, approximately half of rehospitalizations are not HF-related, which underscores the high burden of comorbidity as well as the challenges of implementing personalized therapeutic interventions [87].

Median survival in HF patients decreases gradually with the number of hospitalizations, ranging from 2.5 years in patients with one hospital admission to 0.5 years in those with four admissions [88].

8. Preventive Strategies

The lifetime risk of HF is approximately 20%, and the prevalence and burden of HF will likely continue to increase in developed countries [77].

In all patients, the cornerstone should be counseling on the importance of healthy lifestyle to optimize CV health [89,90].

In this regard, it is essential to assess modifiable HF risk factors, including HTN, elevated body mass index (BMI), physical inactivity, DM, CAD, and tobacco and alcohol use. It should be highlighted that controlling HTN is associated with a lower risk of incident HF, with current guidelines recommending targeting BP < 130/80 mmHg [90].

Furthermore, in patients with DM, a target HbA1c < 7.0% (53 mmol/mol) is recommended [90].

It is recommended that all patients with HF are regularly screened for anemia and iron deficiency with full blood count, serum ferritin concentration, and transferrin saturation (TSAT). In patients with HF, iron deficiency is defined as either a serum ferritin concentration < 100 ng/mL or 100–299 ng/mL with TSAT < 20% [91].

Ion supplementation with IV ferric carboxymaltose should be considered for the improvement of symptoms, exercise capacity, and quality of life in patients with HF and LVEF < 45%. It should also be considered for the reduction of HF rehospitalizations in patients with LVEF < 50% recently hospitalized for worsening HF [3].

Influenza and pneumococcal vaccination, as well as COVID-19 vaccination, when available, should be considered in patients with HF [92].

9. Conclusions

AHF is a life-threatening medical emergency requiring immediate therapeutic interventions in order to optimize hemodynamic status. Precipitants and comorbid conditions should be addressed, specifically acute decompensation triggers such as ACS, hypertensive emergency and malignant arrythmia. Multidisciplinary comprehensive follow-up and rehabilitation programs are recommended, along with the implementation of digital health (i.e., remote monitoring, teleconsulting, and implantable device interrogation) in order to reduce the risk of recurrent HF hospitalization and mortality. In the near future, we may expect a major practical change towards personalized care.

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References

1. Bozkurt, B.; Coats, A.J.S.; Tsutsui, H.; Abdelhamid, C.M.; Adamopoulos, S.; Albert, N.; Anker, S.D.; Atherton, J.; Böhm, M.; Butler, J.; et al. Universal definition and classification of heart failure: A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur. J. Heart Fail.* **2021**, *23*, 352–380. [CrossRef] [PubMed]
2. Felker, G.M.; Teerlink, J.R. Diagnosis and Management of Acute Heart Failure. In *Braunwald's Heart Disease a Textbook of Cardiovascular Medicine*, 11th ed.; Zipes, D.P., Libby, P., Bonow, R., Mann, L.D., Tomaselli, G.F., Eds.; Elsevier: Philadelphia, PA, USA, 2019; pp. 462–489.
3. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef] [PubMed]
4. Arrigo, M.; Jessup, M.; Mullens, W.; Reza, N.; Shah, A.M.; Sliwa, K.; Mebazaa, A. Acute heart failure. *Nat. Rev. Dis. Primer* **2020**, *6*, 16. [CrossRef] [PubMed]

5. Nieminen, M.S.; Brutsaert, D.; Dickstein, K.; Drexler, H.; Follath, F.; Harjola, V.-P.; Hochadel, M.; Komajda, M.; Lassus, J.; Lopez-Sendon, J.L.; et al. EuroHeart Failure Survey II (EHFS II): A survey on hospitalized acute heart failure patients: Description of population. *Eur. Heart J.* **2006**, *27*, 2725–2736. [CrossRef]
6. Urbich, M.; Globe, G.; Pantiri, K.; Heisen, M.; Bennison, C.; Wirtz, H.S.; Di Tanna, G.L. A Systematic Review of Medical Costs Associated with Heart Failure in the USA (2014–2020). *PharmacoEconomics* **2020**, *38*, 1219–1236. [CrossRef]
7. Farmakis, D.; Filippatos, G. Acute heart failure: Epidemiology, classification, and pathophysiology. In *The ESC Textbook of Intensive and Acute Cardiovascular Care*, 3rd ed.; Tubaro, M., Vranckx, P., Bonnefoy, E., Price, S., Vrints, C., Eds.; Oxford University Press: Oxford, UK, 2021; pp. 603–616.
8. Di Palo, K.E.; Barone, N.J. Hypertension and Heart Failure. *Heart Fail. Clin.* **2020**, *16*, 99–106. [CrossRef]
9. Kim, I.-C. Atrial Fibrillation and Heart Failure with Preserved Ejection Fraction. *Heart Fail. Clin.* **2021**, *17*, 377–386. [CrossRef]
10. Pellicori, P.; Cleland, J.G.F.; Clark, A.L. Chronic Obstructive Pulmonary Disease and Heart Failure. *Heart Fail. Clin.* **2020**, *16*, 33–44. [CrossRef]
11. Ananthram, M.G.; Gottlieb, S.S. Renal Dysfunction and Heart Failure with Preserved Ejection Fraction. *Heart Fail. Clin.* **2021**, *17*, 357–367. [CrossRef]
12. Sugimoto, T. Acute Decompensated Heart Failure in Patients with Heart Failure with Preserved Ejection Fraction. *Heart Fail. Clin.* **2020**, *16*, 201–209. [CrossRef]
13. Fonarow, G.C.; Stough, W.G.; Abraham, W.T.; Albert, N.M.; Gheorghiade, M.; Greenberg, B.H.; O'Connor, C.M.; Sun, J.L.; Yancy, C.W.; Young, J.B. Characteristics, Treatments, and Outcomes of Patients With Preserved Systolic Function Hospitalized for Heart Failure. *J. Am. Coll. Cardiol.* **2007**, *50*, 768–777. [CrossRef]
14. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; Deswal, A.; Drazner, M.H.; Dunlay, S.M.; Evers, L.R.; et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* **2022**, *145*, e895–e1032. [CrossRef] [PubMed]
15. Mebazaa, A.; Yilmaz, M.B.; Levy, P.; Ponikowski, P.; Peacock, W.F.; Laribi, S.; Ristic, A.D.; Lambrinou, E.; Masip, J.; Riley, J.P.; et al. Recommendations on pre-hospital & early hospital management of acute heart failure: A consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergenc: Recommendations on pre-hospital & early hospital management of acute heart failure. *Eur. J. Heart Fail.* **2015**, *17*, 544–558. [CrossRef] [PubMed]
16. Masip, J.; Gayà, M.; Páez, J.; Betbesé, A.; Vecilla, F.; Manresa, R.; Ruíz, P. Pulsioximetría en el diagnóstico de insuficiencia cardiaca aguda. *Rev. Esp. Cardiol.* **2012**, *65*, 879–884. [CrossRef] [PubMed]
17. Ponikowski, P.; Voors, A.A.; Anker, S.D.; Bueno, H.; Cleland, J.G.F.; Coats, A.J.S.; Falk, V.; González-Juanatey, J.R.; Harjola, V.-P.; Jankowska, E.A.; et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **2016**, *37*, 2129–2200. [CrossRef] [PubMed]
18. Weng, C.-L. Meta-analysis: Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema. *Ann. Intern. Med.* **2010**, *152*, 590. [CrossRef] [PubMed]
19. Collet, J.-P.; Thiele, H.; Barbato, E.; Barthélémy, O.; Bauersachs, J.; Bhatt, D.L.; Dendale, P.; Dorobantu, M.; Edvardsen, T.; Folliguet, T.; et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Rev. Esp. Cardiol. Engl. Ed.* **2021**, *74*, 544. [CrossRef]
20. Ibanez, B.; James, S.; Agewall, S.; Antunes, M.J.; Bucciarelli-Ducci, C.; Bueno, H.; Caforio, A.L.P.; Crea, F.; Goudevenos, J.A.; Halvorsen, S.; et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur. Heart J.* **2018**, *39*, 119–177. [CrossRef]
21. Zeppenfeld, K.; Tfelt-Hansen, J.; de Riva, M.; Winkel, B.G.; Behr, E.R.; Blom, N.A.; Charron, P.; Corrado, D.; Dagres, N.; de Chillou, C.; et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur. Heart J.* **2022**, *43*, 3997–4126. [CrossRef]
22. Hindricks, G.; Potpara, T.; Dagres, N.; Arbelo, E.; Bax, J.J.; Blomström-Lundqvist, C.; Boriani, G.; Castella, M.; Dan, G.-A.; Dilaveris, P.E.; et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* **2021**, *42*, 373–498. [CrossRef]
23. Glikson, M.; Nielsen, J.C.; Kronborg, M.B.; Michowitz, Y.; Auricchio, A.; Barbash, I.M.; Barrabés, J.A.; Boriani, G.; Braunschweig, F.; Brignole, M.; et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur. Heart J.* **2021**, *42*, 3427–3520. [CrossRef] [PubMed]
24. Tschöpe, C.; Ammirati, E.; Bozkurt, B.; Caforio, A.L.P.; Cooper, L.T.; Felix, S.B.; Hare, J.M.; Heidecker, B.; Heymans, S.; Hübner, N.; et al. Myocarditis and inflammatory cardiomyopathy: Current evidence and future directions. *Nat. Rev. Cardiol.* **2021**, *18*, 169–193. [CrossRef] [PubMed]
25. Habib, G.; Lancellotti, P.; Antunes, M.J.; Bongiorni, M.G.; Casalta, J.-P.; Del Zotti, F.; Dulgheru, R.; El Khoury, G.; Erba, P.A.; Iung, B.; et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur. Heart J.* **2015**, *36*, 3075–3128. [CrossRef] [PubMed]

26. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adultThe Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur. Heart J.* **2014**, *35*, 2873–2926. [CrossRef]
27. Konstantinides, S.V.; Meyer, G.; Becattini, C.; Bueno, H.; Geersing, G.-J.; Harjola, V.-P.; Huisman, M.V.; Humbert, M.; Jennings, C.S.; Jiménez, D.; et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur. Heart J.* **2020**, *41*, 543–603. [CrossRef]
28. Williams, B.; Mancia, G.; Spiering, W.; Agabiti Rosei, E.; Azizi, M.; Burnier, M.; Clement, D.L.; Coca, A.; de Simone, G.; Dominiczak, A.; et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur. Heart J.* **2018**, *39*, 3021–3104. [CrossRef]
29. Jobs, A.; Simon, R.; de Waha, S.; Rogacev, K.; Katalinic, A.; Babaev, V.; Thiele, H. Pneumonia and inflammation in acute decompensated heart failure: A registry-based analysis of 1939 patients. *Eur. Heart J. Acute Cardiovasc. Care* **2018**, *7*, 362–370. [CrossRef]
30. Halpin, D.M.G.; Criner, G.J.; Papi, A.; Singh, D.; Anzueto, A.; Martinez, F.J.; Agusti, A.A.; Vogelmeier, C.F. Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **2021**, *203*, 24–36. [CrossRef]
31. Leung, A.M. Thyroid Emergencies. *J. Infus. Nurs.* **2016**, *39*, 281–286. [CrossRef]
32. Sirbu, O. Anemia in heart failure—From guidelines to controversies and challenges. *Anatol. J. Cardiol.* **2018**, *20*, 52. [CrossRef]
33. Rosano, G.; Jankowska, E.A.; Ray, R.; Metra, M.; Abdelhamid, M.; Adamopoulos, S.; Anker, S.D.; Bayes-Genis, A.; Belenkov, Y.; Ben Gal, T.; et al. COVID-19 vaccination in patients with heart failure: A position paper of the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **2021**, *23*, 1806–1818. [CrossRef] [PubMed]
34. Bartoletti, M.; Azap, O.; Barac, A.; Bussini, L.; Ergonul, O.; Krause, R.; Paño-Pardo, J.R.; Power, N.R.; Sibani, M.; Szabo, B.G.; et al. ESCMID COVID-19 living guidelines: Drug treatment and clinical management. *Clin. Microbiol. Infect.* **2022**, *28*, 222–238. [CrossRef] [PubMed]
35. Núñez, J.; de la Espriella, R.; Rossignol, P.; Voors, A.A.; Mullens, W.; Metra, M.; Chioncel, O.; Januzzi, J.L.; Mueller, C.; Richards, A.M.; et al. Congestion in heart failure: A circulating biomarker-based perspective. A review from the Biomarkers Working Group of the Heart Failure Association, European Society of Cardiology. *Eur. J. Heart Fail.* **2022**, *24*, 1751–1766. [CrossRef] [PubMed]
36. Salzano, A.; D'Assante, R.; Israr, M.Z.; Eltayeb, M.; D'Agostino, A.; Bernieh, D.; De Luca, M.; Rega, S.; Ranieri, B.; Mauro, C.; et al. Biomarkers in Heart Failure. *Heart Fail. Clin.* **2021**, *17*, 223–243. [CrossRef]
37. Mueller, C.; McDonald, K.; de Boer, R.A.; Maisel, A.; Cleland, J.G.F.; Kozhuharov, N.; Coats, A.J.S.; Metra, M.; Mebazaa, A.; Ruschitzka, F.; et al. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur. J. Heart Fail.* **2019**, *21*, 715–731. [CrossRef]
38. Hollenberg, S.M.; Warner Stevenson, L.; Ahmad, T.; Amin, V.J.; Bozkurt, B.; Butler, J.; Davis, L.L.; Drazner, M.H.; Kirkpatrick, J.N.; Peterson, P.N.; et al. 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized With Heart Failure. *J. Am. Coll. Cardiol.* **2019**, *74*, 1966–2011. [CrossRef]
39. Harjola, V.-P.; Mullens, W.; Banaszewski, M.; Bauersachs, J.; Brunner-La Rocca, H.-P.; Chioncel, O.; Collins, S.P.; Doehner, W.; Filippatos, G.S.; Flammer, A.J.; et al. Organ dysfunction, injury and failure in acute heart failure: From pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC): Organ dysfunction and failure in AHF. *Eur. J. Heart Fail.* **2017**, *19*, 821–836. [CrossRef]
40. Via, G.; Hussain, A.; Wells, M.; Reardon, R.; ElBarbary, M.; Noble, V.E.; Tsung, J.W.; Neskovic, A.N.; Price, S.; Oren-Grinberg, A.; et al. International Evidence-Based Recommendations for Focused Cardiac Ultrasound. *J. Am. Soc. Echocardiogr.* **2014**, *27*, 683.e1–683.e33. [CrossRef]
41. Mitchell, C.; Rahko, P.S.; Blauwet, L.A.; Canaday, B.; Finstuen, J.A.; Foster, M.C.; Horton, K.; Ogunyankin, K.O.; Palma, R.A.; Velazquez, E.J. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. *J. Am. Soc. Echocardiogr.* **2019**, *32*, 1–64. [CrossRef]
42. Gargani, L. Ultrasound of the Lungs. *Heart Fail. Clin.* **2019**, *15*, 297–303. [CrossRef]
43. Picano, E.; Scali, M.C.; Ciampi, Q.; Lichtenstein, D. Lung Ultrasound for the Cardiologist. *JACC Cardiovasc. Imaging* **2018**, *11*, 1692–1705. [CrossRef] [PubMed]
44. Lichtenstein, D.A.; Mezière, G.A. Relevance of Lung Ultrasound in the Diagnosis of Acute Respiratory Failure*: The BLUE Protocol. *Chest* **2008**, *134*, 117–125. [CrossRef]
45. Coiro, S.; Rossignol, P.; Ambrosio, G.; Carluccio, E.; Alunni, G.; Murrone, A.; Tritto, I.; Zannad, F.; Girerd, N. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure: Prognostic value of B-lines after discharge from HF hospitalisation. *Eur. J. Heart Fail.* **2015**, *17*, 1172–1181. [CrossRef] [PubMed]
46. Pellicori, P.; Platz, E.; Dauw, J.; Maaten, J.M.; Martens, P.; Pivetta, E.; Cleland, J.G.F.; McMurray, J.J.V.; Mullens, W.; Solomon, S.D.; et al. Ultrasound imaging of congestion in heart failure: Examinations beyond the heart. *Eur. J. Heart Fail.* **2021**, *23*, 703–712. [CrossRef]
47. Iida, N.; Seo, Y.; Sai, S.; Machino-Ohtsuka, T.; Yamamoto, M.; Ishizu, T.; Kawakami, Y.; Aonuma, K. Clinical Implications of Intrarenal Hemodynamic Evaluation by Doppler Ultrasonography in Heart Failure. *JACC Heart Fail.* **2016**, *4*, 674–682. [CrossRef] [PubMed]
48. Puchalski, M.D.; Lui, G.K.; Miller-Hance, W.C.; Brook, M.M.; Young, L.T.; Bhat, A.; Roberson, D.A.; Mercer-Rosa, L.; Miller, O.I.; Parra, D.A.; et al. Guidelines for Performing a Comprehensive Transesophageal Echocardiographic. *J. Am. Soc. Echocardiogr.* **2019**, *32*, 173–215. [CrossRef]

49. Suciadi, L.P.; William, Y.; Jorizal, P.; Tarigan, V.N.; Santoso, A.H.; Henrina, J.; Tedjasukmana, F.; Kristanti, N.M. Comparing Lung CT in COVID-19 Pneumonia and Acute Heart Failure: An Imaging Conundrum. *Cureus* **2021**, *13*, e15120. [CrossRef]
50. Bernheim, A.; Mei, X.; Huang, M.; Yang, Y.; Fayad, Z.A.; Zhang, N.; Diao, K.; Lin, B.; Zhu, X.; Li, K.; et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology* **2020**, *295*, 200463. [CrossRef] [PubMed]
51. Mangalat, D.; Kalogeropoulos, A.; Georgiopoulou, V.; Stillman, A.; Butler, J. Value of cardiac CT in patients with heart failure. *Curr. Cardiovasc. Imaging Rep.* **2009**, *2*, 410–417. [CrossRef]
52. Pontone, G.; Baggiano, A.; Conte, E.; Teruzzi, G.; Cosentino, N.; Campodonico, J.; Rabbat, M.G.; Assanelli, E.; Palmisano, A.; Esposito, A.; et al. "Quadruple Rule-Out" With Computed Tomography in a COVID-19 Patient With Equivocal Acute Coronary Syndrome Presentation. *JACC Cardiovasc. Imaging* **2020**, *13*, 1854–1856. [CrossRef]
53. Neumann, F-J.; Sousa-Uva, M.; Ahlsson, A.; Alfonso, F.; Banning, A.P.; Benedetto, U.; Byrne, R.A.; Collet, J.-P.; Falk, V.; Head, S.J.; et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur. Heart J.* **2019**, *40*, 87–165. [CrossRef] [PubMed]
54. Andreucci, M.; Solomon, R.; Tasanarong, A. Side Effects of Radiographic Contrast Media: Pathogenesis, Risk Factors, and Prevention. *BioMed Res. Int.* **2014**, *2014*, 741018. [CrossRef] [PubMed]
55. Felker, G.M.; Ellison, D.H.; Mullens, W.; Cox, Z.L.; Testani, J.M. Diuretic Therapy for Patients With Heart Failure. *J. Am. Coll. Cardiol.* **2020**, *75*, 1178–1195. [CrossRef] [PubMed]
56. Mullens, W.; Damman, K.; Harjola, V.-P.; Mebazaa, A.; Brunner-La Rocca, H.-P.; Martens, P.; Testani, J.M.; Tang, W.H.W.; Orso, F.; Rossignol, P.; et al. The use of diuretics in heart failure with congestion—A position statement from the Heart Failure Association of the European Society of Cardiology: Diuretics in heart failure. *Eur. J. Heart Fail.* **2019**, *21*, 137–155. [CrossRef]
57. Carlson, M.D.; Eckman, P.M. Review of Vasodilators in Acute Decompensated Heart Failure: The Old and the New. *J. Card. Fail.* **2013**, *19*, 478–493. [CrossRef]
58. Peacock, W.F.; Hollander, J.E.; Diercks, D.B.; Lopatin, M.; Fonarow, G.; Emerman, C.L. Morphine and outcomes in acute decompensated heart failure: An ADHERE analysis. *Emerg. Med. J.* **2008**, *25*, 205–209. [CrossRef]
59. Sethi, N.J.; Nielsen, E.E.; Safi, S.; Feinberg, J.; Gluud, C.; Jakobsen, J.C. Digoxin for atrial fibrillation and atrial flutter: A systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *PLoS ONE* **2018**, *13*, e0193924. [CrossRef]
60. Uretsky, B.F.; Young, J.B.; Shahidi, F.E.; Yellen, L.G.; Harrison, M.C.; Jolly, M.K. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: Results of the PROVED trial. *J. Am. Coll. Cardiol.* **1993**, *22*, 955–962. [CrossRef]
61. Tebbe, U.; Schellong, S.M.; Haas, S.; Gerlach, H.E.; Abletshauser, C.; Sieder, C.; Bramlage, P.; Riess, H. Certoparin versus unfractionated heparin to prevent venous thromboembolic events in patients hospitalized because of heart failure: A subgroup analysis of the randomized, controlled CERTIFY study. *Am. Heart J.* **2011**, *161*, 322–328. [CrossRef]
62. Francis, G.S.; Bartos, J.A.; Adatya, S. Inotropes. *J. Am. Coll. Cardiol.* **2014**, *63*, 2069–2078. [CrossRef]
63. Masarone, D.; Melillo, E.; Gravino, R.; Errigo, V.; Martucci, M.L.; Caiazzo, A.; Petraio, A.; Pölzl, G.; Pacileo, G. Inotropes in Patients with Advanced Heart Failure. *Heart Fail. Clin.* **2021**, *17*, 587–598. [CrossRef] [PubMed]
64. Mebazaa, A.; Parissis, J.; Porcher, R.; Gayat, E.; Nikolaou, M.; Boas, F.V.; Delgado, J.F.; Follath, F. Short-term survival by treatment among patients hospitalized with acute heart failure: The global ALARM-HF registry using propensity scoring methods. *Intensive Care Med.* **2011**, *37*, 290–301. [CrossRef] [PubMed]
65. Biegus, J.; Voors, A.A.; Collins, S.P.; Kosiborod, M.N.; Teerlink, J.R.; Angermann, C.E.; Tromp, J.; Ferreira, J.P.; Nassif, M.E.; Psotka, M.A.; et al. Impact of empagliflozin on decongestion in acute heart failure: The EMPULSE trial. *Eur. Heart J.* **2023**, *44*, 41–50. [CrossRef] [PubMed]
66. Voors, A.A.; Angermann, C.E.; Teerlink, J.R.; Collins, S.P.; Kosiborod, M.; Biegus, J.; Ferreira, J.P.; Nassif, M.E.; Psotka, M.A.; Tromp, J.; et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: A multinational randomized trial. *Nat. Med.* **2022**, *28*, 568–574. [CrossRef]
67. Mullens, W.; Dauw, J.; Martens, P.; Verbrugge, F.H.; Nijst, P.; Meekers, E.; Tartaglia, K.; Chenot, F.; Moubayed, S.; Dierckx, R.; et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. *N. Engl. J. Med.* **2022**, *387*, 1185–1195. [CrossRef]
68. Racioppi, M.F.; Burgos, J.I.; Morell, M.; Gonano, L.A.; Vila Petroff, M. Cellular Mechanisms Underlying the Low Cardiotoxicity of Istaroxime. *J. Am. Heart Assoc.* **2021**, *10*, e018833. [CrossRef]
69. Torre, E.; Arici, M.; Lodrini, A.M.; Ferrandi, M.; Barassi, P.; Hsu, S.-C.; Chang, G.-J.; Boz, E.; Sala, E.; Vagni, S.; et al. SERCA2a stimulation by istaroxime improves intracellular Ca2+ handling and diastolic dysfunction in a model of diabetic cardiomyopathy. *Cardiovasc. Res.* **2022**, *118*, 1020–1032. [CrossRef]
70. Carubelli, V.; Zhang, Y.; Metra, M.; Lombardi, C.; Felker, G.M.; Filippatos, G.; O'Connor, C.M.; Teerlink, J.R.; Simmons, P.; Segal, R.; et al. Treatment with 24 hour istaroxime infusion in patients hospitalised for acute heart failure: A randomised, placebo-controlled trial. *Eur. J. Heart Fail.* **2020**, *22*, 1684–1693. [CrossRef]
71. Metra, M.; Chioncel, O.; Cotter, G.; Davison, B.; Filippatos, G.; Mebazaa, A.; Novosadova, M.; Ponikowski, P.; Simmons, P.; Soffer, J.; et al. Safety and efficacy of istaroxime in patients with acute heart failure-related pre-cardiogenic shock—A multicentre, randomized, double-blind, placebo-controlled, parallel group study (SEISMIC). *Eur. J. Heart Fail.* **2022**, *24*, 1967–1977. [CrossRef] [PubMed]
72. Teerlink, J.R.; Davison, B.A.; Cotter, G.; Maggioni, A.P.; Sato, N.; Chioncel, O.; Ertl, G.; Felker, G.M.; Filippatos, G.; Greenberg, B.H.; et al. Effects of serelaxin in patients admitted for acute heart failure: A meta-analysis. *Eur. J. Heart Fail.* **2020**, *22*, 315–329. [CrossRef]
73. Teerlink, J.; Alburikan, K.; Metra, M.; Rodgers, J. Acute Decompensated Heart Failure Update. *Curr. Cardiol. Rev.* **2014**, *11*, 53–62. [CrossRef] [PubMed]

74. Gattis, W.A.; O'Connor, C.M. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure. *Am. J. Cardiol.* **2004**, *93*, 74–76. [CrossRef] [PubMed]
75. Masip, J.; Peacock, W.F.; Price, S.; Cullen, L.; Martin-Sanchez, F.J.; Seferovic, P.; Maisel, A.S.; Miro, O.; Filippatos, G.; Vrints, C.; et al. Indications and practical approach to non-invasive ventilation in acute heart failure. *Eur. Heart J.* **2018**, *39*, 17–25. [CrossRef] [PubMed]
76. Atkinson, T.M.; Ohman, E.M.; O'Neill, W.W.; Rab, T.; Cigarroa, J.E. A Practical Approach to Mechanical Circulatory Support in Patients Undergoing Percutaneous Coronary Intervention. *JACC Cardiovasc. Interv.* **2016**, *9*, 871–883. [CrossRef] [PubMed]
77. Schocken, D.D.; Benjamin, E.J.; Fonarow, G.C.; Krumholz, H.M.; Levy, D.; Mensah, G.A.; Narula, J.; Shor, E.S.; Young, J.B.; Hong, Y. Prevention of Heart Failure: A Scientific Statement From the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation* **2008**, *117*, 2544–2565. [CrossRef] [PubMed]
78. Wachter, R.; Senni, M.; Belohlavek, J.; Straburzynska-Migaj, E.; Witte, K.K.; Kobalava, Z.; Fonseca, C.; Goncalvesova, E.; Cavusoglu, Y.; Fernandez, A.; et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: Primary results of the randomised TRANSITION study. *Eur. J. Heart Fail.* **2019**, *21*, 998–1007. [CrossRef]
79. Velazquez, E.J.; Morrow, D.A.; DeVore, A.D.; Duffy, C.I.; Ambrosy, A.P.; McCague, K.; Rocha, R.; Braunwald, E. Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure. *N. Engl. J. Med.* **2019**, *380*, 539–548. [CrossRef]
80. Solomon, S.D.; McMurray, J.J.V.; Claggett, B.; de Boer, R.A.; DeMets, D.; Hernandez, A.F.; Inzucchi, S.E.; Kosiborod, M.N.; Lam, C.S.P.; Martinez, F.; et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N. Engl. J. Med.* **2022**, *387*, 1089–1098. [CrossRef]
81. Anker, S.D.; Butler, J.; Filippatos, G.; Ferreira, J.P.; Bocchi, E.; Böhm, M.; Brunner–La Rocca, H.-P.; Choi, D.-J.; Chopra, V.; Chuquiure-Valenzuela, E.; et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N. Engl. J. Med.* **2021**, *385*, 1451–1461. [CrossRef]
82. Dixit, N.M.; Ziaeian, B.; Fonarow, G.C. SGLT2 Inhibitors in Heart Failure. *Heart Fail. Clin.* **2022**, *18*, 587–596. [CrossRef]
83. Greene, S.J.; Fonarow, G.C.; Vaduganathan, M.; Khan, S.S.; Butler, J.; Gheorghiade, M. The vulnerable phase after hospitalization for heart failure. *Nat. Rev. Cardiol.* **2015**, *12*, 220–229. [CrossRef] [PubMed]
84. Bossone, E.; Mauro, C.; Maiellaro, A.; Raiola, E.; Cocchia, R.; Ranieri, B.; Sepe, C.; Capone, V.; Chianese, S.; Maramaldi, R.; et al. Cardiac teleconsulting in the time of COVID-19 global pandemic: The "Antonio Cardarelli" Hospital project. *Monaldi Arch. Chest Dis.* **2021**, *91*, 1779. [CrossRef] [PubMed]
85. Humbert, M.; Kovacs, G.; Hoeper, M.M.; Badagliacca, R.; Berger, R.M.F.; Brida, M.; Carlsen, J.; Coats, A.J.S.; Escribano-Subias, P.; Ferrari, P.; et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur. Heart J.* **2022**, *43*, 3618–3731. [CrossRef] [PubMed]
86. Chioncel, O.; Mebazaa, A.; Harjola, V.-P.; Coats, A.J.; Piepoli, M.F.; Crespo-Leiro, M.G.; Laroche, C.; Seferovic, P.M.; Anker, S.D.; Ferrari, R.; et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: The ESC Heart Failure Long-Term Registry: Outcome of patients hospitalized for acute heart failure. *Eur. J. Heart Fail.* **2017**, *19*, 1242–1254. [CrossRef]
87. O'Connor, C.M.; Miller, A.B.; Blair, J.E.A.; Konstam, M.A.; Wedge, P.; Bahit, M.C.; Carson, P.; Haass, M.; Hauptman, P.J.; Metra, M.; et al. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: Results from efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) program. *Am. Heart J.* **2010**, *159*, 841–849. [CrossRef]
88. Lund, L.H.; Edwards, L.B.; Dipchand, A.I.; Goldfarb, S.; Kucheryavaya, A.Y.; Levvey, B.J.; Meiser, B.; Rossano, J.W.; Yusen, R.D.; Stehlik, J. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Heart Transplantation Report—2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J. Heart Lung Transplant.* **2016**, *35*, 1158–1169. [CrossRef]
89. Piepoli, M.F.; Adamo, M.; Barison, A.; Bestetti, R.B.; Biegus, J.; Böhm, M.; Butler, J.; Carapetis, J.; Ceconi, C.; Chioncel, O.; et al. Preventing heart failure: A position paper of the Heart Failure Association in collaboration with the European Association of Preventive Cardiology. *Eur. J. Heart Fail.* **2022**, *24*, 143–168. [CrossRef]
90. Visseren, F.L.J.; Mach, F.; Smulders, Y.M.; Carballo, D.; Koskinas, K.C.; Bäck, M.; Benetos, A.; Biffi, A.; Boavida, J.-M.; Capodanno, D.; et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur. Heart J.* **2021**, *42*, 3227–3337. [CrossRef]
91. McDonagh, T.; Damy, T.; Doehner, W.; Lam, C.S.P.; Sindone, A.; van der Meer, P.; Cohen-Solal, A.; Kindermann, I.; Manito, N.; Pfister, O.; et al. Screening, diagnosis and treatment of iron deficiency in chronic heart failure: Putting the 2016 European Society of Cardiology heart failure guidelines into clinical practice. *Eur. J. Heart Fail.* **2018**, *20*, 1664–1672. [CrossRef]
92. Zhang, Y.; Coats, A.J.S.; Zheng, Z.; Adamo, M.; Ambrosio, G.; Anker, S.D.; Butler, J.; Xu, D.; Mao, J.; Khan, M.S.; et al. Management of heart failure patients with COVID-19: A joint position paper of the Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **2020**, *22*, 941–956. [CrossRef]

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Review

Efficacy of the New Inotropic Agent Istaroxime in Acute Heart Failure

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Abstract: Current therapeutic strategies for acute heart failure (AHF) are based on traditional inotropic agents that are often associated with untoward effects; therefore, finding new effective approaches with a safer profile is dramatically needed. Istaroxime is a novel compound, chemically unrelated to cardiac glycosides, that is currently being studied for the treatment of AHF. Its effects are essentially related to its inotropic and lusitropic positive properties exerted through a dual mechanism of action: activation of the sarcoplasmic reticulum Ca^{2+} ATPase isoform 2a (SERCA2a) and inhibition of the Na^+/K^+-ATPase (NKA) activity. The advantages of istaroxime over the available inotropic agents include its lower arrhythmogenic action combined with its capability of increasing systolic blood pressure without augmenting heart rate. However, it has a limited half-life (1 hour) and is associated with adverse effects including pain at the injection site and gastrointestinal issues. Herein, we describe the main mechanism of action of istaroxime and we present a systematic overview of both clinical and preclinical trials testing this drug, underlining the latest insights regarding its adoption in clinical practice for AHF.

Keywords: acute heart failure; calcium; inotropic agents; istaroxime; lusitropic agents; Na^+/K^+-ATPase; NKA; PST2744; SERCA2a

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1. Introduction

Heart failure (HF) is a clinical syndrome characterized by several symptoms, including dyspnea, ankle swelling, and fatigue, and signs, including peripheral edema, elevated jugular venous pressure, and pulmonary crackles. It is mainly due to structural and/or functional cardiac abnormalities causing a failure of the heart to pump enough to satisfy the metabolic requirements of the organism or generating an elevated intracardiac pressure to provide them [1].

With the aging of the population, HF incidence and prevalence are increasing worldwide [2,3]. HF incidence is about 6.0–7.9 per 1000 person-years in people >45 years old and about 21 per 1000 in people >65 years old [4,5]. The total percentage of people affected by HF is expected to rise from 2.4% in 2012 to 3.0% in 2030. HF prevalence is extremely variable with the lowest numbers in sub-Saharan Africa, but prevalence is projected to rise even in low- and middle-income countries as populations age and the burden of HF risk factors, such as elevated blood pressure, continues to increase [6,7]. HF has different classifications, based on the ejection fraction (EF), according to European Society of Cardiology (ESC)

and the American Heart Association (AHA) guidelines. The ESC guidelines define HF as follows: HF with preserved ejection fraction (HFpEF) is characterized by an EF $\geq$ 50%, HF with mildly reduced ejection fraction (HFmrEF) is characterized by an 40% $\leq$EF < 49%, and HF with reduced ejection fraction (HFrEF) is characterized by an EF < 40%. The AHA defines: HFpEF with EF $\geq$ 50%; HFmrEF with 41% $\leq$ EF $\leq$ 49%; HF with improved EF (HFimpEF) for patients who have EF improved from a lower level to an EF >40% at follow-up; and HFrEF has EF $\leq$ 40% [1,8,9].

Acute HF (AHF) is universally considered as a gradual or rapid onset of signs and symptoms of HF resulting in a need for urgent therapy or hospitalization [8,10–13]. AHF can lead to cardiogenic shock, characterized by a life-threatening low-cardiac-output state causing end-organ hypoperfusion and hypoxia [8,14–18]. AHF in-hospital mortality ranges from 4 to 13% and the mortality rate at 1-year post-discharge is 25–30%, with more than 45% of readmissions [19–23].

Current therapy for AHF is based on inotropic agents that are often associated with serious adverse effects. Indeed, catecholamines, inhibitors of Na^+/K^+-ATPase (NKA), phosphodiesterase-3 inhibitors, and calcium (Ca^{2+}) sensitizers, have been associated with tachycardia, ischemia, hypotension, and even with an excess of mortality, presumably related to arrhythmias in the short-term and the activation of signaling pathways that aggravate maladaptive remodeling of the failing heart in the long-term [24–26]. Therefore, there is an urgent need to identify new effective inotropic modulators with a safer profile.

Istaroxime is a relatively novel compound, a derivative of androstenedione, is chemically unrelated to cardiac glycosides, and possesses inotropic and lusitropic actions exerted through a dual mechanism: inhibition of the Na^+/K^+-ATPase (NKA) and activation of the sarcoplasmic reticulum calcium ATPase isoform 2a (SERCA2a) [27].

2. NKA: Na^+/K^+-ATPase Pump

NKA, first described in 1957 [28], is a ubiquitous enzyme that actively transports three Na^+-ions through the cell membrane outside the cytoplasm in exchange for two K^+ ions imported inside the cytoplasm [29,30]. NKA is a pump made up of two subunits: α and β. Subunit β does not seem to contain functional sites, but it is necessary to stabilize the α subunit and to guarantee the passage from the endoplasmic reticulum to the cell membrane [30]. The transport is accomplished by enzyme conformational changes between two states, E1 and E2. Using energy derived from ATP hydrolysis, NKA produces electrochemical gradients across the membrane necessary for electrical excitability as well as cellular uptake of ions, nutrients, and neurotransmitters. Electrochemical gradients across the membrane are necessary to regulate cell volume as well as intracellular pH [31].

NKA is a target of cardiotonic glycosides (CG), such as ouabain, digoxin, and digitoxin, which can bind NKA in the E2 state, inhibiting it [32–34]. This inhibition causes an increase in intracellular [Na^+]. Consequently, the Na^+/Ca^{2+} exchanger (NCX) ejects Na^+ in exchange for Ca^{2+}, thereby increasing the cytosolic concentration of Ca^{2+}, activating excitation-contraction coupling, ultimately enhancing myocardial contractility [24,32,35,36].

3. SERCA2a: Sarcoendoplasmic Reticular Adenosine Triphosphate-Driven Ca^{2+} Pump

The family of the sarco/endoplasmic reticulum Ca^{2+} ATPase gene, also known as SERCA, counts different isoforms. The SERCA2 gene is known to codify for SERCA2a-d, whereas SERCA2a encodes for a 997-aminoacid protein, a specific isoform located in the cardiac muscle, slow-twitch skeletal muscle, and smooth muscle cells [37]. In cardiomyocytes, SERCA2a is able to generate an influx of Ca^{2+} from the cytosol into the sarcoplasmic reticulum (SR) against the gradient.

This process guarantees the relaxation of cardiac muscle fibers and a sufficient Ca^{2+} storage in the SR that can be utilized to start a new contractile activity for the ensuing contraction.

SERCA2a is inhibited by phospholamban (PLB) and this regulation depends on its state of phosphorylation mediated by protein kinase A (PKA): in its de-phosphorylated form,

PLB inhibits SERCA2a, whereas in its phosphorylated form SERCA2a is released from such inhibition [38,39]. Stimulation of β-adrenergic receptors causes the phosphorylation of PLB by PKA, inactivating PLB and stimulating SERCA2a, improving myocardial contraction and relaxation (inotropic and lusitropic positive effects [40,41]). These processes explain why the dysregulation of SERCA2a and PLB interaction is intimately related to HF, along with the desensitization and downregulation of myocardial β-adrenergic receptors due to their chronic activation [42–51].

4. Ca^{2+} and SERCA2a Function in Cardiac Contractility

The contractile activity of the heart is due to the interaction of myosin and actin filaments, an interaction finely tuned by cytoplasmic Ca^{2+} levels [24]. Ca^{2+} fluxes in the myocardium are dysregulated in HF, producing a depression of myocardial contractility.

Ca^{2+} enters the cardiomyocyte during depolarization through L-type Ca^{2+} channels localized in the cell membrane in proximity of the SR. This Ca^{2+} influx induces a further release of Ca^{2+} from the SR in the cytoplasm, through intracellular Ca^{2+} release channels known as type 2 ryanodine receptors (RyR2) [52–54]. Thus, cytosolic [Ca^{2+}] rises up to a critical concentration that activates the contractile system of the myocyte. To complete the contraction and start the relaxation phase, Ca^{2+} previously released by the SR needs to be re-uptaken. This step is possible thanks to SERCA2a, which brings intracytoplasmic Ca^{2+} into the SR against a concentration gradient [55–57].

Dysregulation of Ca^{2+} fluxes could be caused by alterations of RyR2 and/or loss of function of SERCA2a. Altered RyR2 generates an inappropriate diastolic release of Ca^{2+} from the SR, known as a Ca^{2+} leak; this diastolic leak reduces Ca^{2+} content in the SR and consequently, Ca^{2+} is available for the subsequent myocardial contraction [58–61].

Even the loss of function of SERCA2a reduces the availability of Ca^{2+} for the next contraction because of the inability of this pump to reuptake a sufficient amount of the ion. Moreover, SERCA2a loss of function compromises ventricular relaxation and causes diastolic dysfunction, reducing the quantity and speed of Ca^{2+} re-uptake from the cytosol [58,62].

5. Istaroxime

Istaroxime *-(E,Z)-3-[(2-aminoethoxy)imino] androstane-6,17-dione hydrochloride-* is a compound derived from androstenedione, hence considered a cardiotonic steroid, developed for the treatment of AHF [63]. Its application is limited to acute intravenous therapy due to its short plasma half-life (less than 1 h) because of the extensive hepatic processing that generates a long-lasting metabolite named PST3093 (E,Z)-[(6-beta-hydroxy-17-oxoandrostan-3-ylidene)amino]oxyacetic acid [64]. Istaroxime is a first-in-class drug with both inotropic and lusitropic effects without vasodilator properties; on the contrary, one of its characteristics is to rise systolic blood pressure (SBP) [65]. As mentioned above, istaroxime properties are related to its dual mechanism of action: NKA inhibition and SERCA2a stimulation. Istaroxime inhibits NKA by binding its E2 state from the extracellular side [66] (Figure 1).

Its inhibition of NKA is similar to that of digoxin [67] and leads to an increased [Ca^{2+}], obtaining an inotropic effect. At nanomolar concentrations, istaroxime stimulates SERCA2a activity and Ca^{2+} uptake through a direct interaction with the SERCA2a/PLB complex, independent of cAMP/PKA and PLB phosphorylation [68] (Figure 2).

Henceforth, an influx of Ca^{2+} into the SR is generated during the diastolic phase, promoting myocardial relaxation, with a lusitropic effect [48,69,70] without inducing spontaneous Ca^{2+} efflux from the SR [68,71]. The increase in Ca^{2+} reserves through SERCA2a into the SR contributes to augment Ca^{2+} ions available for the following cardiac cycle, contributing to the inotropic effect of the compound [58]. The peculiar combination of istaroxime targets (Figure 3) seems to confer a better safety profile compared to digoxin; for instance, treatment with istaroxime has been associated with a lower risk of arrhythmias [72].

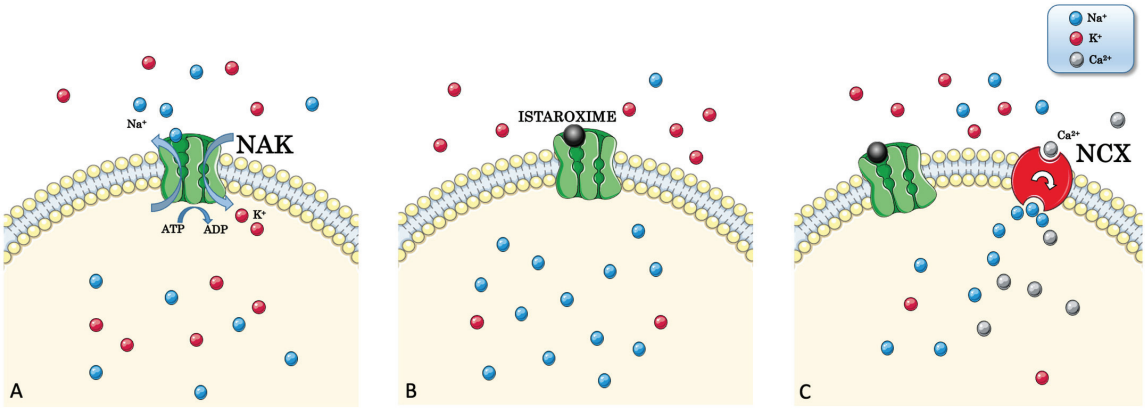

Figure 1. Istaroxime inhibits the Na^+/K^+-ATPase (NAK) pump. (**A**) NAK actively transports three Na^+-ions through the cell membrane outside the cytosol in exchange for two K^+ ions inside the cytoplasm. (**B**) Istaroxime inhibits NAK by binding it from the extracellular side with a consequent raise of $[Na^+]$ in the intracellular side. (**C**) Increased $[Na^+]$ leads to the activation of the Na^+/Ca^{2+} exchanger (NCX), which exchanges three Na^+ ions for one Ca^{2+} ion, eventually increasing intracytoplasmatic $[Ca^{2+}]$.

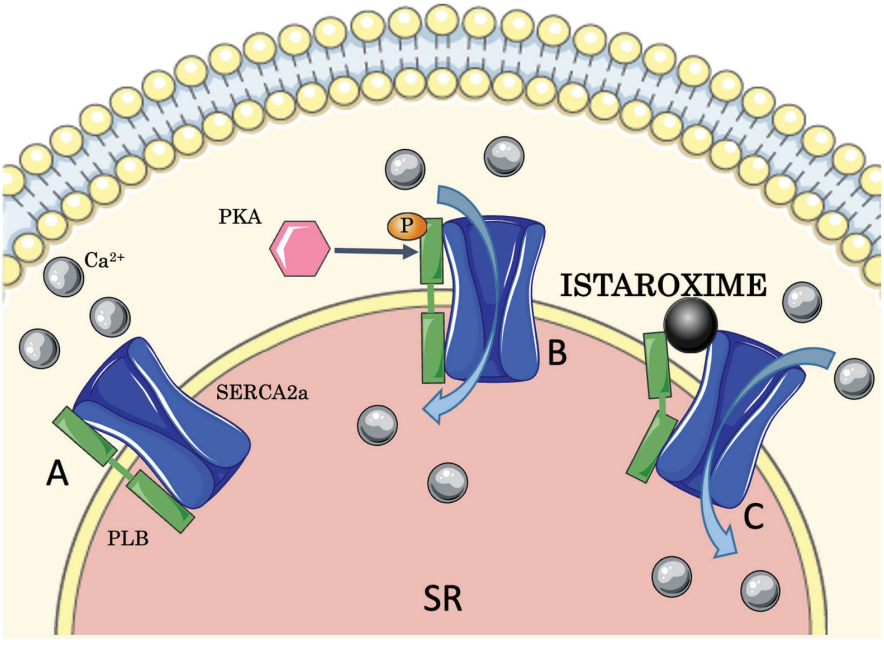

Figure 2. Istaroxime activates SERCA2a. (**A**) PLB, in its dephosphorylated form, inhibits SERCA2a. (**B**) PKA phosphorylates PLB releasing SERCA2a inhibition, thereby Ca^{2+} can be re-uptaken from the cytosol to the sarcoplasmic reticulum (SR). (**C**) Istaroxime activates SERCA2a with a direct interaction with the SERCA2a/PLB complex, independent of PLB phosphorylation. PKA: protein kinase A; PLB: phospholamban; SERCA2a: sarco/endoplasmic reticulum Ca^{2+} ATPase 2a.

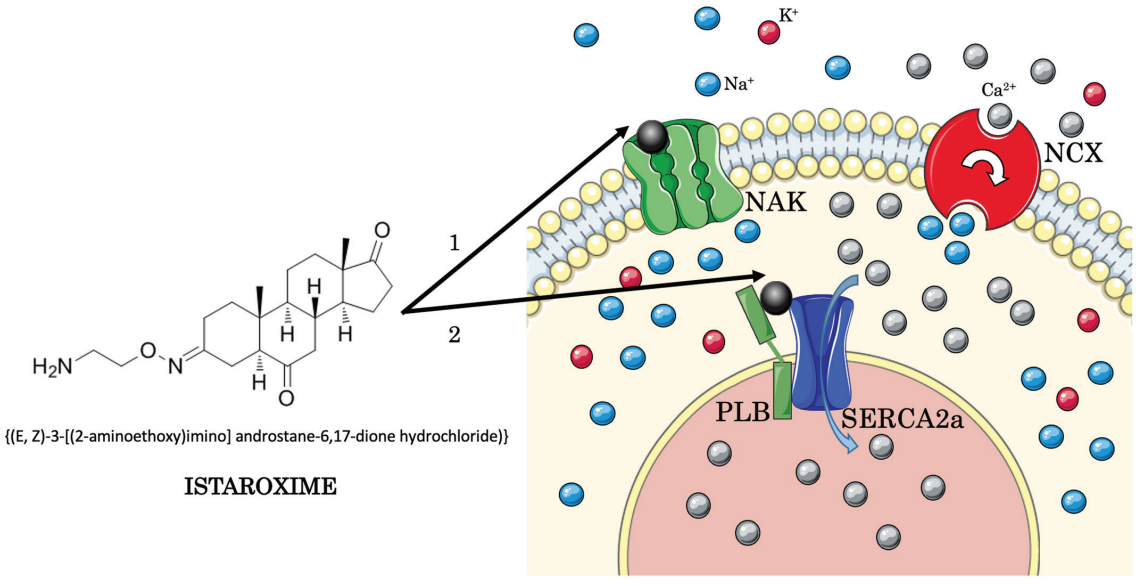

Figure 3. Dual mechanism of action of istaroxime. Istaroxime (structure depicted on the left) inhibits NAK by binding it from the extracellular side. NAK inhibitions increase [Na^+] inside the cytoplasm, activating NCX that expels three Na^+ -ions in one Ca^{2+} ion exchange, raising [Ca^{2+}] inside the cytoplasm, increasing myocardial contractility (inotropic effect); istaroxime activates SERCA with a direct interaction with the complex formed by SERCA2a and PLB, independent of PLB phosphorylation. SERCA2a stimulation triggers an influx of Ca^{2+} against the gradient from the cytosol to the SR, guaranteeing the relaxation of cardiac muscle fibers (lusitropic effect) and a sufficient amount of Ca^{2+} storage in the SR that can be utilized to start a new contractile activity for the ensuing contraction (empowerment of inotropic effect). NAK: Na^+/K^+-ATPase pump; NCX: Na^+/Ca^{2+} exchanger; PKA: protein kinase A; PLB: phospholamban; SERCA: sarco/endoplasmic reticulum Ca^{2+} ATPase.

Other Therapeutical Applications of Istaroxime

Istaroxime has also been shown to have anti-cancer actions due to its antiproliferative capacity exhibited in tumor cell lines [73]. Its use could be taken into account in prostate cancer [74]. Indeed, the use of androgen deprivation therapy in prostate cancer can be limited by the onset of cardiovascular events, including HF. In this sense, istaroxime could combine its antineoplastic and inotropic actions [75]; remarkably, the antiproliferative capacity of istaroxime is shared with other cardiotonic steroids, so these compounds are being proposed as new antitumoral drugs [34,76].

6. Preclinical Studies

In an animal model of diabetic cardiomyopathy, istaroxime was shown to improve diastolic dysfunction (DD) stimulating SERCA2a and reducing alterations in intracellular Ca^{2+} handling [77]; equally important, in animal models of acute decompensated HF it significantly improved hemodynamic and echocardiographic parameters [78]. Istaroxime was also compared to dobutamine in a preclinical study investigating chronic ischemic HF, showing to be an effective inotropic agent without positive chronotropic actions [79]. The chronic use of istaroxime was tested in a hamster model of progressive HF and was demonstrated to improve cardiac function and heart rate variability [80].

Comparing the electrophysiological effects of istaroxime and digoxin in guinea pig ventricular myocytes, istaroxime was shown to inhibit (−43%) the transient inward current (I_{TI}) induced by the transient flux of Ca^{2+} in the presence of a complete block of the

NKA pump; this effect was not evident with digoxin. Therefore, the therapeutic index of istaroxime may be accounted for by inhibition of I_{TI}, a current directly involved in digitalis-induced arrhythmias [81–84]. Furthermore, the toxicity of istaroxime was compared to ouabain in murine cells, showing that istaroxime can reach a significant inotropic effect without activating Ca^{2+}/calmodulin-dependent kinase II (CaMKII) whose over-stimulation could lead to cardiomyocyte death. Interestingly, at its inotropic concentration, istaroxime does not evoke a significant increase in diastolic local (Ca^{2+} sparks) or propagated (Ca^{2+} waves) SR Ca^{2+} release. In fact, istaroxime breaks arrhythmogenic Ca^{2+} waves into mini waves, which are less arrhythmogenic. This aspect corroborates the substantial safety compared to digitalis compounds. Remarkably, these results were evident even in PLB-knockout myocytes, suggesting that the safety of istaroxime is not merely related to its capacity to dissociate the SERCA/PLB interaction [85]. The main preclinical studies are summarized in Table 1.

Table 1. Summary of designs and conclusions of preclinical studies investigating istaroxime.

Clinical Condition	Animal Model	Endpoint	Conclusion
DCM	DCM STZ induced in rats	DD	Istaroxime improved DD stimulating SERCA2a and reducing alterations in intracellular Ca^{2+} handling.
ADHF	Canine model of HF produced by multiple sequential intracoronary embolizations with microspheres	LVEF (%); LVEDV (mL); LVESV (mL).	Istaroxime improved hemodynamic and echocardiographic parameters.
Chronic ischemic HF, comparing istaroxime to dobutamine	Canine model of HF produced by ligation of the left anterior descending coronary artery and intracoronary embolizations	LV function	Istaroxime was shown to be an effective inotropic agent without positive chronotropic actions.
Progressive HF	Hamster model of progressive HF	Heart/body weight ratio; max dP/dT; min dP/dT; LVSP; CFR	Istaroxime improved cardiac function and heart rate variability
Electrophysiological effects of istaroxime and digoxin	Guinea pig isolated ventricular myocytes	Effects on I_{TI}	Istaroxime inhibited I_{TI} (effect not evident with digoxin)
Cardiotoxic effects of equi-inotropic concentrations of istaroxime and ouabain	Rat isolated ventricular myocytes	Cell viability; Apoptosis; CaMKII activation.	Istaroxime had a significant inotropic effect, neither activating CaMKII nor promoting cardiomyocytes death (contrary to digoxin)

ADHF: acute decompensated heart failure; CaMKII: Ca^{2+}/calmodulin-dependent kinase II; CFR: coronary flow rate; DCM: diabetic cardiomyopathy; DD: diastolic dysfunction; dP/dT: derivative of LV pressure; LVEDV: LV end-diastolic volume; LVESV: LV end-systolic volume; HF: heart failure; I_{TI}: transient inward current of Ca^{2+}; LV: left ventricle; LVEF: LV ejection fraction; LVSP: LV systolic pressure; MI: myocardial infarction; STZ: streptozotocin.

7. Clinical Investigations

The first evaluation of istaroxime in humans was a phase I-II dose escalating study evaluating the safety and tolerability of istaroxime and its specific effects on ECG and hemodynamic parameters in patients with chronic HF with reduced systolic function [86]. Three cohorts of six patients were exposed to four sequentially increasing (0.005–5.0 μg/kg/min) 1-h infusions. In addition to safety, hemodynamic parameters were evaluated by an impedance cardiography, a digital Holter recorder, and by electrocardiography. Enhanced contractility was demonstrated with evidence of improvement of the acceleration index. Istaroxime improved the left cardiac work index, cardiac index, and pulse pressure at doses of ≥1 μg/kg/min, with evidence of activity at doses of 0.5 μg/kg/min. Istaroxime also

shortened the QTc. The compound was tolerated at doses of up to 3.33 μg/kg/min with evidence of gastrointestinal symptoms and injection site pain at higher doses [86].

The HORIZON-HF (Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent) trial is a randomized, double-blind, placebo-controlled, dose-escalation trial (*NCT00616161*) in which patients were randomized to istaroxime or placebo (ratio 3:1) [87]; patients treated with istaroxime were randomized to 0.5 μg/kg/min, 1.0 μg/kg/min, or 1.5 μg/kg/min doses [88]. The primary endpoint was the change in pulmonary capillary wedge pressure (PCWP) compared with placebo after a 6 h continuous infusion [87]. All the three doses of istaroxime lowered PCWP (mean ± SD: −3.2 ± 6.8 mm Hg, −3.3 ± 5.5 mm Hg, and −4.7 ± 5.9 mm Hg compared to 0.0 ± 3.6 mm Hg with placebo; $p < 0.05$ for all doses); furthermore, secondary end points (changes in cardiac index, right atrial pressure, SBP, diastolic blood pressure (DBP), heart rate (HR), and stroke work index) improved. In addition, changes in left ventricular (LV) end-diastolic and systolic volumes, LV ejection fraction (EF), diastolic function indexes, neurohormones, renal function, troponin, pharmacokinetics, and safety were evaluated. A significant decrease in HR ($p = 0.008$, 0.02, and 0.006, with 0.5, 1.0, and 1.5 μg/kg/min, respectively) and an increased SBP ($p = 0.005$ and $p < 0.001$, with 1 and 1.5 μg/kg/min, respectively) were observed in patients treated with istaroxime. The cardiac index increased during the 1.5 μg/kg/min infusion vs placebo ($p = 0.04$), but not at the end of the 6 h infusion. At the ultrasound examination (echocardiography), the LV end-systolic volume was reduced in the 1.0 μg/kg/min istaroxime group compared to placebo (−15.8 ± 22.7 mL vs. −2.1 ± 25.5 mL; $p = 0.03$), and LV end-diastolic volume was reduced in the 1.5 μg/kg/min group compared to placebo (−14.1 ± 26.3 mL vs. +3.9 ± 32.4 mL; $p = 0.02$). E-wave deceleration time increased in the 1.5 μg/kg/min group (+30 ± 51 ms vs. +3 ± 51 ms; $p = 0.04$). There were no changes in neurohormones, renal function, or troponin I. Adverse events were dose-related gastrointestinal symptoms and injection site pain. In particular, vomiting and nausea occurred and were dose-related. No deaths occurred during the treatment period [89].

A recent phase II, multicenter, randomized, double-blind, placebo-controlled, parallel group investigation trial (*NCT02617446*) revealed that a 24 h infusion of istaroxime at 0.5 or 1.0 μg/kg/min in patients with AHF and reduced LVEF markedly improves LV diastolic and systolic function without major cardiac adverse effects [90]. The primary endpoint was the E/e' ratio change from baseline to 24 h that was significantly reduced by both doses of istaroxime compared to placebo (cohort 1: −4.55 ± 4.75 istaroxime 0.5 μg/kg/min vs. −1.55 ± 4.11 placebo, $p = 0.029$; cohort 2: −3.16 ± 2.59 istaroxime 1.0 μg/kg/min vs. −1.08 ± 2.72 placebo, $p = 0.009$). Moreover, other parameters including E/A ratio, left atrial dimensions, and inferior cava diameter improved. Among others, there was a decrease in HR (from baseline by about 3 bpm with istaroxime 0.5 μg/kg/min and by 8–9 bpm with istaroxime 1.0 μg/kg/min with significant changes vs. placebo at 3 to 24 h in the high-dose group; 3 h: −10.61 ± 10.04, $p < 0.001$; 6 h: −8.89 ± 9.83, $p = 0.001$; 12 h: −9.49 ± 11.96, $p = 0.005$; 24 h: −9.61 ± 12.10, $p = 0.004$) and a significant increase in SBP with the 1.0 μg/kg/min dose (from baseline by about 3 mmHg with istaroxime 0.5 μg/kg/min and by 6–8 mmHg with istaroxime 1.0 μg/kg/min reaching statistical significance compared to placebo at 3 to 12 h in istaroxime 1.0 μg/kg/min group; 3 h: 7.63 ± 9.22, $p < 0.001$; 6 h: 8.08 ± 11.06, $p = 0.001$; 12 h: 9.00 ± 11.75, $p = 0.006$). These results occurred early after starting the infusion, with a significant difference already evident at 3h, most likely due to the pharmacokinetic profile of istaroxime, characterized by a rapid onset of action and a rapid washout after infusion termination. An increased estimated glomerular filtration rate (eGFR) was observed in the group treated with the high dose of the drug compared to placebo. Self-reported dyspnea and N-terminal pro-brain natriuretic peptide improved in all groups without significant differences between istaroxime and placebo [90].

Also in this trial, the most common adverse events were injection site reactions and gastrointestinal events, the latter primarily with istaroxime 1.0 μg/kg/min. A higher rate of

patients experiencing abdominal pain, nausea, and vomiting was observed with istaroxime 1.0 μg/kg/min. At this dose, a high rate of injection site reaction was observed in patients with short intravenous catheters, leading to a necessary change of the peripheral line or use of peripheral long line or a central line. One case of treatment discontinuation due to injection site problems occurred. Neither major cardiovascular events nor an increase in arrhythmias occurred. These observations confirm the findings of the HORIZON-HF trial and further extend the safety of istaroxime to 24 h compared to the HORIZON-HF trial, in which the compound was tested only for 6 h [88,90].

The clinical effects of istaroxime appear to be favorable for patients with AHF with low or borderline SBP, for which inotropes have been associated with major cardiovascular adverse events and possibly an increased risk of mortality [91,92]. The safety and efficacy of istaroxime in patients with AHF-related pre-cardiogenic shock (stage B of the Classification of the Society for Cardiovascular Angiography and Interventions, SCAI) was tested in the SEISMiC trial (*NCT04325035*), a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel group study [93]. The SEISMiC study was designed to compare the safety and efficacy of istaroxime with placebo in patients hospitalized for AHF-related SCAI stage B pre-cardiogenic shock with persistent hypotension (75 < SBP < 90 mmHg) but no clinical signs of hypoperfusion (both clinically and as evidenced by venous lactate levels <2.0 mml/L). Patients were randomized to continuous 24 h infusion of istaroxime 1.0 μg/kg/min or 1.5 μg/kg/min or placebo. The primary endpoint was the adjusted area under the curve (AUC) representing the change in SBP from baseline, start of study drug infusion, through 6 h. Secondary endpoints included: SBP AUC through 24 h, changes from baseline in SBP, in DBP, and mean arterial pressure (MAP) at 6 and 24 h; changes from baseline in HR, treatment failure score (treatment failure defined as death or need for circulatory, respiratory, or renal mechanical support or need for intravenous inotrope or vasopressor treatment); increase from baseline in SBP $\geq$ 5% and/or $\geq$ 10 mmHg; changes in quality of life (measured by the EuroQol 5 Dimension 5 Level, EQ-5D-5L), change from baseline to 24 h in echocardiography parameters. Secondary endpoints were also considered: changes in troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP), hospital readmission for HF and for any cause by day 30, in-hospital worsening HF to day 5, and length of in-hospital stay. Endpoints of safety were: incidence of adverse events, changes in vital signs, change in 12-lead ECG, incidence of supraventricular and ventricular arrhythmias, changes in laboratory parameters, renal function, cardiac troponin (I and T), and mortality through day 30. In the SEISMiC trial, istaroxime increased SBP and improved echocardiographic measures, including an increase in the cardiac index and a reduction in the left atrial and left ventricular dimensions. The adjusted mean 6 h AUC was 53.1 (standard error [SE] 6.88) mmHg × hour in the istaroxime group vs. 30.9 (SE 6.76) mmHg × hour in the placebo group (p = 0.017); an increase of 72% was observed. The adjusted mean 24 h SBP AUC was 291.2 (SE 27.5) mmHg × hour in istaroxime arm *vs* 208.7 (SE 27.0) mmHg × hour in placebo arm (p = 0.025), with an increase of 40%. The adjusted SBP increase at 6 h was 12.3 (SE 1.71) mmHg in the istaroxime group vs. 7.5 (SE 1.64) mmHg in the placebo group (p = 0.045). The corresponding adjusted changes in SBP at 24 h were 17.1 (SE 2.36) mmHg and 15.1 (SE 2.25) mmHg in the istaroxime group vs. placebo (p = 0.543). Increases were noted in DBP and MAP, as well. Of note, the concomitant increase in both the cardiac index (at 24 h: +0.16 ± 0.1 vs. −0.06 ± 0.1 L/min/m^2; p = 0.016) and SBP had not been observed with any previous intravenous drugs administered to patients with cardiogenic shock related to AHF. Additionally, other echocardiographic measures besides the cardiac index that demonstrated improvements at 24 h in the istaroxime group as compared to the placebo group were: left atrial area (−1.8 ± 0.5 vs. 0.0±0.5 cm^2; p = 0.008), LV end-systolic volume (−8.7 ± 4.2 vs. 3.3 ± 4.2 mL; p = 0.034), and LV end-diastolic volume (−6.5 ± 4.9 vs. 5.6 ± 4.8 mL; p = 0.061). Laboratory parameters did not suggest an effect mediated by istaroxime on end-organ damage. Istaroxime treatment was associated with more adverse events (such as nausea, vomiting, and pain at infusion site) than placebo, but it was not associated with arrhythmias or worsening of renal function. Among

gastrointestinal adverse events, nausea was the most frequent (28%), followed by vomiting (14%). Injection site pain occurred in 14% of the patients [93].

In order to reduce gastrointestinal adverse effects and injection site pain related to istaroxime, several attempts have been made, including the development of a liposomal formulation of the molecule, encapsulating istaroxime in a drug delivery system conveniently designed to be quickly destabilized in plasma in order to minimize alterations of the pharmacokinetic profile of istaroxime. *Poly ethylene glycol 660-hydroxystearate* (PEG-HS) was chosen as an excipient to modulate the bilayer fluidity and the release properties of the liposomes, obtaining an almost complete release in physiological conditions in less than 10 min [94]. It is important to emphasize that istaroxime use may also be considered in pediatric patients [95].

In summary, istaroxime was shown to be a potential new inotropic agent, safer than currently available treatments for AHF. Its ability to improve overall cardiac function in HF with reduced arrhythmogenic risk launched a new field of investigation in AHF treatment, which has most recently led to the development of other molecules with highly selective SERCA2a activation and longer half-time starting from istaroxime long-lasting metabolite PST3093 [64,96]. The main clinical trials investigating istaroxime are summarized in Table 2.

Table 2. Results of the main clinical trials on Istaroxime.

Clinical Trial	Primary Endpoint	Main Results
HORIZON-HF (*NCT00616161*)	Change in PCWP (mmHg)	Istaroxime: -3.2 ± 6.8, -3.3 ± 5.5, and -4.7 ± 5.9 vs. placebo: 0.0 ± 3.6; $p < 0.05$ (for all doses)
The Clinical Study of the Safety and Efficacy of Istaroxime in Treatment of ADHF (*NCT02617446*)	E/e' ratio change from baseline to 24 h	cohort 1: istaroxime 0.5 μg/kg/min: -4.55 ± 4.75 vs. placebo: -1.55 ± 4.11, $p = 0.029$; cohort 2: 59 istaroxime 1.0 μg/kg/min: $-3.16 \pm 2.$ vs. placebo: -1.08 ± 2.72, $p = 0.009$
SEISMiC (*NCT04325035*)	AUC (mmHg × hour; change in SBP from baseline through 6 h)	Istaroxime: 53.1 ± 6.88 vs. placebo: 30.9 ± 6.76, $p = 0.017$

ADHF: acute decompensated heart failure; AUC: area under curve; PCWP: pulmonary capillary wedge pressure; SBP: systolic blood pressure.

Intriguingly, therapies based on cardiac contractility modulation (CCM) take advantage of SERCA2a upregulation in patients with chronic HF. CCM therapy is based on an implantable device that delivers a non-excitatory high-voltage bipolar signal to the right ventricle (RV) synchronized on the absolute refractory period of the action potential [97,98]. It stimulates SERCA and RyR upregulation, PLB phosphorylation, and downregulation of NCX. Its modulation of Ca^{2+} flux and increase of re-uptake of the ion into SR results in the increase of myocardial contractility [97]. CCM has been approved by the FDA based on the results of several randomized clinical trials [99–104], which revealed that CCM improves the signs and symptoms of HF, particularly in patients with a LVEF between 25% and 45%, NYHA III symptoms despite guideline-directed medical therapy, and a sinus rhythm with normal QRS length. CCM therapy is associated with a reduction in hospitalization for HF compared with the rate of hospitalization the year before the device implantation [105,106]. Furthermore, a recent study revealed that CCM improves LVEF, global longitudinal strain, and myocardial mechano-energetic efficiency in patients with HFrEF [107]. These pieces of evidence suggest that the production of a metabolite derived from istaroxime, harboring a selective SERCA2a action and a longer half-time, could overcame the pharmacodynamic limitations of istaroxime itself, making it a new effective pharmacologic tool not only for AHF but for chronic HF as well [108].

8. Future Perspectives

HF is a clinical syndrome with considerable medical implications in our society, both in terms of morbidity and mortality [109–111]. Specifically, de novo AHF and acute decompensated HF (ADHF) represent life-threatening conditions [112–115]. According to

recent evidence examining its effectiveness and safety, it is reasonable to consider istaroxime as the first example of a new useful and safe category of drugs against HF in contraposition with traditional inotropic agents whose uses are often limited by several adverse effects. The development of new molecules derived from istaroxime with longer lifetime and less adverse effects is ongoing and current results are quite promising. Nonetheless, more investigations are warranted.

9. Conclusions

Istaroxime is a cardiotonic steroid currently under investigation for AHF treatment. Compared to the inotropic agents presently used for AHF in clinical practice with which it shares inotropic actions, it also has a lusitropic positive effect and a better safety profile. Its properties are exerted through a dual mechanism of action: activation of SERCA2a and inhibition of NKA activity. Istaroxime is being tested exclusively for acute intravenous therapy due to its half-time of only 1 h because of its rapid hepatic metabolism. Available data indicate that istaroxime has an overall safe profile with a reduced arrhythmogenic risk. Adverse events include gastrointestinal discomfort, most likely attributable to the systemic inhibition of NKA, and pain at the injection site. Hitherto, only studies on animal models and phase I and II trials are available; therefore, albeit there are promising perspectives for istaroxime as a new inotropic agent for AHF treatment, it is necessary to further expand the investigation on this compound to assess its effectiveness and long-term safety.

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References

1. Santulli, G.; Wang, X.; Mone, P. Updated ACC/AHA/HFSA 2022 guidelines on heart failure: What is new? From epidemiology to clinical management. *Eur. Heart J. Cardiovasc. Pharmacother.* **2022**, *8*, e23–e24. [CrossRef]
2. Savarese, G.; Becher, P.M.; Lund, L.H.; Seferovic, P.; Rosano, G.M.C.; Coats, A. Global burden of heart failure: A com-prehensive and updated review of epidemiology. *Cardiovasc. Res.* **2022**, *Online ahead of print*. [CrossRef] [PubMed]
3. Jenca, D.; Melenovsky, V.; Stehlik, J.; Stanek, V.; Kettner, J.; Kautzner, J.; Adamkova, V.; Wohlfahrt, P. Heart failure after myocardial infarction: Incidence and predictors. *ESC Heart Fail.* **2021**, *8*, 222–237. [CrossRef]
4. Huffman, M.D.; Berry, J.D.; Ning, H.; Dyer, A.R.; Garside, D.B.; Cai, X.; Daviglus, M.L.; Lloyd-Jones, D.M. Lifetime risk for heart failure among white and black Americans: Cardiovascular lifetime risk pooling project. *J. Am. Coll. Cardiol.* **2013**, *61*, 1510–1517. [CrossRef]
5. Emmons-Bell, S.; Johnson, C.; Roth, G. Prevalence, incidence and survival of heart failure: A systematic review. *Heart* **2022**, *108*, 1351–1360. [CrossRef]
6. Virani, S.S.; Alonso, A.; Aparicio, H.J.; Benjamin, E.J.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Cheng, S.; Delling, F.N.; et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. *Circulation* **2021**, *143*, e254–e743. [CrossRef]

7. Heidenreich, P.A.; Albert, N.M.; Allen, L.A.; Bluemke, D.A.; Butler, J.; Fonarow, G.C.; Ikonomidis, J.S.; Khavjou, O.; Konstam, M.A.; Maddox, T.M.; et al. Forecasting the impact of heart failure in the United States: A policy statement from the American Heart Association. *Circ. Heart Fail.* **2013**, *6*, 606–619. [CrossRef]
8. Masip, J.; Frank Peacok, W.; Arrigo, M.; Rossello, X.; Platz, E.; Cullen, L.; Mebazaa, A.; Price, S.; Bueno, H.; Di Somma, S.; et al. Acute Heart Failure in the 2021 ESC Heart Failure Guidelines: A scientific statement from the Association for Acute CardioVascular Care (ACVC) of the European Society of Cardiology. *Eur. Heart J. Acute Cardiovasc. Care* **2022**, *11*, 173–185. [CrossRef]
9. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; Deswal, A.; Drazner, M.H.; Dunlay, S.M.; Evers, L.R.; et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* **2022**, *145*, e895–e1032. [CrossRef]
10. Kurmani, S.; Squire, I. Acute Heart Failure: Definition, Classification and Epidemiology. *Curr. Heart Fail. Rep.* **2017**, *14*, 385–392. [CrossRef]
11. Nieminen, M.S.; Harjola, V.P. Definition and epidemiology of acute heart failure syndromes. *Am. J. Cardiol.* **2005**, *96*, 5G–10G. [CrossRef] [PubMed]
12. Gheorghiade, M.; Zannad, F.; Sopko, G.; Klein, L.; Pina, I.L.; Konstam, M.A.; Massie, B.M.; Roland, E.; Targum, S.; Collins, S.P.; et al. Acute heart failure syndromes: Current state and framework for future research. *Circulation* **2005**, *112*, 3958–3968. [CrossRef] [PubMed]
13. ter Maaten, J.M.; Valente, M.A.; Damman, K.; Hillege, H.L.; Navis, G.; Voors, A.A. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. *Nat. Rev. Cardiol.* **2015**, *12*, 184–192. [CrossRef] [PubMed]
14. Masip, J.; Peacock, W.F.; Price, S.; Cullen, L.; Martin-Sanchez, F.J.; Seferovic, P.; Maisel, A.S.; Miro, O.; Filippatos, G.; Vrints, C.; et al. Indications and practical approach to non-invasive ventilation in acute heart failure. *Eur. Heart J.* **2018**, *39*, 17–25. [CrossRef]
15. Schumann, J.; Henrich, E.C.; Strobl, H.; Prondzinsky, R.; Weiche, S.; Thiele, H.; Werdan, K.; Frantz, S.; Unverzagt, S. Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome. *Cochrane Database Syst. Rev.* **2018**, *1*, CD009669. [CrossRef] [PubMed]
16. Choi, M.S.; Shim, H.; Cho, Y.H. Mechanical Circulatory Support for Acute Heart Failure Complicated by Cardiogenic Shock. *Int. J. Heart Fail.* **2020**, *2*, 23–44. [CrossRef]
17. Mebazaa, A.; Tolppanen, H.; Mueller, C.; Lassus, J.; DiSomma, S.; Baksyte, G.; Cecconi, M.; Choi, D.J.; Cohen Solal, A.; Christ, M.; et al. Acute heart failure and cardiogenic shock: A multidisciplinary practical guidance. *Intensive Care Med.* **2016**, *42*, 147–163. [CrossRef]
18. Thiele, H.; Zeymer, U.; Neumann, F.J.; Ferenc, M.; Olbrich, H.G.; Hausleiter, J.; Richardt, G.; Hennersdorf, M.; Empen, K.; Fuernau, G.; et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N. Engl. J. Med.* **2012**, *367*, 1287–1296. [CrossRef]
19. Abraham, W.T.; Adams, K.F.; Fonarow, G.C.; Costanzo, M.R.; Berkowitz, R.L.; LeJemtel, T.H.; Cheng, M.L.; Wynne, J.; Committee, A.S.A.; ADHERE Scientific Advisory Committee and Investigators; et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: An analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J. Am. Coll. Cardiol.* **2005**, *46*, 57–64. [CrossRef]
20. Nieminen, M.S.; Brutsaert, D.; Dickstein, K.; Drexler, H.; Follath, F.; Harjola, V.P.; Hochadel, M.; Komajda, M.; Lassus, J.; Lopez-Sendon, J.L.; et al. EuroHeart Failure Survey II (EHFS II): A survey on hospitalized acute heart failure patients: Description of population. *Eur. Heart J.* **2006**, *27*, 2725–2736. [CrossRef]
21. Abraham, W.T.; Fonarow, G.C.; Albert, N.M.; Stough, W.G.; Gheorghiade, M.; Greenberg, B.H.; O'Connor, C.M.; Sun, J.L.; Yancy, C.W.; Young, J.B.; et al. Predictors of in-hospital mortality in patients hospitalized for heart failure: Insights from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *J. Am. Coll. Cardiol.* **2008**, *52*, 347–356. [CrossRef] [PubMed]
22. De Matteis, G.; Covino, M.; Burzo, M.L.; Della Polla, D.A.; Franceschi, F.; Mebazaa, A.; Gambassi, G. Clinical Characteristics and Predictors of In-Hospital Mortality among Older Patients with Acute Heart Failure. *J. Clin. Med.* **2022**, *11*, 439. [CrossRef] [PubMed]
23. Spinar, J.; Parenica, J.; Vitovec, J.; Widimsky, P.; Linhart, A.; Fedorco, M.; Malek, F.; Cihalik, C.; Spinarova, L.; Miklik, R.; et al. Baseline characteristics and hospital mortality in the Acute Heart Failure Database (AHEAD) Main registry. *Crit. Care* **2011**, *15*, R291. [CrossRef] [PubMed]
24. Kansakar, U.; Varzideh, F.; Jankauskas, S.S.; Gambardella, J.; Trimarco, B.; Santulli, G. Advances in the understanding of excitation-contraction coupling: The pulsing quest for drugs against heart failure and arrhythmias. *Eur. Heart J. Cardiovasc. Pharmacother.* **2021**, *7*, e91–e93. [CrossRef] [PubMed]
25. Psotka, M.A.; Gottlieb, S.S.; Francis, G.S.; Allen, L.A.; Teerlink, J.R.; Adams, K.F., Jr.; Rosano, G.M.C.; Lancellotti, P. Cardiac Calcitropes, Myotropes, and Mitotropes: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* **2019**, *73*, 2345–2353. [CrossRef]
26. van Diepen, S.; Katz, J.N.; Albert, N.M.; Henry, T.D.; Jacobs, A.K.; Kapur, N.K.; Kilic, A.; Menon, V.; Ohman, E.M.; Sweitzer, N.K.; et al. Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation* **2017**, *136*, e232–e268. [CrossRef]

27. Tavares, M.; Rezlan, E.; Vostroknoutova, I.; Khouadja, H.; Mebazaa, A. New pharmacologic therapies for acute heart failure. *Crit. Care Med.* **2008**, *36*, S112–S120. [CrossRef]
28. Skou, J.C. The influence of some cations on an adenosine triphosphatase from peripheral nerves. *Biochim. Biophys. Acta* **1957**, *23*, 394–401. [CrossRef]
29. Manoj, K.M.; Gideon, D.A.; Bazhin, N.M.; Tamagawa, H.; Nirusimhan, V.; Kavdia, M.; Jaeken, L. Na,K-ATPase: A murzyme facilitating thermodynamic equilibriums at the membrane-interface. *J. Cell Physiol.* **2022**, *in press*. [CrossRef]
30. Fedosova, N.U.; Habeck, M.; Nissen, P. Structure and Function of Na,K-ATPase-The Sodium-Potassium Pump. *Compr. Physiol.* **2021**, *12*, 2659–2679. [CrossRef]
31. Morth, J.P.; Pedersen, B.P.; Toustrup-Jensen, M.S.; Sorensen, T.L.; Petersen, J.; Andersen, J.P.; Vilsen, B.; Nissen, P. Crystal structure of the sodium-potassium pump. *Nature* **2007**, *450*, 1043–1049. [CrossRef]
32. Kanai, R.; Cornelius, F.; Ogawa, H.; Motoyama, K.; Vilsen, B.; Toyoshima, C. Binding of cardiotonic steroids to Na(+),K(+)-ATPase in the E2P state. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2020438118. [CrossRef]
33. Kravtsova, V.V.; Bouzinova, E.V.; Matchkov, V.V.; Krivoi, I.I. Skeletal Muscle Na,K-ATPase as a Target for Circulating Ouabain. *Int. J. Mol. Sci.* **2020**, *21*, 2875. [CrossRef]
34. Triana-Martinez, F.; Picallos-Rabina, P.; Da Silva-Alvarez, S.; Pietrocola, F.; Llanos, S.; Rodilla, V.; Soprano, E.; Pedrosa, P.; Ferreiros, A.; Barradas, M.; et al. Identification and characterization of Cardiac Glycosides as senolytic compounds. *Nat. Commun.* **2019**, *10*, 4731. [CrossRef]
35. Altamirano, J.; Li, Y.; DeSantiago, J.; Piacentino, V., 3rd; Houser, S.R.; Bers, D.M. The inotropic effect of cardioactive glycosides in ventricular myocytes requires Na+-Ca2+ exchanger function. *J. Physiol.* **2006**, *575*, 845–854. [CrossRef]
36. Shattock, M.J.; Ottolia, M.; Bers, D.M.; Blaustein, M.P.; Boguslavskyi, A.; Bossuyt, J.; Bridge, J.H.; Chen-Izu, Y.; Clancy, C.E.; Edwards, A.; et al. Na+/Ca2+ exchange and Na+/K+-ATPase in the heart. *J. Physiol.* **2015**, *593*, 1361–1382. [CrossRef]
37. Primeau, J.O.; Armanious, G.P.; Fisher, M.E.; Young, H.S. The SarcoEndoplasmic Reticulum Calcium ATPase. *Subcell. Biochem.* **2018**, *87*, 229–258. [CrossRef]
38. Tada, M.; Kadoma, M.; Fujii, J.; Kimura, Y.; Kijima, Y. Molecular structure and function of phospholamban: The regulatory protein of calcium pump in cardiac sarcoplasmic reticulum. *Adv. Exp. Med. Biol.* **1989**, *255*, 79–89. [CrossRef]
39. Gruber, S.J.; Haydon, S.; Thomas, D.D. Phospholamban mutants compete with wild type for SERCA binding in living cells. *Biochem. Biophys. Res. Commun.* **2012**, *420*, 236–240. [CrossRef]
40. Arnold, M.E.; Dostmann, W.R.; Martin, J.; Previs, M.J.; Palmer, B.; LeWinter, M.; Meyer, M. SERCA2a-phospholamban interaction monitored by an interposed circularly permutated green fluorescent protein. *Am. J. Physiol. Heart Circ. Physiol.* **2021**, *320*, H2188–H2200. [CrossRef]
41. Liu, Y.; Chen, J.; Fontes, S.K.; Bautista, E.N.; Cheng, Z. Physiological and pathological roles of protein kinase A in the heart. *Cardiovasc. Res.* **2022**, *118*, 386–398. [CrossRef] [PubMed]
42. Izzo, R.; Cipolletta, E.; Ciccarelli, M.; Campanile, A.; Santulli, G.; Palumbo, G.; Vasta, A.; Formisano, S.; Trimarco, B.; Iaccarino, G. Enhanced GRK2 expression and desensitization of betaAR vasodilatation in hypertensive patients. *Clin. Transl. Sci.* **2008**, *1*, 215–220. [CrossRef] [PubMed]
43. Santulli, G.; Campanile, A.; Spinelli, L.; Assante di Panzillo, E.; Ciccarelli, M.; Trimarco, B.; Iaccarino, G. G protein-coupled receptor kinase 2 in patients with acute myocardial infarction. *Am. J. Cardiol.* **2011**, *107*, 1125–1130. [CrossRef]
44. Sorriento, D.; Ciccarelli, M.; Santulli, G.; Illario, M.; Trimarco, B.; Iaccarino, G. Trafficking GRK2: Cellular and Metabolic consequences of GRK2 subcellular localization. *Transl. Med. UniSa* **2014**, *10*, 3–7.
45. Sorriento, D.; Santulli, G.; Franco, A.; Cipolletta, E.; Napolitano, L.; Gambardella, J.; Gomez-Monterrey, I.; Campiglia, P.; Trimarco, B.; Iaccarino, G.; et al. Integrating GRK2 and NFkappaB in the Pathophysiology of Cardiac Hypertrophy. *J. Cardiovasc. Transl. Res.* **2015**, *8*, 493–502. [CrossRef]
46. Selby, D.E.; Palmer, B.M.; LeWinter, M.M.; Meyer, M. Tachycardia-induced diastolic dysfunction and resting tone in myocardium from patients with a normal ejection fraction. *J. Am. Coll. Cardiol.* **2011**, *58*, 147–154. [CrossRef] [PubMed]
47. Dhalla, N.S.; Panagia, V.; Singal, P.K.; Makino, N.; Dixon, I.M.; Eyolfson, D.A. Alterations in heart membrane calcium transport during the development of ischemia-reperfusion injury. *J. Mol. Cell. Cardiol.* **1988**, *20* (Suppl. S2), 3–13. [CrossRef] [PubMed]
48. Gambardella, J.; Wang, X.J.; Ferrara, J.; Morelli, M.B.; Santulli, G. Cardiac BIN1 Replacement Therapy Ameliorates Inotropy and Lusitropy in Heart Failure by Regulating Calcium Handling. *JACC Basic Transl. Sci.* **2020**, *5*, 579–581. [CrossRef]
49. Santulli, G.; Iaccarino, G. Adrenergic signaling in heart failure and cardiovascular aging. *Maturitas* **2016**, *93*, 65–72. [CrossRef] [PubMed]
50. Ciccarelli, M.; Santulli, G.; Pascale, V.; Trimarco, B.; Iaccarino, G. Adrenergic receptors and metabolism: Role in development of cardiovascular disease. *Front. Physiol.* **2013**, *4*, 265. [CrossRef] [PubMed]
51. Santulli, G. Adrenal signaling in heart failure: Something more than a distant ship's smoke on the horizon. *Hypertension* **2014**, *63*, 215–216. [CrossRef] [PubMed]
52. Gambardella, J.; Jankauskas, S.S.; D'Ascia, S.L.; Sardu, C.; Matarese, A.; Minicucci, F.; Mone, P.; Santulli, G. Glycation of ryanodine receptor in circulating lymphocytes predicts the response to cardiac resynchronization therapy. *J. Heart Lung Transplant.* **2022**, *41*, 438–441. [CrossRef] [PubMed]

53. Jin, X.; Amoni, M.; Gilbert, G.; Dries, E.; Donate Puertas, R.; Tomar, A.; Nagaraju, C.K.; Pradhan, A.; Yule, D.I.; Martens, T.; et al. InsP(3)R-RyR Ca(2+) channel crosstalk facilitates arrhythmias in the failing human ventricle. *Basic Res. Cardiol.* **2022**, *117*, 60. [CrossRef] [PubMed]
54. Santulli, G.; Lewis, D.; des Georges, A.; Marks, A.R.; Frank, J. Ryanodine Receptor Structure and Function in Health and Disease. *Subcell. Biochem.* **2018**, *87*, 329–352. [CrossRef]
55. Braunwald, E. Heart failure. *JACC Heart Fail.* **2013**, *1*, 1–20. [CrossRef]
56. Maning, J.; Desimine, V.L.; Pollard, C.M.; Ghandour, J.; Lymperopoulos, A. Carvedilol Selectively Stimulates betaArrestin2-Dependent SERCA2a Activity in Cardiomyocytes to Augment Contractility. *Int. J. Mol. Sci.* **2022**, *23*, 11315. [CrossRef]
57. Chung, Y.J.; Luo, A.; Park, K.C.; Loonat, A.A.; Lakhal-Littleton, S.; Robbins, P.A.; Swietach, P. Iron-deficiency anemia reduces cardiac contraction by downregulating RyR2 channels and suppressing SERCA pump activity. *JCI Insight* **2019**, *4*, e125618. [CrossRef]
58. Gambardella, J.; Trimarco, B.; Iaccarino, G.; Santulli, G. New Insights in Cardiac Calcium Handling and Excitation-Contraction Coupling. *Adv. Exp. Med. Biol.* **2018**, *1067*, 373–385. [CrossRef]
59. Kushnir, A.; Santulli, G.; Reiken, S.R.; Coromilas, E.; Godfrey, S.J.; Brunjes, D.L.; Colombo, P.C.; Yuzefpolskaya, M.; Sokol, S.I.; Kitsis, R.N.; et al. Ryanodine Receptor Calcium Leak in Circulating B-Lymphocytes as a Biomarker in Heart Failure. *Circulation* **2018**, *138*, 1144–1154. [CrossRef]
60. Santulli, G.; Nakashima, R.; Yuan, Q.; Marks, A.R. Intracellular calcium release channels: An update. *J. Physiol.* **2017**, *595*, 3041–3051. [CrossRef]
61. Sardu, C.; Santulli, G.; Guerra, G.; Trotta, M.C.; Santamaria, M.; Sacra, C.; Testa, N.; Ducceschi, V.; Gatta, G.; Amico, M.; et al. Modulation of SERCA in Patients with Persistent Atrial Fibrillation Treated by Epicardial Thoracoscopic Ablation: The CAMAF Study. *J. Clin. Med.* **2020**, *9*, 544. [CrossRef]
62. Hoydal, M.A.; Kirkeby-Garstad, I.; Karevold, A.; Wiseth, R.; Haaverstad, R.; Wahba, A.; Stolen, T.L.; Contu, R.; Condorelli, G.; Ellingsen, O.; et al. Human cardiomyocyte calcium handling and transverse tubules in mid-stage of post-myocardial-infarction heart failure. *ESC Heart Fail.* **2018**, *5*, 332–342. [CrossRef]
63. Rocchetti, M.; Alemanni, M.; Mostacciuolo, G.; Barassi, P.; Altomare, C.; Chisci, R.; Micheletti, R.; Ferrari, P.; Zaza, A. Modulation of sarcoplasmic reticulum function by PST2744 [istaroxime; (E,Z)-3-((2-aminoethoxy)imino) androstane-6,17-dione hydrochloride)] in a pressure-overload heart failure model. *J. Pharmacol. Exp. Ther.* **2008**, *326*, 957–965. [CrossRef] [PubMed]
64. Arici, M.; Ferrandi, M.; Barassi, P.; Hsu, S.C.; Torre, E.; Luraghi, A.; Ronchi, C.; Chang, G.J.; Peri, F.; Ferrari, P.; et al. Istaroxime metabolite PST3093 selectively stimulates SERCA2a and reverses disease-induced changes in cardiac function. *J. Pharmacol. Exp. Ther.* **2022**, *in press*. [CrossRef] [PubMed]
65. Khan, H.; Metra, M.; Blair, J.E.; Vogel, M.; Harinstein, M.E.; Filippatos, G.S.; Sabbah, H.N.; Porchet, H.; Valentini, G.; Gheorghiade, M. Istaroxime, a first in class new chemical entity exhibiting SERCA-2 activation and Na-K-ATPase inhibition: A new promising treatment for acute heart failure syndromes? *Heart Fail. Rev.* **2009**, *14*, 277–287. [CrossRef] [PubMed]
66. Cornelius, F.; Mahmmoud, Y.A.; Toyoshima, C. Metal fluoride complexes of Na,K-ATPase: Characterization of fluoride-stabilized phosphoenzyme analogues and their interaction with cardiotonic steroids. *J. Biol. Chem.* **2011**, *286*, 29882–29892. [CrossRef] [PubMed]
67. Micheletti, R.; Mattera, G.G.; Rocchetti, M.; Schiavone, A.; Loi, M.F.; Zaza, A.; Gagnol, R.J.; De Munari, S.; Melloni, P.; Carminati, P.; et al. Pharmacological profile of the novel inotropic agent (E,Z)-3-((2-aminoethoxy)imino)androstane-6,17-dione hydrochloride (PST2744). *J. Pharmacol. Exp. Ther.* **2002**, *303*, 592–600. [CrossRef]
68. Ferrandi, M.; Barassi, P.; Tadini-Buoninsegni, F.; Bartolommei, G.; Molinari, I.; Tripodi, M.G.; Reina, C.; Moncelli, M.R.; Bianchi, G.; Ferrari, P. Istaroxime stimulates SERCA2a and accelerates calcium cycling in heart failure by relieving phospholamban inhibition. *Br. J. Pharmacol.* **2013**, *169*, 1849–1861. [CrossRef] [PubMed]
69. Bossu, A.; Kostense, A.; Beekman, H.D.M.; Houtman, M.J.C.; van der Heyden, M.A.G.; Vos, M.A. Istaroxime, a positive inotropic agent devoid of proarrhythmic properties in sensitive chronic atrioventricular block dogs. *Pharmacol. Res.* **2018**, *133*, 132–140. [CrossRef] [PubMed]
70. Schwinger, R.H.; Brixius, K.; Bavendiek, U.; Hoischen, S.; Muller-Ehmsen, J.; Bolck, B.; Erdmann, E. Effect of cyclopiazonic acid on the force-frequency relationship in human nonfailing myocardium. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 286–292. [PubMed]
71. Abrol, N.; de Tombe, P.P.; Robia, S.L. Acute inotropic and lusitropic effects of cardiomyopathic R9C mutation of phospholamban. *J. Biol. Chem.* **2015**, *290*, 7130–7140. [CrossRef] [PubMed]
72. Alemanni, M.; Rocchetti, M.; Re, D.; Zaza, A. Role and mechanism of subcellular Ca^{2+} distribution in the action of two inotropic agents with different toxicity. *J. Mol. Cell. Cardiol.* **2011**, *50*, 910–918. [CrossRef] [PubMed]
73. Alevizopoulos, K.; Dimas, K.; Papadopoulou, N.; Schmidt, E.M.; Tsapara, A.; Alkahtani, S.; Honisch, S.; Prousis, K.C.; Alarifi, S.; Calogeropoulou, T.; et al. Functional characterization and anti-cancer action of the clinical phase II cardiac Na^+/K^+ ATPase inhibitor istaroxime: In vitro and in vivo properties and cross talk with the membrane androgen receptor. *Oncotarget* **2016**, *7*, 24415–24428. [CrossRef] [PubMed]
74. Stagno, M.J.; Zacharopoulou, N.; Bochem, J.; Tsapara, A.; Pelzl, L.; Al-Maghout, T.; Kallergi, G.; Alkahtani, S.; Alevizopoulos, K.; Dimas, K.; et al. Istaroxime Inhibits Motility and Down-Regulates Orai1 Expression, SOCE and FAK Phosphorylation in Prostate Cancer Cells. *Cell. Physiol. Biochem.* **2017**, *42*, 1366–1376. [CrossRef]

75. Wallner, M.; Khafaga, M.; Kolesnik, E.; Vafiadis, A.; Schwantzer, G.; Eaton, D.M.; Curcic, P.; Kostenberger, M.; Knez, I.; Rainer, P.P.; et al. Istaroxime, a potential anticancer drug in prostate cancer, exerts beneficial functional effects in healthy and diseased human myocardium. *Oncotarget* **2017**, *8*, 49264–49274. [CrossRef]
76. Mijatovic, T.; Van Quaquebeke, E.; Delest, B.; Debeir, O.; Darro, F.; Kiss, R. Cardiotonic steroids on the road to anti-cancer therapy. *Biochim. Biophys. Acta* **2007**, *1776*, 32–57. [CrossRef]
77. Torre, E.; Arici, M.; Lodrini, A.M.; Ferrandi, M.; Barassi, P.; Hsu, S.C.; Chang, G.J.; Boz, E.; Sala, E.; Vagni, S.; et al. SERCA2a stimulation by istaroxime improves intracellular Ca2+ handling and diastolic dysfunction in a model of diabetic cardiomyopathy. *Cardiovasc. Res.* **2022**, *118*, 1020–1032. [CrossRef]
78. Sabbah, H.N.; Imai, M.; Cowart, D.; Amato, A.; Carminati, P.; Gheorghiade, M. Hemodynamic properties of a new-generation positive luso-inotropic agent for the acute treatment of advanced heart failure. *Am. J. Cardiol.* **2007**, *99*, 41A–46A. [CrossRef]
79. Adamson, P.B.; Vanoli, E.; Mattera, G.G.; Germany, R.; Gagnol, J.P.; Carminati, P.; Schwartz, P.J. Hemodynamic effects of a new inotropic compound, PST-2744, in dogs with chronic ischemic heart failure. *J. Cardiovasc. Pharmacol.* **2003**, *42*, 169–173. [CrossRef]
80. Lo Giudice, P.; Mattera, G.G.; Gagnol, J.P.; Borsini, F. Chronic istaroxime improves cardiac function and heart rate variability in cardiomyopathic hamsters. *Cardiovasc. Drugs Ther.* **2011**, *25*, 133–138. [CrossRef]
81. Rocchetti, M.; Besana, A.; Mostacciuolo, G.; Ferrari, P.; Micheletti, R.; Zaza, A. Diverse toxicity associated with cardiac Na+/K+ pump inhibition: Evaluation of electrophysiological mechanisms. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 765–771. [CrossRef] [PubMed]
82. Tseng, G.N.; Wit, A.L. Characteristics of a transient inward current that causes delayed afterdepolarizations in atrial cells of the canine coronary sinus. *J. Mol. Cell. Cardiol.* **1987**, *19*, 1105–1119. [CrossRef] [PubMed]
83. Hancox, J.C.; Levi, A.J. Actions of the digitalis analogue strophanthidin on action potentials and L-type calcium current in single cells isolated from the rabbit atrioventricular node. *Br. J. Pharmacol.* **1996**, *118*, 1447–1454. [CrossRef] [PubMed]
84. Holmes, M.; Hurley, M.E.; Sheard, T.M.D.; Benson, A.P.; Jayasinghe, I.; Colman, M.A. Increased SERCA2a sub-cellular heterogeneity in right-ventricular heart failure inhibits excitation-contraction coupling and modulates arrhythmogenic dynamics. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **2022**, *377*, 20210317. [CrossRef]
85. Racioppi, M.F.; Burgos, J.I.; Morell, M.; Gonano, L.A.; Vila Petroff, M. Cellular Mechanisms Underlying the Low Cardiotoxicity of Istaroxime. *J. Am. Heart Assoc.* **2021**, *10*, e018833. [CrossRef]
86. Ghali, J.K.; Smith, W.B.; Torre-Amione, G.; Haynos, W.; Rayburn, B.K.; Amato, A.; Zhang, D.; Cowart, D.; Valentini, G.; Carminati, P.; et al. A phase 1-2 dose-escalating study evaluating the safety and tolerability of istaroxime and specific effects on electrocardiographic and hemodynamic parameters in patients with chronic heart failure with reduced systolic function. *Am. J. Cardiol.* **2007**, *99*, S47–S56. [CrossRef]
87. Blair, J.E.; Macarie, C.; Ruzyllo, W.; Bacchieri, A.; Valentini, G.; Bianchetti, M.; Pang, P.S.; Harinstein, M.E.; Sabbah, H.N.; Filippatos, G.S.; et al. Rationale and design of the hemodynamic, echocardiographic and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: A randomized controlled trial in patients hospitalized with heart failure (HORIZON-HF) trial. *Am. J. Ther.* **2008**, *15*, 231–240. [CrossRef]
88. Shah, S.J.; Blair, J.E.; Filippatos, G.S.; Macarie, C.; Ruzyllo, W.; Korewicki, J.; Bubenek-Turconi, S.I.; Ceracchi, M.; Bianchetti, M.; Carminati, P.; et al. Effects of istaroxime on diastolic stiffness in acute heart failure syndromes: Results from the Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: A Randomized Controlled Trial in Patients Hospitalized with Heart Failure (HORIZON-HF) trial. *Am. Heart J.* **2009**, *157*, 1035–1041. [CrossRef]
89. Gheorghiade, M.; Blair, J.E.; Filippatos, G.S.; Macarie, C.; Ruzyllo, W.; Korewicki, J.; Bubenek-Turconi, S.I.; Ceracchi, M.; Bianchetti, M.; Carminati, P.; et al. Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: A randomized controlled trial in patients hospitalized with heart failure. *J. Am. Coll. Cardiol.* **2008**, *51*, 2276–2285. [CrossRef]
90. Carubelli, V.; Zhang, Y.; Metra, M.; Lombardi, C.; Felker, G.M.; Filippatos, G.; O'Connor, C.M.; Teerlink, J.R.; Simmons, P.; Segal, R.; et al. Treatment with 24 hour istaroxime infusion in patients hospitalised for acute heart failure: A randomised, placebo-controlled trial. *Eur. J. Heart Fail.* **2020**, *22*, 1684–1693. [CrossRef]
91. Thomas, S.S.; Nohria, A. Hemodynamic classifications of acute heart failure and their clinical application:—An update. *Circ. J.* **2012**, *76*, 278–286. [CrossRef] [PubMed]
92. Weatherley, B.D.; Milo-Cotter, O.; Felker, G.M.; Uriel, N.; Kaluski, E.; Vered, Z.; O'Connor, C.M.; Adams, K.F.; Cotter, G. Early worsening heart failure in patients admitted with acute heart failure—A new outcome measure associated with long-term prognosis? *Fundam. Clin. Pharmacol.* **2009**, *23*, 633–639. [CrossRef]
93. Metra, M.; Chioncel, O.; Cotter, G.; Davison, B.; Filippatos, G.; Mebazaa, A.; Novosadova, M.; Ponikowski, P.; Simmons, P.; Soffer, J.; et al. Safety and efficacy of istaroxime in patients with acute heart failure-related pre-cardiogenic shock—A multicentre, randomized, double-blind, placebo-controlled, parallel group study (SEISMiC). *Eur. J. Heart Fail.* **2022**, *24*, 1967–1977. [CrossRef] [PubMed]
94. Luciani, P.; Fevre, M.; Leroux, J.C. Development and physico-chemical characterization of a liposomal formulation of istaroxime. *Eur. J. Pharm. Biopharm.* **2011**, *79*, 285–293. [CrossRef] [PubMed]
95. Hoffman, T.M. Newer inotropes in pediatric heart failure. *J. Cardiovasc. Pharmacol.* **2011**, *58*, 121–125. [CrossRef] [PubMed]

96. Luraghi, A.; Ferrandi, M.; Barassi, P.; Arici, M.; Hsu, S.C.; Torre, E.; Ronchi, C.; Romerio, A.; Chang, G.J.; Ferrari, P.; et al. Highly Selective SERCA2a Activators: Preclinical Development of a Congeneric Group of First-in-Class Drug Leads against Heart Failure. *J. Med. Chem.* **2022**, *65*, 7324–7333. [CrossRef]
97. Lyon, A.R.; Samara, M.A.; Feldman, D.S. Cardiac contractility modulation therapy in advanced systolic heart failure. *Nat. Rev. Cardiol.* **2013**, *10*, 584–598. [CrossRef]
98. Abi-Samra, F.; Gutterman, D. Cardiac contractility modulation: A novel approach for the treatment of heart failure. *Heart Fail. Rev.* **2016**, *21*, 645–660. [CrossRef]
99. Neelagaru, S.B.; Sanchez, J.E.; Lau, S.K.; Greenberg, S.M.; Raval, N.Y.; Worley, S.; Kalman, J.; Merliss, A.D.; Krueger, S.; Wood, M.; et al. Nonexcitatory, cardiac contractility modulation electrical impulses: Feasibility study for advanced heart failure in patients with normal QRS duration. *Heart Rhythm* **2006**, *3*, 1140–1147. [CrossRef]
100. Borggrefe, M.M.; Lawo, T.; Butter, C.; Schmidinger, H.; Lunati, M.; Pieske, B.; Misier, A.R.; Curnis, A.; Bocker, D.; Remppis, A.; et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. *Eur. Heart J.* **2008**, *29*, 1019–1028. [CrossRef] [PubMed]
101. Kadish, A.; Nademanee, K.; Volosin, K.; Krueger, S.; Neelagaru, S.; Raval, N.; Obel, O.; Weiner, S.; Wish, M.; Carson, P.; et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. *Am. Heart J.* **2011**, *161*, 329–337.e2. [CrossRef] [PubMed]
102. Abraham, W.T.; Nademanee, K.; Volosin, K.; Krueger, S.; Neelagaru, S.; Raval, N.; Obel, O.; Weiner, S.; Wish, M.; Carson, P.; et al. Subgroup analysis of a randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. *J. Card. Fail.* **2011**, *17*, 710–717. [CrossRef] [PubMed]
103. Abraham, W.T.; Kuck, K.H.; Goldsmith, R.L.; Lindenfeld, J.; Reddy, V.Y.; Carson, P.E.; Mann, D.L.; Saville, B.; Parise, H.; Chan, R.; et al. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation. *JACC Heart Fail.* **2018**, *6*, 874–883. [CrossRef] [PubMed]
104. Wiegn, P.; Chan, R.; Jost, C.; Saville, B.R.; Parise, H.; Prutchi, D.; Carson, P.E.; Stagg, A.; Goldsmith, R.L.; Burkhoff, D. Safety, Performance, and Efficacy of Cardiac Contractility Modulation Delivered by the 2-Lead Optimizer Smart System: The FIX-HF-5C2 Study. *Circ. Heart Fail.* **2020**, *13*, e006512. [CrossRef]
105. Muller, D.; Remppis, A.; Schauerte, P.; Schmidt-Schweda, S.; Burkhoff, D.; Rousso, B.; Gutterman, D.; Senges, J.; Hindricks, G.; Kuck, K.H. Clinical effects of long-term cardiac contractility modulation (CCM) in subjects with heart failure caused by left ventricular systolic dysfunction. *Clin. Res. Cardiol.* **2017**, *106*, 893–904. [CrossRef]
106. Liu, M.; Fang, F.; Luo, X.X.; Shlomo, B.H.; Burkhoff, D.; Chan, J.Y.; Chan, C.P.; Cheung, L.; Rousso, B.; Gutterman, D.; et al. Improvement of long-term survival by cardiac contractility modulation in heart failure patients: A case-control study. *Int. J. Cardiol.* **2016**, *206*, 122–126. [CrossRef] [PubMed]
107. Masarone, D.; Kittleson, M.M.; De Vivo, S.; D'Onofrio, A.; Ammendola, E.; Nigro, G.; Contaldi, C.; Martucci, M.L.; Errigo, V.; Pacileo, G. The Effects of Device-Based Cardiac Contractility Modulation Therapy on Left Ventricle Global Longitudinal Strain and Myocardial Mechano-Energetic Efficiency in Patients with Heart Failure with Reduced Ejection Fraction. *J. Clin. Med.* **2022**, *11*, 5866. [CrossRef]
108. Avvisato, R.; Jankauskas, S.S.; Santulli, G. Istaroxime and Beyond: New Therapeutic Strategies to Specifically Activate SERCA and Treat Heart Failure. *J. Pharmacol. Exp. Ther.* **2023**, *384*, 1–3. [CrossRef]
109. Sze, S.; Pellicori, P.; Zhang, J.; Weston, J.; Clark, A.L. Which frailty tool best predicts morbidity and mortality in ambulatory patients with heart failure? A prospective study. *Eur. Heart J. Qual. Care Clin. Outcomes* **2022**, *in press*. [CrossRef]
110. Pocock, S.J.; Ferreira, J.P.; Gregson, J.; Anker, S.D.; Butler, J.; Filippatos, G.; Gollop, N.D.; Iwata, T.; Brueckmann, M.; Januzzi, J.L.; et al. Novel biomarker-driven prognostic models to predict morbidity and mortality in chronic heart failure: The EMPEROR-Reduced trial. *Eur. Heart J.* **2021**, *42*, 4455–4464. [CrossRef]
111. Rich, J.D.; Burns, J.; Freed, B.H.; Maurer, M.S.; Burkhoff, D.; Shah, S.J. Meta-Analysis Global Group in Chronic (MAGGIC) Heart Failure Risk Score: Validation of a Simple Tool for the Prediction of Morbidity and Mortality in Heart Failure With Preserved Ejection Fraction. *J. Am. Heart Assoc.* **2018**, *7*, e009594. [CrossRef] [PubMed]
112. Lee, W.C.; Wu, P.J.; Fang, H.Y.; Fang, Y.N.; Chen, H.C.; Tong, M.S.; Sung, P.H.; Lee, C.H.; Chung, W.J. Levosimendan Administration May Provide More Benefit for Survival in Patients with Non-Ischemic Cardiomyopathy Experiencing Acute Decompensated Heart Failure. *J. Clin. Med.* **2022**, *11*, 3997. [CrossRef] [PubMed]
113. Dass, B.; Dimza, M.; Singhania, G.; Schwartz, C.; George, J.; Bhatt, A.; Radhakrishnan, N.; Bansari, A.; Bozorgmehri, S.; Mohandas, R. Renin-Angiotensin-Aldosterone System Optimization for Acute Decompensated Heart Failure Patients (ROAD-HF): Rationale and Design. *Am. J. Cardiovasc. Drugs* **2020**, *20*, 373–380. [CrossRef] [PubMed]
114. Scrutinio, D.; Ammirati, E.; Guida, P.; Passantino, A.; Raimondo, R.; Guida, V.; Sarzi Braga, S.; Canova, P.; Mastropasqua, F.; Frigerio, M.; et al. The ADHF/NT-proBNP risk score to predict 1-year mortality in hospitalized patients with advanced decompensated heart failure. *J. Heart Lung Transplant.* **2014**, *33*, 404–411. [CrossRef]
115. Arrigo, M.; Jessup, M.; Mullens, W.; Reza, N.; Shah, A.M.; Sliwa, K.; Mebazaa, A. Acute heart failure. *Nat. Rev. Dis. Primers* **2020**, *6*, 16. [CrossRef]

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Dapsone-Associated Anemia in Heart Transplant Recipients with Normal Glucose-6-Phosphate Dehydrogenase Activity

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Abstract: Dapsone is considered an alternative for pneumocystis jirovecii pneumonia (PJP) prophylaxis in sulfa-allergic or -intolerant transplant patients with normal glucose-6-phosphate dehydrogenase (G6PD) activity. Despite normal G6PD activity, anemia can still occur while on dapsone therapy. We retrospectively reviewed heart transplant patients transplanted at our center between January 2016 and June 2018 and identified those taking dapsone prophylaxis. There were 252 heart transplant recipients at our center between January 2016 and June 2018. 36 patients received dapsone prophylaxis. All had normal G6PD activity assessed prior to dapsone initiation. 8 (22%) patients developed significant anemia attributed to dapsone: 2 were hospitalized for anemia, 1 of whom required blood transfusion. These patients had a median reduction in hemoglobin of 2.1 g/dL from baseline prior to dapsone initiation. Overt evidence of hemolysis was present in six patients. Once dapsone was discontinued, Hgb increased by at least 2 g/dL in a median of 30 days. Anemia from dapsone may occur in a significant proportion of patients despite normal G6PD activity and resulting in significant morbidity. Careful monitoring of transplant recipients on dapsone prophylaxis is warranted, as well as consideration of alternative agents.

Keywords: dapsone; transplant; G6PD; anemia

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1. Introduction

Pneumocystis jirovecii is a ubiquitous fungus that can cause pneumonia in up to 15% of transplant recipients in the absence of appropriate antimicrobial prophylaxis. The drug of choice for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis is trimethoprim-sulfamethoxazole for a duration of 6 to 12 months, but its utility can be limited by allergic reactions present in approximately 3% of the population [1,2].

In patients with trimethoprim-sulfamethoxazole intolerance or allergy, dapsone is often used for PJP prophylaxis. Dapsone inhibits bacterial and protozoan synthesis of dihydrofolic acid [3]. Before initiation, glucose-6-phosphate dehydrogenase (G6PD) function should be checked as a deficiency increases the risk of hemolytic anemia and methemoglobinemia [1,4].

Dapsone may also cause dose-dependent anemia [5–7], though the incidence of anemia in heart transplant patients with normal G6PD activity on dapsone is not well characterized [3,8–12]. The purpose of this study was to report the incidence and characterization of dapsone-associated anemia with normal G6PD function in heart transplant recipients at our center.

2. Materials and Methods

The study was approved by our Institutional Review Board at Cedars Sinai. We reviewed patients transplanted at our medical center between January 2016 and June 2018 to identify those who received dapsone prophylaxis. The electronic medical record was

used to extract clinical data including demographic information, clinical characteristics, and laboratory values. All patients had normal G6PD activity prior to initiating dapsone. G6PD activity was a send-out lab to Quest Diagnostics Nichols Institute with normal values 7.0–20.5 units/gram of hemoglobin. All patients were maintained on a calcineurin inhibitor, mycophenolate mofetil, and prednisone. While patients were admitted, basic metabolic panel (BMP) and complete blood count (CBC) labs were drawn daily. Outpatient BMP and CBC labs were drawn twice weekly until month 1 after transplant, weekly until month 2, every other week until month 3, monthly until month 6, then every 3 months until the first year, unless patients were re-admitted. Additional labs were ordered only when deemed necessary.

Hemolytic anemia was defined by a decreased hemoglobin with any of the following: presence of spherocytes, schistocytes, or bite cells on peripheral blood smear, symptoms such as brown urine or jaundice; and laboratory findings such as elevated lactate dehydrogenase (>220 U/L), elevated indirect bilirubin (>1 mg/dL), decreased haptoglobin (<36 mg/dL), elevated reticulocyte percentage (>2%) and macrocytosis (>100 fL) [13]. As reticulocytes are larger than mature erythrocytes, the presence of macrocytosis can be a surrogate for reticulocytosis, after ruling out other causes of macrocytosis like vitamin B-12 or folate deficiencies [14].

Statistics were calculated using the chi-squared test and paired *t*-test.

3. Results

Between January 2016 and June 2018, 252 patients underwent heart transplantation at our center. Of these, 36 patients (14%) received dapsone, most commonly 100 mg daily, for PJP prophylaxis. G6PD activity was assessed prior to initiation of dapsone in all patients and was normal. Dapsone was initiated at a median of 12.5 days (range 2 to 157 days) post heart transplantation. The reasons for the use of dapsone included: documented sulfa allergy causing a rash or anaphylaxis (21 patients), acute kidney injury (8 patients), leukopenia (4 patients), hyperkalemia (2 patients) and elevated alkaline phosphatase (1 patient).

Of the 36 patients who received dapsone for PJP prophylaxis, 8 (22%) developed anemia that resolved with discontinuation of dapsone. There was no difference in age, gender, prior durable mechanical circulatory support device, antithymocyte induction use, ethnicity, dapsone dosage, and reason for dapsone initiation between those patients with anemia and without anemia (Table 1). Of these 8 patients with anemia, 2 were hospitalized for anemia and one required blood transfusion.

Table 1. Demographics.

	Hemolytic Anemia (n = 8)	**No Hemolytic Anemia (n = 28)**	***p*-Value**
Mean age +/− SD	54.9 +/− 14.2	57.0 +/− 10.3	0.64
Female (%)	4 (50)	5 (18)	0.07
Prior durable MCS device (%)	2 (25)	10 (36)	0.57
ATG induction (%)	8 (100)	22 (79)	0.16
Ethnicity			
White	4 (50)	18 (64)	0.06
African American	0 (0)	7 (25)	
Hispanic	3 (37)	2 (7)	
Asian	1 (13)	1 (4)	
Daily dapsone dose			
100 mg	7 (87)	25 (89)	0.88
50 mg	1 (13)	3 (11)	
Reason for dapsone initiation			
Sulfa intolerance	6 (75)	15 (54)	0.21
Kidney injury	0 (0)	8 (29)	
Leukopenia	1 (13)	3 (11)	
Hyperkalemia	0 (0)	2 (7)	
Elevated alkaline phosphatase	1 (13)	0 (0)	

Six of the patients met at least one laboratory or clinical criteria for hemolytic anemia, but none of the patients had complete hemolysis labs and four had peripheral blood smears (Table 2).

Table 2. Evidence of hemolysis.

Patient Number	G6PD Level	Baseline Hgb (g/dL)	Hgb Nadir (g/dL)	Hgb (g/dL) at Least 30 Days after Dapsone Discontinuation	Trans-Fusion (no. of PRBC Units)	Hapto-Globin (Normal: 36–195 mg/dL)	LDH (Normal: 125–220 U/L)	Reticul-ocyte % (Normal: 0.5–2%)	Schisto-Cytes
1	Normal	8.5	7.5	9.4	0	85	244	10.7	no
2	Normal	8.5	7.4	12.3	0	<8	---	3.5	---
3	Normal	11.4	6	10.6	0	138	468	7.4	yes
4	Normal	8.7	6.9	10.8	0	215	266	3.6	no
5	Normal	11.1	8.3	11.3	0	<8	---	11.2	---
6	Normal	9.2/10.8	8.6/9	10.5/11.1	0	---	---	---	---
7	Normal	10.3	7.8	10.2	2	208	248	6.3	no
8	Normal	11.6	8.7	11.7	0	---	---	---	---

Dapsone was discontinued after a median of 52 days (range 21–90 days) from initiation and replaced with atovaquone (Table 3). At least 30 days after dapsone discontinuation, at a median of 40 days (range 30–55 days), the hemoglobin increased 39% from nadir, a median of 3 g/dL (range 1.9–4.9 g/dL). Figure 1 depicts the degree of anemia while on dapsone therapy and hemoglobin recovery at least 30 days after dapsone was discontinued. The time course of resolution was that hemoglobin increased by 2 g/dL from nadir occurred after a median of 30 days (range 15–54 days). Seven patients had macrocytosis. MCV decreased to normal, under 100 fL, at a median of 42 days (range 30–65 days) post dapsone discontinuation. One patient was restarted on dapsone 51 days after discontinuation, which resulted in recurrent anemia, hemoglobin 10.8 g/dL off dapsone to a nadir of 8.2 g/dL after 73 days on dapsone for which dapsone was stopped a second time. Another patient reported only "dark brown urine" per chart description without anemia after one week of dapsone therapy, which resolved after discontinuation. Upon rechallenge six days later, this patient again reported "dark urine" and developed anemia over 2 weeks.

Table 3. Dapsone duration and recognition of anemia.

Patient Number	Daily Dose (mg)	Days from Date of Transplant to Dapsone Initiation	Days from Dapsone Initiation to Onset of First Hgb Drop	Days from Dapsone Initiation to Hgb Nadir	Days from Date of Transplant to Dapsone Discontinuation	Days to Discontinuation of Dapsone after Initial Hgb Drop
1	100	3	15	22	30	15
2	100	5	11	23	47	31
3	100	7	7	50	57	43
4	100	6	11	21	27	10
5	100	63	46	46	116	7
6 *	100	25/166	90/45	90/101	115/267	0/56
7	50	18	13	76	94	63
8	100	58	59	59	117	0

* Patient 6 was rechallenged with dapsone and exhibited anemia when dapsone was restarted that again resolved when it was discontinued.

Patients were scored on the Naranjo Adverse Drug Reaction (ADR) Probability Scale which provides a standardized assessment of causality for adverse drug reactions [15]. The reaction is considered definite if the score is 9 or higher, probable if 5 to 8. Two patients scored +11, indicating a definite causal relationship and the rest scored +8, indicating a probable causal relationship between dapsone use and anemia (Table 4).

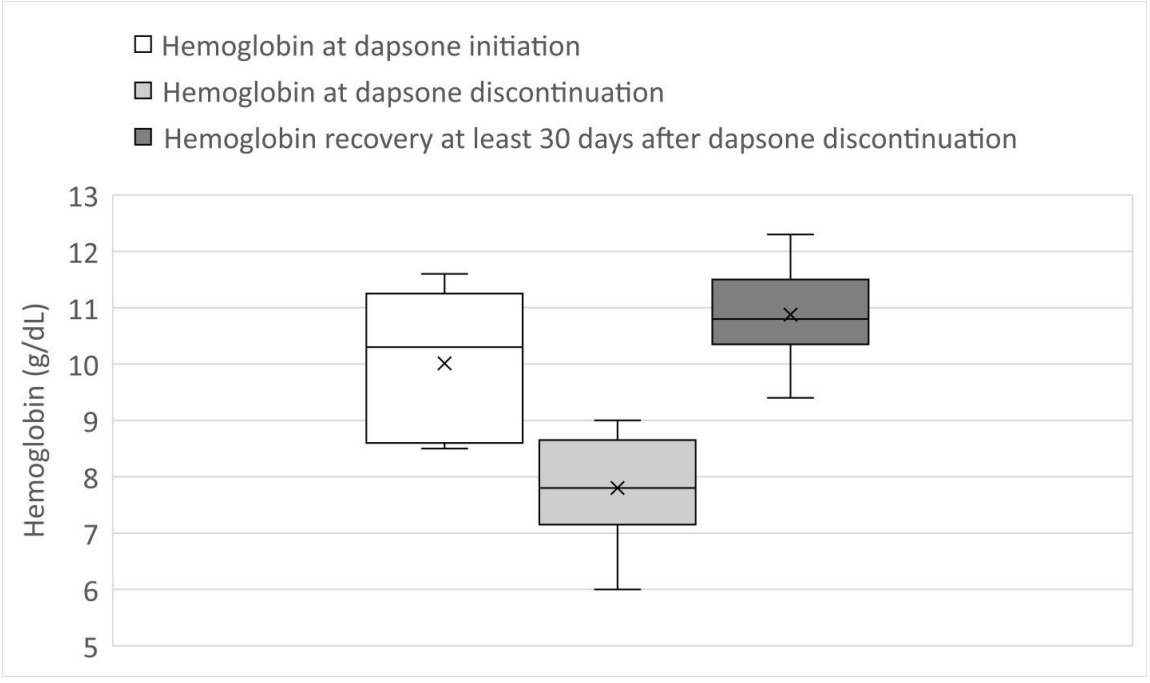

Figure 1. Hemoglobin levels at dapsone initiation, at dapsone discontinuation and at least 30 days after dapsone discontinuation with interquartile ranges, ranges, medians, and means (marked by x). $p = 0.0018$ comparing hemoglobin at dapsone initiation to hemoglobin at dapsone discontinuation. $p < 0.0001$ comparing hemoglobin at dapsone discontinuation to hemoglobin recovery.

Table 4. The Naranjo probability scale to determine the likelihood of causation of dapsone and anemia. Two patients scored definite causal relationship while six patients scored probable causal relationship. Adapted from Naranjo et al. [15].

Patient	1	2	3	4	5	6	7	8
Has this adverse event been documented before? (+1 Y, 0 N)	+1	+1	+1	+1	+1	+1	+1	+1
Did the adverse reaction occur after suspected drug was given? (+2 Y, −1 N)	+2	+2	+2	+2	+2	+2	+2	+2
Did the adverse reaction resolve after cessation of drug or was it reversible? (+1 Y, 0 N)	+1	+1	+1	+1	+1	+1	+1	+1
Did the adverse reaction recur after re-challenge with suspected drug? (+2 Y, −1 N)	+2	0	0	0	0	+2	0	0
Have other causes been ruled out? (−1 Y, +2 N) *	+2	+2	+2	+2	+2	+2	+2	+2
When an alternative was given, did the reaction occur? (−1 Y, +1 N)	+1	+1	+1	+1	+1	+1	+1	+1
Was there any determination of toxic drug levels in the blood or other fluids? (+1 Y, 0 N)	0	0	0	0	0	0	0	0
Did changing the dose change the severity of the reaction? (+1 Y, 0 N)	0	0	0	0	0	0	0	0
When the patient was given the drug or alternative previously, did they experience a reaction? (+1 Y, 0 N)	+1	0	0	0	0	+1	0	0
Was there any objective evidence to verify the adverse effect? (+1 Y, 0 N)	+1	+1	+1	+1	+1	+1	+1	+1
Total (> +9: definite, +5–8 probable, possible +1–4, doubtful < +1	+11	+8	+8	+8	+8	+11	+8	+8

* +2 chosen because the anemia recovered after stopping dapsone and the onset of anemia was 30 days or later after transplant, so post-surgical anemia unlikely. In addition, the anemia occurred and resolved with initiation and discontinuation of dapsone regardless of maintenance on all other potential contributing medications including mycophenolate mofetil and valganciclovir.

4. Discussion

Despite normal G6PD activity, 22% of heart transplant recipients receiving dapsone for PJP prophylaxis developed anemia with at least a probable causal association by the Naranjo Adverse Drug Reaction Probability scale. This anemia resulted in significant morbidity, with 2 patients requiring hospitalization and one requiring blood transfusion.

To our knowledge, this is the first reported case series of dapsone-associated anemia in heart transplant recipients with normal G6PD activity though this observation has been made in other solid organ transplant (SOT) recipients. Dapsone-related anemia has been reported in the setting of normal G6PD activity resulting in dapsone discontinuation in 46% of kidney transplant recipients [12] and 23% of lung transplant recipients [11]. One small study observed dapsone-related anemia in kidney, lung, liver, and heart transplant recipients though G6PD activity was not documented in all patients [9]. Dapsone-related anemia has also been observed in non-SOT patients, up to 87% in stem cell transplant recipients with normal G6PD activity [10], 4% in patients with HIV [16], and 25% of patients with leprosy [3]. The incidence of dapsone-related anemia of 22% in our study is comparable to that observed in lung transplant recipients but lower than that seen in kidney or stem cell transplant recipients, which may be related to comorbidities or duration or dosage of dapsone used.

Dapsone is absorbed almost completely with 80–100% bioavailability. Only 20% of dapsone is renally eliminated unchanged while 70–85% of dapsone metabolites are renally eliminated [5]. All of the patients with dapsone-associated anemia did not have any renal dysfunction to explain any dapsone or dapsone metabolite accumulation.

One putative mechanism for dapsone-induced hemolytic anemia in patients with normal G6PD activity is the accumulation of the toxic metabolite dapsone hydroxylamine which forms free radicals in erythrocytes [17,18]. This accumulation may be modified based on genetic polymorphisms. Dapsone undergoes metabolism via acetylation by N-acetyltransferase to an inactive metabolite (monoacetyldapsone) and oxidation primarily by the cytochrome P450 2E1, but also 3A4 and 2C9 [5,19,20], to its toxic metabolite dapsone hydroxylamine. It is possible that patients who are both slow acetylators and fast oxidizers are more prone to dapsone-induced anemia as the predominant metabolite would be shifted from the inactive metabolite to the toxic one [17,21,22]. The role of pharmacogenomics on the metabolism and toxicity of dapsone is an important area of future study.

This study has several limitations. First, the small size precludes clear assessment of causality. The retrospective nature also prevented clear assessment of hemolysis as relevant laboratory assessments for the diagnosis of hemolysis were not performed in all patients. Patients were managed as an outpatient which contributed to delays in recognition of anemia or extended duration of dapsone. Furthermore, in some patients the anemia was gradual, whereas in others, the anemia was pronounced. However, once dapsone was discontinued, the anemia gradually resolved regardless of the onset of anemia. Although only 2 of 6 patients exhibited low haptoglobin, the haptoglobin levels could have been falsely elevated by corticosteroids which are given post heart transplantation, thereby overlooking the diagnosis of hemolysis [23]. Nonetheless, these real-world observations provide important insight for clinicians managing solid organ transplant patients with worsening anemia while receiving dapsone prophylaxis.

5. Conclusions

Dapsone is used regularly for PJP prophylaxis in patients who are allergic or intolerant to sulfonamide antibiotics. Despite normal G6PD function, hemolytic anemia can still occur in patients on dapsone prophylaxis leading to potential hospitalizations and blood transfusions. Careful monitoring is necessary and alternative agents for PJP prophylaxis should be considered.

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References

1. Martin, S.I.; Fishman, J.A. The AST Infectious Disease Community of Practice. Pneumocystis pneumonia in solid organ transplantation. *Am. J. Transplant.* **2013**, *13*, 272–279. [CrossRef] [PubMed]
2. Bigby, M.; Jick, S.; Jick, H.; Arndt, K. Drug-induced cutaneous reactions: A report from the Boston collaborative drug surveillance program on 15438 consecutive inpatients, 1975 to 1982. *JAMA* **1986**, *256*, 3358–3363. [CrossRef] [PubMed]
3. Deps, P.; Guerra, P.; Nasser, S.; Simon, M. Hemolytic anemia in patients receiving daily dapsone for the treatment of leprosy. *Lepr Rev.* **2012**, *83*, 305–307. [CrossRef] [PubMed]
4. Belfield, K.D.; Tichy, E.M. Review of drug therapy implications of glucose-6-phosphate dehydrogenase deficiency. *Am. J. Health-Syst. Pharm.* **2018**, *75*, 97–104. [CrossRef] [PubMed]
5. Wozel, G.; Blasum, C. Dapsone in dermatology and beyond. *Arch. Dermatol. Res.* **2014**, *306*, 103–124. [CrossRef]
6. Luzzatto, L.; Seneca, E. G6PD deficiency: A classic example of pharmacogenetics with on-going clinical implications. *Br. J. Haematol.* **2014**, *164*, 469–480. [CrossRef] [PubMed]
7. Hughes, W.T. Use of dapsone in the prevention and treatment of Pneumocystis carinii pneumonia: A review. *Clin. Infect. Dis.* **1998**, *27*, 191–204. [CrossRef] [PubMed]
8. Esbenshade, A.J.; Ho, R.H.; Shintani, A.; Zhao, Z.; Smith, L.A.; Friedman, D.L. Dapsone-induced methemoglobinemia: A dose-related occurrence? *Cancer* **2011**, *117*, 3485–3492. [CrossRef]
9. Lee, I.; Barton, T.D.; Goral, S.; Doyle, A.M.; Bloom, R.D.; Chojnowski, D.; Korenda, K.; Blumberg, E.A. Complications related to dapsone use for Pneumocystis Jirovecii pneumonia prophylaxis in solid organ transplant recipients. *Am. J. Transplant.* **2005**, *5*, 2791–2795. [CrossRef]
10. Olteanu, H.; Harrington, A.M.; George, B.; Hari, P.N.; Bredeson, C.; Kroft, S.H. High prevalence of dapsone-induced oxidant hemolysis in North American SCT recipients without glucose-6-phosphate-dehydrogenase deficiency. *Bone Marrow Transplant.* **2012**, *47*, 399–403. [CrossRef]
11. Naik, P.M.; Lyon, G.M., III; Ramirez, A.; Lawrence, E.C.; Neujahr, D.C.; Force, S.; Pelaez, A. Dapsone-induced hemolytic anemia in lung allograft recipients. *J. Heart Lung Transplant.* **2008**, *27*, 1198–1202. [CrossRef] [PubMed]
12. Hedvat, J.; Poladi, N.; Salerno, D.M.; Dube, G.K.; Lange, N.W. An evaluation of PJP prophylaxis and anemia among renal transplant recipients. *Transpl. Infect. Dis.* **2021**, *23*, e13543. [CrossRef] [PubMed]
13. Phillips, J.; Henderson, A.C. Hemolytic Anemia: Evaluation and differential diagnosis. *Am. Fam. Physician* **2018**, *98*, 354–361.
14. Kaferle, J.; Strzoda, C.E. Evaluation of macrocytosis. *Am. Fam. Physician* **2009**, *79*, 203–208.
15. Naranjo, C.A.; Busto, U.; Sellers, E.M.; Sandor, P.; Ruiz, I.; Roberts, E.A.; Janecek, E.; Domecq, C.; Greenblatt, D.J. A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther.* **1981**, *30*, 239–245. [CrossRef] [PubMed]
16. Beumont, M.G.; Graziani, A.; Ubel, P.A.; MacGregor, R.R. Safety of dapsone as Pneumocysitis carinii pneumonia prophylaxis in human immunodeficiency virus-infected patients with allergy to trimethoprim/sulfamethoxazole. *Am. J. Med.* **1996**, *100*, 611–616. [CrossRef]
17. Bordin, L.; Fiore, C.; Zen, F.; Coleman, M.D.; Ragazzi, E.; Clari, G. Dapsone hydroxylamine induces premature removal of human erythrocytes by membrane reorganization and antibody binding. *Br. J. Pharmacol.* **2010**, *16*, 1186–1199. [CrossRef] [PubMed]
18. Bradshaw, T.P.; McMillan, D.C.; Crouch, R.K.; Jollow, D.J. Formation of free radicals and protein mixed disulfides in rat red cells exposed to dapsone hydroxylamine. *Free Radic. Biol. Med.* **1997**, *22*, 1183–1193. [CrossRef]
19. May, D.G.; Porter, J.A.; Uetrecht, J.P.; Wilkinson, G.R.; Branch, R.A. The contribution of N-hydroxylation and acetylation to dapsone pharmacokinetics in normal subjects. *Clin. Pharmacol. Ther.* **1990**, *48*, 619–627. [CrossRef]
20. Mitra, A.K.; Thummel, K.E.; Kalhorn, T.F.; Kharasch, E.D.; Unadkat, J.D.; Slattery, J.T. Metabolism of dapsone to its hydroxylamine by CYP2E1 in vitro and in vivo. *Clin. Pharmacol. Ther.* **1995**, *58*, 556–566. [CrossRef]
21. Bluhm, R.E.; Adedoyin, A.; McCarver, D.G.; Branch, R.A. Development of dapsone toxicity in patients with inflammatory dermatoses: Activity of acetylation and hydroxylation of dapsone as risk factors. *Clin. Pharmacol. Ther.* **1999**, *65*, 598–605. [CrossRef]

22. Cappellini, M.D.; Fiorelli, G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* **2008**, *371*, 64–74. [CrossRef]
23. Shih, A.W.Y.; McFarlane, A.; Verhovsek, M. Haptoglobin testing in hemolysis: Measurement and interpretation. *Am. J. Hematol.* **2014**, *89*, 443–447. [CrossRef] [PubMed]

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Effects of Cardiac Contractility Modulation Electrodes on Tricuspid Regurgitation in Patients with Heart Failure with Reduced Ejection Fraction: A Pilot Study

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Abstract: Background: Cardiac contractility modulation (CCM) is an innovative therapy for heart failure with reduced ejection fraction delivered by a cardiac implantable device (Optimizer Smart®). One of the most prominent periprocedural complications common to all cardiac implantable devices (CIDs) is tricuspid regurgitation (TR) due to the placement of the right ventricular endocardial leads. To date, no published studies have assessed the changes in the TR degree in patients with heart failure with reduced ejection fraction (HFrEF) who received an implantable cardioverter-defibrillator (ICD) after the implantation of cardiac contractility modulation therapy devices. Objective: This study aimed to evaluate the effect of the implantation of the trans-tricuspid leads required to deliver CCM therapy on the severity of TR in patients with HFrEF who previously underwent ICD implantation. Methods: We enrolled 30 HFrEF patients who underwent CCM therapy between November 2020 and October 2021. For all the patients, echocardiographic evaluations of TR were performed according to current guidelines 24 h before and six months after the Optimizer Smart® implant was applied. Results: At the 6-month follow-up, the grade of TR remained unchanged compared to the preimplant grade. The value of the vena contracta (VC) of TR was 0.40 ± 0.19 cm in the preimplant period and 0.45 ± 0.21 cm at the 6-month follow-up (p = 0.33). Similarly, the TR proximal isovelocity surface area (PISA) radius value was unchanged at follow-up (0.54 ± 0.22 cm vs. 0.62 ± 0.20 cm; p = 0.18). No statistically significant difference existed between the preimplant VC and PISA radius values, irrespective of the device type. Conclusions: The implantation of right ventricular electrodes for the delivery of CCM therapy did not worsen tricuspid regurgitation in patients with HFrEF and ICD.

Keywords: cardiac contractility modulation; optimizer smart; heart failure reduced ejection fraction; tricuspid regurgitation

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1. Introduction

Cardiac contractility modulation (CCM) is an innovative therapy for the treatment of heart failure (HF) with mildly reduced (HFmrEF) and reduced ejection fraction (HFrEF) that modulates the myocardial contraction force through the delivery of non-excitatory impulses [1]. The device used for CCM therapy delivery, the Optimizer Smart®, generates high-amplitude (from 4.0 V to 7.5 V) biphasic electrical signals during the absolute refractory period of the cardiac cycle, leading to an improvement in calcium handling and, consequently, in cardiac contractility and performance [2].

In patients with HFmrEF and HFrEF, CCM therapy improves the symptoms and quality of life, reduces the number of hospitalizations, and promotes biventricular reverse

remodeling [3]. However, Optimizer Smart implantation is an invasive procedure that is potentially subject to several theorized early and late complications. It should be noted that the actual 30-day significant adverse event (SAE) rate of Optimizer implantation is similar to that of dual-chamber pacemaker implantation (8.8% vs. 9.1%, respectively) [4,5].

One of the most prominent periprocedural complications common to all cardiac implantable devices (CIDs) is tricuspid regurgitation (TR) due to the placement of the right ventricular endocardial leads [6].

The mechanisms through which endocardial leads can result in TR are numerous and can be characterized as structural [7] (due to valve deformity from the impingement of the leads to the valve leaflet or valve perforation), functional [8] (recurrent embolization from lead thrombosis, resulting in pulmonary hypertension and TR secondary to right ventricular dilatation), or physiologic [9] (due to TR resulting from the RV-pacing-induced worsening of HF).

However, more than 650 patients with HFmrEF and HFrEF who participated in two randomized controlled trials and a large CCM therapy registry had Optimizer Smart® devices and concomitant implantable defibrillators fitted (with at least three leads crossing the tricuspid valve), and there were no reported cases of worsening TR [3,4,10].

As no specific published studies exist, the purpose of this study was to evaluate the effect of the implantation of the trans-tricuspid leads required to deliver CCM therapy on the severity of TR in patients with HFrEF who had previously received implantable cardioverter-defibrillator (ICD) implants by echocardiography.

2. Methods

2.1. Study Population

We prospectively and consecutively enrolled all the patients diagnosed with HFrEF who underwent CCM therapy between November 2020 and December 2021 according to the European Society of Cardiology guidelines.

The following inclusion criteria were used:

- Left ventricular ejection fraction of <40%;
- New York Heart Association (NYHA) class II–III;
- Referral for CCM implant due to the >2 unplanned visits or hospitalization in the last 12 months and/or the persistence of HF-related symptoms despite the use of optimal medical therapy;
- A QRS duration of <120 msec.

The following exclusion criteria were used:

- Acute coronary syndrome in the previous three months;
- ICD implantation in the previous twelve months;
- Severe tricuspid regurgitation (i.e., vena contracta >7 mm, proximal isosurface radius >9 mm).

The demographic, clinical, and laboratory data were acquired from stable patients 24 h before the Optimizer Smart® implantation.

The study was conducted according to the Declaration of Helsinki. For all the patients, signed informed consent was obtained, and approval was received from the institutional review board of AORN dei Colli-Ospedale Monaldi (deliberation No. 903/2020).

2.2. Echocardiographic Evaluation

Standard transthoracic echocardiography and Doppler evaluation were performed using commercially available equipment (Vivid E9, GE Healthcare, Milwaukee, WI, USA) according to the international guidelines [11,12].

Two independent observers, who were blinded to the clinical details of the patients enrolled, analyzed all the echocardiographic studies, and an average of 3–5 cardiac cycles were performed for each parameter.

According to the international recommendations, TR was assessed by color Doppler evaluation in the apical four-chamber view [13]. The degree of TR was classified as mild in the presence of a vena contracta (VC) <0.3 cm and proximal isovelocity surface area (PISA) radius <0.5 cm, as moderate with a VC >0.3 cm and <0.7 cm and PISA radius >0.5 cm and <0.9 cm, and as severe with a VC >0.7 cm and PISA radius >0.9 cm.

For all the patients, echocardiographic evaluations were performed 24 h before and six months after the Optimizer Smart® implant was applied.

2.3. Optimizer Smart® Implant

The implantation procedure of the Smart Optimizer (Impulse Dynamics Inc., Marlton, NJ, USA) was performed after the patient's sedation under local anesthesia.

Two electrodes, which are necessary for detecting ventricular activity and the subsequent CCM therapy delivery, were attached to the right side of the interventricular septum through the right subclavian vein. These leads were then connected to the Optimizer Smart, and the device was implanted in a subcutaneous pocket with the charging coil facing in the anterior direction.

2.4. Statistical Analysis

Statistical analyses were performed using Prism 9 (GraphPad Software, San Diego, CA, USA). The demographic and clinical variables were expressed as the mean ± standard deviation. The categorical variables were expressed as numbers and percentages. Differences between the baseline and treatment values were compared using Wilcoxon's rank test for a non-normal distribution and the paired t-test for a normal distribution.

Receiver operating characteristic curve analysis was performed to select the optimal cut-off values for the echocardiographic measurements. In addition, the reproducibility of the measurements was determined in the case of all the patients. The inter-observer and intra-observer variability of the echocardiographic measures were examined using Pearson's two-tailed bivariate correlations and Bland–Altman analysis. Correlation coefficients, 95% confidence limits, and percentage errors were reported.

All the p-values were two-sided, and $p < 0.05$ indicated statistical significance.

3. Results

Thirty-two patients with HfrEF underwent Optimizer Smart® implantation during the study period. Of these, two patients has severe tricuspid regurgitation; thus, they were not enrolled in the study.

The demographic, clinical, and echocardiographic characteristics of the 30 patients enrolled in the study are presented in Table 1.

Table 1. Demographic, clinical, and echocardiographic characteristics of the study population.

Variable	Total Population (n = 30)
Age (mean ± SD)	59.5 ± 12.9 years
Female sex (n, %)	5 (16.6%)
Ischemic etiology (n, %)	13 (43.3%)
Hypertension (n, %)	10 (33.3%)
Diabetes (n, %)	8 (26.6%)
NYHA class II (n, %)	6 (20%)
NYHA class III (n, %)	24 (80%)
SBP (mean ± SD)	108 ± 12.3 mmHg
DBP (mean ± SD)	62 ± 5.7 mmHg

Table 1. *Cont.*

Variable	Total Population (n = 30)
HR (mean ± SD)	62 ± 10.2 b/m
NT-pro-BNP (mean ± SD)	3956 ± 2872 pg/mL
Atrial fibrillation	12 (40%)
ICD-DR	14 (46.6%)
ICD-VR	2 (6.6%)
S-ICD	2 (6.6%)
CRT-D	12 (40%)
Hb (mean ± SD)	11.3 ± 1.2 g/dL
Creatinine (mean ± SD)	1.2 ± 0.7 mg/d:
e-GFR (mean ± SD)	45.9 ± 13.6 mL/min/1.73 m^2
LVEDV (mean ± SD)	225.8 ± 51.6 mL
LVESV (mean ± SD)	162.4 ± 41.8 mL
LVEF (mean ± SD)	30.5 ± 3.6%
E wave (mean ± SD)	110.5 ± 38.7 cm/sec
E' average (mean ± SD)	5.8 ± 3.2 cm/sec
E/e' average (mean ± SD)	15.5 ± 4.2
DecT (mean ± SD)	142.8 ± 45.3 m/sec
LAVi (mean ± SD)	47.3 ± 11.5 mL/m^2
RVOT prox (mean ± SD)	28.7 ± 4.2 mm
RVOT dist (mean ± SD)	25.3 ± 3.8 mm
RVD 1 (mean ± SD)	29.2 ± 4.8 mm
RVD 2 (mean ± SD)	27.5 ± 5.2 mm
RVD3 (mean ± SD)	63.4 ± 6.2 mm
TAPSE (mean ± SD)	13.6 ± 5.6 mm
S wave (mean ± SD)	10.3 ± 1.5 cm/sec
PASP (mean ± SD)	37.6 ± 8.2 mmHg
TR mild (n, %)	17 (56.6%)
TR moderate (n, %)	13 (43.4%)

NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate, NT-pro-BNP: NT-pro-brain natriuretic peptides; ICD-DR: implantable cardioverter-defibrillator dual chamber; ICD-VR: implantable cardioverter-defibrillator single chamber; S-ICD: subcutaneous implantable cardioverter-defibrillator; CRT-D: cardiac resynchronization therapy with defibrillator back-up; Hb: hemoglobin; e-GFR: estimated glomerular filtration rate; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; E wave: peak early mitral inflow velocity; e′ average: average septal and lateral peak early diastolic mitral annular velocity; DecT: deceleration time; LAVi: left atrium volume index; RVOT prox.: right ventricle outflow tract dimension on the proximal sub-valvular level; RVOT distal: right ventricle outflow tract dimension on the distal or pulmonic valve level; RVD1: right ventricle basal dimension; RVD2: right ventricle mid-cavity dimension; RVD3: right ventricle longitudinal dimension; TAPSE: tricuspid annular plane systolic excursion; S wave: peak systolic of the free wall of the right ventricle; PASP: pulmonary artery systolic pressure; TR: tricuspid regurgitation.

All the patients had a previously implanted device. In total, 14 (46.7%) had a dual-chamber implantable cardioverter-defibrillator (ICD-DR), 12 (40%) had a device for cardiac resynchronization therapy with defibrillation back-up (CRT-D), and 4 (13.3%) had a single-chamber implantable cardioverter-defibrillator (ICD-VR).

The r coefficients for Pearson's two-tailed bivariate correlations were 0.92 and 0.87 according to the Bland–Altman analysis.

At the 6-month follow-up, the grade of TR remained unchanged compared to the pre-implant grade (Figure 1). The VC value of TR was 0.40 ± 0.19 cm in the pre-implant period and 0.45 ± 0.21 cm at 6 months ($p = 0.33$). Similarly, the PISA radius value of TR was unchanged at follow-up (0.54 ± 0.22 cm vs. 0.62 ± 0.20 cm; $p = 0.18$). No statistically significant difference existed between the pre-implant VC and PISA radius values, irrespective of the device type (Figure 2A,B).

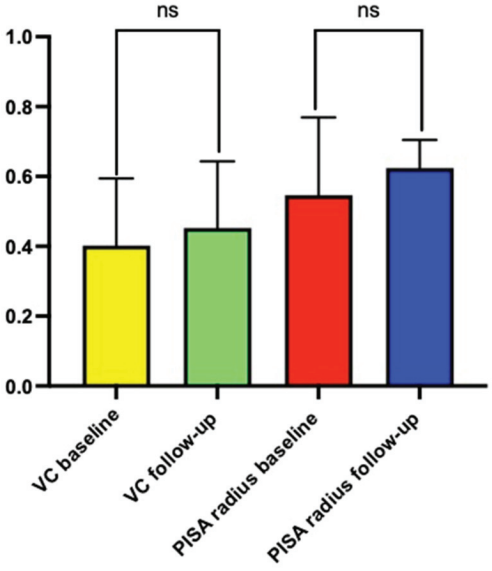

Figure 1. Value of vena contracta and proximal isosurface area radius of tricuspid regurgitation before and after Optimizer® Smart implantation. VC: vena contracta; PISA: proximal isosurface area radius. ns: non-significance.

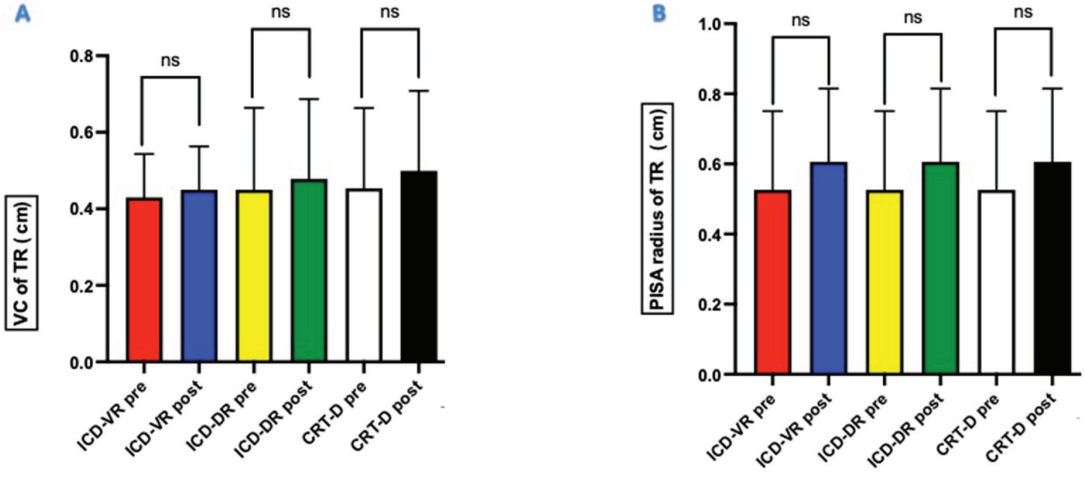

Figure 2. Value of vena contract (panel (**A**)) and proximal isosurface area radius (panel (**B**)) of tricuspid regurgitation before and after Optimizer® Smart implantation. ns: non-significance. ICD-VR: single-chamber implantable cardioverter-defibrillator; ICD-DR: dual-chamber implantable cardioverter-defibrillator; CRT-D: cardiac resynchronization therapy with implantable cardioverter-defibrillator back-up.

In addition, as shown in Table 2 and Figure 3, at the six-month follow-up, the CCM therapy induced right ventricular reverse remodeling and reduced systolic pulmonary pressure values.

Table 2. Effects of CCM on the right ventricular dimensions, systolic function, and hemodynamic parameters at the six-month follow-up.

Parameter	Baseline	6-Month Follow-Up	*p*-Value
RVOT prox (mean ± SD)	28.7 ± 4.2 mm	26.3 ± 3.8	0.042
RVOT dist (mean ± SD)	25.3 ± 3.8 mm	22.9 ± 4.5 mm	0.037
RVD 1 (mean ± SD)	29.2 ± 4.8 mm	27.2 ± 3.3 mm	0.026
RVD 2 (mean ± SD)	27.5 ± 5.2 mm	26.2 ± 4.8 mm	0.022
RVD3 (mean ± SD)	63.4 ± 6.2 mm	61.9 ± 3.8 mm	0.031
TAPSE (mean ± SD)	13.6 ± 5.6 mm	16.7 ± 4.6 mm	0.012
S wave (mean ± SD)	10.3 ± 1.5 cm/s	12.3 ± 2.8 cm/s	0.017
PASP (mean ± SD)	37.6 ± 8.2 mmHg	33.6 ± 4.7 mmHg	0.035
PAMP	20.3 ± 7.5 mmHg	15.8 ± 4.2 mmHg	0.043
PCWP	12.6 ± 5.8 mmHg	9.3 ± 2.9 mmHg	0.031

RVOT prox.: right ventricular outflow tract proximal diameter; RVOT dist.: right ventricular outflow tract distal diameter; RVD 1: right ventricular basal dimension; RVD 2: right ventricular mid-cavity dimension; RVD 3: right ventricular longitudinal dimension; TAPSE: tricuspid annular plane excursion; S wave: peak systolic of the free wall of the right ventricle; PASP: pulmonary artery systolic pressure; PAMP: pulmonary artery mean pressure; PCWP: pulmonary capillary wedge pressure.

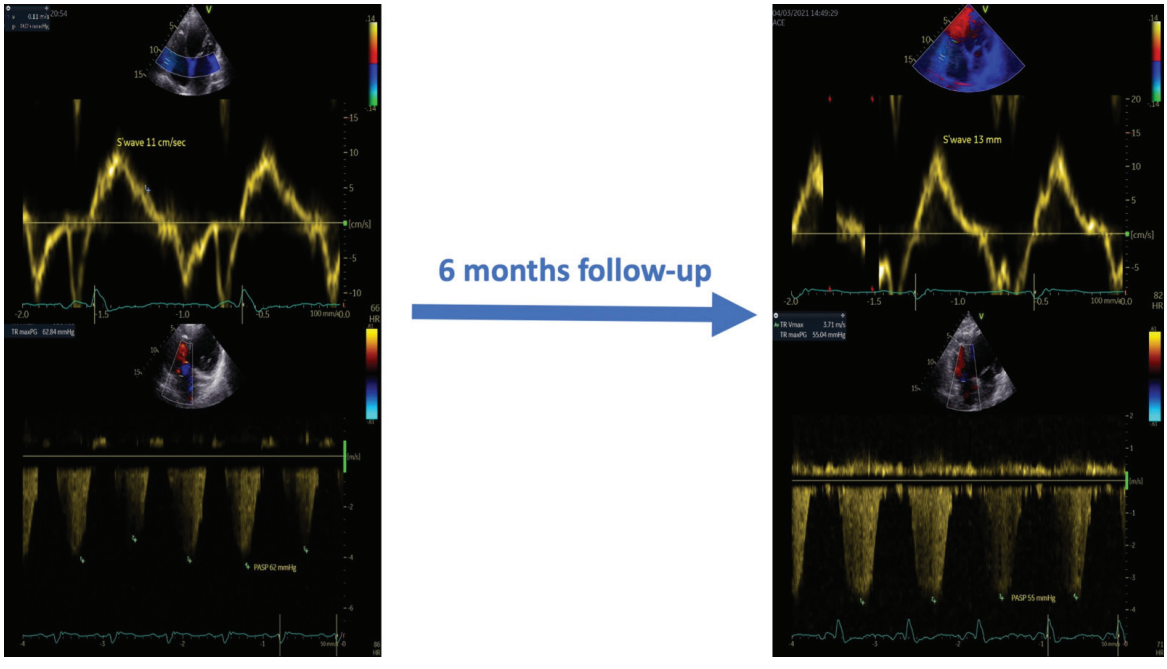

Figure 3. Effects of CCM therapy on the systolic function and pulmonary artery systolic pressure at the six-month follow-up.

These data confirm the absence of hemodynamically significant worsening of tricuspid regurgitation after the implantation of the electrodes that deliver CCM therapy. In the multivariable analysis (Table 3), the non-significant worsening of TR was associated with left ventricular ejection fraction and pulmonary artery systolic pressure.

Table 3. Multiple linear regression analysis of the Δ TR.

Variable	Mean ± SD	B	t	*p*-Value
Δ TR degree at six months	2.5 ± 0.03	-	-	-
Age (years)	59.5 ± 12.9	−0984	0.756	0.082
SBP (mmHg)	108 ± 12.3	−0.063	0.250	0.767
HR (b/m)	62 ± 10.2	−0.265	0.371	0.428
LVEF (%)	30.5 ± 3.6%	0.189	0.465	0.021
PCWP (mmHg)	12.6 ± 5.8	−0543	0.751	0.065
PASP (mmHg)	37.6 ± 8.2	−0345	0.651	0.048
TAPSE (mm)	13.6 ± 5.6	−0012	0.345	0.061

TR: tricuspid regurgitation; SBP: systolic blood pressure; HR: heart rate; LVEF: left ventricular ejection fraction; PCWP: pulmonary capillary wedge pressure; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion. In bold *p*-value with statistical significance.

4. Discussion

The main findings of this study are as follows:

(1) The implantation of pacemaker leads to deliver CCM therapy did not result in a worsening of TR at six months compared with the baseline.
(2) The absence of TR worsening was independent of the type of CIED previously implanted and, therefore, the presence and number of endocardial leads already implanted.

With the advent of CIED-based therapies for HfrEF, several investigations have shown a worsening of TR associated with the implantation of an ICD and CRT-D [14].

However, to the best of our knowledge, no prospective study in the literature has evaluated the effects of implanting endocardial leads for CCM therapy delivery on tricuspid valve function.

Our results demonstrate, for the first time, that CCM implantation does not increase the severity of TR. This finding is particularly important, because most patients enrolled in the study had a pre-existing CIED with one or more endocardial leads.

In our population, adding two leads on the right side of the interventricular septum did not worsen the extent of TR in the patients with a CRT-D, ICD-DR, or ICD-VR.

After the implantation of the CIED leads, the worsening of TR (described in 16–25% of the patients) could develop or worsen because of several proposed mechanisms, including the physical impingement of the lead on the valve [15], fibrous tissue formation on the valve leaflets [16], and, rarely, the perforation and entrapment of the lead in the valve apparatus. Additionally, and perhaps most commonly, RV-pacing-induced worsening heart failure worsens the RV hemodynamics, resulting in the worsening of TR [17].

Lead implantation for CCM therapy is not associated with any of these mechanisms for various reasons. Firstly, though both leads used for CCM delivery are placed in the right ventricle, CCM does not result in the pacing of the heart (that is, no excitatory event is produced), so that the normal depolarization patterns remain unaltered.

Thus, RV-pacing-induced HF and the subsequent deterioration of tricuspid valve function do not occur.

Additionally, CCM improves left ventricular systolic and diastolic function and induces left ventricular remodeling [18]. These effects could be protective against heart-failure-induced TR [19]. After reducing the LV filling pressures, the tricuspid valve pressure gradient is similarly decreased, and TR is not likely to worsen but may, indeed, improve [20].

In addition, in our population, CCM improved the right ventricle function and right ventricular–pulmonary artery coupling. These effects are mediated by both the improvement in myocardial contractility and reduction in pulmonary artery systolic pressure (PASP) [21].

In our study, the Δ of TR at six months was associated with left ventricular ejection fraction (LVEF) and pulmonary artery systolic pressure (PASP).

A previous study showed that in patients with HfrEF, the degree of TR was correlated with left ventricular ejection fraction (LVEF), which is associated with the tethering of the leaflet of tricuspid valve [22]. This fact suggests that ventricular interdependence plays a significant role in determining tricuspid valve competence, presumably via the effect of left ventricular dysfunction on the interventricular septum, to which the septal leaflet of the tricuspid valve is attached [23].

PASP is one of the main determinants of TR in patients with HfrEF who have previously received CIEDs implants [24]. However, it appears that the remodeling of the right heart in response to elevated pulmonary pressure, and not only the increase in PASP, represents the major mechanism responsible for TR in these patients [25].

Thus, the increase in LVEF and reduction in PASP induced by CCM could represent the main mechanisms that contribute to the "neutral" effects that the implantation of CCM electrodes have on the degree of TR in patients with HFrEF.

5. Study Limitations

Our study had some limitations. Firstly, we used 2D echocardiography to assess the TR and RV function, whereas 3D echocardiography might have been more accurate in quantifying TR. However, we used more quantitative parameters determined by the guidelines to optimally evaluate TR in standard clinical practice.

Secondly, despite the prospective nature of our study, our study population was small. Therefore, our results will need to be confirmed in a larger population. Finally, the endpoints were assessed at six months post-implantation, and it has yet to be seen what long-term effects may occur in the future. In particular, the fibrotic scarring of leads of the tricuspid apparatus may take years to develop and manifest effects.

6. Conclusions

In this pilot study, the implantation of right ventricular electrodes for the delivery of CCM therapy did not appear to worsen TR in patients with HFrEF who had previously undergone CIED implantation. The mechanisms that may prove to be particularly important are (1) the lack of RV pacing through CCM delivery (thus preventing RV-pacing-induced heart failure) and (2) biventricular function improvement, which secondarily improves the RV hemodynamics. HF specialists and electrophysiologists should be aware of this so as to avoid depriving patients of a safe and effective therapy for HFrEF due to the fear of worsening TR.

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Informed Consent Statement: Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The dataset generated and analyzed in the study is available from the corresponding author on reasonable request.

Conflicts of Interest: Ishu Rao is employed as the medical director of Impulse Dynamics and is the owner of stocks of Impulse Dynamics. The other authors declare no conflict of interest.

References

1. Patel, P.A.; Nadarajah, R.; Ali, N.; Gierula, J.; Witte, K.K. Cardiac contractility modulation for the treatment of heart failure with reduced ejection fraction. *Heart Fail Rev.* **2021**, *26*, 217–226. [CrossRef] [PubMed]
2. Rao, I.V.; Burkhoff, D. Cardiac contractility modulation for treating moderate to severe HF. *Expert Rev. Med. Devices* **2021**, *18*, 15–21. [CrossRef] [PubMed]
3. Kuschyk, J.; Falk, P.; Demming, T.; Marx, O.; Morley, D.; Rao, I.; Burkhoff, D. Long-term clinical experience with cardiac contractility modulation therapy delivered by the Optimizer Smart system. *Eur. J. Heart Fail.* **2021**, *23*, 1160–1169. [CrossRef] [PubMed]
4. Abraham, W.T.; Lindenfeld, J.; Reddy, V.Y.; Hasenfuss, G.; Kuck, K.H.; Boscardin, J.; Gibbons, R.; Burkhoff, D. FIX-HF-5C Investigators and Coordinators. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with moderately reduced left ventricular ejection fraction and a narrow QRS duration: Study rationale and design. *J. Card Fail.* **2015**, *21*, 16–23.
5. Cantillon, D.J.; Exner, D.V.; Badie, N.; Davis, K.; Gu, N.Y.; Nabutovsky, Y.; Doshi, R. Complications and Health Care Costs Associated With Transvenous Cardiac Pacemakers in a Nationwide Assessment. *JACC Clin. Electrophysiol.* **2017**, *3*, 1296–1305. [CrossRef]
6. Chang, J.D.; Manning, W.J.; Ebrille, E.; Zimetbaum, P.J. Tricuspid Valve Dysfunction Following Pacemaker or Cardioverter-Defibrillator Implantation. *J. Am. Coll. Cardiol.* **2017**, *69*, 2331–2341. [CrossRef]
7. Trankle, C.R.; Gertz, Z.M.; Koneru, J.N.; Kasirajan, V.; Nicolato, P.; Bhardwaj, H.L.; Ellenbogen, K.A.; Kalahasty, G. Severe tricuspid regurgitation due to interaction with right ventricular permanent pacemaker or defibrillator leads. *Pacing Clin. Electrophysiol.* **2018**, *41*, 845–853. [CrossRef]
8. Ebrille, E.; Chang, J.D.; Zimetbaum, P.J. Tricuspid Valve Dysfunction Caused by Right Ventricular Leads. *Card. Electrophysiol. Clin.* **2018**, *10*, 447–452. [CrossRef]
9. Van De Heyning, C.M.; Elbarasi, E.; Masiero, S.; Brambatti, M.; Ghazal, S.; Al-Maashani, S.; Capucci, A.; Leong, D.; Shivalkar, B.; Saenen, J.B.; et al. Prospective Study of Tricuspid Regurgitation Associated With Permanent Leads After Cardiac Rhythm Device Implantation. *Can. J. Cardiol.* **2019**, *35*, 389–395. [CrossRef]
10. Abraham, W.T.; Burkhoff, D.; Nademanee, K.; Carson, P.; Bourge, R.; Ellenbogen, K.A.; Parides, M.; Kadish, A. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with systolic heart failure: Rationale, design, and baseline patient characteristics. *Am. Heart J.* **2008**, *156*, 641–648. [CrossRef]
11. Lang, R.M.; Badano, L.P.; Mor-Avi, V.; Afilalo, J.; Armstrong, A.; Ernande, L.; Flachskampf, F.A.; Foster, E.; Goldstein, S.A.; Kuznetsova, T.; et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J. Am. Soc. Echocardiogr.* **2015**, *28*, 1–39. [CrossRef]
12. Quiñones, M.A.; Otto, C.M.; Stoddard, M.; Waggoner, A.; Zoghbi, W.A. Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: A report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J. Am. Soc. Echocardiogr.* **2002**, *1*, 167–184.
13. Zoghbi, W.A.; Adams, D.; Bonow, R.O.; Enriquez-Sarano, M.; Foster, E.; Grayburn, P.A.; Hahn, R.T.; Han, Y.; Hung, J.; Lang, R.M.; et al. Recommendations for Non invasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J. Am. Soc. Echocardiogr.* **2017**, *30*, 303–371. [CrossRef] [PubMed]
14. Addetia, K.; Harb, S.C.; Hahn, R.T.; Kapadia, S.; Lang, R.M. Cardiac Implantable Electronic Device Lead-Induced Tricuspid Regurgitation. *JACC Cardiovasc. Imaging* **2019**, *12*, 622–636. [CrossRef] [PubMed]
15. Zhang, X.X.; Wei, M.; Xiang, R.; Lu, Y.M.; Zhang, L.; Li, Y.D.; Zhang, J.H.; Xing, Q.; Tang, B.P.; Zhou, X.H. Incidence, Risk Factors, and Prognosis of Tricuspid Regurgitation After Cardiac Implantable Electronic Device Implantation: A Systematic Review and Meta-analysis. *J. Cardiothorac. Vasc. Anesth.* **2021**, *25*, 1741–1755. [CrossRef]
16. Al-Mohaissen, M.A.; Chan, K.L. Prevalence and mechanism of tricuspid regurgitation following implantation of endocardial leads for pacemaker or cardioverter-defibrillator. *J. Am. Soc. Echocardiogr.* **2012**, *25*, 245–252. [CrossRef]
17. Alizadeh, A.; Sanati, H.R.; Haji-Karimi, M.; Yazdi, A.H.; Rad, M.A.; Haghjoo, M.; Emkanjoo, Z. Induction and aggravation of atrioventricular valve regurgitation in the course of chronic right ventricular apical pacing. *Europace* **2011**, *13*, 1587–1590. [CrossRef]
18. Yücel, G.; Fastner, C.; Hetjens, S.; Toepel, M.; Schmiel, G.; Yazdani, B.; Husain-Syed, F.; Liebe, V.; Rudic, B.; Akin, I.; et al. Impact of baseline left ventricular ejection fraction on long-term outcomes in cardiac contractility modulation therapy. *Pacing Clin. Electrophysiol.* **2022**, *45*, 639–648. [CrossRef]
19. Dreyfus, G.D.; Martin, R.P.; Chan, K.M.; Dulguerov, F.; Alexandrescu, C. Functional tricuspid regurgitation: A need to revise our understanding. *J. Am. Coll. Cardiol.* **2015**, *65*, 2331–2336. [CrossRef]

20. Margonato, D.; Ancona, F.; Ingallina, G.; Melillo, F.; Stella, S.; Biondi, F.; Boccellino, A.; Godino, C.; Margonato, A. Tricuspid Regurgitation in Left Ventricular Systolic Dysfunction: Marker or Target? *Front. Cardiovasc. Med.* **2021**, *8*, 702589. [CrossRef]
21. Contaldi, C.; De Vivo, S.; Martucci, M.L.; D'Onofrio, A.; Ammendola, E.; Nigro, G.; Errigo, V.; Pacileo, G.; Masarone, D. Effects of Cardiac Contractility Modulation Therapy on Right Ventricular Function: An Echocardiographic Study. *Appl. Sci.* **2022**, *12*, 7917–7923. [CrossRef]
22. Fukuda, S.; Gillinov, A.M.; Song, J.M.; Daimon, M.; Kongsaerepong, V.; Thomas, J.D.; Shiota, T. Echocardiographic insights into atrial and ventricular mechanisms of functional tricuspid regurgitation. *Am. Heart J.* **2006**, *152*, 1208–1214. [CrossRef] [PubMed]
23. Kim, H.K.; Kim, Y.J.; Park, J.S.; Kim, K.H.; Kim, K.B.; Ahn, H.; Sohn, D.W.; Oh, B.H.; Park, Y.B.; Choi, Y.S. Determinants of the severity of functional tricuspid regurgitation. *Am. J. Cardiol* **2006**, *98*, 236–242. [CrossRef]
24. Lin, G.; Nishimura, R.A.; Connolly, H.M.; Dearani, J.A.; Sundt, T.M., 3rd; Hayes, D.L. Severe symptomatic tricuspid valve regurgitation due to permanent pacemaker or implantable cardioverter-defibrillator leads. *J. Am. Coll. Cardiol.* **2005**, *45*, 1672–1675. [CrossRef]
25. Vinciguerra, M.; Sitges, M.; Luis Pomar, J.; Romiti, S.; Domenech-Ximenos, B.; D'Abramo, M.; Wretschko, E.; Miraldi, F.; Greco, E. Functional Tricuspid Regurgitation: Behind the Scenes of a Long-Time Neglected Disease. *Front. Cardiovasc. Med.* **2022**, *9*, 836441. [CrossRef] [PubMed]

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Review

Use of Levosimendan in Patients with Advanced Heart Failure: An Update

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Abstract: Levosimendan is an inodilator drug that, given its unique pharmacological actions and safety profile, represents a viable therapeutic option in patients with heart failure with reduced ejection fraction in the advanced stage of the disease (advHFrEF). Pulsed levosimendan infusion in patients with advHFrEF improves symptoms and clinical and hemodynamic status, prevents recurrent hospitalizations, and enables optimization of guidelines-directed medical therapy. Furthermore, considering its proprieties on right ventricular function and pulmonary circulation, levosimendan could be helpful for the prevention and treatment of the right ventricular dysfunction post-implanting a left ventricular assist device. However, to date, evidence on this issue is scarce and has yielded mixed results. Finally, preliminary experiences indicate that treatment with levosimendan at scheduled intervals may serve as a "bridge to transplant" strategy in patients with advHFrEF. In this review, we summarized the clinical pharmacology of levosimendan, the available evidence in the treatment of patients with advHFrEF, as well as a hypothesis for its use in patients with advanced heart failure with preserved ejection fraction.

Keywords: advanced heart failure; inodilators; levosimendan; pharmacologic therapy

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1. Introduction

Although pharmacologic and non-pharmacologic treatment of patients with heart failure (HF) with reduced ejection fraction (HFrEF) improves quality of life and survival rates [1], a variable percentage (up to 13%) of patients do not respond to conventional therapy, resulting in progression to the more advanced stage of the disease (advHFrEF) [2]. Because patients with advHFrEF often have a reduced tolerance to disease-modifying drugs [3], inotropes are frequently used to improve symptoms and quality of life and to reduce hospitalizations [4]. Among the inotropes, levosimendan has been demonstrated to achieve these goals in patients with advHFrEF [5]. In addition, it has been shown that levosimendan may be helpful in the prevention and treatment of the right ventricular dysfunction after a left ventricular assist device (LVAD) implant and as a "bridge to transplant" strategy in patients on a waiting list for a heart transplant [6]. In this review, we summarize the clinical pharmacology of levosimendan and the research outcomes for levosimendan in patients with advHFrEF, while also providing practical advice regarding the use of levosimendan in clinical practice

2. Pharmacology of Levosimendan

2.1. Pharmacokinetic of Levosimendan

Levosimendan is a pro-drug that presents linear kinetics without renal and hepatic impairment [7]. In clinical practice, it is administered intravenously, but levosimendan has an oral bioavailability of 85%, a volume of distribution of 0.2 L/Kg, and very high plasma protein binding (97–98%) [8]. In addition, levosimendan is extensively metabolized before excretion in urine and feces, primarily through conjugation with glutathione to form inactive metabolites [8]. The minor route of metabolization (approximately 6% of the total dose of levosimendan) is the intestinal transformation in an intermediate metabolite (OR-1855), which is further metabolized by acetylation into the active metabolite (OR-1896, Figure 1).

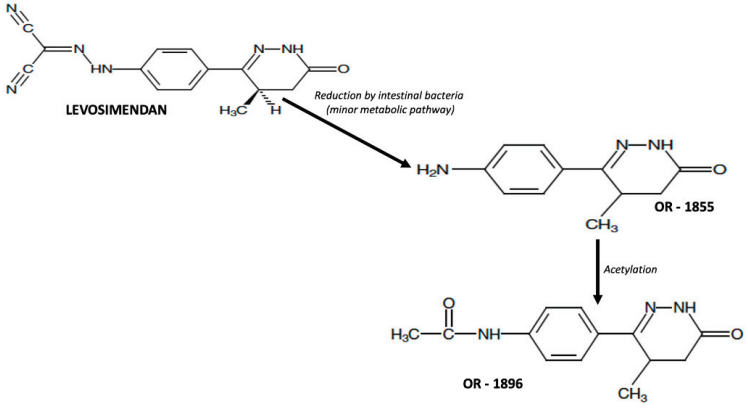

Figure 1. Metabolic pathway of transformation of levosimendan in its active metabolites.

Levosimendan has a half-life of around 1 h; therefore, even in patients with HFrEF, it has a rapid elimination from circulation at the end of the infusion. On the other hand, the half-life of levosimendan metabolites is roughly 80 h, with both OR-1855 and OR-1896 reaching their peak plasma concentrations at 48–72 after the levosimendan administration. This means that the pharmacodynamic effects persist for 10–14 days after infusion [9,10]. Comparative studies have shown that levosimendan's pharmacokinetics are not significantly affected by HF, mild to moderate renal and hepatic impairment [11,12]. In contrast, in patients with severe renal dysfunction, the half-life of OR-1855 and OR-1896 is prolonged by 1.5, and their area under the curve and peak concentrations are 2-fold higher [13].

Therefore, it has been suggested that the dose and infusion rate be reduced when levosimendan is used in patients with severe chronic kidney disease [14].

2.2. Pharmacodynamics of Levosimendan

Levosimendan possesses a triple mechanism of action [15]. First, the inotropic effect is due to calcium sensitization achieved through selective binding to the calcium-bound form of cardiac troponin C, resulting in increased cardiac contractility in the absence of alterations in cardiomyocyte electrophysiological homeostasis and with myocardial relaxation [16]. The second mechanism is the activation (resulting in the opening) of K^+ adenosine triphosphate (ATP)-dependent channels present in vascular smooth muscle cells; this mechanism results in improved oxygen delivery to the myocardium in the absence of increased oxygen demand [17] while also promoting arterial and venous vasodilation [18,19]. The third mechanism is the opening up of ATP-dependent K^+ channels in the mitochondria, producing a cardioprotective and organ-protective effect [20,21]. Finally, systemic effects have also been demonstrated, including anti-inflammatory [22] and antiapoptotic effects [23], although the clinical relevance of these effects is uncertain.

2.3. Side Effects and Contraindications of Levosimendan

Levosimendan is generally well tolerated in patients with HF. The most common adverse effects are secondary to vasodilatation and include hypotension, headache, and nausea [24].

Regarding arrhythmias, levosimendan infusion is associated with an increased incidence of atrial fibrillation compared with dobutamine and placebo [25,26].

However, unlike the other inotropes, levosimendan does not increase intracellular calcium concentration and myocardial oxygen consumption, meaning that ventricular arrhythmias are unlikely during levosimendan treatment [27].

Finally, hypokalemia is a typical side effect of levosimendan administration, but the mechanism responsible for this effect is not yet known [28].

Contraindications to the use of levosimendan include severe symptomatic hypotension (systolic blood pressure <70 mmHg), significant mechanical obstruction affecting ventricular filling or outflow, or both (i.e., severe mitral stenosis, severe aortic stenosis), severe renal impairment (i.e., creatinine clearance <30 mL/min/1.73 m^2), and severe hepatic impairment (i.e., MELD score >30).

3. Intermittent Levosimendan Infusion in Patients with advHFrEF

Several small-scale, non-randomized trials and registries of advHFrEF patients not eligible or waiting for a heart transplant or an LVAD implant have shown that repeated infusions of levosimendan improve symptoms [29] and clinical and hemodynamic status [30–32], prevent recurrent hospitalizations [33], and enable the optimization of guideline-directed medical therapy [34]. However, as highlighted in Table 1, different administration protocols were used in these studies, so the optimal administration strategy has not yet been identified.

Table 1. Summary of the clinical study on the repetitive infusion of levosimendan in patients with advHFrEF.

Study	N° of Patients	Levosimendan Dose	Time of Infusion	Interval of Infusion	Results
Nanas 2005 [35]	36	Bolus dose (6 mg/kg) plus Infusion rate (0.2 mcg/Kg/min). Levosimendan was added to dobutamine infusion	24 h	2 weeks for 45 days	Improvement in survival (6% vs. 61% $p = 0.0002$)
Parissis 2006 [36]	25	Bolus dose (6 mg/kg) plus Infusion rate (0.1–0.4 mcg/Kg/min)	24 h	3 weeks for 114 days	Reduction of LVEDVi (120 vs. 156 mL/m^2; $p < 0.01$), LVESVi (80 vs. 106 mL/m^2; $p < 0.01$) and NT-proBNP plasma levels (966 vs.1529 pg/mL; $p < 0.01$) increase of LVEF (26 vs. 22%, $p < 0.01$)
Mavrogeni 2007 [37]	50	Bolus dose (6 mg/kg) plus Infusion rate (0.1–0.2 mcg/Kg/min)	24 h	30 days for 6 months	Increase of LVEF (28 + 7 vs. 21 + 4%, $p = 0.003$) and LVFS (15 + vs. 11 + 3%, $p = 0.006$).
Papadopoulou [38]	20	No bolus dose Infusion rate (0.1 mcg/kg/min)	24 h	30 days for 6 months	Increase of LVEF (30.3 ± 6.9 vs. 32.1 ± 7.4%; $p = 0.01$) and quality of life (LIhFE score i 35.4 ± 18.6 vs. 22.2 ± 13.0; $p < 0.0001$).

Table 1. *Cont.*

Study	N° of Patients	Levosimendan Dose	Time of Infusion	Interval of Infusion	Results
Malfatto 2012 [39]	33	No bolus dose Infusion rate (0.1–0.4 mcg/kg/min)	24 h	30 days for 12 months	Increase of LVEF (25.9 + 5.1 vs. 28.7 ± 5.4%; $p < 0.05$) and CI (2.34 + 0.58 vs. 2.77 + 0.65 L/min/m2; $p < 0.05$). Reduction of PASP (51.8 ± 15.4 vs. 42.6 ± 13.0 mmHg; $p < 0.05$), E/e' ratio (18.3 ± 8.9 vs. 13.8 ± 4.1; $p < 0.05$)
Oliva (RELEVANT-HF) 2018 [33]	185	No bolus dose Infusion rate (0.2 mcg/Kg/min)	24 h	3–4 weeks for 6 months	Reduction of days in hospital (9.4 vs. 2.8 days; $p < 0.0001$) and length of HF admissions (17.4 vs. 21.6 days; $p = 0.0001$)
Masarone 2020 [29]	15	No bolus dose Infusion rate (0.2 mcg/Kg/min	6 h	2 weeks for 12 months	Reduction of HF-related hospitalizations (2 vs. 10; $p < 0.05$) and increase of distance walked at six-minute walking test (282 ± 52 vs. 248 ± 30 meters; $p < 0.05$)
Altenberger (LevoRep) 2014 [40]	120	No bolus dose Infusion rate (0.2 mcg/Kg/min)	6 h	2 weeks for 42 days	No increase in the distance walked on the 6-minute walking test and no increase in score on the Kansas City Cardiomyopathy Questionnaire (19% vs. 15%; OR.25; 95% CI 0.44–3.59; $p = 0.810$).
Comín-Colet (LION HEART) 2018 [41]	69	No bolus dose Infusion rate (0.2 mcg/Kg/min)	6 h	2 weeks for 6 months	Reduction of NT-proBNP plasma levels (mean change in NT-proBNP–1446 vs. –1320 pg/mL; $p < 0.001$) and of the rate of HF-related hospitalization (hazard ratio 0.25; 95% CI 0.11–0.56; $p = 0.001$)
García-González (LAICA) 2021 [42]	97	No bolus dose Infusion rate (0.1 mcg/Kg/min)	24 h	4 weeks for 12 months	No reduction in HF-related hospitalizations (HR 0.66; 95% CI, 0.32–1.32; $p = 0.24$). Reduction of cumulative incidence of HF-related hospitalizations and death at 1 month (5.7% vs. 25.9%; $p = 0.004$) and 3 months (17.1% vs. 48.1%; $p = 0.001$). Improvement in survival (log-rank: 4.06; $p = 0.044$).

LVEDVi: left ventricular end-diastolic diameter index, LVESVi: left ventricular end-systolic volume index, NT-proBNP: N-terminal pro-brain natriuretic peptides, LVEF: left ventricular ejection fraction, LVFS: left ventricular fractional shortening, CI: cardiac index, PASP: pulmonary artery systolic pressure, HF: heart failure.

Three randomized clinical trials on the use of levosimendan in advHFrEF patients have also been conducted. The trial LevoRep (efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure) enrolled 120 outpatients with advHFrEF randomized to levosimendan (0.2 μg/kg/min for 6 hours at 2-week intervals over 6 weeks) or placebo [40]. In this trial, levosimendan failed to achieve the primary endpoint (a composite endpoint of improvement in the 6-min walk test ≥20% and increase in score on the Kansas City Cardiomyopathy Questionnaire ≥15%) (19% vs. 15%; OR 1.25; 95% CI 0.44–3.59; $p = 0.810$). In the LIONHEART (efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure) trial, 69 patients with advHFrEF were randomized to levosimendan (0.2 μg/kg/min for 6 hours every 2 weeks for 12 weeks) versus placebo [41]. At the end of the study, patients in the levosimendan arm significantly reduced NT-proBNP plasma levels more than the

placebo group (mean change in NT-proBNP–1446 vs.–1320 pg/mL; $p < 0.001$). Moreover, the patients treated with levosimendan experienced a reduction in HF-related hospitalization (HR 0.25; 95% CI 0.11–0.56; $p = 0.001$) and were shown to have the lowest probability of a clinically significant decline in quality of life ($p = 0.022$).

In the LAICA (efficacy and safety of intermittent repeated levosimendan infusions in advanced heart failure patients) study, 97 patients were randomized to levosimendan (0.1 μg/kg/min as a continuous 24-h intravenous infusion administered once monthly for 1 year) vs. placebo [42]. In this trial, levosimendan did not reduce the rate of readmissions for acute decompensated HF (HR 0.66; 95% CI, 0.32–1.32; $p = 0.24$). However, patients in the treatment arm exhibited a significantly lower cumulative incidence of acute decompensation of HF and/or death at 1 month (5.7% vs. 25.9%; $p = 0.004$) and 3 months (17.1% vs. 48.1%; $p = 0.001$) and a significant improvement in survival during 12 months of treatment (log-rank: 4.06; $p = 0.044$).

A recent meta-analysis of 984 patients (727 treated with levosimendan and 257 in the control group) showed that levosimendan treatment was associated with an improvement in NYHA class ($p < 0.001$), left ventricular ejection fraction ($p < 0.001$), as well as a reduction in natriuretic peptide levels ($p < 0001$) [43]. Furthermore, although all-cause mortality did not differ between the two groups, cardiovascular death was lower in levosimendan-treated patients than in controls ($p = 0.02$). Taking into account the data from both these studies and the meta-analyses [44,45], the generally accepted conclusion is that the repetitive application of levosimendan is likely to be effective, feasible, and safe in patients with advHFrEF. Furthermore, the author believes that both 6-h and 24-h pulsed administration of levosimendan are effective in patients with advHFrEF.

The ongoing trial LEODOR (Repetitive Levosimendan Infusion for Patients with Advanced Chronic Heart Failure trial; NCT03437226) will test the efficacy and safety of intermittent levosimendan therapy in patients with advHFrEF in the vulnerable phase, offering additional evidence regarding the use of levosimendan in this challenging patient population [46]. The LEIA-HF (Levosimendan In Ambulatory Heart Failure Patients; NCT04705337) is another multicenter, randomized, double-blind, placebo-controlled trial whose purpose is to evaluate whether the repetitive use of continuous 24-h infusions of levosimendan every 4 weeks for 48 weeks reduces the incidence of adverse cardiovascular events in outpatients with chronic advHFrEF [47].

4. Levosimendan in Patients with advHFrEF Undergoing LVAD Implantation

Left ventricular assist device (LVAD) implant is an effective management strategy for patients with advHFrEF [48]. In particular, the new generation devices (specifically the HeartMate 3) have short- and medium-term survival rates comparable to heart transplantation [49]. Unfortunately, though, up to 25% of patients who undergo LVAD implantation develop post-implanted right ventricular heart failure with significantly increased morbidity and mortality rates [50]. Given the pharmacological effects of levosimendan on the right ventricle and pulmonary circulation [51,52], the impact of pretreatment with levosimendan on right ventricular dysfunction after LVAD implantation has been evaluated.

Sponga et al. analyzed, in a single-center study, the effects of levosimendan infusion on hemodynamic parameters in patients with borderline right ventricular function before urgent LVAD implantation and the prognostic effect of response to levosimendan infusion [53]. Treatment with levosimendan resulted in a dose-dependent increase in cardiac index by 21% ($p = 0.014$), a decrease in pulmonary pressure by 12% ($p = 0.003$), S and a decrease in pulmonary capillary wedge pressure and central venous pressure by 15% ($p = 0.028$ and $p = 0.016$). Notably, hemodynamic improvements persisted for 24 h after discontinuing levosimendan infusion in patients who survived but not in those who subsequently died of right ventricular failure. Based on these results, the authors stated that hemodynamic response after levosimendan infusion could predict mortality and right ventricular dysfunction in advHFrEF patients undergoing urgent LVAD implantation. In a retrospective post hoc analysis, 9 patients with LVAD support received levosimendan

without experiencing any adverse effects. At 24 months, the survival rate was 89%, which is a better result than that seen in the data from the fifth INTERMACS registry, which reports a 2-year survival of 75% [54]. However, the lack of a control group does not allow firm conclusions to be made regarding the benefit of levosimendan in these patients; also, in this study, post-LVAD right ventricular dysfunction was not assessed.

In a retrospective single-center study, 85 patients with advHFrEF and LVAD exhibited improved right ventricular stroke work index (406.26 ± 251.30 vs. 275.48 ± 200.51 g/m^2/b/min; $p = 0.025$) and reduced pulmonary vascular resistance (4.0 ± 1.8 vs. 3.0 ± 1.4 wood units; $p = 0.038$) when levosimendan was added to other inotropes; however, no significant difference in early and late right ventricular dysfunction occurred [55]. In another single-center study, 84 patients with advHFrEF who underwent LVAD implant were randomized to levosimendan and placebo. No difference in the right ventricular failure rate was observed between the two groups (7.5% vs. 13.6%; $p = 0.43$) as well as no significant difference in in-hospital (5% vs. 4.5%; $p > 0.999$) and long-term mortality (10% vs. 27.3%; $p = 0.64$) rates [56].

Moreover, a recent meta-analysis of 106 patients with advHFrEF who underwent LVAD implant [57] showed that levosimendan administration was associated with hemodynamic improvements and improved organ perfusion. However, such hemodynamic benefits are not associated with a reduction in mortality, which is likely a result of the low statistical power of the studies conducted to date.

A multicenter randomized, placebo-controlled trial is needed to obtain conclusive results.

5. Levosimendan in Patients with advHFrEF on the Waiting List for a Heart Transplant

Heart transplantation remains the gold-standard treatment for selected patients with advanced HF [58].

However, organ shortages continue to limit the number of transplants that can be performed each year, thus increasing the waiting time for patients to receive a compatible and suitable heart [59].

Intermittent use of levosimendan may be helpful in this challenging clinical setting. For example, in a single-center study, 11 patients on the waiting list for heart transplantation [60] were given scheduled infusions of levosimendan (a 6-h infusion every 2 months at a dose of 0.1–0.2 mg/kg/min, depending on the patient's blood pressure). This therapeutic strategy reduced both the rate of rehospitalization and the need for urgent heart transplantation (22% vs. 44% in Spanish registries). Although these results are preliminary and inconclusive, expert consensus points to levosimendan as a viable therapeutic option as a bridge to transplantation [61] in patients who are not candidates for LVAD to ensure adequate end-organ perfusion (and thus prevent the onset of multiorgan failure) and to avoid increased pulmonary vascular pressures and resistances (and therefore avoid patient exclusion from the heart transplant waiting list or the need for heart-lung transplantation).

6. Levosimendan in Patients with advHFpEF as a Future Perspective

In this review, we summarize the available evidence on the use of levosimendan in patients with advHFrEF; however, a sizeable proportion of patients with advanced HF have a preserved ejection fraction (advHFpEF) [62]. In addition, such patients have unique hemodynamic features such as a persistent elevation of pulmonary capillary wedge pressures (PCWP) and pulmonary pressure at rest or during exertion as well as an inability to appropriately augment the cardiac index during exercise [63,64].

In the Levosimendan Improves Hemodynamics and Exercise Tolerance in PH-HFpEF (HELP) trial, 37 patients with advHFpEF were randomized to levosimendan and placebo. In this preliminary study, levosimendan reduced PCWP during exercise (−3.9 ± 2.0 mm Hg; $p = 0.047$) with a trend in the increase of cardiac index during exercise (2.5 ± 0.8 at baseline vs. 3.2 ± 1.1 at 25 watts). Furthermore, levosimendan treatment resulted in a 29.3-meter rise in the distance walked during the 6-minute walking test compared with placebo (95% CI: 2.5 to 56.1; $p = 0.033$) [65].

Although these data are preliminary, further studies may confirm that levosimendan improves exercise capacity and quality of life in patients with advHFpEF.

7. Tips and Tricks for the Use of Levosimendan in Clinical Practice

In the previous sections, we reviewed the evidence on the use of levosimendan in patients with advanced heart failure; in this section, we will offer practical advice regarding how to use levosimendan in patients with advHFrEF to facilitate the use of this drug in common clinical practice.

According to European Society of Cardiology guidelines [66], periodic infusion of levosimendan may be considered a palliative strategy or as a "bridge to transplant/LVAD" strategy in patients with advHFrEF with evidence of organ hypoperfusion.

For both indications, we recommend the first administration of levosimendan be performed in an inpatient setting and in 24 h at a dose of 0.2 µg/kg/min to verify both safety (particularly in terms of the appearance of symptomatic hypotension and ventricular tachycardias) and efficacy. For palliative purposes, the response to levosimendan infusion can be assessed as a subjective reduction of symptoms and improvement of quality of life; in doubtful cases, the assessment of NT-proBNP plasma values can be helpful. In contrast, in the case of a "bridge to transplant/LVAD" strategy, we recommend objectifying the efficacy of levosimendan by echocardiography (improvement of biventricular systolic function, reduction of pulmonary circulation pressures) or, in doubtful cases, by right heart catheterization.

Subsequent dosing can be given in either 24-h or 6-h periods, depending on the patient's profile (Figure 2).

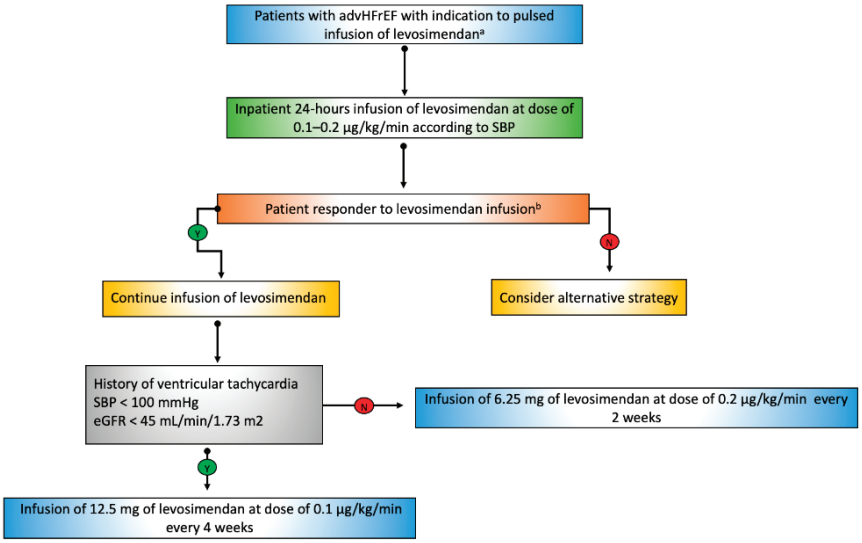

Figure 2. Therapeutic algorithm for the use of pulsed infusion of levosimendan in patients with advHFrEF. SBP: systolic blood pressure, eGFR: estimated glomerular filtration rate. a: Indication to pulsed infusion of levosimendan INTERMACS Class IV (frequent-flyers patients), progressive deterioration of kidney function, combined precapillary and post-capillary pulmonary hypertension, persistently high levels of NT-proBNP despite guidelines-directed medical therapy. b: subjective reduction of symptoms and improvement of quality of life; in doubtful cases, the assessment of NT-proBNP plasma values (palliative purpose); improvement of biventricular systolic function and reduction of pulmonary circulation pressures.

In patients with systolic blood pressure >100 mmHg, mildly or moderately reduced renal function (estimated glomerular filtrate > 45 mL/min/1.73 m^2), and no history of complex ventricular arrhythmias, we perform administration of 6.25 mg levosimendan at a dosage of 0.2 μg/kg/min every two weeks.

In contrast, in patients with systolic blood pressure <100 mmHg, severely reduced renal function (estimated glomerular filtrate >30 <45 mL/min/1.73 m^2), and a history of complex ventricular arrhythmias, we recommend administration of 12.5 mg levosimendan at a dosage of 0.1 μg/kg/min every four weeks.

The latter administration scheme can also be used in carefully selected advHFrEF patients with glomerular filtrate >15 mL/min/1.73 m^2 <30 mL/min/1.73 m^2 when levosimendan infusion for palliative purposes documents marked improvement in symptoms and quality of life.

Finally, in patients with an indication for LVAD implantation, we recommend the day before the implant, 24-h administration of levosimendan at a dose of 0.2 μg/kg/min combined with noradrenaline or adrenaline 0.1–0.2 μg/kg/min in patients with a high risk of right ventricular dysfunction post-implantation of LVAD (e.g., patients with right ventricular failure risk score >5.5).

8. Conclusions

With its unique pharmacological action and safety profile, levosimendan represents a viable therapeutic option in patients with advHFrEF to prevent HF-related hospitalizations, improve quality of life, and serve as a "bridge to transplant" strategy. In its first twenty years, levosimendan has been transformed from an innovative infusion for the management of acute HF to a safe and potentially effective option for outpatients with advHFrEF.

Over the next several years, randomized trials will hopefully establish a role for levosimendan in preventing right ventricular dysfunction post LVAD implantation and in the treatment of advHFpEF.

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References

1. Metra, M.; Teerlink, J.R. Heart failure. *Lancet* **2017**, *390*, 1981–1995. [CrossRef]
2. Kępińska, K.; Adamczak, D.M.; Kałużna-Oleksy, M. Advanced heart failure: A review. *Adv. Clin. Exp. Med.* **2019**, *28*, 1143–1148. [CrossRef] [PubMed]
3. Masarone, D.; Kittleson, M.; Petraio, A.; Pacileo, G. Advanced heart failure: State of the art and future directions. *Rev. Cardiovasc. Med.* **2022**, *23*, 48–58. [CrossRef] [PubMed]
4. Fang, J.C.; Ewald, G.A.; Allen, L.A.; Butler, J.; Canary, C.A.W.; Colvin-Adams, M.; Dickinson, M.G.; Levy, P.; Stough, W.G.; Sweitzer, N.K.; et al. Advanced (Stage D) Heart Failure: A Statement from the Heart Failure Society of America Guidelines Committee. *J. Card. Fail.* **2015**, *21*, 519–534. [CrossRef] [PubMed]
5. Vishram-Nielsen, J.K.K.; Tomasoni, D.; Gustafsson, F.; Metra, M. Contemporary Drug Treatment of Advanced Heart Failure with Reduced Ejection Fraction. *Drugs* **2022**, *82*, 375–405. [CrossRef] [PubMed]
6. Masarone, D.; Melillo, E.; Gravino, R.; Errigo, V.; Martucci, M.L.; Caiazzo, A.; Petraio, A.; Pölzl, G.; Pacileo, G. Inotropes in Patients with Advanced Heart Failure: Not only palliative care. *Heart Fail. Clin.* **2021**, *17*, 587–598. [CrossRef] [PubMed]
7. Antila, S.; Sundberg, S.; Lehtonen, L.A. Clinical pharmacology of levosimendan. *Clin. Pharm.* **2007**, *46*, 535–552. [CrossRef] [PubMed]

8. Lehtonen, L.A.; Antila, S.; Pentikäinen, P.J. Pharmacokinetics and pharmacodynamics of intravenous inotropic agents. *Clin. Pharm.* **2004**, *43*, 187–203. [CrossRef] [PubMed]
9. Cleland, J.G.F.; Nikitin, N.; James, M. Levosimendan: First in a new class of inodilator for acute and chronic severe heart failure. *Expert Rev. Cardiovasc. Ther.* **2004**, *2*, 9–19. [CrossRef]
10. Figgitt, D.P.; Gillies, P.S.; Goa, K.L. Levosimendan. *Drugs* **2001**, *61*, 613–627. [CrossRef] [PubMed]
11. Papp, Z.; Agostoni, P.; Alvarez, J.; Bettex, D.; Bouchez, S.; Brito, D.; Černý, V.; Comin-Colet, J.; Crespo-Leiro, M.G.; Delgado, J.F.; et al. Levosimendan efficacy and safety: 20 years of SIMDAX in clinical use. *Card Fail Rev.* **2020**, *6*, e19. [CrossRef]
12. Puttonen, J.; Kantele, S.; Ruck, A.; Ramela, M.; Hakkinen, S.; Kivikko, M.; Pentikainen, P.J. Pharmacokinetics of intravenous levosimendan and its metabolites in subjects with hepatic impairment. *J. Clin. Pharmacol.* **2008**, *48*, 445–454. [CrossRef] [PubMed]
13. Puttonen, J.; Kantele, S.; Kivikko, M.; Häkkinen, S.; Harjola, V.-P.; Koskinen, P.; Pentikäinen, P.J. Effect of severe renal failure and haemodialysis on the pharmacokinetics of levosimendan and its metabolites. *Clin Pharm.* **2007**, *46*, 235–246. [CrossRef] [PubMed]
14. Farmakis, D.; Agostoni, P.; Baholli, L.; Bautin, A.; Comin-Colet, J.; Crespo-Leiro, M.G.; Fedele, F.; García-Pinilla, J.M.; Giannakoulas, G.; Grigioni, F.; et al. A pragmatic approach to the use of inotropes for the management of acute and advanced heart failure: An expert panel consensus. *Int. J. Cardiol.* **2019**, *297*, 83–90. [CrossRef]
15. Papp, Z.; Csapo, K.; Pollesello, P.; Haikala, H.; Edes, I. Pharmacological mechanisms contributing to the clinical efficacy of levosimendan. *Cardiovasc. Drug Rev.* **2005**, *23*, 71–98. [CrossRef] [PubMed]
16. Haikala, H.; Kaivola, J.; Nissinen, E.; Wall, P.; Levijoki, J.; Linden, I.B. Cardiac troponin C as a target protein for a novel calcium sensitizing drug, levosimendan. *J. Mol. Cell Cardiol.* **1995**, *27*, 1859–1866. [CrossRef]
17. Nieminen, M.S.; Pollesello, P.; Vajda, G.; Papp, Z. Effects of levosimendan on the energy balance: Preclinical and clinical evidence. *J. Cardiovasc. Pharmacol.* **2009**, *53*, 302–310. [CrossRef] [PubMed]
18. Kopustinskiene, D.M.; Pollesello, P.; Saris, N.E. Levosimendan is a mitochondrial K (ATP) channel opener. *Eur. J. Pharmacol.* **2011**, *428*, 311–314. [CrossRef]
19. Burkhoff, D.; Rich, S.; Pollesello, P.; Papp, Z. Levosimendan-induced venodilation is mediated by opening of potassium channels. *ESC Heart Fail.* **2021**, *8*, 4454–4464. [CrossRef] [PubMed]
20. Milligan, D.J.; Fields, A.M. Levosimendan: Calcium sensitizer and inodilator. *Anesthesiol. Clin.* **2010**, *28*, 753–760. [CrossRef] [PubMed]
21. Ng, T.M.; Akhter, M.W. Levosimendan: Dual mechanisms for acute heart failure and beyond? *Minerva Cardioangiol.* **2005**, *53*, 565–584. [PubMed]
22. Trikas, A.; Antoniades, C.; Latsios, G.; Vasiliadou, K.; Karamitros, I.; Tousoulis, D.; Tentolouris, C.; Stefanadis, C. Long-term effects of levosimendan infusion on inflammatory processes and sFas in patients with severe heart failure. *Eur. J. Heart Fail.* **2006**, *8*, 804–809. [CrossRef] [PubMed]
23. Parissis, J.T.; Adamopoulos, S.; Antoniades, C.; Kostakis, G.; Rigas, A.; Kyrzopoulos, S.; Iliodromitis, E.; Kremastinos, D. Effects of levosimendan on circulating pro-inflammatory cytokines and soluble apoptosis mediators in patients with decompensated advanced heart failure. *Am. J. Cardiol.* **2004**, *93*, 1309–1312. [CrossRef] [PubMed]
24. Mebazaa, A.; Erhardt, L. Levosimendan: A new dual-action drug in the treatment of acute heart failure. *Int. J. Clin. Pract.* **2003**, *57*, 410–416.
25. Mebazaa, A.; Nieminen, M.S.; Packer, M.; Cohen-Solal, A.; Kleber, F.X.; Pocock, S.J.; Thakkar, R.; Padley, R.J.; Põder, P.; Kivikko, M.; et al. Levosimendan vs. dobutamine for patients with acute decompensated heart failure: The SURVIVE randomized trial. *JAMA* **2007**, *297*, 1883–1891. [CrossRef]
26. Packer, M.; Colucci, W.; Fisher, L.; Massie, B.M.; Teerlink, J.R.; Young, J.; Padley, R.J.; Thakkar, R.; Delgado-Herrera, L.; Salon, J.; et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC Heart Fail.* **2013**, *1*, 103–111. [CrossRef]
27. Silva-Cardoso, J.; Ferreira, J.; Oliveira-Soares, A.; Martins-de-Campos, J.; Fonseca, C.; Lousada, N.; Ilídio-Moreira, J.; Rabaçal, C.; Damasceno, A.; Amorim, S.; et al. Effectiveness and safety of levosimendan in clinical practice. *Rev. Port. Cardiol.* **2009**, *28*, 143–154.
28. Moreno, N.; Tavares-Silva, M.; Lourenço, A.P.; Oliveira-Pinto, J.; Henriques-Coelho, T.; Leite-Moreira, A.F. Levosimendan: The current situation and new prospects. *Rev. Port. Cardiol.* **2014**, *33*, 795–800. [CrossRef]
29. Masarone, D.; Valente, F.; Verrengia, M.; Ammendola, E.; Gravino, R.; D'Alterio, G.; Petraio, A.; Pacileo, G. Efficacy and safety of repeated infusion of levosimendan in outpatients with advanced heart failure: A real-world experience. *J. Cardiovasc. Med.* **2020**, *21*, 919–921. [CrossRef]
30. Masarone, D.; Melillo, E.; Errigo, V.; Martucci, M.L.; Pacileo, R.; Pollesello, P.; Petraio, A.; Pacileo, G. Hemodynamic Effects of Levosimendan in Outpatients with Advanced Heart Failure: An Echocardiographic Pilot Study. *J. Cardiovasc. Pharmacol.* **2022**, *79*, e36–e40. [CrossRef]
31. Mushtaq, S.; Andreini, D.; Farina, S.; Salvioni, E.; Pontone, G.; Sciomer, S.; Volpato, V.; Agostoni, P. Levosimendan improves exercise performance in patients with advanced chronic heart failure. *ESC Heart Fail.* **2015**, *2*, 133–141. [CrossRef] [PubMed]
32. Apostolo, A.; Vignati, C.; Della Rocca, M.; De Martino, F.; Berna, G.; Campodonico, J.; Contini, M.; Muratori, M.; Palermo, P.; Mapelli, M.; et al. Why Levosimendan Improves the Clinical Condition of Patients with Advanced Heart Failure: A Holistic Approach. *J. Card. Fail.* **2022**, *28*, 509–514. [CrossRef] [PubMed]

33. Oliva, F.; Perna, E.; Marini, M.; Nassiacos, D.; Cirò, A.; Malfatto, G.; Morandi, F.; Caico, I.; Perna, G.; Meloni, S.; et al. Scheduled intermittent inotropes for Ambulatory Advanced Heart Failure. The RELEVANT-HF multicentre collaboration. *Int. J. Cardiol.* **2018**, *272*, 255–259. [CrossRef] [PubMed]
34. Masarone, D.; Kittleson, M.M.; Martucci, M.L.; Valente, F.; Gravino, R.; Verrengia, M.; Ammendola, E.; Contaldi, C.; Di Palma, V.; Caiazzo, A.; et al. Levosimendan as a "Bridge to Optimization" in Patients with Advanced Heart Failure with Reduced Ejection-A Single-Center Study. *J. Clin. Med.* **2022**, *11*, 4227. [CrossRef] [PubMed]
35. Nanas, J.N.; Papazoglou, P.; Tsagalou, E.P.; Ntalianis, A.; Tsolakis, E.; Terrovitis, J.V.; Kanakakis, J.; Nanas, S.N.; Alexopoulos, G.P.; Anastasiou-Nana, M.I. Efficacy and safety of intermittent, long-term, concomitant dobutamine and levosimendan infusions in severe heart failure refractory to dobutamine alone. *Am. J. Cardiol.* **2005**, *95*, 768–771. [CrossRef]
36. Parissis, J.T.; Adamopoulos, S.; Farmakis, D.; Filippatos, G.; Paraskevaidis, I.; Panou, F.; Iliodromitis, E.; Kremastinos, D.T. Effects of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal and immune activation in patients with advanced heart failure. *Heart* **2006**, *92*, 1768–1772. [CrossRef]
37. Mavrogeni, S.; Giamouzis, G.; Papadopoulou, E.; Thomopoulou, S.; Dritsas, A.; Athanasopoulos, G.; Adreanides, E.; Vassiliadis, I.; Spargias, K.; Panagiotakos, D.; et al. A 6-month follow-up of intermittent levosimendan administration effect on systolic function, specific activity questionnaire, and arrhythmia in advanced heart failure. *J. Card. Fail.* **2007**, *13*, 556–559. [CrossRef]
38. Papadopoulou, E.F.; Mavrogeni, S.I.; Dritsas, A.; Cokkinos, D.V. Assessment of quality of life using three activity questionnaires in heart failure patients after monthly, intermittent administration of levosimendan during a six-month period. *Hellenic. J. Cardiol.* **2009**, *50*, 269–274.
39. Malfatto, G.; Della Rosa, F.; Villani, A.; Rella, V.; Branzi, G.; Facchini, M.; Parati, G. Intermittent levosimendan infusions in advanced heart failure: Favourable effects on left ventricular function, neurohormonal balance, and one-year survival. *J. Cardiovasc. Pharmacol.* **2012**, *60*, 450–455. [CrossRef]
40. Altenberger, J.; Parissis, J.T.; Costard-Jaeckle, A.; Winter, A.; Ebner, C.; Karavidas, A.; Sihorsch, K.; Avgeropoulou, E.; Weber, T.; Dimopoulos, L.; et al. Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: A multicentre randomized trial. *Eur. J. Heart Fail.* **2014**, *16*, 898–906. [CrossRef]
41. Comín-Colet, J.; Manito, N.; Segovia-Cubero, J.; Delgado, J.; Pinilla, J.M.G.; Almenar, L.; Crespo-Leiro, M.G.; Sionis, A.; Blasco, T.; Pascual-Figal, D.; et al. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: The LION-HEART multicentre randomised trial. *Eur. J. Heart Fail.* **2018**, *20*, 1128–1136. [CrossRef] [PubMed]
42. García-González, M.J.; Perona, A.A.; Padron, A.L.; Rull, J.L.M.; Martínez-Sellés, M.; Martin, M.D.M.; Díaz, J.L.; Fernandez, S.L.; Oficialdegui, P.O.; Sosa, A.J. Efficacy and safety of intermittent repeated levosimendan infusions in advanced heart failure patients: The LAICA study. *ESC Heart Fail.* **2021**, *8*, 4820–4831. [CrossRef] [PubMed]
43. Elsherbini, H.; Soliman, O.; Zijderhand, C.; Lenzen, M.; Hoeks, S.E.; Kaddoura, R.; Izham, M.; Alkhulaifi, A.; Omar, A.S.; Caliskan, K. Intermittent levosimendan infusion in ambulatory patients with end-stage heart failure: A systematic review and meta-analysis of 984 patients. *Heart Fail. Rev.* **2022**, *27*, 493–505. [CrossRef] [PubMed]
44. Cui, D.; Liao, Y.; Li, G.; Chen, Y. Levosimendan Can Improve the Level of B-Type Natriuretic Peptide and the Left Ventricular Ejection Fraction of Patients with Advanced Heart Failure: A Meta-analysis of Randomized Controlled Trials. *Am. J. Cardiovasc. Drugs* **2021**, *21*, 73–81. [CrossRef] [PubMed]
45. Silvetti, S.; Belletti, A.; Fontana, A.; Pollesello, P. Rehospitalization after intermittent levosimendan treatment in advanced heart failure patients: A meta-analysis of randomized trials. *ESC Heart Fail.* **2017**, *4*, 595–604. [CrossRef]
46. Pölzl, G.; Birgani, S.A.; Comín-Colet, J.; Delgado, J.F.; Fedele, F.; García-Gonzáles, M.J.; Gustafsson, F.; Masip, J.; Papp, Z.; Störk, S.; et al. Repetitive levosimendan infusions for patients with advanced chronic heart failure in the vulnerable post-discharge period. *ESC Heart Fail.* **2019**, *6*, 174–181. [CrossRef]
47. Tycińska, A.; Gierlotka, M.; Bartuś, S.; Gąsior, M.; Główczyńska, R.; Grześk, G.; Jaguszewski, M.; Kasprzak, J.D.; Kubica, J.; Legutko, J.; et al. Repetitive use of LEvosimendan in Ambulatory Heart Failure patients (LEIA-HF)—The rationale and study design. *Adv. Med. Sci.* **2022**, *67*, 18–22. [CrossRef]
48. Jefferson, H.L.; Kent, W.D.T.; MacQueen, K.T.; Miller, R.J.H.; Holloway, D.D.; Hassanabad, A.F. Left ventricular assist devices: A comprehensive review of major clinical trials, devices, and future directions. *J. Card. Surg.* **2021**, *36*, 1480–1491. [CrossRef]
49. McNamara, N.; Narroway, H.; Williams, M.; Brookes, J.; Farag, J.; Cistulli, D.; Bannon, P.; Marasco, S.; Potapov, E.; Loforte, A. Contemporary outcomes of continuous-flow left ventricular assist devices-a systematic review. *Ann. Cardiothorac. Surg.* **2021**, *10*, 186–208. [CrossRef]
50. Kapelios, C.J.; Lund, L.H.; Wever-Pinzon, O.; Selzman, C.H.; Myers, S.L.; Cantor, R.S.; Stehlik, J.; Chamogeorgakis, T.; McKellar, S.H.; Koliopoulou, A.; et al. Right Heart Failure Following Left Ventricular Device Implantation: Natural History, Risk Factors, and Outcomes: An Analysis of the STS INTERMACS Database. *Circ. Heart Fail.* **2022**, *15*, e008706. [CrossRef]
51. Hansen, M.S.; Andersen, A.; Nielsen-Kudsk, J.E. Levosimendan in pulmonary hypertension and right heart failure. *Pulm. Circ.* **2018**, *8*, 2045894018790905. [CrossRef] [PubMed]
52. Hu, Y.; Wei, Z.; Zhang, C.; Lu, C.; Zeng, Z. The effect of levosimendan on right ventricular function in patients with heart dysfunction: A systematic review and meta-analysis. *Sci. Rep.* **2021**, *11*, 24097. [CrossRef]
53. Sponga, S.; Ivanitskaia, E.; Potapov, E.; Krabatsch, T.; Hetzer, R.; Lehmkuhl, H. Preoperative treatment with levosimendan in candidates for mechanical circulatory support. *ASAIO J.* **2012**, *58*, 6–11. [CrossRef] [PubMed]

54. Theiss, H.D.; Grabmaier, U.; Kreissl, N.; Hagl, C.; Steinbeck, G.; Sodian, R.; Franz, W.-M.; Kaczmarek, I. Preconditioning with levosimendan before implantation of left ventricular assist devices. *Artif. Organs.* **2014**, *38*, 231–234. [CrossRef] [PubMed]
55. Kocabeyoglu, S.S.; Kervan, U.; Sert, D.E.; Karahan, M.; Aygun, E.; Beyazal, O.F.; Unal, E.U.; Akin, Y.; Demirkan, B.; Pac, M. Optimization with levosimendan improves outcomes after left ventricular assist device implantation. *Eur. J. Cardio-Thoracic Surg.* **2020**, *57*, 176–182. [CrossRef] [PubMed]
56. Segev, A.; Lavee, J.; Kassif, Y.; Shemesh, Y.; Kogan, A.; Freimark, D.; Morgan, A.; Lotan, D.; Itelman, E.; Grupper, A. Effect of levosimendan infusion prior to left ventricular assist device implantation on right ventricular failure. *J. Cardiothorac. Surg.* **2022**, *17*, 158–164. [CrossRef]
57. Abdelshafy, M.; Elsherbini, H.; Elkoumy, A.; Simpkin, A.J.; Elzomor, H.; Caliskan, K.; Soliman, O. Perioperative Levosimendan Infusion in Patients with End-Stage Heart Failure Undergoing Left Ventricular Assist Device Implantation. *Front. Cardiovasc. Med.* **2022**, *9*, 888136. [CrossRef]
58. Shah, K.S.; Kittleson, M.M.; Kobashigawa, J.A. Updates on Heart Transplantation. *Curr. Heart Fail. Rep.* **2019**, *16*, 150–156. [CrossRef]
59. Bastani, B. The present and future of transplant organ shortage: Some potential remedies. *J. Nephrol.* **2020**, *33*, 277–288. [CrossRef]
60. Ponz de Antonio, I.; de Juan Bagudá, J.S.; Rodríguez Chaverri, A.; García-Cosío, C.; Arribas Ynsaurriaga, F.; Delgado Jiménez, J.F. Levosimendan as bridge to transplant in patients with advanced heart failure. *Rev. Esp. Cardiol.* **2020**, *73*, 422–424. [CrossRef]
61. Agostoni, P.; Farmakis, D.T.; García-Pinilla, J.M.; Harjola, V.P.; Karason, K.; von Lewinski, D.; Parissis, J.; Pollesello, P.; Pölzl, G.; Recio-Mayoral, A.; et al. Haemodynamic Balance in Acute and Advanced Heart Failure: An Expert Perspective on the Role of Levosimendan. *Card. Fail. Rev.* **2019**, *5*, 155–161. [CrossRef] [PubMed]
62. Dunlay, S.M.; Roger, V.L.; Killian, J.M.; Weston, S.A.; Schulte, P.J.; Subramaniam, A.V.; Blecker, S.B.; Redfield, M.M. Advanced Heart Failure Epidemiology and Outcomes: A Population-Based Study. *JACC Heart Fail.* **2021**, *9*, 722–732. [CrossRef] [PubMed]
63. Gevaert, A.B.; Boen, J.R.A.; Segers, V.F.; Van Craenenbroeck, E.M. Heart Failure with Preserved Ejection Fraction: A Review of Cardiac and Noncardiac Pathophysiology. *Front. Physiol.* **2019**, *10*, 634–638. [CrossRef] [PubMed]
64. Deis, T.; Wolsk, E.; Mujkanovic, J.; Komtebedde, J.; Burkhoff, D.; Kaye, D.; Hasenfuß, G.; Hayward, C.; Van der Heyden, J.; Petrie, M.; et al. Resting and exercise haemodynamic characteristics of patients with advanced heart failure and preserved ejection fraction. *ESC Heart Fail.* **2022**, *9*, 186–195. [CrossRef] [PubMed]
65. Burkhoff, D.; Borlaug, B.A.; Shah, S.J.; Zolty, R.; Tedford, R.J.; Thenappan, T.; Zamanian, R.T.; Mazurek, J.A.; Rich, J.D.; Simon, M.A.; et al. Levosimendan Improves Hemodynamics and Exercise Tolerance in PH-HFpEF: Results of the Randomized Placebo-Controlled HELP Trial. *JACC Heart Fail.* **2021**, *9*, 360–370. [CrossRef]
66. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **2021**, *42*, 3599–3726.

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The Effects of Device-Based Cardiac Contractility Modulation Therapy on Left Ventricle Global Longitudinal Strain and Myocardial Mechano-Energetic Efficiency in Patients with Heart Failure with Reduced Ejection Fraction

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Abstract: Background: Virtually all patients with heart failure with reduced ejection fraction have a reduction of myocardial mechano-energetic efficiency (MEE). Cardiac contractility modulation (CCM) is a novel therapy for the treatment of patients with HFrEF, in whom it improves the quality of life and functional capacity, reduces hospitalizations, and induces biventricular reverse remodeling. However, the effects of CCM on MEE and global longitudinal strain (GLS) are still unknown; therefore, this study aims to evaluate whether CCM therapy can improve the MEE of patients with HFrEF. Methods: We enrolled 25 patients with HFrEF who received an Optimizer Smart implant (the device that develops CCM therapy) between January 2018 and January 2021. Clinical and echocardiographic evaluations were performed in all patients 24 h before and six months after CCM therapy. Results: At six months, follow-up patients who underwent CCM therapy showed an increase of left ventricular ejection fraction (30.8 ± 7.1 vs. 36.1 ± 6.9%; $p = 0.032$) as well a rise of GLS 10.3 ± 2.7 vs. −12.9 ± 4.2; $p = 0.018$), of MEE (32.2 ± 10.1 vs. 38.6 ± 7.6 mL/s; $p = 0.013$) and of MEE index (18.4 ± 6.3 vs. 24.3 ± 6.7 mL/s/g; $p = 0.022$). Conclusions: CCM therapy increased left ventricular performance, improving left ventricular ejection fraction, GLS, as well as MEE and MEEi.

Keywords: cardiac contractility modulation; heart failure with reduced ejection fraction; global longitudinal strain; myocardial mechano-energetics efficiency

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1. Introduction

Myocardial mechano-energetic efficiency (MEE) expresses the heart's ability to convert adenosine triphosphate (ATP), obtained from aerobic metabolism, into mechanical work [1]. Increased energy dissipation is a pathophysiologic hallmark of heart failure (HF) with reduced ejection fraction (HFrEF), in which MEE is reduced [2]. Although the gold standard for quantification of MEE is cardiac catheterization (bilateral and of the coronary sinus) [3], recently, an echocardiographic approach has been proposed, enabling more extensive clinical applications [4,5]. Cardiac contractility modulation (CCM) is an innovative therapy for the treatment of patients with HF [6] that through delivery, via an implantable device (Optimizer Smart®, Impulse Dynamics, Marlton, NJ, USA), of high-energy biphasic non-excitatory impulses during the absolute refractory period of the cardiomyocytes results in improved calcium handling [7], reverses titin downregulation and fetal gene expression [8,9] and reduces adrenergic tone and myocardial fibrosis [10,11]. These effects on failing myocardium biology result in an improvement of quality of life and functional capacity [12], reduction of hospitalizations [13], and a biventricular reverse

remodeling [14,15] in patients with HFrEF. However, the effects of CCM on the MEE of patients with HFrEF are still unknown; therefore, in this study, we evaluate whether CCM therapy can improve the MEE of patients with HFrEF.

2. Materials and Methods

2.1. Study Design

We evaluated for inclusion in the study all patients who underwent an Optimizer Smart implant between January 2018 and January 2021 at the Heart Failure Unit of Monaldi Hospital.

The following inclusion criteria were used:

(1) left ventricular ejection fraction $\leq$ 40%,
(2) New York Heart Association Class (NYHA) II-IV,
(3) Persistence of HF-related symptoms and/or >2 unplanned HF-related visits or hospitalization in the last 12 months despite optimal medical therapy (OMT),
(4) QRS duration < 120 ms.

The following exclusion criteria were used:

(1) acute coronary syndrome in the previous three months,
(2) cardiac resynchronization therapy device implantation in the previous 12 months,
(3) absence of aortic stenosis or left ventricular outflow tract (LVOT) obstruction,
(4) non-target dose of OMT for HFrEF,
(5) end-stage kidney disease required renal replacement therapy.

During the study period, 27 patients underwent an Optimizer Smart®implant, however, 2 patients died before the six-months follow-up, so the final enrolled population consisted of 25 patients.

Study data were obtained from all patients 24 h before and six months after CCM therapy. In addition, all patients signed informed consent, the recommendations of the Helsinki Declaration were followed, and the ethics committee of the AORN dei Colli-Monaldi Hospital approved the study (resolution No. 903/2020).

2.2. Echocardiography

Standard transthoracic echocardiography and Doppler assessment were performed with Vivid E9 (GE Healthcare, Chicago, IL, USA) as recommended elsewhere [16–18]. Three cardiologists with expertise in echocardiography, blinded to this study, acquired and analyzed all echocardiographic images.

An average of 3 cardiac cycles in patients with sinus rhythm and 5 cardiac cycles in patients with atrial fibrillation was used for the individual measures. According to common practice [19], stroke volume (SV) was calculated as:

$$SV = \text{Left ventricular outflow tract (LVOT) radius}^2 \times \text{time velocity integral (TVI) of LVOT.}$$

The global longitudinal strain (GLS) of the left ventricle was measured using the Q-Analysis software package (EchoPAC BT2.02; GE Vingmed, Horten, Norway).

After manually identifying the end-systolic endocardial boundary of the left ventricle by locating three points, a region of interest (ROI) was automatically generated. Next, the ROI was adjusted by the operator in order to include the entire left ventricular walls. Finally, according to international recommendations, we calculated the GLS value as the average of the values obtained from the four chambers, two chambers, and three chambers' views. The echocardiographic evaluations were performed 24 h before and six months after CCM therapy.

2.3. MEE Evaluation

The MEE of a system is the ratio of the work produced to the amount of energy required to produce that work [20]. The MEE of the left ventricle is determined by the ratio

of systolic work (SW) to myocardial volume oxygen (MVO2), which expresses the amount of oxygen used by the cardiomyocytes [21].

The following formula were used for calculations:

$$SW = \text{systolic blood pressure (SBP)} \times \text{stroke volume (SV)},$$

$$MVO2 = SBP \times \text{heart rate (HR)},$$

$$MEE = SV/HR \text{ (where HR is expressed in second, HR/60)},$$

$$MEEi = MEE/\text{body surface area (BSA)}.$$

2.4. Statistical Analysis

Prism 9 statistical software (GraphPad Software, San Diego, CA, USA) was used to do all statistical analyses. Clinical and population variables are shown as mean ± standard deviation, and categorical variables are expressed as numbers and percentages. Variations between variables at baseline and follow-up were compared using the Wilcoxon test for variables with nonnormal distribution and the t-test for variables with normal distribution. All p values were two-sided; statistical significance was considered for p values < 0.05.

3. Results

The final study population consisted of 25 patients, whose clinical and echocardiographic characteristics are shown in Table 1.

Table 1. Clinical and echocardiographic patients' characteristics at baseline.

Variable	Overall Population (25)
Age (mean ± SD)	62.8 ± 9.7 years
Female sex (n,%)	3 (12%)
Ischemic etiology (n%)	13 (52%)
Hypertension (n, %)	12 (48%)
Diabetes (n,%)	9 (36%)
COPD (n,%)	7 (28%)
NYHA class II (n,%)	4 (16%)
NYHA class III (n,%)	13 (52%)
NYHA class IV (n, %)	8 (32%)
ICD-DR (n,%)	16 (64%)
S-ICD	2 (8%)
CRT-D	7 (28%)
SBP (mean ± SD)	101 ± 11 mmHg
DBP (mean ± SD)	72 ± 6 mmHg
NT-pro BNP (mean ± SD)	2185 ± 1738 pg/mL
e-GFR (CKD-EPI)	62.3 ± 12 ml/min/1.73 m^2
BUN/Creatinine	18.4 ± 9.7 mg/dL
Atrial fibrillation	9 (36%)
LVEDV (mean ± SD)	208.2 ± 73.2 mL
LVESV (mean ± SD)	125.3 ± 43.5 mL
LVEF (mean ± SD)	32.8 ± 7.1%

Table 1. *Cont.*

Variable	Overall Population (25)
LAVi	41.9 ± 4.3 mL/m^2
E/e' ratio	16.3 ± 7.5 cm/sec
Loop diuretic (n,%)	16 (64%)
Beta-Blockers (n,%)	25 (100%)
ARNI (n%)	25 (100%)
MRA (n,%)	18 (72%)

COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; ICD-DR: dual chamber implantable cardioverter defibrillator; S-ICD: subcutaneous implantable cardioverter defibrillator; CRT-D: cardiac resynchronization therapy with defibrillator back-up SBP: systolic blood pressure; DBP: diastolic blood pressure; NT-pro BNP: N terminal-pro brain natriuretic peptide; e-GFR: estimated glomerular filtration rate; CKD-EPI: chronic kidney disease epidemiology collaboration; BUN: blood urea nitrogen; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; LAVi: left atrium volume index; E/e' ratio: Ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity ARNI: angiotensin receptor-neprilysin inhibitor; MRA: mineral receptor antagonist.

Most of the patients were male (22; 88%), 13 patients (52%) had an ischemic etiology, and 9 patients (36%) had atrial fibrillation. Additionally, all patients have a previous implantable cardioverter defibrillator, and 7 patients (28%) have a device for cardiac resynchronization therapy.

3.1. Effects of CCM Therapy on Left Ventricular Function

The echocardiographic index of left ventricular systolic function improved at the six-months follow-up (Table 2).

Table 2. Echocardiographic index of left ventricular systolic function of the study population.

Variable	Baseline	6 Months Follow-Up	*p*-Value
LVEDV (mL)	211.8 ± 45.8	188.3 ± 38.5	0.041
LVESV (mL)	141.8 ± 51.5	119.6 ± 49.7	0.024
LVEF (%)	32.8 ± 7.1	36.1 ± 6.9	0.032
GLS (%)	−10.3 ± −2.7	−12.9 ± −4.2	0.018

LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain.

There was a significant left ventricular reverse remodeling with a reduction of end-diastolic (211.8 ± 45.8 vs. 88.3 ± 38.5 mL; $p = 0.041$) and end-systolic volumes (141.8 ± 51.5 vs. 119.6 ± 49.7 mL; $p = 0.024$), with a consequent improvement of left ventricular ejection fraction (30.8 ± 71 vs. 36.1 ± 6.9%; $p = 0.032$). In addition, there was a significant increase in the most specific and reproducible echocardiographic index of left ventricular function, the GLS (−10.3 ± −2.7 vs. −12.9 ± −4.2%; $p = 0.018$; Figure 1). In addition, diastolic function indices also improved, particularly the E/e' ratio was significantly reduced at six-month follow-up (16.3 ± 7.5 vs. 10.8 ± 4.2; $p = 0.041$).

3.2. Effects of CCM Therapy on Natriuretic Peptides, NYHA Class, and Quality of Life

As shown in Figure 2 (panel A) at the six months follow-up, a significant reduction of plasma levels of N-terminal Brian Natriuretic Peptide (NT-proBNP) was observed in the enrolled patients (2975 ± 1988 vs. 1911 ± 1268 pg/mL; $p = 0.029$).

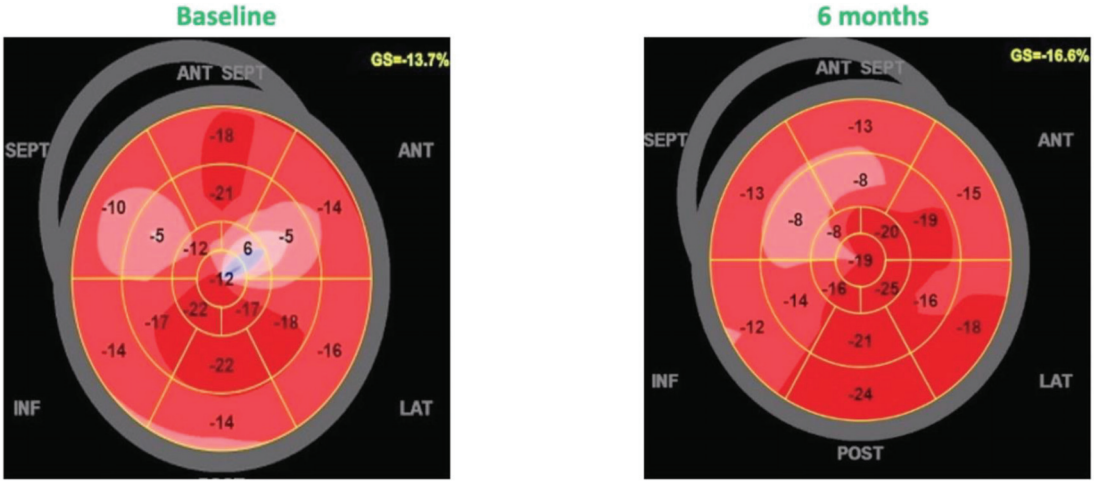

Figure 1. Effects of CCM on global longitudinal strain.

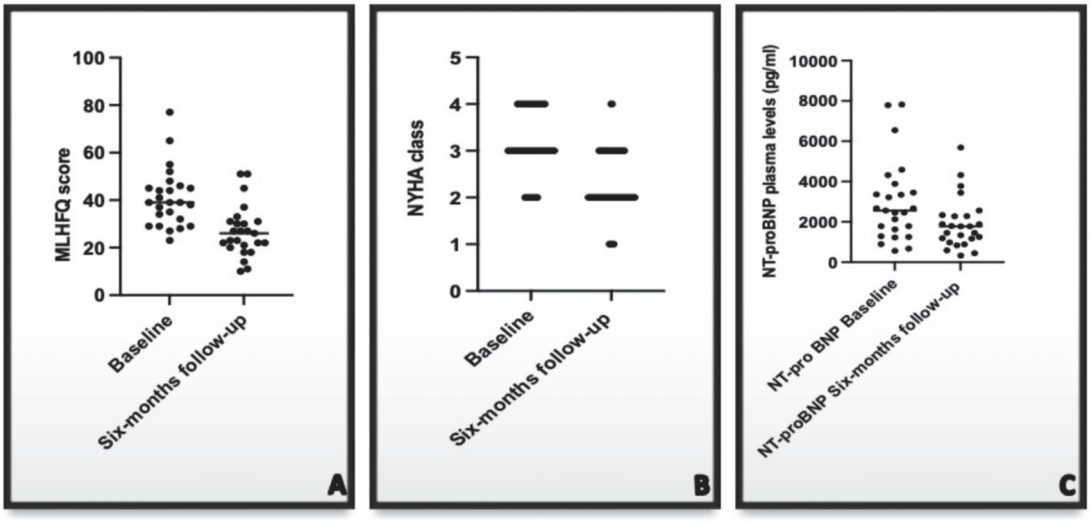

Figure 2. Effects of CCM therapy on NT-proBNP plasma levels (panel (**A**)), NYHA class (panel (**B**)), and MLHFQ score (panel (**C**)). NT-proBNP: N terminal-pro brain natriuretic peptide; NYHA: New York Heart Association; MLHFQ: Minnesota Living with Heart Failure Questionnaire.

Simultaneously with the reduction of natriuretic peptides plasma levels, an improvement in the symptom reported by the patients occurred; in fact, at follow-up, a statistical reduction in both NYHA class (3.1 ± 0.62 vs. 2.3 ± 0.56; $p = 0.0001$; Figure 2B) and of the Minnesota Living with Heart Failure score occurred (40.08 ± 12.31 vs. 26.9 ± 10.8; $p = 0.0001$—Figure 2C).

3.3. Effects of CCM on MEE

As showed in Figure 3, both MEE (32.2 ± 10.1 vs. 38.6 ± 7.6; mL/s $p = 0.013$) and MEEi (18.4 ± 6.3 vs. 24.3 ± 6.7 mL/s/g; $p = 0.022$) increased after six months of CCM therapy. The improvement of these indexes was due essentially due to the increase of SV without a concomitant increase in HR (Figure 4). From a pathophysiological point of view, this

indicates an increase in cardiac contractility in the absence of a corresponding increase in myocardial oxygen consumption, thus leading to an improved mechano-energetic coupling of the heart.

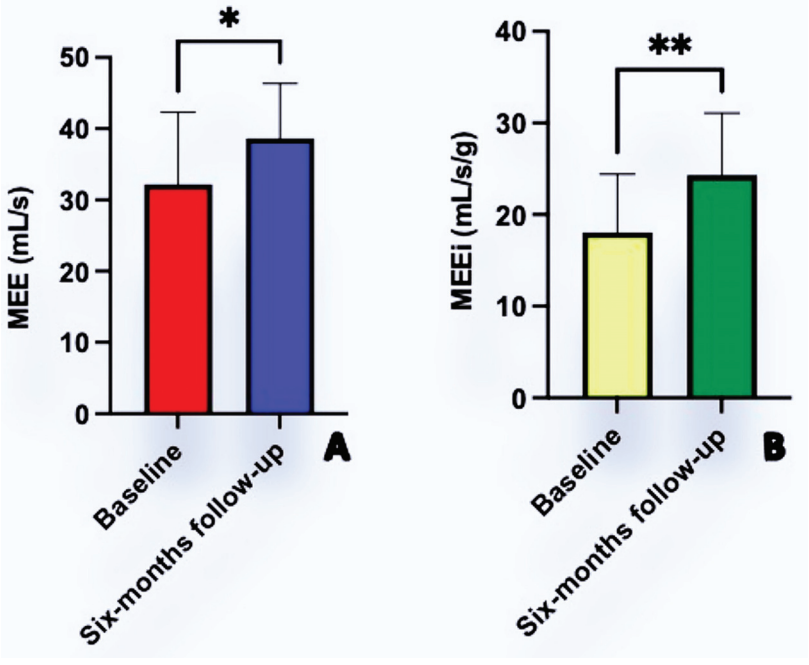

Figure 3. Improvements of Myocardial Mechano-Energetic Efficiency (MEE; Panel (**A**)) and Mechano-Energetic Efficiency index (MEEi; Panel (**B**)) after six months of CCM therapy. * = $p < 0.05$; ** = $p < 0.001$.

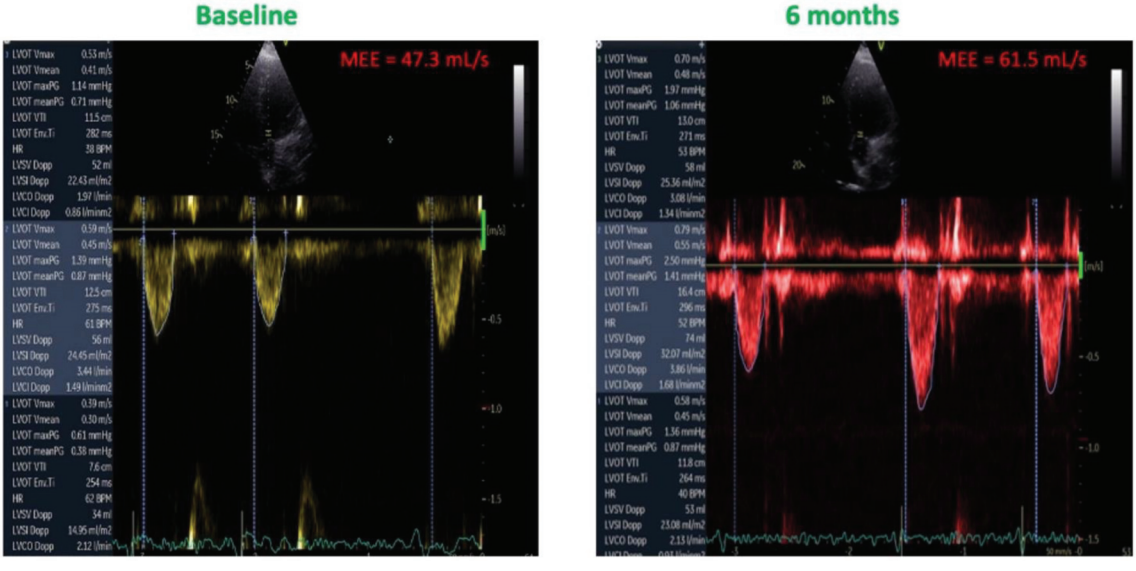

Figure 4. Effects of CCM therapy on MME. Note the increase in stroke volume without an increase in heart rate.

4. Discussion

In this study, for the first time, we demonstrate that left ventricular GLS and MEE increased after 6 months of CCM therapy in patients with HFrEF. Longitudinal deformation of the left ventricle is due to the contraction of subendocardial fibers, which are the most susceptible to altered calcium handling [22], increased myocardial stiffness [23], and myocardial fibrosis [24], typical features of the failing heart.

Therefore, longitudinal left ventricular dysfunction and consequentially reduced GLS values develop early in patients with HFrEF [25]. In ex vivo intact hearts, CCM therapy improves calcium handling through several mechanisms, such as rapid normalization of phospholamban phosphorylation [26], upregulation of L-type calcium channels, and increased calcium uptake into the sarcoplasmic reticulum [27]. The latter mechanism results in a rise of extracellular calcium flux during the subsequent cardiac cycle and increased calcium release from the SR itself (the so-called "calcium-induced calcium release") mechanism [28].

Animal models have demonstrated benefits of CCM therapy. In a canine HFrEF model, CCM therapy reduced left ventricular filling pressure due to the improvement of ventricular compliance and relaxation and improved diastolic Ca^{++} physiology [29]. In a rabbit HFrEF model, CCM therapy reduced cardiac expression of connective tissue growth factor and galectin-3 (a pro-fibrotic marker involved in myocardial structural remodeling) with a reduction of myocardial fibrosis [11]. These effects of CCM therapy observed in animal models may explain the improvement in diastolic function and GLS observed in this study, as well as a reduction of the E/e' ratio and of the NT-proBNP plasma levels both expression of left ventricular filling pressure.

The improvement in diastolic function justifies the improvement in NYHA class and quality of life observed in patients enrolled in the study. In fact, diastolic function is the main determinant of functional capacity and quality of life in patients with HF [30–32], and therefore its improvement is associated with an improvement in these parameters [33].CCM has also been shown to increase stroke volume in a canine HFrEF model [34]; in our study, we documented for the first time that CCM therapy results in an increase in SV at 6 months, even in a population of patients with HFrEF in optimal medical treatment.

Notably, the improvement in MME observed in our study was caused by an increase in SV without a rise in HR and, consequently, of MVO2. This confirms the findings of a prior study in which CCM increased dP/dt (an index of myocardial contractility) without an increase of MVO2 in nine patients with HFrEF [35].

In conclusion, CCM induces an increase of SV and consequently of cardiac output without a concomitant increase in myocardial oxygen demand acting as a smart inotropic therapy.

5. Study Limitations

The relatively small number of patients as well as the single-center, observational design of the study with the lack of a control group may influence our results. In addition, although the echocardiographic evaluations were performed in stable patients, the assessments of SV and GLS may be influenced by loading conditions. Seven patients have a CRT-D implanted 12 months before the inclusion in the study; for these patients, late response to this therapy cannot be excluded.

6. Conclusions

At six months of follow-up, CCM therapy increased left ventricular performance, improving left ventricular ejection fraction, E/e' ratio, GLS, as well as MEE and MEEi in patients with HFrEF on optimal medical therapy.

These echocardiographic improvements are associated with a clear clinical benefit documented by reduction of NT-pro BNP plasma levels NYHA class and MLHFQ score.

Additional larger studies are needed to provide a greater understanding of the long-term impact of CCM on left ventricular function, as well as the prognostic significance of these observations.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the AORN dei Colli-Monaldi Hospital (resolution No. 903/2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ferrara, F.; Capone, V.; Cademartiri, F.; Vriz, O.; Cocchia, R.; Ranieri, B.; Franzese, M.; Castaldo, R.; D'Andrea, A.; Citro, R.; et al. Physiologic Range of Myocardial Mechano-Energetic Efficiency among Healthy Subjects: Impact of Gender and Age. *J. Pers. Med.* **2022**, *12*, 996. [CrossRef] [PubMed]
2. Kim, I.S.; Izawa, H.; Sobue, T.; Ishihara, H.; Somura, F.; Nishizawa, T.; Nagata, K.; Iwase, M.; Yokota, M. Prognostic value of mechanical efficiency in ambulatory patients with idiopathic dilated cardiomyopathy in sinus rhythm. *J. Am. Coll. Cardiol.* **2002**, *39*, 1264–1268. [CrossRef]
3. Knaapen, P.; Germans, T.; Knuuti, J.; Paulus, W.J.; Dijkmans, P.A.; Allaart, C.P.; Lammertsma, A.A.; Visser, F.C. Myocardial energetics and efficiency: Current status of the noninvasive approach. *Circulation* **2007**, *115*, 918–927. [CrossRef] [PubMed]
4. Losi, M.A.; Izzo, R.; Mancusi, C.; Wang, W.; Roman, M.J.; Lee, E.T.; Howard, B.V.; Devereux, R.B.; de Simone, G. Depressed Myocardial Energetic Efficiency Increases Risk of Incident Heart Failure: The Strong Heart Study. *J. Clin. Med.* **2019**, *8*, 1044. [CrossRef] [PubMed]
5. Manzi, M.V.; Mancusi, C.; Lembo, M.; Esposito, G.; Rao, M.A.; de Simone, G.; Morisco, C.; Trimarco, V.; Izzo, R.; Trimarco, B. Low mechano-energetic efficiency is associated with future left ventricular systolic dysfunction in hypertensives. *ESC Heart Fail.* **2022**, *9*, 2291–2300. [CrossRef]
6. Patel, P.A.; Nadarajah, R.; Ali, N.; Gierula, J.; Witte, K.K. Cardiac contractility modulation for the treatment of heart failure with reduced ejection fraction. *Heart Fail Rev.* **2021**, *26*, 217–226. [CrossRef]
7. Gupta, R.C.; Mishra, S.; Rastogi, S.; Wang, M.; Rousso, B.; Mika, Y.; Remppis, A.; Sabbah, H.N. Ca(2+)-binding proteins in dogs with heart failure: Effects of cardiac contractility modulation electrical signals. *Clin. Transl. Sci.* **2009**, *2*, 211–215. [CrossRef]
8. Rastogi, S.; Mishra, S.; Zacà, V.; Mika, Y.; Rousso, B.; Sabbah, H.N. Effects of chronic therapy with cardiac contractility modulation electrical signals on cytoskeletal proteins and matrix metalloproteinases in dogs with heart failure. *Cardiology* **2008**, *110*, 230–237. [CrossRef]
9. Butter, C.; Rastogi, S.; Minden, H.H.; Meyhöfer, J.; Burkhoff, D.; Sabbah, H.N. Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. *J. Am. Coll Cardiol.* **2008**, *51*, 1784–1789. [CrossRef]
10. Tschöpe, C.; Kherad, B.; Klein, O.; Lipp, A.; Blaschke, F.; Gutterman, D.; Burkhoff, D.; Hamdani, N.; Spillmann, F.; Van Linthout, S. Cardiac contractility modulation: Mechanisms of action in heart failure with reduced ejection fraction and beyond. *Eur. J. Heart Fail.* **2019**, *21*, 14–22. [CrossRef]
11. Ning, B.; Zhang, F.; Song, X.; Hao, Q.; Li, Y.; Li, R.; Dang, Y. Cardiac contractility modulation attenuates structural and electrical remodeling in a chronic heart failure rabbit model. *J. Int. Med. Res.* **2020**, *48*, 300060520962910. [CrossRef] [PubMed]
12. Giallauria, F.; Cuomo, G.; Parlato, A.; Raval, N.Y.; Kuschyk, J.; Stewart Coats, A.J. A comprehensive individual patient data meta-analysis of the effects of cardiac contractility modulation on functional capacity and heart failure-related quality of life. *ESC Heart Fail.* **2020**, *7*, 2922–2932. [CrossRef] [PubMed]
13. Anker, S.D.; Borggrefe, M.; Neuser, H.; Ohlow, M.-A.; Röger, S.; Goette, A.; Remppis, B.A.; Kuck, K.; Najarian, K.B.; Gutterman, D.D.; et al. Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction. *Eur. J. Heart Fail.* **2019**, *21*, 1103–1111. [CrossRef]
14. Yücel, G.; Fastner, C.; Hetjens, S.; Toepel, M.; Schmiel, G.; Yazdani, B.; Husain-Syed, F.; Liebe, V.; Rudic, B.; Akin, I.; et al. Impact of baseline left ventricular ejection fraction on long-term outcomes in cardiac contractility modulation therapy. *Pacing Clin. Electrophysiol.* **2022**, *45*, 639–648. [CrossRef]

15. Contaldi, C.; De Vivo, S.; Martucci, M.L.; D'Onofrio, A.; Ammendola, E.; Nigro, G.; Errigo, V.; Pacileo, G.; Masarone, D. Effects of Cardiac Contractility Modulation Therapy on Right Ventricular Function: An Echocardiographic Study. *Appl. Sci.* **2022**, *2*, 7917. [CrossRef]
16. Lang, R.M.; Badano, L.P.; Mor-Avi, V.; Afilalo, J.; Armstrong, A.; Ernande, L.; Flachskampf, F.A.; Foster, E.; Goldstein, S.A.; Kuznetsova, T.; et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J. Am. Soc. Echocardiogr.* **2015**, *28*, 1–39.e14. [CrossRef]
17. Quiñones, M.A.; Otto, C.M.; Stoddard, M.; Waggoner, A.; Zoghbi, W.A. Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: A report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J. Am. Soc Echocardiogr.* **2002**, *15*, 167–184.
18. Mitchell, C.; Rahko, P.S.; Blauwet, L.A.; Canaday, B.; Finstuen, J.A.; Foster, M.C.; Horton, K.; Ogunyankin, K.O.; Palma, R.A.; Velazquez, E.J. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. *J. Am. Soc. Echocardiogr.* **2019**, *32*, 1–64. [CrossRef] [PubMed]
19. Sattin, M.; Burhani, Z.; Jaidka, A.; Millington, S.J.; Arntfield, R.T. Stroke Volume Determination by Echocardiography. *Chest* **2022**, *161*, 1598–1605. [CrossRef] [PubMed]
20. Tran, P.; Maddock, H.; Banerjee, P. Myocardial Fatigue: A Mechano-energetic Concept in Heart Failure. *Curr. Cardiol. Rep.* **2022**, *24*, 711–730. [CrossRef]
21. Juszczyk, A.; Jankowska, K.; Zawiślak, B.; Surdacki, A.; Chyrchel, B. Depressed Cardiac Mechanical Energetic Efficiency: A Contributor to Cardiovascular Risk in Common Metabolic Diseases-From Mechanisms to Clinical Applications. *J. Clin. Med.* **2020**, *9*, 2681. [CrossRef]
22. Ong, G.; Yan, A.T.; Connelly, K.A. Clinical application of echocardiographic-derived myocardial strain imaging in subclinical disease: A primer for cardiologists. *Curr. Opin. Cardiol.* **2019**, *34*, 147–155. [CrossRef]
23. Haji, K.; Marwick, T.H. Clinical Utility of Echocardiographic Strain and Strain Rate Measurements. *Curr. Cardiol. Rep.* **2021**, *23*, 18–25. [CrossRef] [PubMed]
24. Tops, L.F.; Delgado, V.; Marsan, N.A.; Bax, J.J. Myocardial strain to detect subtle left ventricular systolic dysfunction. *Eur. J. Heart Fail.* **2017**, *19*, 307–313. [CrossRef] [PubMed]
25. Russo, C.; Jin, Z.; Elkind, M.S.; Rundek, T.; Homma, S.; Sacco, R.L.; Di Tullio, M.R. Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort. *Eur. J. Heart Fail.* **2014**, *16*, 1301–1309. [CrossRef] [PubMed]
26. Brunckhorst, C.B.; Shemer, I.; Mika, Y.; Ben-Haim, S.A.; Burkhoff, D. Cardiac contractility modulation by non-excitatory currents: Studies in isolated cardiac muscle. *Eur. J. Heart Fail.* **2006**, *8*, 7–15. [CrossRef]
27. Burkhoff, D.; Shemer, I.; Felzen, B.; Shimizu, J.; Mika, Y.; Dickstein, M.; Prutchi, D.; Darvish, N.; Ben-Haim, S.A. Electric currents applied during the refractory period can modulate cardiac contractility in vitro and in vivo. *Heart Fail. Rev.* **2001**, *6*, 27–34. [CrossRef]
28. Endo, M. Calcium-induced calcium release in skeletal muscle. *Physiol. Rev.* **2009**, *89*, 1153–1176. [CrossRef]
29. Imai, M.; Rastogi, S.; Gupta, R.C.; Mishra, S.; Sharov, V.G.; Stanley, W.C.; Mika, Y.; Rousso, B.; Burkhoff, D.; Ben-Haim, S.; et al. Therapy with cardiac contractility modulation electrical signals improves left ventricular function and remodeling in dogs with chronic heart failure. *J. Am. Coll. Cardiol.* **2007**, *49*, 2120–2128. [CrossRef] [PubMed]
30. Smart, N.; Haluska, B.; Leano, R.; Case, C.; Mottram, P.M.; Marwick, T.H. Determinants of functional capacity in patients with chronic heart failure: Role of filling pressure and systolic and diastolic function. *Am. Heart J.* **2005**, *149*, 152–158. [CrossRef]
31. Terzi, S.; Sayar, N.; Bilsel, T.; Enc, Y.; Yildirim, A.; Ciloğlu, F.; Yesilcimen, K. Tissue Doppler imaging adds incremental value in predicting exercise capacity in patients with congestive heart failure. *Heart Vessel.* **2007**, *22*, 237–244. [CrossRef] [PubMed]
32. Daullxhiu, I.; Haliti, E.; Poniku, A.; Ahmeti, A.; Hyseni, V.; Olloni, R.; Vela, Z.; Elezi, S.; Bajraktari, G.; Daullxhiu, T.; et al. Predictors of exercise capacity in patients with chronic heart failure. *J. Cardiovasc. Med.* **2011**, *12*, 223–225. [CrossRef] [PubMed]
33. Bussoni, M.F.; Guirado, G.N.; Roscani, M.G.; Polegato, B.F.; Matsubara, L.S.; Bazan, S.G.; Matsubara, B. Diastolic function is associated with quality of life and exercise capacity in stable heart failure patients with reduced ejection fraction. *Braz. J. Med. Biol. Res.* **2013**, *46*, 803–838. [CrossRef] [PubMed]
34. Mohri, S.; He, K.L.; Dickstein, M.; Mika, Y.; Shimizu, J.; Shemer, I.; Yi, G.H.; Wang, J.; Ben-Haim, S.; Burkhoff, D. Cardiac contractility modulation by electric currents applied during the refractory period. *Am. J. Physiol. Heart Circ. Physiol.* **2002**, *282*, 1642–1647. [CrossRef]
35. Butter, C.; Wellnhofer, E.; Schlegl, M.; Winbeck, G.; Fleck, E.; Sabbah, H.N. Enhanced inotropic state of the failing left ventricle by cardiac contractility modulation electrical signals is not associated with increased myocardial oxygen consumption. *J. Card. Fail.* **2007**, *13*, 137–142. [CrossRef]

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Levosimendan as a "Bridge to Optimization" in Patients with Advanced Heart Failure with Reduced Ejection—A Single-Center Study

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Abstract: *Background*: Patients with advanced heart failure with reduced ejection fraction often cannot tolerate target doses of guideline-directed medical therapy due to symptomatic hypotension, renal dysfunction, and associated electrolyte abnormalities. While levosimendan can facilitate the titration of β-blockers in patients with advanced HFrEF, it is unclear whether ambulatory levosimendan infusions would offer the same benefit. In this prospective study, we investigate the effects of intermittent ambulatory levosimendan infusions on the uptitration of disease-modifying drugs. *Methods*: We enrolled 37 patients with advanced HFrEF who received repeated ambulatory infusions of levosimendan between January 2018 and January 2021. The demographic, clinical, and laboratory data were acquired 24 h before the first and the last ambulatory levosimendan infusion. *Results*: At the 1 year follow-up, the enrolled patients were on significantly higher doses of guideline-directed medical therapy, including bisoprolol (3.2 ± 2.8 mg vs. 5.9 ± 4.1 mg; $p = 0.02$), sacubitril/valsartan (41.67 ± 32.48 mg vs. 68.5 ± 35.72 mg; $p = 0.01$), and eplerenone (12.7 ± 8.5 mg vs. 22.8 ± 13.6 mg; $p = 0.03$). Furthermore, a substantial decrease in the furosemide dose was observed (123.2 ± 32.48 mg vs. 81.6 ± 19.47 mg; $p < 0.0001$). *Conclusions*: Levosimendan facilitates the optimization of disease-modifying heart failure medications in previously intolerant advanced HFrEF patients.

Keywords: levosimendan; disease modifier drugs; advanced heart failure; heart failure reduced ejection fraction

1. Introduction

Despite improvements in pharmacological and nonpharmacological treatments for patients with heart failure (HF) with reduced ejection fraction (HFrEF), approximately 10% of patients have a progressively worsening functional status culminating in advanced HF [1]. Furthermore, patients with advanced HFrEF develop distinct haemodynamic features that affect their natural history and disease-modifying drugs tolerance [2]. Symptomatic hypotension, renal dysfunction, and hyperkalaemia render the uptitration of β-blockers, angiotensin receptor-neprilysin inhibitors (ARNIs), and mineral receptor antagonists (MRAs) challenging [3]. Levosimendan is a calcium-sensitising medication [4] with two mechanisms of action, increased inotropy and vasodilation, and positive haemodynamic effects

in acute HF [5]. Several studies of levosimendan in advanced HFrEF have been performed; however, they all included a bolus dose mimicking acute treatment [6,7]. More recently, the LIONHEART study showed that ambulatory intermittent levosimendan infusions reduced NT-proBNP plasma levels and hospitalisations [8]. Following this pivotal trial, subsequent studies demonstrated that intermittent ambulatory infusions of levosimendan improved haemodynamic parameters [9] and functional capacity [10], while reducing hospitalisation [11,12] in patients with advanced HFrEF. In addition, a 24-h infusion of levosimendan could facilitate the titration of β-blockers in previously intolerant advanced HFrEF patients [13]. However, the role of levosimendan ambulatory infusions in the optimization of guideline-directed medical therapy for HFrEF remains unknown. Therefore, the purpose of this prospective study was to investigate whether intermittent infusions of levosimendan could facilitate the titration of β-blockers, ARNIs, and MRAs in advanced patients with HFrEF and a documented intolerance to disease-modifying drugs uptitration.

2. Materials and Methods

2.1. Study Population

We enrolled the study population at the Heart Failure Unit of Monaldi Hospital between January 2018 and January 2021 (Figure 1).

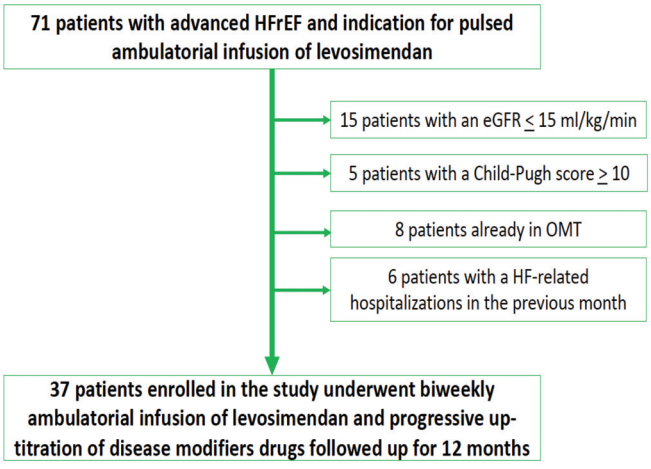

Figure 1. Study protocol. eGFR: estimated glomerular filtration rate. OMT: optimal medical therapy. HF: Heart failure. HFrEF: heart failure with reduced ejection fraction.

The following inclusion criteria were used:

(1) HFrEF with a left ventricular ejection fraction <35%,
(2) NYHA class III-IV,
(3) NT-proBNP >2500 pg/mL,
(4) walking distance at 6-min walking test <300 m,
(5) indication for intermittent ambulatory levosimendan infusion due to episodes of pulmonary or systemic congestion requiring a high dose i.v. diuretics or episodes of low output requiring inotropes or causing >2 unplanned visits or hospitalisations in the last 12 months, and
(6) guideline-directed medical therapy for HFrEF not at target dose [14–16], with documented intolerance to their uptitration in the six months prior to levosimendan infusion.

The following exclusion criteria were used:

(1) End-stage renal disease (i.e., estimated glomerular filtration rate <15 mL/kg/min according to the CKD-EPI equation),
(2) severe liver impairment (i.e., Child–Pugh score >10).

Signed informed consent was obtained, the Declaration of Helsinki was followed, and the institutional review board of AORN dei Colli–Ospedale Monaldi granted approval (deliberation n° 345 of November 2017). Demographic, clinical, and laboratory data were acquired from stable patients 24 h before the first and the last ambulatory levosimendan administration. The patients were followed up for 1 year during ambulatory infusions of levosimendan, and the follow-up was started at the first infusion of levosimendan.

2.2. Levosimendan Infusion

In all patients, levosimendan (Simdax®) was intravenously administered at 0.2 μg/kg/min for a total dosage of 6.25 mg every two weeks in an ambulatory setting. Levosimendan was administered in all patients for at least 1 year. No change in the dose of levosimendan occurred during the follow-up.

2.3. Evaluation of Disease Modifiers Drug Dose

During follow-up, the doses of disease-modifying drugs were uptitrated according to clinical judgment by two physicians with experience treating patients with advanced HFrEF (D.M., F.V.). The uptitration of the drugs was performed in an ambulatory setting on the same day as the levosimendan infusion. The doses of guideline-directed medical therapy were recorded 24 h before the first and the last ambulatory infusion of levosimendan; the latter doses were considered the maximum doses for each patient.

2.4. Statistical Analysis

All statistical analyses were performed using Prism 9 (GraphPad Software, San Diego, CA, USA). All demographic and clinical variables are expressed as the mean ± standard deviation. Categorical variables are expressed as numbers and percentages. Differences between the baseline and treatment values were compared using a Wilcoxon rank test for non-normal distribution and using a *t*-test for normal distribution. All *p*-values were two-sided; $p < 0.05$ indicated statistical significance.

3. Results

A total of 71 patients meeting the diagnostic criteria for advanced HFrEF with an indication for intermittent infusion of levosimendan were screened in our unit during the study period. Of these patients, fifteen (21%) did not receive an ambulatory infusion of levosimendan for end-stage renal disease, and five patients (7%) did not for severe liver failure. In addition, six patients (8%) had HF-related hospitalisations in the month before levosimendan administration, and eight patients (11%) had already achieved the target dose of disease-modifying drugs, so they were excluded from the study. The final population comprised 37 patients (mean age 55.8 ± 13.2 years, 84% male, mean ejection fraction 26.8 ± 9.4%). The demographic, clinical, and echocardiographic characteristics of the study population are presented in Table 1.

At the one-year follow-up, the ambulatory infusion of levosimendan had allowed a significant increase in the mean dose of sacubitril/valsartan compared with the dose before levosimendan treatment (41.67 ± 32.48 mg vs. 68.5 ± 35.72 mg; $p = 0.01$; Figure 2A).

Likewise, we observed a significant increase in the mean dose of bisoprolol compared with the dose before levosimendan administration (3.2 ± 2.8 mg vs. 5.9 ± 4.1 mg; $p = 0.02$; Figure 2B), and the same change was seen with eplerenone (12.7 ± 8.5 mg vs. 22.8 ± 13.6 mg, $p = 0.03$; Figure 2C). Simultaneously with the increase in the dose of disease-modifying drugs, a substantial decrease in the dose of furosemide was observed compared with the dose before levosimendan treatment (123.2 ± 32.48 mg vs. 81.6 ± 19.47 mg; $p < 0.0001$; Figure 2D).

Table 1. Baseline clinical and echocardiographic characteristics of the study population.

Variable	Total Population (n = 37)
Age (mean ± SD)	55.8 ± 13.2 years
Female sex (n, %)	6 (16%)
Ischaemic (n, %)	20 (54%)
Hypertension (n, %)	18 (48%)
Diabetes (n, %)	17 (45%)
COPD (n, %)	12 (32%)
NYHA class III (n, %)	25 (67%)
NYHA class IV (n, %)	12 (33%)
SBP (mean ± SD)	97 ± 10 mmHg
DBP (mean ± SD)	62 ± 8 mmHg
NT-pro BNP (mean ± SD)	3448 ± 1187 pg/mL
Atrial fibrillation	15 (40%)
Hb (mean ± SD)	11.7 ± 1.8 g/dL
Creatinine (mean ± SD)	1.4 ± 1.3 mg/dL
eGFR (mean ± SD)	36.7 ± 18.1 mL/min/1.73 m^2
LVEDV (mean ± SD)	2321.2 ± 85.9 mL
LVESV (mean ± SD)	192.7 ± 80.2 mL
LVEF (mean ± SD)	26.8 ± 9.4%
E wave (mean ± SD)	128.1 ± 39.5 cm/s
e' average (mean ± SD)	6.9 ± 3.5 cm/s
E/e' average (mean ± SD)	21.2 ± 6.3
DecT (mean ± SD)	165.2 ± 28.3 m/s
LAVi (mean ± SD)	52.5 ± 13.5 mL/m^2
PASP (mean ± SD)	40.8 ± 12.6 mmHg
TAPSE (mean ± SD)	14.1 ± 5.4 mm
Peak systolic s wave (mean ± SD)	8.7 ± 3.2 cm/s
Loop diuretic (n, %)	37 (100%)
Furosemide dose (mean ± SD)	123.2 ± 32.48 mg
β-blocker (n, %)	37 (100 %)
Bisoprolol dose (mean ± SD)	3.2 ± 2.8 mg
ARNI (n, %)	37 (100%)
ARNI dose (mean ± SD)	41.67 ± 32.48 mg
MRA (n, %)	37 (100%)
Eplerenone dose	9.7 ± 8.8 mg

COPD: chronic obstructive pulmonary disease; NYHA: New York Health Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; NT-pro BNP: N terminal-pro brain natriuretic peptide; Hb: haemoglobin; eGFR: estimated glomerular filtration rate; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; E wave: peak early mitral inflow velocity; e′ average: average of septal and lateral peak early diastolic mitral annular velocity; DecT: deceleration time; LAVi, left atrium volume index; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion; ARNI: angiotensin receptor-neprilysin inhibitor; MRA: mineral receptor antagonist.

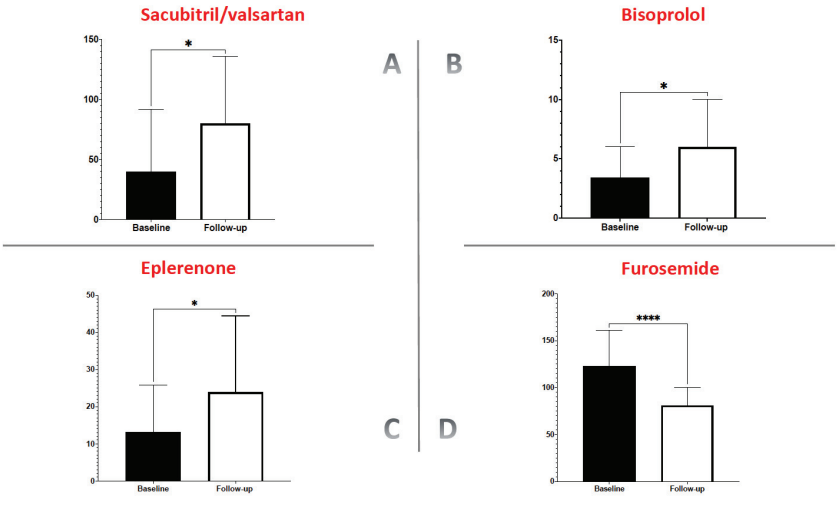

Figure 2. Change in the dose of disease modifier drugs (panel **A**–**C**) and diuretics at follow-up (panel **D**). *: $p < 0.05$; ****: $p < 0.0001$.

4. Discussion

One of the most complex clinical challenges in patients with advanced HFrEF is their intolerance to guideline-directed medical therapy or, if administered, inability to titrate to recommended doses due to hypotension, renal failure, and hyperkalaemia [17,18]. The poor tolerance of neurohormonal modulatory drugs in patients with advanced HFrEF could be related to the progression of the disease itself, leading to a critical reduction in the stroke volume resulting in hypotension and renal dysfunction. Alternatively, it could be associated with the direct effect of neurohormonal modulators or a combination of both [19]. Regardless of the cause, suboptimal doses of guideline-directed medical therapy in patients with advanced HFrEF are associated with poor prognoses. In this clinical scenario, levosimendan can assist in optimising therapy with β-blockers and drugs interfering with the renin-angiotensin-aldosterone system. Berger and colleagues demonstrated that levosimendan allowed the uptitration of β-blockers in previously intolerant HF patients. Levosimendan was periodically infused every four weeks, with a loading dose of 12 μg/kg for 10 min and an infusion rate of 0.1 μg/kg/min for 24 h. This protocol allowed for an increased dose of bisoprolol in patients in whom this had not been previously possible [13]. In our study, the use of levosimendan allowed for an increase in the dose of bisoprolol; this may have been due to the increase in cardiac output and consequent increase in blood pressure. The ability of levosimendan to increase cardiac output and cardiac performance, in addition to its positive effect on renal haemodynamics [20,21], may have allowed the uptitration of sacubitril/valsartan. Additionally, the positive impact on the renal performance, the reduction in the diuretic dose, and the reduction in potassium levels associated with levosimendan may have allowed the increase in the dose of MRAs [22]. Finally, in our study as well as in clinical trials [23] and in previous real-world experiences [24], the increasing dose of sacubitril/valsartan reduced the relative need for diuretics in patients with advanced HFrEF. This is potentially related to the natriuretic effects of sacubitril [25] or the presumed improvement in renal haemodynamics that may occur with sacubitril/valsartan [26].

5. Study Limitations

We recognise that the relatively small sample size, single-centre study design, the study's observational nature, and the absence of a control arm could have affected our results. However, the data from our observational study should be taken into consideration when planning properly powered randomised clinical trials in this therapeutic setting.

6. Conclusions

Levosimendan facilitates the optimisation of guideline-directed medical therapy in patients with advanced HFrEF who were previously unable to achieve target doses. This therapeutic strategy may be used as a 'bridge to optimisation' and may justify, at least in part, the improvement in clinical outcomes that the intermittent infusion of levosimendan produces in patients with advanced HFrEF.

Author Contributions: Conceptualization D.M., M.M.K., M.L.M. and G.P.; investigation F.V., R.G., M.V., E.A., A.C. and A.P.; writing—original draft preparation D.M., C.C. and V.D.P.; writing—review and editing, G.P., M.M.K. and P.P. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of AORN dei Colli-Ospedale Monaldi (deliberation n° 345 of November 2017).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: D.M., M.M.K., M.L.M., F.V., R.G., M.V., E.A., C.C., V.D.P., A.C., A.P. and G.P. report no conflicts of interest in this work. P.P. is a full-time employee of Orion Pharma, where levosimendan was discovered and developed.

References

1. Truby, L.K.; Rogers, J.G. Advanced Heart Failure: Epidemiology, Diagnosis, and Therapeutic Approaches. *JACC Heart Fail.* **2020**, *8*, 523–536. [CrossRef]
2. Masarone, D.; Kittleson, M.; Petraio, A.; Pacileo, G. Advanced heart failure: State of the art and future directions. *Rev. Cardiovasc. Med.* **2022**, *23*, 48. [CrossRef]
3. Iacoviello, M.; Vitale, E.; Corbo, M.D.; Correale, M.; Brunetti, N.D. Disease-modifier Drugs in Patients with Advanced Heart Failure: How to Optimize Their Use? *Heart Fail. Clin.* **2021**, *17*, 561–573. [CrossRef]
4. Masarone, D.; Melillo, E.; Gravino, R.; Errigo, V.; Martucci, M.L.; Caiazzo, A.; Petraio, A.; Pölzl, G.; Pacileo, G. Inotropes in Patients with Advanced Heart Failure: Not Only Palliative Care. *Heart Fail. Clin.* **2021**, *17*, 587–598. [CrossRef]
5. Long, Y.X.; Cui, D.Y.; Kuang, X.; Hu, S.; Hu, Y.; Liu, Z.Z. Effect of Levosimendan on Ventricular Systolic and Diastolic Functions in Heart Failure Patients: A Meta-Analysis of Randomized Controlled Trials. *J. Cardiovasc. Pharmacol.* **2021**, *77*, 805–813. [CrossRef]
6. Mavrogeni, S.; Giamouzis, G.; Papadopoulou, E.; Thomopoulou, S.; Dritsas, A.; Athanasopoulos, G.; Adreanides, E.; Vassiliadis, I.; Spargias, K.; Panagiotakos, D.; et al. A 6-month follow-up of intermittent levosimendan administration effect on systolic function, specific activity questionnaire, and arrhythmia in advanced heart failure. *J. Card. Fail.* **2007**, *13*, 556–559. [CrossRef]
7. Parissis, J.T.; Adamopoulos, S.; Farmakis, D.; Filippatos, G.; Paraskevaidis, I.; Panou, F.; Iliodromitis, E.; Kremastinos, D.T. Effects of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal and immune activation in patients with advanced heart failure. *Heart* **2006**, *92*, 1768–1772. [CrossRef]
8. Comín-Colet, J.; Manito, N.; Segovia-Cubero, J.; Delgado, J.; Pinilla, J.M.G.; Almenar, L.; Crespo-Leiro, M.G.; Sionis, A.; Blasco, T.; Pascual-Figal, D.; et al. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: The LION-HEART multicentre randomised trial. *Eur. J. Heart Fail.* **2018**, *20*, 1128–1136. [CrossRef]
9. Masarone, D.; Melillo, E.; Errigo, V.; Martucci, M.L.; Pacileo, R.; Pollesello, P.; Petraio, A.; Pacileo, G. Hemodynamic Effects of Levosimendan in Outpatients With Advanced Heart Failure: An Echocardiographic Pilot Study. *J. Cardiovasc. Pharmacol.* **2021**, *79*, e36–e40. [CrossRef]
10. Apostolo, A.; Vignati, C.; Della Rocca, M.; De Martino, F.; Berna, G.; Campodonico, J.; Contini, M.; Muratori, M.; Palermo, P.; Mapelli, M.; et al. Why Levosimendan Improves the Clinical Condition of Patients With Advanced Heart Failure: A Holistic Approach. *J. Card. Fail.* **2021**, *28*, 509–514. [CrossRef]
11. Masarone, D.; Valente, F.; Verrengia, M.; Ammendola, E.; Gravino, R.; D'Alterio, G.; Petraio, A.; Pacileo, G. Efficacy and safety of repeated infusion of levosimendan in outpatients with advanced heart failure: A real-world experience. *J. Cardiovasc. Med.* **2020**, *21*, 919–921. [CrossRef]
12. Oliva, F.; Perna, E.; Marini, M.; Nassiacos, D.; Cirò, A.; Malfatto, G.; Morandi, F.; Caico, I.; Perna, G.; Meloni, S.; et al. Scheduled intermittent inotropes for Ambulatory Advanced Heart Failure. The RELEVANT-HF multicentre collaboration. *Int. J. Cardiol.* **2018**, *272*, 255–259. [CrossRef]

13. Berger, R.; Moertl, D.; Huelsmann, M.; Bojic, A.; Ahmadi, R.; Heissenberger, I.; Pacher, R. Levosimendan and prostaglandin E1 for uptitration of beta-blockade in patients with refractory, advanced chronic heart failure. *Eur. J. Heart Fail.* **2007**, *9*, 202–208. [CrossRef]
14. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef]
15. Rosano, G.M.; Moura, B.; Metra, M.; Böhm, M.; Bauersachs, J.; Ben Gal, T.; Adamopoulos, S.; Abdelhamid, M.; Bistola, V.; Čelutkienė, J.; et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **2021**, *23*, 872–881. [CrossRef]
16. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; Deswal, A.; Drazner, M.H.; Dunlay, S.M.; Evers, L.R.; et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* **2022**, *145*, e895–e1032. [CrossRef]
17. Ameri, P.; Bertero, E.; Maack, C.; Teerlink, J.R.; Rosano, G.; Metra, M. Medical treatment of heart failure with reduced ejection fraction: The dawn of a new era of personalized treatment? *Eur. Heart J. Cardiovasc. Pharmacother.* **2021**, *7*, 539–546. [CrossRef]
18. Komajda, M.; Follath, F.; Swedberg, K.; Cleland, J.; Aguilar, J.; Cohen-Solal, A.; Dietz, R.; Gavazzi, A.; van Gilst, W.; Hobbs, R.; et al. The EuroHeart Failure Survey programme–a survey on the quality of care among patients with heart failure in Europe. Part 2: Treatment. *Eur. Heart J.* **2003**, *24*, 464–474. [CrossRef]
19. Crespo-Leiro, M.G.; Barge-Caballero, E. Advanced Heart Failure: Definition, Epidemiology, and Clinical Course. *Heart Fail. Clin.* **2021**, *17*, 533–545. [CrossRef]
20. Caira, C.; Brasolin, B.; Maestrini, V.; Scardala, R.; Orvieto, G.; Mancone, M.; Fedele, F. 475 Effects of Levosimendan on renal function and renal hemodynamic parameters in patients with acute heart failure. *Eur. J. Heart Fail. Suppl.* **2007**, *6*, 103. [CrossRef]
21. Zemljic, G.; Bunc, M.; Yazdanbakhsh, A.P.; Vrtovec, B. Levosimendan Improves Renal Function in Patients With Advanced Chronic Heart Failure Awaiting Cardiac Transplantation. *J. Card. Fail.* **2007**, *13*, 417–421. [CrossRef]
22. Nieminen, M.S.; Akkila, J.; Hasenfuss, G.; Kleber, F.X.; Lehtonen, L.A.; Mitrovic, V.; Nyquist, O.; Remme, W.J. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. *J. Am. Coll. Cardiol.* **2000**, *36*, 1903–1912. [CrossRef]
23. Mcmurray, J.J.V.; Packer, M.; Desai, A.S.; Gong, J.; Lefkowitz, M.P.; Rizkala, A.R.; Rouleau, J.L.; Shi, V.C.; Solomon, S.D.; Swedberg, K.; et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. PARADIGM-HF Investigators and Committees. *N. Engl. J. Med.* **2014**, *371*, 993–1004. [CrossRef]
24. Masarone, D.; Melillo, E.; Errigo, V.; Valente, F.; Pacileo, G. Clinical relevance of transient worsening renal function after initiation of sacubitril/valsartan. *Curr. Med. Res. Opin.* **2020**, *37*, 9–12. [CrossRef]
25. Wang, T.-D.; Tan, R.S.; Lee, H.-Y.; Ihm, S.-H.; Rhee, M.-Y.; Tomlinson, B.; Pal, P.; Yang, F.; Hirschhorn, E.; Prescott, M.F.; et al. Effects of Sacubitril/Valsartan (LCZ696) on Natriuresis, Diuresis, Blood Pressures, and NT-proBNP in Salt-Sensitive Hypertension. *Hypertension* **2017**, *69*, 32–41. [CrossRef]
26. Pontremoli, R.; Borghi, C.; Filardi, P.P. Renal protection in chronic heart failure: Focus on sacubitril/valsartan. *Eur. Heart J. Cardiovasc. Pharmacother.* **2021**, *7*, 445–452. [CrossRef]

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Review

Novel Therapeutic Devices in Heart Failure

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Abstract: Heart failure (HF) constitutes a significant clinical problem and is associated with a sizeable burden for the healthcare system. Numerous novel techniques, including device interventions, are investigated to improve clinical outcome. A review of the most notable currently studied devices targeting pathophysiological processes in HF was performed. Interventions regarding autonomic nervous system imbalance, i.e., baroreflex activation therapy; vagus, splanchnic and cardiopulmonary nerves modulation; respiratory disturbances, i.e., phrenic nerve stimulation and synchronized diaphragmatic therapy; decongestion management, i.e., the Reprieve system, transcatheter renal venous decongestion system, Doraya, preCardia, WhiteSwell and Aquapass, are presented. Each segment is divided into subsections: potential pathophysiological target, existing evidence and weaknesses or unexplained issues. Novel therapeutic devices represent great potential in HF therapy management; however, further evidence is necessary to fully evaluate their utility.

Keywords: heart failure; cardiorenal syndrome; autonomic dysregulation; respiratory disturbances; novel devices

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1. Introduction

Heart failure (HF) is a clinical syndrome resulting from structural and/or functional abnormality of the heart, leading to elevated intracardiac pressures and/or insufficient cardiac output. Increased cardiac filling pressures and neuro-hormonal disturbances resulting in fluid retention and redistribution are major factors responsible for congestion development and acute decompensation in heart failure [1].

As the HF pathophysiology is multidimensional, device interventions allow direct or indirect targeting of biological HF pathways, e.g. methods to manipulate sympathetic nervous system (SNS) imbalance, respiratory dysregulation or volume overload have been developed (Table 1). To preserve the article's coherence and compactness, we decided not to describe all promising techniques, but we focused on selected pathophysiological processes crucial in HF (Figure 1).

Table 1. Summary of the proposed novel methods.

Method	Pathophysiological Mechanism	Solution	Trial Design and Size	Primary Outcomes	Evidence	Adverse Events
Baroreflex activation therapy	Overactivity of SNS (increased heart rate, arterial pressure, RAAS activity and negative cardiac remodeling).	Stimulation of carotid bodies to restore autonomic system balance.	Multicenter, prospective, controlled trial $n = 408$	Rate of cardiovascular and HF morbidity, MANCE, Change in: NT-proBNP, 6 MHW, MLWHF QOL	BeAT-HF showed improvements of quality of life, exercise capacity, functional status and decrease of NT-proBNP [2]	MANCE event-free rate: 97%. A system or procedure-related serious adverse event occurred in seven patients.
			Single-center, open-label $n = 11$	Not reported	Dell'Oro et al. demonstrated significant improvement of EF and reduction in hospitalization [3]	No adverse effects were reported.
Vagus nerve stimulation	Overactivity of SNS (increased heart rate, arterial pressure, RAAS activity and negative cardiac remodeling).	Increase of PNS activity.	Multicenter, prospective, randomized, controlled trial $n = 95$	Change in LVESD, Percentage of surviving patients.	NECTAR-HF presented significant improvement in quality of life, NYHA class and functional status [4]	There were no significant differences in serious adverse events between control and therapy groups. The overall rate of implantation-related infections was 7.4%
			Multicenter, open-label, uncontrolled trial $n = 60$	Change in: LVESV EF, Adverse events.	ANTHEM-HF showed positive, durable improvement of cardiac function [5]	Serious adverse events occurred in 16 patients. There was one death related to system implantation due to an embolic stroke that occurred 3 days after surgery.
Splanchnic nerve stimulation	Excessive cardiac filling pressure due to overactivity of SNS resulting in visceral vasoconstriction and rapid volume shift from visceral to central compartment during exercise.	GSN modulation preventing exercise provoked visceral vasoconstriction and subsequent fluid shift from the visceral compartment to the central venous system.	Single-center, prospective, open-label, uncontrolled trials $n = 11$, $n = 15$	Change in CVPPAMP PCWP	Splanchnic-HF 1, and Splanchnic-HF 2 showed a reduction in PCPW and improvement of the cardiac index during exercise [6,7]	No adverse events were reported.
			Multicenter, prospective, uncontrolled, pilot study	Change in: mean PCPW at rest and exercise (20 W). Adverse events.	REBALANCE-HF confirmed the reduction in exercise PCPW in HFpEF and NYHA class improvement [8]	There were three non-serious device-related adverse events reported in this study: HF decompensation due to periprocedural fluid overload, transient hypertension and back pain following ablation.

Table 1. *Cont.*

Method	Pathophysiological Mechanism	Solution	Trial Design and Size	Primary Outcomes	Evidence	Adverse Events
Cardiopulmonary nerve stimulation	Impaired LV contractility and relaxation.	Stimulation of the autonomic system area responsible for LV contractility resulting in positive lusitropic and inotropic effects.	Single-center, first-in-human, proof-of-concept study $n = 15$	Adverse events.	A proof-of-concept study showed improvement of LV contractility and an increase in mean arterial pressure without affecting the heart rate [9]	No device-related serious adverse events were reported.
Phrenic nerve stimulation	Central apnea due to periodic drop in CO_2 partial pressure to below the threshold for triggering the action potential in the respiratory center caused by greater sensitivity to carbon dioxide leading to potent stimulus of rhythmic breathing.	Transvenous stimulation of phrenic nerve during apneas.	Multicenter, randomized, open-label study $n = 151$	Reduction in AHI and freedom from serious adverse events	The remedē System Pivotal Trial showed significant reduction in AHI, arousal index, desaturation and apnea episodes. It also revealed improvement in quality of life, sleep structure and EF [10,11]	Cumulatively, 21 (14%) serious adverse events were observed in 5-year follow-ups (15; (10%) in the first 12 months). It predominantly included electrode dysfunction, electrode dislocation and infection of the implantation site [10]
Asymptomatic diaphragmatic stimulation	High left ventricle pre-load and after-load pressures increase remodeling and HF progression.	Stimulation of diaphragm muscle fibers synchronized with cardiac cycle to decrease intrathoracic pressures.	Single-center, randomized, open-label study $n = 33$	LVEF improvement	EPIPHRENIC II Study showed significant improvement of LVEF, maximal power on effort, reduction in NYHA class, without differences in 6-min walking test or BNP concentration [12,13]	Three patients were excluded due to dysfunctional diaphragmatic electrode. No adverse events were observed [12]
			Multicenter, non-randomized, open-label study $n = 15$	Freedom from serious adverse events during procedural recovery or acute therapy	VisONE study showed improvement in LVEF and life quality (evaluated in SF-36); extended walking distance during the 6 MWT was observed at a 1-year follow-up. [13]	No adverse events were observed during procedural recovery, acute therapy (primary outcome) and in 12month follow-up (secondary outcome) [13]
Reprieve system	Problems with controlling decongestive therapy to avoid too rapid diuretic response and hypovolemia and, on the other hand, providing too much fluid, which worsens volume overload.	Sustaining the accurate fluid balance by measuring the urine output and providing the exact amount of replacement solution to achieve preset fluid balance.	Non-randomized, single-center, prospective, open-label, studies, both $n = 19$	Device and procedure-related adverse events and decongestive efficacy	Higher urine output and decrease in CVP in comparison to the baseline. Actual fluid loss did not exceed target fluid loss at the end of therapy in every patient [14]	No serious adverse events were observed. One case of hypokalemia occurred.

Table 1. *Cont.*

Method	Pathophysiological Mechanism	Solution	Trial Design and Size	Primary Outcomes	Evidence	Adverse Events
Transcatheter renal venous decongestion system	Congestion in renal veins.	Transfemoral inserted flow pump, which reduces renal vein pressure to the desired level.	No results have been published so far.	Device and procedure-related adverse events, technical and procedural feasibility	The trial to evaluate TRVD was terminated prematurely, no results have been published so far.	No results have been published so far.
Doraya Catheter	Congestion in renal veins.	Partial obstruction of the flow in the inferior vena cava below the level of the renal veins reduces renal vein pressure	First in-human, single-arm, open-label study $n = 9$	Serious adverse events.	The catheter was successfully deployed in all patients. Clinical symptoms, as well as diuresis and natriuresis, improved [15]	No device-related or embolic events were reported. One serious procedure-related adverse event: bleeding hematoma from the injection site, resolved without sequelae.
preCARDIA	Increased right ventricle preload.	Obstruction of the superior vena cava leading to an intermittent decrease in preload.	Multicenter, prospective, single-arm exploratory safety and feasibility, open-label, trial $n = 30$	Freedom from device or procedure-related serious adverse events	Successful decrease in right atrial pressure and PCWP, increase in net fluid balance and urine output [16]	No device or procedure-related serious adverse events were observed.
WhiteSwell	Increased preload causes lymphatic congestion, which impairs interstitial drainage and exacerbates oedema.	Reduction in the pressure in the area of lymphatic duct outflow into venous vessels.	The animal model study, $n = 7$ sheep, used in 1 human, $n = 1$	Serious adverse events.	Examined in a ovine model. Trend toward improved oxygenation an diuresis was noticed [17]	No adverse events were reported in in-human application.
AquaPass	Insufficient urine volume removal.	Enhancing the sweat rate to remove fluid directly from interstitial space.	Feasibility and short-term performance, single-arm, open-label study, $n = 16$	Serious adverse events, treatment tolerance, ability to control skin temperature between 33 and 38 Celsius degrees).	The procedure was safe in HF patients, successful weight loss was observed. Increased skin temperature without elevating core temperature above average was achieved in each patients [18]	No adverse event occurred.

Abbreviations: CVP—Central Venous Pressure, SNS—Sympathetic Nervous System, RAAS—Renin-Angiotensin-Aldosterone System, HF—Heart Failure, MANCE—major adverse neurological or cardiovascular system or procedure-related event rate, MLWHF QOL—Minnesota Living With Heart Failure Quality of Life, NT-proBNP—N-terminal pro brain natriuretic peptide, EF—ejection fraction, PNS—parasympathetic nervous system, NYHA—New York Heart Association, PAMP—Pulmonary Arterial Mean Pressure, PCPW—Pulmonary Capillary Wedge Pressure, HFpEF—Heart Failure with Preserved Ejection Fraction, LV—left ventricle, AHI—Apnea-Hypopnea Index, LVESV—Left ventricle end-systolic volume, LVESD—Left ventricle end-systolic dimension, TRVD—transcatheter renal venous decongestion system, 6 MHW—Six Minute Hall Walk Test.

HF remains a major medical problem and is associated with a high occurrence of rehospitalization and deaths, which constitute a huge problem for patients as well as healthcare systems worldwide [19]. Given that, numerous methods to improve outcome in HF have arisen, some including device-based treatment techniques.

Novel devices are supported by a strong theoretical background and a number of positive early signs from several small studies. Nevertheless, all device therapies, especially those that are permanently implanted in the patient, should undergo thorough assessment in large-scale prospective studies before they can be used in clinical practice.

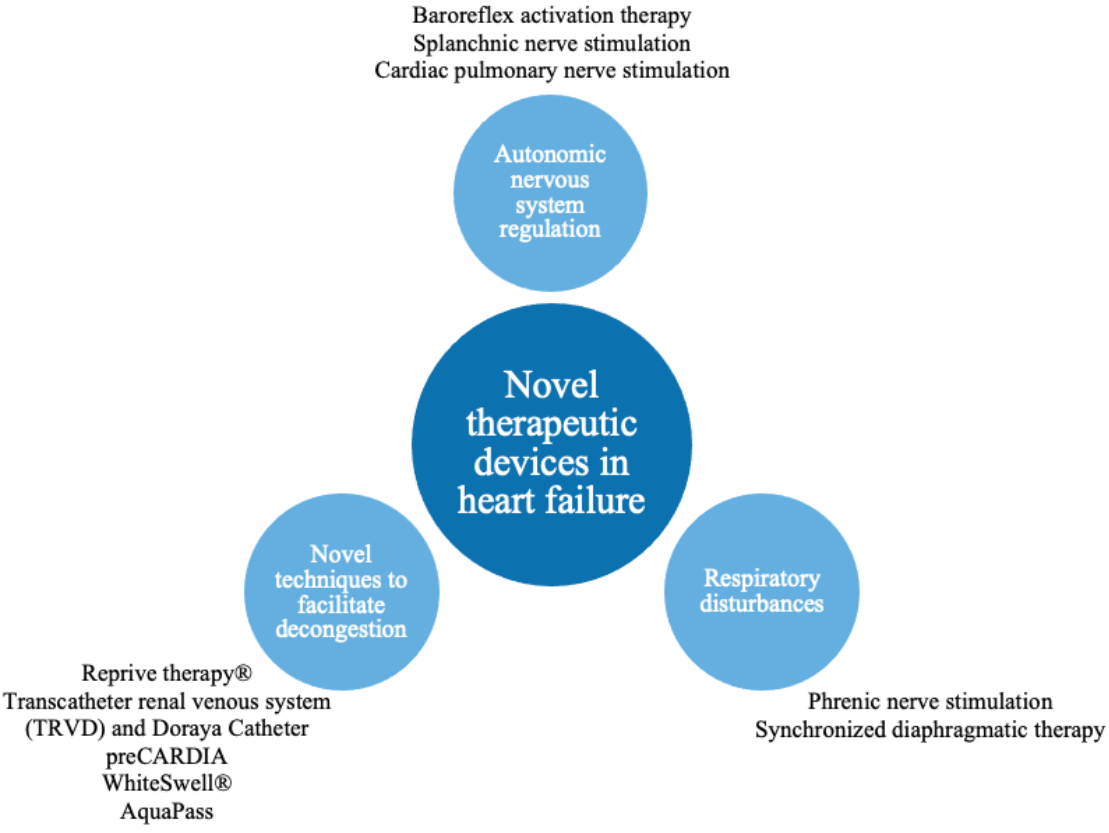

Figure 1. Pathophysiological pathways addressed by novel therapeutic devices.

2. Targeting Autonomic Nervous System Regulation

2.1. Potential Pathophysiological Target

Physiologically, the autonomic nervous system (ANS) may be described as a highly dynamic structure, driven by uncountable neurohormonal reactions to maintain homeostasis. The imbalance of the ANS plays a crucial role in the pathogenesis of HF as the SNS exceeds the buffer capabilities of the parasympathetic nervous system (PNS). The ANS is responsible for modulation of the heart rate, systemic vascular resistance, arterial blood pressure and cardiac afterload, whereby constant overactivity of SNS leads to undesired maladaptations and cardiovascular remodeling. This phenomenon is reflected in the treatment of HF. From the clinical point of view, there are several possible targets for ANS modulation. Modulation of selected subtypes of receptors (e.g., baroreflex activation therapy) allows for interaction with specific ANS branches (sympathetic or parasympathetic). Via the afferent nerves, stimuli are transmitted from receptors to the central nervous system (CNS). On this level, impulses are analyzed and transferred to the effector pathways. The efferent nerves transmit impulses from the CNS to the neurochemical synapses. Modulation of this process directly influences PNS (Vagus nerve stimulation) or SNS (Splanchnic nerve modulation). In the end, impulses reach the presynaptic membrane resulting in the secretion of neurochemical transmitters (e.g., epinephrine, norepinephrine and acetylcholine), which react with receptors localized in the effector tissue. Crucial for HF is the overactivity of SNS mediated by adrenergic receptors [20]. Numerous studies of beta-adrenergic receptor blockers have proven their impact on survival in HFpEF patients [21,22]. Additionally, the SNS is directly connected with the Renin-Angiotensin-Aldosterone system (RAAS), responsible

for increased sodium and water reabsorption with subsequent fluid accumulation, which elevates cardiac filling pressure and promotes congestion development, the indisputable targets of HF therapy [1]. Although the role of the SNS in HF is certain, the knowledge about its mechanisms responsible for HF is still unclear, and the ANS is an area for ongoing research in HF therapies especially using novel biomedical technologies.

2.2. Baroreflex Activation Therapy

Baroreflex activation therapy (BAT) uses a physiological reflex pathway to rebalance the activity of the ANS. Electrical stimulation of the carotid bodies sends afferent nerve impulses to the CNS that reacts by increasing PNS firing and decreasing SNS outflow [23]. The cardiovascular system response is acute and results in the decrease of heart rate and systemic vascular resistance with subsequent reduction in both systolic and diastolic blood pressure [23].

2.2.1. Existing Evidence

Several clinical studies have evaluated the effectiveness and safety of BAT. A multicenter, prospective, randomized, controlled trial–Baroreflex Activation Therapy for Heart Failure (BeAT-HF, NCT02627196)–showed that in the group of 264 patients with the FDA-approved enrolment criteria for BAT (EF $\leq$ 35%, NT-proBNP < 1.600 pg/mL, NYHA functional class III and without Class I indication for CRT), BAT is a safe procedure that significantly improves quality of life, exercise capacity and functional status, while it decreases NT-proBNP and reduces the number of HF hospitalizations per year. The study reported that the overall major adverse neurological and cardiovascular event-free rate was 97.2%, while the system and procedure-related complication event-free rate was 85.9% [2]. Cardiovascular mortality and HF morbidity rates are still under investigation (1200 participants, 5 years of observation, NCT02627196) Dell'Oro et al. demonstrated that in the group of seven patients who completed follow-up, BAT significantly improved EF (from 32.3 $\pm$ 2 to 36.7 $\pm$ 3% in 43 months, $p < 0.05$) and reduced heart failure-related hospitalization rate. There were no side effects reported in this study [3]. Apart from HF, BAT is also widely investigated as a potential drug-resistant arterial hypertension treatment [23].

2.2.2. Weaknesses or Unexplained Issues

Despite positive early results, there is a need for further, well-powered clinical trials before BAT can be incorporated into HF clinical practice. BAT needs at least larger-scale research that includes longer follow-up, a higher number of patients and clarified outcomes with mortality risks [24]. The study performed by Dell'Oro et al. was not registered as a clinical trial.

2.3. Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is an autonomic system modulation that aims to level autonomic system imbalance by increasing PNS activity. Electrostimulation of the easily accessed right cervical vagus nerve induces neurohormonal reactions that buffer the overactivity of SNS [25].

2.3.1. Existing Evidence

The Neural Cardiac Therapy for Heart Failure (NECTAR-HF, NCT01385176, 95 participants, 63 randomized to therapy) trial was the first study that evaluated the usefulness of VNS in HFrEF. It showed improvements in quality of life, NYHA class and exercise capacity without changes in echocardiographic measures (primary endpoint defined as the change in left ventricle end-systolic diameter) in the VNS treated patients. There were no significant differences in the serious adverse event (SAE) rates between the control and therapy groups. The overall rate of implantation-related infections was 7.4% [4]. The Autonomic Regulation Therapy for the Improvement of Left Ventricular Function and Heart Failure Symptoms (ANTHEM-HF, NCT01823887, 60 participants) uncontrolled design study de-

livered information about the safety of this procedure, and it showed positive, durable improvements in cardiac function and echocardiography parameters after 6 months of treatment. Additionally, this study confirmed significant improvement in NYHA functional class and exercise tolerance. One death related to the device implantation procedure caused by an embolic stroke that occurred 3 days after surgery in a patient suffering from extensive atherosclerosis of the carotid arteries was reported [5]. The promising application of VNS may be heart rate-dependent stimulation, which, apart from balancing the autonomic system, restores physiological relations [26].

2.3.2. Weakness or Unexplained Issues

Although VNS has a significant positive impact on a patient's functional status, it does not impact the prognosis [27]. The ANTHEM-HF study was conducted without a control group, which is a significant limitation. To exclude the placebo effect and assess the safety of the procedure, there is a need for a randomized, controlled clinical trial [5]. Moreover, positive echocardiographic changes are not reported by any studies [27]. Interestingly, positive functional changes observed during VNS therapy are not accompanied by NT-proBNP serum level decrease.

2.4. Splanchnic Nerve Modulation

The splanchnic nerves are responsible for autonomic innervation of the upper abdominal viscera (e.g., liver) and are highly connected with splanchnic vascular volume management, primarily caused by visceral vasoconstriction during exercise. The visceral vascular bed is a natural reservoir of blood volume that can be quickly relocated for an urgent need (like hypovolemia, hemorrhage, or exercise). Redistribution of blood volume from the extra-thoracic compartments into the central circulation is believed to be a significant contributor to elevated filling pressures in HF patients, including HF with preserved ejection fraction (HFpEF) [8]. Modulation (blockage or partial blockage) of the splanchnic nerves (SNM) decreases sympathetic tone. It thereby prevents the rapid shift of blood from the splanchnic bed to the central circulation during physical exercise.

SNM may protect the central venous system from acute volume redistribution and subsequent cardiac filling pressure increase [28]. SNM is reached by uni- or bilateral chemical, electrical or surgical greater splanchnic nerve blockage.

2.4.1. Existing Evidence

The splanchnic-HF 1 (NCT02669407) and 2 (NCT03453151) trials reported promising effects of SNM therapy in both acute decompensated (ADHF) and chronic heart failure (CHF). Eleven ADHF patients with advanced HFrEF underwent bilateral temporary percutaneous splanchnic nerve block with lidocaine. In this group, significant reduction in pulmonary capillary wedge pressure (from 30 ± 7 mmHg at baseline to 22 ± 7 mmHg at 30 min, $p < 0.001$) and an increase in cardiac index (from 2.17 ± 0.74 L/min/m^2 at baseline to 2.59 ± 0.65 L/min/m^2 at 30 min $p = 0.007$) were reported [6]. Similar findings were provided by a study of 18 CHF patients who underwent the same procedure [7]. In HFpEF, permanent ablation of the right greater splanchnic nerve resulted in the reduction of intracardiac filling pressures during exercise, as early as 24 h after the procedure [29]. Moreover, a European two-center study investigated the feasibility of permanent surgical right-sided SNM for the treatment of HFpEF (Surgical Resection of the Greater Splanchnic Nerve in Subjects Having Heart Failure with Preserved Ejection Fraction, NCT03715543) demonstrated a significant reduction of PCPW at a 3-month follow-up and significant improvement in NYHA class and quality of life at 12 months after the procedure [28]. The early results of the REBALANCE-HF study (NCT04592445, the ongoing multicenter evaluation of splanchnic ablation for volume management in HFpEF) delivered auspicious results. In the group of 18 enrolled patients, the 20 W exercise PCWP and peak exercise PCWP decreased significantly 1 month after the procedure. At least one NYHA class improvement was experienced by 39% of patients at 1 month and 50% at 3 months after the

SNM procedure. This study reported three non-serious device-related adverse events (AE): HF decompensation due to periprocedural fluid overload, transient hypertension and back pain following ablation [8].

2.4.2. Weakness or Unexplained Issues

Safety and efficacy of SNM in the treatment of HF needs to be further investigated. Current scientific reports are based on small patient populations and very limited follow-ups. Notably, the abovementioned studies were proof-of-concept clinical trials without a control group. Additionally, a unified procedure for HF SNM application must be established [28].

2.5. Cardiac Pulmonary Nerve Stimulation

This method uses anatomical relations between pulmonary arteries and the cardiac autonomic system elements. An endovascular delivered electrode placed in pulmonary arteries stimulates the surrounding autonomic nerves resulting in positive lusitropic (increasing relaxation of the myocardium during diastole) and positive inotropic (increasing myocardial contractility) effects without an influence on heart rate. Thus, this percutaneous device has at least theoretical potential to improve cardiac function and systemic perfusion and facilitate decongestion in ADHF [9].

2.5.1. Existing Evidence

The first in-human, proof-of-concept, uncontrolled study (NCT04814134) revealed promising cardiac pulmonary nerve stimulation (CPNS) effects. CPNS in HF resulted in LV contractility improvement and an increase in mean arterial pressure without affecting the heart rate. Moreover, the CPNS 2 Feasibility Study demonstrated short-term safety (no SAE reported) and feasibility in chronic HF patients undergoing a catheterization procedure or implantable cardioverter-defibrillator/cardiac resynchronization therapy implantation [9].

2.5.2. Weakness or Unexplained Issues

CPNS is a concept that needs further investigation. Well organized clinical trials are required to provide information about CPNS effectiveness, safety and impact on outcomes.

3. Respiratory Disturbances in Heart Failure

The function of the respiratory system is essential not only in the context of the exchange of respiratory gases but also in generating resistance in the pulmonary circulation and pressure changes inside the chest. The constellation of these factors affects the function of the heart itself and the entire circulatory system.

Sleep-disordered breathing is a common pathology, especially in patients with HF, affecting both cardiovascular and respiratory systems. There are two main types of sleep apnea syndromes: obstructive sleep apnea syndrome (OSA) and central sleep apnea syndrome (CSA) [30].

3.1. Potential Pathophysiological Target

OSA/CSA increases SNS, RAAS activation, oxidative stress, cell apoptosis, endothelial dysfunction and, as a result, remodeling and fibrosis of the heart [31,32]. These effects are common to the OSA/CSA and HF pathophysiology and accelerate HF progression, despite different mechanisms leading to these consequences [33].

In CSA, the lack of respiration is caused by pathological pauses in neurological impulses triggering breathing muscles contraction, which results in periods of apnea [34,35]. It was found that the underlying cause of this pathology is the augmented ventilation response to the high partial pressure of CO2 (pCO2), also enhanced by hypoxia, especially in acute heart failure (AHF) [33]. Thus, hyperventilation occurs during sleep (as a response to high pCO2), leading to a periodic drop in pCO2, which goes below the threshold for

triggering the action potential in the respiratory center. As a result, patients present periodic apnea during night rest [34–36].

The OSA is caused by excessive laxity and, as a result, the upper airways collapse during breathing. Several methods of treatment such as continuous positive airway pressure (CPAP), adaptive servo-ventilation, oral inserts, surgical treatment (e.g., uvulopalatopharyngoplasty or maxillomandibular advancement, tracheostomy or hypoglossal nerve stimulation have been proposed [37]. Nevertheless, meta-analyses showed that treatment with CPAP/ASV improved HF patients' quality of life, with no impact on survival or rehospitalizations. On the other hand, there are signals that the use of ASV in patients with HFrEF and CSA may be even harmful and associated with an increase in all-cause mortality [38,39].

Thus, the main problem in the HF population is the group of patients with CSA, in which there are regular/cyclic pauses in breathing during sleep due to a lack of respiratory effort. Since the act of breathing is mainly caused by the intercostal muscles and the diaphragm, and the cause of the dysfunction lies in the area of the respiratory center, a method of stimulating the phrenic nerve or diaphragm has been proposed for treatment.

3.2. Phrenic Nerve Stimulation

Technically, this method is similar to classic cardiac stimulation. An electrode is implanted into a brachiocephalic or pericardiophrenic vein to sense the diaphragm's contractions during breathing and stimulate the diaphragmatic nerve during apnea. The electrode is connected to the subcutaneously implanted management module.

The task of this device is to maintain a relatively stable pO2 and pCO2 and prevent over-activation of SNS and RAAS. [10,40].

3.2.1. Existing Evidence

The remedē System Pivotal Trial (NCT01816776) was a multicenter, randomized study with 151 participants. It was meant to provide phrenic nerve stimulation and demonstrated a significant reduction in the apnea-hypopnea index (AHI), central apnea index, arousal index, oxygen desaturation $\geq$4% index, percentage of sleep with rapid eye movement and sleepiness (Epworth Sleepiness Scale (ESS)) [41]. Those findings were sustained in a 5-year follow-up [11].

Costanzo et al. found that patients treated with phrenic nerve stimulation had an improvement in life quality and improvement in left ventricle ejection fraction (LVEF), with no significant difference in end-systolic and end-diastolic volumes [10].

This method was relatively safe. In follow-ups, the AE were most common during the first year and predominantly included electrode dysfunction, electrode dislocation and infection of the implantation site. Cumulatively, in 5-year observations, the SAE occurred in 14% of patients. There was one episode of inadequate intervention by the high-energy implantable device related to hypersensitivity, which was resolved by changing the device settings [10,41,42].

3.2.2. Weaknesses or Unexplained Issues

The effect of phrenic nerve stimulation on mortality in HF patients with CSA syndrome is unknown and large scale clinical trials are required.

3.3. Synchronized Diaphragmatic Therapy

Elevation of intrathoracic pressure causes chronic stress on the heart muscle and may worsen HF. The respiratory muscles can significantly influence intrathoracic pressure. Thus, a strategy for synchronic diaphragm stimulation was proposed. It involves implanting a device connected with an electrode that senses the heart rhythm and stimulates the diaphragm.

This system aims to synchronize the cardiac work cycle to changes in diaphragm movement by stimulation of diaphragm's muscle fibers (especially type I), causing cyclical

changes in their tension, which in turn reduces intra-thoracic pressure. It is imperceptible for the patient, as it does not cause contraction of the diaphragm leading to respiratory movement. Thus, it does not cause any discomfort to the patient. In the first study, entitled Epiphrenic II, [12] the electrode-to-diaphragm stimulation was implanted during coronary artery by-pass grafting procedures [12,40]. A minimally invasive method of laparoscopic implantation, which minimizes the risk of complications and shortens the hospitalization period after implantation, has further been developed.

3.3.1. Existing Evidence

In Epiphrenic II (NCT00769678), a randomized study conducted on 33 participants, researchers found improvement in LVEF and HF symptoms on the NYHA scale. There was also an observed increase in maximal power and oxygen consumption during exercise testing. However, no significant improvement in the 6-min walking test (6 MWT) and BNP concentration was recorded in a group with optimized synchronized diaphragmatic stimulation. No SAE were observed [12].

In the VisOne Heart Failure non-randomized study (NCT03484780, 15 participants) improvement of LVEF and quality of life (evaluated in SF-36) and extended walking distance during the 6 MWT were observed at the 1-year follow-up. Best results were achieved in patients with over 80% diaphragm pacing synchronized to the heart cycle. No AE were observed at 12-month follow-up (primary and secondary endpoint) [12,13].

3.3.2. Weaknesses or Unexplained Issues

The VisOne study was non-randomized, and both studies were conducted in a small group of patients. Due to the promising results of the trials, it would be worth performing further studies on an extensive study group with a control population.

4. Novel Techniques to Facilitate Decongestion

4.1. Potential Pathophysiological Target

Loop diuretics remain the cornerstone of the decongestive therapy in HF; however, reduced responsiveness to them, especially in chronic use, constitutes a clinical challenge. Up to nearly 50% of the classically treated HF patients are discharged with residual congestion, which worsens prognosis [43,44]. Extracorporeal ultrafiltration has been proposed as an alternative for pharmacotherapy; however, current results about its safety and the advantage over standard care remain unclear [45]. Given all the exposed deficiencies, interest in novel fluid removal techniques has emerged.

4.2. Reprieve Therapy®

Reprieve therapy is a method which intends to provide a solution for the more accurately controlled decongestion for HF patients. The Reprieve System is designed to measure the urine output (via urinary catheter) and deliver (adjusted to urine output) a precise volume of replacement solution (via peripheral vein cannula) to achieve the preset fluid balance [14]. This technique is meant to decrease the risk of intravascular volume depletion, which is a strong inner signal for urine output drop during decongestion. The urine output is unpredictable in HF, thus, some patients have large urine outputs that may unintentionally lead to intravascular volume depletion and to so-called diuretic resistance. The Reprieve system is meant to prevent excessive intravascular fluid removal and subsequent volume depletion, which may lead to hypovolemia and hemodynamic instability.

4.2.1. Existing Evidence

TARGET-1 and TARGET-2 studies have assessed the safety and efficacy of controlled decongestion by the Reprieve System in AHF patients (NCT05015764). In both studies, patients in the study group achieved higher urine output, reduction in body weight and a decrease in central venous pressure (CVP), in comparison to the status before the initiation of the therapy. It is noteworthy that, while achieving greater fluid loss, the treatment was

safe–systolic blood pressure remained stable. No renal injury makers or a decrease in renal function was observed. There were no SAE, and the most frequent AE was hypokalemia–mean serum potassium dropped from 4.1 to 3.6 mmol/L ($p < 0.05$).

4.2.2. Weaknesses or Unexplained Issues

Data about the Reprieve System comes from two non-randomized, relatively small, prospective single-center studies. Further trials, including randomized controlled trials, are warranted to confirm its value and impact on the outcome, i.e., mortality or HF hospitalizations. Moreover, Reprieve is targeted at AHF patients with preserved diuresis who respond to diuretics. Whether the device holds promise for the facilitation of decongestion in AHF needs further investigation. The new and more advanced device versions are being investigated.

4.3. Transcatheter Renal Venous Decongestion System (TRVD) and Doraya Catheter

As renal vein congestion has been assessed as the most critical factor responsible for the worsening renal function in AHF patients [46], attempts to create novel interventions for renal decongestion have arisen. The novel concept of the renal tamponade caused by the congestion, which additionally impedes the renal outflow and subsequently harms renal function, just added importance to the issue [47]. The transcatheter renal venous decongestion system (TRVD) is inserted through a femoral vein catheter-mounted flow pump, the aim of which is to reduce the pressure in the renal veins to the selected target [48]. The device was tested in a porcine model, where renal pressure was artificially increased by a suprarenal balloon and then reduced by the TRVD, showing an increase in renal flow and subsequently an increase in urine output. The trial to evaluate TRVD in the AHF population (NCT03621436) was terminated prematurely due to the sponsors' decision, and no study results have been published by now.

The Doraya Catheter is deployed in the inferior vena cava below the renal veins. The Doraya catheter was developed to temporarily reduce renal venous pressure by creating a controllable gradient in the inferior vena cava below the renal veins. The device aims to decrease renal venous pressure at the cost of transitory obstruction of the venous outflow from the lower extremities. By partially blocking venous flow, the Doraya creates a gradient of pressure below and above the catheter, which results in a pressure decrease in renal veins and further diminishes the right ventricle preload.

4.3.1. Existing Evidence

The results of the first in-human studies of Doraya are promising (NCT03234647) [15]. No device malfunctions were observed, and all the technical aspects regarding the device deployment and removal were successful. Significant pressure reduction above the catheter was observed as well as a positive diuretic response. Clinical signs of congestion, including dyspnoea, all improved. No device-related or embolic events were observed during the procedure. In a follow-up after 30 days, one SAE was observed, i.e., bleeding hematoma from the injection site, that resolved without sequelae. The Doraya catheter seems to provide an exciting concept for the treatment of AHF patients with inadequate response to the standard diuretic treatment.

4.3.2. Weaknesses or Unexplained Issues

Currently, only pilot studies in a small population, regarding novel renal veins decongestion techniques, have been performed. Studies included a limited population and aimed to assess the feasibility of such strategies, rather than their clinical efficacy and impact on outcome. Further research (which is under way) is necessary to establish the clinical value of the methods mentioned above.

4.4. preCARDIA

The producers of the preCARDIA system proposed a distinct approach for congestion relief therapy. The device is inserted into the superior vena cava to cause intermittent occlusion, leading to a decrease in right ventricular preload.

4.4.1. Existing Evidence

The VENUS-HF early feasibility study (NCT03836079) showed a decrease in right atrial pressure and PCWP compared to the pretreatment values. At 24 h of treatment, a 130 and 156% increase in the urine output and net fluid output, consequently, was observed. No device- or procedure-related SAE were observed [16]. Prior studies have also reported its safety in the preclinical model, in terms of thrombotic events, strokes or neurologic deficits. No examined animal has experienced increased cerebral oedema or thrombotic event [49].

4.4.2. Weaknesses or Unexplained Issues

The studies are the first in-human trials of the device. They had a non-randomized design and included a limited number of patients observed for a short period of time. Furthermore, larger studies with prolonged follow-up are warranted to evaluate the safety and precise clinical utility of the preCARDIA system and its impact on outcome.

4.5. WhiteSwell®

The role of the lymphatic system in HF pathophysiology has been underestimated, but it appears that it could play a role in decongestive therapy. Firstly, lymphatic drainage is essential for interstitial fluid removal. Furthermore, increased central venous pressure disturbs the lymph outflow through the thoracic duct and additionally stimulates lymph production, leading to oedema deterioration [50]. These pathological aspects prompted researchers to create an intervention, which would target the lymphatic flow in HF therapy. WhiteSwell is a device designed to create a low-pressure area in the outflow of the thoracic duct into the venous system. Such a technique aims to facilitate interstitial drainage with simultaneous intravascular fluid removal by diuretic therapy [17].

4.5.1. Existing Evidence

The WhiteSwell (NCT02863796) has been investigated in a sheep model and in one in-human case. In all studied sheep, WhiteSwell was successfully implanted and removed. The desired pressure gradient was achieved. As opposed to the controls with no implanted device, in studied sheep, WhiteSwell not only stopped the further fluid accumulation (understood as the extravascular lung water changes), but effectively initiated its removal [17]. No evidence of hemolysis was noted.

By now, one case of in-human implementation of the device was reported with positive early signals (in terms of serum creatinine, NT-proBNP and CVP change) of the intervention. After the procedure, the patient felt well and reported improvement in the orthopnea and oedema. No AE were reported.

WhiteSwell, and the general perspective for incorporating the lymphatic system into the HF therapy, constitute a promising supplementation to the traditional, intravascular space-based approach.

4.5.2. Weaknesses or Unexplained Issues

Except for all the limitations stemming from the animal model study, some issues need to be solved before wider clinical implementation. No reliable data about the impact of lymphatic system interventions and clinical outcome in HF patients is available. There were also some technical issues regarding the catheter implantation, and the second-generation catheter is now being constructed [17,44].

4.6. AquaPass

The AquaPass system has proposed another novel approach for direct interstitial fluid and sodium removal. The Aquapass system enhances sweat rate and thus fluid removal. It is a wearable machine constructed to increase the skin temperature of the lower parts of the body, with no effect on the core temperature [18].

Existing Evidence

The AquaPass system was evaluated in a study (NCT04578353) including only 6 healthy subjects and 10 HF patients who underwent three treatment sessions for up to 4 h. The skin temperature increased, with no change in core temperature. The median weight loss was 219 ± 67 g/h, and heart rate, systolic and diastolic pressure remained stable. No AE occurred. Enhancing sweat rate in HF patients seems to be a safe possibility for decongestive therapy; however, further studies are warranted to evaluate the precise value of the method and its impact on outcome [18].

5. Limitations

Our study is not free from limitations. Importantly, this is a literature review and was not performed in accordance with systematic review guidelines. Furthermore, to preserve the article compactness, we decided not to include all the promising device-based techniques applied in HF, such as valvular interventions, atrial shunting or cardiac contractility modulation.

6. Conclusions

The abovementioned techniques intend to leverage the pathophysiological aspects of heart failure, which have not been used in therapy by now. Notwithstanding the enormous potential of novel approaches, most are still distant from broad clinical appliance. Further, well-designed, randomized, controlled trials are warranted to evaluate their precise value in HF management.

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References

1. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef] [PubMed]
2. Zile, M.R.; Lindenfeld, J.; Weaver, F.A.; Zannad, F.; Galle, E.; Rogers, T.; Abraham, W.T. Baroreflex Activation Therapy in Patients With Heart Failure With Reduced Ejection Fraction. *J. Am. Coll. Cardiol.* **2020**, *76*, 1–13. [CrossRef] [PubMed]
3. Dell'Oro, R.; Gronda, E.; Seravalle, G.; Costantino, G.; Alberti, L.P.; Baronio, B.; Staine, T.; Vanoli, E.; Mancia, G.; Grassi, G. Restoration of normal sympathetic neural function in heart failure following baroreflex activation therapy: Final 43-month study report. *J. Hypertens.* **2017**, *35*, 2532–2536. [CrossRef] [PubMed]

4. Zannad, F.; De Ferrari, G.M.; Tuinenburg, A.E.; Wright, D.; Brugada, J.; Butter, C.; Klein, H.; Stolen, C.; Meyer, S.; Stein, K.M.; et al. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: Results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. *Eur. Heart J.* **2015**, *36*, 425–433. [CrossRef]
5. Premchand, R.K.; Sharma, K.; Mittal, S.; Monteiro, R.; Dixit, S.; Libbus, I.; Dicarlo, L.A.; Ardell, J.L.; Rector, T.S.; Amurthur, B.; et al. Autonomic Regulation Therapy via Left or Right Cervical Vagus Nerve Stimulation in Patients With Chronic Heart Failure: Results of the ANTHEM-HF Trial. *J. Card. Fail.* **2014**, *20*, 808–816. [CrossRef] [PubMed]
6. Fudim, M.; Ganesh, A.; Green, C.; Jones, W.S.; Blazing, M.A.; Devore, A.D.; Felker, G.M.; Kiefer, T.L.; Kong, D.F.; Boortz-Marx, R.L.; et al. Splanchnic nerve block for decompensated chronic heart failure: Splanchnic-HF. *Eur. Heart J.* **2018**, *39*, 4255–4256. [CrossRef]
7. Fudim, M.; Jones, W.S.; Boortz-Marx, R.L.; Ganesh, A.; Green, C.L.; Hernandez, A.F.; Patel, M.R. Splanchnic Nerve Block for Acute Heart Failure. *Circulation* **2018**, *138*, 951–953. [CrossRef]
8. Fudim, M.; Fail, P.S.; Litwin, S.E.; Shaburishvili, T.; Goyal, P.; Hummel, S.L.; Borlaug, B.A.; Mohan, R.C.; Patel, R.B.; Mitter, S.S.; et al. Endovascular ablation of the right greater splanchnic nerve in heart failure with preserved ejection fraction: Early results of the REBALANCE-HF trial roll-in cohort. *Eur. J. Heart Fail.* **2022**. [CrossRef]
9. Goedeke, S.; Emani, S.; Abraham, W.T.; Brandt, M.M.; Schaefer, J.A. Cardiac Pulmonary Nerve Stimulation (CPNSTM)): A Novel Treatment for Acute Decompensated Heart Failure. *JACC Basic Transl. Sci.* **2022**, *7*, 324–325. [CrossRef]
10. Costanzo, M.R.; Ponikowski, P.; Coats, A.; Javaheri, S.; Augostini, R.; Goldberg, L.R.; Holcomb, R.; Kao, A.; Khayat, R.N.; Oldenburg, O.; et al. Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure. *Eur. J. Heart Fail.* **2018**, *20*, 1746–1754. [CrossRef]
11. Costanzo, M.R.; Javaheri, S.; Ponikowski, P.; Oldenburg, O.; Augostini, R.; Goldberg, L.R.; Stellbrink, C.; Fox, H.; Schwartz, A.R.; Gupta, S.; et al. Transvenous Phrenic Nerve Stimulation for Treatment of Central Sleep Apnea: Five-Year Safety and Efficacy Outcomes. *Nat. Sci. Sleep* **2021**, *13*, 515–526. [CrossRef] [PubMed]
12. Beeler, R.; Schoenenberger, A.W.; Bauerfeind, P.G.K.-H.; Kobza, R.; Bergner, M.; Mueller, X.; Schlaepfer, R.; Zuberbühler, M.; Erne, S.; Erne, P. Improvement of cardiac function with device-based diaphragmatic stimulation in chronic heart failure patients: The randomized, open-label, crossover Epiphrenic II Pilot Trial. *Eur. J. Heart Fail.* **2014**, *16*, 342–349. [CrossRef] [PubMed]
13. Cleland, J.G.; Young, R.; Jorbenadze, A.; Shaburishvili, T.; Demyanchuk, V.; Buriak, R.; Todurov, B.; Rudenko, K.; Zuber, M.; Stämpfli, S.F.; et al. A First in Human Multi-center, Open Label, Prospective Study to Evaluate Safety, Usability and Performance of the VisONE System for Heart Failure with a Reduced Left Ventricular Ejection Fraction. *J. Card. Fail.* **2020**, *26*, S64. [CrossRef]
14. Biegus, J.; Zymlinski, R.; Siwolowski, P.; Testani, J.; Szachniewicz, J.; Tycińska, A.; Banasiak, W.; Halpert, A.; Levin, H.; Ponikowski, P. Controlled decongestion by Reprieve therapy in acute heart failure: Results of the TARGET-1 and TARGET-2 studies. *Eur. J. Heart Fail.* **2019**, *21*, 1079–1087. [CrossRef] [PubMed]
15. Zymliński, R.; Dierckx, R.; Biegus, J.; Vanderheyden, M.; Bartunek, J.; Ponikowski, P. Novel IVC Doraya Catheter Provides Congestion Relief in Patients With Acute Heart Failure. *JACC Basic Transl. Sci.* **2022**, *7*, 326–327. [CrossRef]
16. Kapur, N.K.; Kiernan, M.S.; Gorgoshvili, I.; Yousefzai, R.; Vorovich, E.E.; Tedford, R.J.; Sauer, A.J.; Abraham, J.; Resor, C.D.; Kimmelstiel, C.D.; et al. Intermittent Occlusion of the Superior Vena Cava to Improve Hemodynamics in Patients With Acutely Decompensated Heart Failure: The VENUS-HF Early Feasibility Study. *Circ. Heart Fail.* **2022**, *15*, e008934. [CrossRef]
17. Abraham, W.T.; Jonas, M.; Dongaonkar, R.M.; Geist, B.; Ueyama, Y.; Render, K.; Youngblood, B.; Muir, W.; Hamlin, R.; del Rio, C.L. Direct Interstitial Decongestion in an Animal Model of Acute-on-Chronic Ischemic Heart Failure. *JACC Basic Transl. Sci.* **2021**, *6*, 872–881. [CrossRef]
18. Aronson, D.; Nitzan, Y.; Petcherski, S.; Bravo, E.; Habib, M.; Burkhoff, D.; Abraham, W.T. Enhancing sweat rate using a novel device for the treatment of congestion in heart failure. *Eur. Heart J.* **2021**, *42*, ehab724.1056. [CrossRef]
19. Lesyuk, W.; Kriza, C.; Kolominsky-Rabas, P. Cost-of-illness studies in heart failure: A systematic review 2004–2016. *BMC Cardiovasc. Disord.* **2018**, *18*, 74. [CrossRef]
20. McCorry, L.K. Physiology of the Autonomic Nervous System. *Am. J. Pharm. Educ.* **2007**, *71*, 78. [CrossRef]
21. Florea, V.G.; Cohn, J.N. The Autonomic Nervous System and Heart Failure. *Circ. Res.* **2014**, *114*, 1815–1826. [CrossRef] [PubMed]
22. Kishi, T. Heart failure as an autonomic nervous system dysfunction. *J. Cardiol.* **2012**, *59*, 117–122. [CrossRef] [PubMed]
23. Victor, R.G. Carotid baroreflex activation therapy for resistant hypertension. *Nat. Rev. Cardiol.* **2015**, *12*, 451–463. [CrossRef] [PubMed]
24. Babar, N.; Giedrimiene, D. Updates on Baroreflex Activation Therapy and Vagus Nerve Stimulation for Treatment of Heart Failure With Reduced Ejection Fraction. *Cardiol. Res.* **2022**, *13*, 11–17. [CrossRef]
25. De Ferrari, G.M.; Crijns, H.J.; Borggrefe, M.; Milasinovic, G.; Smid, J.; Zabel, M.; Gavazzi, A.; Sanzo, A.; Dennert, R.; Kuschyk, J.; et al. Chronic vagus nerve stimulation: A new and promising therapeutic approach for chronic heart failure. *Eur. Heart J.* **2011**, *32*, 847–855. [CrossRef]
26. Schwartz, P.J.; De Ferrari, G.M.; Sanzo, A.; Landolina, M.E.; Rordorf, R.; Raineri, C.; Campana, C.; Revera, M.; Ajmone-Marsan, N.; Tavazzi, L.; et al. Long term vagal stimulation in patients with advanced heart failure First experience in man. *Eur. J. Heart Fail.* **2008**, *10*, 884–891. [CrossRef]
27. Gold, M.R.; Van Veldhuisen, D.J.; Hauptman, P.J.; Borggrefe, M.; Kubo, S.H.; Lieberman, R.A.; Milasinovic, G.; Berman, B.J.; Djordjevic, S.; Neelagaru, S.; et al. Vagus Nerve Stimulation for the Treatment of Heart Failure. *J. Am. Coll. Cardiol.* **2016**, *68*, 149–158. [CrossRef]

28. Fudim, M.; Ponikowski, P.P.; Burkhoff, D.; Dunlap, M.E.; Sobotka, P.A.; Molinger, J.; Patel, M.R.; Felker, G.M.; Hernandez, A.F.; Litwin, S.E.; et al. Splanchnic nerve modulation in heart failure: Mechanistic overview, initial clinical experience, and safety considerations. *Eur. J. Heart Fail.* **2021**, *23*, 1076–1084. [CrossRef]
29. Gajewski, P.; Fudim, M.; Kittipibul, V.; Engelman, Z.J.; Biegus, J.; Zymliński, R.; Ponikowski, P. Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction. *J. Clin. Med.* **2022**, *11*, 1063. [CrossRef]
30. Fudim, M.; Abraham, W.T.; von Bardeleben, R.S.; Lindenfeld, J.; Ponikowski, P.P.; Salah, H.M.; Khan, M.S.; Sievert, H.; Stone, G.W.; Anker, S.D.; et al. Device Therapy in Chronic Heart Failure: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2021**, *78*, 931–956. [CrossRef]
31. Chen, Y.-L.; Su, M.-C.; Liu, W.-H.; Wang, C.-C.; Lin, M.-C.; Chen, M.-C. Influence and Predicting Variables of Obstructive Sleep Apnea on Cardiac Function and Remodeling in Patients without Congestive Heart Failure. *J. Clin. Sleep Med.* **2014**, *10*, 57–64. [CrossRef] [PubMed]
32. Wang, Y.; Schöbel, C.; Penzel, T. Management of Obstructive Sleep Apnea in Patients With Heart Failure. *Front. Med.* **2022**, *9*, 803388. [CrossRef] [PubMed]
33. Costanzo, M.R.; Khayat, R.; Ponikowski, P.; Augostini, R.; Stellbrink, C.; Mianulli, M.; Abraham, W.T. Mechanisms and Clinical Consequences of Untreated Central Sleep Apnea in Heart Failure. *J. Am. Coll. Cardiol.* **2015**, *65*, 72–84. [CrossRef] [PubMed]
34. Sanders, M.H. Article reviewed: A mechanism of central sleep apnea in patients with heart failure. *Sleep Med.* **2000**, *1*, 63–64. [CrossRef]
35. Javaheri, S. A Mechanism of Central Sleep Apnea in Patients with Heart Failure. *N. Engl. J. Med.* **1999**, *341*, 949–954. [CrossRef]
36. Carlisle, T.; Ward, N.R.; Atalla, A.; Cowie, M.; Simonds, A.K.; Morrell, M.J. Investigation of the link between fluid shift and airway collapsibility as a mechanism for obstructive sleep apnea in congestive heart failure. *Physiol. Rep.* **2017**, *5*, e12956. [CrossRef]
37. Gottlieb, D.J.; Punjabi, N.M. Diagnosis and Management of Obstructive Sleep Apnea: A review. *JAMA* **2020**, *323*, 1389–1400. [CrossRef]
38. Voigt, J.; Emani, S.; Gupta, S.; Germany, R.; Khayat, R. Meta-Analysis Comparing Outcomes of Therapies for Patients With Central Sleep Apnea and Heart Failure With Reduced Ejection Fraction. *Am. J. Cardiol.* **2020**, *127*, 73–83. [CrossRef]
39. Yu, J.; Zhou, Z.; McEvoy, D.; Anderson, C.; Rodgers, A.; Perkovic, V.; Neal, B. Association of Positive Airway Pressure With Cardiovascular Events and Death in Adults With Sleep Apnea: A Systematic Review and Meta-analysis. *JAMA J. Am. Med. Assoc.* **2017**, *318*, 156–166. [CrossRef]
40. Fudim, M.; Mirro, M.; Goldberg, L.R. Synchronized Diaphragmatic Stimulation for the Treatment of Symptomatic Heart Failure: A Novel Implantable Therapy Concept. *JACC Basic Transl. Sci.* **2022**, *7*, 322–323. [CrossRef]
41. Costanzo, M.R.; Ponikowski, P.; Javaheri, S.; Augostini, R.; Goldberg, L.; Holcomb, R.; Kao, A.; Khayat, R.N.; Oldenburg, O.; Stellbrink, C.; et al. Transvenous neurostimulation for central sleep apnoea: A randomised controlled trial. *Lancet* **2016**, *388*, 974–982. [CrossRef]
42. Ponikowski, P.; Javaheri, S.; Michalkiewicz, D.; Bart, B.A.; Czarnecka, D.; Jastrzebski, M.; Kusiak, A.; Augostini, R.; Jagielski, D.; Witkowski, T.; et al. Transvenous phrenic nerve stimulation for the treatment of central sleep apnoea in heart failure. *Eur. Heart J.* **2012**, *33*, 889–894. [CrossRef] [PubMed]
43. Gheorghiade, M.; Filippatos, G. Reassessing treatment of acute heart failure syndromes: The ADHERE Registry. *Eur. Heart J. Suppl.* **2005**, *7*, B13–B19. [CrossRef]
44. Costanzo, M.R. Novel Devices for the Cardiorenal Syndrome in Heart Failure. *Curr. Treat. Options Cardiovasc. Med.* **2020**, *22*, 23. [CrossRef]
45. Urban, S.; Blaziak, M.; Biegus, J.; Zymlinski, R. Ultrafiltration in acute heart failure: Current knowledge and fields for further research. *Adv. Clin. Exp. Med.* **2021**, *30*, 737–746. [CrossRef]
46. Mullens, W.; Abrahams, Z.; Francis, G.S.; Sokos, G.; Taylor, D.O.; Starling, R.C.; Young, J.B.; Tang, W.W. Importance of Venous Congestion for Worsening of Renal Function in Advanced Decompensated Heart Failure. *J. Am. Coll. Cardiol.* **2009**, *53*, 589–596. [CrossRef]
47. Boorsma, E.M.; ter Maaten, J.M.; Voors, A.A.; van Veldhuisen, D.J. Renal Compression in Heart Failure: The Renal Tam-ponade Hypothesis. *JACC Heart Fail.* **2022**, *10*, 175–183. [CrossRef]
48. Clinical Evaluation of the TRVDTM System in ADHF—Full Text View—ClinicalTrials.gov, (n.d.). Available online: https://clinicaltrials.gov/ct2/show/study/NCT03621436 (accessed on 20 May 2022).
49. Kapur, N.K.; Karas, R.H.; Newman, S.; Jorde, L.; Chabrashvili, T.; Annamalai, S.; Esposito, M.; Kimmelstiel, C.D.; Lenihan, T.; Burkhoff, D. First-in-human experience with occlusion of the superior vena cava to reduce cardiac filling pressures in congestive heart failure. *Catheter. Cardiovasc. Interv.* **2019**, *93*, 1205–1210. [CrossRef]
50. Fudim, M.; Salah, H.M.; Sathananthan, J.; Bernier, M.; Pabon-Ramos, W.; Schwartz, R.S.; Rodés-Cabau, J.; Côté, F.; Khalifa, A.; Virani, S.A.; et al. Lymphatic Dysregulation in Patients With Heart Failure: JACC Review Topic of the Week. *J. Am. Coll. Cardiol.* **2021**, *78*, 66–76. [CrossRef]

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Effects of Sacubitril/Valsartan on the Renal Resistance Index

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Abstract: Background: Sacubitril/valsartan plays a key role in improving left ventricular remodeling and prognosis in patients with heart failure with a reduced ejection fraction (HFrEF). Moreover, some data support its role in preserving renal function. In order to better clarify the effects of sacubitril/valsartan in cardiorenal syndrome, this study evaluated its effects on the renal resistance index (RRI). Methods: A group of patients with HFrEF was enrolled. The RRI was assessed with renal echo-color Doppler at enrollment and again after at least six months of sacubitril/valsartan treatment. In a subgroup of patients, the RRI was also evaluated at least six months before enrollment. The variations in echocardiographic parameters reflecting the left and right ventricular function, as well as creatinine and the estimated glomerular filtration rate, were also evaluated. Results: After treatment with sacubitril/valsartan, significant improvements in the left ventricular ejection fraction, and a decrease in the left atrial and ventricular volumes were observed. The RRI also showed a significant decrease. No relationship was found between the improvements in the parameters reflecting cardiac function and changes in the RRI. Conclusions: Treatment with sacubitril/valsartan is associated with improvements in both left ventricular function and renal perfusion, through decreasing the renal resistance. These data help to clarify the effects of the drug on cardiorenal syndrome progression.

Keywords: heart failure with reduced ejection fraction; cardiorenal syndrome; angiotensin receptor–neprilysin inhibitors; reverse cardiac remodeling; renal resistance index

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1. Introduction

In patients with heart failure with a reduced left ventricular ejection fraction (HFrEF), sacubitril/valsartan has been demonstrated to be superior to ACE inhibitors (ACEi) in decreasing the risk of heart failure hospitalization and death [1], and in reversing left ventricular remodeling [2,3]. These effects are associated with better neuro-hormonal modulation that is mediated by this drug, which both antagonizes angiotensin II and inhibits the degradation of natriuretic peptides (NPs) [4,5].

Some data have also demonstrated the ability of sacubitril/valsartan to slow the progression of renal dysfunction [6–9]. A secondary analysis of PARADIGM-HF [6] has indicated that, during follow-up studies, the patients taking sacubitril/valsartan had a smaller decrease in the estimated glomerular filtration rate (GFR) than the patients taking enalapril, despite showing a greater blood pressure decrease. These effects were independent of both chronic kidney disease and albuminuria. These findings have been further supported by the PARAMOUNT study and available metanalyses [7–9]. The mechanisms underlying these favorable effects on renal function have not been fully

elucidated but may be mediated by improvements in the renal blood flow, which are mediated by the increased efficiency of the NP system (NPS) [5,10].

In order to better clarify the effects on the renal blood flow, the aim of this study was to evaluate the variation in the renal resistance index (RRI) after treatment with sacubitril/valsartan.

2. Materials and Methods

We evaluated patients referred to the Heart Failure Unit of the University Policlinic Hospital of Bari from 2016 and 2019, and to the Heart Failure Unit of the University Policlinic Hospital of Foggia from 2019 and 2021 for HFrEF (ESC criteria), who had been prescribed sacubitril/valsartan. Patients from Bari were enrolled in a study aimed at evaluating the predictors of cardiorenal syndrome progression whose main results have already been published [11]. Patients from Foggia were enrolled in the Daunia registry. Both of these studies were approved by local ethics committees and all enrolled patients provided written informed consent to participate.

Study design. Patients for whom sacubitril/valsartan was prescribed were evaluated. According to the indications of the Italian Ministry of Health, sacubitril/valsartan was prescribed to the patients with the New York Heart Association (NYHA) class II–IV; left ventricular ejection fraction (LVEF) of $\leq$35%; prior treatment with ACEi or angiotensin II receptor blockers (ARB) for at least 6 months; no history of angioedema; systolic arterial pressure of >95 mm Hg; estimated GFR of >30 mL/min/1.73 m^2; and serum potassium of <5.2 mmol/L. Patients taking an ACEi before study enrollment underwent a 36 h washout before the start of treatment with sacubitril/valsartan. The starting dose of sacubitril/valsartan was 24/26 mg b.i.d. or 49/51 mg b.i.d. depending on arterial pressure, renal function, and the previous ARNi/ARB dose. The dose was then up-titrated, when tolerated, to 97/103 mg b.i.d.

Baseline evaluation (T0) was considered to be the time in which the sacubitril/valsartan therapy was started. Between 6 and 12 months after beginning ARNI, a new complete evaluation was performed (T1). Moreover, an evaluation was performed at 6 and 12 months before ARNI therapy was started (T-1).

At T-1, T0, and T1, the following evaluations were performed:

- Medical examination and ECG. Records were documented, including ischemic heart disease, arterial hypertension, diabetes mellitus, history of ventricular arrhythmic events, NYHA class, arterial pressure, heart rhythm and heart rate at ECG;
- Echocardiographic examinations. Left ventricular end-diastolic volume (LVEDV), end-systolic volume (LVESV), and LVEF were calculated with Simpson's rule. The peak of the E wave (E), through mitral pulsed Doppler at the level of the mitral leaflets, and early diastolic velocity peak (e') at the level of the septal and lateral mitral annulus, through tissue Doppler imaging, were measured. The E/e' ratio was then calculated as the ratio between E and the mean value of septal and lateral e'. The central venous pressure was determined through the assessment of the inferior vena cava diameter and respiratory excursion. The mitral regurgitation (MR) was evaluated and quantified in arbitrary units (a.u. range from 0 to 4). The systolic pulmonary artery pressure (PAP) was estimated by the measurement of the RV–right atrium gradient from the peak velocity of the tricuspid valve regurgitation (TR) with the simplified Bernoulli equation; this value was added to an estimate of the mean right atrium pressure. The RV systolic function was evaluated according to tricuspid annular plane systolic excursion (TAPSE);
- Doppler of interlobular renal arteries. The method to assess the RRI was described previously [12,13]. The renal arterial Doppler was performed after echocardiographic examination by using the same echograph (Vivid 7, GE Vingmed Ultrasound, General Electric or EPIQ CVx system, Philips, Amsterdam, The Netherlands) and the same 4 MHz probe, moving the patient into the sitting position and using a posterior approach to the kidney. The course of the right or left kidney segmental arteries

was visualized by color Doppler flow and then, at the middle tract level of the best visualized one, pulsed Doppler was performed. Every effort was made to achieve the best alignment of the ultrasonic beam. An average of 2–3 measurements of the peak systolic velocity and the end-diastolic velocity were used to calculate the RRI according to Peurcelot's formula, i.e., 100 × [1 − (end-diastolic velocity/peak systolic velocity)].

RRI is a parameter with a high inter-operator and intra-operator reproducibility, as previously demonstrated [12]. To avoid bias in the measurement, the images were acquired by a single operator (M.I.) and analyzed by a single operator for each center (M.I.G. for patients referred to the center of Bari, and G.A. for those referred to the center of Foggia).

- Blood sample analyses. Blood samples were collected to evaluate NT-proBNP (immunoassay Dade Behring, Eschborn, Germany) and creatinine (mg/dL). The glomerular filtration rate was calculated with the abbreviated CKD-EPI formula (GFR-EPI, ml/min/1.73 m^2) [14].

Study end-points. The primary end-point of the study was to evaluate the changes in the RRI between the evaluations before and the evaluation after the introduction of sacubitril/valsartan therapy. As the secondary end-point we evaluated the changes in echocardiographic parameters after sacubitril/valsartan therapy and their relationship with those of the RRI. Reverse remodeling was defined as a relative change in LVESVI of >15% [15].

Statistical analysis. Continuous variables are expressed as mean values ± standard deviation. Discrete variables were summarized as frequencies and percentages. Spearman analysis was used to evaluate the relationship between the changes in the RRI and changes in the other studied parameters. To study the effect of sacubitril/valsartan therapy, we applied a linear regression mixed model on the values obtained at the different time points (before and after the therapy), with patients fitted as subject-specific random intercepts. The effects of sacubitril/valsartan therapy and the interaction at different time points were considered. If the overall effect was significant in the linear model, then pairwise differences were examined. The trends over timing points were displayed by plotting the mean values with standard error. Statistical analyses were performed in STATA software, version 12 (StataCorp LLC, College Station, TX, USA) or Statistica 6.1 software (StatSoft Inc., Tulsa, OK, USA). A p value of <0.05 was considered statistically significant.

3. Results

A total of 80 consecutive patients for whom sacubitril/valsartan was prescribed were evaluated, and 14 patients were excluded as follows: eight because of sacubitril/valsartan intolerance (seven for hypotension and one for muscular pain) and six because of a missing T1 evaluation. The clinical characteristics of the remaining 66 patients are shown in Table 1.

As shown in Table 2, after sacubitril/valsartan administration, significant reverse remodeling was observed, i.e., a significant decrease in the left ventricular volumes, as well as significant improvements in the LVEF. The improvement of the left ventricular volumes and the LVEF were observed after the initiation of the sacubitril/valsartan. In patients in whom T-1 was available, no changes in the left ventricular volumes were observed when the T-1 and T0 evaluations were compared. The parameters reflecting the left ventricular filling pressures, i.e., E/e', left atrial volume, and NT-proBNP, also significantly improved after sacubitril/valsartan, whereas no significant differences were found between the T-1 and T0 measurements. No significant differences were observed in TAPSE, TR, CVP, PAPs, creatinine, or GFR-EPI.

Table 1. Patient baseline clinical characteristics.

Number	66
Age (years)	56 ± 13
Males, *n* (%)	56 (85)
Ischemic etiology *n*, (%)	24 (36)
Diabetes mellitus *n*, (%)	13 (20)
Arterial Hypertension *n*, (%)	31 (47)
Atrial Fibrillation *n*, (%)	5 (8)
NYHA class II, *n* (%)	49 (76)
III, *n* (%)	17 (24)
BMI (kg/m^2)	29.4 ± 6.2
SAP (mm Hg)	120 ± 15
Heart rate (beats/minute)	67 ± 9
LVEF (%)	29 ± 6
Creatinine (mg/dL)	0.99 ± 1.9
GFR-EPI (mL/min/1.73 m^2)	84 ± 22
NT-proBNP (pg/mL)	1052 ± 1321
Concomitant therapy at the enrollment	
ACE-I, *n* (%)	45 (68)
Enalapril-equivalent dose (mg/die)	11 ± 6
ACE-I ≥ 50% target dose *n* (% among treated)	32 (71)
ARB, *n* (%)	21 (32)
Valsartan-equivalent dose (mg/die)	138 ± 75
ARB ≥ 50% target dose (% among treated)	11 (55)
Beta-blockers (%)	65 (98)
Bisoprolol-equivalent dose (mg/die)	7.1 ± 3.2
Beta-blocker ≥ 50% target dose	50 (76)
MRA *n*, (%)	58 (88)
MRA dose	45 ± 26
Loop diuretics *n*, (%)	52 (79)
Furosemide-equivalent dose (mg/die)	76 ± 102
ICD, *n* (%)	61 (95)
CRT, *n* (%)	22 (34)
Sacubitril/Valsartan up-titrated dose	
24/26 mg b.i.d., *n* (%)	34 (51)
49/51 mg b.i.d., *n* (%)	22 (34)
97/103 mg b.i.d., *n* (%)	10 (15)

ACE-I: inhibitors of Angiotensin-Converting Enzyme; ARB: angiotensin II receptor blockers; BMI: body mass index; GFR-EPI: estimated glomerular filtration rate by EPI formula; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; MRA: mineralcorticoid receptor antagonists; NYHA class: New York heart Association class; NT-proBNP: amino terminal brain natriuretic peptide; SAP: systolic arterial pressure.

Table 2. Changes in studied parameters after sacubitril/valsartan treatment.

	Sacubitril/Valsartan			
	Before		**After**	
	T-1	**T0**	**T1**	***p***
SAP (mmHg)	122 ± 16	120 ± 15	116 ± 19 †	0.037
LVEDV (mL)	193 ± 50	184 ± 57	173 ± 56 *†	<0.001
LVESV (mL)	136 ± 41	133 ± 48	116 ± 46 *†	<0.001
LVEF (%)	30 ± 6	29 ± 6 †	34 ± 6 *†	<0.001
MR (a.u.)	1.8 ± 0.8	1.7 ± 0.8	1.6 ± 0.6	0.154
LAV (mL)	83 ± 29	82 ± 32	70 ± 27 *†	<0.001
E/e′	10.8 ± 3.4	10.9 ± 3.4	9.7 ± 3.9 *†	0.033
TAPSE (mm)	19.6 ± 3.8	19.8 ± 3.3	20.4 ± 3.4	0.281
TR (a.u.)	1.6 ± 0.7	1.5 ± 0.6	1.5 ± 0.6	0.541
CVP (mmHg)	4.9 ± 2.6	4.0 ± 2.2	4.4 ± 2.5	0.132
PAPs (mmHg)	32 ± 8	32 ± 7	30 ± 6 *	0.049

Table 2. *Cont.*

	Sacubitril/Valsartan			
	Before		After	
	T-1	T0	T1	*p*
Creatinine (mg/dL)	0.96 ± 0.24	0.99 ± 0.26	1.01 ± 0.22	0.404
GFR-EPI (mL/min/1.73 m^2)	87 ± 20	84 ± 21	83 ± 20	0.268
NTproBNP (pg/mL)	857 ± 1105	1052 ± 1321	614 ± 653 *†	0.017
RRI (%)	66.9 ± 5.5	67.0 ± 5.5	64.9 ± 5.5 *†	<0.001

Data expressed as mean ± standard deviation. *p* refers to linear fixed model. T-1 available in 49 patients. * $p < 0.05$ vs. T0; † $p < 0.05$ vs. T-1. CVP: central venous pressure; E/e': the ratio between the peak of the E wave (E), through mitral pulsed Doppler at the level of the mitral leaflets, and early diastolic velocity peak (e') at the level of the septal and lateral mitral annulus, through tissue Doppler imaging; GFR-EPI: estimated glomerular filtration rate by EPI formula; LAV: left atrial volume; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MR: mitral regurgitation; NT-proBNP: amino-terminal brain natriuretic peptide; PAPs: estimated systolic pulmonary arterial pressure; RRI: renal resistance index; SAP: systolic arterial pressure; TAPSE: peak of tricuspid annulus systolic excursion; TR: tricuspid regurgitation.

When the RRI was analyzed, a significant reduction was demonstrated after the sacubitril/valsartan treatment, whereas no differences were found between the T-1 and T0 evaluations in the 41 patients in whom it was available (Figure 1, left panel).

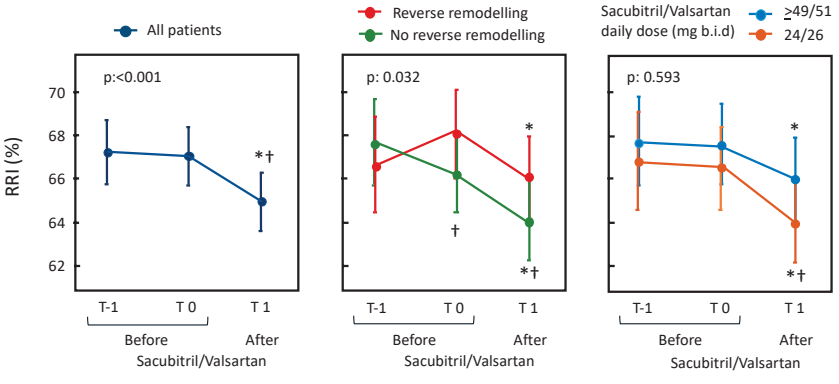

Figure 1. In the left panel, changes in RRI before and after sacubitril/valsartan are presented. In the right panels, changes are presented depending on the occurrence of reverse remodeling after treatment with sacubitril/valsartan and on its dosage. The data are expressed as the mean and 95% confidence interval with a linear mixed model adjusted for repeated measures. *p* refers to the statistical significance of the model; * $p < 0.05$ vs. T0, † $p < 0.05$ vs. T-1.

In order to evaluate the relationship between the RRI changes and the improvements in the left ventricular remodeling and function, we separately evaluated the variation in the RRI in patients with and without reverse remodeling (i.e., a relative decrease in LVESV of >15%) (Figure 1, middle panel). Both patients with and without reverse remodeling showed an improvement of RRI when compared with baseline values. This improvement was even greater and more significant in the patients with reverse remodeling when a comparison with T-1 values was performed. Moreover, as shown in the right panel of Figure 1, no significant changes in RRI were observed according with sacubitril/valsartan dosage.

Finally, the changes in the RRI were not correlated with those of the parameters reflecting the diastolic function, i.e., LAV (Spearman's R 0.014, *p* 0.911) and E/e' (Spearman's R 0.116, *p* 0.391). Analogously, no correlation was found with the absolute changes in TAPSE (Spearman's R −0.027, *p* 0.845) and PAP (Spearman's R 0.008, *p* 0.956). In addition, the changes in the RRI were not correlated with the absolute and relative changes in creatinine (Spearman's R 0.219 and 0.215, *p* 0.087 and 0.093, respectively) and with the relative changes in GFR (Spearman's R −0.122, *p* 0.338).

4. Discussion

The main finding of this study was that, after treatment with sacubitril/valsartan, significant improvements in renal resistances were observed and were not associated with the improvements in the left ventricular function.

Sacubitril/valsartan plays a key role in the treatment of patients with HFrEF [1,16]. The greater efficacy of this drug compared to ACEi [1,2] is related to the contemporary angiotensin II antagonism and the inhibition of neprilysin, the endothelial endopeptidase that is involved in the degradation of NPs. The NPS counteracts the renin-angiotensin system and sympathetic nervous system activity [5] by inducing natriuresis and diuresis, thus exerting an antifibrotic effect at the cardiac level, causing vasodilation and inhibiting the renin-angiotensin II system. These effects explain the improvement in cardiac function, which we observed in our series of patients. In fact, a significant decrease in left ventricular volumes, an improvement in the left ventricular systolic function, and a decrease in the left ventricular filling pressures were also observed in our patients.

However, the beneficial effects of sacubitril/valsartan are mediated not only by cardiac protection but also by renal protection, thus slowing the progression of cardiorenal syndrome [17] in patients with HF. The nephroprotective effects of sacubitril/valsartan are mediated by both antagonism of angiotensin II and by the inhibition of neprylisin [10] (Figure 2). The latter effect, by decreasing the degradation of NPs, increases cGMP-PKG activity, thereby leading to not only natriuretic and diuretic effects, but also other favorable effects, such as afferent arteriole dilation and increased glomerular filtration. Moreover, NPs inhibit sympathetic nervous system activity and angiotensin II, and consequently induce efferent arteriole dilation, glomerular hypertrophy, and scaring, as well as mesangial matrix accumulation. These effects explain the diminished renal fibrosis that is mediated by sacubitril/valsartan at the level of the kidneys [18].

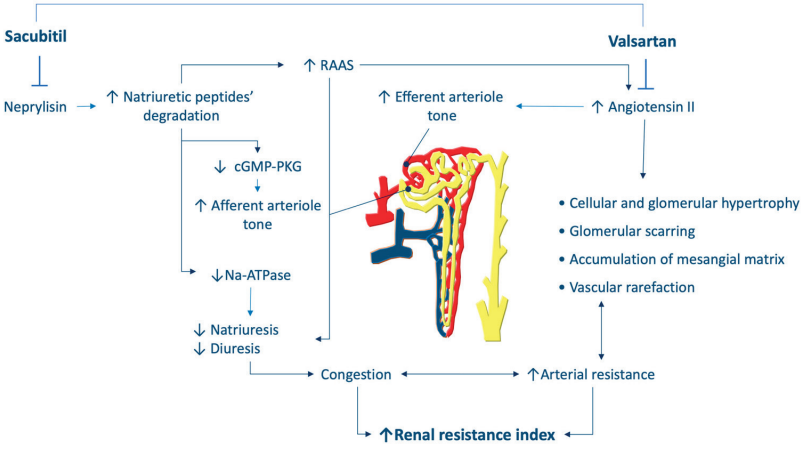

Figure 2. Hypothesis regarding the effects of sacubitril/valsartan on renal resistance. RAAS: renin-angiotensin system.

Our results support the hypothesis that sacubitril/valsartan exerts specific nephroprotective effects that decrease arterial renal resistance and are associated with the progression of renal dysfunction. In fact, the RRI reflects arterial renal resistance [12,19,20], which is closely associated with the pathophysiology of renal dysfunction. The increased RRI is associated with the overactivation of the neuro-hormonal systems, as well as renal parenchymal abnormalities, leading to vascular rarefaction. The increased RRI is also associated with oxidative stress, endothelial dysfunction, and inflammatory cytokine activity [20,21]. Finally, in patients with heart failure, greater intrabdominal and central venous pressure can also increase the RRI, as a consequence of renal congestion [22]. Together, these mechanisms

may explain the prognostic relevance of RRI, as well as the relationship between RRI and the progression of renal dysfunction. The ability of sacubitril/valsartan to decrease the renal resistance indicates that sacubitril/valsartan can modify the pathophysiological background underlying the RRI, thus providing renal protection.

Interestingly, the changes in the RRI that have we observed were not related to those reflecting reverse remodeling, improvements in LVEF, or decreased left ventricular filling pressure and right pressure. As a consequence, sacubitril/valsartan might be hypothesized to have additive and direct renal effects independent from the improvements in cardiac function.

Our study did not include a control group. In order to overcome this limitation and to strengthen the evidence of a causal relationship between sacubitril/valsartan therapy and RRI variation, we evaluated the parameters not only at the time of prescription and after the treatment with sacubitril/valsartan, but also at least six months before the start of the treatment. Interestingly, the RRI, as well as the left ventricular atrial and ventricular volumes and the left ventricular ejection fraction, were similar at T0 and T-1, but changed significantly after the administration of sacubitril/valsartan. These findings provide further support for the drug's role in the observed changes.

Finally, no relationship was found between the RRI changes and the changes in creatinine serum levels and estimated GFR. As previously demonstrated [19], an altered RRI may precede the decline in renal function, because it more accurately reflects the pathophysiological mechanisms leading to nephron loss, when a normal GFR is still present due to compensatory mechanisms.

However, our study presents several limitations. It was not a randomized study, and we did not have data to compare the effects of sacubitril/valsartan with those of ACE-inhibitors or angiotensin II receptor blockers. However, all of our patients were taking one of these two classes of drugs before sacubitril/valsartan and no change was observed between T-1 and T0 evaluations, whereas the changes were observed after the initiation of sacubitril/valsartan. The changes in RRI were statistically significant but small. This could be due to the short follow-up. However, it is worth noting that no significant changes in GFR were observed during the same period. Consequently, despite the above-mentioned limitations, our results could be useful to generate hypotheses about the effects of sacubitril/valsartan on renal resistances that could occur earlier than those of GFR. Future studies should confirm our results and evaluate the RRI changes in a larger population with a longer follow-up.

5. Conclusions

Sacubitril/valsartan appears to have favorable effects on arterial renal resistances and kidney function. These variations are likely to be related to the combined renal effects of the inhibition of the renin-angiotensin system and the inhibition of neprylisin. Moreover, these effects are not related to reverse remodeling, changes in creatinine serum levels, or the estimated GFR. In this sense, more evidence is needed in order to better characterize the effects on renal function and hemodynamics.

Author Contributions: M.I.G. and M.I. conceived the study; M.I.G., G.P., D.G., M.A., G.A., M.C. and M.I. enrolled patients, collected data, and executed and analyzed the echocardiograms; M.I.G. and G.A. analyzed the Renal Resistance Index; M.I. completed the statistical analysis; M.I.G. and M.I. completed the draft of the paper; M.C., N.D.B. and M.M.C. critically revised the results of the study and the first draft. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki. It pooled data from two protocols, one approved by the Institutional Ethics Committee of the Polyclinic University Hospital of Bari, Bari, Italy (study number 4282 approved on 6 November 2013) and a second approved by the Institutional Ethics Committee of the Polyclinic

University Hospital of Foggia, Foggia, Italy (protocol code 68/CE/20, date of approval 26 May 2020). In both protocols M.I. was the principal investigator.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Mcmurray, J.J.V.; Packer, M.; Desai, A.S.; Gong, J.; Lefkowitz, M.P.; Rizkala, A.R.; Rouleau, J.L.; Shi, V.C.; Solomon, S.D.; Swedberg, K.; et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. PARADIGM-HF Investigators and Committees. *N. Engl. J. Med.* **2014**, *371*, 993–1004. [CrossRef] [PubMed]
2. Desai, A.S.; Solomon, S.D.; Shah, A.M.; Claggett, B.L.; Fang, J.C.; Izzo, J.; McCague, K.; Abbas, C.A.; Rocha, R.; Mitchell, G.F.; et al. Effect of Sacubitril-Valsartan vs. Enalapril on Aortic Stiffness in Patients with Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. *JAMA* **2019**, *322*, 1–10. [CrossRef] [PubMed]
3. Januzzi, J.L., Jr.; Prescott, M.F.; Butler, J.; Felker, G.M.; Maisel, A.S.; McCague, K.; Camacho, A.; Piña, I.L.; Rocha, R.A.; Shah, A.M.; et al. Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction. *JAMA* **2019**, *322*, 1–11. [CrossRef] [PubMed]
4. Buggey, J.; Mentz, R.J.; DeVore, A.D.; Velazquez, E.J. Angiotensin receptor neprilysin inhibition in heart failure: Mech-anistic action and clinical impact. *J. Card. Fail.* **2015**, *21*, 741–750. [CrossRef] [PubMed]
5. Díez, J. Chronic heart failure as a state of reduced effectiveness of the natriuretic peptide system: Implications for therapy. *Eur. J. Heart Fail.* **2017**, *19*, 167–176. [CrossRef]
6. Damman, K.; Gori, M.; Claggett, B.; Jhund, P.; Senni, M.; Lefkowitz, M.P.; Prescott, M.F.; Shi, V.C.; Rouleau, J.L.; Swedberg, K.; et al. Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure. *JACC Heart Fail.* **2018**, *6*, 489–498. [CrossRef]
7. Solomon, S.D.; Zile, M.; Pieske, B.; Voors, A.; Shah, A.; Kraigher-Krainer, E.; Shi, V.; Bransford, T.; Takeuchi, M.; Gong, J.; et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: A phase 2 double-blind randomised controlled trial. *Lancet* **2012**, *380*, 1387–1395. [CrossRef]
8. Wang, Y.; Zhou, R.; Lu, C.; Chen, Q.; Xu, T.; Li, D. Effects of the Angiotensin-Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis. *J. Am. Heart Assoc.* **2019**, *8*, e012272. [CrossRef]
9. Damman, K.; Valente, M.A.; Voors, A.A.; O'Connor, C.M.; Van Veldhuisen, D.J.; Hillege, H.L. Renal impairment, worsening renal function, and outcome in patients with heart failure: An updated meta-analysis. *Eur. Heart J.* **2014**, *35*, 455–469. [CrossRef]
10. Judge, P.; Haynes, R.; Landray, M.J.; Baigent, C. Neprilysin inhibition in chronic kidney disease. *Nephrol. Dial. Transplant.* **2015**, *30*, 738–743. [CrossRef]
11. Iacoviello, M.; Di Serio, F.; Rizzo, C.; Leone, M.; Grande, D.; Guida, P.; Gioia, M.I.; Parisi, G.; Leopizzi, T.; Caldarola, P.; et al. Association between high Gal-3 serum levels and worsening of renal function in chronic heart failure outpatients. *Biomark. Med.* **2019**, *13*, 707–713. [CrossRef] [PubMed]
12. Ciccone, M.M.; Iacoviello, M.; Gesualdo, L.; Puzzovivo, A.; Antoncecchi, V.; Doronzo, A. The renal arterial resistance index: A marker of renal function with an independent and incremental role in predicting heart failure progression. *Eur. J. Heart Fail.* **2014**, *16*, 210–216. [CrossRef] [PubMed]
13. Bigé, N.; Levy, P.; Callard, P.; Faintuch, J.-M.; Chigot, V.; Jousselin, V.; Ronco, P.; Boffa, J.-J. Renal arterial resistive index is associated with severe histological changes and poor renal outcome during chronic kidney disease. *BMC Nephrol.* **2012**, *13*, 139. [CrossRef] [PubMed]
14. Levey, A.S.; Stevens, L.A.; Schmid, C.H.; Zhang, Y.L.; Castro, A.F., 3rd; Feldman, H.I.; Kusek, J.W.; Eggers, P.; Van Lente, F.; Greene, T.; et al. A new equation to estimate glomerular fil-tration rate. *Ann. Intern. Med.* **2009**, *150*, 604–612. [CrossRef] [PubMed]
15. Pitzalis, M.V.; Iacoviello, M.; Romito, R.; Massari, F.; Rizzon, B.; Luzzi, G.; Guida, P.; Andriani, A.; Mastropasqua, F.; Rizzon, P. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J. Am. Coll. Cardiol.* **2002**, *40*, 1615–1622. [CrossRef]
16. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Bohm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; ESC Scientific Document Group; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the Eu-ropean Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. J. Heart Fail.* **2022**, *24*, 4–131.
17. Rangaswami, J.; Bhalla, V.; Blair, J.E.A.; Chang, T.I.; Costa, S.; Lentine, K.L.; Lerma, E.V.; Mezue, K.; Molitch, M.; Mullens, W.; et al. American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology. Car-diorenal syndrome: Classification, pathophysiology, diagnosis, and treatment strategies: A scientific statement from the American Heart Association. *Circulation* **2019**, *139*, e840–e878.

18. Ushijima, K.; Ando, H.; Arakawa, Y.; Aizawa, K.; Suzuki, C.; Shimada, K.; Tsuruoka, S.; Fujimura, A. Prevention against renal damage in rats with subtotal nephrectomy by sacubitril/valsartan (LCZ696), a dual-acting angiotensin receptor-neprilysin inhibitor. *Pharmacol. Res. Perspect.* **2017**, *5*, e00336. [CrossRef]
19. Iacoviello, M.; Monitillo, F.; Leone, M.; Citarelli, G.; Doronzo, A.; Antoncecchi, V.; Puzzovivo, A.; Rizzo, C.; Lattarulo, M.S.; Massari, F.; et al. The Renal Arterial Resistance Index Predicts Worsening Renal Function in Chronic Heart Failure Patients. *Cardiorenal Med.* **2016**, *7*, 42–49. [CrossRef]
20. Ciccone, M.M.; Iacoviello, M.; Puzzovivo, A.; Scicchitano, P.; Monitillo, F.; De Crescenzo, F.; Caragnano, V.; Sassara, M.; Quistelli, G.; Guida, P.; et al. Clinical correlates of endothelial function in chronic heart failure. *Clin. Res. Cardiol.* **2011**, *100*, 515–521. [CrossRef]
21. Chade, A.R. Renal vascular structure and rarefaction. *Compr. Physiol.* **2013**, *3*, 817–831.
22. Braam, B.; Cupples, W.A.; Joles, J.A.; Gaillard, C. Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. *Heart Fail. Rev.* **2012**, *17*, 161–175. [CrossRef] [PubMed]

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Review

The Treatment of Heart Failure in Patients with Chronic Kidney Disease: Doubts and New Developments from the Last ESC Guidelines

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Abstract: Patients with heart failure (HF) and associated chronic kidney disease (CKD) are a population less represented in clinical trials; additionally, subjects with more severe estimated glomerular filtration rate reduction are often excluded from large studies. In this setting, most of the data come from post hoc analyses and retrospective studies. Accordingly, in patients with advanced CKD, there are no specific studies evaluating the long-term effects of the traditional drugs commonly administered in HF. Current concerns may affect the practical approach to the traditional treatment, and in this setting, physicians are often reluctant to administer and titrate some agents acting on the renin angiotensin aldosterone system and the sympathetic activity. Therefore, the extensive application in different HF subtypes with wide associated conditions and different renal dysfunction etiologies remains a subject of debate. The role of novel drugs, such as angiotensin receptor blocker neprilysin inhibitors and sodium glucose linked transporters 2 inhibitors seems to offer a new perspective in patients with CKD. Due to its protective vascular and hormonal actions, the use of these agents may be safely extended to patients with renal dysfunction in the long term. In this review, we discussed the largest trials reporting data on subjects with HF and associated CKD, while suggesting a practical stepwise algorithm to avoid renal and cardiac complications.

Keywords: heart failure; chronic kidney disease; estimated glomerular filtration rate; sodium glucose linked transporters 2 inhibitors; treatment; angiotensin receptor blocker neprilysin inhibitors

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1. Introduction

The most recent HF guidelines propose a revised algorithm for the treatment of heart failure with reduced ejection fraction (HFrEF), with the "quadruple therapy" approach with the use of SGLT-2 inhibitors, angiotensin receptor blocker neprilysin inhibitors (ARNI) (as a replacement of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) or in de novo HFrEF patients with class of recommendation IIb), on top on B-blockers, and mineralocorticoid receptor antagonists (MRAs), with a substantial improvement in clinical outcomes in terms of hospitalization and mortality [1]. However, renin angiotensin system (RAAS) inhibitors, MRAs, angiotensin receptor blocker neprilysin inhibitors (ARNI), and sodium glucose linked transporters 2 (SGLT2) inhibitors significantly impact the renal function due to changes in renal physiology. These drugs reset the renal function curve, affecting the intraglomerular hydrostatic pressures–natriuresis relationship through the tubule-glomerular feedback mechanism and by contrasting the effects on the afferent and efferent glomerular arteriola induced by different agents. These effects modify the physiological filtration fraction, have different baroceptorial and chemotactic repercussion on the macula densa, and may impact the tubular function (Figure 1). The concomitant

use of RAAS inhibitors, MRAs, and novel drug such as SGLT2 inhibitors and ARNI may amplify the process of transitory renal impairment occurring after the early administration, resulting in the inertia of the start and up-titration of these lifesaving therapies. In most of cases, renal impairment is transitory, and the kidney function tends to return to its prior conditions or remain stable in the long term [2]. However, the effect on the renal function induced by polytherapy is not being sufficiently analyzed. Therefore, HF patients with concomitant renal dysfunction are less likely to receive guideline-recommended therapies, even though this is not always justified. In this review, we reported the effects on the kidney of heart failure (HF) drugs in patients with HF and chronic kidney disease (CKD), and we suggested the correct application of these lifesaving therapies in clinical practice.

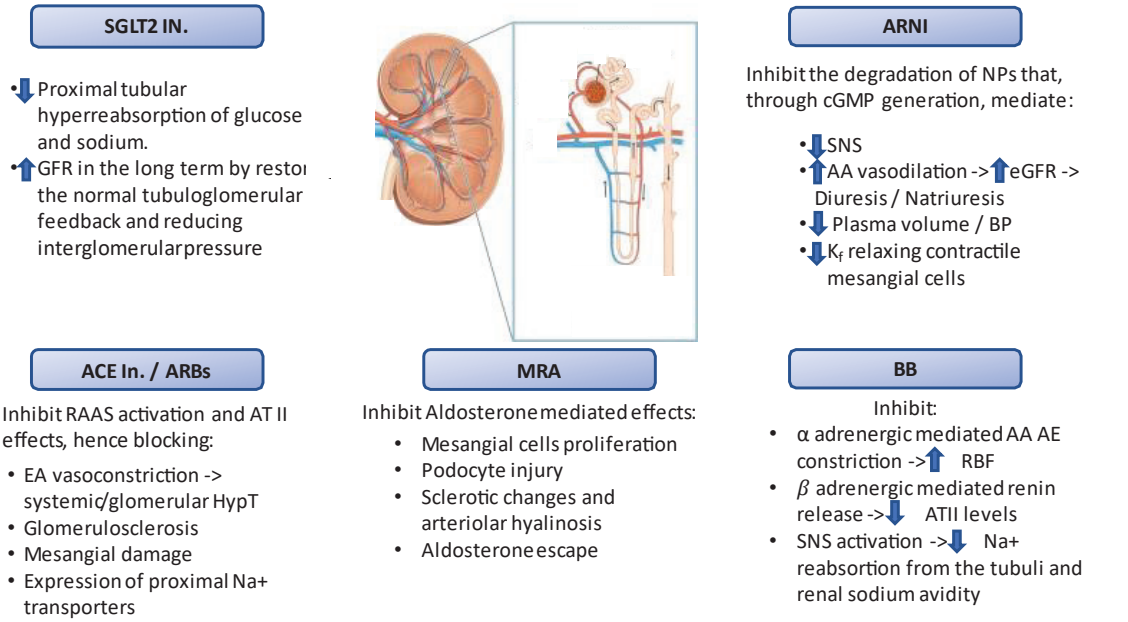

Figure 1. The effects of heart failure drugs on renal physiology. AA: afferent arteriole; ACE In.: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers; ARNI: angiotensin receptor neprilisin inhibitor; ATII: angiotensin II; BB: beta blockers; BP: blood pressure; cGMP: cyclic guanosine monophosphate; eGFR: estimated glomerular filtration rate; EA: efferent arteriole; HypT: hypertension; K_f: glomerular capillary ultrafiltration coefficient; MRA: mineralcorticoid receptor antagonist; NPs: natriuretic peptides; RAAS: renin angiotensin aldosterone system; RBF: renal blood flow; SGLT2 In.: sodium glucose transporter protein 2 inhibitors; SNS: sympathetic nervous system.

2. Clinical Characteristics of Patients with Chronic Kidney Disease and Heart Failure

Previous studies on outpatients with chronic HF showed that one of the highest prevalence among the non-cardiovascular comorbidities was related to a renal failure ranging from 30% to 50% [3]. The heart and kidneys were strictly related; the dysfunction of either of those organs led to a functional deterioration of the other due to various mechanisms, such as inflammation, oxidative stress, impaired hydro-saline homeostasis, and diuretic resistance [4,5]. In chronic HF, there was decreased cardiac output, predominantly due HFrEF results in decreased organ perfusion. In patients with HFpEF, elevated filling pressures were the main hemodynamic feature and decreased systolic filling resulted in inadequate stroke volume reserved, ultimately causing a decreased cardiac output. A reduction in cardiac output in patients with chronic HF has been shown to result in a decrease in renal blood flow. Additionally, in response to a diminished cardiac output, the kidney promotes

mechanisms that result in water and sodium retention, ultimately causing subclinical congestion, which in turn causes further kidney dysfunction. Both in experimental settings and in patients with either chronic or acute HF, an increase in central venous pressures or abdominal pressure was associated with an increased risk of worsening renal function. In cardiorenal syndrome type 2, CKD has been observed in 45 to 63% of patients. Renal congestion, hypoperfusion, and increased right atrial pressure represent hallmarks of this clinical condition [6]. HF and CKD patients shared a poor quality of life and showed a high burden of cardiovascular (CV) risk due to several common risk factors, such as diabetes, hypertension, and coronary artery disease (CAD) [7]. Phenotyping patients with renal dysfunction remains a real challenge; the pathophysiological mechanisms and the prognostic role of renal dysfunction may differ across HFrEF, HFmrEF, and HFpEF. CKD is often associated with more severe HF conditions and stages, independently of left ventricular ejection fraction (LVEF). The relationships between CKD, older age, female sex, diabetes, and HF stage were similar in the three HF groups, but several studies demonstrated that CKD was more prevalent in heart failure with preserved ejection fraction (HFpEF) than in heart failure with mildly reduced ejection fraction (HFmrEF) and HFrEF [8,9]. Other studies showed a higher prevalence of CKD in HFrEF patients [10]. The association between HFpEF and the deterioration of the renal function was independent of the presence of CKD at baseline. Renal dysfunction in HFpEF may be considered a major comorbidity, with a general prognostic impact without any relation with a worse HF status: conversely, in HFrEF patients, kidney dysfunction may reflect the progression of HF, perhaps due to low cardiac output, hemodynamic hypoperfusion, and sympathetic and neurohormonal activation [11].

Among non-CV comorbidities, CKD was the disease more frequently associated with hospitalization [12]. Renal dysfunction, regardless of its definition and screening method, conferred a clinically significant risk for excess mortality in patients with HF [13]. CKD was associated with worse outcomes in all HF phenotype; however, the literature on mortality in HFpEF and CKD shows conflicting results. In the larger meta-analyses, which included a cohort of HFpEF patients, CKD was a more powerful predictor of death [14]. Conversely, a meta-analysis of the Global Group in Chronic Heart Failure (MAGGIC) showed a lower mortality rate and a lower association between CKD and death in patients with HFpEF than in those with HFrEF [15]. This result was confirmed in the Swedish Heart Failure registry, in which the association between CKD and mortality risk was less pronounced in HFpEF patients [16].

In patients with acute heart failure (AHF), we can discern between two distinct phenotypes: patients with baseline renal dysfunction, defined as CKD, and patients developing worsening renal function (WRF) during hospitalization [17]. A new classification of WRF has been proposed, according to the time frame resolution or persistence. The first clinical scenario was a patient with good renal function and occurrence of a "pseudo" WRF during hospitalization for acute HF, that was considered secondary to the decongestion therapy. The increase of in-hospital creatinine did not usually persist after discharge, without consequences for the prognosis if the patient was well treated, with efficient decongestion at discharge. The second scenario was a patient with true WRF due to congestion (increased renal venous pressure) and hypoperfusion (reduced arterial perfusion), in which renal deterioration persisted, with an increase in creatinine also in the post-discharge period and with a higher burden of HF re-hospitalization [18]. Finally, in the third scenario, WRF could occur in the presence of CKD related to reduced cortical blood flow and chronic glomerulosclerosis with reduced cortical wall. This subtype was common in older patients with several comorbidities, where WRF reflected the real deterioration of the renal function, with worse prognostic value. Current classification was uncompleted, because it did not account for serial kidney evaluation after discharge and the severity of an effective estimated glomerular filtration rate (eGFR) impairment (Table 1).

Table 1. Clinical scenarios and RIFLE (risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, end-stage renal failure) criteria and AKIN (acute kidney injury network) criteria for diagnosis of acute kidney injury.

Clinical Scenarios		
(1) "Pseudo" WRF	Good renal function at baseline and occurrence of WRF during hospitalization for acute HF, usually secondary to the decongestion therapy.	
(2) "True" WRF	WRF due to congestion and hypoperfusion, in which renal deterioration persisted also in the post-discharge period with a higher burden of HF re-hospitalization.	
(3) WRF in CKD	WRF could occur in the presence of CKD. This subtype was common in older patients with several comorbidities, where WRF reflected the real deterioration of the renal function, with worse prognostic value.	
Laboratory/urine Output Criteria		
	eGFR Criteria	Urine output criteria
RIFLE (an acute rise in SCr over 7d)		
Risk	Increased SCr $\geq \times 1.5$ or eGFR decrease > 25%	UO < 0.5 mL/kg/h $\times$ 6 h
Injury	Increase in SCr $\geq \times 2$ or eGFR decrease > 50%	UO < 0.5 mL/kg/h $\times$ 12 h
Failure	Increase in SCr $\geq \times 3$ or eGFR decrease > 75% or SCr $\geq$ 4.0 mg/dL	UO < 0.5 mL/kg/h $\times$ 24 h or anuria $\times$ 12 h
Loss	Persistent ARF = Complete loss of kidney function > 4 wk	
ESKD	End stage renal disease (>3 months)	
AKIN (an acute rise in SCr within 48 h)		
Stage 1	Same as RIFLE Risk or increase in SCr $\geq$ 0.3 mg/dL ($\geq$26.4 µmol/L)	Same as RIFLE Risk
Stage 2	Same as RIFLE Injury	Same as RIFLE Injury
Stage 3	Increase in SCr $\geq \times 3$ or serum creatinine of $\geq$4.0 mg/dL with an acute increase of at least 0.5 mg/dL or RRT	Same as RIFLE Failure

WRF: worsening renal function; CKD: chronic kidney disease; HF: heart failure; AKIN: acute kidney injury network; ARF: acute renal failure; d: days; ESKD: end-stage kidney disease; eGFR: estimated glomerular filtration rate; h: hour; RIFLE: risk of renal failure, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal failure; RRT: renal replacement therapy; SCr: serum creatinine; UO: urine output; and wk: weeks.

3. Therapeutic Target and Limitations in Patients with Heart Failure and Chronic Kidney Disease

All drugs used in HF patients have potentially detrimental effects on the renal function, and they expose HF patients with renal dysfunction to a greater risk of adverse renal complications, such as hyperkalemia and dialysis. Historically, data from randomized controlled trials on the effect of HF medications in HF patients and CKD were limited, due to the exclusion of patients with CKD.

The studies of left ventricular dysfunction (SOLVD) trial enrolled 36% of patients with CKD and eGFR < 60 mL/min/1.73 m^2; 33% of all patients presented a >0.5 mg/dL increase in serum creatinine; in the final analyses, the benefits on all-cause mortality were maintained across the entire CKD spectrum [19]. This finding was confirmed by the survival and ventricular enlargement (SAVE) trial, which demonstrated the improvement in survival and reduced morbidity in patients with asymptomatic left ventricular dysfunction treated with captopril vs. placebo regardless of CKD (exclusion criteria Cr > 2.5 mg/dL, 33% of patients with CKD). After 42 months of follow-up, the risk for death associated with renal

events was hazard ratio (HR) 1.63 (95% CI 1.05–2.52) in the placebo group, versus HR 1.33 (95% CI 0.81–2.21) in the captopril group (p = 0.49 for interaction) [20]. Similar findings were found in the trandolapril cardiac evaluation (TRACE) study group, in which 40% of patients with post-myocardial infarct LV dysfunction had CKD. In this group, trandolapril significantly reduced the risk of CV mortality and HF progression [21]. More recently, in the NETWORK and ATLAS trials, patients with Cr > 2.3 mg/dL and Cr > 2.5 mg/dL were excluded, and no specific therapeutic data on advanced CKD could be extrapolated. The valsartan heart failure trial (Val-HeFT) included the higher percentage of patients with HF and CKD (58% of the entire cohort); valsartan significantly reduced the combined endpoint of mortality and morbidity and improved HF symptoms also in HF patients with CKD [22]. Notably, candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM)-added and CHARM-alternative trials, which included a significant proportion of CKD population, confirmed the previous data. However, patients with more severe CKD (creatinine > 3.0 mg/dL) were excluded. In this study, a significant percentage of patients (7.1%) discontinued the therapy due to an increase in creatinine, in the absence of sufficient data regarding the permanent effect on the renal outcome [23].

The Cox proportional hazards regression models in the SOLVD trial showed that, compared to placebo, ACE-I did not reduce the decline in eGFR, that was similar in both groups. However, the study recommended to avoid the withdrawal of ACE-I in patients with low and moderate eGFR decline due to the beneficial effect on the overall CV outcome [24]. Moreover, both ACE-I and ARBs showed to significantly slow the eGFR decline in diabetes and nephropathy due to their favorable physiological effect [25] (Table 2).

In patients in sinus rhythm with HF and LVEF < 50%, B-blockers reduced mortality versus placebo without any deterioration in renal function over time in patients with moderate or moderate to severe renal impairment [26]. These beneficial results were lost in patients with HF and atrial fibrillation (AF) at any level of eGFR. Metoprolol was analyzed in three renal function subgroups and demonstrated an effective reduction in all-cause death and hospitalizations for worsening HF in patients with eGFR < 45 mL/min/1.73 m^2 and eGFR 45 to 60 mL/min/1.73 m^2, as in those with eGFR > 60 mL/min/1.73 m^2 [27]. Meta-analyses from the CAPRICORN (carvedilol postinfarct survival control in left ventricular dysfunction study) and COPERNICUS (carvedilol prospective randomized, cumulative survival study) studies showed that carvedilol was well tolerated in patients with and without CKD, with an increased relative incidence in the transient increase in serum creatinine, without serious adverse kidney effects and electrolyte changes in CKD patients. Carvedilol therapy reduced the composite outcome of CV mortality or HF hospitalization, without significant effects on sudden death in the presence of mild to moderate CKD [28]. Carvedilol reduced morbidity and mortality in dialyzed patients with dilated cardiomyopathy [29]. Current contrasting findings show that the use of B-blockers in dialysis or in patients with severe kidney deterioration needs to be further investigated (Table 3).

Table 2. Comparison in renal function outcome between trials evaluating therapy with ACE-I, ARBs, and MRAs in HF patients.

Trial; Author; Year	Pts (*n*)	Design	Main Eligibility Criteria	Primary Outcome	Mean Follow up (years)	Renal Function Exclusion	CKD Groups (eGFR, mL/min/ 1.73 m^2)	Main Findings
Angiotensin Converting Enzyme inhibitors								
CONSENSUS; 1987; The CONSENSUS Trial Study Group	253	Enalapril vs. Pl.	Congested HF, NYHA IV, cardiomegaly on chest X-ray	ACM	0.5	Serum creatinine concentration > 3.4 mg/dL	NA	Enalapril significantly reduced ACM in patients with sCr > 1.39 mg/dL compared to pl. (30% vs. 55%) but did not have a significant effect in those with sCr < 1.39 mg/dL.
SOLVD treatment; 1991; The SOLVD Investigators [19]	2569	Enalapril vs. Pl.	LVEF ≤ 35%, NYHA I–IV (90% NYHA II, III)	ACM	3.4	Creatinine > 2 mg/dL	≥60 (*n* = 1466) (59, 7%) <60 (*n* = 1036) (40, 3%)	Enalapril reduced mortality and hospitalization in SHF patients without significant heterogeneity between those with and without CKD.
SOLVD prevention; 1992; The SOLVD Investigators	4228	Enalapril vs. Pl.	Receiving digitalis, diuretics, or vasodilators (remainder same as SOLVD treatment trial)	ACM	3.08	Creatinine > 2 mg/dL	<45 (*n* = 450) 10.6% ≥45 <60 (*n* = 669) 15.8% ≥60 <75 (*n* = 640) 15.1% >75 (*n* = 863) 20.4	No significant interaction between CKD and treatment
SAVE; 1992; Tokmakova et al. [20]	2331	Captopril vs. Pl.	Acute myocardial infarction (age 21–80 years) LVEF < 40%	ACM	3.5	Creatinine > 2.5 mg/dL	≥60 (*n* = 1562) 67% <60 (*n* = 769) 33%	Captopril reduced CV events irrespective of baseline kidney function. CKD was associated with a heightened risk for all major CV events after MI, particularly among subjects with an eGFR < 45 mL/min/1.73 m^2.
AIRE; 1997; Hall et al.	2006	Ramipril vs. Pl.	Acute myocardial infarction (ECG and enzymes) and transient or persistent congestive heart failure after index infarct. Clinical CHF by physical examination or radiography.	ACM	1.25	NA	NA	ACM significantly lower for Ramipril (17%) than pl. (23%).

Table 2. *Cont.*

Trial; Author; Year	Pts (*n*)	Design	Main Eligibility Criteria	Primary Outcome	Mean Follow up (years)	Renal Function Exclusion	CKD Groups (eGFR, mL/min/ 1.73 m^2)	Main Findings
TRACE; 1995; Køber et al. [21]	1749	Trandolapril vs. Pl.	Able to tolerate a test dose of 0.5 mg trandolapril adults with acute myocardial infarction 2–6 days prior to trial entry. Echocardiographic ejection fraction < 35%	ACM	3	Creatinine > 2.5 mg/dL	NA	Trandalopril reduced relative risk of death. Trandolapril also reduces the risk of death from CV causes.
NETWORK; 1998; The NETWORK investigators	1532	Enalapril 2.5 vs. 5 vs. 10 mg BID	Age 18 to 85 years, NYHA II–IV, abnormality of the heart and current treatment for heart failure	ACM, HFH, WHF	0.5	Creatinine > 2.3 mg/dL		No relationship between dose of enalapril and clinical outcome in patients with HF.
ATLAS; 1999; Packer et al.	3174	Lisinopril high vs. low dose	LVEF ≤ 30 NYHA II–IV	ACM	3.8	Creatinine > 2.5 mg/dL	Creatinine > 1.5 mg/dL 2176 (68.5%) Creatinine < 1.5 mg/dL 998 (31.5%)	ACM was non-significantly reduced both in patients with and without CKD.
Angiotensin Receptor Blockers								
Val-HeFT; 2003; Carson et al. [22]	5010	Valsartan vs. Pl.	LVEF < 40%; clinically stable CHF NYHA II–IV; treatment with ACE inhibitors; LVDD > 2.9 cm/bsa	ACM	1.9	Creatinine > 2.5 mg/dL	<60 2114 (47%) ≥60 2196 (53%)	Patients with WRF demonstrated the same benefits with valsartan treatment compared with pl. in the overall population.
CHARM added, 2001; McMurray et al. [23]	2548	Candesartan vs. Pl.	LVEF ≤ 40%; NYHA II–IV; treatment with ACE inhibitor	CV death or HFH	3.4	Creatinine >3 mg/dL	≥60 67% <60 33%	The risk for CV death or hospitalization for worsening CHF as well as the risk for ACM increased significantly below an eGFR of 60 mL/min per 1.73 m^2.
CHARM alternative, 2003; Granger et al.	2028	Candesartan vs. Pl.	CHF NYHA II–IV, LVEF ≤ 40%, ACE inhibitors intolerance	CV death or HFH	2.8	Creatinine > 3 mg/dL	≥60 57.4% <60 42.6%	See above
HEEAL; 2009; Konstam et al.	3846	High dose vs. Low dose Losartan	LVEF ≤ 40%; NYHA II–IV; ACE inhibitors intolerance	ACM or HFH	4.7	Creatinine > 2.5 mg/dL	NA	Losartan 150 mg vs. 50 mg maintained its net clinical benefit and was associated with reduced risk of death or HFH, despite higher rates of WRF and greater rates of eGFR decline.

Table 2. *Cont.*

Trial; Author; Year	Pts (*n*)	Design	Main Eligibility Criteria	Primary Outcome	Mean Follow up (years)	Renal Function Exclusion	CKD Groups (eGFR, mL/min/ 1.73 m^2)	Main Findings
Mineralcorticoid Receptor Antagonist								
RALES; 1999; Kulbertus et al.	1663	Spironolactone vs. Pl.	LVEF < 35%; NYHA III–IV; creatinine ≤ 2.5 mmol/L	ACM	2	creatinine ≥ 2.5 mg/dL	<60 (*n* = 792) 47.62% ≥60 (*n* = 866) 52.07%	Individuals with reduced baseline eGFR exhibited similar relative risk reductions in all-cause death and the combined. Endpoint of death or hospital stayed for HF as those with normal renal function and greater absolute risk reduction compared with those with a higher baseline eGFR.
EMPHASIS-HF, 2001; Zannad et al. [30]	2737	Eplerenone vs. Pl.	LVEF ≤ 35%; NYHA II; eGFR ≥ 30 mL/min/1.73 m	CV death or HFH	1.75	eGFR < 30 mL/min/1.73 m	<60 (*n* = 912) 33.32% ≥60 (*n* = 1821) 66.53%	Eplerenone, as compared with placebo, reduced both the risk of death and the risk of hospitalization in HFrEF patients with CKD.
TOPCAT; 2021; Khumbanj, et al.	3445	Spironolactone vs. placebo (*n* = 3445)	LVEF ≥ 45%; HF hospitalization or elevated NP level; eGFR ≥ 30 mL/min/1.73 m^2 or creatinine ≤ 2.5	CV death or aborted cardiac arrest or hospitalization for HF	3.3	eGFR < 30 mL/min/1.73 m or serum creatinine >2.5 mg/dL	<45 (*n* = 411) 11.9% 45–60 (*n* = 533) 15.47% ≥60 (*n* = 823) 23.88%	The primary endpoint was similar between the spironolactone and placebo arms. The risk of adverse events was amplified in the lower eGFR categories. These data supported use of spironolactone to treat HFpEF patients with advanced CKD only when close laboratory surveillance was possible.

ACE: angiotensin-converting enzyme inhibitor; ACM: all-cause mortality; CHF: congestive heart failure; CKD: chronic kidney disease; CV: cardiovascular; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; HF: heart failure; HFH: hospitalization for heart failure; HR: hazard ratio; LVEF: left ventricular ejection fraction; LVDD: left ventricular diastolic diameter; MI: myocardial infarction; NYHA: New York Heart Association; Pts: patients; NA: not available; Pl.: placebo; sCr: serum creatinine; SHF: sever heart failure; WHF: worsening heart failure; and WRF: worsening renal function.

Table 3. Comparison in renal function outcome between trials evaluating therapy with Beta Blockers in HF patients.

Trial; Author; Year	Pts (*n*)	Design	Main Eligibility Criteria	Primary out-come	Mean Follow up (years)	Renal Function Exclusion	CKD Groups (eGFR, mL/min/ 1.73 m^2)	Main Findings
Beta-Blockers								
MDC; 1993; Waagstein et al.	383	Metoprolol vs. Pl.	LVEF $\leq$ 40%; NYHA II, III	ACM	0.9	NA	NA	Treatment with Metoprolol improved symptoms, LVEF, exercise time. It reduced PCWP and clinical deterioration.
CIBIS; 1994; CIBIS Investigators and Committees	641	Bisoprolol vs. Pl.	LVEF $\leq$ 40% NYHA III–IV Age 18–75 Treatment with diuretic and vasodilator	ACM	1.9	Creatinine > 3.4 mg/dL	Renal insufficiency being a non-inclusion criterion	No significant difference in mortality or sudden death. Improvements in functional status in the bisoprolol arm.
US-Carvedilol; 1996; Packer et al.	1094	Carvedilol vs. Pl.	LVEF $\leq$ 35%; NYHA II, III despite at least two months of treatment with diuretics and an ACE inhibitor	ACM	0.5	Clinical impor-tant renal disease	NA	Carvedilol reduced overall mortality rate, CV risk, hospitalization for CV reasons.
MERIT HF; 1999; MERIT-HF Study Group [27]	3991	Metoprolol vs. Pl.	LVEF $\leq$ 40%; NYHA II–IV	ACM	1.0	NA	<45 (n = 493) $\geq$ 45 $\leq$ 60 (n = 976) >60 (n = 2496)	Metoprolol CR/XL was effective in reducing death and hospitalizations for worsening HF in patients with eGFR < 45 as in those with eGFR > 60. eGFR was a powerful predictor of death and hospitalizations from HF.
CIBIS-II; 1999; CIBIS-II Investigators and Committees	2289	Bisoprolol vs. Pl.	LVEF $\leq$ 35%; NYHA III, IV	ACM	1.3	Creatinine > 3.4 mg/dL	<60 mL/min (n = 849) 37.1% $\geq$60 mL/min (n = 1198) 52.3%	Patients with eGFR <60 mL/min had a markedly higher mortality rate than patients with less compromised renal function; however, they benefited to the same extent from bisoprolol treatment.
COPERNICUS; 2001; Eric J Eichhorn et al.	2289	Carvedilol vs. Pl.	LVEF $\leq$ 25%; NYHA IV	ACM	0.9	Creatinine > 2.8 mg/dL	$\leq$60 (n = 2566) 61% >60 (n = 1651) 39% Data to be referred to both the COPERNICUS and CAPRICORN studies considered together	Among the CKD group, treatment with carvedilol was associated with decreased risks of ACM, CV mortality, HF mortality, first HFH. Treatment with carvedilol did not have a statistically significant impact on sudden cardiac death in HF patients with CKD.
CAPRICORN; 2005; McMurray et al.	1959	Carvedilol vs. Pl.	CHF LVEF $\leq$ 35%	ACM	1.3	Renal Im-pairment	$\leq$60 (n = 2566) 61% >60 (n = 1651) 39% Data to be referred to both the COPERNICUS and CAPRICORN studies Considered together.	See Copernicus results above.

Table 3. *Cont.*

Trial; Author; Year	Pts (*n*)	Design	Main Eligibility Criteria	Primary out-come	Mean Follow up (years)	Renal Function Exclusion	CKD Groups (eGFR, mL/min/ 1.73 m^2)	Main Findings
COMET; 2003; Pool Wilson et al.	3029	Carvedilol vs. Meto-prolol	LVEF ≤ 35%; NYHA II to IV; ACE inhibitor therapy for at least 4 weeks; Diuretic therapy for at least 2 weeks. Prior hospitalization for CV reasons at least once in the year preceding inclusion.	ACM	4.8	NA	NA	Carvedilol improved vascular outcomes better than metoprolol.
SENIORS; 2005; Flather et al.	2128	Nebivolol vs. Placebo	Age ≥ 70 y, HF confirmed as HF hospitalization in recent 12 months and/or LVEF ≤ 35% in recent 6 months	ACM or CV hos-pitaliza-tion	1.8	Significant renal disease	<55.5 (*n* = 704) 33% 55.5–72.8 (*n* = 704) 33% >72.8 (*n* = 704) 33%	SENIORS was not powered to detect reductions in the primary outcome for the renal sub-groups and hence none of the eGFR tertiles reached statistical significance. Nebivolol was safe for use in those with renal dysfunction, albeit with a marginal increase in bradycardia-related treatment discontinuation.

ACM: all-cause mortality; CHF: congestive heart failure; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; Pts: patients; HFH: hospitalization for heart failure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; pts: patients; NA: not available; PCWP: pulmonary capillary wedge pressure; Pl.: placebo; WHF: worsening heart failure; and WRF: worsening renal function.

Historically, MRAs were considered contra-indicated in patients with renal dysfunction, due to the higher risk of hyperkalemia. The beneficial effect of both spironolactone and eplerenone on the outcomes of HF patients has recently extended to those with renal dysfunction; however, no trials focused on the effects of MRAs on the renal outcome and related mortality in patients with HF and eGFR < 30 mL/min/1.73 m^2 [30]. A recently published secondary analysis of the eplerenone in mild patients hospitalized and survival study in heart failure (EMPHASIS-HF) examined the beneficial and adverse effects of eplerenone on renal function. Even though patients with an eGFR < 50 mL/min/1.73 m^2 were assigned lower target doses of eplerenone (25 mg versus 50 mg), the drug showed a beneficial effect on the outcome versus placebo; however, patients with eGFR 30–49 mL/min/1.73 m^2 experienced higher incidences of hyperkalemia, renal failure, and drug discontinuation [31]. Patients with moderate renal dysfunction should be monitored closely after the initiation of a MRAs, with frequent K^+ analyses and a slower up-titration of therapy, due to the higher risk of hyperkalemia and the potential arrhythmic and renal consequences. MRAs treatment did not affect renal function in subjects without evidence of HF; finerenone, a non-steroidal selective MRA, resulted in a lower risk of CKD progression and CV events than placebo in patients with CKD and type two diabetes [32]. The aforementioned data reinforced the use of MRAs in patients with either HF and mild to moderate CKD, or in patients with high CV risk associated with renal dysfunction, but a larger use in more advanced HF and CKD stages was not extensively carried out, and it deserves specific analyses.

In patients with HF, the beneficial effect of ARNI showed several physiological mechanisms, including the increase in intracellular cyclic GMP that counteracts the constrictive effects of the tubule-glomerular feedback on the afferent arteriole. In a retrospective analysis of the prospective comparison of ARNI with ACE-i to determine impact on global mortality and morbidity in heart failure (PARADIGM-HF) trial, sacubitril and valsartan improved CV outcomes and led to a slower rate of eGFR decline versus enalapril (difference of 0.4 mL/min/1.73 m^2 per year). The relative risk reduction associated with sacubitril and valsartan was similar in patients with and without renal dysfunction, despite causing a modest increase in the urinary albumin to creatinine ratio [33]. The extent of the benefit was larger in patients with diabetes than those without [34]. This effect was also confirmed in HFpEF patients, in whom sacubitril and valsartan reduced the risk of a $\geq$50% reduction in eGFR, end-stage renal disease, or death from renal cause, and slowed the decline in eGFR during the follow-up versus valsartan. The renal benefits were more evident in patients with LVEF between 30–60%; however, the entire population enrolled in the study experienced an eGFR reduction of 1.8 mL/min/1.73 m^2 per year in the sacubitril and valsartan group, versus 2.4 mL/min/1.73 m^2 per year in the RAAS inhibitors group, regardless of the LVEF [35].

SGLT-2 co-transporters are mainly located in the renal proximal convoluted tubule; by inhibiting Na+ and glucose reabsorption, SGLT-2 inhibitors promote glucosuria and natriuresis and reduce extracellular fluid and plasma volume. These effects reduced the left ventricular afterload and preload and decreased blood pressure and arterial stiffness, while improving the subject-endocardial blood flow [36]. The renal hemodynamic effects of SGLT-2 inhibition were ascribable to the reduction in intra-glomerular pressure. The effect of SGLT-2 to counterbalance the glomerular hypertension and hyperfiltration was crucial in type two diabetes mellitus (T2DM), where hyperglycemia leads to renal Na+ reabsorption, causing an afferent renal vasodilatory response through the tubuloglomerular feedback [37]. Empaglifozin improves the diabetic kidney disease by alleviating mitochondrial fission via AMPK/SP1/PGAM5 pathway [38,39]. With all these favorable effects, SGLT-2 inhibitors led to nephron protection and reduced the progression of diabetic nephropathy. Moreover, sodium-hydrogen exchanger 3 (NHE3) is expressed in proximal tubule and exchanges Na+ into the cell with proton export [40]. NHE3 increases the expression of SGLT-2 in the nephron membrane, leading to sympathetic/RAAS activation and acidosis. The restoration of Na+ homeostasis depends also on the inhibition of renal NHE3 by SGLT-2 inhibitors. Finally, in a meta-analysis of randomized controlled trials, SGLT-2 decreased albuminuria,

slowing the progression of microalbuminuria to macroalbuminuria and reducing the risk of end-stage renal disease [41].

In recent years, landmark trials established the CV benefits and renal outcome of SGLT-2 inhibitors in the HFrEF population. The empagliflozin outcome trial in patients with chronic heart failure and a reduced ejection fraction (EMPEROR-Reduced) showed that empagliflozin reduced both CV death and HF hospitalization in patients with HFrEF, despite OMT. The trial included patients with eGFR higher than 20 mL/min/1.73 m^2, and 48% of the subjects enrolled had an eGFR < 60 mL/min/1.73 m^2 [42]. Empagliflozin reduced the primary outcome and total number of HF hospitalizations in patients with and without CKD, and had the beneficial effect of reducing the decline of the renal function, regardless of the severity of renal function at baseline [43]. The analyses of the CREDENCE (canagliflozin and renal events in diabetes with established nephropathy clinical evaluation) trial showed the effects of canagliflozin in reducing the incidence of kidney-related adverse events in patients with T2DM and CKD [44]. Moreover, the dapagliflozin and prevention of adverse outcomes in heart failure (DAPA-HF) trial included 41% of patients with eGFR < 60 mL/min/1.73 m^2 and excluded those with eGFR < 25 mL/min/1.73 m^2 [45]. The results of the trial showed that the benefits of dapagliflozin on morbidity and mortality in HFrEF did not differ by eGFR category or by examining eGFR as a continuous variable, with a significantly slower rate of decline in eGFR, regardless of the presence of diabetes [46]. In the DAPA-CKD (dapagliflozin and prevention of adverse outcomes in chronic kidney disease) trial, properly designed for patients with CKD, dapagliflozin significantly reduced the decline in eGFR, the end-stage kidney disease, or death from renal or CV causes [47] (Table 4).

Table 4. Comparison in renal function outcome between trials evaluating HF therapy with SGLT2 inhibitors, ARNI, and agents considered in selected HFrEF patients.

Trial; Author; Year	Pts (*n*)	Design	Main Eligibility Criteria	Primary Outcome	Mean Follow up (years)	Renal Function Exclusion	CKD Groups (eGFR, mL/min/ 1.73 m^2)	Main Findings
Sodium Glucose Linked Transporter 2 Inhibitors								
DAPA-HF; 2019; Mc Murray et al. [45]	4744	Dapaglifozin vs. Pl.	LVEF $\leq$ 40%; NYHA III–V; eGFR $\geq$ 30 mL/min/ 1.73 m^2	WHF or CV death	1.5	eGFR < 30 mL/min/ 1.73 m^2	<60 (*n* = 1926) 41% $\geq$60 (*n* = 2816) 59, 35%	The effect of dapagliflozin on the primary and secondary outcomes did not differ by eGFR category or examining eGFR as a continuous variable.
EMPEROR reduced; 2020; Packer et al.;	3730	Empaglifozin vs. Pl.	LVEF $\leq$ 40%; NYHA IIIV; eGFR $\geq$ 20 mL/min/ 1.73 m^2	WHF or CV death	1.3	eGFR < 20 mL/min/ 1.73 m^2	<60 (*n* = 1978) 53, 2% $\geq$60 (*n* = 1746) 46.8%	Empagliflozin reduced the primary outcome and total HF hospitalizations in patients with and without CKD.
SOLOIST-WHF; 2021; Bhatt et al.	1222	Sotaglifozin vs. Pl.	18–85 years old; symptoms or sign of HF; type II diabetes; recent hospitalization for WHF.	Total WHF and CV death	0.75	eGFR < 30 mL/min/ 1.73 m^2	<60 (*n* = 854) 69.9% $\geq$60 (*n* = 368) 30.1%	Sotaglifozin therapy resulted in lower total number of deaths from CV causes and hospitalizations or urgent visits for HF than placebo even in patients with CKD across the full range of proteinuria.

Table 4. *Cont.*

Trial; Author; Year	Pts (*n*)	Design	Main Eligibility Criteria	Primary Outcome	Mean Follow up (years)	Renal Function Exclusion	CKD Groups (eGFR, mL/min/ 1.73 m^2)	Main Findings
Angiotensin Receptor Neprylisin Inhibitors								
PARADIGM-HF; 2014; Solomon et al.	8442	Enalapril vs. Sac/Val	LVEF $\leq$ 40%; NYHA III–V; eGFR $\geq$ 30 mL/min/ 1.73 m^2	CV death or HFH	2.25	eGFR $\leq$ 30 mL/min/ 1.73 m^2	<60 (*n* = 3061) 36.2% $\geq$60 (*n* = 5338) 63.2%	Compared with enalapril, sacubitril and valsartan led to a slower rate of decrease in the eGFR and improved CV outcomes, even in patients with CKD.
PARAGON-HF; 2019; Solomon et al.	4822	Sac/Val vs. Valsartan	LVEF $\geq$ 45%; NYHA III–V; eGFR $\geq$ 30 mL/min/ 1.73 m^2	CV death or HFH	2.92	eGFR $\leq$ 30 mL/min/ 1.73 m^2	<60 (*n* = 2341) 48.5% $\geq$60 (*n* = 2454) 50.9%	Sacubitril–valsartan did not result in a significantly lower rate of total HFH and death from CV causes both in patients with CKD and without CKD.
Agents Considered in Selected HFrEF Patients								
SHIFT; 2012; Bohrer et al.	6558	Ivabradine vs. Pl.	LVEF < 35%; synus rhythm; Heart rate > 70 bpm	CV Death or HFH	1.9	Sever renal disease	<60 (*n* = 1579) 24.07% $\geq$60 (*n* = 4581) 69.85%	Ivabradine significantly reduced the combined primary end point of CV mortality or HFH compared with pl. The incidence of the primary end point was similar in both patients with (CKD stages 3–5) and without CKD.
VICTORIA; 2020; Armstrong et al.	5050	Vericiguat vs. Pl.	LVEF < 45%; NYHA III–V; recent hospitalization; eGFR 15 $\geq$ mL/min/ 1.73 m^2 (no more than 15% of subjects with an eGFR in the 15 L/min/ 1.73 m^2 to 30 mL/min/ 1.73 m^2 range).	CV Death or HFH	0.8	eGFR < 15 mL/min/ 1.73 m^2	$\leq$30 (*n* = 506) 10% >30 $\leq$60 (*n* = 2118) 41.94% >60 (*n* = 2335) 46.23%	Vericiguat reduced the primary composite endpoint of CV death or HFH across all eGFR spectrum. the beneficial effects of vericiguat were similar in patients with and without WRF.
GALACTIC-HF; 2021; Teerlink et al.	8256	Omecamtiv /Mecarbil vs. Pl.	LVEF $\leq$ 35%; symptomatic chronic HF	CV Death or HFH/WHF	1.8	eGFR < 15 mL/min/ 1.73 m^2	NA	Lower incidence of HF event or death from CV causes in the omecamtiv mecarbil arm compared with placebo.

ACM: all-cause mortality; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; HFH: hospitalization for heart failure; Pts: patients; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; pts: patients; NA: not available; Pl.: placebo; and WRF: worsening renal function.

In clinical practice, as demonstrated in several trials, the initiation of SGLT-2 inhibitors was associated with an initially mild drop of eGFR over the first weeks. This decrease in eGFR was reversible, and the renal function gradually returned to its baseline levels, with a stabilization of the renal function during the follow-up. The initial mild drop in eGFR should not lead to a premature discontinuation of the SGLT-2 inhibitors treatment.

Recently, novel therapies in HFrEF have been proposed. The vericiguat global study in subjects with heart failure with reduced ejection fraction (VICTORIA) trial demonstrated

the effect of vericiguat, a soluble guanylate cyclase stimulator, in reducing the primary composite outcome of CV death or HF hospitalization. For the first time in HF therapies, the study included patients with eGFR higher than 15 mL/min/1.73 m^2; the beneficial effects of vericiguat were consistent across the entire range of eGFR, irrespectively of WRF [48].

The use of hydralazine and isosorbide dinitrate (H-ISDN) in HFrEF is rarely used in clinical practice. However, treatment with H-ISDN was recommended in the last guidelines for HFrEF patients who are intolerant to RAAS inhibitors, and in African-American HFrEF patients who are symptomatic despite optimal neurohumoral therapy. The treatment with H-ISDN is safe in patients with CKD. However, in a recent trial, H-ISDN on the top of standard medical therapy did not improve exercise capacity in patients with cardiorenal syndrome and HFrEF [49]. These findings are in agreement with real-world data on a large cohort of HFpEF and HFmrEF patients enrolled in the Swedish Heart Failure Registry where patients in the sub-group analyses with HF and CKD (eGFR 30–59 mL/min/1.73 m^2 and eGFR < 30 mL/min/1.73 m^2) benefitted from nitrate administration [50].

4. Renal Diagnostic Exams and Comparison between Different Criteria

Several methods and diagnostic approaches have been proposed for the evaluation of renal function in chronic conditions. So far, no universal definition and classification exists, and this contributes to complicate the definition and severity of CKD.

The simplified modification of diet in renal disease (MDRD) formula showed a few limitations, such as the use of body mass and age of patients showing an incorrect relationship between serum creatinine and muscle mass variability. The Cockcroft-Gault formula showed the worst accuracy in measuring eGFR; however, it was accurate in improving the risk stratification for death in HF patients, perhaps due to the inclusion of weight in its formula (not included in MDRD) [51]. The simplified modification of diet in renal disease the chronic kidney epidemiology collaboration (CKD-EPI) formula, based on serum creatinine and serum cystatin C, estimated more accurately the real eGFR in all HF patients, particularly in those with preserved or moderately impaired renal function [52,53]. Cystatin C concentration was less affected by age, sex, muscle mass, or diet than creatinine. In detail, CKD-$EPI_{crea/cys}$ and CKD-EPI_{cys} (CKD-EPI creatinine and cystatin formula: $177.6 \times (\text{serum creatinine (mg dL)}) - 0.65 \times (\text{serum cystatin C (mg L)}) - 0.57 \times \text{age} - 0.2$) provided less bias and more accurate estimates of eGFR than CKD-EPI_{crea} [54]. Recently, the new European Kidney Function Consortium equation showed improved accuracy and precision with lower age-related bias compared with the commonly used equations for estimating GFR from serum creatinine (SCr) levels [55].

The limitation of eGFR and creatinine in assessing renal function should lead to the addition of several marker and laboratory exams, in order to deeply monitor renal function. Blood urea nitrogen (BUN) was commonly assessed in association with renal function and reflected glomerular filtration, tubular reabsorption, and neurohormonal activation. The main difference between sCr and BUN was the reabsorption of BUN at the tubular level. Recently, the BUN to creatinine ratio was able to differentiate pre-renal and intrinsic renal diseases; in particular, neurohormonal activation led to a disproportional reabsorption of BUN in comparison with creatinine. Both BUN and the BUN to creatinine ratio identified HF patients with an increased risk of adverse outcomes. Moreover, the urine BUN to creatinine ratio predicted diuretic efficiency and a significant difference for HF rehospitalization and death rate at 180 days [56]. Albuminuria was mainly a marker of increased glomerular permeability and failure of tubular reabsorption, and affected around 20–30% of patients with HF, particularly those with associated CKD. Albuminuria was a marker of endothelial dysfunction, inflammation, podocyte damage, disrupted tubular reabsorption, and congestion, and provided additional information regarding the mechanism of renal impairment on top of the eGFR or BUN to creatinine ratio [57]. Micro- and macro-albuminuria were associated with increased mortality in the HF population, independently from eGFR, thus highlighting the concept that albuminuria itself could accelerate the progression of renal dysfunction via an impairment in the recovery cells in

Bowman's space and a chronic overload and damage to the megalin cubilin transporter system in the proximal tubule.

The tubulo-interstitial injury in HF, as measured by increased urinary neutrophil gelatinase-associated lipocalin (NGAL) concentrations, may indicate renal damage, even in the presence of normal glomerular filtration. Poniatowski et al. had recognized serum and urine NGAL as sensitive early markers of renal dysfunction in patients with chronic HF and normal serum creatinine but reduced eGFR [58]. In detail, the extension of tubular damage was related to increased urinary concentrations of three urinary markers of tubular damage: NGAL, *N*-acetyl-beta-D-glucosaminidase (NAG), and kidney injury molecule 1 (KIM-1). The increases in these tubular markers were related to a poorer outcome in HF patients, even when eGFR was normal.

Recently, urinary sodium—assessed in spot urinary samples—showed interesting data in both acute and chronic HF patients; measuring natriuresis early after hospitalization could reliably identify patients with a poor diuretic response during hospitalization, who might require an adjustment of their diuretic strategies [59]. In a single-center study of HF outpatients, a drop in urinary spot sodium concentration was found a week before hospitalization for HF. The outpatient assessment of spot urinary sodium may therefore be a readily applicable marker to guide or initiate treatment and prevent hospitalization for AHF [60]. The etiology of hypochloremia in patients with HF was not only related to the diuretic used, but was also associated with the activation of RAAS and a stimulatory effect on the with-no-lysine kinases, which may increase the renal sodium-chloride co-transporter activity [61]. A sub-analysis of the beta-blocker evaluation of survival (BEST) trial showed that both urinary hypochloremia and hyponatremia were related to a poor prognosis in HF patients, suggesting the routine use of spot urinary samples to monitor the renal response and adjust the treatment of HF [62].

5. Potential Strategy for the Correct Use of Neuro-Hormonal Inhibition Treatments According to Renal Dysfunction Severity

Historically, CKD represents a real "nightmare" when tailoring and optimizing the HF therapy. Although the latest ESC guidelines recommended the concomitant use of four agents after the diagnosis of HF, the potential treatment strategy across CKD spectrum was not elucidated. Based on the analysis of a larger trial evaluating the sympathetic antagonism and the treatment with RAAS inhibitors, the use of common neuro-hormonal inhibitory therapy was recommended in mild to moderate CKD, even if some studies seemed to suggest a protective role of B-blockers in patients with more severe renal dysfunction. The new ESC guidelines recommended the quadruple therapy in patients with eGFR > 60 mL/min/1.73 m^2. SGLT-2 inhibitors were recommended for all patients with HFrEF in addition to ACE-I/ARNI, a beta-blocker, and an MRA. This combined approach may suddenly change the renal physiology, which could lead to a higher risk of a progressive decline in eGFR, even in patients with normal renal function. In those patients, a careful monitoring of the renal function and electrolytes should be performed 3 or 4 weeks after the start of the therapy, in order to avoid sudden eGFR deterioration and potassium (K^+) increase. In patients with eGFR 30–60 mL/min/1.73 m^2, a triple therapy with low dose B-blocker, RAAS inhibitors, or ARNI and a full dosage of SGLT-2 inhibitors should be prescribed. During follow-up, we can add low-dose MRAs if creatinine levels remain stable—or increase by less than 30%—and if K is < 5 meq/L. More attention should be paid in patients with eGFR 15–30 mL/min/1.73 m^2, where we suggest starting with low-dose B-blockers and SGLT-2 inhibitors, adding RAAS inhibitors after the up-titration of the first two agents only if creatinine increases by <30% or K^+ is < 5 mmol/L. In patients with severe renal dysfunction, the multi-drug approach may become deleterious, and the administration of lower dosages of B-blocker with the subsequent addition of ACE-I without up-titration may be considered.

Overall, in patients with renal dysfunction, we recommend checking renal function and K^+ after 15 days of starting therapy and then every 2 to 3 months in order to reach

the maximum tolerated dose. If serum creatinine increases by >50% or above 3.5 mg/dL, treatment should be discontinued. Hyperkalemia was the most frequent cause for drug discontinuation; the down-titration of HF drugs was recommended if K^+ was between 5.5 meq/L and 6 meq/L, and temporary discontinuation was advised if potassium was above 6 meq/L (Figure 2). When adjusting for the discontinuation of ACE-I/ARB, hyperkalemia was no longer associated with mortality, suggesting that it may be a risk marker for the discontinuation of ACE-I/ARB rather than a risk factor for worse outcomes. In patients with normal renal function and isolated K^+ increase, novel K^+ binder such as patiromer and sodium zirconium cyclosilicate substantially reduced serum K^+ levels in the long term, allowing up-titration and the maintenance of the RAAS inhibitors and ARNI therapy. Therefore, both agents have been safety tested in patients with chronic HF as providing beneficial effects on the CV risk [63].

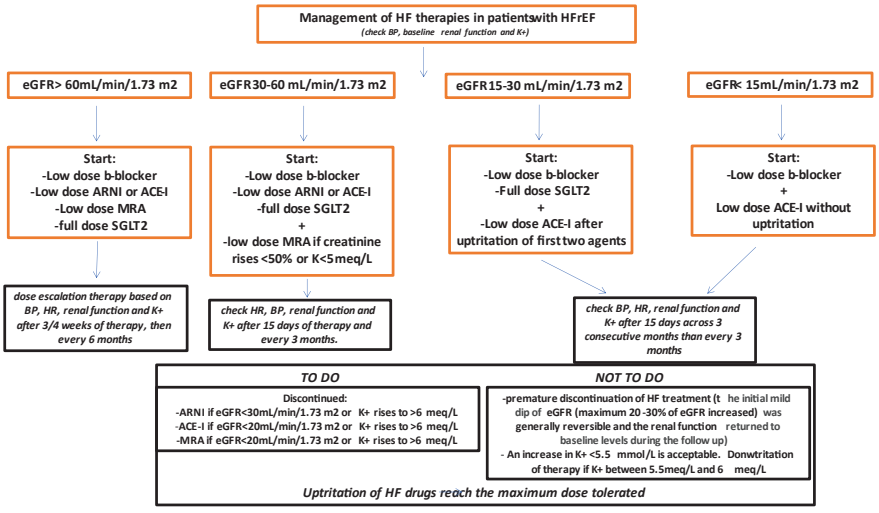

Figure 2. Management of HF therapies in patients with HFrEF. HFrEF: Heart Failure with reduced ejection fraction; ACE-I: angiotensin converting enzyme inhibitor; ARNI: angiotensin receptor neprilisin inhibitor; B-Blocker: beta blocker; BP: blood pressure; eGFR: estimated glomerular filtration rate; HR: heart rate; K^+: potassium; HF: heart failure MRA: mineralcorticoid receptor antagonist; SGLT2: sodium glucose late transporter 2 inhibitors.

Therefore, combining current HF lifesaving drugs significantly improved the hard endpoints in the HF population; thus, the aim was to use a sequential up-titration of single agents while checking renal function, electrolytes, and blood pressure, thus avoiding the risks of treatment side effects.

6. Conclusions

CKD in HF is associated with a worse prognosis across the entire eGFR spectrum. The recently proposed HF "quadruple therapy" significantly reduces mortality and HF hospitalization also in patients with HF and CKD. Despite the favorable effects of these HF medications, specific studies investigating the effect of the treatment with an eGFR lower than 30 mL/min/m^2 remain scarce, and their safety should be confirmed over a long observational period. Conversely, the false myth of administering inadequate target dose or withdrawing HF therapies to avoid end-stage renal disease resulted in a lower use of these lifesaving therapies, with a significant impact on the HF prognosis. The extensive application of multiple HF agents needs caution and a frequent monitoring of specific laboratory patterns, with particular attention during the titration phase and the recurrence of HF.

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References

1. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Bohm, M.; Burri, H.; Butler, J.; Celutkiene, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic. *Eur. Heart J.* **2021**, *42*, 4901. [CrossRef] [PubMed]
2. Onyali, C.B.; Anim-Koranteng, C.; Shah, H.E.; Bhawnani, N.; Ethirajulu, A.; Alkasabera, A.; Mostafa, J.A. Role of Selective Sodium-Glucose Co-Transporter-2 Inhibitors in Managing Cardio-Renal Complications in Type 2 Diabetes Mellitus: Beyond Glycemic Control. *Cureus* **2021**, *13*, e17452. [CrossRef] [PubMed]
3. Ruocco, G.; Palazzuoli, A.; Ter Maaten, J.M. Loop diuretics in acute heart failure: Beyond the decongestive relief for the kidney. *Crit. Care* **2015**, *19*, 296.
4. Palazzuoli, A.; Ruocco, G.; Pellegrini, M.; Martini, S.; Del Castillo, G.; Beltrami, M.; Franci, B.; Lucani, B.; Nuti, R. Patients with cardiorenal syndrome revealed increased neurohormonal activity, tubular and myocardial damage compared to heart failure patients with preserved renal function. *Cardiorenal Med.* **2014**, *4*, 257–268. [CrossRef] [PubMed]
5. Beltrami, M.; Ruocco, G.; Ibrahim, A.; Lucani, B.; Franci, B.; Nuti, R.; Palazzuoli, A. Different trajectories and significance of B-type natriuretic peptide, congestion and acute kidney injury in patients with heart failure. *Intern. Emerg. Med.* **2017**, *12*, 593–603. [CrossRef]
6. Di Lullo, L.; Bellasi, A.; Barbera, V.; Ronco, C. Cardionephrology and cardiorenal disease in Italy: State of the art. *Rev. Cardiovasc. Med.* **2021**, *22*, 563–572. [CrossRef]
7. Palazzuoli, A.; Beltrami, M.; Nodari, S.; McCullough, P.A.; Ronco, C. Clinical impact of renal dysfunction in heart failure. *Rev. Cardiovasc. Med.* **2011**, *12*, 186–199. [CrossRef]
8. Lofman, I.; Szummer, K.; Evans, M.; Carrero, J.J.; Lund, L.H.; Jernberg, T. Incidence of, associations with and prognostic impact of worsening renal function in heart failure with different ejection fraction categories. *Am. J. Cardiol.* **2019**, *124*, 1575–1583. [CrossRef]
9. Quiroz, R.; Doros, G.; Shaw, P.; Liang, C.S.; Gauthier, D.F.; Sam, F. Comparison of characteristics and outcomes of patients with heart failure preserved ejection fraction versus reduced left ventricular ejection fraction in an urban cohort. *Am. J. Cardiol.* **2014**, *113*, 691–696. [CrossRef]
10. Ather, S.; Chan, W.; Bozkurt, B.; Aguilar, D.; Ramasubbu, K.; Zachariah, A.A.; Wehrens, X.H.; Deswal, A. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J. Am. Coll. Cardiol.* **2012**, *59*, 998–1005. [CrossRef]
11. McAlister, F.A.; Ezekowitz, J.; Tarantini, L.; Squire, I.; Komajda, M.; Bayes-Genis, A.; Gotsman, I.; Whalley, G.; Earle, N.; Poppe, K.K.; et al. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: Impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. *Circ. Heart Fail.* **2012**, *5*, 309–314. [CrossRef] [PubMed]
12. Streng, K.W.; Nauta, J.F.; Hillege, H.L.; Anker, S.D.; Cleland, J.G.; Dickstein, K.; Filippatos, G.; Lang, C.C.; Metra, M.; Ng, L.L.; et al. Non-cardiac comorbidities in heart failure with reduced, mid-range and preserved ejection fraction. *Int. J. Cardiol.* **2018**, *271*, 132–139. [CrossRef] [PubMed]
13. Smith, G.L.; Lichtman, J.H.; Bracken, M.B.; Shlipak, M.G.; Phillips, C.O.; DiCapua, P.; Krumholz, H.M. Renal impairment and outcomes in heart failure: Systematic review and meta-analysis. *J. Am. Coll. Cardiol.* **2006**, *47*, 1987–1996. [CrossRef] [PubMed]
14. Damman, K.; Valente, M.A.; Voors, A.A.; O'Connor, C.M.; van Veldhuisen, D.J.; Hillege, H. Renal impairment, worsening renal function, and outcome in patients with heart failure: An updated meta-analysis. *Eur. Heart J.* **2014**, *35*, 455–469. [CrossRef] [PubMed]
15. Meta-Analysis Global Group in Chronic Heart Failure. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: An individual patient data meta-analysis. *Eur. Heart J.* **2012**, *33*, 1750–1757. [CrossRef]
16. Lofman, I.; Szummer, K.; Dahlstrom, U.; Jernberg, T.; Lund, L.H. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. *Eur. J. Heart Fail.* **2017**, *19*, 1606–1614. [CrossRef]
17. Ruocco, G.; Palazzuoli, A.; Ter Maaten, J.M. The role of the kidney in acute and chronic heart failure. *Heart Fail. Rev.* **2020**, *25*, 107–118. [CrossRef]
18. Beldhuis, I.E.; Streng, K.W.; van der Meer, P.; Ter Maaten, J.M.; O'Connor, C.M.; Metra, M.; Dittrich, H.C.; Ponikowski, P.; Cotter, G.; Cleland, J.G.F.; et al. Trajectories of Changes in Renal Function in Patients with Acute Heart Failure. *J. Card Fail.* **2019**, *25*, 866–874. [CrossRef]

19. Bowling, C.B.; Sanders, P.W.; Allman, R.M.; Rogers, W.J.; Patel, K.; Aban, I.B.; Rich, M.W.; Pitt, B.; White, M.; Bakris, G.C.; et al. Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: Insights from the SOLVD Treatment trial. *Int. J. Cardiol.* **2013**, *167*, 151–156. [CrossRef]
20. Jose, P.; Skali, H.; Anavekar, N.; Tomson, C.; Krumholz, H.M.; Rouleau, J.L.; Moye, L.; Pfeffer, M.A.; Solomon, S.D. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. *J. Am. Soc. Nephrol.* **2006**, *17*, 2886–2891. [CrossRef]
21. Køber, L.; Torp-Pedersen, C.; Carlsen, J.E.; Bagger, H.; Eliasen, P.; Lyngborg, K.; Videbaek, J.; Cole, D.S.; Auclert, L.; Pauly, N.C. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. *N. Engl. J. Med.* **1995**, *333*, 1670–1676. [CrossRef] [PubMed]
22. Cohn, J.N.; Tognoni, G.; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N. Engl. J. Med.* **2001**, *345*, 1667–1675. [CrossRef] [PubMed]
23. Young, J.B.; Dunlap, M.E.; Pfeffer, M.A.; Probstfield, J.L.; Cohen-Solal, A.; Dietz, R.; Granger, C.B.; Hradec, J.; Kuch, J.; McKelvie, R.S.; et al. Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Investigators and Committees. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: Results of the CHARM low-left ventricular ejection fraction trials. *Circulation* **2004**, *110*, 2618–2626. [PubMed]
24. McCallum, W.; Tighiouart, H.; Ku, E.; Salem, D.; Sarnak, M.J. Acute declines in estimated glomerular filtration rate on enalapril and mortality and cardiovascular outcomes in patients with heart failure with reduced ejection fraction. *Kidney Int.* **2019**, *96*, 1185–1194. [CrossRef] [PubMed]
25. Brenner, B.M.; Cooper, M.E.; de Zeeuw, D.; Keane, W.F.; Mitch, W.E.; Parving, H.H.; Remuzzi, G.; Snapinn, S.M.; Zhang, Z.; Shahinfar, S.; et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N. Engl. J. Med.* **2001**, *345*, 861–869. [CrossRef]
26. Badve, S.V.; Roberts, M.A.; Hawley, C.M.; Cass, A.; Garg, A.X.; Krum, H.; Tonkin, A.; Perkovic, V. Effects of beta-adrenergic antagonists in patients with chronic kidney disease: A systematic review and meta-analysis. *J. Am. Coll. Cardiol.* **2011**, *58*, 1152–1161. [CrossRef]
27. Ghali, J.K.; Wikstrand, J.; Van Veldhuisen, D.J.; Fagerberg, B.; Goldstein, S.; Hjalmarson, A.; Johansson, P.; Kjekshus, J.; Ohlsson, L.; Samuelsson, O.; et al. The influence of renal function on clinical outcome and response to beta-blockade in systolic heart failure: Insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF). *J. Card. Fail.* **2009**, *15*, 310–318. [CrossRef]
28. Wali, R.K.; Iyengar, M.; Beck, G.J.; Chartyan, D.M.; Chonchol, M.; Lukas, M.A.; Cooper, C.; Himmelfarb, J.; Weir, M.R.; Berl, T.; et al. Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease: A meta-analysis of randomized trials. *Circ. Heart Fail.* **2011**, *4*, 18–26. [CrossRef]
29. Cice, G.; Ferrara, L.; D'Andrea, A.; D'Isa, S.; Di, B.A.; Cittadini, A.; Russo, P.E.; Golino, P.; Calabro, R. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: A prospective, placebo-controlled trial. *J. Am. Coll. Cardiol.* **2003**, *41*, 1438–1444. [CrossRef]
30. Zannad, F.; McMurray, J.J.; Krum, H.; van Veldhuisen, D.J.; Swedberg, K.; Shi, H.; Vincent, J.; Pocock, S.J.; Pitt, B.; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med.* **2011**, *364*, 11–21. [CrossRef]
31. Ferreira, J.P.; Abreu, P.; McMurray, J.J.V.; van Veldhuisen, D.J.; Swedberg, K.; Pocock, S.J.; Vincent, J.; Lins, K.; Rossignol, P.; Pitt, B. Renal function stratified dose comparisons of eplerenone versus placebo in the EMPHASIS-HF trial. *Eur. J. Heart Fail.* **2019**, *21*, 345–351. [CrossRef] [PubMed]
32. Bakris, G.L.; Agarwal, R.; Anker, S.D.; Pitt, B.; Ruilope, L.M.; Rossing, P.; Kolkhof, P.; Nowack, C.; Schloemer, P.; Joseph, A. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. *N. Engl. J. Med.* **2020**, *383*, 2219–2229. [CrossRef] [PubMed]
33. Damman, K.; Gori, M.; Claggett, B.; Jhund, P.S.; Senni, M.; Lefkowitz, M.P.; Prescott, M.F.; Shi, V.C.; Rouleau, J.L.; Swedberg, K.; et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. *JACC Heart Fail.* **2018**, *6*, 489–498. [CrossRef] [PubMed]
34. Packer, M.; Claggett, B.; Lefkowitz, M.P.; McMurray, J.J.V.; Rouleau, J.L.; Solomon, S.D.; Zile, M.R. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: A secondary analysis of the PARADIGM-HF trial. *Lancet Diabetes Endocrinol.* **2018**, *6*, 547–554. [CrossRef]
35. Mc Causland, F.R.; Lefkowitz, M.P.; Claggett, B.; Anavekar, N.S.; Senni, M.; Gori, M.; Jhund, P.S.; McGrath, M.M.; Packer, M.; Shi, V.; et al. Angiotensin-Neprilysin Inhibition and Renal Outcomes in Heart Failure With Preserved Ejection Fraction. *Circulation* **2020**, *142*, 1236–1245. [CrossRef] [PubMed]
36. Lytvyn, Y.; Bjornstad, P.; Udell, J.A.; Lovshin, J.A.; Cherney, D.Z.I. Sodium Glucose Cotransporter-2 Inhibition in Heart Failure: Potential Mechanisms, Clinical Applications, and Summary of Clinical Trials. *Circulation* **2017**, *136*, 1643–1658. [CrossRef]
37. Seferović, P.M.; Fragasso, G.; Petrie, M.; Mullens, W.; Ferrari, R.; Thum, T.; Bauersachs, J.; Anker, S.D.; Ray, R.; Çavuşoğlu, Y.; et al. Sodium-glucose co-transporter 2 inhibitors in heart failure: Beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **2020**, *22*, 1495–1503. [CrossRef]

38. Liu, X.; Xu, C.; Xu, L.; Li, X.; Sun, H.; Xue, M.; Li, T.; Yu, X.; Sun, B.; Chen, L. Empagliflozin improves diabetic renal tubular injury by alleviating mitochondrial fission via AMPK/SP1/PGAM5 pathway. *Metabolism* **2020**, *111*, 154334. [CrossRef]
39. Hawley, S.A.; Ford, R.J.; Smith, B.K.; Gowans, G.J.; Mancini, S.J.; Pitt, R.D.; Day, E.A.; Salt, I.P.; Steinberg, G.R.; Hardie, D.G. The Na+/Glucose Cotransporter Inhibitor Canagliflozin Activates AMPK by Inhibiting Mitochondrial Function and Increasing Cellular AMP Levels. *Diabetes* **2016**, *65*, 2784–2794. [CrossRef]
40. Zeng, Q.; Zhou, Q.; Liu, W.; Wang, Y.; Xu, X.; Xu, D. Mechanisms and Perspectives of Sodium-Glucose Co-transporter 2 Inhibitors in Heart Failure. *Front. Cardiovasc. Med.* **2021**, *10*, 636152. [CrossRef]
41. Bae, J.H.; Park, E.G.; Kim, S.; Kim, S.G.; Hahn, S.; Kim, N.H. Effects of sodium-glucose cotransporter 2 inhibitors on renal outcomes in patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Sci. Rep.* **2019**, *9*, 13009. [CrossRef] [PubMed]
42. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Pocock, S.J.; Carson, P.; Januzzi, J.; Verma, S.; Tsutsui, H.; Brueckmann, M.; et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N. Engl. J. Med.* **2020**, *383*, 1413–1424. [CrossRef] [PubMed]
43. Zannad, F.; Ferreira, J.P.; Pocock, S.J.; Zeller, C.; Anker, S.D.; Butler, J.; Filippatos, G.; Hauske, S.J.; Brueckmann, M.; Pfarr, E.; et al. Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced. *Circulation* **2021**, *143*, 310–321. [CrossRef] [PubMed]
44. Heerspink, H.J.L.; Oshima, M.; Zhang, H.; Li, J.; Agarwal, R.; Capuano, G.; Charytan, D.M.; Craig, J.; de Zeeuw, D.; Di Tanna, G.L.; et al. Canagliflozin and Kidney-Related Adverse Events in Type 2 Diabetes and CKD: Findings From the Randomized CREDENCE Trial. *Am. J. Kidney Dis.* **2022**, *79*, 244–256.e1. [CrossRef]
45. McMurray, J.J.V.; Solomon, S.D.; Inzucchi, S.E.; Kober, L.; Kosiborod, M.N.; Martinez, F.A.; Ponikowski, P.; Sabatine, M.S.; Anand, I.S.; Belohlavek, J.; et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* **2019**, *381*, 1995–2008. [CrossRef]
46. Jhund, P.S.; Solomon, S.D.; Docherty, K.F.; Heerspink, H.J.L.; Anand, I.S.; Bohm, M.; Chopra, V.; de Boer, R.A.; Desai, A.S.; Ge, J.; et al. Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. *Circulation* **2021**, *143*, 298–309. [CrossRef]
47. Heerspink, H.J.L.; Stefánsson, B.V.; Correa-Rotter, R.; Chertow, G.M.; Greene, T.; Hou, F.-F.; Mann, J.F.E.; McMurray, J.J.V.; Lindberg, M.; Rossing, P.; et al. Dapagliflozin in patients with chronic kidney disease. *N. Engl. J. Med.* **2020**, *383*, 1436–1446. [CrossRef]
48. Voors, A.A.; Mulder, H.; Reyes, E.; Cowie, M.R.; Lassus, J.; Hernandez, A.F.; Ezekowitz, J.A.; Butler, J.; O'Connor, C.M.; VICTORIA Study Group. Renal function and the effects of vericiguat in patients with worsening heart failure with reduced ejection fraction: Insights from the VICTORIA (Vericiguat Global Study in Subjects with HFrEF) trial. *Eur. J. Heart Fail.* **2021**, *23*, 1313–1321. [CrossRef]
49. Lim, S.L.; Gandhi, M.; Woo, K.L.; Chua, H.R.; Lim, Y.C.; Sim, D.K.L.; Lee, S.S.G.; Teoh, Y.L.; Richards, A.M.; Lam, C.S.P. Nitrates in combination with hydralazine in cardiorenal syndrome: A randomized controlled proof-of-concept study. *ESC Heart Fail.* **2020**, *7*, 4267–4276. [CrossRef]
50. Lim Shir, L.; Benson, L.; Dahlström, U.; Lam Carolyn, S.P.; Lund Lars, H. Association between use of long-acting nitrates and outcomes in heart failure with preserved ejection fraction. *Circ. Heart Fail.* **2017**, *10*, e003534.
51. Zamora, E.; Lupón, J.; Vila, J.; Urrutia, A.; de Antonio, M.; Sanz, H.; Grau, M.; Ara, J.; Bayés-Genís, A. Estimated glomerular filtration rate and prognosis in heart failure: Value of the Modification of Diet in Renal Disease Study-4, chronic kidney disease epidemiology collaboration, and cockroft-gault formulas. *J. Am. Coll. Cardiol.* **2012**, *59*, 1709–1715. [CrossRef] [PubMed]
52. Valente, M.A.; Hillege, H.L.; Navis, G.; Voors, A.A.; Dunselman, P.H.; van Veldhuisen, D.J.; Damman, K. The Chronic Kidney Disease Epidemiology Collaboration equation outperforms the Modification of Diet in Renal Disease equation for estimating glomerular filtration rate in chronic systolic heart failure. *Eur. J. Heart Fail.* **2014**, *16*, 86–94. [CrossRef] [PubMed]
53. Mullens, W.; Damman, K.; Testani, J.M.; Martens, P.; Mueller, C.; Lassus, J.; Tang, W.H.W.; Skouri, H.; Verbrugge, F.H.; Orso, F.; et al. Evaluation of kidney function throughout the heart failure trajectory—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **2020**, *22*, 584–603. [CrossRef] [PubMed]
54. Zou, L.X.; Sun, L.; Nicholas, S.B.; Lu, Y.; Sinha, S.K.; Hua, R. Comparison of bias and accuracy using cystatin C and creatinine in CKD-EPI equations for GFR estimation. *Eur. J. Intern. Med.* **2020**, *80*, 29–34. [CrossRef]
55. Pottel, H.; Bjork, J.; Courbebaisse, M.; Couzi, L.; Ebert, N.; Eriksen, B.O.; Dalton, R.N.; Dubourg, L.; Gaillard, F.; Garrouste, C.; et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate: A cross-sectional analysis of pooled data. *Ann. Intern. Med.* **2020**, *174*, 183–191. [CrossRef]
56. Ando, T.; Okuhara, Y.; Orihara, Y.; Nishimura, K.; Yamamoto, K.; Masuyama, T.; Hirotani, S. Urinary composition predicts diuretic efficiency of hypertonic saline solution with furosemide therapy and heart failure prognosis. *Heart Vessels* **2018**, *33*, 1029–1036. [CrossRef]
57. Palazzuoli, A.; Tecson, K.M.; Ronco, C.; McCullough, P.A. Nomenclature for Kidney Function from KDIGO: Shortcomings of Terminology Oversimplification. *Cardiorenal Med.* **2021**, *11*, 119–122. [CrossRef]
58. Poniatowski, B.; Malyszko, J.; Bachorzewska-Gajewska, H.; Malyszko, J.S.; Dobrzycki, S. Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in patients with chronic heart failure and coronary artery disease. *Kidney Blood Press Res.* **2009**, *32*, 77–80. [CrossRef]

59. Ter Maaten, J.M.; Beldhuis, I.E.; van der Meer, P.; Krikken, J.A.; Coster, J.E.; Nieuwland, W.; van Veldhuisen, D.J.; Voors, A.A.; Damman, K. Natriuresis guided therapy in acute heart failure: Rationale and design of the Pragmatic Urinary Sodium-based Treatment algoritHm in Acute Heart Failure (PUSH-AHF) trial. *Eur. J. Heart Fail.* **2021**, *24*, 385–392. [CrossRef]
60. Martens, P.; Dupont, M.; Verbrugge, F.H.; Damman, K.; Degryse, N.; Nijst, P.; Reynders, C.; Penders, J.; Tang, W.H.W.; Testani, J.; et al. Urinary sodium profiling in chronic heart failure to detect development of acute decompensated heart failure. *JACC Heart Fail.* **2019**, *7*, 404–414. [CrossRef]
61. Cuthbert, J.J.; Bhandari, S.; Clark, A.L. Hypochloraemia in Patients with Heart Failure: Causes and Consequences. *Cardiol. Ther.* **2020**, *9*, 333–347. [CrossRef] [PubMed]
62. Eichhorn, E.J.; Domanski, M.J.; Krause-Steinrauf, H.; Bristow, M.R.; Lavori, P.W. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N. Engl. J. Med.* **2001**, *344*, 1659–1667. [PubMed]
63. Silva-Cardoso, J.; Brito, D.; Frazão, J.M.; Ferreira, A.; Bettencourt, P.; Branco, P.; Fonseca, C. Management of RAASi-associated hyperkalemia in patients with cardiovascular disease. *Heart Fail Rev.* **2021**, *26*, 891–896. [CrossRef] [PubMed]

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Early Hemodynamic Changes following Surgical Ablation of the Right Greater Splanchnic Nerve for the Treatment of Heart Failure with Preserved Ejection Fraction

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Abstract: Background: Permanent ablation of the right greater splanchnic nerve (GSN) has previously been demonstrated to improve quality of life and functional outcomes, as well as reduce abnormally high intracardiac filling pressures, in patients with heart failure with preserved ejection fraction (HFpEF) at 1, 3 and 12 months following the procedure. We hypothesize that hemodynamic changes that ensue from surgical right GSN ablation would be apparent as early as 24 h after the medical intervention. Methods and Results: This is a prespecified analysis of a single-arm, two-center, open-label study evaluating the effects of right GSN ablation via thoracoscopic surgery in HFpEF patients with pulmonary capillary wedge pressure (PCWP) $\geq$15 mmHg at rest or $\geq$25 mmHg with supine cycle ergometry. A total of seven patients (median age 67 years, 29% female) underwent GSN removal followed by invasive right heart catheterization within 24 h. GSN ablation resulted in a significant reduction in PCWP 24 h after the procedure compared to baseline for both 20 W exercise (baseline (28.0 $\pm$ 4.3 mmHg) to 24 h (19.6 $\pm$ 6.9 mmHg); p = 0.0124) and peak exercise (baseline (25.6 $\pm$ 2.4 mmHg) to 24 h (17.4 $\pm$ 5.9 mmHg); p = 0.0025). There were no significant changes in resting or leg-up hemodynamics. Conclusions: Permanent right GSN ablation leads to a reduction in intracardiac filling pressures during exercise, apparent as early as 24 h following the procedure.

Keywords: heart failure; HFpEF; greater splanchnic nerve ablation

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1. Background

Heart failure with preserved ejection fraction (HFpEF) comprises about 50% of today's heart failure population, and its incidence is constantly increasing [1,2]. Unlike heart failure with reduced ejection fraction (HFrEF), in HfpEF, there are no well-established drug therapies. Current clinical approaches focus on modifying risk factors and comorbidities to control symptoms in HFpEF [3,4]. The results of the EMPEROR-Preserved study published in 2021 indicate a new option for pharmacological treatment to reduce the combined risk of death from cardiovascular causes and hospitalization due to heart failure [5]. Preliminary evidence suggests that lowering exercise induces intracardiac pressures with the interatrial shunt procedure, yet the pivotal study results are pending.

The hallmark of HFpEF is exercise intolerance, which is manifested by exertional dyspnea or fatigue. Growing evidence shows that an uncontrolled hemodynamic response to exercise, as manifested by a rapid increase in intracardiac filling pressures (which usually return to baseline in the rest) can be responsible for this condition [6]. Volume redistribution,

in addition to total body fluid retention, is increasingly being recognized as an important contributor of elevated intracardiac pressures and clinical congestion in heart failure [7]. The splanchnic venous reservoir plays a critical role in controlling the distribution of blood between stressed and unstressed compartments in the body [8]. In heart failure, there is a decreased capacity of the splanchnic vascular reservoir to buffer volume shifts in the body, leading to an abnormal rise in central pressures during exertion, even in the setting of normal hemodynamics at rest as commonly seen in patients with HFpEF [9]. Various interventions aimed at selectively affecting the splanchnic system to improve outcomes in patients with HF have been investigated, with specific focus on targeted modulation of the greater splanchnic nerve (GSN) [10]. The potential benefits of splanchnic nerve modulation in HF are believed to be related to sympathetically mediated improvement in vascular compliance and a decrease in inappropriately high intracardiac filling pressures at rest and especially with exertion [11].

Recently, the feasibility and safety of permanent right GSN ablation in HFpEF were examined in a small proof-of-concept study [12]. This study demonstrated that right GSN ablation in HFpEF was safe, with no adverse events related to the absence of the GSN for at least 12 months. Mechanistically, there was a significant reduction in intracardiac filling pressures during exercise right-heart catheterization at 1, 3, and 12 months after the procedure compared to baseline. Clinically, patients demonstrated significant improvement in quality of life and functional capacity following GSN ablation through 12-month follow-ups as compared to baseline. The early hemodynamic changes following GSN ablation have not yet been described. In this study, we sought to examine the changes in invasive hemodynamic measurements within 24 h following surgical GSN ablation in patients with HFpEF.

2. Methods

The study design and the primary results have been previously published [11]. Briefly, patients were enrolled in a single-arm, two-center, open-label, prospective study aimed at the feasibility of elective blockade of sympathetic signaling to the splanchnic circulation by surgical ablation of the right GSN (clinicaltrial.gov, NCT03715543). To be considered for enrollment, patients had to be $\geq$18 years of age with guideline-defined HFpEF, New York Heart Association (NYHA) functional class III/IV, and pulmonary capillary wedge pressure (PCWP) $\geq$15 mmHg at rest or $\geq$25 mmHg during exercise. The original study enrolled a total of 10 patients (from 15 patients screened) between June 2016 and July 2017. All patients underwent surgical ablation of the right GSN using a multi-port video-assisted thoracoscopic approach. Seven of the ten patients who recovered from the surgical intervention underwent repeat hemodynamic testing approximately 24 h after the original procedure.

The early clinical effectiveness of GSN ablation was assessed by examining changes in hemodynamic measurements obtained from invasive right heart catheterization approximately 24 h after the procedure compared with baseline. Central hemodynamic profiles (i.e., central venous pressure (CVP) and systolic pulmonary artery pressure (PAP-S), PCWP) were measured at rest, during leg-up maneuver, and during supine bicycle exercise. Supine bicycle exercise protocol was implemented by commencing at 20 watts (W) with 10 W increments every 90 s until the patient achieved maximum effort as defined by symptom-limiting dyspnea or fatigue. The same central hemodynamic measurements were taken after a five-minute recovery from the end of maximal exertion. Summaries within a visit are presented as mean $\pm$ standard deviation or median (Q1, Q3), unless otherwise noted, and change from baseline is presented as median (95% confidence interval [CI]). Hemodynamic data were compared using Wilcoxon Signed Rank test (SAS v9.4 for Windows, SAS Institute Inc., Cary, NC, USA). A p value < 0.05 was considered statistically significant.

3. Results

Baseline characteristics of seven enrolled patients are summarized in Table 1. Patients had a median age of 67 years, were 29% female and had high burden of comorbidities

(86% with atrial fibrillation and 71% with arterial hypertension). All patients were on diuretics and had a high utilization of anti-hypertensive/HF medications. At 24 h after undergoing surgical right GSN ablation, there was no significant change in resting CVP (baseline (9.9 ± 5.0 mmHg) to 24 h (7.43 ± 2.99 mmHg); $p = 0.199$), resting PAP-S (baseline (37.0 ± 8.7 mmHg) to 24 h (37.1 ± 8.7 mmHg); $p = 0.898$) or resting PCWP (baseline (15.7 ± 2.7 mmHg) to 24 h (14.9 ± 3.5 mmHg); $p > 0.999$). In contrast, there was a significant reduction in PWCP with 20 W (baseline (28.0 ± 4.3 mmHg) to 24 h (20.7 ± 6.0 mmHg); $p = 0.0124$) and peak exercise (baseline (25.6 ± 2.4 mmHg) to 24 h (18.6 ± 5.4 mmHg); $p = 0.0025$) (Figure 1). There was a non-significant trend toward reduction in PCWP with leg-up (baseline (21.9 ± 3.6 mmHg) to 24 h (17.6 ± 4.2 mmHg); $p = 0.0714$).

Table 1. Baseline demographic characteristics (n = 7).

Age ± SD (years)	67 ± 11
Female (%)	2 (29)
Body Mass Index, median (Interquartile range) (kg/m^2)	30 (29–35)
Comorbidities	
History of Atrial Fibrillation (%)	6 (86)
Hypertension (%)	5 (71)
Diabetes (%)	3 (43)
Coronary Artery Disease (%)	4 (57)
Previous Myocardial Infarction (%)	3 (43)
Left Ventricular Ejection Fraction ± SD (%)	54 ± 7
NYHA Class I/II/III/IV (%)	0/0/100/0
Arterial Blood Pressure, systolic/diastolic ± SD (mmHg)	126/80 ± 15/14
Resting Heart Rate (beats/min)	80 ± 9
NT-proBNP, median (Interquartile range) (pg/mL)	1220 (51–2797)
Creatinine, median (Interquartile range) (mg/dL)	1.1 (1.0-1.5)
eGFR ± SD (mL/min/1.73 m^2)	63 ± 16
Heart failure or anti-hypertension medication	
Loop Diuretic (%)	7 (100)
ACEi or ARB (%)	6 (86)
Beta-Blocker (%)	6 (86)
MRA (%)	6 (86)
CCB (%)	2 (29)
Other vasodilators (%)	1 (14)

Abbreviations: NYHA, New York Heart Association; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; CCB, calcium channel blockers; NT-proBNP, N terminal pro-natriuretic peptide; eGFR, estimated glomerular filtration rate. Results are presented as mean ± standard deviation (SD) unless otherwise specified.

The early (24 h) hemodynamic changes after the GSN ablation correlated well with long-term post-procedure hemodynamic adaptations. There was a similar statistically significant reduction in PCWP with leg-up (16.9 ± 3.8 mmHg; $p = 0.0278$) and 20 W exercise (20.3 ± 6.4 mmHg; $p = 0.0217$) one year after GSN resection compared to baseline. Although the 24 h PCWPs were often lower than those measured after one year, there was no statistically significant differences between the groups for either rest ($p = 0.379$), leg-up ($p = 0.745$), or 20 W exercise ($p = 0.843$).

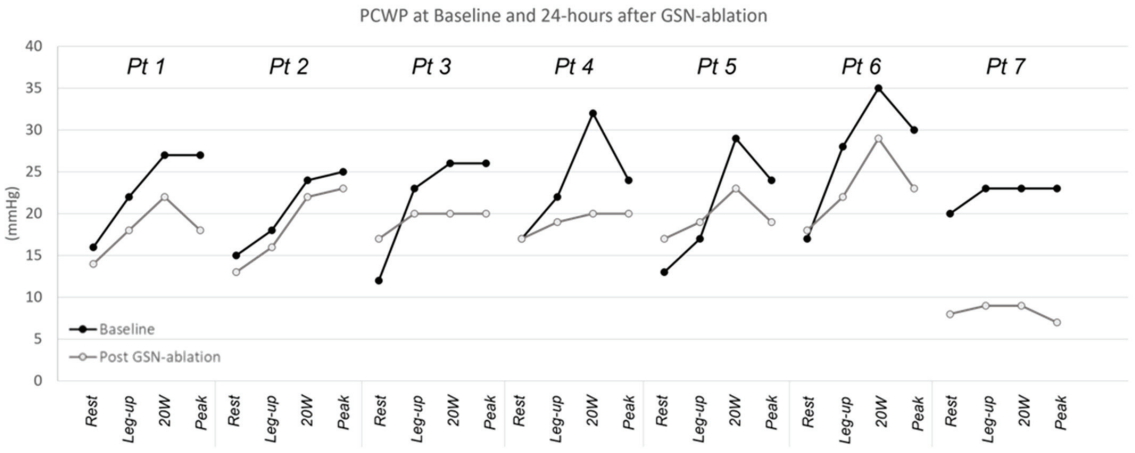

Figure 1. Resting and exercise pulmonary capillary wedge pressure. Abbreviations: GSN, greater splanchnic nerve; PCWP, pulmonary capillary wedge pressure.

Changes were also observed in the intracardiac pressure during the recovery phase of exercise. In all patients, there was a decrease in recovery PCWP in the first 24 h after the procedure vs. baseline (15.6 ± 4.7 vs. 20.4 ± 5.0 mmHg, $p < 0.027$). A similar trajectory was observed in the annual follow-up with mean recovery PCWP of 17.3 ± 9.1 mmHg, although this did not meet statistical significance compared to baseline ($p = 0.31$).

4. Discussion

The persistent hemodynamic and clinical benefits of permanent GSN ablation have been described previously [12]; herein, we describe for the first time in HFpEF patients undergoing permanent right GSN ablation that hemodynamic improvements occur as early as 24 h after the procedure. These results of permanent GSN ablation in HFpEF support the mechanistic insights and immediate hemodynamic benefits seen with temporary GSN modulation in both decompensated hospitalized HF (splanchnic HF-1) [13] and chronic ambulatory HF (splanchnic HF-2) [14]. As opposed to these studies, which enrolled predominantly HFrEF patients (91% HFrEF in splanchnic HF-I and 93% HFrEF in splanchnic HF-II), the current study exclusively enrolled patients with HFpEF. The consistent and favorable effects of GSN modulation on hemodynamics in the HFpEF phenotype is encouraging, as this group historically does not derive the same therapeutic benefits from HFrEF treatments.

Similar to follow-ups at 1, 3, and 12 months [12], the early hemodynamic changes following permanent GSN ablation appear to be more prominent during exercise than at rest, and they failed to reach statistical significance at 24 h follow-up. Conversely, a significant reduction in resting filling pressures was observed in splanchnic HF-I and splanchnic HF-II trials. The greater administration of supporting intravenous fluid and blood product during the surgical procedure as opposed to temporary block procedures may explain, in part, some of the observation differences in resting pressures. Despite this, patients still exhibited significant improvement in exercise hemodynamics, signifying the promising benefits of GSN ablation even in the setting of increased fluid retention. The observed difference may potentially be explained by the incremental effect of bilateral block over unilateral ablation. Nevertheless, the differential effects of GSN ablation on reducing filling pressures only during exercise highlight the important role of the splanchnic nervous system in reducing stressed blood volume that underlies exercise intolerance in HFpEF.

The consistency of hemodynamic and clinical benefits seen across these studies speaks to the importance of the splanchnic vascular reservoir in the pathophysiology of heart

failure independent of ejection fraction. These encouraging results, together with a reasonable safety profile of GSN modulation [10], pave the way for larger randomized controlled studies needed to show long-term benefits, tolerability, and safety in HF, as well as the best technical approach for GSN modulation.

5. Limitations

This study has some limitations, in addition to what was described in the original study, that need to be considered. First, not all patients underwent right heart catheterization at 24 h following surgical GSN ablation at the discretion of the treating physician. This subjects the results to possible selection bias in that only patients who recovered well enough for the catheterization and exercise could have derived greater benefits from the procedure. Second, clinical variables (e.g., weight, NT-proBNP) other than invasive hemodynamic measurements were not recorded at 24 h and were not available for comparison.

6. Conclusions

From the retrospective analysis of the single-arm, open-label, prospective study, a reduction in intracardiac filling pressures during exercise was observed as early as 24 h following permanent right GSN ablation in patients with HFpEF.

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References

1. Shah, K.S.; Xu, H.; Matsouaka, R.A.; Bhatt, D.L.; Heidenreich, P.A.; Hernandez, A.F.; Devore, A.D.; Yancy, C.W.; Fonarow, G.C. Heart Failure with Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J. Am. Coll. Cardiol.* **2017**, *70*, 2476–2486. [CrossRef] [PubMed]
2. Steinberg, B.A.; Zhao, X.; Heidenreich, P.A.; Peterson, E.D.; Bhatt, D.L.; Cannon, C.P.; Hernandez, A.F.; Fonarow, G.C. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: Prevalence, therapies, and outcomes. *Circulation* **2012**, *126*, 65–75. [CrossRef] [PubMed]
3. Yancy, C.W.; Jessup, M.; Bozkurt, B.; Butler, J.; Casey, D.E., Jr.; Colvin, M.M.; Drazner, M.H.; Filippatos, G.S.; Fonarow, G.C.; Givertz, M.M.; et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J. Card. Fail.* **2017**, *23*, 628–651. [CrossRef] [PubMed]

4. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef] [PubMed]
5. Anker, S.D.; Butler, J.; Filippatos, G.; Ferreira, J.P.; Bocchi, E.; Böhm, M.; Brunner-La Rocca, H.P.; Choi, D.J.; Chopra, V.; Chuquiure-Valenzuela, E.; et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N. Engl. J. Med.* **2021**, *385*, 1451–1461. [CrossRef] [PubMed]
6. Borlaug, B.A. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction. *Circ. J.* **2014**, *78*, 20–32. [CrossRef] [PubMed]
7. Fudim, M.; Hernandez, A.F.; Felker, G.M. Role of Volume Redistribution in the Congestion of Heart Failure. *J. Am. Heart Assoc.* **2017**, *6*, e006817. [CrossRef] [PubMed]
8. Greenway, C.V.; Lister, G.E. Capacitance effects and blood reservoir function in the splanchnic vascular bed during non-hypotensive haemorrhage and blood volume expansion in anaesthetized cats. *J. Physiol.* **1974**, *237*, 279–294. [CrossRef] [PubMed]
9. Borlaug, B.A.; Nishimura, R.A.; Sorajja, P.; Lam, C.S.; Redfield, M.M. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ. Heart Fail.* **2010**, *3*, 588–595. [CrossRef] [PubMed]
10. Fudim, M.; Ponikowski, P.P.; Burkhoff, D.; Dunlap, M.E.; Sobotka, P.A.; Molinger, J.; Patel, M.R.; Felker, G.M.; Hernandez, A.F.; Litwin, S.E.; et al. Splanchnic nerve modulation in heart failure: Mechanistic overview, initial clinical experience, and safety considerations. *Eur. J. Heart Fail.* **2021**, *23*, 1076–1084. [CrossRef] [PubMed]
11. Fudim, M.; Patel, M.R.; Boortz-Marx, R.; Borlaug, B.A.; DeVore, A.D.; Ganesh, A.; Green, C.L.; Lopes, R.D.; Mentz, R.J.; Patel, C.B.; et al. Splanchnic Nerve Block Mediated Changes in Stressed Blood Volume in Heart Failure. *JACC Heart Fail.* **2021**, *9*, 293–300. [CrossRef] [PubMed]
12. Málek, F.; Gajewski, P.; Zymliński, R.; Janczak, D.; Chabowski, M.; Fudim, M.; Martinca, T.; Neužil, P.; Biegus, J.; Mates, M.; et al. Surgical ablation of the right greater splanchnic nerve for the treatment of heart failure with preserved ejection fraction: First-in-human clinical trial. *Eur. J. Heart Fail.* **2021**, *23*, 113443. [CrossRef] [PubMed]
13. Fudim, M.; Ganesh, A.; Green, C.; Jones, W.S.; Blazing, M.A.; DeVore, A.D.; Felker, G.M.; Kiefer, T.L.; Kong, D.F.; Boortz-Marx, R.L.; et al. Splanchnic nerve block for decompensated chronic heart failure: Splanchnic-HF. *Eur. Heart J.* **2018**, *39*, 4255–4256. [CrossRef] [PubMed]
14. Fudim, M.; Boortz-Marx, R.L.; Ganesh, A.; DeVore, A.D.; Patel, C.B.; Rogers, J.G.; Coburn, A.; Johnson, I.; Paul, A.; Coyne, B.J.; et al. Splanchnic Nerve Block for Chronic Heart Failure. *JACC Heart Fail.* **2020**, *8*, 742–752. [CrossRef] [PubMed]

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Prognostic Benefit of New Drugs for HFrEF: A Systematic Review and Network Meta-Analysis

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Abstract: Background: The new heart failure (HF) therapies of sodium-glucose cotransporter 2 inhibitors (SGLT2i), vericiguat, and omecamtiv mecarbil do not act primarily through the neurohormonal blockade, but have shown clinical benefits in patients with HF with reduced ejection fraction (HFrEF). However, their respective efficacies remain unclear. Our aim was to evaluate the relative efficacy of new drugs for HFrEF. Methods: We performed a network meta-analysis (NMA) of randomized controlled trials (RCTs) comparing SGLT2i, vericiguat, omecamtiv mecarbil, and placebo in HFrEF patients. The primary endpoint was the composite of cardiovascular death (CVD) or HF hospitalization (CVD-HF); secondary endpoints were CVD, all-cause death, and HF hospitalization (HFH). Results: Twelve RCTs (n = 23,861 patients) were included. A significant reduction in CVD-HF was observed with SGLT2i compared with placebo (risk ratio (RR) 0.77, 95% confidence interval (CI) 0.71–0.83), vericiguat (RR 0.84, 95% CI 0.75–0.93), and omecamtiv mecarbil (RR 0.80, 95% CI 0.72–0.88). No significant difference was observed between vericiguat and omecamtiv mecarbil (RR 0.95, 95% CI 0.87–1.04). SGLT2i were superior to placebo and omecamtiv mecarbil for all individual secondary endpoints (CVD, all-cause death, and HFH), and also to vericiguat for HFH. SGLT2i ranked as the most effective therapy for all endpoints, and vericiguat, omecamtiv mecarbil, and placebo ranked as the second, third, and last options, respectively, for the primary endpoint. Conclusions: In patients with HFrEF on standard-of-care therapy, SGLT2i therapy was associated with a reduced risk of CVD-HF compared to placebo, vericiguat, and omecamtiv mecarbil. Furthermore, SGLT2i were superior to placebo and omecamtiv mecarbil for CVD, all-cause death, and HFH, and also to vericiguat for HFH.

Keywords: heart failure; ejection fraction; network meta-analysis; SGLT2-inhibitors; vericiguat; omecamtiv mecarbil

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1. Introduction

Heart failure (HF) is a major cause of morbidity and mortality worldwide [1]. Medical therapies targeting the neuro-hormonal axes (classically represented by β-blockers, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA)) have significantly improved the clinical outcomes of patients with HF and reduced ejection fraction (HFrEF), and represent the mainstay of treatment for this condition [1–3]. The angiotensin receptor-neprilysin inhibitor

(ARNI) sacubitril/valsartan has been proven to be superior to ACEi in HFrEF, and is recommended by HF guidelines, with American guidelines even recommending sacubitril/valsartan as the first-line therapy [2–5]. Over the last few years, further advances have been made in HFrEF pharmacotherapy with new drugs not acting directly through neurohormonal blockade (the sodium-glucose cotransporter 2 inhibitors (SGLT2i) dapagliflozin and empagliflozin, vericiguat, and omecamtiv mecarbil) showing a prognostic benefit in randomized controlled trials (RCTs) [6–11]. Of note, according to the latest European HF guidelines, SGLT2i are now considered as a first-line therapy for HFrEF, along with ACEi/ARNI, β-blockers, and MRA [3]. As head-to-head comparisons are lacking, and are unlikely to be performed in the future, the present network meta-analysis (NMA) aimed to evaluate the relative efficacy of SGLT2i, vericiguat, and omecamtiv mecarbil in patients with HFrEF.

2. Materials and Methods

Search strategy, study selection, and data extraction.

Three authors (M.P., L.B. and D.T.) independently searched PubMed, Embase, Google Scholar, and the Cochrane Central Register of Controlled Trials (up to 18 March 2021), using the following combinations of keywords: "SGLT2" OR "dapagliflozin" OR "empagliflozin" OR "sotagliflozin" OR "vericiguat" OR "omecamtiv mecarbil" AND "heart failure". Reference lists of the identified articles and pertinent reviews were also screened. All RCTs investigating SGLT2i, vericiguat, or omecamtiv mecarbil in patients with HFrEF were selected for inclusion. Studies including patients with acute decompensated HF or HF with preserved ejection fraction (as defined by investigators) were not included. Both phase 2 and phase 3 studies were considered for inclusion; furthermore, subgroup analyses from RCTs were also considered for inclusion. Studies with an observational design, not reporting data on primary or secondary endpoint at follow-up (as number of events and event rates), and reporting data on overlapping populations were excluded (Figure 1). Studies focused on sacubitril/valsartan were not considered for inclusion, as this drug was already included in 2016–2017 HF guidelines [2,5], targets the neuro-hormonal axis, and was already prescribed at baseline in a relevant proportion of patients enrolled in the other included trials (up to 40%).

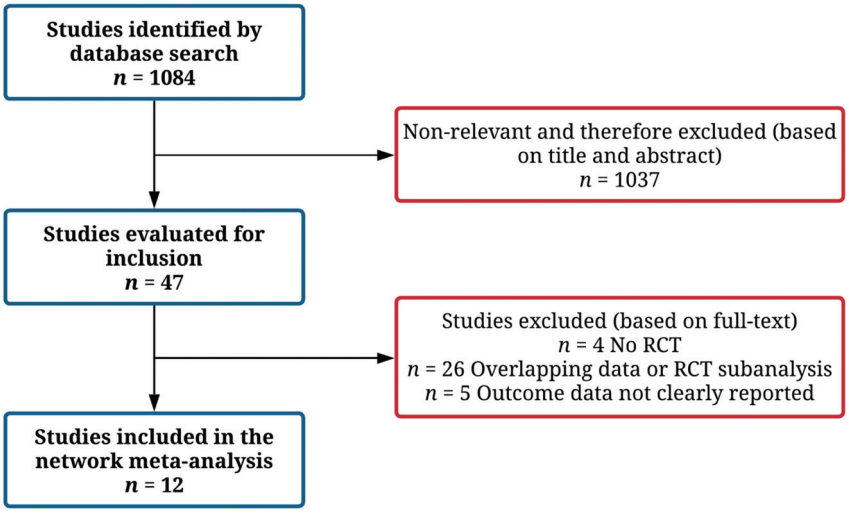

Figure 1. Study flow-chart.

The figure shows the study selection process. A total of 12 studies were included in the final analysis.

Two authors (M.P. and L.B.) independently assessed the identified studies for possible inclusion and performed data extraction (study designs, patient characteristics, and clinical outcomes). Conflicts regarding study inclusion, data extraction, and analysis were discussed and resolved with another author (C.M.L.). Two authors (D.T. and L.B.) assessed the risk of bias of the included studies using the Cochrane Collaboration tool (results available in Table S1).

This NMA was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses recommendations [12].

2.1. Study Endpoints

The primary endpoint was the composite of cardiovascular death (CVD) or HF hospitalization (CVD-HF). Secondary endpoints of interest were the following individual endpoints: CVD, all-cause death, and HF hospitalization (HFH).

2.2. Statistical Analysis

Treatment effects were compared with an NMA technique to provide more precise effect estimates, combining both direct and indirect evidence. In addition, this allowed for the comparison of pairs of interventions that were not directly assessed in randomized trials. This comprehensive comparison of all interventions in a single analysis also provided an estimation of their relative efficacy ranking for a given outcome [13–15]. This technique is extensively described in the Cochrane Handbook for Systematic Reviews of Interventions [15]. The present NMA included RCTs comparing the study drugs (SGLT2i, vericiguat, or omecamtiv mecarbil) with the placebo on top of standard-of-care therapy for HFrEF, thus obtaining indirect comparisons of the relative efficacy of the investigated study drugs [16,17]. The transitivity of the included studies was checked by a qualitative comparison of the baseline patient characteristics. A random-effects NMA was performed on the cumulative event rates for primary and secondary endpoints based on a frequentist approach with the DerSimonian−Laird estimator [18]. Effect estimates were based on relative risk (RR) per study, and were analyzed by considering their point estimates and 95% confidence interval (CI). The NMA results were summarized by means of league tables. No locally closed loop to calculate both the direct and indirect evidence exists to evaluate inconsistency.

To establish a relative ranking of the effectiveness of the available treatments, the surface under the cumulative ranking area (SUCRA) method and the probability of being the best treatment for a given outcome were calculated through a Bayesian approach [19]. Pre-specified sensitivity analyses were performed by including only phase 3 studies and by performing a random-effects NMA on hazard ratio (HR) estimates (instead of event counts).

The NMA was conducted in RStudio version 1.3.1093 (RStudio PBC, Boston, MA, USA) with the "netmeta" package for the frequentist approach and "bnma" package for the Bayesian analysis. Statistical significance was set at p value < 0.05 (two-sided) for the frequentist NMA.

3. Results

As shown in Figure 1, the study selection process led to the final inclusion of 12 studies in the NMA, for an overall population of 23,861 patients [6–9,20–27]. The network map is available in Figure 2. The included trials compared SGLT2i (eight studies), vericiguat (two studies), and omecamtiv mecarbil (two studies) versus placebo, on top of standard medical therapy for HFrEF. As shown in Table 1, there were some differences regarding the study characteristics across the included trials (such as sample size, baseline NT-proBNP values, or percentage of patients already treated with ARNI).

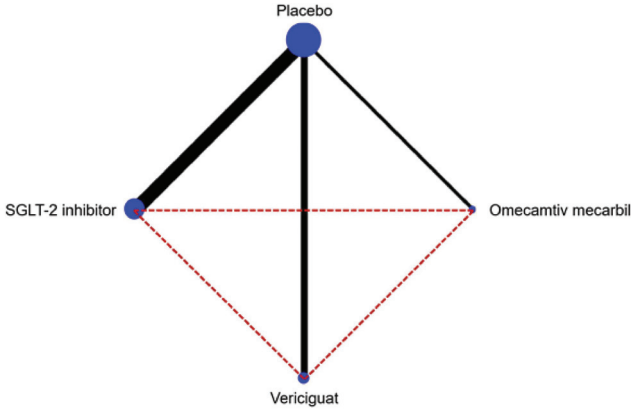

Figure 2. Network map of the study treatments.

Table 1. Main characteristics of the included studies.

Study	Year	Treatment	*n* Patients	Age (Years)	Male Sex (%)	EF (%)	Diabetes (%)	NT-proBNP (pg/mL)	Background HF Therapy				Follow-Up
									ACEi/ARB (%)	Beta-Blocker (%)	ARNI (%)	MRA (%)	
GALACTIC-HF [9]	2021	Omecamtiv mecarbil vs. Placebo	8232	65	79	27	40	1971	87 *	94	19	78	22 months (median)
COSMIC-HF [22]	2016	Omecamtiv mecarbil vs. Placebo	298	63	82	29	39	1719	93	97	0	61	24 weeks
VICTORIA [8]	2020	Vericiguat vs. Placebo	5050	67	76	29	47	2816	73	93	15	70	11 months (median)
SOCRATES-REDUCED [23]	2015	Vericiguat vs. Placebo	183	68	82	29	49	3076	81	92	0	62	12 weeks
EMPEROR-Reduced [7]	2020	Empagliflozin vs. Placebo	3730	67	76	27	50	1907	70	95	19	71	16 months (median)
EMPERIAL-Reduced [24]	2020	Empagliflozin vs. Placebo	311	70	74	30	60	1489	55	95	37	58	12 weeks
Empire HF [25]	2020	Empagliflozin vs. Placebo	190	64	85	30	17	594	96 *	95	31	66	12 weeks
SUGAR-DM-HF [26]	2021	Empagliflozin vs. Placebo	105	69	73	33	78	466	61	91	34	60	40 weeks
EMPA-TROPISM (ATRU-4) [27]	2021	Empagliflozin vs. Placebo	84	62	64	36	0	NA	42	88	43	33	6 months
DAPA-HF [6]	2019	Dapagliflozin vs. Placebo	4744	66	77	31	42	1437	84	96	11	71	18 months (median)
DECLARE-TIMI 58 (HFrEF subgroup) [20]	2019	Dapagliflozin vs. Placebo	671	63	84	38	100	NA	88	88	NA	30	4.2 years (median)
DEFINE-HF [21]	2019	Dapagliflozin vs. Placebo	263	61	73	26	62	1136	59	97	33	61	12 weeks

* ACEi, ARB, or ARNI. ACEi—angiotensin-converting enzyme inhibitors; ARB—angiotensin receptor blockers; ARNI—angiotensin receptor-neprilysin inhibitor; EF—ejection fraction; HF—heart failure; MRA—mineralocorticoid receptor antagonist; NA—not available; NT-proBNP—N-terminal pro-B-type natriuretic peptide. This graph shows available comparisons between study treatments (with respect to the primary endpoint). The bullet diameter represents the size of the included randomized controlled trials, and line thickness represents the number of trials with direct comparisons. Direct comparisons are represented by continuous lines, while indirect comparisons are represented by dashed lines.

3.1. Primary Endpoint

A total of seven studies (n = 22,694 patients) evaluated the primary endpoint of CVD-HF. Sample size, event counts, and summary measures are reported in Figure S1. Both SGLT2i and vericiguat were found to be superior to the placebo, while omecamtiv mecarbil was not (Figure S2). Furthermore, SGLT2i proved superior to vericiguat and omecamtiv mecarbil, whereas no significant difference was observed between vericiguat and omecamtiv mecarbil (Table 2).

Table 2. League table showing pooled risk ratios for primary and secondary endpoints.

Endpoint	Placebo	SGLT2i	Vericiguat	Omecamtiv Mecarbil
CV death or HF hospitalization				
	Placebo	0.77 (0.71–0.83)	0.92 (0.85–0.99)	0.96 (0.91–1.02)
	1.30 (1.20–1.41)	SGLT2i	1.19 (1.07–1.33)	1.25 (1.13–1.39)
	1.09 (1.01–1.17)	0.84 (0.75–0.93)	Vericiguat	1.05 (0.96–1.15)
	1.04 (0.98–1.10)	0.80 (0.72–0.88)	0.95 (0.87–1.04)	Omecamtiv mecarbil
CV death				
	Placebo	0.85 (0.75–0.96)	0.94 (0.83–1.06)	1.01 (0.93–1.10)
	1.18 (1.04–1.33)	SGLT2i	1.10 (0.93–1.31)	1.19 (1.03–1.38)
	1.07 (0.95–1.21)	0.91 (0.76–1.08)	Vericiguat	1.08 (0.93–1.25)
	0.99 (0.91–1.08)	0.84 (0.72–0.98)	0.93 (0.80–1.08)	Omecamtiv mecarbil
All-cause death				
	Placebo	0.86 (0.77–0.95)	0.96 (0.86–1.07)	1.00 (0.93–1.07)
	1.16 (1.05–1.29)	SGLT2i	1.11 (0.96–1.29)	1.16 (1.02–1.32)
	1.05 (0.94–1.16)	0.90 (0.77–1.04)	Vericiguat	1.04 (0.92–1.19)
	1.00 (0.93–1.08)	0.86 (0.76–0.98)	0.96 (0.84–1.09)	Omecamtiv mecarbil
HF hospitalization				
	Placebo	0.73 (0.66–0.81)	0.92 (0.84–1.00)	0.97 (0.90–1.04)
	1.37 (1.24–1.52)	SGLT2i	1.26 (1.10–1.44)	1.33 (1.17–1.50)
	1.09 (1.00–1.19)	0.79 (0.69–0.91)	Vericiguat	1.05 (0.94–1.18)
	1.03 (0.97–1.11)	0.75 (0.67–0.85)	0.95 (0.85–1.06)	Omecamtiv mecarbil

Values are reported as pooled risk ratios and 95% confidence intervals. The pooled effect estimates obtained from the network meta-analysis are reported for column intervention relative to raw. CV—cardiovascular; HF—heart failure; SGLT2i—sodium-glucose cotransporter 2 inhibitors.

In the probability analyses, SGLT2i had the highest probability of being the best agent to reduce CVD-HF, whereas vericiguat, omecamtiv mecarbil, and placebo ranked as the second, third, and worst therapies, respectively (Table 3 and Table S1).

Table 3. Probability ranks for primary and secondary endpoints.

Treatment	P_{best}	SUCRA
CV death or HF hospitalization		
Placebo	0.29	3.91
SGLT2i	77.24	99.97
Vericiguat	15.92	61.54
Omecamtiv mecarbil	6.55	34.58
CV death		
Placebo	1.49	24.76
SGLT2i	61.14	95.09
Vericiguat	25.89	60.85
Omecamtiv mecarbil	11.48	19.30
Any death		
Placebo	3.66	23.49
SGLT2i	64.97	96.92
Vericiguat	28.40	53.75
Omecamtiv mecarbil	2.97	25.83
HF hospitalization		
Placebo	0.48	6.40

Table 3. *Cont.*

Treatment	P_{best}	SUCRA
SGLT2i	78.21	99.99
Vericiguat	19.12	59.60
Omecamtiv mecarbil	2.19	34.01

CV—cardiovascular; HF—heart failure; P_{best}—probability of each treatment being the best (%); SGLT2i—sodium-glucose cotransporter 2 inhibitors; SUCRA—surface under the cumulative ranking.

3.2. Secondary Endpoints

A total of 10 studies (*n* = 23,550 patients) were available for the secondary endpoint of CVD (Figure S4). Only SGLT2i were proven to be superior to placebo, while vericiguat and omecamtiv mecarbil were not (Figure S5). SGLT2i were also superior to omecamtiv mecarbil, but not to vericiguat, and no significant difference was observed between vericiguat and omecamtiv mecarbil (Table 2). In the probability analyses, SGLT2i had the highest probability of being the best agent to reduce CVD (Table 3 and Figure S6).

A total of 12 studies (*n* = 23,861 patients) evaluated the secondary endpoint of all-cause death (Figure S7). Only SGLT2i were proven to be significantly more effective than placebo (Figure S8). SGLT2i were also proven to be superior to omecamtiv mecarbil, but not to vericiguat, and no significant difference was observed between vericiguat and omecamtiv mecarbil (Table 2). In the probability analyses, SGLT2i ranked as the best agent to reduce all-cause death (Table 3 and Figure S9).

A total of 10 studies (*n* = 23,445 patients) were available for the secondary endpoint of HFH (Figure S10). Only SGLT2i were found to be superior to the placebo (Figure S11). SGLT2i were also superior to vericiguat and omecamtiv mecarbil, whereas no difference was observed between vericiguat and omecamtiv mecarbil (Table 2). Again, SGLT2i had the highest probability of being the best agent to reduce HFH (Table 3 and Figure S12).

3.3. Sensitivity Analyses

A pre-specified random-effects NMA on HR estimates from the included studies was performed for the primary endpoint. A total of six studies were included. All three active treatments (SGLT2i, vericiguat, and omecamtiv mecarbil) were proven to be superior to the placebo (Figure S13), and SGLT2i were also superior to vericiguat and omecamtiv mecarbil (Table S2).

A pre-specified sensitivity analysis (random-effects NMA) including only phase 3 studies was also conducted for the primary endpoint. A total of four studies were included. Both SGLT2i and vericiguat were proven to be superior to the placebo (Figure S14). SGLT2i were also superior to vericiguat and omecamtiv mecarbil (Table S3).

4. Discussion

In our NMA including patients with HFrEF on standard medical therapy, SGLT2i (dapagliflozin/empagliflozin) were proven to be superior to the placebo, vericiguat, and omecamtiv mecarbil for the primary endpoint of CVD-HF. Furthermore, SGLT2i were proven to be superior to placebo and omecamtiv mecarbil for all secondary endpoints (CVD, all-cause death, and HFH), and also to vericiguat for the secondary endpoint of HFH. Accordingly, SGLT2i had the highest probability of being the best therapy to reduce all of the evaluated endpoints and ranked first in the probability analyses for all of the evaluated endpoints.

A variety of different drugs are becoming available in the treatment of HF, yet the relative superiorities over each other have not been formally investigated to date. In this NMA, we performed a quantitative assessment of drug efficacy on hard clinical endpoints in patients with HFrEF, on top of standard-of-care therapy based on ACEi/ARBs/ARNI, β-blockers, and MRA [2,3,5]. SGLT2i demonstrated a clear favorable effect in all of the investigated endpoints, a finding that further supports their role as potent disease-modifying drugs in HF and the recent proposal of an early start of SGLT2i therapy in HFrEF [28,29].

Indeed, SGLT2i were included as first-line therapy for HFrEF in the latest European HFrEF guidelines, along with neuro-hormonal antagonists (ACEi/ARNI, β-blockers, and MRA) [3]. Conversely, omecamtiv mecarbil and vericiguat are, at this time, intended for the treatment of patients with more advanced HFrEF.

In patients with type 2 diabetes mellitus, with or without a history of HF and cardiovascular disease, the use of SGLT2i (empagliflozin, dapagliflozin, and canagliflozin) has largely shown a reduction in the risk of HF hospitalization and an improvement in CV outcome [30]. The DApagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) was the first randomized trial to investigate the benefits of dapagliflozin in a population with HFrEF, regardless of diabetes history. Dapagliflozin reduced the risk of CVD or worsening HF compared to the placebo (HR 0.74; 95% CI 0.65–0.85) [6]. More recently, the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trial confirmed and expanded the positive results of DAPA-HF in patients with a more advanced disease (lower ejection fraction, higher natriuretic peptides levels, and worse renal function) [7]. In both trials, the benefits were primarily driven by a significant reduction in HF hospitalizations. A recent meta-analysis of these two large trials confirmed these promising results and demonstrated that treatment with SGLT2i led to a significant reduction in all-cause mortality (HR 0.87, 95% CI 0.77–0.98), CVD (HR 0.86, 95% CI 0.76–0.98), CVD-HF (HR 0.86, 95% CI 0.76–0.98), and renal outcome (HR 0.62, 95% CI 0.43–0.90) [31].

The mechanisms behind the beneficial effects of SGLT2i are not completely clear [32,33]. The levels of glycated haemoglobin, both at baseline and over time, do not seem to affect the course of treatment, suggesting favorable effects beyond glycemic control. SGLT2i also present diuretic properties—exerting their action on the proximal tubule, these drugs enhance glycosuria and natriuresis and ensure osmotic diuresis, which is more pronounced in diabetic patients [32,34]. The hemodynamic consequence with a reduction in preload and decongestion might justify the prominent reduction in HF hospitalizations. However, SGLT2i could also improve cardiomyocyte metabolism and blunt the progression of myocardial fibrosis, leading to an improved diastolic function and reverse cardiac remodeling [32,35]. The recent Effect of Empagliflozin on Left Ventricular Volumes in Patients with Type 2 Diabetes, or Prediabetes, and Heart Failure with Reduced Ejection Fraction (SUGAR-DM-HF) trial showed that empagliflozin therapy caused a significant reduction in left ventricular volumes compared to the placebo, even if without an improvement in global longitudinal strain, after 36 weeks of treatment [26]. Similar results were observed after 12 weeks of treatment in a sub-study of the Empagliflozin in Heart Failure Patients with Reduced Ejection Fraction (Empire HF) trial [36]. Furthermore, a rapid reduction in pulmonary artery pressures was recently demonstrated with empagliflozin in patients with HF and CardioMEMS pulmonary artery pressure sensor, independently of diuretic management [37]. SGLT2i are generally safe and well tolerated, with genital tract infections being the most common adverse event, while hypotension, hyperkalaemia, and renal dysfunction, the most feared adverse effects of neuro-hormonal antagonists, have a similar incidence in patients treated with SGLTi or placebo [6,7].

In our NMA, besides the superiority of SGLT2i over placebo in HFrEF, we found a significant reduction in the primary endpoint of CVD-HF with SGLT2i compared to vericiguat and omecamtiv mecarbil, two drugs that were recently associated with benefits compared to the placebo in the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) and Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure (GALACTIC-HF) trials, respectively [8,9]. The mechanism associated with the benefits of vericiguat in HFrEF is a direct stimulation of the soluble guanylate cyclase, sensitizing it to endogenous nitric oxide and leading to an enhancement of the cyclic guanosine monophosphate pathway, with positive effects on hemodynamics and vascular and myocardial function [8,23]. Conversely, omecamtiv mecarbil is a cardiac myosin activator that ameliorates myocardial function and contractility by direct improvement of the cardiac sarcomere function [9,22]. It is

important to underline that this superiority of SGLT2i over vericiguat and omecamtiv mecarbil was based only on indirect comparisons. Furthermore, some heterogeneity in the baseline characteristics of the included RCTs may be responsible for some of the observed differences: for example, left ventricular ejection fraction and use of ARNI at baseline tended to be slightly higher in SGLT2i trials, whereas median NT-proBNP values were higher and patients were less stable in vericiguat trials.

Recent NMA studies have focused on omecamtiv mecarbil and tested this drug in the comparisons. Of note, we found a superiority of SGLT2i over placebo, vericiguat, and omecamtiv mecarbil for CVD-HF, hence supporting the use of SGLT2i in HFrEF patients already treated with conventional neuro-hormonal blockers.

Limitations

A relevant limitation of the present analysis is that all comparisons between SGLT2i, omecamtiv mecarbil, and vericiguat are indirect, as trials directly comparing these treatments have not been performed to date (and are unlikely to be performed in the future). Nonetheless, NMA is an established tool to indirectly compare the relative efficacy of different therapies in the absence of RCTs involving direct comparisons between them [38]. Furthermore, although most patients were randomized upon optimized medical therapy, some differences in the baseline characteristics and medical treatments across trials may have contributed to the observed superiority among different drugs. For example, the different rate of ARNI prescription across the included studies could be particularly relevant, as ARNI is already part of the standard-of-care therapy for HFrEF [2,5], and the prognostic impact of novel drugs should be tested on a similar background of baseline medical therapy for HF. Furthermore, the SGLT2i trials included only 25–30% of patients with NYHA class III−IV [6,7], whereas the omecamtiv mecarbil and vericiguat trials included up to 45% of patients with NYHA III−IV [8,9]. Another potential limitation may be related to differences between empagliflozin and dapagliflozin, leading to non-class effects of SGLT2i, an issue that is not addressed by our analysis.

5. Conclusions

SGLT2i were associated with a reduced risk of CVD-HF compared to placebo, vericiguat, and omecamtiv mecarbil, given on top of standard therapy for HFrEF. Furthermore, SGLT2i were superior to placebo and omecamtiv mecarbil for CVD, all-cause death, and HFH, and also to vericiguat for HFH.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm11020348/s1, Figure S1: Forest plot summarizing data from individual studies for primary endpoint (main analysis), Figure S2: Forest plot of each treatment versus PLACEBO for primary endpoint (main analysis), Figure S3: Cumulative probability rank plots for each treatment being the best with respect to primary endpoint (main analysis), Figure S4: Forest plot summarizing data from individual studies for CV death (main analysis), Figure S5: Forest plot of each treatment versus PLACEBO for CV death (main analysis), Figure S6: Cumulative probability rank plots for each treatment being the best with respect to CV death (main analysis), Figure S7: Forest plot summarizing data from individual studies for all-cause death (main analysis), Figure S8: Forest plot of each treatment versus PLACEBO for all-cause death (main analysis), Figure S9: Cumulative probability rank plots for each treatment being the best with respect to all-cause death (main analysis), Figure S10: Forest plot summarizing data from individual studies for HF hospitalization (main analysis), Figure S11: Forest plot of each treatment versus PLACEBO for HF hospitalization (main analysis), Figure S12: Cumulative probability rank plots for each treatment being the best with respect to HF hospitalization (main analysis), Figure S13: Forest plot of each treatment versus PLACEBO for primary endpoint (sensitivity analysis – NMA on HR estimates), Table S1: Risk of bias of individual studies by revised Cochrane Risk Assessment tool, Table S2: League table showing pooled HRs for primary and secondary endpoints (sensitivity analysis – NMA on HR estimates), Table S3: League table showing pooled risk ratios for primary and secondary endpoints (sensitivity analysis – NMA including phase 3 trials only).

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Abbreviations

ACEi	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor-neprilysin inhibitor
CI	confidence interval
CVD	cardiovascular death
CVD-HF	cardiovascular death or heart failure hospitalization
HF	heart failure
HFH	heart failure hospitalization
HR	hazard ratio
HFrEF	heart failure with reduced ejection fraction
MRA	mineralocorticoid receptor antagonist

References

1. Metra, M.; Teerlink, J.R. Heart failure. *Lancet* **2017**, *390*, 1981–1995. [CrossRef]
2. Ponikowski, P.; Voors, A.A.; Anker, S.D.; Bueno, H.; Cleland, J.G.F.; Coats, A.J.S.; Falk, V.; González-Juanatey, J.R.; Harjola, V.-P.; Jankowska, E.A.; et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2016**, *37*, 2129–2200. [CrossRef]
3. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef]
4. Mcmurray, J.J.V.; Packer, M.; Desai, A.S.; Gong, J.; Lefkowitz, M.P.; Rizkala, A.R.; Rouleau, J.L.; Shi, V.C.; Solomon, S.D.; Swedberg, K.; et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *N. Engl. J. Med.* **2014**, *371*, 993–1004. [CrossRef]
5. Yancy, C.W.; Jessup, M.; Bozkurt, B.; Butler, J.; Casey, D.E.; Colvin, M.M.; Drazner, M.H.; Filippatos, G.S.; Fonarow, G.C.; Givertz, M.M.; et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of Amer. *Circulation* **2017**, *136*, e137–e161. [CrossRef] [PubMed]
6. McMurray, J.J.V.; Solomon, S.D.; Inzucchi, S.E.; Køber, L.; Kosiborod, M.N.; Martinez, F.A.; Ponikowski, P.; Sabatine, M.S.; Anand, I.S.; Bělohlávek, J.; et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* **2019**, *381*, 1995–2008. [CrossRef]
7. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Pocock, S.J.; Carson, P.; Januzzi, J.; Verma, S.; Tsutsui, H.; Brueckmann, M.; et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N. Engl. J. Med.* **2020**, *383*, 1413–1424. [CrossRef] [PubMed]
8. Armstrong, P.W.; Pieske, B.; Anstrom, K.J.; Ezekowitz, J.; Hernandez, A.F.; Butler, J.; Lam, C.S.; Ponikowski, P.; Voors, A.A.; Jia, G.; et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* **2020**, *382*, 1883–1893. [CrossRef] [PubMed]
9. Teerlink, J.R.; Diaz, R.; Felker, G.M.; McMurray, J.J.V.; Metra, M.; Solomon, S.D.; Adams, K.F.; Anand, I.; Arias-Mendoza, A.; Biering-Sørensen, T.; et al. Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. *N. Engl. J. Med.* **2021**, *384*, 105–116. [CrossRef]

10. O'Meara, E.; McDonald, M.; Chan, M.; Ducharme, A.; Ezekowitz, J.A.; Giannetti, N.; Grzeslo, A.; Heckman, G.A.; Howlett, J.G.; Koshman, S.L.; et al. CCS/CHFS Heart Failure Guidelines: Clinical Trial Update on Functional Mitral Regurgitation, SGLT2 Inhibitors, ARNI in HFpEF, and Tafamidis in Amyloidosis. *Can. J. Cardiol.* **2020**, *36*, 159–169. [CrossRef]
11. Lombardi, C.M.; Cimino, G.; Pagnesi, M.; Dell'Aquila, A.; Tomasoni, D.; Ravera, A.; Inciardi, R.; Carubelli, V.; Vizzardi, E.; Nodari, S.; et al. Vericiguat for Heart Failure with Reduced Ejection Fraction. *Curr. Cardiol. Rep.* **2021**, *23*, 144. [CrossRef]
12. Hutton, B.; Salanti, G.; Caldwell, D.M.; Chaimani, A.; Schmid, C.H.; Cameron, C.; Ioannidis, J.P.A.; Straus, S.; Thorlund, K.; Jansen, J.P.; et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. *Ann. Intern. Med.* **2015**, *162*, 777–784. [CrossRef]
13. Cooper, N.J.; Peters, J.; Lai, M.C.; Juni, P.; Wandel, S.; Palmer, S.; Paulden, M.; Conti, S.; Welton, N.J.; Abrams, K.R.; et al. How Valuable are Multiple Treatment Comparison Methods in Evidence-Based Health-Care Evaluation? *Value Health* **2011**, *14*, 371–380. [CrossRef] [PubMed]
14. Caldwell, D.M.; Dias, S.; Welton, N.J. Extending Treatment Networks in Health Technology Assessment: How Far Should We Go? *Value Health* **2015**, *18*, 673–681. [CrossRef]
15. Higgins, J.P.T.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. (Eds.) Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (Updated February 2021); Cochrane: 2021. Available online: www.training.cochrane.org/handbook (accessed on 10 November 2021).
16. Lumley, T. Network meta-analysis for indirect treatment comparisons. *Stat. Med.* **2002**, *21*, 2313–2324. [CrossRef]
17. Caldwell, D.M.; Ades, T.; Higgins, J. Simultaneous comparison of multiple treatments: Combining direct and indirect evidence. *BMJ* **2005**, *331*, 897–900. [CrossRef] [PubMed]
18. Lu, G.; Ades, A.E. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat. Med.* **2004**, *23*, 3105–3124. [CrossRef] [PubMed]
19. Salanti, G.; Ades, A.E.; Ioannidis, J.P. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. *J. Clin. Epidemiol.* **2011**, *64*, 163–171. [CrossRef] [PubMed]
20. Kato, E.; Silverman, M.G.; Mosenzon, O.; Zelniker, T.A.; Cahn, A.; Furtado, R.H.M.; Kuder, J.; Murphy, S.A.; Bhatt, D.L.; Leiter, L.A.; et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. *Circulation* **2019**, *139*, 2528–2536. [CrossRef] [PubMed]
21. Nassif, M.E.; Windsor, S.L.; Tang, F.; Khariton, Y.; Husain, M.; Inzucchi, S.E.; Mc-Guire, D.K.; Pitt, B.; Scirica, B.M.; Austin, B.; et al. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients with Heart Failure With Reduced Ejection Fraction. *Circulation* **2019**, *140*, 1463–1476. [CrossRef] [PubMed]
22. Teerlink, J.R.; Felker, G.M.; McMurray, J.J.V.; Solomon, S.D.; Adams, K.F.; Cleland, J.G.F.; Ezekowitz, J.A.; Goudev, A.; Macdonald, P.; Metra, M.; et al. Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): A phase 2, pharmacokinetic, randomised, placebo-controlled trial. *Lancet* **2016**, *388*, 2895–2903. [CrossRef]
23. Gheorghiade, M.; Greene, S.J.; Butler, J.; Filippatos, G.; Lam, C.S.P.; Maggioni, A.P.; Ponikowski, P.; Shah, S.J.; Solomon, S.D.; Kraigher-Krainer, E.; et al. Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction: The SOCRATES-REDUCED Randomized Trial. *JAMA* **2015**, *314*, 2251–2262. [CrossRef] [PubMed]
24. Abraham, W.T.; Lindenfeld, J.; Ponikowski, P.; Agostoni, P.; Butler, J.; Desai, A.S.; Filippatos, G.; Gniot, J.; Fu, M.; Gullestad, L.; et al. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. *Eur. Heart J.* **2021**, *42*, 700–710. [CrossRef] [PubMed]
25. Jensen, J.; Omar, M.; Kistorp, C.; Poulsen, M.K.; Tuxen, C.; Gustafsson, I.; Køber, L.; Gustafsson, F.; Faber, J.; Fosbøl, E.L.; et al. Twelve weeks of treatment with empagliflozin in patients with heart failure and reduced ejection fraction: A double-blinded, randomized, and placebo-controlled trial. *Am. Heart J.* **2020**, *228*, 47–56. [CrossRef]
26. Lee, M.M.Y.; Brooksbank, K.J.M.; Wetherall, K.; Mangion, K.; Roditi, G.; Campbell, R.T.; Berry, C.; Chong, V.; Coyle, L.; Docherty, K.F.; et al. Effect of Empagliflozin on Left Ventricular Volumes in Patients with Type 2 Diabetes, or Prediabetes, and Heart Failure with Reduced Ejection Fraction (SUGAR-DM-HF). *Circulation* **2020**, *143*, 516–525. [CrossRef]
27. Santos-Gallego, C.G.; Vargas-Delgado, A.P.; Requena-Ibanez, J.A.; Garcia-Ropero, A.; Mancini, D.; Pinney, S.; Macaluso, F.; Sartori, S.; Roque, M.; Sabatel-Perez, F.; et al. Randomized Trial of Empagliflozin in Nondiabetic Patients with Heart Failure and Reduced Ejection Fraction. *J. Am. Coll. Cardiol.* **2021**, *77*, 243–255. [CrossRef]
28. McMurray, J.J.V.; Packer, M. How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction? A Redefinition of Evidence-Based Medicine. *Circulation* **2021**, *143*, 875–877. [CrossRef]
29. Vaduganathan, M.; Claggett, B.L.; Jhund, P.S.; Cunningham, J.W.; Ferreira, J.P.; Zannad, F.; Packer, M.; Fonarow, G.C.; McMurray, J.J.V.; Solomon, S.D. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: A comparative analysis of three randomised controlled trials. *Lancet* **2020**, *396*, 121–128. [CrossRef]
30. Seferović, P.M.; Coats, A.J.; Ponikowski, P.; Filippatos, G.; Huelsmann, M.; Jhund, P.S.; Polovina, M.M.; Komajda, M.; Seferović, J.; Sari, I.; et al. European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. *Eur. J. Heart Fail.* **2020**, *22*, 196–213. [CrossRef]

31. Zannad, F.; Ferreira, J.P.; Pocock, S.J.; Anker, S.D.; Butler, J.; Filippatos, G.; Brueckmann, M.; Ofstad, A.P.; Pfarr, E.; Jamal, W.; et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: A meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* **2020**, *396*, 819–829. [CrossRef]
32. Lopaschuk, G.D.; Verma, S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors. *JACC Basic Transl. Sci.* **2020**, *5*, 632–644. [CrossRef] [PubMed]
33. Seferović, P.M.; Fragasso, G.; Petrie, M.; Mullens, W.; Ferrari, R.; Thum, T.; Bauersachs, J.; Anker, S.D.; Ray, R.; Çavuşoğlu, Y.; et al. Sodium–glucose co-transporter 2 inhibitors in heart failure: Beyond glycaemic control. The position paper of the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **2020**, *22*, 1495–1503. [CrossRef] [PubMed]
34. Verma, S.; McMurray, J.J.V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: A state-of-the-art review. *Diabetologia* **2018**, *61*, 2108–2117. [CrossRef] [PubMed]
35. Petrie, M.C.; Verma, S.; Docherty, K.; Inzucchi, S.E.; Anand, I.; Belohlávek, J.; Böhm, M.; Chiang, C.-E.; Chopra, V.K.; De Boer, R.A.; et al. Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients with Heart Failure With and Without Diabetes. *JAMA J. Am. Med Assoc.* **2020**, *323*, 1353–1368. [CrossRef]
36. Omar, M.; Jensen, J.; Ali, M.; Frederiksen, P.H.; Kistorp, C.; Videbæk, L.; Poulsen, M.K.; Tuxen, C.D.; Möller, S.; Gustafsson, F.; et al. Associations of Empagliflozin with Left Ventricular Volumes, Mass, and Function in Patients With Heart Failure and Reduced Ejection Fraction. *JAMA Cardiol.* **2021**, *6*, 836. [CrossRef]
37. Nassif, M.E.; Qintar, M.; Windsor, S.L.; Jermyn, R.; Shavelle, D.M.; Tang, F.; Lamba, S.; Bhatt, K.; Brush, J.; Civitello, A.; et al. Empagliflozin Effects on Pulmonary Artery Pressure in Patients with Heart Failure. *Circulation* **2021**, *143*, 1673–1686. [CrossRef]
38. Jansen, J.P.; Fleurence, R.; Devine, B.; Itzler, R.; Barrett, A.; Hawkins, N.; Lee, K.; Boersma, C.; Annemans, L.; Cappelleri, J.C. Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. *Value Health* **2011**, *14*, 417–428. [CrossRef] [PubMed]

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