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Insights in heart failure and transplantation 2022

Edited by
Matteo Cameli and Emma Birks

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Insights in heart failure and transplantation: 2022

Topic editors

Matteo Cameli — University of Siena, Italy

Emma Birks — University of Kentucky, United States

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EDITED AND REVIEWED BY
Masanori Aikawa,
Harvard Medical School, United States

*CORRESPONDENCE
Matteo Cameli
matteo.cameli@yahoo.com
Federico Landra
f.landra@student.unisi.it

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Editorial: Insights in heart failure and transplantation: 2022

Matteo Cameli[1]*, Emma J. Birks[2] and Federico Landra[1]*

[1]Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy, [2]Division of Cardiovascular Medicine, University of Kentucky, Lexington, KY, United States

KEYWORDS

heart failure, heart transplant, cardiac surgery, donation, diabetes

Editorial on the Research Topic
Insights in heart failure and transplantation: 2022

Heart transplant: expanding the donor pool

Just over 50 years from the first Heart Transplant ever performed by Dr Christiaan Barnard in 1967 in Cape Town, heart transplantation has become the mainstay therapy for patients with advanced heart failure. Today, the main limitation of the applicability of such treatment is the well-recognized shortage of organ donors in the modern era. Not only are donor hearts lacking but also the number of patients requiring a heart transplant is incessantly increasing, due to population aging and improved survival of patients living with heart failure. As a result, between 5% and 10% of patients die while on waiting lists.

Even though bridge solutions to heart transplant are becoming more and more familiar with left ventricular assist devices, the problem overall remains largely unsolved. Different proposals have been advanced over the last decades trying to face this brain teaser. Some of them have already become reality in some countries, such as acceptance of hearts from HCV-positive donors, thanks to curative treatments now available, and protocols to widen the spectrum of donors. Particularly, the ADONHERS protocol, developed in Italy in Emilia-Romagna and Tuscany regions, aims at assessing the eligibility of the so-called marginal donors, namely those with >55 years or <55 years with multiple cardiovascular risk factors, employing stress-echocardiography to rule out subtle coronary artery disease (Cameli et al.).

Other promising solutions not widely used yet are *ex-vivo* heart perfusion platforms and donation after circulatory death, the latter coming as a revolutionary paradigm. Actually, the first heart transplant performed by Dr Barnard was from a donation after circulatory death and at the beginning of heart transplant history donation after circulatory death was common practice. Later, with the introduction of brain-death legislation, donation after brain death became the standard method, which also permitted to minimize organ hypoxia. Nowadays, heart transplant is routinely performed from brain-dead donors using cold storage, but from the early 2000 donation after circulatory death has raised renewed interest following successful experience from abdominal and pulmonary transplantations. Donation after circulatory death is performed in patients who do not fulfill brain death criteria but have no chance for recovery. The main difference with donation after brain death is the occurrence of warm ischemia after withdrawal of life support. Nowadays, substantial body of research has been done to limit the ischemic injury by different protocols. Recent clinical data suggest noninferiority compared to donations after brain death, making donation after circulatory death a potential solution to the shortage of organs.

Cardiac surgery after heart transplantation

The largest available dataset of heart transplant patients undergoing cardiac surgery from three different continents and sixty high-volume centers has been published in this Research Topic (Gökler et al.). One hundred ten patients have been collected and results show valvular disease to be the most common indication for cardiac surgery in this special population. Among them, tricuspid valve disease was the one most largely observed, mostly as a results of intense surveillance protocols requiring frequent endomyocardial biopsies to rule out rejection. Another relatively common indication was coronary artery vasculopathy, even though percutaneous coronary intervention is usually preferred in this case. Surgery in heart transplant patients may be challenging because of surgical reintervention and may be complicated by a higher rate of infections due to the immunosuppressive regimens. For these reasons, surgery after heart transplantation is rarely performed unless in highly selected cases. According to data from this register, the Authors conclude that surgery in this context is relatedly safe, with low in-hospital mortality and postoperative complications in carefully selected patients. Nonetheless, the overall in-hospital and 1-year mortality after surgery were 9.1% and 13.8%, respectively, which are not neglectable after all. Therefore, the surgical option is certainly feasible but not free from safety concerns and should be considered only in specific conditions with indubitable benefit as compared to the interventional alternative.

Diabetes in heart failure with preserved ejection fraction

The relevance of comorbidities in patients with heart failure with preserved ejection fraction is already largely recognized. Treatment of non-cardiovascular comorbidities has recently received a class I recommendation in the latest ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure for patients with a preserved ejection fraction. Diabetes is one of the major risk factors for cardiovascular diseases and specifically for heart failure. There is a close interplay between diabetes and heart failure which is not completely understood yet. Complex pathophysiological processes may eventually lead to heart failure in diabetic patients, also independently from the presence of ischemic heart disease or hypertension, which has led to the discussed definition of diabetic cardiomyopathy in the past years. Beside the hermetic etiological process, heart failure patients with concomitant type 2 diabetes experience a more relevant reduction in the functional capacity. Also, diabetes showed to be the most powerful predictor of limited exercise capacity in patients with heart failure with preserved ejection fraction (Berisha-Muharremi et al.).

Sodium-glucose co-transporter 2 inhibitors were originally thought to be used in diabetic patients, but they have unexpectedly seen a massive spread among the cardiological community because of their clear benefit in patients with heart failure. Initially their use has been assessed in patients with a reduced ejection fraction, but recent randomized controlled trails have shown significant prognostic benefit also for that orphan disease which is heart failure with preserved ejection fraction. Indeed, besides diuretics for fluid retention, no drugs have ever proved benefit in this subset of patients. Sodium-glucose co-transporter 2 inhibitors come as the first specific therapy, notably with a class I recommendation, for patients with a preserved ejection fraction. As such, they represent the only drugs with a class IA recommendation across the whole range of ejection fraction in patients with heart failure. A systematic review and meta-analysis from Treewaree et al. published in the present issue has proved their benefit in terms of improvement of cardiovascular outcomes and quality of life in patients with heart failure with preserved and mildly reduced ejection fraction, anticipating the proposed recommendations in the 2023 Focus Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.

Final considerations

Much evidence regarding both heart transplant and heart failure is continuously emerging, providing deeper insights into diseases' pathophysiology which eventually improve their clinical management. Aside from the papers highlighted herein, many other high-quality works have been published in this topic which well deserve a lecture. From biomarkers to echocardiography, from cardiac resynchronization therapy to left ventricular assist devices, this Research Topic covers a wide range of important subjects concerning heart failure.

Author contributions

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Diabetes Is the Strongest Predictor of Limited Exercise Capacity in Chronic Heart Failure and Preserved Ejection Fraction (HFpEF)

*Venera Berisha-Muharremi[1,2], Michael Y. Henein[3], Frank L. Dini[4], Edmond Haliti[1,5], Ibadete Bytyçi[3,5], Pranvera Ibrahimi[3,5], Afrim Poniku[1,5], Arlind Batalli[1,5], Rina Tafarshiku[1,2], Shpend Elezi[1,5] and Gani Bajraktari[1,3,5]**

[1] Medical Faculty, University of Prishtina, Prishtina, Kosovo, [2] Clinic of Endocrinology, University Clinical Centre of Kosova, Prishtina, Kosovo, [3] Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden, [4] Cardiovascular Diseases Unit 1, Cardiac, Thoracic and Vascular Department, University of Pisa, Pisa, Italy, [5] Clinic of Cardiology, University Clinical Centre of Kosova, Prishtina, Kosovo

Background and Aim: Type 2 diabetes mellitus (T2DM) is a known risk factor in patients with heart failure (HF), but its impact on phenotypic presentations remains unclear. This study aimed to prospectively examine the relationship between T2DM and functional exercise capacity, assessed by the 6-min walk test (6-MWT) in chronic HF.

Methods: We studied 344 chronic patients with HF (mean age 61 ± 10 years, 54% female) in whom clinical, biochemical, and anthropometric data were available and all patients underwent an echo-Doppler study and a 6-MWT on the same day. The 6-MWT distance divided the cohort into; Group I: those who managed ≤ 300 m and Group II: those who managed >300 m. Additionally, left ventricular (LV) ejection fraction (EF), estimated using the modified Simpson's method, classified patients into HF with preserved EF (HFpEF) and HF with reduced EF (HFrEF).

Results: The results showed that 111/344 (32%) patients had T2DM, who had a higher prevalence of arterial hypertension ($p = 0.004$), higher waist/hips ratio ($p = 0.041$), higher creatinine ($p = 0.008$) and urea ($p = 0.003$), lower hemoglobin ($p = 0.001$), and they achieved shorter 6-MWT distance ($p < 0.001$) compared with those with no T2DM. Patients with limited exercise (<300 m) had higher prevalence of T2DM ($p < 0.001$), arterial hypertension ($p = 0.004$), and atrial fibrillation ($p = 0.001$), higher waist/hips ratio ($p = 0.041$), higher glucose level ($p < 0.001$), lower hemoglobin ($p < 0.001$), larger left atrium (LA) ($p = 0.002$), lower lateral mitral annular plane systolic excursion (MAPSE) ($p = 0.032$), septal MAPSE ($p < 0.001$), and tricuspid annular plane systolic excursion (TAPSE) ($p < 0.001$), compared with those performing >300 m. In the cohort as a whole, multivariate analysis, T2DM ($p < 0.001$), low hemoglobin ($p = 0.008$), atrial fibrillation ($p = 0.014$), and reduced septal MAPSE ($p = 0.021$) independently predicted the limited 6-MWT distance.

In patients with HFpEF, diabetes [6.083 (2.613–14.160), $p < 0.001$], atrial fibrillation [6.092 (1.769–20.979), $p = 0.002$], and septal MAPSE [0.063 (0.027–0.184), $p = 0.002$], independently predicted the reduced 6-MWT, whereas hemoglobin

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Inna P. Gladysheva, University of Arizona, United States

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Markus Strauß, University Muenster, Germany
Giuseppe Caminiti, San Raffaele Pisana (IRCCS), Italy

***Correspondence:**
Gani Bajraktari
ganibajraktari@gmail.com

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[0.786 (0.624–0.998), $p = 0.049$] and TAPSE [0.462 (0.214–0.988), $p = 0.041$] predicted it in patients with HFrEF.

Conclusion: Predictors of exercise intolerance in patients with chronic HF differ according to LV systolic function, demonstrated as EF. T2DM seems the most powerful predictor of limited exercise capacity in patients with HFpEF.

Keywords: diabetes mellitus, heart failure, 6-min walk test, exercise capacity, Doppler echocardiography

INTRODUCTION

Heart failure (HF) has become a major public health problem in the past decades (1, 2), and it remains a clinical syndrome with poor prognosis in both patients with reduced ejection fraction (HFrEF) and preserved (HFpEF) (3–6). In those patients, exercise intolerance is one of the most important clinical manifestations and has been shown to be a strong predictor of all-cause mortality (7). Assessment of exercise capacity using the 6-min walk test (6-MWT) has been used as a simple, reproducible, and inexpensive method (8, 9). Indeed, 6-MWT has been shown to have a good correlation with objective measures of exercise tolerance, such as exercise duration and oxygen uptake at peak exercise (10). Type 2 diabetes mellitus (T2DM) is one of the most frequently seen risk factors and comorbidities in patients with congestive heart failure (CHF) (11, 12), and it adversely affects outcomes in these patients (13, 14). The impact of T2DM on different phenotypic presentations of HF, especially in patients with HF and preserved ejection fraction (HFpEF), remains unclear (15, 16). Impaired energy metabolism and muscle fiber-type switches (17, 18) found in T2DM, similar to what is seen in CHF, have been previously shown. Accordingly, it can be assumed that T2DM may further reduce the aerobic capacity of patients with HF as a potential mechanism for the known limited exercise tolerance, as has been previously suggested (16, 19, 20). However, the evidence regarding the direct relationship between 6-MWT and phenotypic type of HF, reduced EF (HFrEF), and preserved (HFpEF), remains lacking. In this study, we aimed to investigate the direct impact of T2DM on the reduced 6-MWT distance in patients with CHF due to various presentations, HFrEF and HFpEF.

METHODS

Study Population

We studied 344 (mean age 61 ± 10 years, 54% female) patients with the clinical diagnosis of symptomatic CHF, and New York Heart Association (NYHA) functional class I–III, secondary to ischemic or non-ischemic etiology, based on the current definitions (21). Patients were referred to the Clinic of Cardiology, University Clinical Centre of Kosovo, between May 2013 and September 2017. At the time of the study, all patients were on optimum HF medications, optimized at least 2 weeks prior to enrollment. Based on patient's symptoms and renal function: 85% were receiving ACE inhibitors or ARB, 76% beta-blockers, 11% calcium-blockers, 8% digoxin, 54% spironolactone, and 58% diuretics. Of the enrolled patients, 45% had ischemic etiology, 38% hypertensive, and 17% had unknown etiology. Furthermore, 17% of the included patients were in atrial fibrillation. Patients with clinical evidence for cardiac decompensation (NYHA class IV, those with peripheral edema), limited physical activity due to factors other than cardiac symptoms (e.g., arthritis), severe mitral regurgitation, more than mild renal failure (in patients with raised creatinine, the glomerular filtration rate (GFR) was measured and patients with values <60 ml/min/1.73 m^2 were excluded), chronic obstructive pulmonary disease or those with recent acute coronary syndrome, stroke, or anemia were excluded from the study. Type 2 DM was defined as a fasting blood glucose level ≥7.0 mmol/L, a glycohemoglobin A1c (HbA1c) level ≥6.5%, and/or the need for oral hypoglycemic medications or insulin. All patients gave written informed consent to participate in the study, which was approved by the local Ethics Committee.

Data Collection

Detailed history and clinical assessment were obtained in all patients, in whom routine biochemical tests were also performed, such as hemoglobin, lipid profile, blood glucose level, and kidney function tests. Estimated body mass index (BMI) was calculated from weight and height measurements. Body surface area (BSA) was calculated using the Du Bois formula: BSA (m^2) = 0.007184 × (height in cm) $^{0.725}$ × (weight in kg)$^{0.425}$ (22). Waist and hip measurements were also made and a waist/hips ratio was calculated.

Echocardiographic Examination

A single operator performed all echocardiographic examinations using a Philips Intelligent E-33 system with a multi-frequency transducer, and harmonic imaging as appropriate. Images were obtained with the patient in the left lateral decubitus position and during quiet expiration. Measurements of interventricular septal thickness, posterior wall thickness, and LV dimensions were made at end-diastole and end-systole, as recommended by the American Society of Echocardiography (23).

Left ventricular volumes and EF were calculated from the apical 2 and 4 chamber views using the modified Simpson's method. Ventricular long axis motion was studied by placing the M-mode cursor at the lateral and septal angles of the mitral annulus and the lateral angle of the tricuspid annulus. The total amplitude of ventricular long-axis motion was measured as previously described (24) from peak inward to peak outward points. The indices were registered as lateral and septal mitral annular plane systolic excursion (MAPSE) and tricuspid annular plane systolic excursion (TAPSE). LV and right ventricular

(RV) long-axis myocardial velocities were also studied using the Doppler myocardial imaging technique. From the apical 4-chamber view, longitudinal velocities were recorded with the sample volume placed at the basal part of LV lateral and septal segments as well as the RV free wall. Systolic (s′) as well as early and late (e′ and a′) diastolic myocardial velocities were measured with the gain optimally adjusted. A mean value of lateral and septal LV velocities was calculated. The left atrial diameter was measured from aortic root recordings with the M-mode cursor positioned at the level of the aortic valve leaflets.

Diastolic LV and RV functions were assessed from filling velocities using spectral pulsed wave Doppler with the sample volume positioned at the tips of the mitral and tricuspid valve leaflets, respectively, during a brief apnea. Peak LV and RV early (E wave) and late (A wave) diastolic velocities were measured and E/A ratios were calculated. E wave deceleration time (DT) was also measured from the peak E wave to the end of its deceleration. The E/e′ ratio was calculated from the trans-mitral E wave and mean lateral and septal segments myocardial e′ wave velocities. The LV filling pattern was considered "restrictive" when the E/A ratio was >2.0, the E wave deceleration time <140 ms, and the left atrium (LA) dilated >40 mm in transverse diameter (25). Total LV filling time was measured from the onset of the E wave to the end of the A wave and ejection time from the onset to the end of the aortic Doppler flow velocity.

Mitral regurgitation severity was assessed by color and continuous wave Doppler and was graded as mild, moderate, or severe according to the relative jet area to that of the LA as well as the flow velocity profile, in line with the recommendations of the American and European Society of Echocardiography (26, 27). Similarly, tricuspid regurgitation was assessed by color Doppler and continuous-wave Doppler. Retrograde trans-tricuspid pressure drop >35 mmHg was taken as evidence for pulmonary hypertension (27, 28). All M-mode and Doppler

TABLE 1 | Clinical data in diabetic and non-diabetic patients with chronic heart failure (HF).

Variable	Non-diabetic (n = 233)	Diabetic (n =111)	p value
Age (years)	61 ±9	62 ±8	0.213
Female (%)	55	53	0.817
Smoking (%)	28	24	0.517
Arterial hypertension (%)	78	62	0.004
Waist/hips ratio	0.95 ±0.05	0.97 ±0.05	0.041
Body-mass index (kg/m^2)	28.2 ±4.2	29.1 ±5	0.094
Body-surface area (m^2)	1.88 ±1.6	1.89 ±1.7	0.551
Fasting glucose (mmol/L)	5.7 ±1.3	9.4 ±3.6	< 0.001
Total cholesterol (mmol/L)	4.7 ±1.2	4.6 ±1.3	0.805
Triglycerides (mmol/L)	1.6 ±0.8	1.8 ±0.9	0.129
Blood urea nitrogen(mmol/l)	8.3 ±4.2	10 ±4.8	0.003
Creatinine (μmol/L)	95 ±34	108 ±51	0.008
Hemoglobin (g/dl)	12.7 ±1.6	12.0 ±2.0	0.001
6-minute walk distance (m)	307 ±111	258 ±109	< 0.001
Baseline heart rate (beats/min)	77 ±14	81 ±12	0.808

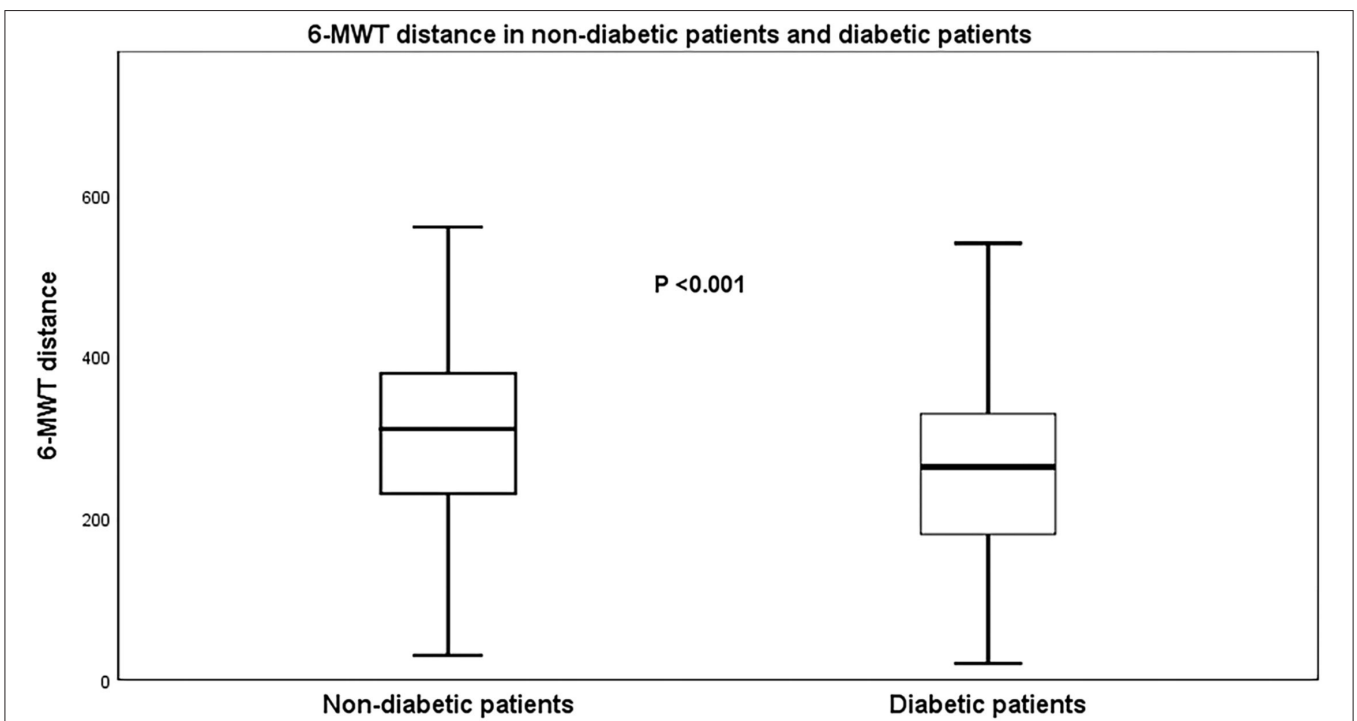

FIGURE 1 | A 6-min walk test (6-MWT) distance in non-diabetic and diabetic patients with heart failure (HF).

recordings were made at a fast speed of 100 mm/s with a superimposed ECG (lead II).

6-Min Walk Test

Within 24 h of the echocardiographic examination, a 6-MWT was performed on a level hallway surface, administered by a specialized nurse who was blinded to the results of the echocardiogram. According to the method of Gyatt et al. (29), patients were informed of the purpose and protocol of the 6 MWT, which was conducted in a standardized fashion while patients were on their regular medications (30, 31). A 15-m flat, obstacle-free corridor was used and patients were instructed to walk as far as they can, turning 180 degrees after they have reached the end of the corridor, during the allocated time of 6 min. Patients walked unaccompanied so as not to influence their walking speed. At the end of the 6 min, the supervising nurse measured the total distance walked by the patient.

Statistical Analysis

Data are presented as mean ± SD or proportions (% of patients). Continuous data were compared with two-tailed unpaired Student's *t*-test and discrete data with a chi-square test. Correlations were tested with Pearson's coefficients. Predictors of the 6MWT distance were identified with univariate analysis, and multivariate logistic regression was performed using the step-wise method. A significant difference was defined as $p < 0.05$ (two-tailed). Patients were divided according to their ability to walk >300 m into good and limited exercise performance groups, and were compared using unpaired Student's *t*-test. Additionally, patients with HFpEF (LVEF ≥ 40%) were compared with those with HFrEF (LVEF < 40%) using the unpaired *t*-test. Due to the possible interaction of age with echocardiographic parameters, we used the general linear model to compare age-adjusted mean values of echocardiographic indices between groups.

TABLE 2 | Echocardiographic data in diabetic and non-diabetic patients with chronic HF.

Variable	Non-diabetic (n = 233)	Diabetic (n =111)	*P* value
Ejection fraction (%)	47 ±16	45 ±16	0.245
IVSd/BSA (cm)	0.6 ±0.1	0.6 ±0.1	0.388
Left atrium/BSA (cm)	2.4 ±0.5	2.4 ±0.4	0.952
LV EDD/BSA (cm)	3.2 ±0.8	3.1 ±0.7	0.135
LV ESD/BSA (cm)	2.4 ±0.7	2.4 ±0.6	0.740
Lateral MAPSE (cm)	1.2 ±0.4	1.2 ±0.3	0.955
Septal MAPSE (cm)	1.0 ±0.3	1.0 ±0.4	0.848
TAPSE (cm)	2.2 ±0.5	2.1 ±0.6	0.353
LV posterior wall/BSA (cm)	0.5 ±0.1	0.5 ±0.1	0.704
E wave (mm)	69 ±25	70 ±31	0.286
E/A ratio	1.2 ±0.8	1.2 ±0.9	0.804
Filling time (ms)	379 ±112	347 ±94	0.076
IVRT (ms)	103 ±27	117 ±36	0.068
E/e′ ratio	11.5 ±7.2	11 ±5.9	0.487
Lateral e′ (cm/s)	6.5 ±2.8	6.5 ±2.6	0.851
Lateral a′(cm/s)	7.5 ±3.2	7.6 ±3.1	0.876
Lateral s′ (cm/s)	5.6 ±1.9	5.7 ±1.7	0.088
Septal e′ (cm/s)	5.6 ±2.3	5.5 ±2.3	0.777
Septal a′ (cm/s)	7.5 ±2.5	7.7 ±3.6	0.586
Septal s′ (cm/s)	4.8 ±1.4	5.1 ±1.6	0.203
Right e′ (cm/s)	9.2 ±3.4	9.1 ±3.4	0.892
Right a′ (cm/s)	12.8 ±4.5	13.4 ±4.3	0.285
Right s′ (cm/s)	9.1 ±3.0	9.5 ±3.5	0.494

LV, left ventricle; EDD, end-diastolic dimension; ESD, end-systolic dimension; IVSd, interventricular septum in diastole; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; A, atrial diastolic velocity; E, early diastolic filling velocity; e′, early diastolic myocardial velocity; s′, systolic myocardial velocity.

RESULTS

Patients With HF and T2DM vs. Patients With HF but No T2DM

Patients with HF and T2DM had a higher prevalence of arterial hypertension ($p = 0.004$), higher waist/hips ratio ($p = 0.041$), higher creatinine ($p = 0.008$), urea ($p = 0.003$), and lower hemoglobin ($p = 0.001$), and completed the 6-MWT for a shorter distance (<0.001) than those with HF but no T2DM (**Table 1**; **Figure 1**). The rest of the clinical indices and echocardiographic parameters were not different between groups (**Table 2**).

Patients With Good vs. Limited 6 MWT Performance

Patients with limited exercise capacity had a higher prevalence of T2DM ($p < 0.001$), arterial hypertension ($p = 0.004$), and atrial fibrillation ($p = 0.001$), a higher waist/hips ratio ($p = 0.041$), a level of fasting glucose ($p < 0.001$), and a lower level of hemoglobin ($p < 0.001$), compared with those with good exercise capacity. In addition, they had larger LA ($p = 0.002$), reduced lateral MAPSE ($p = 0.032$), septal MAPSE ($p < 0.001$), and TAPSE ($p < 0.001$), compared to patients with good 6-MWT performance. The rest of the clinical and echocardiographic indices were not different between subgroups (**Tables 3, 4**).

Predictors of Limited 6-MWT Distance in All Patients

In the univariate analysis model, T2DM ($p < 0.001$), low hemoglobin level ($p < 0.001$), atrial fibrillation ($p < 0.001$), and NYHA class ($p = 0.008$) predicted limited 6-MWT distance, as did enlarged LA ($p = 0.003$), increased E wave velocity ($p = 0.019$), raised E/e′ ($p = 0.028$), reduced lateral MAPSE ($p = 0.033$) septal MAPSE ($p < 0.001$), TAPSE ($p < 0.001$) and septal a′ and s′ ($p = 0.032$ and $p = 0.041$, respectively), and increased E/e′ ($p = 0.028$). In multivariate analysis [odds ratio (*OR*) 95% confidence interval (*CI*)], only diabetes [3.366 (1.907–5.939), $p < 0.001$], low hemoglobin [0.847 (0.729–0.985), $p = 0.031$], atrial fibrillation [2.684 (1.273–5.657), $p = 0.009$], and reduced septal MAPSE [0.308 (0.125–0.759), $p = 0.010$], independently predicted the limited 6-MWT distance (**Table 5**).

TABLE 3 | Clinical and biochemical data in patients with limited exercise vs. good exercise capacity.

Variable	6-MWT > 300 m (n = 168)	6-MWT ≤ 300 m (n =176)	p value
Age (years)	61 ±8	62 ±9	0.095
Female (%)	45	47	0.817
Smoking (%)	30	24	0.517
Diabetes (%)	21	43	< 0.001
Arterial hypertension (%)	59	76	0.004
Atrial fibrillation (%)	10	24	0.001
Waist/hips ratio	0.96 ±0.08	0.96 ±0.08	0.041
Body-mass index (kg/m^2)	28.6 ±4	28.2 ±5	0.069
Fasting glucose (mmol/L)	6.5 ±2.5	7.5 ±3.5	< 0.001
Total cholesterol (mmol/L)	4.8 ±1.2	4.5 ±1.2	0.805
Triglycerides (mmol/L)	1.7 ±0.7	1.6 ±1.0	0.129
Creatinine (μmol/L)	99 ±50	99 ±31	0.975
Urea	8.5 ±4.5	9.3 ±4.5	0.147
Hemoglobin (g/dl)	12.9 ±1.6	12.1 ±1.8	< 0.001
Baseline HR (beats/min)	81 ±15	76 ±12	0.808

6-MWT, 6-min walk test.

TABLE 4 | Echocardiographic data in patients with limited exercise vs. good exercise capacity (6-MWT distance).

Variable	6-MWT > 300 m (n = 168)	6-MWT ≤ 300 m (n =176)	p value
Ejection fraction (%)	47 ±17	45 ±16	0.245
IVSd/BSA (cm/m^2)	0.6 ±0.1	0.6 ±0.1	0.407
Left atrium/BSA (cm/m^2)	2.3 ±0.5	2.5 ±0.5	0.002
LV EDD/BSA (cm/m^2)	3.1 ±0.6	3.2 ±0.6	0.065
LV ESD/BSA (cm/m^2)	2.3 ±0.8	2.5 ±0.7	0.090
Lateral MAPSE (cm)	1.2 ±0.4	1.1 ±0.3	0.032
Septal MAPSE (cm)	1.1 ±0.3	0.9 ±0.4	< 0.001
TAPSE (cm)	2.2 ±0.5	2.0 ±0.6	< 0.001
LV posterior wall (cm/m^2)	0.5 ±0.2	0.5 ±0.1	0.584
E wave (mm)	63 ±23	66 ±26	0.286
E/A ratio	1.2 ±0.8	1.2 ±0.9	0.804
DT of E wave (ms)	167 ±53	160 ±55	0.076
E/e′ ratio	10.8 ±5.4	11.9 ±8.0	0.487
Lateral e′ (cm/s)	6.5 ±2.6	6.4 ±2.8	0.851
Lateral a′(cm/s)	7.8 ±3.3	7.3 ±3.1	0.876
Lateral s′ (cm/s)	5.7 ±1.9	5.5 ±1.8	0.088
Septal e′ (cm/s)	5.5 ±2.1	5.5 ±2.4	0.777
Septal a′ (cm/s)	7.7 ±2.5	7.3 ±3.1	0.586
Septal s′ (cm/s)	4.8 ±1.4	4.8 ±1.6	0.203
Right e′ (cm/s)	9.1 ±3.4	9.0 ±3.7	0.892
Right a′ (cm/s)	12.7 ±4.0	13.3 ±4.8	0.285
Right s′ (cm/s)	9.2 ±2.8	9.3 ±3.5	0.494

6-MWT, 6-min walk test; LV, left ventricle; EDD, end-diastolic dimension; ESD, end-systolic dimension; IVSd, interventricular septum in diastole; BSA, body-surface area; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; A, atrial diastolic velocity; E, early diastolic filling velocity; e′, early diastolic myocardial velocity; s′, systolic myocardial velocity; DT, deceleration time.

Predictors of Limited 6 MWT Distance in HFpEF

Type 2 diabetes mellitus ($p < 0.001$), low hemoglobin ($p = 0.022$), atrial fibrillation ($p = 0.020$), NYHA class ($p = 0.005$), LA ($p = 0.03$), septal MAPSE ($p < 0.001$), and lateral MAPSE ($p = 0.044$) predicted limited 6-MWT distance in HFpEF. In multivariate analysis [*OR* 95% *CI*], only diabetes [6.083 (2.613–14.160), $p < 0.001$], atrial fibrillation [6.092 (1.769–20.979), $p = 0.004$], and septal MAPSE [0.063 (0.027–0.184), $p = 0.002$], independently predicted the limited 6-MWT distance in HFpEF (**Tables 6, 7**).

Predictors of Limited 6 MWT Distance in Patients With HFrEF

In univariate analysis, low hemoglobin ($p = 0.001$), reduced TAPSE ($p = 0.001$), and enlarged LA ($p = 0.043$) predicted limited 6-MWT distance in patients with HFrEF. In multivariate analysis, only low hemoglobin [0.786 (0.624–0.998), $p = 0.049$] and reduced TAPSE [0.462 (0.214–0.988), $p = 0.041$] independently predicted the limited 6-MWT distance in HFrEF (**Tables 6, 7**).

DISCUSSION

Findings

Heart failure patients with limited exercise capacity had a higher prevalence of T2DM, arterial hypertension, and atrial fibrillation, compared with those with good exercise capacity. They also had a higher waist/hips ratio, lower hemoglobin, a larger LA, and compromised LV and RV long-axis systolic function. Patients with combined HF and T2DM had a higher prevalence of arterial hypertension, a higher waist/hips ratio, more compromised renal function, lower hemoglobin, and a shorter 6-MWT distance, compared with those with HF with no T2DM. Multivariate analysis showed diabetes, lowered hemoglobin level, atrial fibrillation, and reduced LV long-axis function as independent predictors of limited exercise capacity in patients with HF.

While the above common knowledge on the relationship between atherosclerosis risk factors and HF is confirmed in our patients, their impact on predicting exercise capacity differed significantly according to LVEF. In patients with reduced LVEF, low hemoglobin and compromised RV long-axis systolic function were the two independent predictors of exercise capacity. However, in patients with LV preserved EF, T2DM, low hemoglobin level, atrial fibrillation, higher NYHA class, and compromised LV long-axis systolic function were the respective predictors.

Data Interpretation

Exercise intolerance is the main symptom in patients with HF, regardless of LVEF (32, 33). In these patients, different echocardiographic indices have been shown as important predictors of exercise capacity, particularly raised LV filling pressures (34–42). Such a relationship can be explained on the basis of reduced stroke volume and pulmonary venous

TABLE 5 | Predictors of limited exercise in All patients with HF.

Variable	OR	(CI 95%)	*p* value
Univariate predictors			
Age	1.021	(0.996–1.047)	0.098
Diabetes mellitus	2.723	(1.694–4.376)	< 0.001
NYHA class	1.472	(1.107–1.956)	0.008
Basal heart rate	0.973	(0.947–1.001)	0.055
Smoking	0.833	(0.517–1.344)	0.455
Gender	1.255	(0.801–1.874)	0.349
Left atrium/BSA	2.026	(1.274–3.220)	0.003
E wave	1.023	(1.004–1.043)	0.019
E/A	1.113	(0.862–1.437)	0.410
Hemoglobin	0.770	(0.675–0.878)	< 0.001
LV EDD/BSA	1.381	(0.979–1.950)	0.066
LV ESD/BSA	1.289	(0.961–1.370)	0.090
LV EF	0.995	(0.983–1.009)	0.496
Lateral MAPSE	0.500	(0.264–0.944)	0.033
Septal MAPSE	0.197	(0.088–0.439)	< 0.001
TAPSE	0.426	(0.276–0.657)	< 0.001
Lateral e′	0.995	(0.915–1.081)	0.900
Lateral a′	0.944	(0.875–1.081)	0.135
Lateral s′	0.940	(0.829–1.066)	0.332
Septal e′	1.009	(0.901–1.130)	0.874
Septal a′	0.949	(0.861–1.046)	0.289
Septal s′	1.007	(0.849–1.95)	0.934
BMI	0.981	(0.937–1.027)	0.406
Atrial fibrillation	2.784	(1.513–5.121)	0.001
Arterial hypertension	0.877	(0.563–1.365)	0.561
Creatinine	1.000	(0.994–1.006)	0.975
E/e′	1.092	(1.009–1.181)	0.028
Septal a′	0.786	(0.631–0.979)	0.032
Septal s′	0.661	(0.444–0.984)	0.041
Multivariate predictors			
Type 2 diabetes mellitus	3.366	(1.907–5.939)	< 0.001
Hemoglobina	0.847	(0.729–0.985)	0.031
Atrial fibrillation	2.684	(1.273–5.657)	0.009
Septal MAPSE	0.308	(0.125–0.759)	0.010
TAPSE	0.998	(0.598–1.679)	0.994
Left atrium diameter/BSA	1.771	(0.970–3.108)	0.064
NYHA class	1.167	(0.821–1.658)	0.389

LV, left ventricle; EDD, end-diastolic dimension; ESD, end-systolic dimension; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; A, atrial diastolic velocity; E, early diastolic filling velocity; e′, early diastolic myocardial velocity; s′, systolic myocardial velocity; DT, deceleration time; BSA, body-surface area; NYHA, New York Heart Association.

TABLE 6 | Univariate predictors of limited exercise capacity (6-MWT < 300 m) in patients with non-reduced and those with reduced left ventricular ejection fraction (LVEF).

Variable	HF Patients with LVEF ≥ 40%			HF Patients with LVEF < 40%		
	OR	(CI 95%)	*p value*	OR	(CI 95%)	*p value*
Age	1.027	(0.989–1.066)	0.171	1.017	(0.983–1.051)	0.327
Gender	1.158	(0.627–2.138)	0.639	1.391	(0.747–2.593)	0.299
Basal heart rate	0.974	(0.915–1.036)	0.397	0.976	(0.946–1.007)	0.132
Duhani	0.865	(0.410–1.826)	0.703	0.772	(0.407–1.467)	0.430
Arterial hypertension	0.796	(0.397–1.554)	0.488	0.990	(0.536–1.830)	0.976
BMI	0.978	(0.925–1.033)	0.423	0.989	(0.910–1.074)	0.784
BSA	0.156	(0.024–1.017)	0.052	0.421	(0.071–2.516)	0.343
NYHA class	1.892	(1.202–2.783)	0.005	1.207	(0.779–1.870)	0.400
Atrial fibrillation	3.727	(1.527–8.837)	0.020	2.029	(0.852–4.832)	0.110
Diabetes	3.929	(2.009–7.682)	< 0.001	1.840	(0.935–3.622)	0.078
Creatinine	1.011	(0.997–1.026)	0.128	0.997	(0.990–1.004)	0.411
Hemoglobin	0.811	(0.679–0.970)	0.022	0.726	(0.599–0.882)	0.001
Left atrium dimension/BSA	2.041	(1.070–3.893)	0.030	2.127	(1.025–4.415)	0.043
LV EDD/BSA	1.719	(0.835–3.538)	0.142	1.434	(0.832–2.471)	0.195
LV ESD/BSA	1.823	(0.863–3.851)	0.116	1.466	(0.841–2.553)	0.177
LV EF	0.986	(0.957–1.016)	0.350	1.008	(0.966–1.051)	0.722
E wave	1.008	(0.995–1.021)	0.249	1.004	(0.992–1.016)	0.508
E/A ratio	0.926	(0.547–1.566)	0.774	1.166	(0.849–1.601)	0.343
Lateral MAPSE	0.376	(0.145–0.975)	0.044	0.772	(0.301–1.980)	0.591
Septal MAPSE	0.092	(0.027–0.314)	< 0.001	0.432	(0.128–1.464)	0.178
TAPSE	0.578	(0.306–1.091)	0.091	0.309	(0.157–0.610)	0.001
Lateral e′	0.972	(0.865–1.092)	0.627	1.069	(0.941–1.214)	0.304
Lateral a′	0.897	(0.802–1.003)	0.058	1.013	(0.907–1.130)	0.824
Lateral s′	0.991	(0.809–1.214)	0.933	0.929	(0.791–1.092)	0.374
Septal e′	1.018	(0.887–1.168)	0.801	1.097	(0.874–1.377)	0.426
Septal a′	0.984	(0.874–1.109)	0.792	0.924	(0.780–1.093)	0.356
Septal s′	1.049	(0.823–1.338)	0.697	1.031	(0.797–1.332)	0.818
E/e′	1.027	(0.974–1.083)	0.990	1.019	(0.972–1.068)	0.430

BMI, body-mass index; BSA, body-surface area; LV, left ventricle; EDD, end-diastolic dimension; ESD, end-systolic dimension; IVSd, interventricular septum in diastole; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; A, atrial diastolic velocity; E, early diastolic filling velocity; e′, early diastolic myocardial velocity; s′, systolic myocardial velocity.

hypertension (43). This is, however, only one explanation of exercise intolerance in HF. Our results provide a clearer image as to the potential mechanisms involved in reduced exercise capacity in patients with HF, when they are classified according to EF. HF with reduced EF is commonly caused by ischemic myopathy that involves both ventricles with their impact on cardiac output and kidney function (44). Indeed, our findings confirm that, having shown that low hemoglobin (45) and compromised RV systolic function (46) are the two main predictors of limited exercise. However, in patients with preserved LVEF, the scenario differs having shown that T2DM and atrial fibrillation are two additional predictors of exercise capacity. Atrial fibrillation is a very common finding in HFpEF. Most such patients are known to have long-standing hypertensive LV disease and left atrial enlargement with its known complications (47). Atrial fibrillation loses the atrial systolic filling component of the LV, hence compromising

TABLE 7 | Multivariate predictors of limited exercise capacity (6-MWT < 300 m) in patients with non-reduced and those with reduced LVEF.

Variable	HF patients with LVEF ≥ 40%			HF patients with LVEF < 40%		
	OR	(CI 95%)	*p value*	OR	(CI 95%)	*p value*
Diabetes	6.083	(2.613–14.160)	<0.001	1.587	(0.656–3.732)	0.342
Hemoglobin	0.870	(0.693–1.092)	0.230	0.786	(0.624–0.998)	0.049
Atrial fibrillation	6.092	(1.769–20.979)	0.004	1.312	(0.474–3.594)	0.622
Septal MAPSE	0.063	(0.027–0.184)	0.002	0.892	(0.218–3.497)	0.812
TAPSE	0.779	(0.344–1.766)	0.550	0.462	(0.214–0.988)	0.041
Left atrium diameter/BSA	1.198	(0.498–2.883)	0.687	1.352	(0.854–2.116)	0.246
NYHA class	1.034	(0.597–1.791)	0.905	1.184	(0.745–1.998)	0.592

6-MWT, 6-min walk test; MAPSE, mitral annular plane systolic excursion; TAPSE, tricuspid annular plane systolic excursion; BMI, body-mass index; BSA, body-surface area; NYHA, New York Heart Association.

overall stroke volume with its impact on exercise capacity (48). T2DM, on the other hand, enhances the atherosclerosis pathology at both main coronary arteries level as well as microcirculation with resulting subendocardial fibrosis and LV cavity stiffness, raising the filling pressures and eventually causing atrial fibrillation (49). Through the same atherosclerotic pathophysiology, T2DM also impacts the peripheral circulation and, over the years, causes peripheral neuropathy. Although our analysis identified individual independent predictors of the limited exercise capacity in patients with HF, it must be mentioned that the pathomechanisms are closely related, particularly T2DM and atrial fibrillation, and their impact on LV myocardial function with its consequence on left atrial enlargement, atrial fibrillation, and its complications.

Limitations

The main limitation of our study is that we did not assess the response of echocardiographic measurements to exercise, at the time of symptoms development. However, the main objective of the study was to identify predictors of ordinary walking exercise limitations rather than a heavy exercise in patients with HF. The lack of left atrial pressure invasive measurements is another limitation, but the study was based on conventional Doppler measurements, which have been shown to be reproducible and correlate closely with invasive pressure measurements (50). We did not have myocardial deformation measurements in our cohort, which might have altered the results.

Clinical Implications

Type 2 diabetes mellitus has a significant impact on exercise intolerance in patients with HFpEFEF. While the cardiac pump function looks better preserved than in patients with HFrEF, the multi-system complications associated with diabetes should be acknowledged, particularly myocardial microcirculation and peripheral arterial disease as well as peripheral neuropathic complications.

CONCLUSION

Predictors of exercise intolerance in patients with chronic HF differ according to LV systolic function, judged as EF. T2DM seems the most powerful predictor of limited exercise capacity in patients with HFpEF.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee, Medical Faculty, University of Prishtina, Prishtina, Kosovo. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VB-H, MH, SE, and GB contributed to conception and design of the study. IB, PI, EH, AP, RT, and AB organized the database. GB, PI, and IB performed the statistical analysis. VB-M wrote the first draft of the manuscript. GB, IB, MH, and SE wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Invasive Hemodynamic Assessment and Procedural Success of Transcatheter Tricuspid Valve Repair—Important Factors for Right Ventricular Remodeling and Outcome

Varius Dannenberg[1], Matthias Koschutnik[1], Carolina Donà[1], Christian Nitsche[1], Katharina Mascherbauer[1], Gregor Heitzinger[1], Kseniya Halavina[1], Andreas A. Kammerlander[1], Georg Spinka[1], Max-Paul Winter[1], Martin Andreas[2], Markus Mach[2], Matthias Schneider[3,4], Anna Bartunek[5], Philipp E. Bartko[1], Christian Hengstenberg[1], Julia Mascherbauer[1,6] and Georg Goliasch[1]

[1] Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria, [2] Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria, [3] Department of Internal Medicine and Cardiology, Charité – Universitätsmedizin Berlin (Campus Virchow-Klinikum), Berlin, Germany, [4] Department of Cardiology, German Heart Center Berlin, Berlin, Germany, [5] Department of Anesthesia and Intensive Care, Medical University of Vienna, Vienna, Austria, [6] Department of Internal Medicine 3, University Hospital St. Pölten, Karl Landsteiner University of Health Sciences, Krems, Austria

Introduction: Severe tricuspid regurgitation (TR) is a common condition promoting right heart failure and is associated with a poor long-term prognosis. Transcatheter tricuspid valve repair (TTVR) emerged as a low-risk alternative to surgical repair techniques. However, patient selection remains controversial, particularly regarding the benefits of TTVR in patients with pulmonary hypertension (PH).

Aim: We aimed to investigate the impact of preprocedural invasive hemodynamic assessment and procedural success on right ventricular (RV) remodeling and outcome.

Methods: All patients undergoing TTVR with a TR reduction of ≥1 grade without precapillary or combined PH [mean pulmonary artery pressure (mPAP) ≥25 mmHg, mean pulmonary artery Wedge pressure ≤15 mmHg, pulmonary vascular resistance ≥3 Wood units] were assigned to the responder group. All patients with a TR reduction of ≥1 grade and precapillary or combined PH were classified as non-responders. Patients with a TR reduction ≥2 grade were directly classified as responders, and patients without TR reduction were directly assigned as non-responders.

Results: A total of 107 patients were enrolled, 75 were classified as responders and 32 as non-responders. We observed evidence of significant RV reverse remodeling in responders with a decrease in RV diameters (−2.9 mm, $p = 0.001$) at a mean follow-up of 229 days (±219 SD) after TTVR. RV function improved in responders [fractional area change (FAC) + 5.7%, $p < 0.001$, RV free wall strain +3.9%, $p = 0.006$], but interestingly further deteriorated in non-responders (FAC −4.5%, $p = 0.003$, RV free wall strain −3.9%, $p = 0.007$). Non-responders had more persistent symptoms than responders (NYHA ≥3, 72% vs. 11% at follow-up). Subsequently, non-response was associated

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***Correspondence:**
Georg Goliasch
georg.goliasch@meduniwien.ac.at

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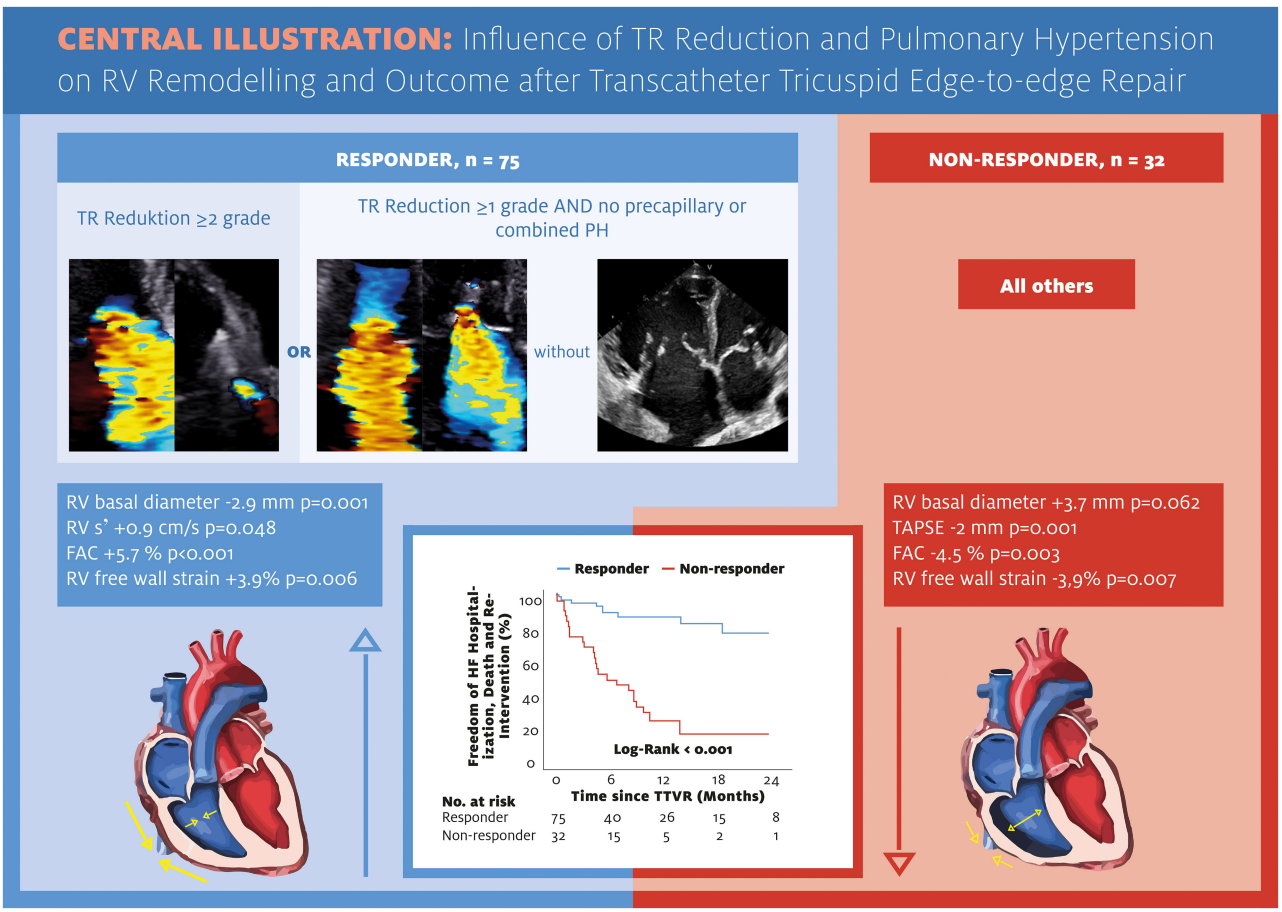
with a poor long-term prognosis in terms of death, heart failure (HF) hospitalization, and re-intervention after 2 years (freedom of death, HF hospitalization, and reintervention at 2 years: 16% vs. 78%, log-rank: $p < 0.001$).

Conclusion: Hemodynamic assessment before TTVR and procedural success are significant factors for patient prognosis. The hemodynamic profiling prior to intervention is an essential component in patient selection for TTVR. The window for edge-to-edge TTVR might be limited, but timely intervention is an important factor for a better outcome and successful right ventricular reverse remodeling.

Keywords: transcatheter repair, pulmonary hypertension, right ventricular remodeling, patient selection, tricuspid regurgitation



GRAPHICAL ABSTRACT | Influence of TR reduction and pulmonary hypertension on RV remodeling and outcome after transcatheter tricuspid edge-to-edge repair. TR, tricuspid regurgitation; PH, pulmonary hypertension; RV, right ventricle; TAPSE, tricuspid annulus plane systolic excursion; FAC, fractional area change; TTVR, transcatheter tricuspid valve repair; HF, heart failure.

INTRODUCTION

Tricuspid regurgitation (TR) is a common condition in the general population. Around 2% are affected by at least moderate TR, compared to 23% in patients with heart failure (HF) (1, 2). Severe TR is associated with increased hospitalization rates due to right heart failure and death (3–6). TR is mostly secondary and can develop in combination with left-sided valvular heart disease and as an isolated valvular lesion (7). Besides medical therapy, surgery has long been the only treatment, but isolated tricuspid valve surgery is associated with increased perioperative mortality (8, 9). Several devices for transcatheter tricuspid valve repair (TTVR) have been recently introduced to clinical practice, but transcatheter edge-to-edge repair is currently the most commonly used method (10). Several prospective observational studies have shown that TTVR can improve symptoms, right

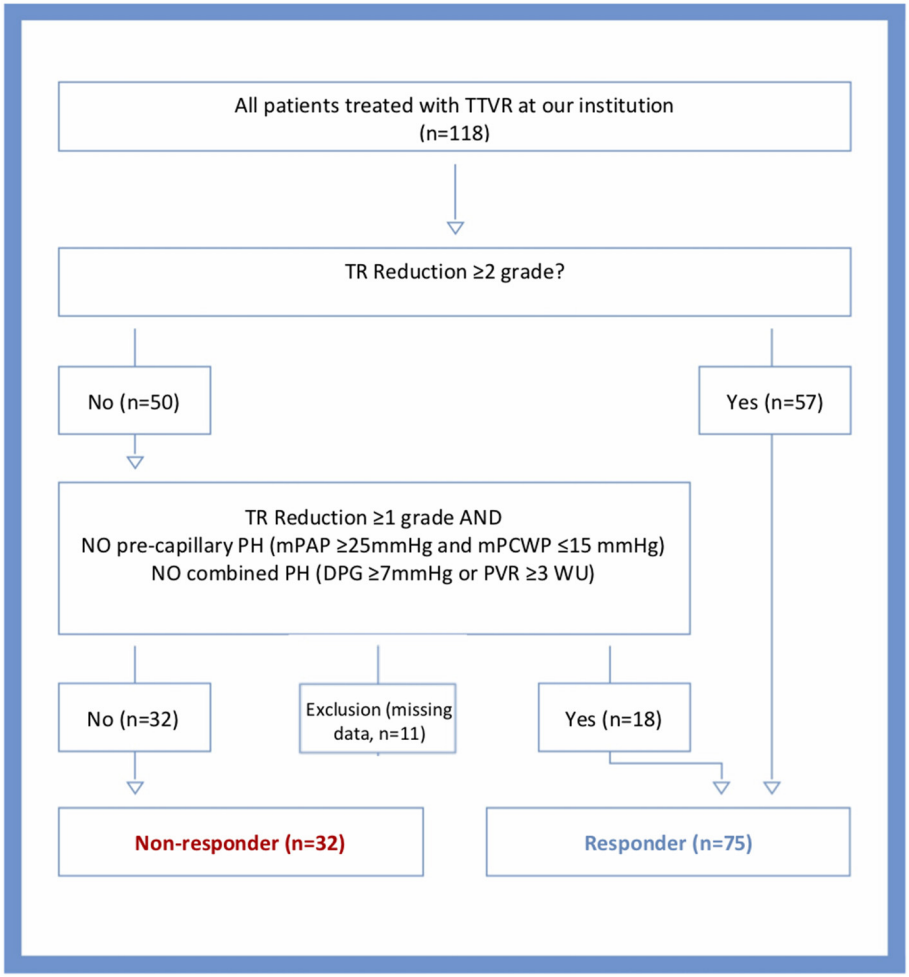


FIGURE 1 | Algorithm for the allocation of patients to responders or non-responders. TTVR, transcatheter tricuspid valve repair; TR, tricuspid regurgitation; PH, pulmonary hypertension; mPCWP, mean pulmonary capillary Wedge pressure; DPG, diastolic pulmonary gradient; PVR, pulmonary vascular resistance; WU, Wood units.

ventricular function, and outcome but might be unfavorable in patients with pulmonary hypertension (PH) (11–13). Based on these results, the European Society of Cardiology (ESC) implemented a 2b recommendation for TTVR in the 2021 guidelines for the management of patients with valvular heart disease (14). However, the ACC/AHA guidelines published in 2020 did not include a recommendation for TTVR due to missing evidence (15). Therefore, further studies and randomized controlled trials (RCT) are needed to firmly establish TTVR in the treatment of TR. The study focuses on i) the outcome of TTVR patients separated into different PH groups, ii) the effects of TR reduction and PH on outcome and RV remodeling after TTVR, iii) the (pre)procedural conditions for improved outcome and RV remodeling after TTVR.

MATERIALS AND METHODS

Study Design and Study Population

We included all patients treated with edge-to-edge TTVR between September 2018 and December 2021 at the Medical University of Vienna. Patients were separately analyzed according to their PH group and were enrolled and classified as either responders or non-responders according to an algorithm illustrated in **Figure 1**. All patients undergoing TTVR with a TR reduction of ≥1 grade without precapillary or combined PH (mean pulmonary artery pressure (mPAP) ≥25 mmHg, mean pulmonary artery Wedge pressure ≤15 mmHg, pulmonary vascular resistance ≥3 Wood units) were assigned to the responder group. All patients with a TR reduction of ≥1 grade and precapillary or combined PH were classified as non-responders. Patients with a TR reduction ≥2 grade were directly classified as responders, and patients without TR reduction were directly assigned as non-responders. Baseline characteristics were recorded before the procedure. The multidisciplinary Heart Team of our center individually discussed and assigned all patients to TTVR based on current guidelines and recommendations. The study protocol was approved by the Ethics Committee of the Medical University of Vienna, and all patients consented to participate.

TABLE 1 | Baseline Characteristics for all patients.

Clinical characteristics	*n* = 107
Age, yrs	76 (9)
Female	69 (65)
NYHA ≤2	16 (15)
Leg edema	71 (66)
Coronary artery disease	44 (41)
Previous myocardial infarction	12 (11)
Previous PCI	24 (22)
Previous CABG	22 (21)
Previous valve surgery	22 (21)
Atrial fibrillation	96 (90)
CIED	33 (31)
Chronic lung disease	26 (24)
Cerebral vascular disease	12 (11)
Peripheral arterial disease	6 (6)
Hypertension	95 (89)
Diabetes	30 (28)
Dyslipidemia	55 (51)
eGFR, mL/min	45 (18)
NT-proBNP, ng/L	3,770 (4,428)
Bilirubin, mg/dL	0.88 (4.9)
EuroSCORE II, %	8.5 (6.8)
TRI-SCORE, %	18 (16)
Pulmonary hypertension class	
No PH	35 (40)
Precapillary PH	2 (2)
Postcapillary PH	32 (36)
Combined PH	19 (18)
Procedural data	
Concomitant TMVR	41 (38)
Baseline TR Vena contracta, mm	16 (5)
Baseline TR EROA, cm²	0.80 (0.54)
Baseline TR RegVol, mL	60 (26)
Residual TR Vena contracta, mm	8.5 (5.7)
Residual TR EROA, cm²	0.34 (0.34)
Residual TR RegVol, mL	25 (21)
TV inflow gradient, mmHg	1.3 (0.7)
Echocardiography	
RV basal diameter, mm	49.6 (8.8)
TV annulus, mm	43.1 (7.7)
TAPSE, mm	17.4 (5.5)
RV s', cm/s	10.2 (2.6)
FAC, %	40.2 (9.3)
RV enddiastolic area, cm²	26 (8.2)
RV endsystolic area, cm²	15.7 (6.0)
RA volume, ml	136 (21)
sPAP, mmHg	45 (14)
LVEF Simpson, %	52 (13)
RV free wall strain, %	20.9 (6.5)
RV free wall strain rate, 1/s	1.2 (0.4)
Invasive hemodynamic measurements	
sPAP, mmHg	43.7 (13.6)
dPAP, mmHg	17 (6.7)
mPAP, mmHg	27.3 (8.7)
mPCWP, mmHg	18.4 (6.9)
vRA, mmHg	16.4 (8.6)
mRA, mmHg	12.1 (6.4)
PVR, WU	2.7 (1.8)
DPG, mmHg	−1.5 (4.6)
TPG, mmHg	8.9 (5.2)

Values are numbers (%) or mean (standard deviation).

NYHA, New York Heart Association; PCI, percutanous coronary intervention; CABG, coronary artery bypass graft; CIED, cardiac implantable eletronic device; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminales pro-B-type natriuretic peptide; EuroSCORE, European Sytem for Cardiac Operative Risk Evaluation; PH, pulmonary hypertension; TMVR, transcatheter mitral valve repair; TR, tricuspid regurgitation; EROA, effective regurgitant orifice area; RegVol, regurgitant volume; TV, tricuspid valve; TAPSE, tricuspid annulus plane systolic excursion; RV, right ventricle; FAC, fractional area change; RA, right atrium; sPAP, systolic pulmonary artery pressure; LVEF, left ventricular ejection fraction; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary Wedge pressure; vRA, v-wave pressure right atrium; mRA, mean pressure right atrium; PVR, pulmonary vascular resistance; WU, Wood units; DPG diastolic pulmonary pressure gradient; TPG, transpulmonary pressure gradient.

Echocardiographic Assessment

A comprehensive echocardiographic assessment, including transesophageal echocardiography (TEE), was performed according to the American Society of Echocardiography guidelines (16, 17). Physicians and sonographers examined all patients using commercially available equipment (Vivid 7, E9, E95, GE Healthcare; and EPIQ 7, Philips Medical Systems), and board-certified physicians interpreted echocardiograms. Cardiac chamber sizes were evaluated according to the American Society of Echocardiography guideline recommendation (16). A comprehensive assessment of the tricuspid valve and TR was performed with an integrated, multiparametric approach, including the tricuspid valve morphology, vena contracta (VC), effective regurgitation orifice area (EROA), and regurgitant volume (RegVol) using the proximal isovelocity surface area (PISA) method (18). We applied a grading scale ranging from 1 to 5 to define TR severity: grade 1 indicates "mild", 2 "moderate", 3 "severe", 4 "massive", and 5 "torrential," as recently proposed (19). Right ventricular systolic function was assessed using tricuspid annular plane systolic excursion (TAPSE), tissue Doppler velocity of the lateral tricuspid annulus (RV s'), fractional area change (FAC), and RV freewall strain and strainrate (20, 21). Systolic pulmonary artery pressure ($sPAP_{echo}$) was calculated by adding the peak tricuspid regurgitation systolic gradient to the estimated central venous pressure (16). All analyses were performed using GE EchoPac software version 203 (GE Vingmed, Horten, Norway).

Invasive Hemodynamic Assessment

Invasive hemodynamic assessment was performed routinely in study participants before TTVR. Hemodynamic measurements were performed using a 7F Swan-Ganz catheter (Edwards

TABLE 2 | Baseline characteristics by groups.

Clinical characteristics	Responder $n = 75$	Non-responder $n = 32$	*p*
Age, yrs	76 (10)	77 (7)	0.919
Female	50 (67)	19 (59)	0.512
NYHA ≤2	13 (17)	3 (9)	0.293
Leg edema	48 (64)	23 (72)	0.432
Coronary artery disease	29 (39)	15 (47)	0.521
Previous myocardial infarction	8 (11)	4 (13)	0.749
Previous PCI	12 (16)	12 (36)	**0.022**
Previous CABG	15 (20)	7 (22)	0.800
Previous valve surgery	13 (17)	9 (28)	0.295
Atrial fibrillation	67 (89)	29 (91)	1.000
CIED	24 (32)	9 (28)	0.820
Chronic lung disease	17 (23)	9 (28)	0.624
Cerebral vascular disease	7 (9)	5 (16)	0.338
Peripheral arterial disease	5 (7)	1 (3)	0.666
Hypertension	66 (88)	29 (91)	1.000
Diabetes	17 (23)	13 (41)	0.065
Dyslipidemia	37 (49)	18 (56)	0.534
eGFR, mL/min	47 (19)	41 (16)	0.180
NT-proBNP, ng/L	3,785 (4,362)	4,083 (4,896)	0.796
Bilirubin, mg/dL	0.85 (0.5)	0.96 (0.48)	0.291
EuroSCORE II, %	7.8 (6.8)	10 (6.8)	0.137
TRI-SCORE, %	14 (12)	27 (20)	**0.003**
Pulmonary hypertension class			0.133
No PH	27 (44)	8 (31)	
Precapillary PH	0 (0)	2 (8)	
Postcapillary PH	22 (36)	10 (39)	
Combined PH	13 (21)	6 (23)	
Procedural data			
Concomitant TMVR	26 (35)	15 (47)	0.280
Baseline TR Vena contracta, mm	16 (5)	17 (5)	0.516
Baseline TR EROA, cm²	0.77 (0.49)	0.85 (0.63)	0.769
Baseline TR RegVol, mL	60 (26)	60 (27)	0.992
Residual TR Vena contracta, mm	6 (3)	15 (5)	**<0.001**
Residual TR EROA, cm²	0.18 (0.14)	0.68 (0.37)	**<0.001**
Residual TR RegVol, mL	15 (11)	47 (22)	**<0.001**
TV inflow gradient, mmHg	1.2 (0.6)	1.4 (0.9)	0.354
Echocardiography			
RV basal diameter, mm	49 (8.3)	51.1 (10)	0.215
TV annulus, mm	42.3 (7.2)	44.9 (8.6)	0.114
TAPSE, mm	17.5 (5.5)	17 (5.7)	0.661
RV s', cm/s	10.6 (2.7)	9.3 (2.3)	**0.036**
FAC, %	40.7 (9.1)	39 (10)	0.406
RV enddiastolic area, cm²	25 (7.4)	28.9 (9.5)	**0.036**
RV endsystolic area, cm²	14.8 (5.1)	17.9 (7.4)	**0.035**
RA volume, ml	122 (59)	171 (86)	0.008
sPAP, mmHg	46 (14)	43 (14)	0.372
LVEF Simpson, %	52 (12)	51 (15)	0.510
RV free wall strain, %	20 (6.4)	22.3 (6.7)	0.292
RV free wall strain rate, 1/s	1.3 (0.4)	1.2 (0.3)	0.741
Invasive hemodynamic measurements			
sPAP, mmHg	43.5 (7.5)	44.7 (14.1)	0.619
dPAP, mmHg	16.3 (6.5)	18.6 (7)	0.157
mPAP, mmHg	26.8 (8.5)	28.5 (9.4)	0.402
mPCWP, mmHg	18.2 (6.9)	18.9 (7)	0.671
vRA, mmHg	15 (7)	19.5 (11.1)	0.071
mRA, mmHg	10.9 (5.2)	15 (8.1)	**0.022**
PVR, WU	2.6 (1.5)	3 (2.2)	0.301
DPG, mmHg	−2 (4.5)	−0.3 (4.9)	0.120
TPG, mmHg	8.6 (4.6)	9.6 (6.3)	0.393

Values are numbers (%) or mean (standard deviation). Bold p-values are statistically significant.

NYHA, New York Heart Association; PCI, percutanous coronary intervention; CABG, coronary artery bypass graft; CIED, cardiac implantable eletronic device; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminales pro-B-type natriuretic peptide; EuroSCORE, European Sytem for Cardiac Operative Risk Evaluation; PH, pulmonary hypertension; TMVR, transcatheter mitral valve repair; TR, tricuspid regurgitation; EROA, effective regurgitant orifice area; RegVol, regurgitant volume; TV, tricuspid valve; TAPSE, tricuspid annulus plane systolic excursion; RV, right ventricle; FAC, fractional area change; RA, right atrium; sPAP, systolic pulmonary artery pressure; LVEF, left ventricular ejection fraction; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary Wedge pressure; vRA, v-wave pressure right atrium; mRA, mean pressure right atrium; PVR, pulmonary vascular resistance; WU, Wood units; DPG diastolic pulmonary pressure gradient; TPG, transpulmonary pressure gradient.

Lifesciences GmbH, Austria) *via* femoral access. Pressures were documented as the average of eight measurements over eight consecutive heart cycles using CathCorLX (Siemens AG, Berlin and Munich, Germany). In addition to pulmonary artery Wedge pressure (PAWP), the systolic (sPAP), diastolic (dPAP), and mean (mPAP) PA pressures were documented. Cardiac output (CO) was measured by Fick's method or thermodilution. If both were available, Fick's method was preferred. Furthermore, the transpulmonary gradient (TPG) and diastolic pulmonary vascular pressure gradient (DPG) were calculated according to current guidelines (22). TPG was computed by subtracting PAWP from mPAP; DPG was calculated as the difference between dPAP and PAWP during a pull-back; pulmonary vascular resistance (PVR) was calculated by dividing TPG by CO. Precapillary PH was defined as mPAP ≥25mmHg and mPCWP ≤15 mmHg and combined pre-/postcapillary PH was defined as DPG ≥7mmHg or PVR ≥3 WU (**Figure 1**) (22). Moreover, coronary angiography was performed in all patients to detect possible coronary artery disease.

Procedural Characteristics

TTVR was performed using the Tri-/MitraClip (Abbott Laboratories, North Chicago, Illinois, size XT and XTW) or PASCAL system (Edwards Lifesciences, Irvine, California, size Ace). Both systems were inserted *via* a steerable guide with a delivery catheter through a right femoral vein access site. Precise valve anatomy and pathophysiology were assessed by transesophageal and transgastric echocardiographic windows

using TEE according to recently published literature (23). The devices were positioned in the right atrium in front of the tricuspid valve. Steering of the guide and delivery catheter, rotation of the device arms, loading and grasping of the leaflets, device closure, and release were performed under fluoroscopic and echocardiographic guidance, as recently described (24).

The treating physician determined treatment strategy, device selection, and the number of implants based on the anatomic and clinical conditions of the individual patient.

Outcome Analyses

Patients were followed up prospectively in a specialized outpatient clinic after TTVR at 3 months, 6 months, and annually. We defined the primary endpoint as all-cause mortality during a follow-up period of 2 years. In addition, we defined heart failure (HF) hospitalization as a secondary study endpoint and a composite endpoint, including death, HF hospitalization, and reintervention. Endpoints were collected *via* the Austrian death registry, telephone calls to patients or relatives, and electronic medical records. All patients gave written informed consent, and the study was approved by the Ethics Committee of the Medical University of Vienna.

Statistical Analysis

Continuous baseline characteristics are presented for all patients and separately for the responder and non-responder groups as mean (SD) and compared with a 2-sided Student's *t*-test or Wilcoxon rank-sum test. Categorical variables were described as frequencies and compared with chi-square or Fisher's exact test. We compared follow-up data with baseline data for responders and non-responders, applying a paired Student's t-test or Wilcoxon rank-sum test. For different PH groups, we compared RV functional parameters at baseline and follow-up. Using described endpoints, Kaplan-Meier curves were plotted for all PH groups, responders, and non-responders. The log-rank test was applied to estimate the differences between survival curves. A two-sided p-value <0.05 was considered statistically significant. Furthermore, univariate and multivariate logistic regression were performed using invasive hemodynamic data and patients with one or more and two or more grade TR reduction after TTVR. All analyses were performed using SPSS 27 (IBM SPSS, USA).

RESULTS

Clinical Characteristics

A total of 118 patients were treated with TTVR at our institution between September 2018 and December 2021. One hundred and seven patients were included in the study, 75 in the responder group and 32 in the non-responder group. Eleven patients were excluded due to 1 grade TR reduction without invasive hemodynamic measurements. 35 patients had no PH, 2 had precapillary, 32 had postcapillary, and 19 had combined PH. Baseline data are displayed for all patients in **Table 1** and for responders and non-responders in **Table 2**. The mean age of responders was 76 years, and 67% were female. In the non-responder group, the mean age was 77 years, and 59% were female. Concomitant transcatheter mitral valve repair (TMVR) was performed in 35% of the responders and in 47% of the non-responders. A significant difference in baseline characteristics between groups was in the presence of previous percutaneous coronary intervention (PCI, responders: 16% vs. non-responders: 36%, $p = 0.022$) and TRI-SCORE risk evaluation (responders: 14% vs. non-responders: 27%, $p = 0.003$) (25).

Invasive Hemodynamics and TR Reduction

Logistic regression analysis showed a significant relationship between mean RA pressure and ≥1 grade TR reduction in uni- and multivariate analysis (univariate: odds ratio 0.894, conf-interval 0.821–0.974, $p = 0.010$; multivariate: odds ratio 0.848, conf-interval 0.734–0.979, $p = 0.025$) and between PVR and ≥1 grade reduction in multivariate analysis (odds ratio 1.008, conf-interval 1.000–1.015, $p = 0.047$). sPAP, mPAP, and mPCWP and ≥1 grade reduction showed no significant relationship. No value showed a significant association with two or more grade reduction in uni- or multivariate logistic regression.

TR Reduction and RV Remodeling

Follow-up visits were performed at a mean of 229 days post TTVR for responders and 187 days post TTVR for non-responders. For patients undergoing reintervention, outcome data were obtained before reintervention. Leg edema and NYHA classification improved in the responder group significantly (64% to 17% for leg edema, $p < 0.001$ and 17% to 89% for NYHA ≤2, $p < 0.001$, **Figures 2A,C**) and did not change significantly in the non-responder group (72% to 78% for leg edema, $p = 0.180$ and 9% to 18% for NYHA ≤2, $p = 0.157$, **Figures 2B,D**). The following TR echocardiographic parameter were significantly reduced in the responder group: TR VC [16 (6) to 6 (3) mm, $p < 0.001$], TR EROA [0.75 (0.48) vs. 0.18 (0.14) cm², $p < 0.001$] and TR RegVol [60 (27) vs. 15 (11) mL, $p < 0.001$] while in the non-responder group only TR RegVol decreased significantly [60 (28) vs. 48 (22) mL, $p = 0.016$] (**Tables 3**, **4**).

In the group of responders, RV basal diameter [46.4 (6.2) vs. 43.5 (7.5) mm, $p = 0.001$] and tricuspid valve (TV) annulus [40.2 (5.9) vs. 38.3 (6.9) mm, $p = 0.004$] decreased, while RV s' [10.8 (2.5) vs. 11.7 (2.4) m/s, $p = 0.048$], FAC [38.6 (8.6) vs. 44.3 (10) %, $p < 0.001$, **Figures 2E,F**], RV free wall strain [19.8 (6.6) vs. 23.7 (5.6) %, $p = 0.006$, **Figures 2G,H**] and RV free wall strain rate [1.2 (0.4) vs. 1.4 (0.4) 1/s, $p = 0.016$] increased significantly. Furthermore, RV free wall strain basal [18.2 (7.4) vs. 24.2 (6.4) %, $p = 0.002$] and RV free wall strain mid [20.5 (7.6) vs. 25.1 (6.6) %, $p = 0.009$] improved (**Table 4**).

And in the group of non-responders, TAPSE [16.4 (5.3) vs. 14.4 (5) mm, $p = 0.001$], FAC [37.7 (9.3) vs. 33.1 (9.8) %, $p = 0.003$] and RV free wall strain [22.6 (6.7) vs. 18.7 (4.5) %, $p = 0.007$] decreased significantly. Moreover, RV free wall strain mid [22.7 (6.6) vs. 19.4 (5.1) %, $p = 0.038$] and RV free wall strain apical [24.5 (7.6) vs. 17.8 (6.4) %, $p = 0.004$] deteriorated (**Table 4**).

RV functional parameters did not change significantly at follow-up when patients were divided into the different PH groups (**Table 5**).

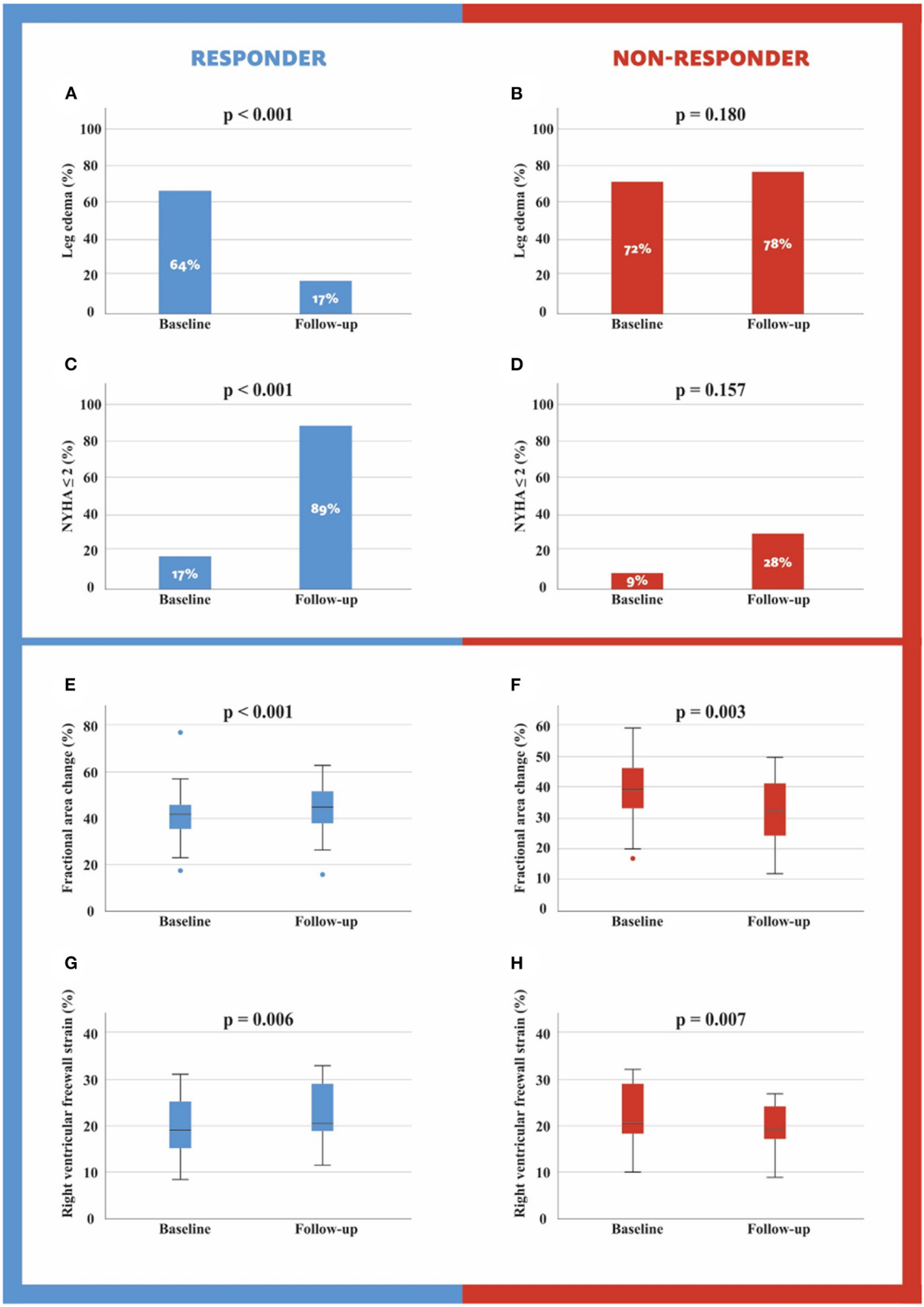


FIGURE 2 | Leg edema and NYHA score at baseline and follow-up for responders and non-responders **(A–C)**. Fractional area change and right ventricular freewall strain at baseline and follow-up for responders and non-responders **(D–H)**.

TABLE 3 | Logistic regression analysis for ≥1 and ≥2 grade TR reduction after TTVR and invasive hemodynamic parameters.

	≥1 grade TR reduction					
	Univariate			Multivariate		
	Odds ratio	95% Conf-interval	*p*	Odds ratio	95% Conf-interval	*p*
sPAP	0.998	0.959–1.038	0.998	1.092	0.939–1.270	0.252
mPAP	0.977	0.918–1.039	0.458	0.898	0.681–1.184	0.445
mPCWP	0.936	0.866–1.012	0.098	0.984	0.827–1.171	0.856
mRA	0.894	0.821–0.974	**0.010**	0.848	0.734–0.979	**0.025**
PVR	1.005	0.999–1.012	0.090	1.008	1.000–1.015	**0.047**
	≥2 grade TR reduction					
	Univariate			Multivariate		
	Odds ratio	95% Conf-interval	*p*	Odds ratio	95% Conf-interval	*p*
sPAP	1.009	0.978–1.041	0.561	1.036	0.945–1.136	0.454
mPAP	1.009	0.961–1.058	0.728	0.929	0.775–1.113	0.424
mPCWP	1.021	0.960–1.086	0.504	1.085	0.958–1.229	0.198
mRA	0.974	0.911–1.041	0.430	0.923	0.832–1.025	1.025
PVR	1.001	0.998–1.005	0.377	1.003	0.999–1.007	0.181

sPAP, systolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary Wedge pressure; mRA, mean pressure right atrium; PVR, pulmonary vascular resistance. Bold p-values are statistically significant.

Clinical Endpoints and Outcome

A total of 39 events (18 deaths, 14 HF hospitalizations, 7 re-interventions) occurred during the observational period of 24 months [mean observational period 9 (8) months per patient]. In the responder group, 5 deaths, 5 HF hospitalizations, and no reintervention were recorded, whereas in the non-responder group, 13 patients died, 9 were hospitalized for HF, and 7 received reintervention. Rates for the combined endpoint of death, HF hospitalization, and re-intervention at 6 months, 1 year, and 2 years were for responders 11, 13, and 22%; and for non-responders, 51, 75, and 84% (log-rank: $p < 0.001$, **Figure 3D**). Similarly, a significant difference between responders and non-responders was found for the combined endpoint of death and HF hospitalization (22% vs. 66%, log-rank: $p < 0.001$, **Figure 3C**), for the isolated endpoint of death (12% vs. 47%, log-rank: $p < 0.001$, **Figure 3A**), and for the isolated endpoint of HF hospitalization (11% vs. 29%, log-rank: $p = 0.021$, **Figure 3B**). In addition, we analyzed outcome according to different PH groups. Rates for the combined endpoint of death and HF hospitalization at 6 months, 1 year, and 2 years for patients without PH were 0, 14, and 14%; for patients with postcapillary PH, 27, 37, and 37%; and for patients with precapillary or combined PH, 51, 51, and 100% (log-rank: $p < 0.001$, **Figure 4A**).

DISCUSSION

This prospective observational study divided TTVR patients into responders and non-responders according to pre-interventional hemodynamic assessment and procedural success. We were able to demonstrate three main findings: 1) Significant RV remodeling after TTVR, 2) Subsequent improvement or worsening of RV function depending on preinterventional hemodynamic status and procedural success, 3) Significantly lower mortality in patients with favorable hemodynamics and successful intervention, and 4) differences in outcome between the PH groups but no difference in RV remodeling.

Patient Selection for TTVR

TR is a common disease with multiple causes that had long been treated only with guideline-directed medical therapy. The high prevalence of concomitant TR in various underlying diseases like left heart disease or PH makes patient selection a central issue for TTVR. Procedural success in TTVR is currently an ongoing matter of debate resulting in different definitions. Some authors advocate procedural success as a TR ≤2 after the procedure, whereas other authors define success based on the extent of reduction (12, 26). If procedural success is defined as TR ≤2 after TTVR, patients with massive or torrential TR have a lower procedural success rate and a higher HF hospitalization rate but a similar mortality rate compared with patients with severe TR (27). Our analysis demonstrated that reduction in TR was an important factor for a favorable outcome, regardless of baseline TR or residual TR after TTVR. We also analyzed invasive hemodynamic parameters and their predictive value for the success of the procedure (**Table 3**). Only right atrial mean pressure showed univariate and multivariate predictive value for TR reduction after TTVR. Elevated right atrial pressure could be a marker of advanced disease stage and should be considered in patient selection. Other values, such as mPAP or mPCWP, may not have prognostic significance because the number of patients in whom these values were strongly elevated was rather small. Furthermore, in our cohort, a substantial number of patients underwent concomitant TMVR (38%). TMVR is known

TABLE 4 | Comparison of baseline and follow-up data divided by responder and non-responder.

	Responder			Non-responder		
	Baseline	**Follow-up**	***p***	**Baseline**	**Follow-up**	***p***
NYHA ≤2	13 (17)	32 (89)	**<0.001**	3 (9)	5 (28)	0.157
Leg edema	48 (64)	6 (17)	**<0.001**	23 (72)	14 (78)	0.180
eGFR, mL/min	47 (22)	41 (16)	**0.006**	47 (16)	42 (20)	0.260
NT-proBNP, ng/L	4,200 (5,271)	2,540 (2,872)	**0.032**	2,231 (1,744)	3,660 (3,181)	0.096
RV basal diameter, mm	46.4 (6.2)	43.5 (7.5)	**0.001**	51.3 (11.1)	54.4 (8.6)	0.062
TV annulus, mm	40.2 (5.9)	38.3 (6.9)	**0.004**	45.6 (9.2)	46.2 (6.7)	0.690
TAPSE, mm	17 (5.3)	18.2 (4.7)	0.083	16.4 (5.3)	14.4 (5)	**0.001**
RV s', cm/s	10.8 (2.5)	11.7 (2.4)	**0.048**	9.1 (2)	9.1 (3)	0.927
FAC, %	38.6 (8.6)	44.3 (10)	**<0.001**	37.7 (9.3)	33.1 (9.8)	**0.003**
RA volume, ml	109 (42)	110 (49)	0.793	180 (78)	181 (83)	0.917
$sPAP_{echo}$, mmHg	46 (13)	40 (10)	**0.003**	43.7 (14.2)	40 (8.6)	0.092
RV free wall strain, %	19.8 (6.6)	23.7 (5.6)	**0.006**	22.6 (6.7)	18.7 (4.5)	**0.007**
RV free wall strain rate, 1/s	1.2 (0.4)	1.4 (0.4)	**0.016**	1.2 (0.3)	1.1 (0.2)	0.281
RV free wall strain basal, %	18.2 (7.4)	24.2 (6.4)	**0.002**	20.7 (7.3)	19 (5.3)	0.393
RV free wall strain mid, %	20.5 (7.6)	25.1 (6.6)	**0.009**	22.7 (6.6)	19.4 (5.1)	**0.038**
RV free wall strain apical, %	20.6 (8.9)	21.7 (6.2)	0.550	24.5 (7.6)	17.8 (6.4)	**0.004**
TR grade ≥3	70 (93)	4 (11)	**<0.001**	31 (97)	16 (89)	0.564
TR Vena contracta, mm	16 (6)	6 (3)	**<0.001**	17 (4.8)	15 (4.8)	0.077
TR EROA, cm^2	0.75 (0.48)	0.18 (0.14)	**<0.001**	0.85 (0.66)	0.69 (0.39)	0.158
TR RegVol, mL	60 (27)	15 (11)	**<0.001**	60 (28)	48 (22)	**0.016**
TV inflow gradient, mmHg	1.2 (0.6)	2.1 (1.1)	**<0.001**	1.4 (0.7)	2.8 (1.8)	**<0.001**

Values are numbers (%) or mean (standard deviation). Bold p-values are statistically significant.
NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminales pro-B-type natriuretic peptide; RV, right ventricle; TV, tricuspid valve; TAPSE, tricuspid annulus plane systolic excursion; FAC, fractional area change; RA, right atrium; $sPAP_{echo}$, systolic pulmonary artery pressure by echocardiography; TR, tricuspid regurgitation; EROA, effective regurgitant orifice area; RegVol, regurgitant volume.

to reduce pulmonary pressure and tricuspid regurgitation (28). In addition, patients with severe MR and TR who receive TMVR and TTVR might have a better outcome than patients who receive TMVR alone (29). Concomitant TMVR is a potential bias for our results, but responders and non-responders had no significant difference regarding the number of patients undergoing TMVR (responders: 35%, non-responders: 47%, $p = 0.280$).

Stocker et al. recently demonstrated that patients with precapillary PH who undergo TTVR have a worse outcome than patients without or with postcapillary PH (13). We also demonstrated that outcomes differed between PH groups and were worst in patients with combined or precapillary PH (**Figure 4**). Postcapillary PH due to left heart disease is a known factor for the occurrence of TR, but an additional precapillary PH component seems to worsen the outcome. Therefore, we included the PH group in our algorithm but also emphasized the success of the procedure. In our cohort, only two patients had precapillary PH and a TR reduction of one grade and were therefore assigned to the non-responder group. This can be explained by our screening for TTVR, which mostly excluded patients with precapillary PH due to early data of TTVR patients (30). The other 9 non-responders with a TR reduction of one TR grade met the criteria for combined PH according to guidelines (22). Still, pulmonary pressure and pulmonary resistance did not differ significantly between responders and non-responders (**Table 6**). This occurs because only patients with a decrease of one grade were placed in one of the groups according to PH, but still, the outcome in responders is much better. This suggests that, on the one hand, the benefit of a large TR reduction may overcome the poor prognosis of patients with PH. On the other hand, a TR reduction of one grade is not sufficient to compensate for the worse outcome of PH patients.

Interestingly, despite the worse outcome of non-responders, both groups differ not much in terms of baseline characteristics. Non-responders had a significantly higher incidence of previous PCI, a larger RV, and RA. The EuroSCORE II was also higher in the non-responder group, but not significantly, whereas the recently introduced TRI-SCORE was able to show a significant difference (25). This is further suggestive that the EuroSCORE II may not be sufficiently prognostic for TR patients and may be inferior to the TRI-SCORE. Nevertheless, the small differences between responders and non-responders in baseline characteristics underline the impact of TR reduction and PH on the outcome.

Right Ventricular Remodeling and Outcome

At echocardiographic follow-up, we observed a significant improvement in RV function and a decrease in RV size in

TABLE 5 | Comparison of right ventricular parameters at baseline and follow-up for different PH groups.

	No PH			Postcapillary PH			Precapillary and combined PH		
	Baseline	**Follow-up**	***p***	**Baseline**	**Follow-up**	***p***	**Baseline**	**Follow-up**	***p***
RV basal diameter, mm	47.4 (7.9)	47.7 (8.8)	0.773	48 (7.6)	47.7 (7.6)	0.754	45.4 (8)	43.9 (8.5)	0.592
TV annulus, mm	42.6 (7.1)	42.6 (8.7)	0.958	42 (7.8)	40.1 (5.6)	0.097	39.4 (6.3)	39.4 (6.8)	1.000
TAPSE, mm	18 (5)	17.3 (4.5)	0.471	17.3 (4.9)	17.8 (4)	0.463	16.3 (5.8)	17 (6.1)	0.592
RV s', cm/s	10.4 (2.2)	11.3 (2.9)	0.228	10.3 (2.1)	10.7 (2.4)	0.487	9.6 (3.1)	10.1 (2.9)	0.578
FAC, %	42.6 (6.7)	43.3 (10.4)	0.660	37.8 (8.8)	39.7 (10.9)	0.359	39.1 (8.5)	42.4 (11.4)	0.459
RA volume, ml	128 (59)	139 (58)	0.217	144 (77)	136 (65)	0.375	102 (42)	106 (93)	0.845
sPAP, mmHg	39.2 (9.7)	37.6 (6.9)	0.328	47.7 (13.1)	43.2 (12.1)	0.106	48.8 (15.3)	42 (8.2)	0.095
RV free wall strain, %	23.4 (5.3)	22.2 (4.9)	0.492	21.1 (5.7)	22.3 (5.7)	0.532	22.9 (9.2)	24.4 (6.2)	0.673
RV free wall strain rate, 1/s	1.4 (0.3)	1.3 (0.4)	0.292	1.3 (0.4)	1.3 (0.4)	0.503	1.2 (0.5)	1.4 (0.4)	0.323

Values are numbers (%) or mean (standard deviation). Bold p-values are statistically significant.
PH, pulmonary hypertension; RV, right ventricle; TV, tricuspid valve; TAPSE, tricuspid annulus plane systolic excursion; FAC, fractional area change; RA, right atrium; $sPAP_{echo}$, systolic pulmonary artery pressure by echocardiography; TR, tricuspid regurgitation; EROA, effective regurgitant orifice area; RegVol, regurgitant volume.

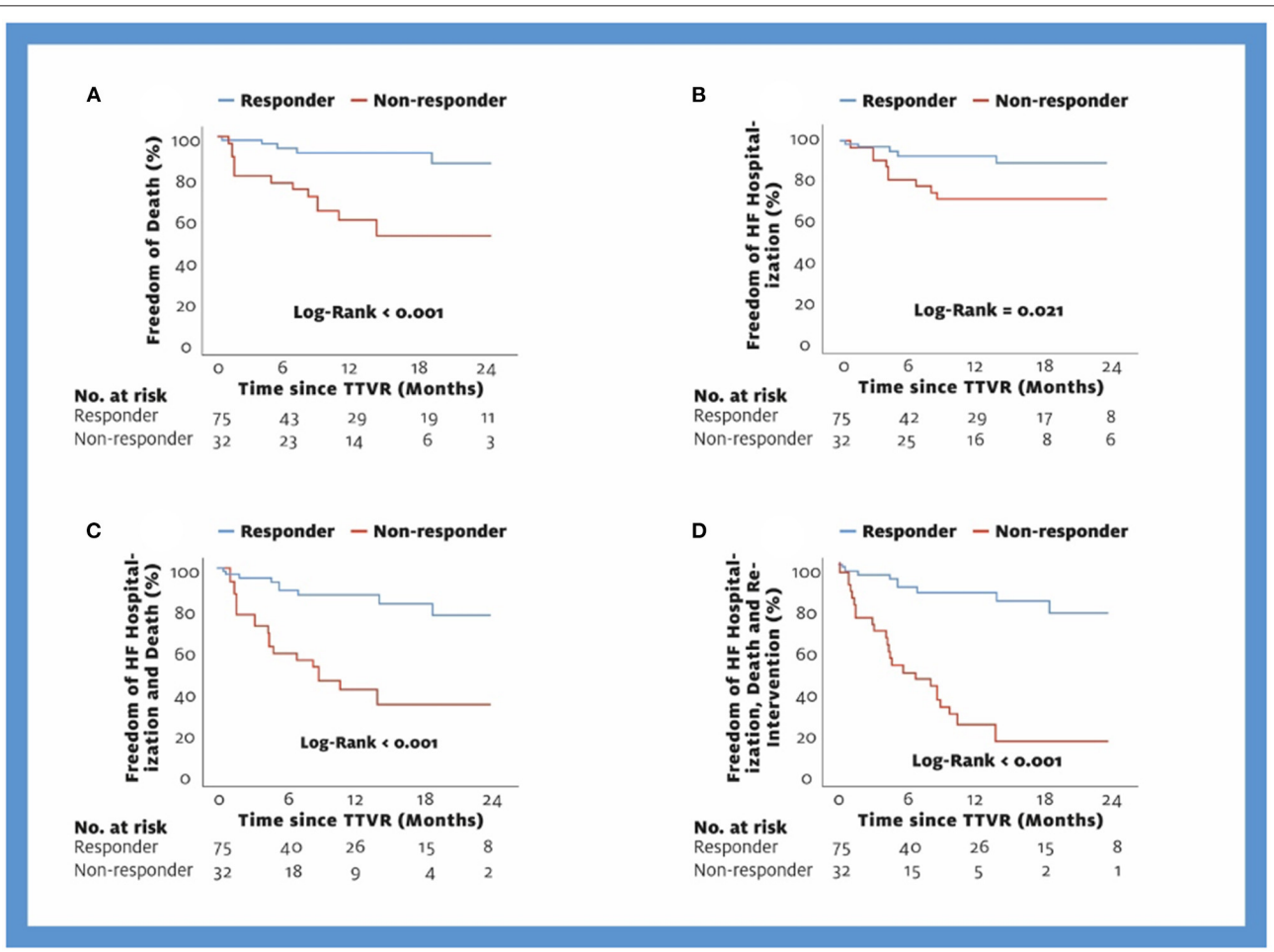


FIGURE 3 | Kaplan-Meier Curves for the endpoints Death **(A)**, HF hospitalization **(B)**, Death and HF hospitalization **(C)**, and Death, HF hospitalization, Re-intervention **(D)**. TTVR, transcatheter tricuspid valve repair; HF, heart failure.

the responder group (**Table 4**), similar to previous studies (11, 31, 32). However, for the first time, we also analyzed the group of non-responders who showed a decline in RV functional parameters (**Table 4**). This information supports the value of successful TTVR for TR patients. Interestingly, in the responder group, RV freewall strain increased more in

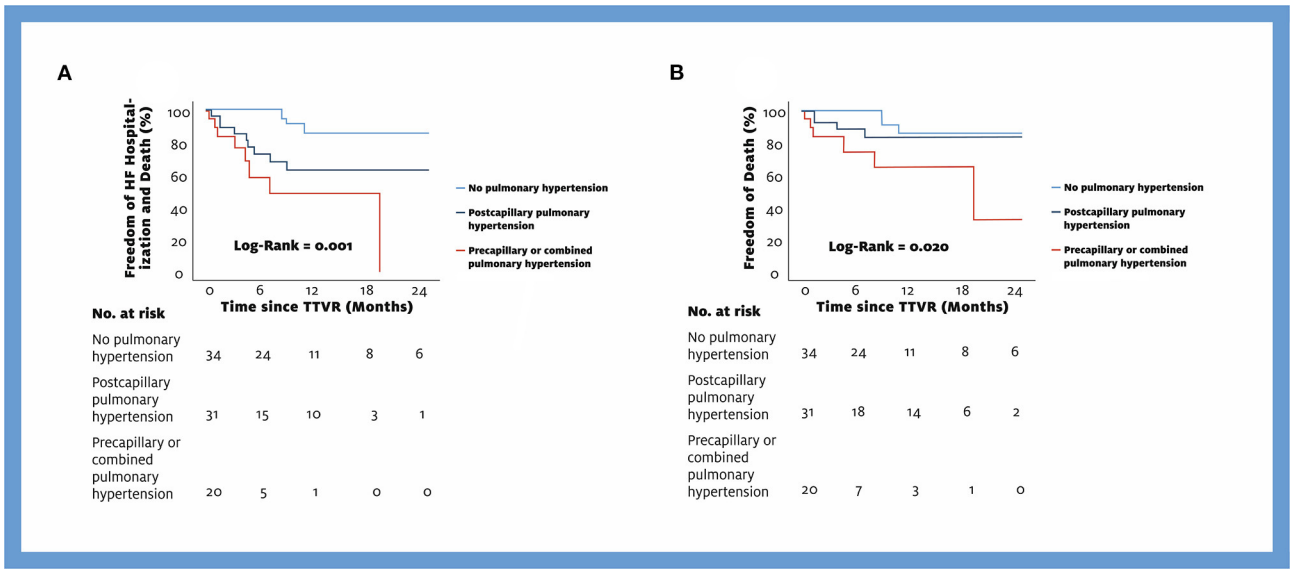


FIGURE 4 | Kaplan-Meier Curves for the endpoints Death and HF hospitalization **(A)** and Death **(B)** by different PH groups. TTVR, transcatheter tricuspid valve repair; HF, heart failure.

the basal segments than in the apical segments. In contrast, it was reversed in the non-responder group concerning strain decrease (**Table 4**). The reason for this could be the indirect annuloplasty that occurs during TTVR. In the responder group, this annuloplasty combined with reduced volume overload after substantial TR reduction leads to reverse RV remodeling, especially in the large basal portions. In the group of non-responders, annuloplasty also takes place and probably has a protective effect on the basal parts of the RV, keeping them from deteriorating. However, due to volume overload following an incompletely repaired TR or an increased PVR, apical RV function deteriorates.

In addition to RV remodeling, we also analyzed the outcome with the endpoints of HF hospitalization, death, and re-intervention, also in combined analyses. We demonstrated a clear advantage for the responders (freedom of all endpoints after 2 years: responders 78%, non-responders: 16%, **Figure 3D**). Taramasso et al. compared TTVR patients with medical-treated patients in a propensity-matched analysis and demonstrated a survival rate of 64% in control patients and 77% in TTVR patients at 1 year (10). In our cohort, 60% of non-responders and 92% of responders survived after 1 year. The comparable outcome of our non-responders and the control patients by Taramasso et al. show that TR reduction of 1 grade in precapillary or combined PH is similar to no intervention in terms of survival. The higher survival of our responders compared with the TTVR group of Taramasso et al. can be explained by the assignment of procedural failures with no TR reduction to the non-responder group. Procedural failures also showed a significantly worse outcome in a separate analysis in the study by Taramasso et al. (10).

Clinical Implications

We observed a significant clinical improvement in the responder group as measured by NYHA score, which demonstrated an increase in patients with NYHA ≤II from 17 to 89% (**Table 4**, $p < 0.001$). In comparison, in the TRILUMINATE cohort, the number of NYHA ≤II patients increased from 31 to 83% 1 year after TTVR ($p < 0.0001$) (11). Our responder patients seem to benefit even more compared to an entire TTVR cohort. However, in our non-responders, NYHA score did not change significantly ($p = 0.157$), consistent with the worse outcome of this group. We also observed no significant changes in the non-responder group in terms of leg edema ($p = 0.180$), while leg edema significantly improved in the responder group ($p < 0.001$). These clinical changes indicate that TTVR can help patients suffering from symptoms of right heart decompensation if PH is not precapillary or combined and at least 1 grade TR reduction is achieved. Finally, we can conclude that our study provides important insights into patient selection and TR reduction required for a good outcome. In addition, we were able to provide more detailed information on RV (reverse) remodeling after TTVR. Upcoming RCTs, such as the TRILUMINATE pivotal trial (unique identifier: NCT03904147), are eagerly awaited to clarify the impact of TTVR on TR patients.

LIMITATIONS

There are several limitations to be considered in this study. We could not include all patients with TTVR from our center because invasive hemodynamic measurements were not available in all patients, mainly if TMVR was performed simultaneously. The changes in RV function and differences in outcome may also be

TABLE 6 | Comparison of responder and non-responder data divided by baseline and follow-up examination.

	Baseline			Follow-up		
	Responder	**Non-responder**	***p***	**Responder**	**Non-responder**	***p***
NYHA ≤2	13 (17)	3 (9)	0.293	32 (89)	5 (28)	**<0.001**
Leg edema	48 (64)	23 (72)	0.432	6 (17)	14 (78)	**<0.001**
eGFR, mL/min	47 (19)	41 (16)	0.180	41 (20)	41 (16)	0.967
NT-proBNP, ng/L	3,785 (4,362)	4,083 (4,896)	0.796	2,370 (2,522)	3,932 (3,260)	0.099
RV basal diameter, mm	49 (8.3)	51.1 (10)	0.215	43.5 (7.5)	53.8 (8.8)	**<0.001**
TV annulus, mm	42.3 (7.2)	44.9 (8.6)	0.114	38.3 (6.9)	45.5 (7.5)	**<0.001**
TAPSE, mm	17.5 (5.5)	17 (5.7)	0.661	18.2 (4.7)	14.4 (5)	**0.003**
RV s', cm/s	10.6 (2.7)	9.3 (2.3)	**0.036**	11.6 (3)	8.9 (3)	**<0.001**
FAC, %	40.7 (9.1)	39 (10)	0.406	44.3 (10.1)	32.3 (10.4)	**<0.001**
RA volume, ml	122 (59)	171 (86)	**0.008**	110 (49)	174 (87)	**0.003**
sPAP, mmHg	46 (14)	43 (14)	0.372	39.6 (10.3)	39.6 (8.6)	0.971
RV free wall strain, %	20 (6.4)	22.3 (6.7)	0.292	22.8 (5.5)	19.1 (4.7)	**0.031**
RV free wall strain rate, 1/s	1.3 (0.4)	1.2 (0.3)	0.741	1.5 (0.5)	1.1 (0.2)	**0.002**
RV free wall strain basal, %	18.8 (7.4)	20.4 (7.2)	0.520	23.1 (6.7)	19.7 (5.7)	0.091
RV free wall strain mid, %	20.6 (7.4)	22.4 (6.5)	0.424	24.1 (6.3)	19.8 (5.2)	**0.025**
RV free wall strain apical, %	20.7 (8.4)	24 (7.6)	0.208	21.2 (6.0)	17.9 (6.6)	0.105
TR grade ≥3	70 (93)	31 (97)	0.468	4 (11)	16 (89)	**<0.001**
TR Vena contracta, mm	16 (5)	17 (5)	0.516	6 (3)	15 (5)	**<0.001**
TR EROA, cm^2	0.77 (0.49)	0.85 (0.63)	0.769	0.18 (0.14)	0.68 (0.39)	**<0.001**
TR RegVol, mL	60 (26)	60 (27)	0.992	15 (11)	47 (22)	**<0.001**
TV inflow gradient, mmHg	1.2 (0.6)	1.4 (0.9)	0.354	2 (1.1)	2.8 (1.8)	**0.031**

Values are numbers (%) or mean (standard deviation). Bold p-values are statistically significant.
NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminales pro-B-type natriuretic peptide; RV, right ventricle; TV, tricuspid valve; TAPSE, tricuspid annulus plane systolic excursion; FAC, fractional area change; RA, right atrium; $sPAP_{echo}$, systolic pulmonary artery pressure by echocardiography; TR, tricuspid regurgitation; EROA, effective regurgitant orifice area; RegVol, regurgitant volume.

attributable to concomitant TMVR, even though both groups had a similar repair rate (**Table 1**). Our procedural results are from a highly specialized center, nevertheless, patients from the beginning of TTVR were included. Therefore, the success rate of patients treated today might be higher. No echocardiography core laboratory was involved in image evaluation.

CONCLUSION

TTVR patients divided into responders and non-responders by preinterventional hemodynamic assessment and procedural success show a marked difference in RV (reverse) remodeling and outcome. While RV function improves in responders, it deteriorates in non-responders. The endpoints of death, HF hospitalization, and reintervention were much more frequently reached by non-responders. Preprocedural hemodynamic assessment may help in patient selection. These encouraging results strengthen the usefulness of TTVR in routine clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethik Kommision der Medizinischen Universität Wien. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VD and GG: conception and design and analysis and interpretation of data. VD, GG, JM, and MS: drafting of the manuscript. GG, JM, MK, CD, KM, GH, KH, AB, MM, and GS: critical revision of the manuscript for important intellectual content. M-PW, PB, CH, GG, MA, AK, and CN: final approval of the submitted manuscript. All authors contributed to the article and approved the submitted version.

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Indications, Complications, and Outcomes of Cardiac Surgery After Heart Transplantation: Results From the Cash Study

Johannes Gökler[1], Arezu Z. Aliabadi-Zuckermann[1], Alexandra Kaider[2], Amrut V. Ambardekar[3], Herwig Antretter[4], Panagiotis Artemiou[5], Alejandro M. Bertolotti[6], Udo Boeken[7], Vicens Brossa[8], Hannah Copeland[9], Maria Generosa Crespo-Leiro[10], Andrea Eixerés-Esteve[11], Eric Epailly[12], Mina Farag[13], Michal Hulman[5], Kiran K. Khush[14], Marco Masetti[15], Jignesh Patel[16], Heather J. Ross[17], Igor Rudež[18], Scott Silvestry[19], Sofia Martin Suarez[20], Amanda Vest[21] and Andreas O. Zuckermann[1]*

[1] Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria, [2] Center for Medical Statistics, Informatics, and Intelligent Systems (CeMSIIS), Medical University of Vienna, Vienna, Austria, [3] Division of Cardiology, University of Colorado School of Medicine, Aurora, CO, United States, [4] Department of Cardiac Surgery, Medical University Innsbruck, Innsbruck, Austria, [5] National Institute of Cardiovascular Diseases, Medical Faculty of the Comenius University, Bratislava, Slovakia, [6] Heart and Lung Transplant Service, Favaloro Foundation University Hospital, Buenos Aires, Argentina, [7] Department of Cardiac Surgery, Medical Faculty, Heinrich Heine University Hospital, Düsseldorf, Germany, [8] Heart Transplant Division, Hospital Santa Creu i Sant Pau, Universitat Autònoma, Barcelona, Spain, [9] Division Cardiac Surgery, Lutheran Hospital, Indiana University School of Medicine, Indiana, IA, United States, [10] Complejo Hospitalario Universitario a Coruña (CHUAC), Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares (CIBERCV), La Coruña, Spain, [11] Department of Cardiac Surgery, University Hospital 12 de Octubre, Madrid, Spain, [12] Heart and Heart-Lung Transplant Unit Medical, Department of Cardiovascular Surgery, Les Hôpitaux Universitaires NHC, Strasbourg, France, [13] Department of Cardiac Surgery, Heidelberg University Hospital, Heidelberg, Germany, [14] Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, United States, [15] Heart Failure and Heart Transplant Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico S. Orsola, Bologna, Italy, [16] Heart Transplant Program, Cedars-Sinai Medical Center, Los Angeles, CA, United States, [17] Cardiac Transplant Program, Peter Munk Cardiac Centre, Toronto, ON, Canada, [18] Department of Cardiac Surgery, University Hospital Dubrava, Zagreb, Croatia, [19] Thoracic Transplant Program, AdventHealth Transplant Institute, Florida, FL, United States, [20] Cardiac Surgery Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico S. Orsola, Bologna, Italy, [21] Cardiac Transplantation Program, Tufts Medical Center, Boston, MA, United States*

Background: Allograft pathologies, such as valvular, coronary artery, or aortic disease, may occur early and late after cardiac transplantation. Cardiac surgery after heart transplantation (CASH) may be an option to improve quality of life and allograft function and prolong survival. Experience with CASH, however, has been limited to single-center reports.

Methods: We performed a retrospective, multicenter study of heart transplant recipients with CASH between January 1984 and December 2020. In this study, 60 high-volume cardiac transplant centers were invited to participate.

Results: Data were available from 19 centers in North America (n = 7), South America (n = 1), and Europe (n = 11), with a total of 110 patients. A median of 3 (IQR 2–8.5) operations was reported by each center; five centers included ≥ 10 patients. Indications for CASH were valvular disease (n = 62), coronary artery disease (CAD) (n = 16), constrictive pericarditis (n = 17), aortic pathology (n = 13), and myxoma

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***Correspondence:**
Johannes Gökler
johannes.goekler@meduniwien.ac.at

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(*n* = 2). The median age at CASH was 57.7 (47.8–63.1) years, with a median time from transplant to CASH of 4.4 (1–9.6) years. Reoperation within the first year after transplantation was performed in 24.5%. In-hospital mortality was 9.1% (*n* = 10). 1-year survival was 86.2% and median follow-up was 8.2 (3.8–14.6) years. The most frequent perioperative complications were acute kidney injury and bleeding revision in 18 and 9.1%, respectively.

Conclusion: Cardiac surgery after heart transplantation has low in-hospital mortality and postoperative complications in carefully selected patients. The incidence and type of CASH vary between international centers. Risk factors for the worse outcome are higher European System for Cardiac Operative Risk Evaluation (EuroSCORE II) and postoperative renal failure.

Keywords: cardiac transplantation, heart transplantation, cardiac surgery, heart failure, cardiac retransplantation

INTRODUCTION

Heart transplantation (HTX) confers excellent long-term survival in select patients with symptomatic end-stage heart failure. Cardiac surgery after heart transplantation (CASH) is a rarely used approach to improve allograft function and quality of life, and prolong survival (1), but has been described only in case reports and single-center experiences (2, 3). Although symptomatic tricuspid regurgitation is known as the most common cause for CASH (2), other valvular diseases, aortic pathology, and cardiac allograft vasculopathy (CAV) can occur in the HTX population (1–3). Coronary artery bypass grafting (CABG) is a safe surgical therapy for CAV, in selected cases, with acceptable long-term outcomes (1, 2). Furthermore, transcatheter and minimally invasive strategies to treat allograft pathologies have been reported with excellent short-term outcomes (4–9).

In this retrospective, multicenter, cohort study, we evaluated the safety of CASH and risk factors for subsequent morbidity and mortality.

MATERIALS AND METHODS

The study cohort was comprised of heart transplant recipients who underwent CASH between January 1984 and December 2020. CASH includes cardiac and aortic transcatheter interventions but does not include retransplantation, pacemaker/defibrillator placement, or reoperation due to bleeding complications. In total, 60 high-volume cardiac transplant centers performing more than 15 HTXs per year were invited to participate in the study. Each participating center obtained ethics approval from its institutional review board (Vienna ethics committee reference number: 1894/2017) and a data use agreement was executed with each center.

Relevant data on demographics, medical history, medications, surgeries, cardiac testing, outcomes, and complications were collected from the patients' medical records and were de-identified by each center's study coordinator. A password-protected, validated Excel file was sent to the primary investigator for statistical analysis. The European System for Cardiac Operative Risk Evaluation (EuroSCORE II) (10, 11), a validated scoring system that predicts the risk of in-hospital mortality after major cardiac surgery, was calculated.

The inverse Kaplan–Meier method was used to quantify median follow-up (12). To evaluate the effect of selected clinical factors on in-hospital mortality, we used univariate logistic regression models accounting for the center as a random effect. Survival after reoperation was described using the Kaplan–Meier method. Two-sided $p < 0.05$ were considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Study Population

Data from 110 patients were submitted by 19 centers (the United States-6; Spain-3; Austria-2; Germany-2; Argentina-1; Canada-1; Croatia-; France-1; Italy-1; and Slovakia-1) with a median of 3 (interquartile range [IQR] 2–8.5) patients per center; five centers reported ≥ 10 patients. The incidence of CASH was 0.86% (lowest 0.17%, highest 2.46%; and total number of HTX: 14,185). The median age at CASH was 57.7 (IQR 47.8–63.1) years with a median interval between HTX and CASH of 4.4 (IQR 1–9.6) years. Indications for surgery was valvular disease (*n* = 62), coronary artery disease (CAD) (*n* = 16), constrictive pericarditis (*n* = 17), aortic disease (*n* = 13), and myxoma (*n* = 2). Five patients (4.5%) had infectious etiology, including two fungal constrictive pericarditis, one aortic and one tricuspid valve endocarditis, and one infectious aortic pseudoaneurysm at the suture line. In 27 (24.5%) patients, CASH was performed in the first year,

Abbreviations: BiVAD, biventricular assist device; CABG, coronary artery bypass grafting; CAV, cardiac allograft vasculopathy; CASH, cardiac surgery after heart transplantation; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; EuroSCORE II, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; HTX, heart transplantation; IQR, interquartile range; LVEF, left ventricular ejection fraction; OR, odds ratio; PCI, percutaneous coronary intervention; POD, postoperative day; TAVR, transcatheter aortic valve replacement.

including 10 in the first 30 days. Thirty-six patients (32.7%) had an urgent indication for surgery. The surgical approaches were redo-sternotomy (n = 104), thoracotomy (n = 4), and transcatheter (TAVR; n = 2). Patient characteristics are provided in **Table 1**.

Outcome

The most common postoperative complication was acute kidney injury (**Table 1**). A permanent pacemaker was needed due to atrioventricular block in five patients, all after tricuspid valve surgery. Postoperative graft failure resulted in early death after tricuspid valve surgery in two patients and after pericardiectomy in one patient. In another patient, graft function recovered with postoperative extracorporeal membrane oxygenation (ECMO) support after total aortic arch replacement, aortic valve replacement, and CABG. Causes of death after discharge were cardiac (n = 14), infectious (n = 10), malignancy (n = 9), neurological complications (n = 3), and other (n = 8).

Overall survival was 86.2 ± 3.3 and 76.7 ± 4.2% after 1 and 3 years, respectively (**Figure 1A**). The 3-year survival stratified by indication for CASH is shown in **Figure 1B**. In-hospital mortality was 9.1% (n = 10), with systemic infection (n = 6), graft failure (n = 3), and bleeding (n = 1) as causes of death. Patients with urgent (compared with elective) CASH had worse in-hospital, 1-, and 3-year survival (Kaplan–Meier estimate: 83.3, 80.4, and 63.6% vs. 94.6, 89.1, and 82.8%, respectively; **Figure 1C**). In-hospital mortality was higher in patients with postoperative acute kidney injury (n = 20, 19.1%; 35.0 vs. 3.5% for urgent vs. elective, respectively). In univariate logistic regression analysis, postoperative acute kidney injury (odds ratio [*OR*] 14.7 [95% confidence interval [*CI*] 3.3–65.6], p = 0.0006) and higher EuroSCORE II (*OR* for 2-fold increase 2.0 [1.0–3.7], p = 0.04) were statistically significantly associated with in-hospital mortality. Higher in-hospital mortality was associated with urgent indication for surgery (*OR* 3.5 [0.9–13.6], p = 0.07), as well as older age at the time of reoperation (*OR* for 10-year increase 1.8 [0.9–3.6], p = 0.08). However, these effects were not statistically significant. Heart transplant recipient sex (p = 0.32), time since HTX (p = 0.89), and baseline serum creatinine (p = 0.55) were not statistically significantly associated with in-hospital mortality in univariate logistic regression models (**Supplementary Table 1**).

TABLE 1 | Patient Characteristics, including postoperative details.

N	110
Sex (male), *n*	90 (82%)
Age at HTX, IQR, y	51.8 (40.7–57.5)
Donor age, IQR, y	42 (28–49)
EuroSCORE II, IQR	4.7 (2.9–8.2)
LVEF < 50%, *n*	13 (11.8%)
Diabetes, n	27 (24.5%), 14 NIDDM/13 IDDM
Creatinine pre-op (mg/dL), IQR	1.6 (1.3–2.2)
CKD (GFR < 60 mL/min), n	59 (53.6%), 5 dialysis dependent
CPB-time, IQR, min	109 (91.5–165)
Cross-clamp time, IQR, min	65 (46–94.5)
ICU stay, IQR, d	3.5 (1–6.3)
In-hospital stay, IQR, d	15 (10–24.5)
Perioperative complication, *n*	
Acute kidney injury	20 (18.2%)
Bleeding revision	10 (9.1%)
Pneumonia	8 (7.3%)
Wound infection	5 (4.5%)
Need for pacemaker	5 (4.5%)
Allograft failure	4 (3.6%)
Stroke	2 (1.8%)
In-hospital mortality, *n*	10 (9.1%)
1-year survival (SE)	86.2% (3.3)
Follow-up, IQR, y	8.2 (3.8–14.6)

CKD, chronic kidney disease; CPB-time, cardiopulmonary bypass time; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; HTX, heart transplantation; ICU, intensive care unit; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; SE, standard error.

Valvular Disease

Tricuspid Valve Surgery

Tricuspid valve surgery was the most common CASH (n = 48) at 14 centers (**Table 2**): 7 centers with one patient, 4 centers with two, and 4 centers with more than two (n = 3, 8, 10, and 12). Of these 48 patients, 5 had tricuspid valve surgery in combination with surgical procedures involving the mitral valve (n = 3), aortic valve (n = 1), and aorta (n = 1).

For isolated tricuspid valve surgeries, the indication was severe, symptomatic tricuspid regurgitation. Biopsy-induced tricuspid regurgitation was the most common indication for surgery. Twelve patients (27.9%) underwent CASH in the first year post-transplant, most within the first 90 days (n = 9).

Major complications were comprised of intraoperative aortic dissection at the cannulation site, which required hemiarch replacement in one patient. Two patients developed intraoperative right heart failure, and both died perioperatively. One patient underwent biological tricuspid valve replacement 4 months after repair due to severe recurrent regurgitation. Four early deaths occurred on postoperative days (PODs) 0, 12, 26, and 34.

Mitral Valve Surgery

Five centers reported 12 patients who had mitral valve surgery (**Table 3**). One patient with concomitant mitral and aortic valve replacement and tricuspid valve reconstruction is described in the aortic valve surgery section. Three patients had tricuspid valve surgery (2 repairs; 1 replacement) as a concomitant procedure. The median age at CASH was 61.5 (IQR 51.6–62.6) years, and the time to CASH was 7.2 (IQR 3.1–10.1) years. One procedure was performed on postoperative day (POD) 2 due to severe mitral regurgitation with a ruptured cord in the anterior leaflet. Surgical access was usually sternotomy, except for one patient who had a thoracotomy. The median postoperative intensive care unit (ICU) stay was 5 (IQR 1–8) days and the in-hospital stay was 15 (IQR 10–21.8) days. No early perioperative (in-hospital) or surgery-related deaths occurred. Postoperative complications were acute kidney injury and reintubation in one patient.

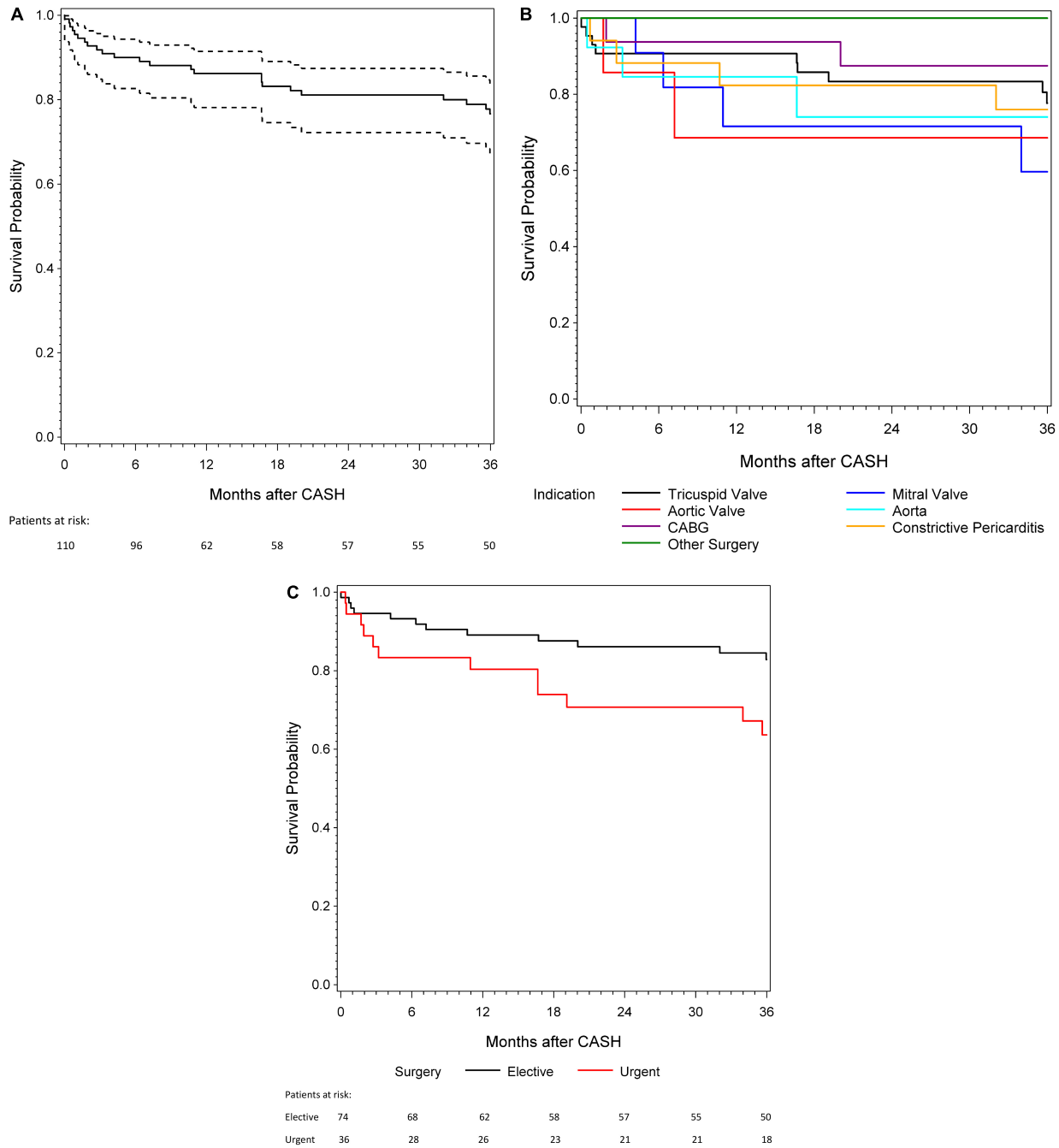

FIGURE 1 | (A) A 3-year survival for patients with cardiac surgery after heart transplantation (CASH). **(B)** A 3-year survival according to the different indications for CASH. **(C)** A 3-year survival in patients with urgent and elective indication for CASH.

Furthermore, 1-year survival was 71.6%, and death was not related to the mitral valve surgery.

Aortic Valve Surgery

Cardiac surgery after heart transplantation due to aortic valve disease was performed in 7 patients at six centers (**Table 4**). The median age and allograft age at CASH were 61.3 (IQR 56.9–68.7) and 59.2 (IQR 45.8–70.6) years, respectively. One patient underwent CASH in the first year (POD 20, unknown cause of aortic regurgitation), and the median time to CASH was 7.1 (IQR 3.7–10.6) years. Surgical access was sternotomy in all but two patients who had transcatheter aortic valve replacement (TAVR). The postoperative ICU stay was 4 days (IQR 1.8–6.3), and the in-hospital stay was 18 days (11–34). Two patients had a complicated postoperative course requiring surgical revision (bleeding) and died 52 and 219 days after CASH, respectively; all the others

are still alive. Four patients underwent aortic valve surgery due to aortic disease (aneurysm/dissection) and are described in the aortic surgery section.

Aortic Surgery

Aortic surgery due to ascending aortic pathologies (dissection, aneurysm, or pseudoaneurysm) was performed in 13 patients at 11 centers (**Table 5**). The median age at CASH was 57.5 (IQR 50.3–61.1) years and the time to CASH was 3.9 (IQR 0.8–7.6) years. Four patients had surgery within the first year (PODs 20, 50, 110, and 235). Allograft function was preserved in all patients. The median preoperative serum creatinine was 1.1 (1.0–1.7) mg/dl. Two patients had reduced kidney function preoperatively, including one patient who was dialysis-dependent.

The median postoperative ICU stay was 5 (IQR 4–6) days, and the in-hospital stay was 18 (IQR 14–24) days. One patient required temporary ECMO due to postoperative stunning and allograft function subsequently recovered. Early postoperative death (PODs 14 and 97) occurred in two patients after a complicated clinical course. The 1-year survival was 84.6%.

TABLE 2 | Tricuspid valve surgery.

N	43
Sex (male), *n*	34 (79.1%)
Age at CASH, y	52.0 (35.4–63.4)
EuroSCORE II	4.4 (2.9–6.3)
LVEF < 50%, *n*	7 (16.3%)
Creatinine pre-op (mg/dL)	1.7 (1.5–2.3)
CKD (GFR < 60 mL/min), *n*	21 (48.8%), 2 dialysis dependent
Time to CASH, y	3.8 (0.9–9.8)
Urgent operation, *n*	14 (32.6%)
Indication, *n*	
Biopsy induced	22
Annular dilation	8
Degenerative	4
Pacemaker lead	1
Endocarditis	1
Unknown cause	7
Operation, *n*	
Repair	22 (51.2%)
biological valve/mechanical valve	19 (44.2%)/2 (4.7%)
Access (sternotomy), *n*	42; thoracotomy *n* = 1
ICU stay, d	3.5 (2–8)
Complications, *n*	
Renal replacement therapy	11 (26.2%)
AVB, PM-implant	5 (11.9%)
Bleeding revision	5 (11.9%)
Right heart failure	2 (4.7%)
Pneumonia	4 (9.3%)
Wound infection	1
Dissection at cannulation site	1
Recurrent severe regurgitation	1 (biological valve replacement)
In-hospital mortality, *n*	4 (9.3%)
1-year survival (SE)	90.7% (9.3)

AVB, atrioventricular block; CASH, cardiac surgery after heart transplantation; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; ICU, intensive care unit; PM-implant, pacemaker implantation; SE, standard error.

Coronary Artery Bypass Grafting Surgery

Sixteen patients (87.5% male) from eight centers who had CAD as the indication for CABG surgery are described in **Table 6**. The median age and allograft age at CASH were 60.3 (IQR 54.6–63.3) and 45.8 (IQR 36.9–54.3) years, respectively. The time to CASH was 8.8 (IQR 5.9–9.8) years. Allograft function, as measured by the left ventricular ejection fraction (LVEF), was severely impaired (< 30%) in two patients, preserved (≥ 50%) in seven patients, and data were not available in seven patients. Eleven patients had reduced kidney function preoperatively, including a patient who was dialysis-dependent.

One patient had percutaneous coronary intervention (PCI) in the allograft prior to CABG surgery. Four patients had diabetes mellitus, including two patients who were insulin-dependent. Coronary angiography was performed in all of the planned CABG surgeries, and computed tomography (CT) was available in only half the patients.

The indications for CASH were CAV (n = 14), iatrogenic left main stem dissection following routine coronary angiography (n = 1), and right coronary artery stenosis unknown at the time of HTX (CABG performed on POD 3). Surgical access was median re-sternotomy in all but two patients who underwent minimally invasive direct coronary artery bypass (MIDCAB). The left internal mammary artery was used as the bypass graft in 81.3% of procedures, and the right internal mammary artery in 37.5%. Saphenous vein grafts were used in half of the patients, radial artery only in one patient.

The median postoperative ICU stay was 2.5 (IQR 1–3.8) days and the in-hospital stay 12.5 (IQR 11–20.8) days. The 1-year survival was 93.8% with only one CASH-related death (POD 59, after iatrogenic left main stem dissection). Due to progression of CAV, half of the patients subsequently had PCI with drug-eluting stents and one patient underwent cardiac retransplantation.

In six additional patients, CABG surgery was a concomitant procedure, and the patients are described in the aortic valve surgery (n = 2), aortic surgery (n = 3), and constrictive pericarditis (n = 1) sections.

Pericardiectomy

Five centers reported 17 patients who had pericardiectomy due to constrictive pericarditis (**Table 7**). Three centers reported more than one case each (n = 4, 5, and 6). The median age at CASH was 56.3 (IQR 54.7–63.5) years and the time to CASH was 1.7 (0.7–3.1) years. Five patients underwent pericardiectomy in the first year. One patient was on vasopressor support with an urgent indication for surgery. Median preoperative serum creatinine was 1.6 (1.5–2.2) mg/dl. Kidney function was reduced preoperatively [glomerular filtration rate (GFR) < 60 ml/min] in 58.8% of patients, and none were dialysis-dependent. Access was *via* a median re-sternotomy for extensive pericardiectomy. The median ICU stay was 1.5 (IQR 1–2.5) days and in-hospital stay was 15 (IQR 8–19) days. In one patient, intraoperative injury of the left anterior descending artery resulted in anastomosis of a

TABLE 3 | Mitral valve surgery.

Pt	Sex	Age	Euro SCORE II	LVEF < 50%	Creatinine	GFR < 60 ml/min	Time to CASH, y	Urgency	Indication	Pathology	Operation	Mortality	Follow-up, y
1	m	47.8	10.27	–	1.3	–	2 days	Urgent	Ruptured chord	Regurgitation	Biological valve	–	5.7
2	f	66.6	6.93	n.a.	2.7	yes	0.6	Elective	Annular dilation	Regurgitation	Repair	–	1.2
3	m	65.1	9.53	yes	1.6	yes	3	Urgent	Degenerative	Regurgitation	Mechanical valve	Cardiac	2.8
4	f	53.1	10.43	–	4	dialysis	3.2	Urgent	Degenerative	Regurgitation	Mechanical valve	Other	0.9
5	m	61.6	2.89	–	1.1	–	5.1	Elective	Degenerative	Regurgitation	Mechanical valve	Other	14.4
6	m	63.7	3.05	–	1.3	–	7.2	Elective	Degenerative	Regurgitation	Mechanical valve	Other	12.3
7	m	61.5	4.8	–	2.5	yes	7.8	Elective	Degenerative	Regurgitation	Repair	Infection	0.4
8	f	50.2	3.42	yes	n.a.	–	9.6	Elective	Degenerative	Both	Mechanical valve	–	0.7
9	m	61.5	8.22	n.a.	3.4	yes	10.6	Elective	Degenerative	Stenosis	Mechanical valve	MOF	5.1
10	m	61.5	5.67	–	1.2	–	10.8	Urgent	Degenerative	Regurgitation	Mechanical valve	Other	9.3
11	m	26.3	3.46	–	0.7	–	13.4	Elective	Degenerative	Regurgitation	Repair	n.a.	0.5
med		61.5 (51.6–62.6)	5.7 (3.4–8.9)		1.5 (1.2–2.7)		7.2 (3.1–10.1)						

CASH, cardiac surgery after heart transplantation; Creatinine, Creatinine pre-op (mg/dL); LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; ICU, intensive care unit; n.a., not available; MOF, multi-organ failure; pt, patient.

TABLE 4 | Aortic valve surgery.

Pt	Sex	Age	Euro SCORE II	Creatinine	Time to CASH, y	Urgency	Pathology	Operation	Concomitant procedure	Complications	Mortality	Follow-up, y
1	m	54.4	16.5	1.4	0.1	Urgent	Regurgitation	Mechanical valve	CABG	Bleeding, RRT, stroke, pneumonia	MOF	0.1
2	m	52.9	6.7	1.2	2.0	Urgent	Endocarditis	Biological valve			–	7.7
3	m	59.3	2.7	n.a.	5.3	Elective	Regurgitation	Mechanical valve			–	0.5
4	m	62.3	15.8	4.4	7.1	Urgent	Stenosis	Mechanical valve	Mitral + tricuspid	RRT	–	0.9
5	m	61.3	2.8	1.7	9.7	Elective	Stenosis	TAVR, femoral			–	3.8
6	m	75.1	7.0	2.1	11.4	Elective	Stenosis	Biological valve		Bleeding	Bleeding	0.6
7	m	83.2	5.1	1.0	22.9	Elective	Stenosis	TAVR, apical			–	2.5
med		61.3 (56.9–68.7)	6.7 (4.0–11.4)	1.5 (1.3–2.0)	7.1 (3.7–10.6)							

CABG, coronary artery bypass graft; CASH, cardiac surgery after heart transplantation; ICU, intensive care unit; n.a not available; MOF, multi-organ failure; MV, mitral valve; pt, patient; RRT, renal replacement therapy.

vein bypass graft. Reintubation was required for pneumonia in one patient, and another patient had a deep sternal infection. One patient had fatal postoperative right heart failure. Overall 1-year survival was 82.4%, and two early deaths were reported (PODs 21 and 83).

Other Operations

Left atrial myxoma resection was performed 1.7 and 14.3 years after HTX (**Table 8**). Both had an uneventful postoperative course and no recurrent disease.

One patient underwent biological pulmonary valve replacement due to regurgitation (valve injury at the time of procurement/implantation) on POD 7. After a complicated postoperative course with surgical revision due to bleeding and pneumonia, the patient is alive 3.8 years after CASH without prosthesis degeneration.

DISCUSSION

Our multicenter study describes the largest cohort of patients with CASH worldwide. We demonstrate that CASH is an acceptable therapy for different cardiovascular pathologies early and late after HTX. Overall in-hospital and 1-year mortality after CASH were acceptable (9.1 and 13.8%, respectively). Urgent indication for CASH, such as endocarditis, infected pseudoaneurysm, aortic dissection, and iatrogenic complications, was strikingly, but not statistically significantly, associated with higher in-hospital mortality. These indications are also associated with high mortality in the general heart surgery population, and in previous reports on CASH (2, 3). Postoperative acute kidney injury requiring renal replacement therapy was the most common complication after CASH and was associated with higher in-hospital mortality. Age at time of CASH and higher EuroSCORE II were also associated with higher in-hospital mortality. However, the effect of age was not statistically significant.

The incidence of postoperative systemic infection and deep sternal wound infection was low (13, 14). Reduction or discontinuation of mammalian target of rapamycin (mTOR) inhibitors several weeks to months prior to elective CASH may be considered due to reports of impaired wound healing (15).

Severe tricuspid regurgitation is the most common reason for CASH (16). HTX-specific tricuspid valve pathologies are biopsy-induced injury to the chordae (leaflets), ischemic injury to the papillary muscle as a consequence of CAV or rejection, and distortion of the valvular apparatus [biatrial implantation technique (2, 17–24). Endocarditis is rare, but is more common than in the general population due to increased risk arising from immunosuppression and frequent central venous access, such as endomyocardial biopsies (25).

Indications for surgery must be carefully considered, especially in patients with ventricular dysfunction and/or pulmonary hypertension because they are at risk of right ventricular failure after CASH. Potential underlying disease processes, such as CAV or acute rejection must be ruled out prior to CASH.

TABLE 5 | Aortic surgery.

Pt	Sex	Age	Euro SCORE II	Time to CASH, y	Urgency	Indication	Operation	Concomitant Procedure	Complications	Mortality	Follow-up, y
1	m	58.6	9.4	20 days	Urgent	Dissection	Bentall, mechanical			–	8.5
2	m	57.1	21.2	0.1	Urgent	Pseudoaneurysm	Supracommissural replacement	TV repair	infection	MOF	0.3
3	m	61.5	10.4	0.3	Urgent	Pseudoaneurysm	Supracommissural replacement			–	2.6
4	m	39.8	7.1	0.8	Elective	Pseudoaneurysm	Supracommissural replacement			–	5.4
5	m	58.0	13.1	1.3	Elective	Aneurysm	Total arch replacement	CABG, aortic valve, stentgraft	ECMO	–	0.9
6	m	61.1	28.3	2.4	Urgent	Pseudoaneurysm	Supracommissural replacement		Bleeding	Bleeding	21 days
7	f	53.8	9.1	3.9	Urgent	Dissection	Supracommissural replacement			Cardiac	5.7
8	m	50.3	23.3	5.1	Urgent	Dissection	Supracommissural replacement	CABG, aortic valve		–	4.0
9	m	57.5	8.7	7.1	Urgent	Aneurysm	Hemiarch replacement	CABG		–	0.3
10	m	48.7	3.8	7.6	Elective	Pseudoaneurysm	Supracommissural replacement			Stroke	3.9
11	f	61.6	6.7	7.7	Elective	Aneurysm	Supracommissural replacement			Cardiac	4.2
12	f	32.7	13.8	10.0	Urgent	Aneurysm	Bentall, biological	CABG		–	1.1
13	m	72.3	31.3	18.1	Urgent	Dissection	Supracommissural replacement			Malignancy	1.4
med		57.5 (50.3–61.1)	10.4 (8.7–21.2)	3.9 (0.8–7.6)							

CABG, coronary artery bypass graft; CASH, cardiac surgery after heart transplantation; ICU, intensive care unit; MOF, multi-organ failure; pt, patient; TV, tricuspid valve.

TABLE 6 | Coronary artery bypass graft surgery.

Pt	Sex	Age	Euro SCORE II	Time to CASH, y	Urgency	Indication	Operation	OP-details	Complications	Mortality	Follow-up, y	PCI/HTX after CASH
1	m	63.0	6.8	3 days	Urgent	Donor stenosis	Vein RCA	RVAD 13d		–	12.3	–
2	m	51.8	2.0	3.6	Elective	CAV	LIMA LAD			Cardiac	5.9	PCI
3	f	62.4	11.5	4.0	Urgent	Iatrogenic dissection	Vein LAD + CX		Sepsis	MOF	0.2	PCI
4	m	59.5	3.7	5.4	Urgent	CAV	LIMA LAD, Vein CX			–	3.8	–
5	m	52.9	2.7	6.1	Elective	CAV	LIMA CX, RIMA DG			Cardiac	9.1	–
6	m	57.4	4.6	7.8	Elective	CAV	Vein LAD + CX			Tumor	7.1	PCI
7	m	65.6	5.5	7.8	Elective	CAV	LIMA LAD, RIMA RCA, Vein CX			–	16.6	PCI
8	m	62.4	4.0	8.5	Elective	CAV	LIMA LAD, RIMA CX			Tumor	7.1	–
9	m	71.4	3.7	9.0	Elective	CAV	LIMA LAD, RIMA RCA (T-graft)			Tumor	8.5	–
10	m	64.3	8.7	9.3	Elective	CAV	LIMA LAD, RIMA DG, Radial CX		Sternal infection	Cardiac	7.6	–
11	m	55.2	2.7	9.3	Elective	CAV	LIMA LAD	off-pump		–	12.3	PCI
12	f	59.6	2.5	9.6	Elective	CAV	LIMA LAD, Vein CX			–	11.8	PCI, Re-HTX
13	m	60.9	2.8	10.4	Elective	CAV	LIMA LAD	MID-CAB		Cardiac	13.3	PCI
14	m	38.4	8.1	10.6	Elective	CAV	LIMA LAD	MID-CAB	RRT	Infection	1.7	–
15	m	48.3	2.7	12.0	Elective	CAV	LIMA LAD + DG, RIMA CX, Vein RCA			–	19.2	PCI
16	m	69.8	29.5	16.2	Urgent	CAV	LIMA LAD, Vein CX + DG + RCA			–	3.9	–
med		60.3 (54.6–63.3)	3.9 (2.7–7.1)	8.8 (5.9–9.8)								

CABG, coronary artery bypass graft; CAV, cardiac allograft vasculopathy; CASH, cardiac surgery after heart transplantation; CX, circumflex artery; DG, diagonal branch; ICU, intensive care unit; LIMA, left internal mammary artery; n.a., not available; MID-CAB, minimally invasive direct coronary artery bypass; MOF, multi-organ failure; PCI, percutaneous coronary intervention; pt, patient; re-HTX, cardiac retransplantation; RIMA, right internal mammary artery; RVAD.

TABLE 7 | Pericardiectomy.

Pt	Sex	Age	Euro SCORE II	Time to CASH, y	Urgency	Complications	Mortality	Follow-up, y
1	m	61.5	2.1	0.2	Urgent		n.a.	2.7
2	m	63.5	4.3	0.2	Elective		Cardiac	0.9
3	m	55.1	4.7	0.3	Elective		–	9.1
4	m	57.4	4.7	0.5	Elective		–	1.5
5	m	65.7	7.7	0.7	Elective	RRT	–	6.9
6	f	47.5	3.4	1.0	Elective	Infection	–	8.2
7	m	63.6	5.2	1.5	Elective		Malignancy	3.5
8	m	45.7	2.7	1.6	Elective		n.a.	4.4
9	m	64.8	3.1	1.7	Elective		Infection	3.5
10	m	56.3	4.7	2.6	Elective		–	0.2
11	m	31.8	2.7	3.0	Elective		Infection	4.2
12	m	26.3	4.7	3.1	Elective		–	9.1
13	m	61.6	2.9	3.1	Elective		n.a.	3.5
14	m	55.9	2.7	3.5	Elective	Right heart failure	Cardiac	0.1
15	f	54.7	4.6	4.3	Elective	Infection, RRT	MOF	0.2
16	m	69.4	4.7	8.3	Urgent		Malignancy	14.1
17	m	55.5	2.7	17.3	Elective		–	3.7
med		56.3 (54.7–63.5)	4.3 (2.7–4.7)	1.7 (0.7–3.1)				

CASH, cardiac surgery after heart transplantation; FU, follow-up; ICU, intensive care unit; n.a., not available; MOF, multi-organ failure; pat, patient; RRT, renal replacement therapy.

TABLE 8 | Other operations.

	Patient 1	Patient 2	Patient 3
Indication	Pulmonary valve regurgitation	Myxoma	Myxoma
CASH	Biological valve	Resection	Resection
Sex	Male	Female	Male
Age	36.1	68	28.5
EuroSCORE II	7.8	9.9	2.7
Time to CASH, y	7 days	1.7	14.3
Urgency	Urgent	Elective	Elective
Complications	Bleeding, pneumonia		
Cause of death	–	–	–
Follow-up, y	3.8	0.7	5

CASH, cardiac surgery after heart transplantation.

Tricuspid valve repair with annuloplasty should only be performed in HTX patients with annular dilation; valve replacement is recommended in complex valvular pathologies or residual regurgitation after repair (21). Besides the risks associated with life-long anticoagulation, mechanical valve replacement rules out the right-sided endomyocardial biopsy. Interventional edge-to-edge repair of the tricuspid valve using the MitraClip system has been reported with perioperative success (26), but long-term data are lacking.

Mitral valve surgery after HTX has been described rarely. Pathology can be related to annular dilation or degeneration of the leaflets or papillary muscles, typically as a consequence of CAV or acute rejection, often accompanied by ventricular dysfunction (27–29). Iatrogenic injury after left-sided endomyocardial biopsy may lead to acute mitral regurgitation. Mitral stenosis has been described in dialysis-dependent HTX patients in association with hyperparathyroidism (30). Mitral valve replacement may be preferred over repair due to complex valvular pathologies in patients with HTX, and to achieve shorter cardiopulmonary bypass times in patients with ventricular dysfunction. In three of our patients, concomitant tricuspid valve repair or replacement was performed without perioperative complications, but postprocedural death occurred 0.5, 0.9, and 2.8 years after CASH.

Minimally invasive CASH *via* thoracotomy confers the advantage of avoiding resternotomy. Transcatheter interventions may be reasonable for patients at high surgical risk with appropriate valvular pathology, but the atrial and atrio-ventricular anatomy can be challenging due to distortions after HTX (9).

Cardiac surgery after heart transplantation due to symptomatic degenerative aortic stenosis in the allograft may occur more often with the acceptance of marginal donor hearts. Single-center case reports have reported acceptable perioperative outcomes (16, 31–33), and case reports on TAVR in HTX patients with high surgical risk have presented data on favorable short-term outcomes (4–8); however, long-term data, as well as data are data on the durability of biological and mechanical valves, are lacking. Aortic valve endocarditis after HTX is extremely rare (34). Our cohort included a patient with biological valve replacement due to endocarditis and 7.7 years of follow-up without valvular degeneration.

Aortic surgery was the most heterogeneous group in our series. Case reports have described successful CASH for ascending aortic aneurysm, dissection, or pseudoaneurysm of the aortic anastomosis (1–3, 35). Aortic pathologies after HTX typically arise at the site of aortic anastomosis due to flow turbulence (donor/recipient aortic size mismatch), infection, or hypertension (36). Due to urgency, the precise preoperative planning of surgery is limited in acute type A dissection and

infected pseudoaneurysm. Our data are in line with previously published data (1). Two patients with urgent surgery due to infected pseudoaneurysm had early surgery-related deaths, highlighting the high risk of mortality associated with this rare disease (36).

Surgical revascularization for CAV is safe, with acceptable long-term results, in HTX patients with acceptable coronary anatomy (type A lesion, Stanford Classification), and elective indication for surgery (1–3, 37). This approach is generally limited, however, by the diffuse nature of CAV (37, 38) and inexorable disease progression in most patients (3, 39), which may necessitate additional interventions (3, 40). The patency of arterial grafts is superior to vein grafts in CASH, with patency of the internal thoracic artery reported up to 20 years (3, 41). Though the left internal thoracic artery was used in most of our patients, the radial artery had good mid-term results in a published case series and may be an adjunct graft in patients with CABG prior to HTX (3).

Constrictive pericarditis after HTX is rare and is typically associated with recurrent pericardial effusions, allograft rejection, or biopsy-related complications (42–44). As most of the participating centers did not report any cases of constrictive pericarditis requiring pericardiectomy, we cannot draw conclusions as to whether patients were undiagnosed at some centers and whether surgical and/or treatment strategies differed at the three centers that reported cases of constrictive pericarditis.

This study is limited by its retrospective nature, the small numbers for each procedure type, and the fact that participation was by invitation only—not all eligible heart transplant centers reported data. It may be of interest, however, for multinational heart transplant registries to begin collecting data on CASH, given the growing population of heart transplant recipients worldwide with improved long-term survival and the increasing use of minimally invasive surgical and transcatheter approaches.

We conclude that CASH is generally safe, with low in-hospital mortality and postoperative complications in carefully selected patients. Nevertheless, it is rarely performed, with differences in practice between heart transplant centers worldwide. Higher EuroSCORE II and postoperative acute kidney injury are associated with higher in-hospital mortality.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

JG and AA-Z designed the study and wrote the manuscript. JG organized the database. AK performed the statistical analysis. All authors contributed to manuscript revision and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.879612/full#supplementary-material

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EDITED BY
Laurens F. Tops,
Leiden University Medical Center, Netherlands

REVIEWED BY
Marco Matteo Ciccone,
University of Bari Aldo Moro, Italy
Alan Gallingani,
University Hospital of Parma, Italy

*CORRESPONDENCE
Maria Concetta Pastore
pastore2411@gmail.com

†These authors have contributed equally to this work and share first authorship

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A multidisciplinary approach for the emergency care of patients with left ventricular assist devices: A practical guide

Matteo Cameli[1†], Maria Concetta Pastore[1*†], Giulia Elena Mandoli[1], Federico Landra[1], Matteo Lisi[1,2], Luna Cavigli[1], Flavio D'Ascenzi[1], Marta Focardi[1], Chiara Carrucola[1], Aleksander Dokollari[3], Gianluigi Bisleri[3], Charilaos Tsioulpas[4], Sonia Bernazzali[4], Massimo Maccherini[4] and Serafina Valente[1]

[1]Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy, [2]Division of Cardiology, Department of Cardiovascular Diseases -AUSL Romagna, Ospedale S. Maria delle Croci, Ravenna, Italy, [3]Department of Cardiac Surgery, Cardiac Surgery, St. Michael Hospital, Toronto, ON, Canada, [4]Department of Cardiac Surgery, Azienda Ospedaliera Universitaria Senese, Siena, Italy

The use of a left ventricular assist device (LVAD) as a bridge-to-transplantation or destination therapy to support cardiac function in patients with end-stage heart failure (HF) is increasing in all developed countries. However, the expertise needed to implant and manage patients referred for LVAD treatment is limited to a few reference centers, which are often located far from the patient's home. Although patients undergoing LVAD implantation should be permanently referred to the LVAD center for the management and follow-up of the device also after implantation, they would refer to the local healthcare service for routine assistance and urgent health issues related to the device or generic devices. Therefore, every clinician, from a bigger to a smaller center, should be prepared to manage LVAD carriers and the possible risks associated with LVAD management. Particularly, emergency treatment of patients with LVAD differs slightly from conventional emergency protocols and requires specific knowledge and a multidisciplinary approach to avoid ineffective treatment or dangerous consequences. This review aims to provide a standard protocol for managing emergency and urgency in patients with LVAD, elucidating the role of each healthcare professional and emphasizing the importance of collaboration between the emergency department, in-hospital ward, and LVAD reference center, as well as algorithms designed to ensure timely, adequate, and effective treatment to patients with LVAD.

KEYWORDS

emergency, heart failure, urgency, LVAD (left ventricular assist device), mechanical circulatory support (MCS)

Introduction

A left ventricular assist device (LVAD) is implanted to support cardiac function in patients with end-stage heart failure (HF), when the myocardium is no more capable of ensuring the necessary hemodynamic conditions to maintain normal vital functions. The device implantation stage is strictly a matter of cardiac surgeons and should take place only in designated centers under the coordination of the National Heart Transplantation Center.

Thanks to rapid improvements in technology using more reliable and durable devices and an increasing incidence of advanced HF, the use of LVAD is widespread in almost all developed countries (1–3); however, few centers have the required expertise and supplies. This entails the referral of many patients coming from the whole country to a reference LVAD center, even many miles away from the local center. After implantation, these patients will have to be permanently referred to the LVAD center for device management and follow-up; however, routine assistance will be demanded by their trusted cardiologists and family doctors. Moreover, in case of urgent health issues, whether device-related or generic, they would refer to the local healthcare service. The concept of "shared-care" was born to optimize the management of severe patients and patients with chronic diseases through improved communication between primary and specialty centers and knowledge sharing. The result is an improvement in the quality of care by primary care hospitals alongside a reduction in the workload for tertiary center and, therefore, the overall cost. It has also proven to be a feasible and effective strategy for patients with LVAD (4).

Therefore, as the number of patients treated with LVAD is increasing, many clinicians, from bigger to smaller centers and from cardiologists to all healthcare professionals, will have to deal with LVAD carriers in the near future, so they should be prepared for the possible risks associated with LVAD management. In fact, emergency treatment of patients with LVAD differs slightly from the conventional emergency protocols and requires specific knowledge to properly manage, avoid ineffective treatment, or provide dangerous consequences (5, 6).

Several authors have already addressed this concern, and a recent expert consensus has been published on this topic (7, 8) However, the importance of a multidisciplinary approach for these patients and cooperation between the emergency department (ED) and in-hospital ward, within the LVAD center or, for local centers, with the LVAD center, and the role of each healthcare professional in the critical management of these sensitive patients has not been fully elucidated.

The main purpose of this paper is to present a standard protocol addressed to all healthcare professionals, based on the available evidence and authors experience, focused on the role of multiple clinical parts for the care and management of patients with LVAD. This would provide algorithms designed to ensure an adequate and timely response of all clinicians involved in the emergency care areas and clear indications for the interaction between dedicated and non-dedicated professionals.

LVAD-associated complications

Left ventricular assist device-associated complications may be classified into LVAD-specific and LVAD-related complications (9). LVAD-specific complications are those directly involving structural or functional properties of the device and include suction event, pump thrombosis, pump failure, pump stoppage, and driveline damage. Besides, complications referred to as "related" are those not directly affecting the device but due to its presence and associated treatment. LVAD-related complications are, therefore, bleeding, hemorrhagic or ischemic stroke, infections, right ventricular failure, dysrhythmia, and aortic regurgitation (10).

In most of the cases, LVAD-related complications present themselves as emergencies, requiring the patient to be admitted to the nearest ED. As reported by the Heart Failure Society of America (HFSA), the Society for Academic Emergency Medicine (SAEM), and the International Society for Heart and Lung Transplantation (ISHLT) in the 2019 consensus for managing emergencies in patients with ventricular assist devices (VAD) (1), among the most worrisome medical emergencies commonly reported in individuals with VADs are cardiac arrest, unstable arrhythmias, myocardial infarction, and unexplained hypotension.

The nearest healthcare center plays a crucial role in readily evaluating patients who arrive in an unstable condition and stabilizing their vital parameters before sending them to a center with appropriate expertise. Situations that typically require immediate transfer to a *primary VAD center are*

- cardiac tamponade,
- mechanical VAD failure,
- pump thrombosis,
- emergency non-cardiac surgery, and
- neurological events.

Many concerns about the management of such patients arise from their intrinsic precarious coagulation balance. In fact, LVAD carriers are both at high thrombotic and high bleeding risk. On one hand, the risk of thrombosis is mainly determined by the presence of a foreign body, a severely reduced ejection

fraction, and possibly atrial fibrillation. On the other hand, bleeding risk is due to the assumption of vitamin K antagonists along with aspirin, the possibility of hepatic congestion consequent to right heart dysfunction, and von Willebrand acquired disease.

Table 1 lists specific recommendations for the primary assistance of the most common LVAD-specific and LVAD-related emergencies.

Emergency care

Patient's approach

There are some pivotal indications that each healthcare worker should respect when dealing with LVAD carriers (Table 2).

- Undress the patient delicately and do not use sharp tools to remove clothes.
- Pay attention to device cables and batteries, and do not use potentially damaging tools (e.g., scissors and scalpel).
- Check that batteries are connected to cables and are correctly working.
- The cardiologist in charge of the coronary care unit (CCU) must be immediately notified of the patient's admission and should take charge of the patient.
- Contact the LVAD reference regional center (telephone number list in the CCU).
- Invite the parent with LVAD to participate (if they are absent, call them quickly).
- Make sure that the patient is provided with an extra battery.

Almost all patients with LVADs have a small tag on their controllers that indicate specific devices, the center of implantation, and an emergency phone number. It is paramount in an emergency to focus on the color of the tag, which could rapidly lead to recognize the type of device, since each color is paired with a specific device following the emergency medical services (EMS) guide (10). Currently, the most widely used devices are HeartMate III, Jarvik 2000, and Heartware. Even if different devices share some characteristics and possible management, there are significant differences from technical to practical aspects, which are fully presented in Table 3.

Clinical evaluation and advanced cardiovascular life support algorithm

Figure 1 shows a practical algorithm to be followed in case of emergency in patients with LVAD (11).

The healthcare worker conducting the clinical evaluation must remember that:

- The patient could have no pulse (LVAD flow could continue, therefore not pulsatile).
- Heart rate at electrocardiogram (ECG) could differ from those evaluated with a pulse if the device has a continuous flow and is not synchronized with the heart rate.
- Blood pressure (BP) assessment could be challenging in the absence of pulsatile blood flow. Arterial BP could be measured manually using the sphygmomanometer (also with Doppler assistance) with the first audible Korotkoff tone corresponding to the medium BP or using an invasive system of BP monitoring. A medium BP value between 70 and 90 mmHg is indicated.
- Pulse oximeter could be less accurate for estimating oxygen blood saturation.
- Heart auscultation is anomalous; heart sounds are partially concealed by continuous LVAD noise. The absence of continuous LVAD noise could indicate a device dysfunction.

Just after the clinical evaluation, the CCU nurse should be informed to check the availability of beds in the CCU. Remember not to stop anticoagulation therapy unless indicated by the CCU cardiologist. The patient should be transferred to the CCU as soon as possible, unless clinical conditions require immediate treatment or urgent transfer to an LVAD center.

If required, resuscitation maneuvers start immediately following the advanced cardiovascular life support (ACLS) LVAD algorithm. Remember that resuscitation maneuvers can provoke LVAD cannula displacement (particularly cannulas positioned at the apex of the left ventricle and in the aorta), leading to sudden death. Therefore, the use of these maneuvers is permitted only in extreme situations as a last chance after excluding other resolvable causes of circulatory arrest. Electrical cardioversion and defibrillation are possible with any device. When performing electrical cardioversion or defibrillation, care should be taken not to place metal plates in a position corresponding to the device. However, aggressive treatment of arrhythmias in asymptomatic patients should be avoided. All drugs listed in ACLS could be administered.

Further assessments

Additional assessments may be required to get to the root of the problem. These include:

a) Laboratory data: A complete blood count should be routinely performed, along with other assessments such as lactate dehydrogenase (LDH), haptoglobin, plasma free hemoglobin, troponin, and brain natriuretic peptide (BNP/N-terminal-pro-BNP) coagulation panel. Anemia may be indicative of ongoing bleeding or hemolysis if

TABLE 1 Management of the main emergency conditions of patients with LVAD according to the Heart Failure Society of America (HFSA), the Society for Academic Emergency Medicine (SAEM), and the International Society for Heart and Lung Transplantation (ISHLT) consensus document (1).

Clinical presentation	Recommendations
Stroke (ischemic or hemorragic)	Ischemic -> endovascular treatment (call LVAD Center first)
	Hemorragic -> blood pressure control, discontinue or reverse anticoagulation, neurologist and neurosurgeon consultation
HF (*inadequate decompression of LV or RV failure)*	Diuretics
	Positive inotropic support (es.milrinone) for subacute/chronic right HF
Abdominal pain	Physical examination and assessment of medical history -> if urgent surgery is needed, send to LVAD center
Bleeding	Assess hemodynamic stability
	Stop source of bleeding (EGDS and/or colonscopy may be necessary
	Balance concomitant antithrombotic risk and the need for reversal agents (vitamin K, fresh frozen plasma, prothrombin complex concentrates)
	Transfusions (reduces rates of future heart transplantation)
VAD-specific emergencies	
Pump thrombosis	IV Heparin and consider surgery treatment (immediate transfer to LVAD center) or mechanical circulatory support (e.g., ECMO)
Pump stoppage or failure	Use ungrounded cable or place patients on batteries only *(less stable long-term choice)*
	Whenever pump stoppage of failure happens, immediate call LVAD center

accompanied by an increase in LDH and free hemoglobin and a decrease in haptoglobin levels. Of note, hemolysis is often due to pump thrombosis in LVAD carriers, so it should be carefully excluded (12–15). On the other hand, abnormalities in the coagulation panel may support a diagnosis of pump thrombosis, if clinically suspected. Also, BNP/NT-pro-BNP could be elevated in this case, as well as in case of device malfunction or a new onset right HF (16–20). Troponin elevation can be found in multiple scenarios and should be specifically requested in case of new onset angor, dyspnea, or new alterations on the ECG.

b) Arterial blood gas analysis: To assess the presence of acidemia. Please consider that arterial puncture will not be easy as usual because the pulse is often diminished and the patients are always on anticoagulation therapy.

c) Imaging:

- **Chest X-Ray**: Easily available and helpful to evaluate pump and inflow–outflow cannula position (11).
- **Echocardiography**: Important to analyze pump flow, possible thrombosis, mechanical complications, LV hemodynamic conditions and filling, and valvular regurgitation [aortic regurgitation can frequently occur in patients with continuous LVAD flow due to multiple factors such as LV unloading (9)]. If available, it is important to perform bedside echocardiography to help focus the diagnosis. Figure 2 shows an algorithm to speed up diagnosis and treatment of the emergence of LVAD starting from echocardiographic findings (15, 16, 21).
- **Computed tomography (CT)**: It could help evaluate areas not visible by echocardiography, such as outflow pump cannula position, and the lack of information due to the poor acoustic window in these patients (22, 23). Moreover, cranial acquisition is crucial in case of suspected stroke, to differentiate hemorrhagic from ischemic ones.

Remember that magnetic resonance imaging (MRI) is contraindicated in patients with LVAD.

Roles and responsibilities

Each healthcare worker plays a specific role in emergency care as described above.

Role of the medical director

a) To ensure the distribution of this document and the comprehension of its content with reference to all possible participants in the management of patients with LVAD.

b) To organize a systematic pathway between LVAD centers and the local hospital to identify all patients with old and new LVAD implantations possibly pertaining to that area. A list of *LVAD carriers* should be placed in a dedicate folder and stored in the ED or CCU.

TABLE 2 Primary practical indications for in-hospital emergency management of patients with LVAD.

1. Immediate approach to LVAD patients in emergency/urgency clinical scenarios. A) Undress the patient delicately and **Don't use sharp tools** to remove clothes. B) Pay attention to the **Cables** and **Batteries** of the device, avoiding the use of tools that could potentially damage them (e.g., scissors, scalpel). C) Check that batteries are **Connected** to cables and that are correctly **Working** D) The **Cardiologist** responsible of **CCU** must be immediately informed about the patient admission and should take charge of the LVAD patient. E) Inform the **LVAD reference regional Center** (telephone number list in CCU) F) Invite the PARENT TRAINED for LVAD use to participate (if he is absent, call him quickly). G) Be sure that the patient is provided with an **Extra-battery.**
2. Evaluation of vital signs and physical examination. A) Patient could present **No pulse** (the LVAD flow could be continue and not pulsating). B) Heart rate at ECG could differ from those evaluated with pulse if the device is continue-flow and is not synchronized with heart rate. C) **Pulse oxymeter** could be less accurate for the estimation of oxygen blood saturation. D) **Heart auscultation** is anomalous: heart sounds are partially concealed by the continuous LVAD noise. E) The absence of the continuos LVAD NOISE could indicate device dysfunction.
3. The resuscitation maneuvres could provoke **LVAD cannulas dislocation** (particularly, the cannulas positioned in LV apex and in aorta) leading to sudden death, therefore the use of these maneuvers is permitted only in extreme situation and, preferably, in presence of selected devices (Table 3) and should be applied only as the last chance after excluding other resolvable causes of circulatory arrest. Electrical cardioversion (ECV) and defibrillation are possible with any device, however, the aggressive treatment of arrhythmias in **asymptomatic patients should be avoided** (also in case of non-sustained ventricular tachycardia): in case of the performance of ECV or defibrillation, beware **not to place the metal plates in correspondence of the device.** All drugs listed in ACLS (Advanced Cardiac Life Support) could be administered.
4. Blood pressure assessment could be challenging for the absence of a pulsatile blood flow. Arterial blood pressures could be manually measured using the sphygmomanometer (also with Doppler assistance) with the first Korotkoff tone audible corresponding to **Medium Blood Pressure,** or alternatively, using an invasive system of blood pressure monitoring. A value of medium BP between 70 and 90 mmHg is considered the medium target in LVAD patients.
5. Don't stop anticoagulation therapy unless indicated by the CCU Cardiologist.
6. CCU nurse should be informed soon in order to check the availability of **beds in CCU.**
7. The patient must be **transferred to CCU** as soon as possible, unless the clinical conditions require an immediate treatment or an urgent transfer to LVAD center.

CCU, coronary care unit; LV, left ventricular; LVAD, left ventricular assist device.

Role of the HF and LVAD multidisciplinary team

A) To ensure continuous update of this document based on the newest evidence.
B) To supervise compliance and correct application of the following procedure when a patient with LVAD is referred to the local hospital.
C) To verify that each patients with LVAD has been correctly identified in the medical records and marked as an "LVAD carrier."
D) To provide a promptly available list of all national LVAD reference centers (to be stored in the CCU).

Role of the physician who is in charge of a patient with LVAD

A) Inform the CCU referral cardiologist of the admission of a patient with LVAD.
B) To ensure that the HF and LVAD multidisciplinary team has been informed of the admission of a patient with LVAD.

TABLE 3 Different LVAD device characteristics and subsequent different emergency management.

Information/devices	Heart MATE 3 / II	Heartware	Jarvik 2000
Mechanism	Centrifugal pump with full magnetic levitation of the rotor / axial continue–flow pump	Centrifugal flow pump	Axial continue–flow pump
Pulse	Normally absent or weak	Normally absent or weak	It could be present depending on myocardial contraction, preload, and afterload
Target vital signs	mBP 70–90 mmHg	mBP 75–90 mmHg (preferably use the doppler method to measure BP)	mBP 65–75 mmHg
Low–flow advices	Heart–shaped red light will appear with a continuous acoustic alarm	Triangular yellow light with acoustic alarm	Low–flow –> Light alarm Pump arrest –> stop signal with red bell and continuous acoustic alarm
Low–flow treatment	*Hypovolemia* –> fluid administration *Right HF* –> inotropes, fluids, hyperventilation	Evaluate if volume expansion is required	
Device flow velocity	Impossible to speed up in out–of–hospital environment	Impossible to speed up in out–of–hospital environment	Normally set on 3 velocity, it could be manually adjusted
Heparin therapy	Generally, not required (discuss with LVAD implantation center)	To decide whether to use heparin, contact LVAD implantation center	Generally, not necessary
Defibrillation	Possible	Possible (don't disconnect device before delivering current)	Possible (don't disconnect device before delivering current)
External or manual pump	Not present	Not present With ECM, high risk of device displacement: evaluate on clinical basis. If ECM has to be performed, evaluate pump function and position first	Not present ECM Possible
External pacing	Possible	Possible	Possible
External cables	One cable emerges from abdomen	One cable emerges from abdomen	One cable emerges from retro–auricular area or abdomen
Battery supply	Patient should have already been equipped with a set of black batteries (3 h duration) and gray batteries (14–17 / 8–10 h duration; charge conditions could be checked pressing the button on the battery cover) –> At least ONE cable must always be connected to a power generator: DON'T remove simultaneously the two batteries, otherwise the pump will stop	Device receive charge from one battery at a time: maximum duration 4–6 h (Both battery and controller have a light signal indicating charge status)	Only battery power source (not electrical current) 2 types of battery: Small and portable, 8–10 h duration (could be quantified pressing on the black button on the battery) Big supply battery, minimum 24 h duration

ECM, external cardiac massage; HF, heart failure; LVAD, left ventricular assist device; mBP, mean blood pressure.

C) To apply the management algorithm reported in Figure 1.
D) To ensure that a phone contact of the closest LVAD reference center is present and that all information about emergency phone numbers, emergency instructions, and battery supply of the device is available to healthcare workers.
E) To ensure systematic follow-up of the patient after discharge [following existing models in other clinical settings (24, 25)] following the Hub–Spoke model in collaboration with the LVAD reference center.

Role of the CCU team

A) If required, to draw up an appropriate treatment plan that integrates clinical and nursing roles for the care of patients with LVAD.
B) To facilitate a timely transfer and admission of the patient with LVAD from the ED to the CCU.
C) To ensure that this protocol is followed specifically in case of the admission of a patient with LVAD.

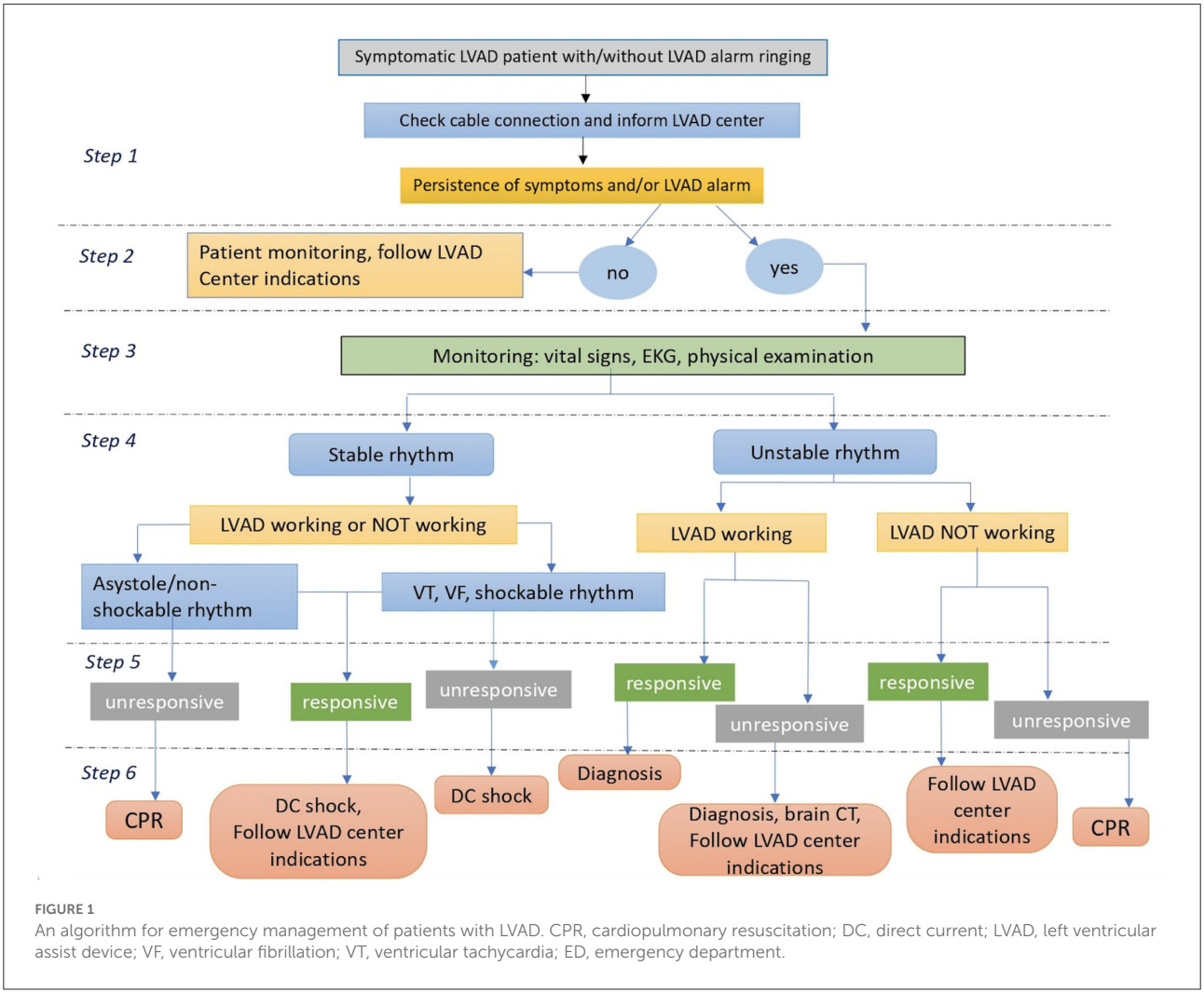

FIGURE 1
An algorithm for emergency management of patients with LVAD. CPR, cardiopulmonary resuscitation; DC, direct current; LVAD, left ventricular assist device; VF, ventricular fibrillation; VT, ventricular tachycardia; ED, emergency department.

D) To inform the LVAD implantation center of the patient's hospitalization as soon as possible (using the phone contacts on the list stored in the CCU-point D in paragraph 2.2).

Role of biomedical engineer

A) Be available for any technical consultation in case of a device malfunction that is not clearly identifiable.
B) Provide technical indications for solving the problem.

Role of nurse care manager

A) Build up and lead the development of a comprehensive, individualized care plan for each hospitalized patient.
B) Contribute to the education of patients and their families by having them fully understand their clinical condition, manage the symptoms associated with their condition, and understand treatment alternatives.
C) Address nonclinical issues that impact quality of life and outcome.

Role of clinicians and nurses in the other departments in which patients with LVAD could be admitted (e.g., surgical department, neurologic department, and so on)

A) Inform the CCU referral cardiologist immediately (if not already done).
B) To ensure that each healthcare operator of the ward is aware of this document.
C) To monitor strict compliance with the advice contained in this document.

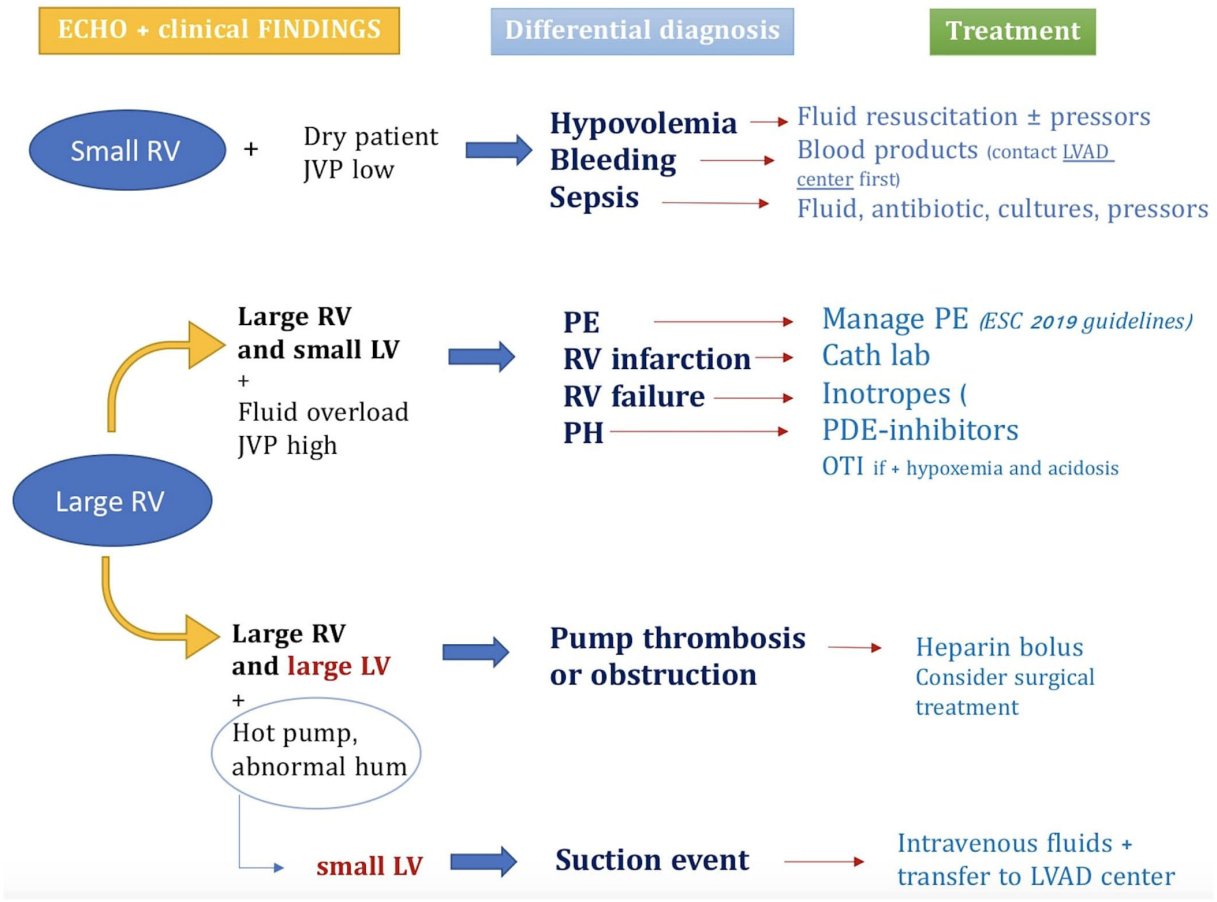

FIGURE 2
An algorithm for the differential diagnosis and treatment of LVAD emergencies that represent an important added value of performing bedside echocardiography. JVP, jugular venous pressure; LV, left ventricle; LVAD, left ventricle assist device; OTI, intubation orotracheal; PDE, phosphodiesterase; PE, pulmonary embolism; PH, pulmonary hypertension; RV right ventricle.

Role of each healthcare professional

A) To be aware of the procedures explained in this document.
B) To perform them correctly in case of the admission of the patient with LVAD.

Conclusions

The growing use of LVAD implantation as destination therapy worldwide has resulted in the need of specific training for clinicians of all specialties to manage patients with LVAD. Particularly, in the emergency setting, a standardized multidisciplinary approach and collaboration between small and VAD centers are essential to ensure the best treatment for patients. This document offers an easy consultation and practical guide for the appropriate management of emergencies in patients with LVAD.

Author contributions

MC, MP, and SV had the idea for this paper. MC, MP, GM, and FL performed the literature search and analysis and drafted the manuscript. ML, LC, CT, MM, SB, FD'A, MF, and SV critically revised the work. All authors contributed to this review conception. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Hendrik Tevaearai Stahel,
Bern University Hospital, Switzerland

*CORRESPONDENCE
Matteo Cameli
matteo.cameli@yahoo.com

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Donor shortage in heart transplantation: How can we overcome this challenge?

Matteo Cameli[1]*, Maria Concetta Pastore[1], Alessandro Campora[1], Matteo Lisi[1,2] and Giulia Elena Mandoli[1]

[1]Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy, [2]Santa Maria delle Croci Hospital, Ravenna, Italy

KEYWORDS

heart transplantation (HT), heart failure, heart donor, ADONHERS protocol, mechanical circulatory support

Introduction

Heart transplantation (HT) is the treatment of choice for carefully selected patients with advanced or end-stage heart failure (HF) in the absence of contraindications (1) (Table 1) with an overall median survival of 12.5 years and conditional survival of 14.8 years for those who surviving after the first year (3).

According to the Global Observatory on Donation and Transplantation, at the end of 2020 (during the COVID-19 pandemic), 2081 patients underwent HT across all European Union countries. In the same year, subjects on the active waiting list were 6,352, among which 435 (7%) died while waiting for a suitable donor (2). Data from 2019 were comparable: 2,269 patients underwent HT, 6,940 subject were on the waiting list, among which 481 (7%) died (4).

Over the past two decades, we registered an increase of 35% in HTs per million population (PMP) rate in Europe, with an annual percentage change (APC) of 1.4% [95% CI (1.1–1.7), $P < 0.0001$]. The increase was particularly relevant in Central Europe, where HTs PMP rate raised from 0.65 in 2000 to 2.93 in 2019 {APC 9.9% [95% CI (8.1–11.8), $P < 0.0001$]} and in Northern Europe, PMP rate from 2.97 in 2000 to 5.18 in 2019 {APC 2.7% [95% CI (1.8–3.7), $P < 0.0001$]} (5).

Despite the reached HT rates, the demand for HTs is persistently higher than the current offer, mainly due to the aging of the global population, the improved overall survival after a myocardial infarction and the better outcome of patients with HF. Solving the current shortage of donor hearts is a major issue, involving medical, legal, religious, cultural, and ethical considerations. This requires combined efforts to expand currently accepted and new selection strategies but also to improve alternative strategies to transplantation. In this editorial, we provide a practical review of selected contemporary advances and challenges in this field.

Increasing the pool of hearts for transplantation with currently accepted methods

The standard cardiac donor selection criteria are listed in Table 2.

TABLE 1 Heart transplantation: Indications and contraindications.

Indications
Advanced HF (2)
No other therapeutic option, except for LVAD as BTT
Contraindications
Assolute
Active infection[a]
Severe peripheral arterial or cerebrovascular disease
Pharmacologic irreversible pulmonary hypertension (LVAD should be considered to reverse elevated pulmonary vascular resistance with subsequent re-evaluation to establish candidacy)
Malignancy with poor prognosis (a collaboration with oncology specialists should occur to stratify each patient as regards their risk of tumor progression or recurrence which increases with the use of immunosuppression)
Irreversible liver dysfunction (cirrhosis) or irreversible renal dysfunction (e.g., creatinine clearance <30 mL/min/1.73 m^2). Combined heart-liver or heart-kidney transplant may be considered
Systemic disease with multiorgan involvement
Other serious comorbidity with poor prognosis
Pre-transplant BMI >35 kg/m^2 (weight loss is recommended to achieve a BMI <35 kg/m^2)
Current alcohol or drug abuse
Psychological instability that jeopardizes proper follow-up and intensive therapeutic regime after heart transplantation
Insufficient social supports to achieve compliant care in the outpatient setting
Relative
Age > 65 years
Obesity (BMI between 30 and 35 kg/m^2)
Cachexia
Irreversible chronic renal failure (clearance <30 ml/min) (except for combined transplant)
Reduced individual compliance and/or poor family support
Diabetes with organ damage (except for non-proliferative retinopathy) or with low glycemic control (HbA1c >7.5 mg/dl or 58 mmol/mol)
Smoking habit (suspension required for at least 6 months)
HCV and/or HBV-related chronic hepatopathy
Severe osteoporosis
Chronic pulmonary disease with severe functional and morphological alterations (GOLD classification)
Severe chronic peripheral vasculopathy based on imaging tests
HIV infection (Useful opinion of the infectious disease specialist)

BMI, body mass index; BTT, bridge to transplantation; HF, heart failure; LVAD, left ventricular assist device.
[a]Active infection is a relative contraindication to transplant although in some cases of infected LVADs it may actually be an indication. Adapted from Crespo-Leiro et al. (2).

Despite strenuous political efforts to promote organ donation and implement donors selection strategies, a lot of differences persists across Europe and other Continents.

TABLE 2 Traditional cardiac donor selection criteria.

Traditional cardiac donor selection criteria
Age <55 years old
No history of chest trauma or cardiac disease
No prolonged hypotension or hypoxemia
Appropriate hemodynamics
Mean arterial pressure >60 mmHg
Central venous pressure 8 to 12 mmHg
Inotropic support <10 mg/kg/min (dopamine or dobutamine)
Normal electrocardiogram
Normal echocardiogram
Normal cardiac angiography (if indicated by donor age and history
Negative serology (hepatitis B surface antigen, hepatitis C virus and human immunodeficiency virus)

Adapted from Sellke et al. (6).

Geography should not represent a determinant of the possibility of a potential candidate to receive HT, but the disparities in HTs rates among European countries suggest many factors needing improvements, including: optimization and coordination of the donation process, education of professionals, patients and the general population, disposal of appropriate financial and legal frameworks. Coordinating the donation process and expanding the criteria for donation are primary elements. Other factors, such as benchmarking, research, and efforts to overcome inequities, might not directly affect the number of HTs, but remain pivotal for ethical reasons and as support for further strategies. Adjustments in the allocation policy have been developed to address these issues, but disparities have not been solved yet. Broader organ sharing was introduced in the national allocation systems for heart, lung, and more recently liver and kidney to reduce geographical differences. However, it is still unclear whether these policy adjustments will eliminate geographical disparities (7).

Age

An effective way to solve the current shortage of donors would be an upward shift of the donor age cut-off limit (from the current 55–65 years). Age-related high prevalence of asymptomatic coronary artery disease and cardiomyopathy severely limit the feasibility of this approach unless a functional screening on the candidate donor heart is performed (8, 9). Although older donors are associated with higher recipient mortality risk, favorable survival has been shown with organs from donors >50 or even >60 years old (10).

For instance, in Italy, about 300 HTs are performed each year with more than 800 patients on the HT list. Over a total of about 1,200/year donor pool, 600 donors are aged <55 years, and

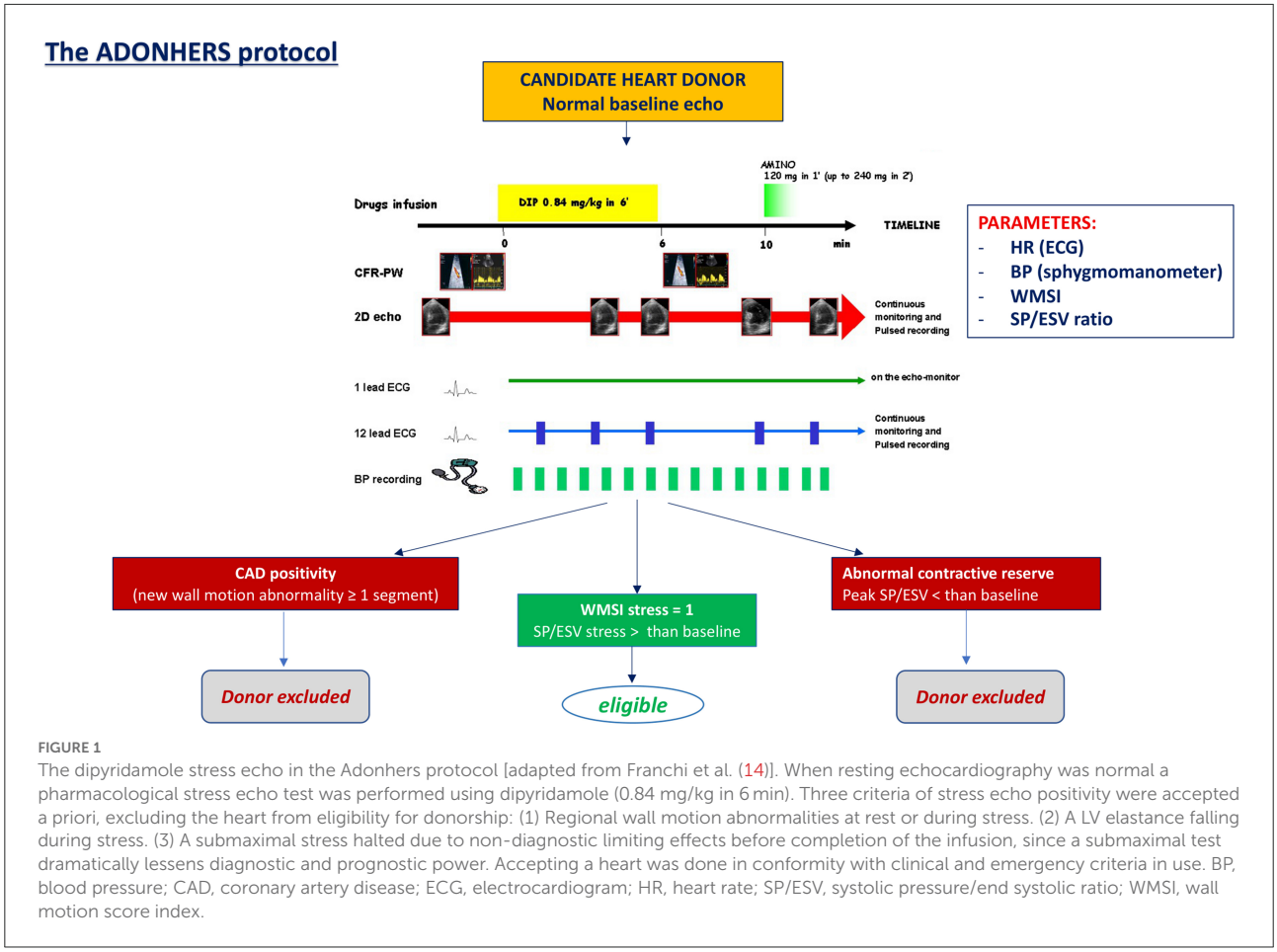

FIGURE 1
The dipyridamole stress echo in the Adonhers protocol [adapted from Franchi et al. (14)]. When resting echocardiography was normal a pharmacological stress echo test was performed using dipyridamole (0.84 mg/kg in 6 min). Three criteria of stress echo positivity were accepted a priori, excluding the heart from eligibility for donorship: (1) Regional wall motion abnormalities at rest or during stress. (2) A LV elastance falling during stress. (3) A submaximal stress halted due to non-diagnostic limiting effects before completion of the infusion, since a submaximal test dramatically lessens diagnostic and prognostic power. Accepting a heart was done in conformity with clinical and emergency criteria in use. BP, blood pressure; CAD, coronary artery disease; ECG, electrocardiogram; HR, heart rate; SP/ESV, systolic pressure/end systolic ratio; WMSI, wall motion score index.

300 of them are eligible for heart donation; since 600 potential donors are aged >55 years, the recruitment of even 25% of the currently dismissed aged donor pool would thereby dramatically decrease the current donor supply shortage (11, 12).

ADONHERS protocol

The ADONHERS protocol has been developed in Italy (first in Emilia-Romagna and Tuscany) with the background of a possible donors age extension (from 55 to 65 years old) after an accurate screening by stress echocardiography to exclude subtle coronary artery disease (13). After excluding global o regional wall motion abnormalities, severe LV hypertrophy, severe valve heart diseases, the brain-dead potential donor, aged >55 years old or <55 years with known multiple cardiovascular risk factors, undergoes dipyridamole stress echocardiography. Inducible ischemia identified by new LV wall motion abnormalities and/or LV abnormal contractile reserve (by Sagawa index) excludes the patient from donation. On the other hand, LV preserved contractile function and normal global and regional function determine marginal donor eligibility (Figure 1) (15). One of the possible limitations of stress echocardiography is the operator dependency. Speckle-tracking echocardiography, offering a quantitative objective analysis of myocardial deformation, may help to overcome this limit, and has showed an excellent feasibility in the analysis of LV myocardial longitudinal deformation both at baseline and peak stress in marginal heart donors. It may be used as a valuable additional mean to better interpret stress echocardiography results in marginal donors (16).

Donor comorbidities, such as diabetes mellitus and hypertension, might affect post-transplant outcomes. Such hearts are now used after excluding irreversible structural cardiac abnormality, and risk scores have been developed to help clinicians in these complex decisions and to guide donors' selection procedures (17, 18).

HCV prophylaxis

Drug abuse in the community raised in the last years resulting in an increased number of organ donors died of overdose. Post-transplant survival in recipients of such organs

seems favorable (19). Curative therapies for Hepatitis C virus (HCV) infection led to the use of HCV-positive donors for organ transplantation (20). An early prophylaxis strategy is correlated to low levels of viral transmission and avoids the development of HCV infection in the recipient, with a shorter duration of therapy and lower costs. In the first year after HX, outcomes of hearts from HCV-positive donors are similar to HCV-negative donors, although longer-term outcomes pertaining immunological activation, allograft rejection, and cardiac allograft vasculopathy remain uncertain (21).

Long-term mechanical circulatory support

Long-term mechanical circulatory support (MCS) might represent an additional strategy to reduce organ shortage. In fact, a wider use of MCS has been described in patients with end-stage HF who show temporary relative contraindications for HT. Current indications for mid-term and long-term MCS include "bridge to transplantation," BTT (patients with severe hemodynamic compromise on a HT waiting list), "bridge to recovery," BTR (recently severe reduction of myocardial function with possible recovery), "bridge to decision," BTD and "bridge to candidacy," BTC (while defining the best management for end stage HF patient). The use of the available different devices should be individualized according to patient characteristics.

Mechanical ventricular assist devices were developed for the left ventricle (LVADs), for the right ventricle (RVADs) or as a full heart replacement. MCS can be divided into short-term and long-term devices. One of the major issue concerning LVAD implantation in the high post operatory mortality rate. In the EUROMACS registry, approximately one out of five patients died within 90 days after LVAD implantation and early mortality was primarily driven by multiorgan failure, followed by sepsis (22, 23).

In the same registry, outcomes of patients receiving MCS were reviewed from January 2011 to June 2020. Totally, 4,834 procedures in 4,486 individual patients (72 hospitals) were included, with a median follow-up of 1.1 (interquartile range: 0.3–2.6) years. During this timeframe, the annual number of implants (range: 346–600) did not significantly change ($P = 0.41$). Two thousands and thirty-six patients died, with an estimated mortality probability of 30.0, 44.5, and 55.5% at 1, 3 and 5 years, respectively. Survival rate was significantly different across different INTERMACS classes, eras, devices, and strategies. Eight hundred and sixty-four patients were successfully given transplants, with a probability of receiving a transplantation of 7.5, 20.2, and 25.2% at 1, 3 and 5 years, respectively. Eleven patients, originally listed as destination therapy (DT), received a transplant while 3 patients were weaned.

Comparative studies on the impact of LVAD implantation on clinical outcome as a BTT are lacking, being difficult to randomize an outpatient, candidate to HT, to a double surgical step (LVAD and HT) vs. a direct HT. However, the available evidence show that LVAD use for BTT guarantees excellent survival and a similar quality of life to that of patients undergoing direct HT. In particular, heart transplanted patients after BTT have a slightly higher mortality rate within 90 days from HT than patients directly sent to HT, but this difference would be probably compensated by the live-years gained using MCS as BTT rather than remaining on the waiting list without advanced therapy (23).

Increasing the pool of hearts for transplantation with new methods

A lot of efforts are currently being invested in the improvement of the current methodologies and in the possibility of exploiting new technologies, to ensure better safety in conservation and transport of the donated organ. Promising data are emerging on the possibility of performing donation after circulatory death (DCD) and another interesting branch of research, which could be fundamental in solving the problem of the shortage of donors, is *xenotransplantation*.

Ex-vivo heart perfusion

In particular, another way to expand the donor pool would be to remove the geographic constraints of ischemic time. This could be obtained with an *ex vivo* heart perfusion platform that maintains the donor heart in a warm, beating state for transplantation. Some small registries have demonstrated the safety of this procedure (24). In the largest randomized trial 130 patients were randomized to receive donor hearts preserved by using either the Organ Care System or standard cold storage. No differences were found in 30-day patient and graft survival rates or serious adverse events (25). The *ex vivo* perfusion platform offers great potential for extended criteria donor hearts, where cold storage would conventionally be associated with poorer outcomes.

Donation after circulatory death

In the last few years, in order to solve the donor shortage, DCD has been studied for HT (26). In DCD, retrieval of hearts for transplantation occurs from patients whose death is declared and confirmed using cardiorespiratory criteria as life support is withdrawn. Particularly, these patients have severe, not reversible, brain damage, that does not meet brain dead criteria. The heart is removed and then, using *ex vivo*

perfusion, resuscitated. The major challenges with HT from DCD are the minimization of ischemic injury of the donor organs, and the after-death assessment of myocardial viability, since, in the DCD, the heart is subjected to an unavoidable period of severe, warm ischemia. Nevertheless, in almost 50 DCD HT performed, post-HT survival and graft function to date seems to be comparable to those observed in contemporary HT performed with donation after brain death (DBD) (27–29).

These outcomes seem to be supported in recent single-center retrospective cohort study. This study analyzed right heart catheterization measurements, inotrope scores, echocardiograms, and clinical outcomes between DCD and DBD heart recipients. Forty-seven DCD and 166 DBD hearts were transplanted. Despite an early significant right heart function impairment in the DCD heart recipient group, the right heart function was similar in the two groups after 3 weeks from HT. Mortality was similar at 30 days (DCD 0 vs. standard 2%; $P = 0.29$) and 1 year post-HT (DCD 3% vs. standard 8%; $P = 0.16$) (30).

Xenotransplantation

Xenotransplantation has required, and is still requiring, scientific advances to overcome challenges of evolutionary distance between species, transmission of zoonosis into the human pool, immunological barriers that cause hyperacute rejection, allograft failure due to thrombotic microangiopathy, and, moreover, it raises ethical concerns of distributive justice. On January 7th, 2022, a successful genetically edited porcine to human HT was performed with 60 days patient survival (31). On autopsy, the xenograft showed findings that were not consistent with typical rejection: it was edematous, nearly doubled in weight, and histologic examination revealed scattered myocyte necrosis, interstitial edema, and red-cell extravasation, without evidence of microvascular thrombosis. Studies are currently under way to identify the mechanisms responsible for these changes (32) and clearly, this experience has highlighted the presence of pathophysiological patterns that have yet to be understood. The topic of xenotransplantation, which could allow new, exciting therapeutic perspectives, raises political, ethical and moral concerns, that will have to be addressed in the years to come. Nevertheless, it represents an interesting new frontier which could make a significant contribution in solving the problem of donor shortage, guaranteeing survival hopes for patients with terminal heart disease currently lacking therapeutic alternatives.

Alternative therapeutic strategies to transplantation

Although HT represents the "gold standard" treatment for patients with advanced HF mainly due to its results in terms of prolongation of life expectancy, competitive technologies are currently under examination as valid therapeutic strategies. The efforts are mainly directed toward long term MCS, such as LVAD and fully implantable mechanical assist systems, or new cutting-edge technologies, such as gene therapy and tissue engineering (33).

Left ventricular assist devices

The most used devices for long-term MCS are those supporting the left ventricle. However, they are burdened by socioeconomic limitations and complications. An accurate selection of candidate by multimodal imaging and right heart catheterization is mandatory to avoid post-implantation right ventricular failure. In particular, an echocardiographic evaluation plays a pivotal role in the evaluation of the patient before, during and after LVAD implantation in the attempt to exclude contraindications (Table 3), guide the implant, optimize pump settings according to patients' hemodynamic profile and exclude complications.

In patients undergoing LVAD implantation, the main long-term complications include infective complications, bleeding and cerebrovascular complications of both ischemic and hemorrhagic nature. In addition, malfunctioning of the LVAD, worsening of aortic regurgitation, ventricular arrhythmias and pump thrombosis may occur. Right ventricular (RV) failure however has however the main relevance on survival. preoperative RV dysfunction should be exclude due to the incapability of the right RV to support the newly increased systemic flow after the implantation. Clinical, echocardiographic, and hemodynamic predictors have been studied but current algorithms for post-LVAD RV failure risk prediction only modestly perform when applied to external populations (34). Recent promising preoperative laboratory and echocardiographic predictors are emerging, like pulmonary artery pulsatility index (PAPi), N-terminal pro brain natriuretic peptide (NT-proBNP) and free wall RV longitudinal strain (fwRVLS) by speckle tracking echocardiography; the latter, representing intrinsic RV myocardial deformation, was the strongest independent predictor of post-LVAD RV failure (35, 36).

The development of durable right-sided mechanical support would improve treatment of patients with RV failure and fully implantable mechanical assist total heart systems, will undoubtedly provide new options for our patients in the future (37, 38).

Total artificial heart

A total artificial heart (TAH) has so far been successfully implanted in over 1,700 patients as a temporary life-saving technology as a BTT (39).

TABLE 3 General evaluation in the patient candidate for left ventricular assist devices.

	Factors conditioning the LVAD implant	Contraindications
Age		>75 years
Life style		Smoking habit, addiction to alcohol and psychotropic substances
Non-cardiological conditions	Multiorgan dysfunction	Irreversible multi-organ failure
	Neurological/psychiatric conditions Coagulation	Degenerative neuro / muscular diseases
	Kidney function	Recent stroke
	Hepatic function	Psychiatric/cognitive and / or psycho-social conditions with poor adherence to treatment
	Respiratory pathology	
	Oncological pathologies	Coagulopathies
	Diabetes mellitus	Uncontrollable bleeding
	Obesity	Irreversible renal failure
		Severe hepatic insufficiency
		Severe respiratory failure (FEV1 <50%) Life expectancy <2 years
		Poor control of blood glucosevalues
Cardiological conditions	Left ventricle	Apical infarction
	- Recent myocardial infarction	
	- Left endoventricularthrombosis	
	Right ventricle	Severe right ventricular dysfunction Pulmonary hypertension
	- Right ventricular function (multiparametric approach) and pulmonarypressures	
	Valvulopathies and valve prostheses	Uncorrectable moderate-severe insufficiency Uncorrectable moderate-severe insufficiency Active endocarditis
	- Aortic valve	
	- Mitral stenosis	
	- Tricuspid insufficiency	
	- Endocarditis	
	Arrhythmias	Uncontrolled ventricular tachyarrhythmias
	- Atrial tachyarrhythmias with a high response rate	
	- Ventriculartachycardias	
	- Previous cardiacsurgery	Previous ventriculoplasty
	Other cardiovascularconditions	
	- Atrial and interventricular septal defects	
	- Restrictive or constricting forms	
	- Anomalies affecting the ascending aorta	
	- (dilation, calcifications, atherosclerotic plaques)	
	- Peripheral vasculopathy	
	- Congenital heartdisease	

FEV1, forced expiratory volume in the firstsecond.

However, after more than six decades of research on TAHs, a device suitable for DT is not yet available. The high rate of complications, bulky devices, poor durability and biocompatibility and low patient quality of life, are some of the main issues limiting TAH. Promising perspective that could help to overcome these limitations are emerging, thanks to the quick developing of innovations in battery technology, wireless energy transmission, biocompatible materials, and soft robotics.

Innovations in the field of biological therapies are leading to bioartificial heart developing, again as possible candidate to overcome shortage of donor hearts. Many intuitions derived from TAHs can also be applied in projecting a bioartificial heart. However, there are some features that are unique to a bioartificial organ, such as the use of cells as an energy source, the necessity of vascularization and the capability of endogenous repair. Many efforts have been addressed on finding cell sources and a suitable vascularized scaffold and now, with the development of inducible pluripotent stem cell technology, autologous tissue engineering is conceivable. It is an exciting era for biomedical engineering, which carries great potential in addressing damaged organs. That could be done either *via* repair or replacement and the development in heart

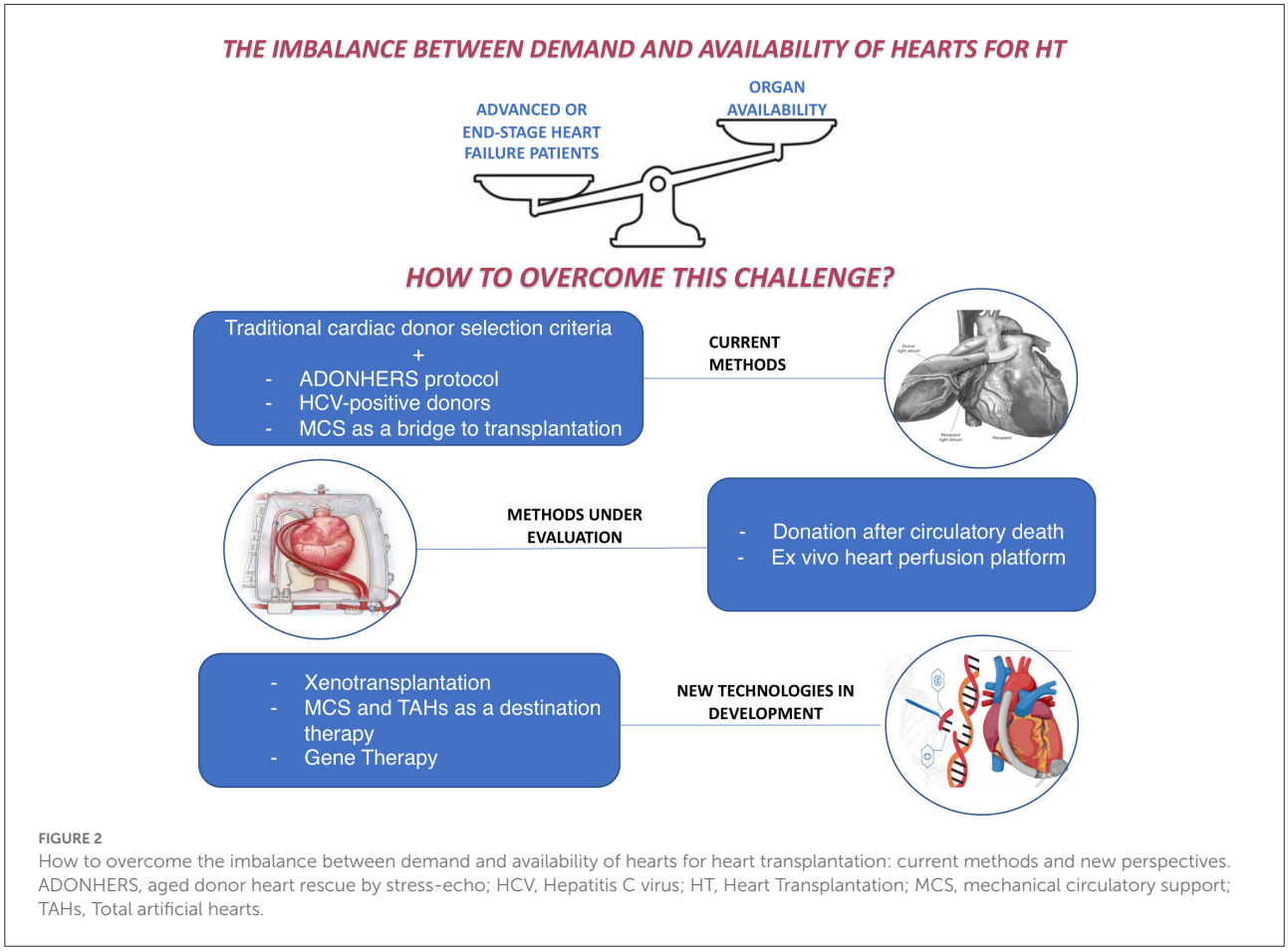

FIGURE 2
How to overcome the imbalance between demand and availability of hearts for heart transplantation: current methods and new perspectives. ADONHERS, aged donor heart rescue by stress-echo; HCV, Hepatitis C virus; HT, Heart Transplantation; MCS, mechanical circulatory support; TAHs, Total artificial hearts.

bioengineering have been astounding. However, further research still needs to be run to provide a mechanically, electrically, and physiologically well-coordinated organ and, ultimately, to successfully transplant it into patients. A coordinated approach between researchers, clinicians, regulatory bodies and society should be promoted to develop unlimited immunotolerant grafts.

Gene therapy

Another innovative therapeutic option is gene therapy. This treatment alters the genetic content of cells to modify target organ therapeutic protein or RNA expression. It has already been successfully introduced into clinical practice for the treatment of various diseases. The greatest benefit of its use in HT would probably be in the prevention of post-transplantation complications, such as primary graft dysfunction, cardiac allograft vasculopathy, and rejection. Additionally, gene therapy can be used to minimize and, potentially, eliminate the need for post-HT immunosuppression. Over the years, researchers have designed and developed several animal models and delivery techniques, with the aim of achieving strong gene expression in the heart. However, none of these methods has been so far successfully translated into clinical practice (40). The recent advances in *ex vivo* perfusion for organ preservation may provide potential ways to overcome many of the barriers that are currently preventing this method from entering clinical practice in HT. Optimizing vector selection for gene-carrying and delivery, and the selection of the therapeutic gene to be conferred are also a key point for implementing gene therapy in HT.

Conclusions

The issue of the imbalance between the demand and the offer of hearts for HT remains a therapeutic obstacle in advanced HF, whose incidence is continuously growing. In the last decades, many options were proposed to improve the selection of candidates, the survival of patients on the waiting list and the number of available donors, as well as to guarantee alternatives in non-eligible patients (Figure 2).

Reasonably, optimization and coordination of the donation process and an improved management of the currently available methods, would not allow to completely overcome the gap

between heart demand and availability. However, it could compensate the difficulties in the treatment of the most critical patients and improve their overall survival.

HT, and transplants in general, remains a complex topic, not only involving clinicians, but also political, economic, and ethical issues. The quick and continuous technological advances could provide new therapeutic alternatives in the near future; however, it would be essential to overcome the obstacles limiting the availability of hearts for transplantation with the means already at our disposal. Certainly, promoting education and raising awareness of the society, greater political commitment and improving international collaboration have a fundamental role in this direction.

Author contributions

MC and MCP contributed to the conception of the manuscript. MCP and AC performed the data research and analysis. MC, MCP, and AC drafted the manuscript. ML and GM contributed to manuscript revision and editing. All authors read and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Timothy P. Fitzgibbons,
University of Massachusetts Medical School, United States

REVIEWED BY
Masashi Amano,
National Cerebral and Cardiovascular Center, Japan
Valeria Pergola,
University Hospital of Padua, Italy

*CORRESPONDENCE
Carlotta Sciaccaluga
carlotta.sciaccaluga@gmail.com

†These authors have contributed equally to this work

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Diastolic function in heart transplant: From physiology to echocardiographic assessment and prognosis

Carlotta Sciaccaluga[1*†], Chiara Fusi[1†], Federico Landra[1], Maria Barilli[1], Matteo Lisi[1,2], Giulia Elena Mandoli[1], Flavio D'Ascenzi[1], Marta Focardi[1], Serafina Valente[1] and Matteo Cameli[1]

[1]Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy, [2]Division of Cardiology, Department of Cardiovascular Diseases - Azienda Unità Sanitaria Locale (AUSL) Romagna, "Santa Maria delle Croci" Hospital, Ravenna, Italy

Heart transplant (HTx) still represents the most effective therapy for end-stage heart failure, with a median survival time of 10 years. The transplanted heart shows peculiar physiology due to the profound alterations induced by the operation, which inevitably influences several echocardiographic parameters assessed during these patients' follow-ups. With these premises, the diastolic function is one of the main aspects to take into consideration. The left atrium (LA) plays a key role in this matter, and that same chamber is significantly impaired with the transplant, with different degrees of altered function based on the surgical technique. Therefore, the traditional echocardiographic evaluation of diastolic function applied to the general population might not properly reflect the physiology of the graft. This review attempts to provide current evidence on diastolic function in HTx starting from defining its different physiology and how the standard echocardiographic parameters might be affected to its prognostic role. Furthermore, based on the experience of our center and the available evidence, we proposed an algorithm that might help clinicians distinguish from actual diastolic dysfunction from a normal diastolic pattern in HTx population.

KEYWORDS

diastolic function, heart transplant, echocardiography, prognosis, physiology

Introduction

The prevalence of people being affected by heart failure worldwide is incessantly increasing and is now over 60 million (1). Consensually, the ranks of those in advanced stages of the disease are expanding. Many treatment strategies are available for such patients with the common goal of supporting the mechanical function of the heart. Heart transplant (HTx) is recognized as the most effective destination therapy since the

median survival time after transplantation exceeds 10 years nowadays (2). More than 5,000 HTx have been performed in 2015 worldwide, reaching the highest number since the technique's introduction back in 1967 (2).

However, survival is still impaired by two groups of transplant-related complications: those dependent on immunosuppressive therapy (e.g., malignancies and infections) and those graft-specific, which include cardiac allograft vasculopathy (CAV) and acute and chronic graft rejection. In a growing donor organ shortage era, avoidance of graft failure as long as possible is of paramount importance.

In addition to invasive methods, such as coronary angiography, endomyocardial biopsy, and right heart catheterization, non-invasive methods have been widely used to track changes in post-transplant cardiac function, such as echocardiography, cardiac computed tomography particularly for CAV detection, and recently, cardiac magnetic resonance (3, 4). It is essential to understand the peculiar physiology of the transplanted heart and how it influences the traditional parameters used during the follow-up, in particular, echocardiographic ones. The transplanted heart is subjected to several changes, myocardial injury and ischemia time of the donor's heart, denervation of the allograft, and peri-operative factors being the most implicated factors. Evidence suggests that both cardiac dimensions and functional parameters might be different from the general population (5), as shown in **Table 1**. Therefore, echocardiographic evaluation after HTx appears further complicated by the lack of standardized specific normal reference values for this population. In this context, one interesting aspect of HTx physiology is diastolic function. In fact, after surgery, the heart is subjected to several modifications, which tend to change over time, particularly the left atrium (LA), which is a major determinant of diastolic function, undergoing profound alterations.

The aim of this review is to attempt to provide current evidence on diastolic function in HTx starting from defining its different physiology and how the standard echocardiographic parameters might be affected to its prognostic role.

Determinants of diastolic function in heart transplant patients

Histological findings in diastolic dysfunction

From a histological standpoint, diastolic dysfunction is related to a substantial subversion of the extracellular matrix due to the presence of edema or fibrosis. Such tissue alterations determine the stiffening of myocardial walls and therefore alter lusitropic properties. In various pathological conditions, they occur before the overt manifestations of the disease, leaving space for pre-clinical detection. This could be true also for early identification of graft-specific complications since edema could be the result of acute graft rejection, while fibrosis may be the manifestation of both chronic graft rejection or CAV. However, recent evidence suggests that diastolic function might also be linked to microvascular density (6). Considering that, Daud et al. found that diastolic dysfunction in patients with severe CAV might be secondary to the loss and/or remodeling of microvasculature rather than a consequence of interstitial fibrosis (7).

Cardiac allograft physiology

Graft physiology is considerably different from normal, as a consequence of various factors such as denervation, altered anatomy, and hemodynamic status of the recipient. First, the electrical impulse originates from the donor atrium and, at least in the first 6–12 months after transplant, it is not under any control of the recipient's nervous system. Because of the reduced variability of heart rate, cardiac output is critically pre-load dependent in HTx. Second, because of the mismatch between the recipient and donor heart dimensions, the cardiac allograft is usually subject to enhanced mobility into the recipient cavity, enlarged by the dilated explanted heart, and clockwise rotated. Finally, atrial contribution to ventricular filling is reduced because of altered anatomy and function consequent to surgical anastomosis. Usually, HTx patients are characterized by restrictive physiology during the first period, probably because of inflammatory edema related to ischemic reperfusion injury, allograft ischemic time, surgery, and/or immune-mediated acute response. During follow-up, the diastolic pattern tends to improve after the first few weeks progressing to a non-restrictive filling pattern during the first year (8, 9). Nonetheless, in some patients, an abnormal diastolic filling can be identified many years after transplantation and this correlates with symptoms of heart failure and a history of acute rejection episodes (10).

The effects of surgical techniques on diastolic function

The atrial function is variably altered in HTx patients according to the employed surgical technique. With the "biatrial technique," in which the posterior cuffs of the recipient atria are left in place and attached to the donor atria, the atria result enlarged with an altered geometry, known as "snowman" configuration. In addition, impaired electrical impulse initiation (due to sinus node injury) or conduction could result in brady- or tachyarrhythmias, including atrial fibrillation (11). To overcome these limitations, two alternative techniques have been introduced over the years: the "bicaval technique" and the "total technique." The former preserves the LA anastomosis but combines it with bicaval anastomosis, whereas the latter

TABLE 1 Reference values for diastolic parameters evaluated by echocardiography in heart transplant patients.

Reference values for diastolic parameters in HTx patients

Echocardiographic parameter	Mean ± SD	Range (2.5th to 97.5th percentile)	95% CI of mean
E/A	1.8 ± 0.6	0.8–3.2	1.7–2.1
e' (lateral) (cm/s)	8.0 ± 3.1	5.5–11.1	7.2–9.1
DT (m/s)	156 ± 31	101–120	146–165
E/e' (lateral)	7.1 ± 3.0	3.1–14.7	6.4–8.4
LA volume/BSA (bicaval) (mL/m^2)	41 ± 16	29–121	71–79
MV E (cm/s)	80 ± 21	50–120	75–87
LVGLS (%)	−16.5 ± 3.3	12–35	15–18

TR velocity and PALS are not reported since no study has determined them yet. Adjusted from Ingvarsson et al. (3). BSA, body surface area; CI, confidence interval; DT, deceleration time; LA, left atrium; LVGLS, left ventricular global longitudinal strain; MV, mitral valve; PALS, peak atrial longitudinal strain; SD, standard deviation; TR, tricuspid regurgitation.

preserves the integrity of both atria but requires to anastomose both the inferior and superior vena cava and the pulmonary veins. However, the "total technique" is infrequently employed because it is technically demanding. The bicaval technique better preserves atrial anatomy and function compared to the biatrial technique (12, 13); therefore, it is the most widely chosen one. **Figure 1** shows the different surgical techniques used in heart transplantation. A recent study showed that both LA and right atrial function, in particular the reservoir phase, are impaired in a population of HTx patients operated with the bicaval technique (14). Particularly, they found that LA reservoir function was more profoundly reduced in presence of a larger LA and increased LV filling pressures, whereas a reduced RA reservoir function was associated with a decreased RV longitudinal function. As mentioned earlier, both atria undergo profound alterations during HTx, even if the bicaval technique is used over the biatrial one, which almost inevitably ends with a certain degree of atrial fibrosis. The atrial reservoir function is significantly dependent not only on ventricular longitudinal function but also on the compliance of the atrium, which is strictly linked to its stiffness and relaxation properties. In particular, since the LA is the chamber mostly and more directly affected by the operation, the association between LA reservoir function and larger LA as well as higher LV filling pressure could be comprehended (14). On the other hand, due to a less extended structural change, it is reasonable to understand a closer correlation between RA function and right ventricular longitudinal function, which is the other major determinant in atrial reservoir function.

Echocardiographic assessment of diastole

Challenges in diastolic evaluation

Echocardiography represents the first-line imaging modality to assess diastolic function and it is the cornerstone exam in the follow-up of HTx patients. However, the evaluation of diastolic function in HTx is challenging since the most widely employed diastolic parameters are sensible to heart motion as well as acoustic angle. Therefore, it is unlikely that the usual cut-off values can be appropriately applied to HTx patients (15). For these reasons, when studying the diastolic function of a cardiac allograft, it is more important to record individual parameters' variability over time instead of focusing on absolute values themselves. The basal echocardiographic assessment should be performed at least 6 months from surgery, since in earlier examinations, many parameters may be physiologically altered (16).

Comprehensive diastolic assessment

According to the latest recommendations (15), at least four echocardiographic variables should always be assessed when evaluating LV diastolic function, including mitral annular e' velocity, preferably both lateral and septal, average E/e' ratio, LA volume index, and peak tricuspid regurgitation velocity. The analysis of mitral inflow velocities and mitral annular tissue Doppler is fundamental for estimating LA pressure, that is LV filling pressure, which in turn correlates better with pulmonary capillary wedge pressure (15). The application of tissue Doppler imaging (TDI) in the assessment of diastolic function improves the accuracy of the echocardiographic exam as Doppler parameters of transvalvular flow are load and heart rate dependent. Furthermore, mainly with the use of the biatrial technique, there is often atrial dissociation and variation in transmitral E and A waves' velocities, limiting their application in the estimation of filling pressures (17). It is also true that TDI velocities may be affected by the exaggerated translation motion of the allograft (18). Additional traditional indexes that should be performed are represented by pulmonary vein velocities and those derived by speckle tracking echocardiography (STE), such as LA strain and LV global longitudinal strain (LV-GLS). **Table 2** summarizes the

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limitations and characteristics of echocardiography-derived diastolic parameters in HTx.

Changes in diastolic function after surgery

Soon after cardiac transplantation, Doppler echocardiographic indexes of LV diastolic function are suggestive of elevated filling pressures. Particularly, isovolumetric relaxation time (IVRT) is shortened and the transmitral inflow pattern shows an increase in E wave velocity and a shortening of deceleration time (DT) (19). The opening of the mitral valve occurs during the rapid ventricular pressure decline resulting in high peak early mitral flow velocity (E wave). Besides, the elevated LV filling pressure and the abrupt rise in early diastolic pressure explain the rapid deceleration of transmitral flow velocity with a shortened DT; also, LA pressure is increased and may contribute to the earlier opening of the mitral valve with a shortened IVRT (10). Moreover, it is common to find low TDI velocities at the mitral annular level, which tend to gradually increase over time, despite the fact that HTx values remain lower compared to the general population, even after 1 year (20). The elevation in filling pressure observed in the first month after surgery is due to the tendency of fluid accumulation due to a systemic inflammatory state and high doses of corticosteroids, in addition to the abovementioned reasons, such as inflammatory edema related to ischemic reperfusion injury, allograft ischemic time, surgery, and/or immune-mediated acute response. The restrictive diastolic pattern occurs irrespective of rejection status, as shown by studies assessing echocardiographic indexes on the day that endomyocardial biopsy was performed (8, 20), as well as independently of the surgical technique used (5) and clinical variables such as pre-operatory pulmonary pressure and the age of the donor's heart (19). In very few cases, the restrictive physiology might be predominantly explained by prolonged donor organ ischemia (21).

As the diastolic function improves with time, a progression to a non-restrictive pattern is seen. IVRT and DT prolong and transmitral early filling velocities decrease (19). However, during follow-up, the mitral E/A ratio could still be $\geq$2, thus indicating a possible restrictive filling pattern, even though LV diastolic function may be normal. LA impairment caused by surgical intervention leads to a reduced atrial component to LV filling explaining the increased E/A ratio (**Figure 2**). Conversely, TD-derived diastolic velocities strongly correlate with altered relaxation and diastolic dysfunction. The ratio E/e', combining TDI parameters with mitral inflow velocities, corrects transmitral velocities for the influence of relaxation and is a valuable index of LV filling pressures and diastolic dysfunction in both the biatrial (17) and bicaval techniques (22). Based on our experience and the available evidence on reference values in HTx patients, we proposed an algorithm that might help clinicians distinguish actual diastolic dysfunction with high LV filling pressure from normal LV filling pressure in the HTx population (**Figure 3**).

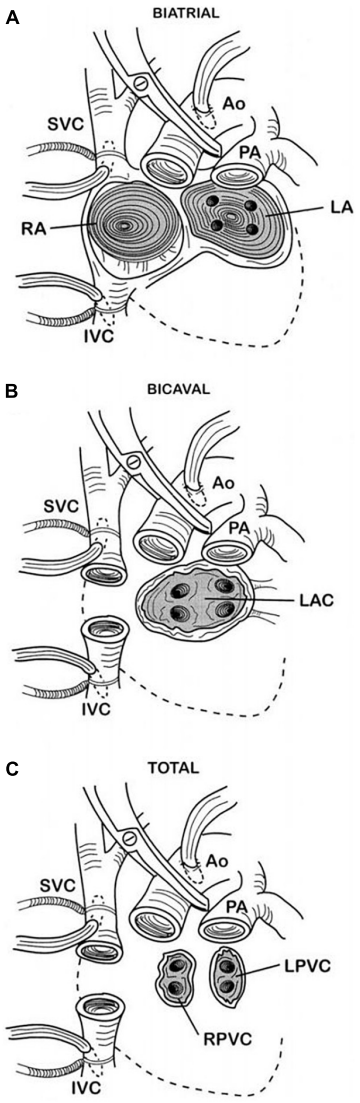

FIGURE 1
Surgical techniques for orthotopic heart transplant. Picture **(A)** shows the biatrial technique in which the anastomoses are at the mid-level of the left and right atria in addition to the aortic and pulmonary artery anastomoses. Picture **(B)** depicts the bicaval technique, the most commonly used nowadays, in which separate superior and inferior vena cava anastomoses are made instead of the right atrial anastomosis. Finally, picture **(C)** shows the total orthotopic heart transplant technique, which is a complete atrioventricular cardiac transplantation with separate cava and pulmonary vein anastomoses. Kindly readapted from Badano et al. (16). Dotted lines, original position of excised native heart; Ao, aorta; IVC, inferior vena cava; LA, left atrium; LAC, left atrial cuff; LPVC, left pulmonary vein cuff; PA, pulmonary artery; RA, right atrium; RPVC, right pulmonary vein cuff; SVC, superior vena cava.

TABLE 2 Advantages and disadvantages of echocardiography-derived diastolic parameters in heart transplant.

Echocardiographic diastolic parameters	Graft specific limitations and characteristics
Mitral inflow velocities (E wave velocity; A wave velocity; E/A ratio)	**Limitations:** Reduced atrial contribution to ventricular filling **Characteristics:** **1.** Restrictive filling pattern soon after cardiac transplantation: Shortened IVRT, high peak E wave velocity, shortened DT **2.** Non-restrictive pattern: Prolonged IVRT and DT, decreased transmitral early filling velocities. **3.** Reduced atrial contribution to LV filling, E/A could still be ≥2 even though LV filling pressures are low
TDI derived velocities (lateral and septal mitral annular e' velocity)	**Limitations:** Exaggerated translation motion (mismatch recipient–donor, enhanced mobility), clockwise rotation of HTx **Characteristics:** Low mitral annular TDI velocities with an increasing trend over time, even though they are lower than general population 1 year after HTx
E/e' ratio	**Limitations:** Exaggerated translation motion (mismatch recipient–donor, enhanced mobility), clockwise rotation of HTx which influence the measurement of TDI derived velocities **Characteristics:** Transmitral velocities corrected for the influence of relaxation; valuable index of LV filling pressures
LA size	**Characteristics:** Atrial enlargement without clear impact on function
Pulmonary veins velocities	**Limitations:** Not valuable index of LV filling pressures
Speckle tracking echocardiography (LA-PALS, LA-PACS, LV-GLS, LV-GCS, Ssr, Esr)	**Limitations:** Susceptible to image quality, low frame rate, which is problematic in higher heart rates as seen in denervated transplanted heart. **Characteristics:** Altered LA and LV parameters (PALS, PACS and GLS, GCS); strong association with LV filling pressures. Ssr and Esr and E/Esr ratio correlate well with LV end-diastolic pressure and detect myocardial dysfunction earlier than LV-GLS.

HTx, heart transplantation; LA, left atrium; LV, left ventricle; IVRT, isovolumetric relaxation time; DT, deceleration time; TDI, tissue Doppler Imaging; PALS, peak atrial longitudinal strain; PACS, peak atrial contraction strain; LV-GLS, left ventricular global longitudinal strain; LV-GCS, left ventricular global circumferential strain; SR, strain rate; Sst, peak systolic strain rate; Esr, early diastolic strain rate.

In particular, the proposed algorithm, shown in **Figure 3**, was created because of the limited application of each diastolic parameter alone. Cut-off values of each parameter were derived from the largest available prospective study by Ingvarsson et al. in a group of 124 clinically stable HTx patients (5), since standardized specific normal reference values for HTx patients are lacking. In particular, the assessment of TDI-derived velocities and DT might carry additional information on the diastolic function when the E/A ratio is above 2. In fact, according to the experience of our center, if these latter two indexes together point toward a restrictive filling pattern, the probability of diastolic dysfunction is high. Otherwise, additional parameters should be used to investigate diastolic function, as mentioned below.

Additional echocardiographic parameters

Pulmonary veins pattern

In HTx, the anastomoses at the level of the pulmonary vein ostia interfere with pulmonary vein flow, except from the biatrial technique (23). In addition to that, because the contractility of the remnant recipient atrial tissue alters the various components of pulmonary veins flow, this variable is not valuable for assessing LV filling pressures, irrespective of the surgical technique used (15).

Left atrial size

A significant atrial enlargement is seen among HTx patients irrespective of surgical technique, although it is more pronounced with the biatrial one because of the remaining atrial roof from the recipient (5, 24). In a prospective study by Ingvarsson et al. (5), they reported the following reference values for atrial dimensions in a group of 124 stable HTx patients: left atrial volume (mL), 96 ± 47 in the biatrial group vs. 75 ± 23 in the bicaval ($p < 0.001$), and left atrial volume/BSA (mL/m^2), 53 ± 23 vs. 39 ± 13 ($p < 0.001$). In patients operated on with the bicaval technique, atrial volume correlates only with allograft age instead (5). However, the impact of LA size on function is not completely clear as there is scarce evidence regarding the comparison of LA function between the two techniques (24, 25).

Left atrial strain

The LA acts as both a reserve and a conduit and also as an ancillary pump. In stable post-transplant patients, LA function is altered in all its functions regardless of the surgical technique as demonstrated in a study by Zhu et al. on 112 clinically well HT patients compared to healthy controls. In this study, functional comparison using STE showed a significant difference between HT patients and controls (PALS: 18.1 ± 5.6% vs. 44.2 ± 6.5% and PACS 4.4 ± 2.3% vs. 17.5 ± 4.7%; both $p < 0.001$) (26). In addition to a reduction in LA-PALS, STE showed a linear negative correlation between PALS and advanced recipient age, larger LA volumes, and worse LV systolic function measured by LV ejection fraction and LVGLS, suggesting that atrial function is altered not only due to surgery but also as a consequence of ventricular dysfunction (26). Also, PALS helps in the detection of diastolic dysfunction as LV end-diastolic pressure is the

afterload on the LA during the reservoir phase (27). An association between increased ventricular filling pressures and reduced atrial strain has been observed (28). Furthermore, a recent study hinted at a possible role of LA-PALS in detecting ACR (29). Rodriguez-Diego et al. found a significant decrease in PALS in presence of any degree of ACR, even though significant inter-vendor strain reproducibility was reported (29). A possible explanation for this finding might be found in the role of PALS in detecting subtle diastolic changes related to ACR episodes, in which different grades of inflammation affect the myocardium.

Left ventricular longitudinal strain

Due to the aforementioned limitations of the traditional indices of diastolic function for the estimation of LV filling pressures in HTx, the performance of myocardial deformation analysis using STE to predict elevated pulmonary capillary wedge pressure in HTx has been studied. Strain and strain rate parameters such as GLS and GCS have stronger diagnostic performance than traditional parameters of diastolic dysfunction, such as E/e' (30). Ingvarsson et al. found a reduction in LV-GLS in a group of HTx patients compared with reported normal values (mean LV-GLS $-16 \pm 3.3\%$; $p < 0.001$ and mean LV-GCS $-22.9 \pm 6.3\%$; P = NS) possibly due to surgical procedure and progressive remodeling including myocardial fibrosis and/or previous rejections (5, 31). LV-GLS and LV-GCS are strongly associated with LV filling pressures as there is a tight coupling of systolic and diastolic functions and also a rise in filling pressures increases wall tension resulting in depressed myocardial systolic deformation (30). Regarding longitudinal diastolic strain rate, defined as the rate of deformation in percent of strain per second during diastole (32), there is evidence that peak systolic (Ssr) and early diastolic (Esr) strain rate and the ratio of transmitral early filling velocity to early diastolic strain rate correlate well with LV end-diastolic pressure and pulmonary capillary wedge pressure, also tracking well the changes of these parameters with time thus detecting myocardial dysfunction earlier than LV-GLS (30).

Prognostic implications of diastolic assessment

Graft failure due to acute cellular rejection is a common complication of HTx and the main cause of mortality in the first years after surgery (33), whereas extensive CAV is seldom seen as early as 1 year after surgery (34). The current gold standard method for diagnosing rejection is an endomyocardial biopsy (35) but other non-invasive imaging methods—of which echocardiography is the first line imaging modality—play an important role in assessing and monitoring allograft function (16). Acute graft rejection is categorized into acute cellular or antibody-mediated rejection (36, 37) and induces myocardial lymphocyte infiltration and edema manifested earlier by impaired LV filling and later by increased wall thickness and systolic dysfunction (38). Acute cellular rejection correlates with shortening of the IVRT and early mitral inflow DT, while changes in E and A wave velocities and E/A ratio have been less consistent (39). Variations in transmitral Doppler flow indices are also rather non-specific in detecting rejection as they are markedly influenced by other variables, such as heart rate, age, and loading conditions. Diastolic function assessed by transmitral Doppler diastolic indexes should allow the sensitive detection of acute rejection but their value is limited as they can be abnormal even in healthy patients (10). Nevertheless, diastolic dysfunction carries a prognostic value (40), and Doppler abnormalities in LV filling patterns have shown a return to baseline following episodes of rejection (41). TDI and relaxation velocities have been studied and results are not univocal, since, in some studies, it has been found that an association between decreased systolic and filling velocities and acute rejection (42, 43) is not confirmed by others (44). It can be said that TDI velocities are highly specific as they have a good negative predictive value, so rejection could be excluded in the presence of <10% reduction in diastolic mitral annular motion velocities (44, 45). The aforementioned markers of acute rejection are based on abnormalities in LV filling; speckle tracking-derived LV-GLS is a sensitive marker for the detection of sub-clinical regional systolic function abnormalities instead (46). Diastolic speckle tracking indexes can detect subclinical dysfunction during acute cellular rejection at an earlier stage than LV-GLS, particularly E/GDSRe, as it can detect functional alterations even in the context of normal E/e' ratio (32). Finally, a completely normal echocardiographic examination provides a high negative predictive value for detecting acute graft rejection at endomyocardial biopsy while there is a significant correlation between the number of abnormal echocardiographic parameters and rejection grade (47).

Diastolic dysfunction carries a significant prognostic value also in chronic graft rejection, which is mainly determined by CAV and, in some patients, triggered by recurring immune responses against the graft resulting in replacement fibrosis and progressive deterioration of myocardial function, especially in patients with alloreactive antibodies. Histologically, CAV is a diffuse vasculopathy secondary to a fibroproliferative process initially resulting in concentric narrowing of both the large epicardial coronary arteries, the coronary veins, and the microcirculation, and later on, in focal luminal stenoses detectable with coronary angiography (16). Diastolic dysfunction is a key element in the grading of CAV; in fact, according to the latest classification of CAV by ISHLT, severe CAV is defined in presence of visual coronary angiographic stenosis and evidence of graft dysfunction such as reduced LVEF end/or restrictive filling pattern (48). It follows that diastolic function is markedly impaired in patients with severe CAV, generally resulting in restrictive cardiac physiology, defined as symptomatic heart failure with an echocardiographic E/A

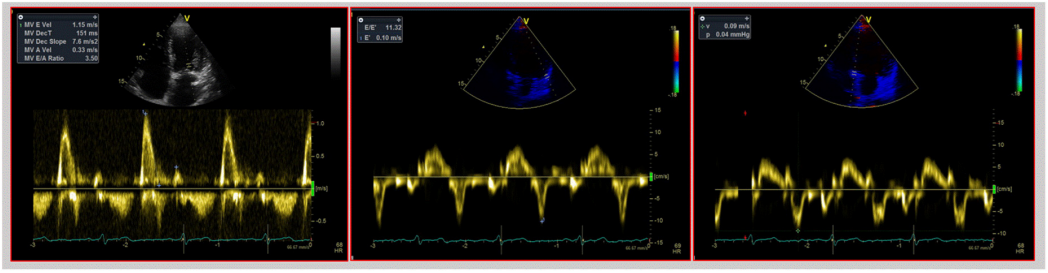

FIGURE 2
Echocardiographic assessment of diastolic function in heart transplant. This figure shows a mitral E/A ratio ≥2 with a deceleration time of E wave of 151 ms, thus indicating a possible restrictive filling pattern in a 3-year heart transplant patient. However, TDI analysis, shown in the middle and right pictures, shows normal e' lateral and septal velocities, thus possibly excluding a restrictive filling pattern.

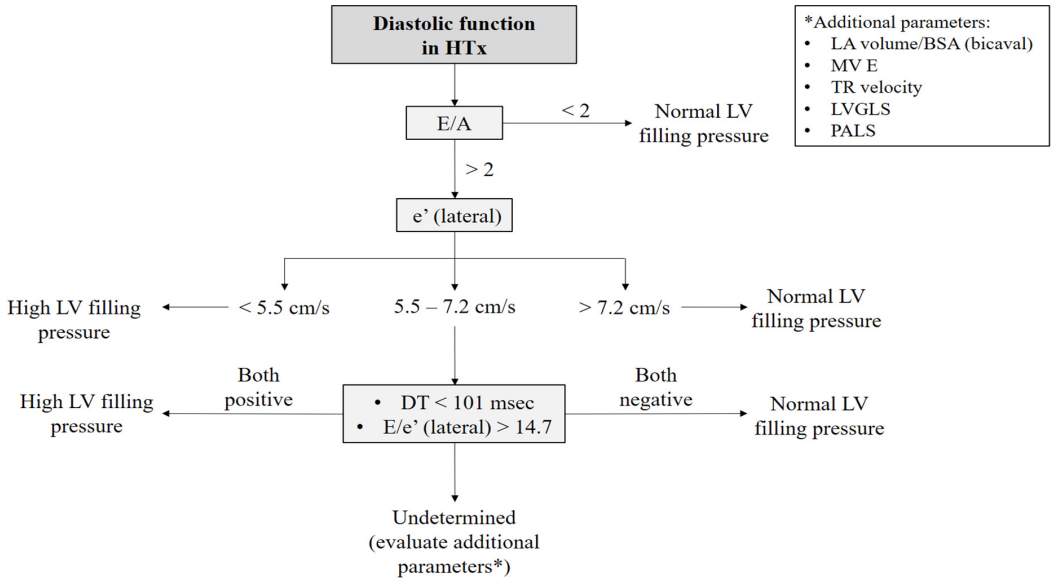

FIGURE 3
Proposed algorithm to evaluate diastolic function in heart transplant patients. The first step in the evaluation of diastolic function in HTx is assessing mitral inflow velocities. In the case of an E/A ratio <2 high LV filling pressure can be fairly excluded. On the other hand, if the E/A ratio >2, it is useful to evaluate TDI-derived velocities. However, when their values lie in a gray zone, DT and E/e' ratio should be considered. If these latter two indexes together cannot exclude high LV filling pressure, additional parameters should be used, such as LAVi (in the case of bicaval technique), LA strain, and LV-GLS and TR velocity. This is the diagnostic algorithm proposed by our center, based on the values derived from the study by Ingvarsson et al. (5). BSA: body mass index; DT: deceleration time; HTx: heart transplantation; LA: left atrial; LAVI: left atrial volume index; LV: left ventricular; LVGLS: left ventricular global longitudinal strain; MV: mitral valve; PALS: peak atrial longitudinal strain; TR: tricuspid regurgitation.

velocity ratio >2, shortened IVRT (<60 ms), shortened DT (<150 ms), or restrictive hemodynamic values (48). Instead, in patients with severe CAV, LVEF is typically preserved, even though it tends to show lower values compared with mild CAV (7); nevertheless, the occurrence of a reduction in LVEF years later after HTx should prompt other investigations to exclude CAV. Earlier detection of ventricular dysfunction may be investigated with TDI-derived velocities and STE with CAV patients presenting with augmented duration and reduced amplitude of TDI-myocardial velocities (39) and the reduced absolute value of LV-GLS (49, 50). Evidence suggests that the key histopathologic finding in CAV-related diastolic dysfunction is increased capillary wall thickness and reduced capillary density, rather than interstitial fibrosis, which has similar extent in severe CAV and non-significant CAV patients (7, 51). Furthermore, the restrictive physiology carries a prognostic significance in CAV patients, as it has been related to a lower 5-year survival (52).

In conclusion, no single diastolic parameter reliably predicts graft-specific complications (47), and a comprehensive echocardiographic evaluation of diastolic function should be performed at every follow-up visit, particularly focusing not on absolute values of the various parameter but rather on

their variation over time. Performing an appropriate baseline echocardiographic exam is fundamental for this purpose.

Conclusion

The assessment of LV diastolic function is considered an integral part of the clinical evaluation of HTx patients. It carries a relevant prognostic value in the follow-up, helping in the early detection of possible complications such as rejections. However, its assessment requires several considerations due to the profound alterations that the transplanted heart undergoes, especially LA which plays a key role in defining diastolic function.

Author contributions

CS, CF, FL, and MB participated in the writing the manuscript. GM and ML provided images and tables as well as a revision of the manuscript, whereas SV, FD'A, MF, and MC critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Matteo Cameli,
University of Siena, Italy

REVIEWED BY
Maria Concetta Pastore,
Università del Piemonte Orientale, Italy
Ahmet Rüçhan Akar,
Ankara University, Turkey

*CORRESPONDENCE
Hanno Grahn
✉ h.grahn@uke.de

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Impact of diastolic pulmonary gradient and pulmonary artery pulse index on outcomes in heart transplant patients—Results from the Eurotransplant database

Tobias Wagner[1], Christina Magnussen[1,2], Alexander Bernhardt[3], Jacqueline M. Smits[4], Katrin Steinbach[5], Hermann Reichenspurner[3], Paulus Kirchhof[1,2,6] and Hanno Grahn[1]*

[1]Department of Cardiology, University Heart and Vascular Center Hamburg, Hamburg, Germany, [2]German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Luebeck, Hamburg, Germany, [3]Department of Cardiovascular Surgery, University Heart and Vascular Center Hamburg, Hamburg, Germany, [4]Eurotransplant International Foundation, Leiden, Netherlands, [5]Department of Cardiology, University Medical Centre, Johannes Gutenberg University Mainz, Mainz, Germany, [6]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom

Background: Predicting complications associated with pulmonary hypertension (PH) after cardiac transplantation is an important factor when considering cardiac transplantation. The transpulmonary gradient (TPG) is recommended to quantify PH in transplant candidates. Nonetheless, PH remains a common driver of mortality. The diastolic pressure gradient (DPG) and pulmonary vascular resistance (PVR) can differentiate post- from combined pre- and post-capillary PH and may improve estimation of PH-associated risks. We used a large European cohort of transplant candidates to assess whether the pulmonary pulsatility index (PAPi), improves prediction of graft failure and mortality compared to DPG and PVR.

Methods: Out of all patients undergoing heart transplantation between 2009 and 2019 in Eurotransplant member states (n = 10,465), we analyzed the impact of PH (mPAP > 25 mmHg) and right heart catheter hemodynamic data on graft failure and mortality within 1–5 years.

Results: In 1,407 heart transplant patients with PH (79% male, median age 54 years, IQR 39–69 years), the median PVR was 2.5 WU (IQR 1.6 WU) with a median mPAP (pulmonary arterial pressure) of 32 mmHg (IQR 9 mmHg). Patients with low (<3 mmHg) DPG had a better 5 year survival than those with higher DPG (log rank p = 0.023). TPG, mPAP, PAPi, and PVR did not improve prediction of survival. Low PAPi (OR = 2.24, p < 0.001) and high PVR (OR = 2.12, p = 0.005) were associated with graft failure.

Conclusion: PAPI and PVR are associated with graft failure in patients with PH undergoing cardiac transplantation. DPG is associated with survival in this cohort.

KEYWORDS

orthotopic heart transplantation, pulmonary hypertension, diastolic pulmonary vascular pressure gradient, transpulmonary pressure gradient, pulmonary pulsatility index

Introduction

Cardiac transplantation is gold standard of care for patients with advanced heart failure. One of the main drivers of morbidity and mortality after cardiac transplantation is right heart failure, often due to pre-existing pulmonary hypertension (PH). PH is often present in patients awaiting cardiac transplant. PH can be a reversible consequence of left heart disease or a sign of irreversible defects in the pulmonary circulation. Differentiating between these etiologies can alter effects on the risk of post-transplant right heart failure (1).

Right heart catheterization (RHC) is commonly used to assess candidates for cardiac transplantation as it allows quantification of cardiac output and calculation of cardiac index. RHC also provides comprehensive right heart and pulmonary hemodynamic information. The (2) pulmonary arterial wedge pressure (PAWP), the derived transpulmonary gradient (TPG) and the calculated pulmonary vascular resistance (PVR) are currently used to differentiate pre- from post-capillary hypertension in candidates for cardiac transplantation (1).

Unfortunately, both TPG and PVR can be increased in patients with cardiac failure and subsequently increased pulmonary venous pressure (3). Therefore, TPG and PVR may over- or under-diagnose the risk of PH-associated morbidity and mortality after cardiac transplantation. The diastolic pulmonary gradient (DPG) can help to further differentiate pre- and postcapillary PH (4). Novel functional parameters like the pulmonary artery pulsatility index (PAPi) were recently proposed to better estimate the risk of right heart failure in cardiac transplant candidates (5, 6).

To quantify the value of these parameters for risk prediction after cardiac transplantation, we analyzed a large European transplant database to determine whether DGP and PAPi are associated with organ failure and death after cardiac transplantation.

Abbreviations: AUC, area under the curve; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient; IQR, interquartile range; LVAD, left ventricular assist device; mPAP, mean pulmonary arterial pressure; OHT, orthotopic heart transplantation; PAPi, pulmonary artery pulsatility index (PAPi, defined as [(systolic pulmonary artery pressure – diastolic pulmonary artery pressure)/central venous pressure]); PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheter; ROC, receiver operating characteristic; sPAP, systolic pulmonary artery pressure; TPG, transpulmonary pressure gradient.

Methods

Data source

All adult patients undergoing orthotopic heart transplantation (OHT) between 2009 to 2019 were extracted from the Eurotransplant database ($n = 10{,}465$). Eurotransplant is an international non-profit organization coordinating organ transplants in Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Netherlands, and Slovenia.

Data management and study design

We examined all adult (age $\geq$ 18 years) OHT patients with a minimum set of pre-transplant hemodynamic data, defined as systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mean pulmonary artery pressure (mPAP), pulmonary artery wedge pressure (PAWP), and cardiac output.

Depending on the implication for OHT and the state of urgency as well as changes in the allocation system, in a vast number of patient RHC was not mandatory of OHT listing. Patients without or with incomplete hemodynamic data excluded. To identify outliers (defined as physiologically impossible parameters), *Z*-standardization of mPAP, PAWP, dPAP, TPG and DPG was performed. All cases with at least one value $>1.5^{*}IQR + 3rd\ quartile$ or $<1.5^{*}IQR + 3rd\ quartile$ were marked as an outlier and excluded from subsequent analysis. Outcomes of interest included survival at 30 days, 1 year, and 5 years as well as graft failure at any time. The cohort was divided into two groups: patients with PH (mPAP $\geq$25 mmHg) and patients without PH (mPAP <25 mmHg). This threshold

was recommended in the time period the patients included in this study were screened to be eligible for OHT. Recently, the revised WHO definition of PH recommend a threshold of >20 mmHg (7).

Statistical analysis

For all variables, descriptive statistics were computed. Depending on the scale of measure, data are presented as numbers and percentages, medians and interquartile ranges, or proportions with 95% confidence intervals (*CI*). For comparison between groups, exclusively non-parametric tests were used. Continuous variables were compared by using the Mann-Whitney *U*-tests and Chi Square test was used to compare categorical variables. The predictive performances of the TPG, DPG, PVR, and PAPi were analyzed with receiver operating characteristic (ROC) curves. Total area under the ROC curve (AUC) values were considered to assess the value of measure. ROC cut points were identified by Youden's index. Kaplan-Meier curves were used to analyze survival and were compared by log-rank test. Spearman rank correlation was used to examine the correlation between variables. Dependent correlations were compared as a variant of Dunn und Clark's z proposed by Hittner et al. (8). Prediction models for survival and graft failure were adjusted for age, sex, listing state and underlying heart disease as possible confounders by logistic regression. For regression models, $p < 0.05$ was used as the entry criterion and $p > 0.10$ as the removal criterion. Data were analyzed with IBM SPSS version 25 for Microsoft Windows. Two-tailed tests of significance were considered to be significant at a $p < 0.05$ and highly significant at $p < 0.01$.

Results

Patients and hemodynamic parameters

Of 10,465 cardiac transplant recipients between 2009 and 2019, 7,938 patients were excluded with incomplete hemodynamic data, and 378 patients with implausible data or outliers (Figure 1). Of the remaining cohort of 2,149 patients, 1,407 patients (65%) had pulmonary hypertension (mPAP ≥ 25 mmHg). Patients with PH were more frequently female and had higher pulmonary pressures, except DPG and PAPi, compared to the 742 transplant recipients without PH. The median time between RHC and OHT was 31 days in patients with PH, while RHC in patients without PH was performed at a median interval of 41 days before OHT ($p < 0.001$). We found a longer median follow-up time after OHT in patients with PH. In patients with PH, left ventricular assist device (LVAD) support as bridge to transplant was present half as frequently (19 vs. 9%, $p < 0.001$). No significant differences

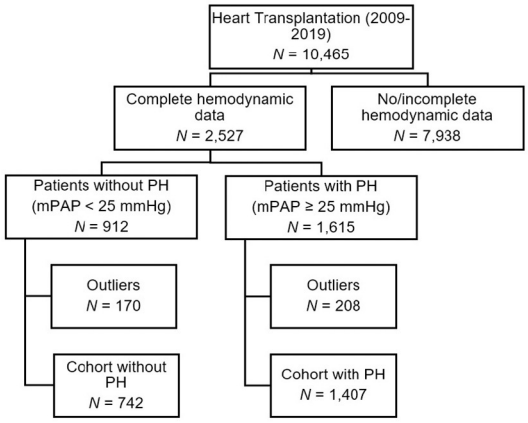

FIGURE 1
Flowchart of study population according broken down by right-heart catheterization data into pulmonary hypertension groups.

in donor characteristics between patients with and without PH were obvious (Table 1). We selected 1,407 patients with PH as the primary analysis population.

Prognostic value of established PH parameters TPG, DPG and PVR

We investigated the ability of the established PH parameters DPG, TPG and PVR to discriminate between survivors and non-survivors in the cohort of patients with PH and found AUC values near 0.5 (Table 2). We took the conventional cut-off value of 3 mmHg for DPG and identified 361 patients (26% of patients with PH) showing a DPG above. We set cut-offs for TPG at 15 mmHg, and 3 WU for PVR.

Kaplan-Meier curves identified a distinct better 1-year survival in patients with a DPG <3 mmHg (log rank $p \leq 0.001$) and a slightly better 5-year survival in the same group of patients (log rank $p = 0.023$, median survival 1,556 vs. 1,318 days). There was no difference in survival in patients with low vs. high TPG, mPAP, and PVR (Figure 2). For the above-mentioned survival analysis, we used a DPG cut point of 3 mmHg chosen a priori. Exploring three different cut points (3, 5, 7, or 10 mmHg) in this cohort of patients with PH, a cut point of 3 mmHg remains the one with best discrimination regarding 5-year survival (Figure 3). TPG and PVR were higher in the high DPG groups (Supplementary Table 2). Analyses of subgroups with PVR >3 WU or TPG >12 mmHg had similar results (Supplementary Table 3).

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TABLE 1 Baseline characteristics.

	No PH (mPAP < 25 mmHg) $N = 742$	PH (≥25 mmHg) $N = 1,407$	p
Demographics			
Age (years)	54 *(39–69)*	54 *(39–69)*	0.190
Female sex	212 *(29)*	298 *(21)*	<0.001
LVAD before OHT	138 *(19)*	119 *(9)*	<0.001
ECMO or IABP before OHT	9 *(1)*	24 *(2)*	0.377
Primary etiology of heart failure			
Ischemic heart disease	139 *(19)*	304 *(22)*	0.117
Dilated cardiomyopathy	410 *(55)*	804 *(57)*	0.402
Congenital heart disease	20 *(3)*	31 *(2)*	0.476
Mixed/others	173 *(23)*	268 *(19)*	
Listing state and donor characteristics			
T	116 *(16)*	179 *(13)*	
HU	626 *(84)*	1,228 *(87)*	0.062
Age of donor (years)	44 *(24–64)*	44 *(23–65)*	0.559
BMI of donor (kg m^{-2})	25 *(20–30)*	25 *(20–29)*	0.182
Female sex of donor	306 *(41)*	569 *(41)*	0.720
Hemodynamics			
sPAP (mmHg)	29 *(17–41)*	48 *(32–64)*	<0.001
mPAP (mmHg)	19 *(13–25)*	33 *(25–41)*	<0.001
dPAP (mmHg)	14 *(7–21)*	25 *(17–33)*	<0.001
PAWP (mmHg)	14 *(6–22)*	24 *(15–33)*	<0.001
PVR (WU)	1.70 *(0.42–2.98)*	2.5 *(0.9–4.1)*	<0.001
TPG (mmHg)	5 *(0–10)*	8 *(2–14)*	<0.001
DPG (mmHg)	0 *(−5–5)*	0 *(−5–5)*	0.323
CI (L min^{-1}) m^{-2})	2.00 *(1.4–2.6)*	1.81 *(1.31–2.31)*	<0.001
CVP (mmHg)	8 *(0–17)*	13 *(3–23)*	<0.001
PAPi	1.93 *(0–4.33)*	1.75 *(0–3.54)*	0.192
Time between RHC and OHT (days)	41 *(0–126)*	31 *(0–75)*	<0.001
Median follow-up time			
Median follow-up (days)	712 *(0–1,557)*	857 *(0–1,780)*	<0.001

Median *(IQR)* or *N (%)*, p-values are calculated by Mann-Whitney U-test or Chi Square test.
CI, cardiac index; CVP, central venous pressure; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient; HU, urgency status "high urgent"; PAPi, pulmonary artery pulsatility index; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; T, urgency status "transplantable"; TPG, transpulmonary gradient; sPAP, systolic pulmonary artery pressure. Italic values was used to delimit interquartile range and % from median and %.

Prognostic value of PAPi

Since there are few data regarding the prognostic impact of PAPi in patients with end stage heart failure, there is no established threshold for PAPi available for OHT patients. We chose 1.84 as threshold as the PAPi cutoff with the best Youden Index for 5-year survival. A PAPi ≥ 1.84 was found in 53% of patients with PH and therefore this cut-off divided the group of recipients with PH in two subgroup with nearly identic size. However, in the Kaplan-Meier curves we found no differences in compare of survival (Figure 2). Likewise, splitting the cohort by a threshold of 3.65—proposed in literature for patients with heart failure (6)—did also not reveal meaningful differences in survival, but in only

TABLE 2 Survival in patients with a mean pulmonary artery pressure ≥25 mmHg.

Variable	AUC	p
DPG		
30-days survival	0.489	0.707
1-year survival	0.464	0.067
5-year survival	0.466	0.123
Transpulmonary gradient		
30-days survival	0.428	0.017
1-year survival	0.459	0.036
5-year survival	0.458	0.059
Peripheral vascular resistance		
30-days survival	0.417	0.051
1-year survival	0.448	0.053
5-year survival	0.415	0.118
Pulmonary artery pulsatility index		
30-days survival	0.500	0.995
1-year survival	0.511	0.584
5-year survival	0.481	0.408

AUC, area under the curve; DPG, diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient.

18% of recipients with PH a PAPi ≥3.65 was found (data not shown).

Adjusted models for survival and graft failure

sPAP correlated considerably weaker with DPG ($r = -0.11$) than TPG ($r = 0.47$). This was consistent in the subgroup of patients with mPAP ≥ 25 mmHg ($r = -0.11$ vs. $r = 0.44$) and in those with PVR >3 WU ($r = -0.15$ vs. $r = 0.43$, (see Supplementary Table 3) for p-values between correlation coefficients). DPG was neither associated with cardiac output in the whole cohort ($r = 0.02$) nor in the subgroup of patients with mPAP ≥ 25 mmHg ($r = 0.04$).

After adjustment for age, sex, listing state and underlying heart disease as possible confounders by use of a logistic regression model, we found that patients with PH and DPG >3 mmHg had a worse survival after 1 year (odds ratio 0.63 [95% confidence interval 0.47–0.85], $p = 0.002$) and 3 years (odds ratio 0.72 [95% confidence interval 0.543–0.959], $p = 0.024$). Five years after transplantation, this difference diminished (odds ratio 0.80 [95% confidence interval 0.56–1.13], $p = 0.181$). Adding TPG as an additional parameter did not change this result (odds ratio 0.60 [95% confidence interval 0.42–0.85], $p = 0.003$ for survival after 1 year, odds ratio 0.66 [95% confidence interval 0.47–0.93], $p = 0.016$ for survival after 3 years and odds ratio 0.81 [95% confidence interval 0.54–1.22], $p = 0.312$ for survival after 5 years) indicating that this prediction is independent from TPG. In contrast, we could not depict a significant difference in survival at any point for patients with TPG > 15 mmHg, PVR > 3 WU. Further, the optimal PAPi threshold of 1.84 did not separate group with differing probability of survival.

With the aforementioned adjustment, PH and DPG > 3 mmHg (odds ratio 1.30 [95% confidence interval 0.93–1.83], $p = 0.125$) or TPG > 15 mmHg (odds ratio 0.83 [95% confidence interval 0.44–1.57], $p = 0.571$) did not increase the risk of graft failure, but PVR >3 WU (odds ratio 2.12 [95% confidence interval 1.25–3.59], $p = 0.005$) did. An optimal PAPi threshold of 2.37 discriminates two groups markedly differing in probability of graft failure (odds ratio 2.24 [95% confidence interval 1.51–3.32], $p < 0.001$, Table 3). Restricting the analysis to patients developing graft failure within the first 90 days after OHT, did not change these results (data not shown).

Discussion

This analysis in a near-complete cohort of cardiac transplant patients with pulmonary hypertension in eight European countries confirms that pulmonary hypertension is common (2/3 of patients) in patients undergoing cardiac transplantation with prior hemodynamic evaluation by RHC. Two new parameters were identified to estimate risk of death and organ failure: A low transpulmonary diastolic pressure gradient (DPG <3 mmHg) is associated with good 5 year survival. Low PAPi and high PVR were associated with graft failure (central illustration, Figure 4). Our findings suggest that quantification of DPG and PAPi in addition to PVR can improve risk estimation in candidates for cardiac transplantation with elevated pulmonary pressure.

Frequently, TPG and PVR are used for ruling-out OHT candidates with irreversible pulmonary remodeling representing a contraindication (1). In left heart disease, TPG can be elevated not only as a result of pulmonary vascular remodeling but also due to the effects of elevated left-sided filling pressures (3). Thus, elevated TPG or PVR does not always reflect irreversible pulmonary vascular disease. TPG may misjudge pulmonary vascular disease in left heart conditions associated with an increased pulmonary venous pressure. Weak prognostic power of PVR and TPG has already been described (9). In this study, we could confirm that TPG do not predict survival or graft failure while increased PVR was associated with graft failure but did not significantly influence survival.

An increase in venous pressure lowers vascular compliance more than solely expressed by PVR (10). This phenomenon majorly increases sPAP and subsequently mPAP but without increase of dPAP. As Naeije et al. (3) describes, TPG and PVR

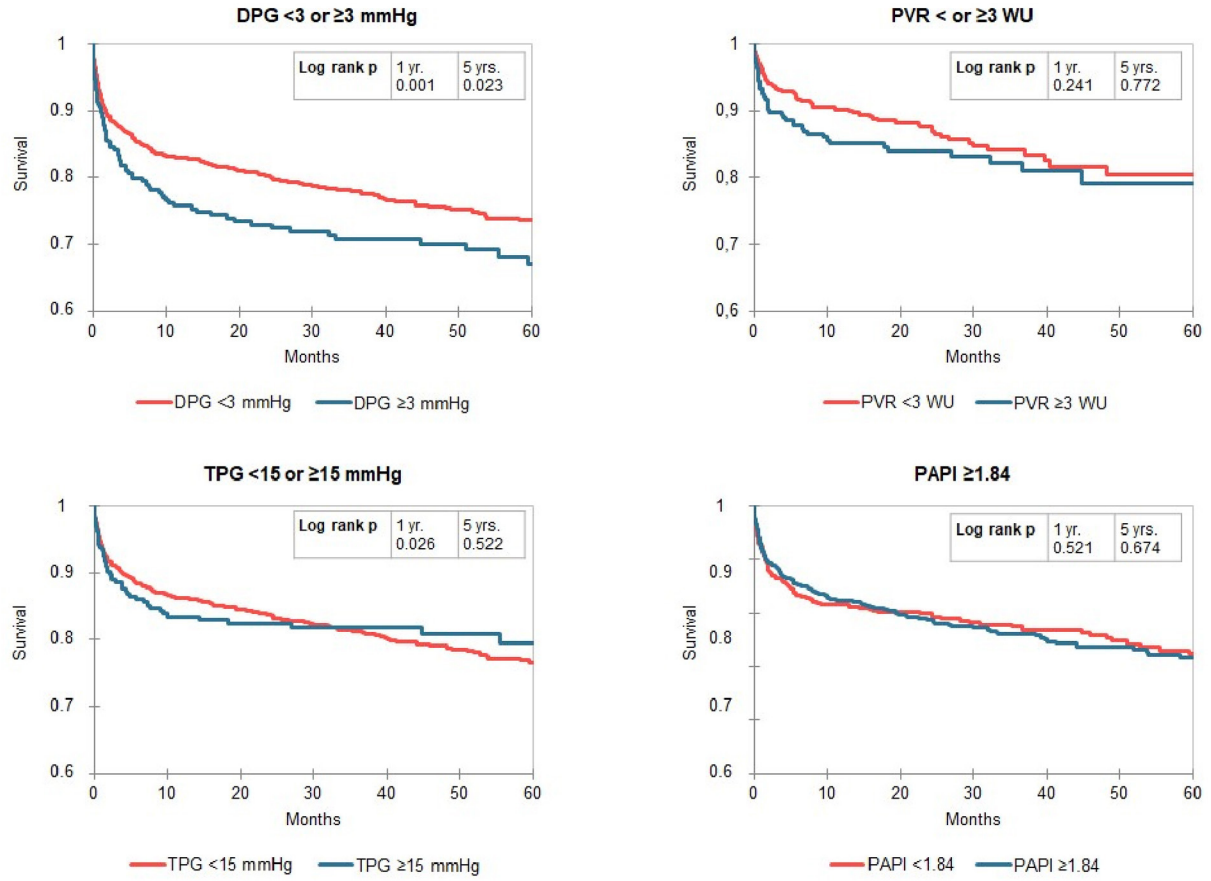


FIGURE 2
Kaplan-Meier curves for Transpulmonary pressure gradient diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient (DPG), transpulmonary pressure gradient (TPG), pulmonary vascular resistance (PVR) and pulmonary pulsatility index (PAPi) dived by cut-off values in patients with pulmonary hypertension (mPAP ≥ 25 mmHg). The numbers of patients at risk are listed in Supplementary Table S4.

are further highly dependent on cardiac output. Our data show that neither TPG > 15 mmHg nor elevated PVR > 3 WU was associated with worse survival.

Comparing TPG and DPG, the latter should be less affected by changes in vascular compliance induced by left heart failure and would appear as an attractive alternative to determine irreversible structural changes in pulmonary vasculature (11). According to this, DPG was independent from sPAP in our study. The evaluation of prognostic significance of the precapillary component of combined PH is complicated by conflicting definitions. While DPG was until recently only considered in the context of elevated mPAP and PAWP (12), the World Symposium on PH favored DPG for the diagnosis of combined post-capillary and pre-capillary PH as the sole discriminator in 2018, but do not longer recommend the use of DPG since 2020 (13).

The effect of elevated DPG on prognosis in PH is controversial. While Tampakakis et al. (14) found that DPG—considered continuously and at multiple cut points—did not demonstrate a significant association with survival in patients with left heart failure, Gerges et al. (15) showed that elevated DPG (≥7 vs. <7 mmHg) was associated with worse median survival in patients with left heart disease with PH and TPG > 12 mmHg. Although Tedford et al. (16) found no impact of DPG on survival in a US cohort of nearly 6,000 patients with advanced heart failure listed for OHT, we could show that DPG > 3 mmHg in OHT candidates with PH was associated with a lower 5-year survival. When favoring DPG, one should notice that even a small error in the measured PAWP might lead to a significant change in the DPG. Therefore, verification than several parameters' suiting to each other is crucial. Further, increases in heart rate lead to an increase in DPG (17). In patients with severe heart failure, this is of interest because tachycardia might occur to compensate low cardiac output or caused by inotropic medications. For further research, especially post-transplant hemodynamic data is required to confirm the importance of DPG and to determine if and to what extent the DPG normalizes after transplantation and if persistently

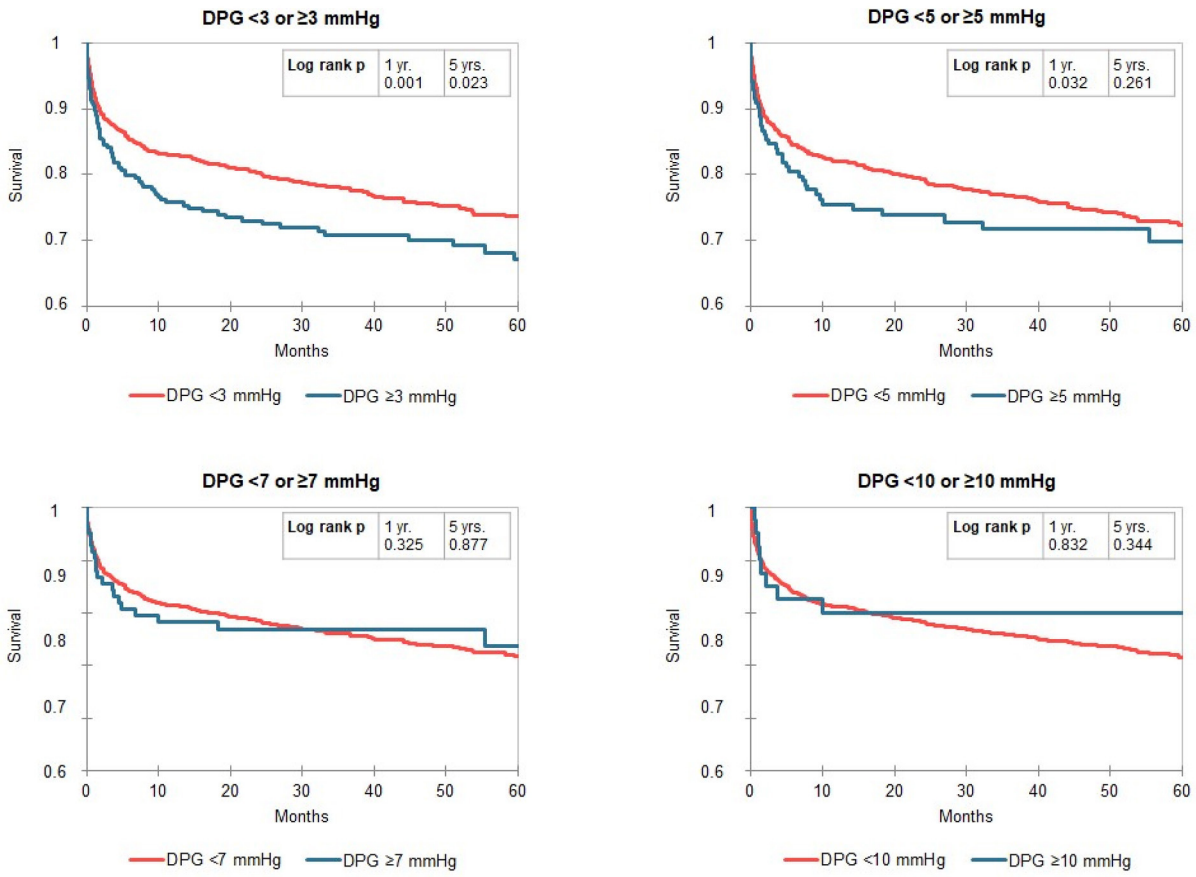


FIGURE 3
Kaplan-Meier curves for the gradient diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient (DPG) split by different cut points (3, 5, 7, or 10 mmHg) in patients with pulmonary hypertension (mPAP ≥ 25 mmHg). The numbers of patients at risk are listed in Supplementary Table S4.

elevated DPG relates to worse outcomes. Goland et al. (18) have shown that failure to normalize PVR to <3 WU after transplantation impacts long-term survival. DPG is not reported in this study.

PAPi is an indicator of right heart function and describes the function of the right ventricular unit against a given afterload. Calculated by pulmonary artery pulse and right atrial pressure its calculation is based on physiology of RV stroke volume, pulmonary arterial capacitance and right atrial pressure. PAPi has been shown to predict 6-month mortality and hospitalization in patients with advanced heart failure. However, no PAPi reference value is available in the setting OHT. Recently Guven et al. (19) found a relevant association between lower PAPi values and higher probability of kidney injury AKI severity in patients with elevated RAP. In out cohort, low PAPi doubled the risk of graft failure. Here we show an impact on graft failure favoring implementation in pre-OHT evaluation as an additional element of patient selection.

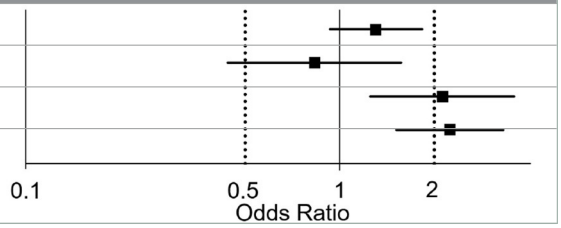
In our cohort, the median time between RHC and OHT was significantly longer in the group of patients without PH. This finding might be partly explained by a higher percentage of patients with LVAD as bridge to transplant and a slightly lower percentage of patients with high urgent listing state in this group. Further, there is less need for hemodynamic follow-up in patients without PH.

Interestingly, RHC was performed more frequent in patients with LVAD. While RHC with complete hemodynamic data was performed in 23% of OHT candidates without LVAD, in 80% of candidates with LVAD hemodynamic data was available. Possibly, some of these patients became hemodynamically eligible for transplantation only after a period of LVAD therapy.

Since LVAD has been shown to lower PVR in PH patients and improve hemodynamics for optimal post OHT outcomes (20), the lower share of PH in LVAD patients is in line with current research. Thresholds for

TABLE 3 Hemodynamic risk factors for graft failure adjusted for age, sex, listing state and underlying heart disease.

Factor	OR	95% CI	*p*	OR and 95% CI
DPG > 3 mmHg	1.30	(0.93–1.83)	0.125	
TPG > 15 mmHg	0.83	(0.44–1.57)	0.571	
PVR > 3 WU	2.12	(1.25–3.59)	0.005	
PAPi < 2.37	2.24	(1.51–3.32)	<0.001	



DPG, diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient; TPG, transpulmonary gradient; PVR, pulmonary vascular resistance; PAPi, pulmonary artery pulsatility index.

FIGURE 4
Hemodynamics risk factors of OHT in patients with PH.

hemodynamic parameters in OHT candidates with LVAD are under debate, but may not fundamentally differ from those in patients without LVAD. Recently, Ruan et al. (21) showed that post-LVAD PVR >3 WU negatively predicts OHT outcomes.

Several limitations of our data should be mentioned. Neither data on vaso-dynamic testing before OHT nor post-OHT hemodynamics were available in a sufficient number of cases. Probably, some patients who did not demonstrate reversibility were excluded as transplant candidates and are therefore not included in this study. Few clinical information on the patients were available, which limits data adjustment. It is likely that co-morbidities influence TPG (e.g., chronic obstructive pulmonary disease) or pulmonary artery pressure (e.g., reduced renal function, anemia, atrial fibrillation). Further, patients evaluated as being not eligible for OHT because of their hemodynamic conditions, were not included. Incomplete data was reported for about 75% of patients of the entire cohort. One can assume that in these patients that were excluded from the analysis, PH might be much less frequent.

We chose overall survival as endpoint, which is influenced by a variety of factors, e.g., infection or rejection. The cause of death was available in post-transplant patients, but not standardized assessed. Alternative causes of death might dilute or distort death because of PH and right heart failure. However, the selective analysis of PH vs. no PH patients should have risen the proportion of deaths from right heart failure. However, these limitations reflect real world conditions, making the study clinically relevant. Multicenter study design and investigation of the impact of two recently popularized hemodynamic parameters (PAPi and DPG) on OHT outcomes are substantial strength of our study.

Conclusion

In the largest European heart transplant database, increased pre-transplant DPG was related to impaired 5-year post-surgical survival. TPG, PVR and PAPi all had poor ability to discriminate survivors from non-survivors. Low PAPi and high PVR were shown to predict graft failure.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to h.grahn@uke.de.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

TW, HG, CM, and PK wrote the manuscript draft. TW performed the data analysis. HG and TW designed the study. JS contributed to data analysis and interpretation. HR, AB, and KS contributed to study design and discussion of results. All authors contributed to manuscript writing and read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1036547/full#supplementary-material

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EDITED BY
Shinichi Okuda,
Yamaguchi Prefectural Grand Medical Center, Japan

REVIEWED BY
Emilia D'Elia,
Papa Giovanni XXIII Hospital, Italy
Andreea Calin,
Carol Davila University of Medicine and Pharmacy, Romania

*CORRESPONDENCE
Giulia Elena Mandoli
✉ giulia_elena@hotmail.it

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The loss of left atrial contractile function predicts a worse outcome in HFrEF patients

Giulia Elena Mandoli [1]*, Maria Concetta Pastore[1], Giovanni Benfari[2], Martina Setti[2], Luca Maritan[2], Enrico Emilio Diviggiano[1], Flavio D'Ascenzi[1], Marta Focardi[1], Luna Cavigli[1], Serafina Valente[1] and Matteo Cameli[1]

[1]Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy, [2]Section of Cardiology, Department of Medicine, University of Verona, Verona, Italy

Background: In chronic heart failure, high intracardiac pressures induce a progressive remodeling of small pulmonary arteries up to pulmonary hypertension. At the end of left atrial conduit function, pulmonary and left heart end-systolic pressures equalization might affect left atrial systole. In this single-center prospective study, we aimed to investigate whether peak atrial contraction strain (PACS), measured by speckle tracking echocardiography, was independently associated with prognosis in heart failure with reduced ejection fraction (HFrEF).

Materials and methods: Outpatients with HFrEF and sinus rhythm referred to our echo-labs were enrolled. After clinical and echocardiographic evaluation, off-line speckle tracking echocardiography analysis was performed. Primary and secondary endpoint were cardiovascular death and heart failure hospitalization, respectively. Spline knotted survival model identified the optimal prognostic cut-off for PACS.

Results: The 152 patients were stratified based on PACS <8% (n = 76) or PACS ≥8% (n = 76). Patients with PACS <8% had lower left ventricle and left atrial reservoir strain and higher New York Heart Association (NYHA) class and left atrial volume index (LAVI). Over a mean follow-up of 3.4 ± 2 years, 117 events (51 cardiovascular death, 66 heart failure hospitalizations) were collected. By univariate and multivariate Cox analysis, PACS emerged as a strong and independent predictor of cardiovascular death and heart failure hospitalization, after adjusting for age, sex, left ventricle strain, and E/e', LAVI (HR 0.6 per 5 unit-decrease in PACS). Kaplan–Meier curves showed a sustained divergence in event-free survival rates for the two groups.

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Conclusion: The reduction of PACS significantly and independently affects cardiovascular outcome in HFrEF. Therefore, its assessment, although limited to patients with sinus rhythm, could offer additive prognostic information for HFrEF patients.

KEYWORDS

speckle tracking, strain, left atrium, heart failure, HFrEF, prognosis

1. Introduction

Chronic heart failure (HF) is a progressive cardiovascular disease with increasing incidence in the last years, parallel to an increasing medium age of the population worldwide. Despite therapeutic novelties, it is still characterized by a poor prognosis, particularly in the advanced stages of the disease (1), and a high burden of symptoms, which strongly affects patients' quality of life. Even though the classification of HF according to the European Society of Cardiology (ESC) guidelines is still based on left ventricular (LV) ejection fraction (EF), this parameter has showed a limited prognostic power, especially within the heart failure with reduced ejection fraction (HFrEF) group. Therefore, in the last years, many scientific investigations focused on the research of new echocardiographic potential prognostic markers in HFrEF, particularly after the introduction of speckle tracking echocardiography (STE) technique in daily clinical practice (2, 3). In fact, the measurement of LV strain by STE provided new insight into early diagnosis and prognostication of HF (4–6); however, in patients with chronic HFrEF including variable etiologies (such as ischemic, dilated, and hypertrophic cardiomyopathy) LV strain is often reduced being the LV the first affected chamber in these patients, so this index often lacks accuracy for risk stratification. On the other hand, left atrial (LA) reservoir strain has recently been introduced in the European association of cardiovascular imaging (EACVI) recommendations as a standard parameter in the diagnostic algorithm of diastolic function in HF with preserved ejection fraction (HFpEF) (7), due to the high amount of evidence regarding its value as early and sensitive marker of elevated LV filling pressures (8, 9) and myocardial fibrosis (10). LA strain has also showed to be a good prognostic marker both in HFrEF (11–14) and HFpEF (15, 16). However, LA reservoir strain is thought to be strictly related to LV strain in chronic HF, because of LV dysfunction in chronic increase of LV filling pressures where LV global longitudinal strain (GLS) is one of the main determinants of reservoir peak atrial longitudinal strain (PALS) (9). Importantly, LA strain could be used to measure all LA function during the cardiac cycle, reservoir one. LA contraction phase is described by peak atrial contraction strain (PACS) (**Figure 1**) (17). Thus, PACS may represent a more independent parameter to merely analyze LA function, being related to intrinsic atrial remodeling and residual contractile function. LA booster function could be affected in chronic HF by the establishment of pulmonary hypertension in adjunction to chronically high filling pressures, leading to pulmonary and left heart pressures equalization at the end of LA conduit phase. PACS has already shown to be a good prognostic parameter in HFrEF if measured together with PALS, however, no study has been developed on the independent value of PACS yet. The aim of our study was to assess the potential value of PACS as an independent prognostic parameter in a cohort of patients with chronic HFrEF.

2. Materials and methods

In this prospective single-center observational study, consecutive patients with HFrEF and sinus rhythm according to the 2016 ESC HF guidelines definition [i.e., patients with signs (pulmonary crackles, peripheral edema, elevated jugular venous pressure) and/or symptoms (dyspnea, fatigue, and ankle swelling) of HF and LV EF <40%] referred to our HF

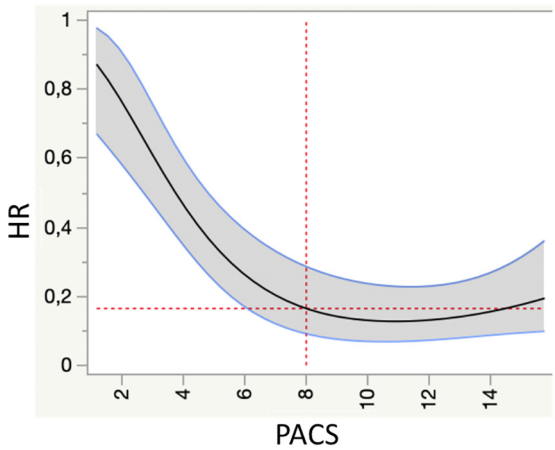

FIGURE 1
Spline knotted survival curve to assess the value of peak atrial contraction strain (PACS) as a predictor of cardiovascular mortality (primary endpoint). HR, hazard ratio.

ambulatories for a cardiologic visit including echocardiography between 2015 and 2017 were enrolled. Exclusion criteria were non-sinus rhythm, previous cardiac surgery or poor acoustic window.

The patients were prospectively followed for a primary and a secondary endpoint, consisting in the occurrence of cardiovascular death and hospitalization for HF, respectively. Follow-up data were collected *via* phone calls and electronic medical records. All subjects gave their written informed consent for participation in this study. All work followed the 1975 Declaration of Helsinki. The study protocol was approved before the enrollment of the first patient by the local Ethics Committee (approval number 11757_2017).

2.1. Basic echocardiography

Echocardiographic examination was performed according to the EACVI/American Society of Echocardiography (ASE) recommendations for chamber quantification (18), using a high-quality ultrasound machine (Vivid E9; GE Medical System, Horten, Norway) with patients in the left lateral recumbent position.

Left ventricular and left atrial dimensions were calculated using standard views. LV ejection fraction (LVEF) and LA volume and area were assessed using the biplane modified Simpson method from the apical 4- and 2-chamber views. LV dimensions and LA volume were indexed to body surface area obtaining LV mass index and LA volume index (LAVI). From the 4-chamber view, tricuspid annular plane systolic excursion (TAPSE) was measured by M-mode; maximum early diastolic (E) and late diastolic (A) velocities were assessed by trans-mitral pulsed wave doppler to calculate E/A ratio; then, peak systolic (S'), early diastolic (E'), and late diastolic (A') annular velocities were obtained by tissue doppler imaging, E/E' ratio was calculated and used as index of the LV filling pressure. Mitral and tricuspid regurgitation (MR, TR) were quantified by bidimensional (2D)-echocardiography according to EACVI/ASE recommendations (18). Systolic pulmonary artery pressure (sPAP) was estimated as the sum of systolic trans-tricuspid pressure gradient and of right atrial

TABLE 1 Clinical and echocardiographic characteristics of heart failure with reduced ejection fraction (HFrEF) patients according to PACS values.

Variable	Overall (*n* = 152)	PACS <8% (*n* = 76)	PACS ≥8% (*n* = 76)	*P*-value
Age	62 ± 12	61 ± 12	62 ± 13	0.8
Male (%, *n*)	79 (120)	82 (62)	76 (58)	0.7
BMI	27 ± 5	27 ± 5	27 ± 5	0.7
sBP (mmHg)	123 ± 21	119 ± 22	127 ± 19	0.02
HR (bpm)	70 ± 10	71 ± 11	70 ± 10	0.7
Hypertension (%, *n*)	39 (60)	34 (26)	45 (34)	0.2
Diabetes mellitus (%,*n*)	16 (25)	16 (12)	17 (13)	0.9
Dyslipidemia (%,*n*)	28 (42)	16 (12)	39 (30)	0.002
NYHA class >2 (%, *n*)	37 (56)	51 (39)	22 (17)	<0.0001
NTpro BNP (pg/L)	1,814 ± 2,059	2,294 ± 1,676	1,335 ± 2,442	0.09
LVEDVi (ml/mq)	82 ± 49	85 ± 55	80 ± 43	0.5
LVESVi (ml/mq)	58 ± 39	62 ± 43	54 ± 33	0.2
LVEF (%)	30 ± 7	28 ± 7	33 ± 7	0.0007
LAVI (ml/mq)	55 ± 18	64 ± 20	45 ± 16	<0.0001
E/A	1.6 ± 1.1	1.9 ± 1.2	1.2 ± 0.9	<0.0001
E/E' ratio	14 ± 8	16 ± 9	12 ± 7	0.003
TAPSE (mm)	17 ± 4	17 ± 4	18 ± 5	0.2
RVFAC (%)	38 ± 9	37 ± 9	40 ± 9	0.09
sPAP (mmHg)	35 ± 11	40 ± 13	30 ± 9	<0.0001
LVGLS (%)	−8.7 ± 3.4	−7.3 ± 3.5	−10.2 ± 3.2	<0.0001
Global PALS (%)	15.0 ± 6.0	9.8 ± 4.9	20.3 ± 7.0	<0.0001

E, peak early diastolic "E" wave; E', medium velocity of early mitral annulus descent; GLS, global longitudinal strain; LAVI, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; PACS, peak atrial contraction strain; PALS, peak atrial longitudinal strain; RVFAC, right ventricular fractional area change, sPAP, systolic pulmonary artery pressure; and TAPSE, tricuspid annular plane excursion.

pressure derived from the diameter and collapsibility of the inferior vena cava.

2.2. Speckle tracking echocardiography

Speckle tracking echocardiography analysis was performed on apical 2-, 3-, and 4- chamber images, obtained by 2D gray-scale echocardiography, with a stable electrocardiographic recording. Care was taken to obtain a good visualization of all chambers and a reliable delineation of the endocardial border. Measurements from three consecutive heart cycles were recorded and averaged. The frame rate was 60–80 frames/sec. Analysis was performed off-line by a single experienced and independent echocardiographer, who was not directly involved in the image acquisition and blinded to basic echocardiographic parameters, using a semiautomated 2D-strain software (EchoPac, GE, Milwaukee, WI, USA). The endocardial border was manually traced in apical views, delineating a region of interest (ROI) of six segments for each view. Then, necessary manual adjustments of the ROI were performed and the longitudinal strain curves for each segment were generated by the software. LV GLS was calculated as the average of 4-, 2-, and 3-chambers longitudinal strain curves. Both apical views were optimized in terms of orientation, depth, and gain to avoid LA foreshortening and to visualize the entire LA throughout the cardiac cycle. Global PALS and PACS were calculated at the end of the reservoir and the contraction phase, respectively, as the average of all LA segments in 4- and 2-chamber views, using QRS as starting point (19). In patients in whom some segments were excluded for impossible adequate tracking, strain was calculated by averaging values measured in the remaining segments.

2.3. Statistical analysis

Data are expressed as means ± SD (continuous variables) or as counts and percentages (binary variables).

Spline-knotted survival model was used to obtain optimal cutoff values of global PACS for the prediction of the primary endpoint (cardiovascular mortality). Using this cutoff, patients were divided into 2 groups based on the presence of PACS lower/higher than the cutoff. Differences between the groups were analyzed using Student *T*-tests for continuous variables and Chi-squared analyses for categorical variables.

Kaplan–Meier curves and Log-Rank test were used to assess the correlation of the two groups with events-free survival. Univariate and multivariate analysis were performed applying the Cox proportional hazard model to investigate the performance of global PACS as a predictor of primary and secondary endpoint; adjustment models were built using age, sex, LV strain, and E/e', LAVI. The covariates were chosen based on their univariable association with the dependent variable as well as based on biological plausibility.

Analyses were performed using the Statistical Package for Social Sciences software, release 20.0 (SPSS, Chicago, IL, USA). *P*-values <0.05 were considered statistically significant.

3. Results

From an initial number of 168 patients, 152 patients were finally enrolled in this study. We excluded 8 patients for previous heart valve surgery, six because of atrial fibrillation during echocardiographic examination and two for poor acoustic window. Intra-operator reproducibility for LA strain analysis was already tested in our center. (19, 20) Mean age was 62 ± 12 years, 21% (n = 32) were female, mean LV EF was 30 ± 9%. All patients were receiving optimized HF therapy (according to current guidelines at the time of enrollment) including ACE inhibitors/angiotensin receptor blockers (91%), mineralcorticoid receptor antagonist (75%), betablockers (78%). Moreover, 81% of the patients had implantable cardiac device (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D). Mean LA maximum volume indexed was 55 ± 18 ml/mq while LA minimum volume was 34 ± 20 ml.

TABLE 2 Univariate and multivariate analysis for the prediction of cardiovascular death.

Parameter	Univariate analysis (HR)	p	Multivariate analysis (HR)	p
LAVI	1.01	0.06		
E/e'	1.03	0.07		
GLS	0.82	0.04	0.88	0.05
Age	1.00	0.49		
Male	1.14	0.52		
PACS	0.71	0.04	0.59	0.03

LAVI, left atrial volume index; GLS, global longitudinal strain; and PACS, peak atrial contraction strain.

TABLE 3 Univariate and multivariate analysis for the prediction of HF hospitalization.

Parameter	Univariate analysis (HR)	p	Multivariate analysis (HR)	p
LAVI	1.00	0.54		
E/e'	1.01	0.54		
GLS	0.81	0.03	1.07	0.17
Age	1.00	0.81		
Male	0.93	0.86		
PACS	0.52	<0.001	0.60	0.01

LAVI, left atrial volume index; GLS, global longitudinal strain; and PACS, peak atrial contraction strain.

Speckle tracking echocardiography analysis revealed severely reduced longitudinal deformation of both left ventricle and atrium (−8.7 ± 3.4 and 15.0 ± 6%, respectively). PACS value showed a moderate, statistically significant correlation with LA minimum volume ($r = 0.54$, $p < 0.001$).

Over a mean follow up of 3.4 ± 2 years, 117 events (51 CV death, 66 HF hospitalizations) were registered. Spline-knotted curves showed a good association of global PACS <8% with risk of cardiovascular mortality (**Figure 1**).

Therefore, this cut-off was used to stratify the population into two risk groups: group 1 with PACS <8% and group 2 with PACS >8%. **Table 1** shows the general and echocardiographic characteristics of the study population. Patients with global PACS <8% showed lower LV GLS and global PALS, higher New York heart association (NYHA) class, N-terminal-pro-brain natriuretic peptide (NTproBNP), LAVI, and sPAP. Then, univariate and multivariate Cox analysis (see **Tables 2**, **3**) was applied after adjusting for age, sex, LV strain, E/e', LAVI (see **Tables 2**, **3** for univariate and multivariate analysis for CV death and HF hospitalization, respectively) showing a strong and independent association of global PACS reduction with the primary endpoint (HR 0.6 per 5 unit decrease in PACS).

Kaplan–Meier curves showed a sustained divergence in event-free survival rates for the two groups for both the primary and the secondary endpoint (**Figure 2**).

4. Discussion

The present study was the first to show an independent prognostic value of PACS in chronic HF, identifying <8% as the optimal cut-off value for risk stratification in HFrEF.

Even though there currently is a lack of studies focused on this parameter alone, there are a lot of evidence on its association with outcome in HF and cardiomyopathies, if measured in adjunction to PALS (21–23). Moreover, Inoue et al. (9) proved that both PALS and PACS are markers of LV filling pressures in patients with reduced LV systolic function, and that PACS predicts LV filling pressures also in patients with normal LV systolic function. Lindqvist and Henein (23) showed that LA contraction strain rate was the strongest predictor of PCWP in symptomatic patients, compared to LA reservoir strain and GLS, particularly in patients with post-capillary PH and with dilated LA cavity. In our population, PACS was moderately correlated with LA minimum volume, which is probably dependent on the fact that the amount of blood remaining in the last atrium at the end of diastole is also determined by LA conduit function and LV compliance.

The rationale in considering PACS as an independent prognostic parameter in HFrEF could be deduced by the pathophysiology of chronic HF: first of all, the direct or indirect myocardial damage which causes overt LV systolic dysfunction in HFrEF and the chronic LV overload impairs myocardial contractility with severe LV GLS reduction accompanying LV EF reduction in the majority of cases. Therefore, although being important for the categorization of overall HF, none of these two parameters seems to be sensitive for risk stratification among patients with chronic systolic dysfunction. Then, the chronic increase of LV filling pressures reflects on the LA myocardium, which initially compensates for the high intracardiac pressures and eventually underwent LA wall ultrastructural changes, with remodeling and fibrosis, leading to LA dilatation and dysfunction. In these phases, LA evaluation

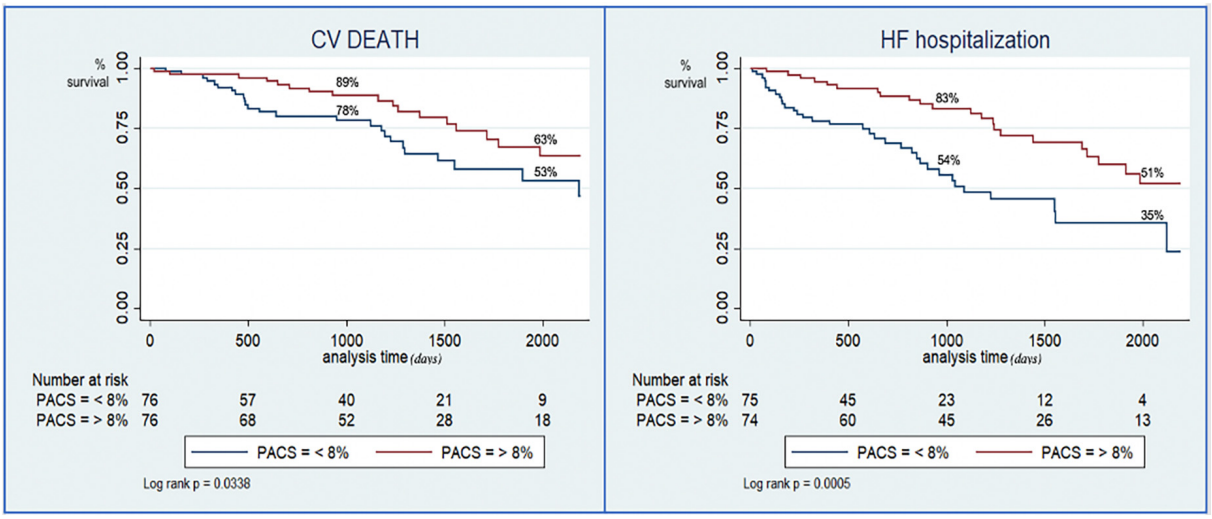

FIGURE 2
Kaplan–Meier curves for the risk stratification of cardiovascular death **(left)** and hospitalization for heart failure **(right)** based on preserved or reduced peak atrial contraction strain (PACS).

is fundamental to assess the stage of the disease and whether the myocardial damage could be reversible or not. Therefore, PALS would be certainly reduced in a grade parallel to the age of the disease, and its value, reflecting the reservoir function in systole, would be probably influenced by LV contractile properties and longitudinal shortening. However, in the advanced phase, when the LA is not capable to face the elevated filling pressures, the transmission of hemodynamic overload on the pulmonary circulation takes place, with a chronic establishment of pulmonary hypertension, up to a point in which pulmonary and LA pressures equalized in diastole, thus affecting LA contraction and its contribution to LV filling. This represents the immediately preceding step before the transition to biventricular failure, due to severe and/or chronic pulmonary hypertension, often irreversible and requiring advance therapies.

Hence, in patients with long-standing chronic HFrEF, the analysis of LA contractile function may offer additional information for risk stratification, identifying those patients who have completely lost the LA contribution to maintain LV filling, in all the cardiac cycle phases, and who are at higher risk of transition to advanced HF.

In the light of the new therapies for HFrEF recommended in the latest ESC HF guidelines (1), there is a timely need of new indices to stratify prognosis to guide clinical choices for the management of these patients.

Considering the high feasibility and availability and low time-consumption of this parameter, the measurement of PACS could help clinicians to provide patients with HF and sinus rhythm a more tailored therapy and to decide whether to be more aggressive with medical therapy and to prescribe stricter follow up to HFrEF patients.

5. Limitations

Although this study shows global PACS promising results for the clinical risk stratification of HFrEF, some limitations should be encountered: first, it was a single center study conducted in a small cohort of patients with HFrEF, therefore, large-scale studies should confirm our findings.

Moreover, PACS was investigated as an independent parameter and was not compared with PALS, which may be associated with it in some way. Finally, an intrinsic limitation of the parameter led to the exclusion of patients with atrial fibrillation, which is a common condition in HF, since PACS is not feasible in these patients.

6. Conclusion

In conclusion, in patients with chronic HFrEF, LA contraction might be affected because of the chronic hemodynamics overload. The assessment of impaired LA contraction as a reduction of global PACS, acquired by speckle tracking echocardiography, significantly and independently affects CV outcome in HFrEF. Therefore, although limited to patients with sinus rhythm, the evaluation of global PACS could provide additive information for risk stratification of HFrEF patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana Sezione: AREA VASTA SUD EST. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GM: conceptualization, methodology, software, formal analysis, writing—original draft, and supervision. MP: software, formal analysis, and investigation. GB: data curation and investigation. MS, LM, LC, and SV: data curation. ED: writing—review and editing, validation, and visualization. MF: investigation. FD'A: conceptualization and methodology. MC: conceptualization, methodology, software, and project administration. All authors have participated in the work and have reviewed and agreed with the content of the article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Francesco Gentile,
Sant'Anna School of Advanced Studies,
Italy

REVIEWED BY
Samit Ghosal,
Nightingale Hospital, India
Hui Gong,
Fudan University,
China

*CORRESPONDENCE
Rungroj Krittayaphong
✉ rungroj.kri@mahidol.ac.th

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Is it time for class I recommendation for sodium-glucose cotransporter-2 inhibitors in heart failure with mildly reduced or preserved ejection fraction?: An updated systematic review and meta-analysis

Sukrit Treewaree[1], Narathorn Kulthamrongsri[2], Weerapat Owattanapanich[3] and Rungroj Krittayaphong[1]*

[1]Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [3]Division of Hematology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: In heart failure with reduced ejection fraction (HFrEF), sodium-glucose cotransporter-2 (SGLT2) inhibitors were demonstrated to lower cardiovascular mortality (CV death) and hospitalization for heart failure (HHF); however, the advantages of SGLT2 inhibitors in heart failure with mildly reduced (HFmrEF) or preserved ejection fraction (HFpEF) are less clear. SGLT2 inhibitors were reported to enhance quality of life (QoL) in HFmrEF or HFpEF patients; however, the findings among studies are inconsistent.

Objective: To conduct an updated systematic review and meta-analysis of recent data to assess the effect of SGLT2 inhibitors on cardiovascular outcomes and QoL in patients with HFmrEF or HFpEF.

Method: Three databases were searched for studies that evaluated SGLT2 inhibitors and their effect on cardiovascular outcomes, including CV death, HHF, all-cause death, and the composite outcome of CV death, HHF, and urgent visit for heart failure (HF), and patient QoL (Kansas City Cardiomyopathy Questionnaire [KCCQ] score compared to baseline, and increase in KCCQ score≥5 points) that were published during January 2000–August 2022. The meta-analysis was performed using the inverse variance method and random-effects model. INPLASY registration: INPLASY202290023.

Results: Sixteen studies (9 recent RCTs) were included, and a total of 16,710 HFmrEF or HFpEF patients were enrolled. SGLT2 inhibitors significantly reduced composite cardiovascular outcome (CV death/HHF/urgent visit for HF; pooled hazard ratio [HR]: 0.80, 95% confidence interval [95%CI]: 0.74–0.86) and HHF alone (HR: 0.74, 95%CI: 0.67–0.82), but there was no significant reduction in CV death alone (HR: 0.93, 95%CI: 0.82–1.05). Benefit of SGLT2 inhibitors for decreasing CV death/HHF was observed across all subgroups, including left ventricular ejection fraction (LVEF) range, diabetes status, New York Heart Association functional class, and baseline renal function. For total HHF, SGLT2 inhibitors conferred benefit in both LVEF 50–60% (HR: 0.64, 95%CI: 0.54–0.76), and LVEF >60% (HR: 0.84, 95%CI: 0.71–0.98). Significant change was observed in the KCCQ-clinical summary score compared to baseline

(mean difference: 1.33, 95%CI: 1.31–1.35), and meaningful improvement in QoL was shown across all 3 types of increase in KCCQ score≥5 points.

Conclusion: This study demonstrates the benefits of SGLT2 inhibitors for improving cardiovascular outcomes and QoL in HFmrEF or HFpEF patients.

KEYWORDS

sodium-glucose cotransporter-2 inhibitors, heart failure with preserved ejection fraction, heart failure with mildly reduced ejection fraction, systematic review, meta-analysis

1. Introduction

Heart failure (HF) is a clinical syndrome that comprises symptoms and signs of abnormal blood pumping and filling from or into the heart. HF is classified according to left ventricular ejection fraction (LVEF) into the 3 following groups: reduced ejection fraction (HFrEF; LVEF ≤40%), mildly reduced ejection fraction (HFmrEF; LVEF 41–49%), and preserved ejection fraction (HFpEF; LVEF ≥50%) (1, 2). The inclusion criteria of many previous clinical trials defined HFpEF as including patients with preserved ejection fraction or with mildly reduced ejection fraction. HF is a global health burden with over 60 million people reported to be affected by HF in 2017 (3). The prevalence of HF is increasing, and HFpEF is most commonly observed (4, 5). As the lifespan of people in most societies continues to increase, HF has emerged as a continuously growing global economic burden. The estimated global cost of treating HF in 2012 was 108 billion US dollars, and the reported direct cost per patient ranged from $800 to $30,000 per year (6–8).

There is robust evidence to support various treatments for reducing mortality and morbidity in patients with HFrEF; however, evidence specific to treatments for reducing mortality and morbidity in patients with HFmrEF or HFpEF is less clear (1, 2). Data from recent clinical trials suggest the benefit of sodium glucose co-transporter 2 (SGLT2) inhibitors as a potential treatment for patients with HFmrEF or HFpEF. The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial reported a significantly reduced risk of composite cardiovascular death (CV death) or hospitalization for heart failure (HHF) in patients with HFmrEF or HFpEF compared to placebo; however, there was no significant effect on CV death alone or all-cause death alone (9).

Recent meta-analysis studies reported benefit of SGLT2 inhibitors for reducing HHF in HFmrEF or HFpEF, but the effects of SGLT2 inhibitors were inconsistent or none for reducing CV death alone or all-cause death alone (10–12). Furthermore, the benefits of SGLT2 inhibitors on HFpEF are not uniform throughout the LVEF spectrum and are mitigated in high LVEF (13).

Recent trials in SGLT2 inhibitors reported improved health status in patients with HFmrEF or HFpEF as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) score; however, there are disparities in findings among studies (9, 14–17).

Given the recent publication of the data from the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial (18), which was a large randomized double-blind trial that compared the effect of dapagliflozin versus placebo in patients with HFmrEF or HFpEF, an updated meta-analysis that focuses on the effect of SGLT2 inhibitor in patients with HFmrEF or HFpEF is urgently needed. Accordingly, the aim of this systematic review and meta-analysis was to evaluate data from recent studies that investigated the effect of SGLT2 inhibitors on patient quality of life (QoL) and cardiovascular (CV) outcomes, including CV death, hospitalization for HF (HHF), urgent visit for HF, and all-cause death, in patients with HFmrEF or HFpEF.

2. Methods

2.1. Data sources and searches

Systematic electronic searches of three online databases (OVID MEDLINE, Embase, and Cochrane CENTRAL) were independently conducted by two investigators (ST and NK) for articles published from 1 January 2000 to 28 August 2022. The search terms included keywords that maximized coverage of HF and SGLT2 inhibitors. Details specific to the search strategies used in this study are presented in Supplementary Data 1. The list of references in eligible studies, included studies, and studies of interest were manually screened to identify other suitable studies. This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (19) (Supplementary Data 2). The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand [COA no. 599/2565(IRB2)]. Written informed consent was not obtained from included patients due to the retrospective nature of this study.

2.2. Selection criteria and data extraction

The following criteria must have been satisfied for a study to be eligible for inclusion in the meta-analysis. First, the study must have been a randomized controlled trial (RCT) or a *post-hoc* analysis of an RCT that compared the outcomes of SGLT2 inhibitors with placebo or other hypoglycemic drugs for the treatment of HF. Second, the study must have reported at least one of the primary outcomes of interest, including CV death, HHF, all-cause death, or the composite outcome of CV death, HHF, and urgent visit for HF. Observational studies, case series, case reports, and reviews were excluded. The same two investigators that performed the database searches (ST, NK) independently determined the eligibility of identified studies. Any lack of agreement between those two investigators was resolved *via* the involvement of a third investigator (WO) until a consensus was reached. The data were independently extracted by the first two investigators (ST, NK) using a standardized data collection form, after which the accuracy and thoroughness of the data were verified by the third investigator (WO). The following data were collected: the name of the first

author, year of publication, median follow-up time, intervention, baseline patient characteristics, and reported outcome(s) of interest.

2.3. Outcomes of interest

The primary outcome was the cardiovascular outcome, including CV death, HHF, all-cause death, and the composite outcome of CV death, HHF, and urgent visit for HF. The secondary outcomes were the change in the KCCQ score compared to baseline, an increase in the KCCQ score of ≥5 points, and total hospitalization due to HF (total HHF). The KCCQ has been used in many clinical trials to assess the health status of HF patients. The KCCQ comprises the following 7 domains: symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life, and self-efficacy. The symptom frequency and symptom burden domain scores can be combined to generate the KCCQ-total symptom (KCCQ-TS) score. The KCCQ-TS score can be merged with the physical limitations domain score to generate the KCCQ-clinical summary (KCCQ-CS) score. The KCCQ-CS score can be combined with the social limitations domain score and quality of life domain score to generate the KCCQ-overall summary (KCCQ-OS) score. All scores are expressed on a 0-to-100 scale with a higher score indicating fewer symptoms, fewer limitations, and greater QoL (20).

2.4. Quality assessment of the included studies

The Cochrane Risk of Bias (RoB) 2 tool (The Cochrane Collaboration, London, United Kingdom) was used to evaluate the quality of included studies by two investigators (ST, NK), and any discrepancies were resolved *via* discussion and consensus between the two investigators (21).

2.5. Statistical analysis

The inverse variance method pooled the hazard ratios (HRs), odds ratios, mean differences, and 95% confidence intervals (95%CI) among the included studies (22). Cochran's Q test was used to determine whether the proportion of 'successes' was equal across three or more groups. The statistical heterogeneity across the eligible studies was demonstrated using the prediction interval (23). A random effects model was used rather than a fixed effects model due to the high likelihood of between-study heterogeneity. A *value of p* of less than 0.05 was considered to reflect statistical significance. Review Manager 5.4 software from the Cochrane Collaboration was used for all statistical analyses. Publication bias was assessed using funnel plots. The study protocol was registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) network (registration number: INPLASY202290023).

3. Results

3.1. Study selection and risk of bias assessment

The initial search yielded 5,327 articles from the three online databases. After the removal of duplicates by the two authors who performed the searches (ST, NK), 3,547 records remained for screening by title and abstract, including 11 papers that were identified *via* a manual search of references. Those same two investigators independently reviewed the full text of 128 publications. Any disagreements between the two reviewing authors were resolved with the help and consultation of a third author (WO). One hundred and twelve articles were excluded for the following reasons: lacked data of interest ($n = 79$), not an RCT or a *post-hoc* analysis of an RCT ($n = 24$), and were ongoing trials or did not publish the results ($n = 9$). The remaining 16 articles that reported data from 9 recent RCTs were included in this meta-analysis (9, 14, 15, 24–36) (Figure 1) (19). The quality assessment using the RoB 2 tool (37) (The Cochrane Collaboration) is shown in Figure 2. We found no publication bias in study selection using funnel plots as shown in Supplementary Data 3.

Among the 112 excluded studies, five studies in HFpEF patients were also excluded from our meta-analysis. A *post-hoc* analysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS) was excluded due to their having a different definition of the reported cardiac composite outcome (38). The Canagliflozin Impact on Health Status, Quality of Life, and Functional Status in Heart Failure (CHIEF-HF) trial, and the Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure (EMPULSE) trial were excluded owing to the use of different statistics to report the change in KCCQ-TS (16, 17). The Prospective Comparison of Luseogliflozin and Alpha-glucosidase on the Management of Diabetic Patients with Chronic Heart Failure and Preserved Ejection Fraction (MUSCAT-HF) trial was excluded because it focused on echocardiographic outcome and had no outcome of interest (39). The Dapagliflozin Effect on Exercise Capacity Using a 6-min Walk Test in Patients with Heart Failure with Preserved Ejection Fraction (DETERMINE-preserved; NCT03877224) was excluded because its study results were publicly available only on the[1] website, so it was an unpublished study.

3.2. Study and patient characteristics

A total of 16,710 HFmrEF or HFpEF patients from 9 RCTs were included in this study. The characteristics of the 9 randomized controlled trials that were included in this study, and from which data were analyzed and reported by the other 7 *post-hoc* studies included in this study are presented in Table 1. The median follow-up time ranged from 3 months in the Effect of Empagliflozin on Exercise Ability and Heart Failure Symptoms in Patients with Chronic Heart Failure (EMPERIAL)-Preserved trial and the Dapagliflozin in Preserved Ejection Fraction Heart Failure (PRESERVED-HF) trial to 50.4 months in the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE–TIMI 58) (14, 15, 36). Except for the Canagliflozin Heart Failure with Preserved Ejection Fraction Study for Type 2 Diabetes Mellitus (CANONICAL) trial (34), which was an open-label randomized trial that compared canagliflozin to standard diabetic therapy, all studies were double-blind and placebo-controlled. Five trials (9, 14, 15, 33, 34) included participants with chronic HF, while the other four trials (24–26, 36) recruited type 2 diabetes patients with CV risk. The Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial

1 clinicaltrials.gov

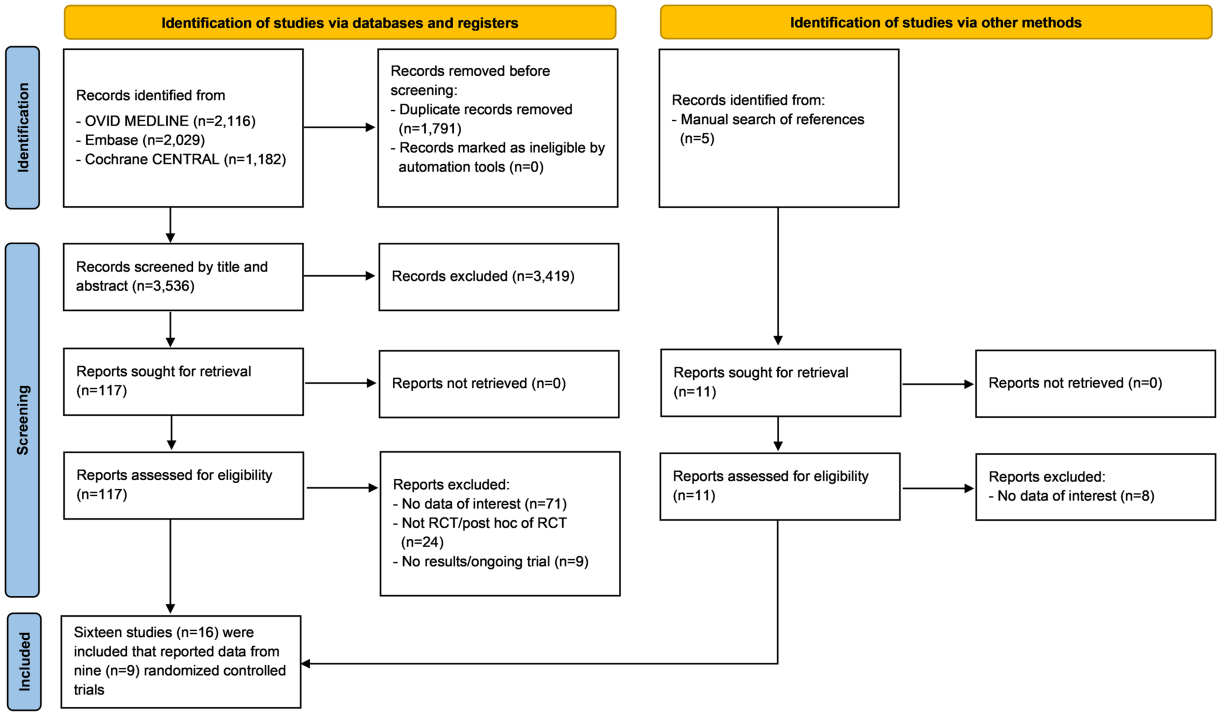

FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram summarizing the systematic review and study selection protocol.

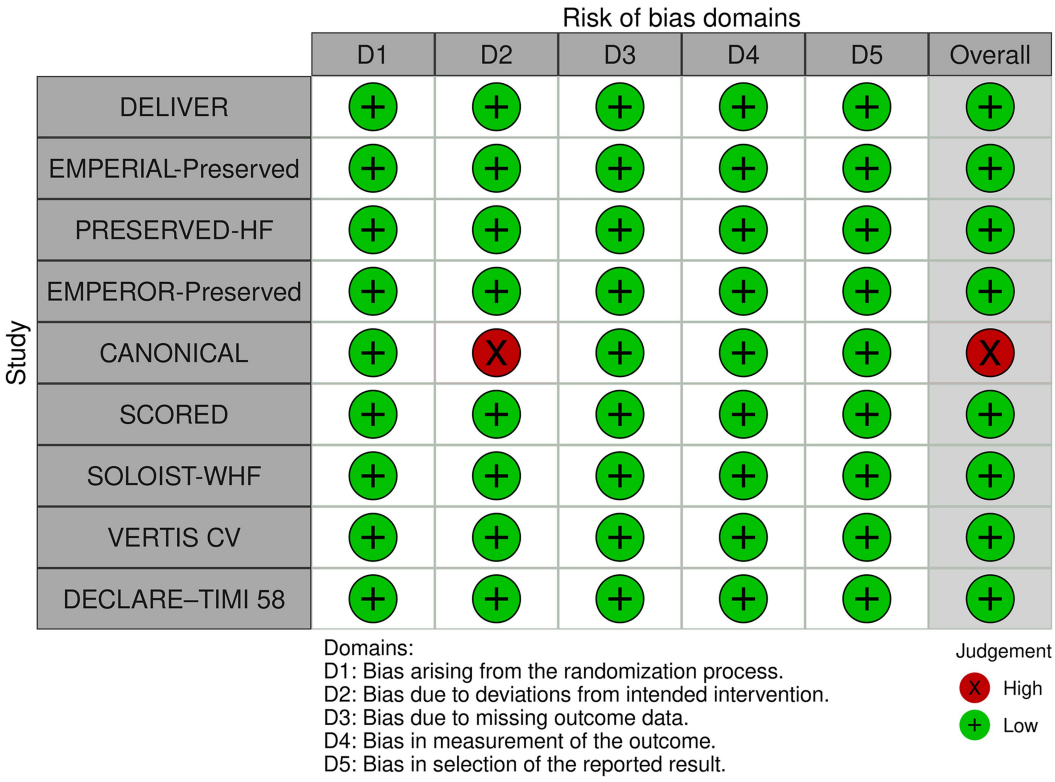

FIGURE 2
Quality assessment of the included randomized controlled trials using the Cochrane Risk of Bias 2 tool.

(25) included type 2 diabetes patients who were hospitalized or had urgent heart failure visits. All trials excluded participants with renal impairment. Exclusion criteria for estimated glomerular filtration rate (eGFR) ranged from <20 ml/min/1.73 m^2 to <30 ml/min/1.73 m^2, or

TABLE 1 The characteristics of the 9 randomized controlled trials that were included in this study, and from which data were analyzed and reported by the other 7 *post-hoc* studies included in this study.

Characteristics	DELIVER (N=6,263)	EMPERIAL-Preserved (N=315)	PRESERVED-HF (N=324)	EMPEROR-Preserved (N=5,988)	CANONICAL (N=82)	SCORED (N=10,584)	SOLOIST-WHF (N=1,222)	VERTIS CV (N=8,246)	DECLARE-TIMI 58 (N=17,160)
Intervention	Dapagliflozin	Empagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin	Sotagliflozin	Sotagliflozin	Ertugliflozin	Dapagliflozin
Year of publication	2022	2021	2021	2021	2021	2020	2020	2020	2018
Median follow-up time (months)	27.6	3.0	3.0	26.2	6.0	16.0	9.0	36.0	50.4
Key inclusion criteria	NYHA functional class II–IV; LVEF >40% and evidence of structural heart disease; Ambulatory or hospitalized patients	NYHA functional class II–IV; LVEF >40%; Evidence of structural heart disease or history of HF hospitalization within 12 months	NYHA functional class II–IV; LVEF ≥45%; Evidence of structural heart disease or history of acute treatment or hospitalization for HF within 12 months	NYHA functional class II–IV; LVEF >40%; Evidence of structural heart disease or history of HF hospitalization within 12 months	NYHA functional class II–III; LVEF ≥50% with history of HF; Type 2 diabetes with $6.5\% \leq HbA_{1c} < 10.0\%$	Type 2 diabetes with $HbA_{1c} \geq 7\%$; $25 \leq eGFR \leq 60$ ml/min/1.73 m^2; Having cardiovascular risk factor	Type 2 diabetes; hospitalized or visit due to worsening HF; Chronic treatment with loop diuretic for >30 days; Previous diagnosis of HF (>3 months); Randomized when hemodynamically stable within 3 days of discharge	Type 2 diabetes with $7.0\% \leq HbA_{1c} \leq 10.5\%$; Evidence or a history of atherosclerosis	Type 2 diabetes; Established cardiovascular disease and/or multiple cardiovascular risk factors
Key exclusion criteria	eGFR <25 ml/min/1.73 m^2	eGFR <20 ml/min/1.73 m^2	eGFR <20 ml/min/1.73 m^2	eGFR <20 ml/min/1.73 m^2	Severe renal dysfunction or hemodialysis; NYHA functional class IV	History of dialysis within 1 year; End-stage HF	eGFR <30 ml/min/1.73 m^2; End-stage HF	eGFR <30 ml/min/1.73 m^2; NYHA functional class IV	CrCl <60 ml/min; NYHA functional class IV
Definition of preserved EF	>40%	>40%	≥45%	>40%	≥50%	≥50%	≥50%	>45%	≥45%
Number of patients with HFpEF	6,263 (100%)	315 (100%)	324 (100%)	5,988 (100%)	82 (100%)	1,667 (15.8%)	256 (20.9%)	1,007 (12.2%)	808 (4.7%)
Reported outcomes of interest*	1, 2, 3, 4, 5, 6	6	3, 6	1, 2, 3, 5, 6	2, 3	5	5	1, 2, 3, 5	1, 2, 3, 5

*Reported outcomes of interest: 1 – CV death; 2 – HHF; 3 – all-cause death; 4 – worsening HF; 5 – cardiac composite; 6 – KCCQ score. Abbreviations: CANONICAL, CANagliflOziN heart faIlure with preserved ejection fraCtion study for type 2 diAbetes meLlitus trial; CrCl, creatinine clearance; CV, cardiovascular; DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events trial; DELIVER, Dapagliflozin Evaluation to improve the LIVEs of patients with pReserved ejection fraction heart failure trial; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EMPERIAL-Preserved, effect of EMPagliflozin on ExeRcise ability and heart failure symptoms In patients with chronic heArt faiLure trial; EMPEROR-Preserved, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction trial; HbA_{1c}, glycated hemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization due to heart failure; KCCQ score, Kansas City Cardiomyopathy Questionnaire score; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PRESERVED-HF, dapagliflozin in PRESERVED ejection fraction Heart Failure trial; SCORED, effect of Sotagliflozin on CardiOvascular and Renal Events in patients with type 2 Diabetes and moderate renal impairment who are at cardiovascular risk trial; SOLOIST-WHF, effect of SOtagLiflOzin on cardiovascular events In patientS with Type 2 diabetes post Worsening Heart Failure trial; VERTIS CV, eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes trial.

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creatinine clearance (CrCl) <60 ml/min. Each trial used different LVEF cut points (range: 40–50%) for recruitment and/or for the analysis of data specific to HFpEF.

Data specific to the outcomes of interest were extracted from the DECLARE-TIMI 58, SOLOIST-WHF, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease (VERTIS-CV), EMPERIAL-preserved, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved), PRESERVED-HF, CANONICAL, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED), and DELIVER trials (9, 14, 15, 24–26, 33, 34, 36).

In the present study, in addition to including data from studies that recruited HFpEF patients only (EMPEROR-Preserved, PRESERVED-HF, and DELIVER), we also included data from studies that recruited both HFpEF and non-HFpEF patients, including the DECLARE-TIMI 58 trial (36), which included diabetes mellitus (DM) patients with and without history of heart failure, and the EMPERIAL trial (14), which recruited HF patients with HFrEF or HFpEF.

The majority of patients in all included trials were male, except for the PRESERVED-HF trial (15). The mean body mass index (BMI) of patients in most trials classified them as overweight or class 1 obesity (40). In all studies, a higher proportion of patients were in New York Heart Association (NYHA) functional class I-II than in functional class III-IV. Approximately half of the patients included in the present study were patients with DM that were enrolled in trials that had HF as part of the inclusion criteria. Patient baseline characteristics from the 9 randomized controlled trials included in this study, and from which data were analyzed and reported by the other 7 *post-hoc* studies included in this study are presented in Table 2.

3.3. SGLT2 Inhibitors reduce the incidence of CV outcomes

For our primary outcome, SGLT2 inhibitors reduced composite CV outcome comprising CV death or HHF or urgent visit for HF (hazard ratio [HR]: 0.80, 95% confidence interval [95%CI]: 0.74–0.86, prediction interval: 0.72–0.89; Figure 3A). The same trends were observed for CV death alone with significant heterogeneity (HR: 0.93, 95%CI: 0.82–1.05, prediction interval: 0.71–1.21; Figure 3B), for HHF alone (HR: 0.74, 95%CI: 0.67–0.82, prediction interval: 0.63–0.87; Figure 3C), and for all-cause death alone (HR: 0.97, 95%CI: 0.89–1.06, prediction interval: 0.86–1.09).

The effect of SGLT2 inhibitors on the composite CV outcome, including CV death or first HHF or urgent visit for HF, was also found to be consistent across 12 clinically relevant subgroups (Figures 4, 5).

Statistically significant benefit of SGLT2 inhibitors for reducing CV death/HHF was observed across ejection fraction groups, as follows: LVEF 40–50% (HR: 0.78, 95%CI: 0.66–0.92, prediction interval: N/A; Figure 4A); LVEF 51–60% (HR: 0.79, 95%CI: 0.68–0.93, prediction interval: N/A; Figure 4B); and, LVEF >60% (HR: 0.81, 95%CI: 0.69–0.96, prediction interval: N/A; Figure 4C).

We found consistent benefit across NYHA functional classification groups, as follows: NYHA functional classification I or II (HR: 0.77, 95%CI: 0.67–0.85, prediction interval: N/A; Figure 5A), and NYHA functional classification III or IV (HR: 0.84, 95%CI: 0.71–0.98, prediction interval: N/A; Figure 5B). We also found consistent benefit across baseline renal function groups [eGFR <60% (HR: 0.77, 95%CI: 0.69–0.87, prediction interval: N/A; Figure 5C), and ≥60% (HR: 0.84, 95%CI: 0.73–0.97, prediction interval: N/A; Figure 5D)], and across DM status groups [DM (HR: 0.80, 95%CI: 0.71–0.90, prediction interval: N/A; Figure 5E), and non-DM (HR: 0.79, 95%CI: 0.69–0.90, prediction interval: N/A; Figure 5F)].

We also observed that SGLT2 inhibitors reduced the total number of HHF across ejection fraction groups, as follows: LVEF 50–60% (HR: 0.64, 95%CI: 0.54–0.76, prediction interval: N/A; Figure 4D), and LVEF >60% (HR: 0.84, 95%CI: 0.71–0.98, prediction interval: N/A; Figure 4E).

3.4. SGLT2 inhibitors improve health status and QoL

More participants in the SGLT2 inhibitor groups experienced clinically significant improvements as measured by the 3 types of KCCQ scores (TS, CS, and OS) when compared to controls, as demonstrated by the mean change in KCCQ-CS score compared to baseline (mean difference: 1.33, 95%CI: 1.31–1.35, prediction interval: N/A; Figure 6A), KCCQ-TS score increase of ≥5 points from baseline (odds ratio [OR]: 1.16, 95%CI: 1.07–1.26, prediction interval: 0.68–1.98; Figure 6B), KCCQ-CS score increase of ≥5 points from baseline (OR: 1.16, 95%CI: 1.07–1.26, prediction interval: 0.68–1.98; Figure 6C), and KCCQ-OS score increase of ≥5 points from baseline (OR: 1.18, 95%CI: 1.08–1.29, prediction interval: 0.66–2.10; Figure 6D).

4. Discussion

The results of this meta-analysis demonstrate that SGLT2 inhibitors, including dapagliflozin, empagliflozin, canagliflozin, and sotagliflozin, significantly or compellingly reduced CV outcome, including any type of death, HHF, or urgent visit due to HF with no or minimal evidence of heterogeneity among trials. The various subanalyses that we performed also revealed that SGLT2 inhibitors improve CV outcomes across LVEF range groups, DM status groups, baseline renal function groups, and NYHA functional class groups.

This meta-analysis also demonstrated that SGLT2 inhibitors improve the health status of patients with HFpEF as measured and supported by both the change in the mean KCCQ-CS score compared to baseline, and the increase in the KCCQ score ≥5 points. The 5-point threshold was considered to reflect a clinically meaningful improvement in health status in many studies, and was also reported to be associated with improvement in functional capacity (41, 42). The benefit of SGLT2 inhibitors on health status has been demonstrated in HFrEF patients but remains controversial in HFpEF. (43) The mean change in the KCCQ-CS score in the PRESERVED-HF and EMPEROR-Preserved studies indicated statistically significant benefits of SGLT2 inhibitors for improving health status, but no statistically significant benefit was found in the EMPERIAL-Preserved trial (9, 14, 15). Incorporating data from the recent DELIVER trial (33, 35), the present meta-analysis found statistically and clinically meaningful improvement in all 3 KCCQ combination scores (KCCQ-TS, KCCQ-CS, and KCCQ-OS). These results strongly suggest that HFmrEF or HFpEF patients that are prescribed SGLT2 inhibitors experience improved health status and QoL.

The mechanisms behind the benefits of SGLT2 inhibitors in HFpEF patients are under investigation. Diastolic dysfunction, subtle systolic dysfunction, atrial dysfunction, and endothelial dysfunction are the main contributors to HFpEF (44, 45). There have been studies

TABLE 2 Patient baseline characteristics from the 9 randomized controlled trials included in this study, and from which data were analyzed and reported by the other 7 *post-hoc* studies included in this study.

Characteristics	DELIVER (N=6,263)		EMPERIAL-Preserved (N=315)		PRESERVED-HF (N=324)		EMPEROR-Preserved (N=5,988)		CANONICAL (N=82)		SCORED (N=10,584)		SOLOIST-WHF (N=1,222)		VERTIS CV (N=8,246)		DECLARE-TIMI 58 (N=17,160)	
Comparison	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Standard diabetic therapy	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
Number of patients	3,131	3,132	157	158	162	162	2,997	2,991	42	40	5,292	5,292	608	614	680 [a]	327 [a]	8,582	8,578
Mean ± SD or median (IQR) age (years)	71.8 ± 9.6	71.5 ± 9.5	74 (68–79)	75 (68–81)	69 (64–77)	71 (63–78)	71.8 ± 9.3	71.9 ± 9.6	76.5 ± 6.4	75.9 ± 5.8	69 (63–74)	69 (63–74)	69 (63–76)	70 (64–76)	63.8 ± 8.3	64.7 ± 8.2	63.9 ± 6.8	64.0 ± 6.8
Female, n (%)	1,364 (43.6%)	1,383 (44.2%)	70 (44.6%)	66 (41.8%)	92 (56.8%)	92 (56.8%)	1,338 (44.7%)	1,338 (44.6%)	NA (33.3%)	NA (32.5%)	2,347 (44.3%)	2,407 (45.5%)	198 (32.6%)	214 (34.9%)	NA (34.4%)	NA (36.7%)	3,171 (36.9%)	3,251 (37.9%)
Mean ± SD or median (IQR) BMI (kg/m^2)	29.8 ± 6.2	29.9 ± 6.1	30.1 (26.5–34.2)	28.8 (26.1–32.8)	35.1 (30.4–41.8)	34.6 (29.7–40.4)	29.77 ± 5.8	29.90 ± 5.9	24.7 ± 3.6	25.2 ± 3.7	31.9 (28.1–36.2)	31.7 (28.0–36.1)	30.4 (26.3–34.3)	31.1 (27.3–34.5)	32.6 ± 5.3	32.9 ± 5.3	32.1 ± 6.0	32.0 ± 6.1
NYHA functional class, *n* (%)																		
I-II	2,314 (73.9%)	2,399 (76.6%)	117 (74.5%)	126 (79.7%)	96 (59.3%)	90 (55.6%)	2,435 (81.2%)	2,452 (82.0%)	88.10%	95.0%					89.6%	93.3%		
III-IV	817 (26.1%)	732 (23.4%)	39 (24.8%)	32 (20.3%)	65 (40.1%)	72 (44.4%)	562 (18.8%)	539 (18.0%)	11.90%	5.0%					7.2%	4.6%		
Mean ± SD or median (IQR) LVEF (%)	54.0 ± 8.6	54.3 ± 8.9	53 (45–58)	53 (46–59)	60 (55–65)	60 (54–65)	54.3 ± 8.8	54.3 ± 8.8	61.1 ± 7.8	61.9 ± 7.6	60 (51–64)	60 (51–65)	35 (28–47)	35 (28–45)				
Median (IQR) NT-ProBNP, pg./ml			966 (572–1,653)	843 (407–1,913)	641 (373–1,210)	710 (329–1,449)	994 (501–1,740)	946 (498–1,725)			196 (75–565)	198 (75–561)	1,817 (855–3,659)	1,741 (843–3,582)				
Diabetes mellitus, n (%)	1,401 (44.7%)	1,405 (44.9%)	86 (54.8%)	75 (47.5%)	90 (55.6%)	91 (56.2%)	1,466 (48.9%)	1,472 (49.2%)	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Mean ± SD or median (IQR) eGFR (mL/min/1.73 m^2)	61 ± 19	61 ± 19	54.5 (41–70)	58.5 (44–71.5)	56 (42–69)	54 (41–69)	60.6 ± 19.8	60.6 ± 19.9	57.8 ± 14.2	56.0 ± 13.8	44.4 (37–51.3)	44.7 (37–51.5)	49.2 (39.5–61.2)	50.5 (40.5–64.6)			85.4 ± 15.8	85.1 ± 16.0

[a]Data from HFmrEF or HFpEF population. Abbreviations: BMI, body mass index; CANONICAL, CANagliflOziN heart faIlure with preserved ejection fraCtion study for type 2 diAbetes meLlitus trial; DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events trial; DELIVER, Dapagliflozin Evaluation to improve the LIVEs of patients with pReserved ejection fraction heart failure trial; eGFR, estimated glomerular filtration rate; EMPERIAL-Preserved, effect of EMPagliflozin on ExeRcise ability and heart failure symptoms In patients with chronic heArt faiLure trial; EMPEROR-Preserved, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction trial; IQR, interquartile range; LVEF, left ventricular ejection fraction; NA, not available; NT-ProBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PRESERVED-HF, dapagliflozin in PRESERVED ejection fraction Heart Failure trial; SCORED, effect of Sotagliflozin on CardiOvascular and Renal Events in patients with type 2 Diabetes and moderate renal impairment who are at cardiovascular risk trial; SD, standard deviation; SOLOIST-WHF, effect of SOtagLiflOzin on cardiovascular events In patientS with Type 2 diabetes post Worsening Heart Failure trial; VERTIS CV, eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial.

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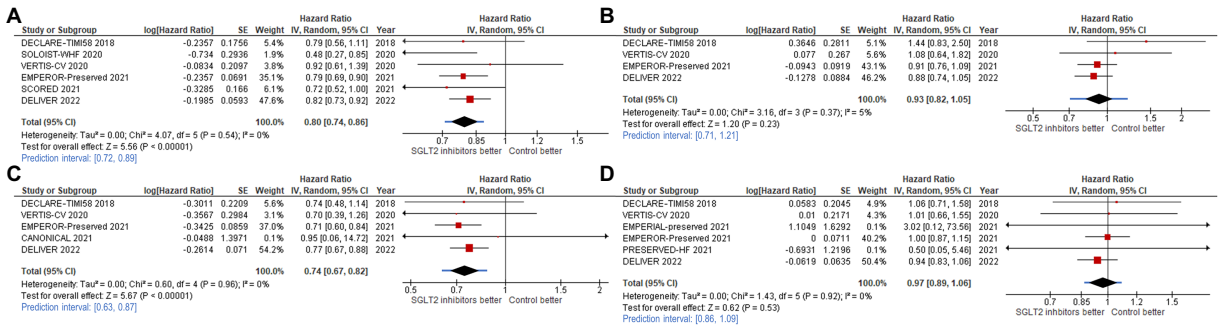

FIGURE 3
Forest plots of studies that investigated **(A)** CV death or HHF or urgent visit for heart failure (HF); **(B)** cardiovascular **(CV)** death; **(C)** hospitalization for heart failure (HHF); and, **(D)** all-cause death compared between patients receiving sodium-glucose cotransporter-2 (SGLT2) inhibitors and controls among all heart failure with mildly reduced (HFmrEF) or preserved ejection fraction (HFpEF) patients.

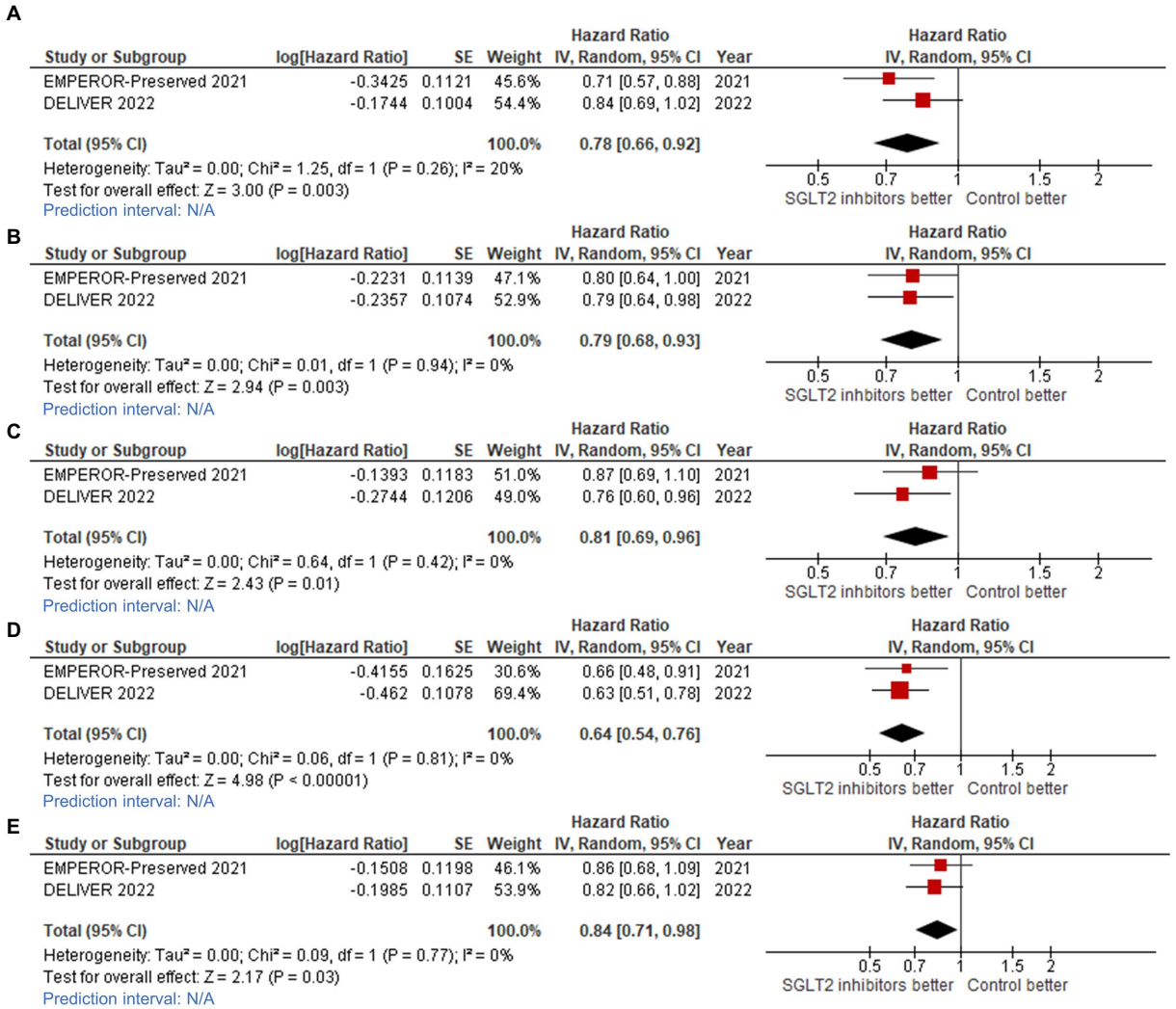

FIGURE 4
Forest plots of studies that compared patients receiving sodium-glucose cotransporter-2 (SGLT2) inhibitors versus controls among patients with **(A)** ejection fraction (EF) 40–50% in cardiovascular (CV) death/hospitalization for heart failure (HHF) outcome; **(B)** EF 50–60% in CV death/HHF outcome; **(C)** EF >60% in CV death/HHF outcome; **(D)** EF 50–60% in total HHF outcome; and, **(E)** EF >60% in total HHF outcome.

that demonstrate that SGLT2 inhibitors alleviate diastolic dysfunction in both HFrEF and HFpEF animal models, which may explain the CV benefits and improved QoL in HFpEF patients (46, 47).

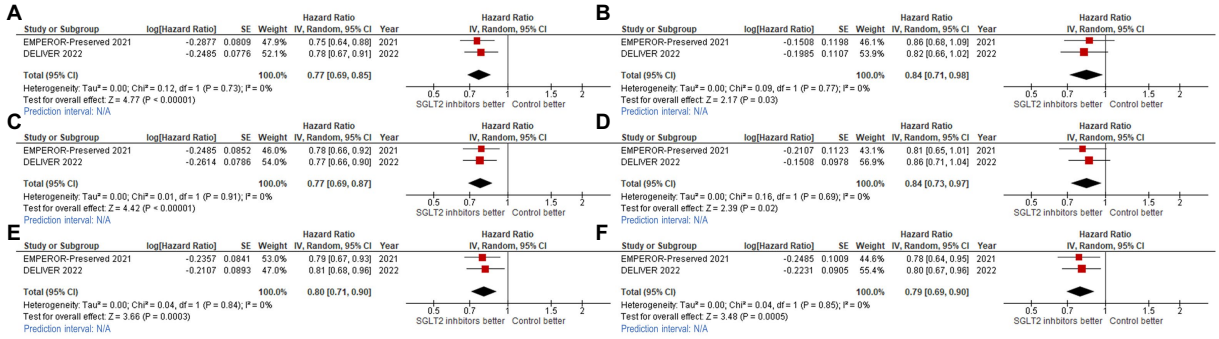

FIGURE 5
Forest plots of studies that compared cardiovascular (CV) death/hospitalization for heart failure (HHF) outcome among patients receiving sodium-glucose cotransporter-2 (SGLT2) inhibitors versus controls in patients with **(A)** New York Heart Association functional class II (NYHA II); **(B)** NYHA III-IV; **(C)** estimated glomerular filtration rate (eGFR) <60ml/min/1.73m2; **(D)** eGFR ≥60ml/min/1.73m2; **(E)** diabetes mellitus (DM); and, **(F)** non-DM.

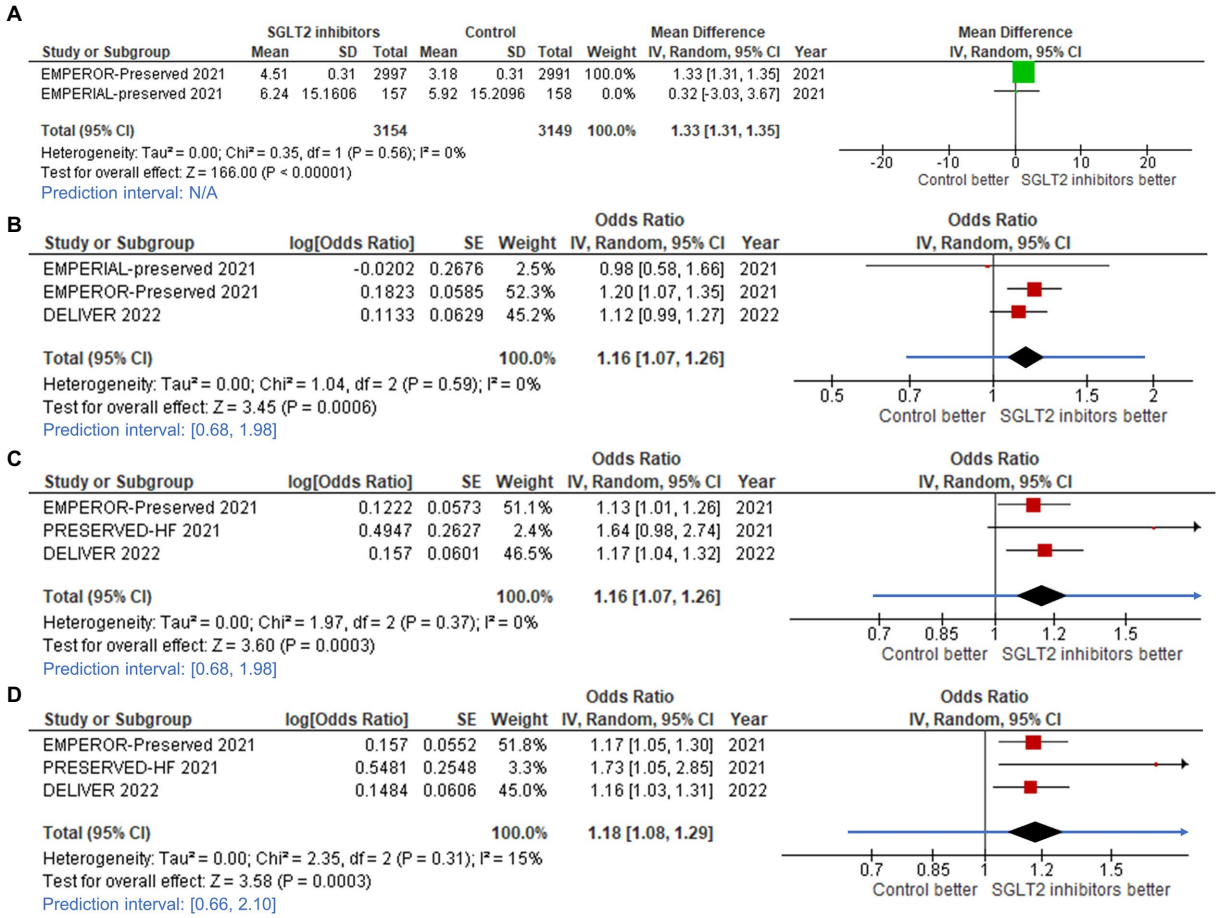

FIGURE 6
Forest plots of studies that evaluated **(A)** change in Kansas City Cardiomyopathy Questionnaire (KCCQ) – clinical summary score; **(B)** increased KCCQ-total symptom (TS) score; **(C)** increased KCCQ-clinical summary (CS) score; and, **(D)** increased KCCQ-overall summary (OS) score compared between patients receiving sodium-glucose cotransporter-2 (SGLT2) inhibitors and controls among all heart failure with mildly reduced (HFmrEF) or preserved ejection fraction (HFpEF) patients.

HFpEF patients were recognized to have more non-cardiac comorbidities than HFrEF patients, which play vital roles in the management and prognosis of HFpEF patients. In addition, atrial fibrillation was common in HFpEF patients and associated with increased adverse CV events (48–50). It is probable that SGLT2 inhibitors could have varying effects on HFpEF patients with different comorbidities. However, there was no statistically significant difference in the effects of SGLT2 inhibitors on reducing the composite of CV mortality or HHF between HFpEF patients with and without the following comorbidities: age, diabetes, obesity (BMI ≥ 30 kg/ m^2),

impaired renal function (eGFR <60 ml/min/1.73 m^2), and history of atrial fibrillation (35). The lack of differences in the effect of SGLT2 inhibitors might be owing to no difference between groups or the inadequate statistical power in subgroup analysis.

To our knowledge, this is the first meta-analysis to study the effect of SGLT2 inhibitors in HFmrEF or HFpEF patients that analyzed extractable data from all of the previously conducted RCTs on this study topic, including DECLARE-TIMI 58, VERTIS CV, SOLOIST-WHF, SCORED, CANONICAL, PRESERVED-HF, EMPERIAL-Preserved, and the 2 most recent large trials – EMPEROR-Preserved and DELIVER. Some earlier meta-analyses that studied the outcome of SGLT2 inhibitors in heart failure patients did not focus solely on HFmrEF or HFpEF patients (12, 51). Moreover, the meta-analyses that did set forth to focus on HFmrEF or HFpEF population did not extensively analyze the same outcome or specific subgroups as our meta-analysis had done (10, 52). Our study also included an increase of at least 5 points in KCCQ score, which reflects new clinical impact on the aspect of patient QoL.

Despite the clinical benefit of SGLT2 inhibitors in HFmrEF or HFpEF relative to CV death and all-cause death being demonstrated in this study, the improvement in those two parameters was not statistically significantly increased. Similarly, previous RCTs reported the benefit of SGLT2 inhibitors for reducing CV outcome and improving patient QoL even though their data did not show statistically significant difference between study and controls. Accordingly, the overriding aim of the present meta-analysis was to compile the current data from focused RCTs, and to use that amplified statistical power to evaluate the effect of SGLT-2 inhibitors on CV outcomes and patient QoL among patients with HFmrEF or HFpEF. The current weaker class IIa recommendations for SGLT-2 inhibitors among HFmrEF and HFpEF patients, were based on the previously reported non-statistically significant improvements in CV outcomes among HFmrEF or HFpEF patients; however, the guideline recommendations for SGLT-2 inhibitor use in HFrEF patients are class I recommendations (1, 2). The present meta-analysis also sheds important light on questions about the efficacy of SGLT2 inhibitors in each specific subgroup of HFmrEF or HFpEF patients. This meta-analysis together with recent data from the DELIVER trial (33) demonstrates the clear and undeniable positive impact of SGLT2 inhibitors on essential clinical events and symptom burden in patients with HFmrEF or HFpEF across various subgroups. Because SGLT2 inhibitors have a favorable but not statistically significant benefit in reducing CV death and all-cause death as individual outcome, further investigation is needed to elevate the recommendation for SGLT2 inhibitors in HFmrEF or HFpEF from class IIa to class I. These findings suggest that SGLT2 inhibitors should be considered for treating patients with HFmrEF or HFpEF. We hope that ongoing studies that are focusing on various outcomes of SGLT2 inhibitors, such as NCT04249778, the DAPPER study (JPRN-jRCTs051180135), EUCTR 2020–004832-48-GB, and EUCTR2015-005715-32-SE, will yield greater insights that will further improve the management of patients with HFmrEF or HFpEF, and support future guideline updates.

Since none of the studies included in this meta-analysis compared one SGLT2 inhibitor against another SGLT2 inhibitor. An RCT study, which was not included in our meta-analysis due to lack of an outcome of interest, showed that Sotagliflozin has greater effects on some of the metabolic and antidiabetic effects when compare with Empagliflozin, which might have implications for the clinical outcome (53). Thus, we cannot deny the possibility of differences in clinical efficacy and safety between and among the different SGLT2 inhibitors.

Despite this meta-analysis demonstrating significant benefits of SGLT2 inhibitors in HFmrEF or HFpEF by pooling data from 9 clinical trials, there are some limitations that must be disclosed and discussed. First, there were variations in the duration of time between the baseline KCCQ and the final KCCQ that ranged from 12 weeks in the PRESERVED-HF and EMPERIAL-Preserved trials to 52 weeks in the EMPEROR-Preserved trial (9, 14, 15). The results of all 3 of these trials favored the use of SGLT2 inhibitors over placebo, except the difference between study and control was statistically significant in the PRESERVED-HF and EMPEROR-Preserved trials, but non-significant in the EMPERIAL-Preserved trial. This difference among groups may be due to the difference in follow-up duration. Second, individual participant-level data from each study were not available to us, so we resorted to using publicly accessible data. As such, some outcomes or subgroup factors might be more accurately represented in pooled analysis if participant-level data were available. The PRESERVED-HF, EMPERIAL-Preserved, CHIEF-HF, and EMPULSE trials (14–16, 54) reported changes in KCCQ-OS score and KCCQ-TS score from baseline using different statistics, including mean difference, Hodges-Lehmann median difference, and least square mean difference. Which means that these data could not be directly included in the pooled analysis. Moreover, two studies (55, 56) reported their methods for estimating the mean or effect size, but they were limited by their data distribution assumptions. We, therefore, decided to omit the aforementioned outcome data to avoid misinterpretation. Among the 9 RCTs that generated all of the data used in all 16 included studies, only the DELIVER, EMPEROR-Preserved, and DECLARE-TIMI 58 trials had LVEF subgroup range data available, and there were differences in the reported cut point used among those 3 studies. DECLARE-TIMI 58 stratified LVEF into 45–54% and ≥55% (30), whereas DELIVER stratified LVEF into 41–49%, 50–59%, and ≥60% (9, 35). Third, due to discrepancies in exclusion criteria between trials, our study may not identify some subtypes of HFpEF. The DELIVER, EMPEROR-Preserved, SOLOIST-WHF, EMPERIAL-preserved, and PRESERVED-HF trials excluded infiltrative and hypertrophic obstructive cardiomyopathy, while other trials in our analysis did not mention this. Therefore, some cases with cardiac amyloidosis and hypertrophic cardiomyopathy (HCM) might be included in this analysis. Because treatment and prognosis differ between HFpEF caused by amyloidosis or HCM and other etiologies, more investigation into each subtype of HFpEF is warranted (1, 57, 58). Finally, renal endpoint was excluded from our meta-analysis. Only the EMPEROR-Preserved trial reported composite renal outcomes, which consisted of chronic dialysis, renal transplantation, sustained decrease in eGFR of ≥40% or sustained eGFR <15 ml/min/1.73 m^2 in patients with a baseline eGFR ≥30 ml/min/1.73 m^2, or < 10 ml/min/1.73 m^2 in patients with a baseline eGFR <30 ml/min/1.73 m^2 (9, 32). The MUSCAT-HF trial reported only percentage change in eGFR (39). Most of the other trials reported adverse renal events only with no clear definition. This finding may influence future trials to integrate renal outcomes into their study design. No adjustment for multiplicity of testing was made for subgroup analyses.

5. Conclusion

The results of this systematic review and meta-analysis demonstrated the benefit of SGLT2 inhibitors for significantly reducing the risk of the composite of CV death, HHF, or urgent visit for HF compared to placebo in patients with HFmrEF or HFpEF, but

their benefit for reducing CV death alone and all-cause death alone could not be established. We also found that SGLT2 inhibitors improve KCCQ scores, which translates to improved patient QoL. The results of this meta-analysis indicate the universal beneficial impact of SGLT2 inhibitors in patients with HFmrEF or HFpEF irrespective of baseline ejection fraction, renal status, NYHA functional class, and diabetes status. Taken together, these results suggest that SGLT2 inhibitors should be considered for treating patients with HFmrEF or HFpEF to improve patient outcomes and QoL. Further study into the effects of SGLT2 inhibitors on CV death, all-cause mortality, and different background therapies, as well as on less-studied outcomes, such as renal outcome, respiratory outcome, and neurological outcome are warranted, Study of the effect of SGLT2 inhibitors in various metabolic and hemodynamic scenarios is also recommended.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: All datasets generated for this study are available from the corresponding author upon reasonable request. Requests to access these datasets should be directed to rungroj.kri@mahidol.ac.th.

Author contributions

All authors participated in the design of the study. ST and NK performed the search and study selection processes. WO analyzed the data and generated the forest plots. ST, NK, and WO wrote the manuscript. ST created all other figures and tables. WO and RK critically assessed the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1046194/full#supplementary-material

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EDITED BY
Matteo Cameli,
University of Siena, Italy

REVIEWED BY
Nicolò Ghionzoli,
University of Siena, Italy
Mahwash Kassi,
Houston Methodist Hospital, United States

*CORRESPONDENCE
Inna P. Gladysheva
✉ innagladysheva@arizona.edu
Guy L. Reed
✉ guyreed@arizona.edu

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Falling corin and ANP activity levels accelerate development of heart failure and cardiac fibrosis

Inna P. Gladysheva*, Ryan D. Sullivan and Guy L. Reed*

Department of Internal Medicine and Translational Cardiovascular Research Center, College of Medicine, University of Arizona, Phoenix, AZ, United States

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1. Introduction

Despite the best available therapies, heart failure with reduced ejection fraction (HFrEF) remains one of the leading causes of morbidity and mortality worldwide (1). Dilated cardiomyopathy (DCM) is one of the leading cause of HFrEF (2). DCM is characterized by progressive heart enlargement with a rEF that is caused by genetic, ischemic, and other disorders (3). Neurohumoral imbalances of the sympathetic nervous system, renin-angiotensin-aldosterone systems (RAAS) and the natriuretic peptide system, are associated with maladaptive cardiac remodeling in HFrEF (4–8). Corin, a cardiac type II transmembrane protease, activates pro-atrial natriuretic peptide (pro-ANP) to biologically active ANP by proteolytic cleavage during pro-ANP secretion from cardiomyocytes (9–12). Through production of biologically active ANP, corin appears to slow the progression of DCM to HFrEF and death, which makes it an attractive therapeutic target in HF management (13–23). Reduced levels of circulating and cardiac corin in patients with symptomatic HFrEF were reported in numerous studies (14, 15, 24–31). The biologically active corin-ANP axis blocked the development of systolic/diastolic dysfunction, low cardiac output, pulmonary and/or systemic fluid retention (edema), dyspnea and elevated blood HF biomarkers (ANP and B-type natriuretic peptide, BNP) (15–18, 23, 30, 31). Pre-clinical studies revealed that the biologically active corin-ANP axis also reduces the development of chronic adverse fibrotic ventricular remodeling (cardiac fibrosis, diffuse accumulation of collagen I/III fibers) (17, 19, 20, 22). Although the protective role of pro-fibrotic angiotensin II (Ang II)-AT1 axis blockage in reverse remodeling in HFrEF is widely accepted, the therapeutic potential of the corin-ANP axis in preventing fibrosis, are less appreciated. Herein, we present and discuss pre-clinical and clinical evidence supporting the targeted restoration of biological activity of the corin-ANP axis as a valuable anti-fibrotic therapeutic strategy in DCM-HFrEF.

2. Role of corin-ANP-cGMP pathway under physiological conditions

Under physiological conditions, corin is expressed by atrial and ventricular cardiomyocytes on the external membrane surface as a zymogen and proteolytically active enzyme (9, 10, 17, 21). In atrial cardiomyocytes, corin is co-expressed with its biological substrate pro-ANP- (10, 32). Upon secretion, pro-ANP is proteolytically cleaved by corin and released into circulation as biologically active ANP (11, 12). Circulating biologically active ANP acts locally in the heart and remotely in the kidneys and vasculature by

preferentially stimulating the transmembrane natriuretic peptide-A receptor, which generates the intracellular cyclic guanosine monophosphate (cGMP) and stimulates protein kinase G-driven signaling pathways (33, 34). Remotely, the ANP-cGMP axis triggers natriuresis and vasodilation and inhibits renal renin secretion; this decreases cardiac volume overload, aldosterone synthesis and Ang II production in the circulation (11, 35–37). In the heart, the ANP-cGMP pathway counters hypertrophy and fibrosis through autocrine/paracrine regulatory mechanisms leading to inhibition of fibroblast-mediated collagen synthesis (33, 38, 39). Specifically, by stimulation of cGMP production and protein kinase G activation, biologically active ANP may transmit extracellular signals and modulate downstream effector molecules into the same cardiomyocytes it was secreted from (an autocrine mechanism) or on neighboring cardiac myocyte and fibroblast cells (a paracrine mechanism) (33, 39).

3. Impairment of corin-ANP-cGMP pathway in symptomatic HFrEF

Dysregulation of ANP-cGMP axis by blunted corin has been shown to contribute to systolic dysfunction, maladaptive cardiac remodeling and edema, leading to HFrEF development (15–19, 21, 22, 30, 40, 41). In DCM, the balance between cardiac anti-fibrotic/pro-fibrotic processes are under control of hemodynamic and humoral modulators such as corin-ANP-cGMP axis and the RAAS. The dysregulation of this balance, its pathological shift and contribution to HFrEF development in DCM are schematically illustrated in **Figure 1** and described below.

In DCM at pre-HF stage, RAAS plays an adaptive protective role compensating for impaired cardiac function and structural changes by stimulating sodium-water retention by the kidney and increasing arterial vasoconstriction. However, prolonged, persistent RAAS activation stimulates DCM progression (4–6, 8, 40, 42–44). In DCM at pre-HF stage, the corin-ANP-cGMP axis, when biologically functional, counters the outcomes of the pathologically activated systemic and cardiac classical RAAS by maintaining cardio-renal homeostasis promoting diuresis, natriuresis, and vasodilation and anti-fibrotic action (4, 6, 40, 45, 46). However, as DCM progress in human and mice, cardiac corin expression and activity are reduced leading to impairment of biological activity of the corin-ANP-cGMP axis (21, 30). Declines in corin levels indicate systolic dysfunction as it happened even before the increases in plasma ANP and BNP levels and the onset of edema (21, 23, 26, 30), which is a major hallmark of HF and a key driver of symptoms (3, 47). Consequently, as the natriuretic peptide system is impaired and becomes insufficient to properly balance

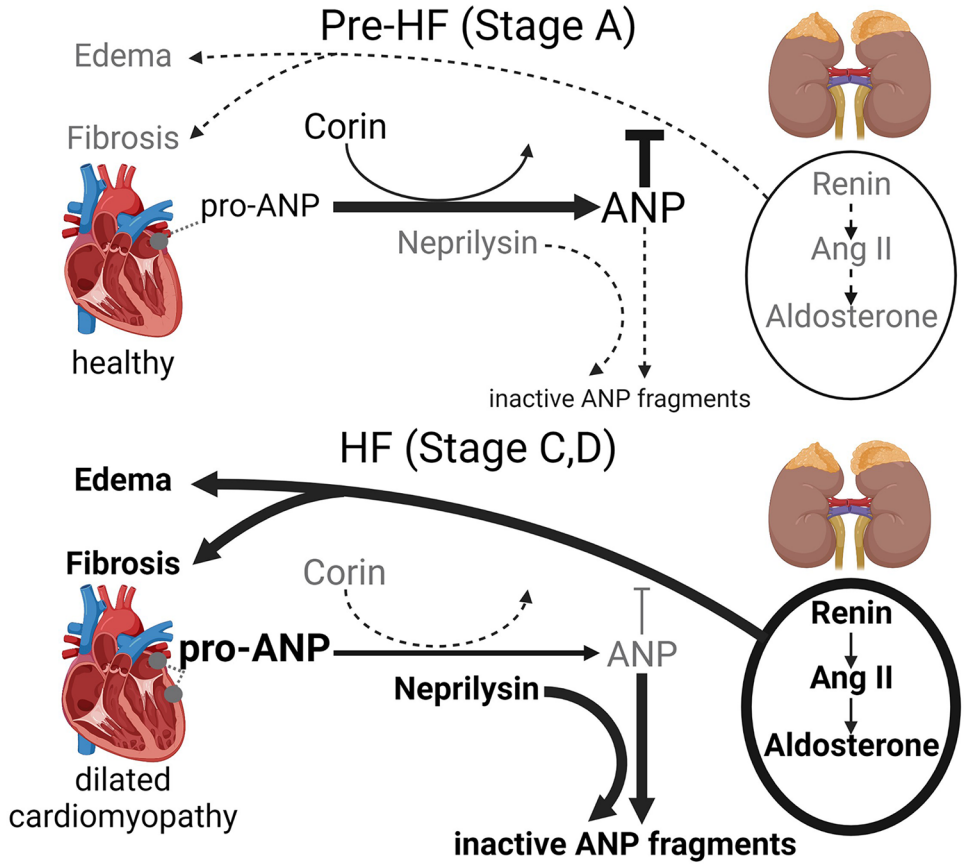

FIGURE 1
Schematic representation of the pathological shift of the cardiac corin-atrial natriuretic peptide (ANP) axis and classical RAAS [renin-angiotensin II (Ang II)—aldosterone] axis in dilated cardiomyopathy, which promotes cardiac fibrosis, edema and accelerates HFrEF progression.

RAAS activity, pathologically active RAAS further promotes cardiac dilation, fibrotic ventricular remodeling, salt-water retention (edema), and HFrEF development in humans and pre-clinical models (4, 6, 40, 42, 44, 46, 48, 49). Although HFrEF (stages C-D) is associated with a boost of pro-ANP expression by the ventricle's cardiomyocytes (21, 37), pro-ANP cleavage and production of biologically active ANP are compromised as the level of corin is significantly reduced (21).

As DCM progresses to HFrEF (stages C-D), renin is over-secreted by the kidneys into circulation. It triggers Ang II activation pathways (systemic and locally within the heart), cardiac Ang II-independent signaling and stimulates aldosterone secretion from the adrenal glands, which fosters fibrotic remodeling (6, 40, 43, 49, 50). Systemic (circulating) Ang II and aldosterone play an important role in cardiac fibrosis development, as increased local production of Ang II in the heart is not enough to induce ventricular hypertrophy or fibrosis (51).

Converging evidence from human and pre-clinical mouse studies indicate that, as DCM progresses to HF Stages C and D, the protective action of the corin-ANP-cGMP axis is impaired as the coordinated relationship between cardiac pro-ANP expression and enzymes responsible for pro-ANP activation (corin) and ANP degradation (neprilysin) become imbalanced. In particular, levels of the ANP degrading enzyme neprilysin begin to rise (30, 34) while levels of ANP activating enzyme corin fall (14, 15–17, 19, 21– 23, 25, 28, 30, 31). Consequently, the blunted ANP homeostasis contributes to the relative cGMP deficiency in HFrEF.

HFrEF is characterized by elevated pro-ANP expression, which is due to increased expression by the atria and reprogramming of cardiac left ventricular gene expression with induction of pro-ANP. However, levels of cardiac and circulating corin significantly decline in patients and preclinical models with DCM and HFrEF (15, 17, 19, 21, 25, 28, 30, 31, 41). In patients with HFrEF, decreases in circulating corin lead to impaired cleavage/activation of pro-ANP and dysregulated relationships between pro-ANP, ANP and cGMP levels (15, 30). At the same time, neprilysin levels progressively increase with severity of clinical HF assessed by Framingham criteria and are negatively correlated with corin levels (23, 30). In a pre-clinical DCM-HFrEF model, restoration of suppressed cardiac corin was associated with normalization of circulating neprilysin and suppression of renin activity and aldosterone in circulation (41). Low plasma corin was associated with poor HF-related clinical outcomes: lower NYHA functional status (increased functional class), increased cardiovascular mortality and major adverse cardiac events. Depressed cardiac and plasma corin reflects the progression of systolic dysfunction (severity of cardiomyopathy), left ventricular remodeling and fibrosis; it promoted the development of symptomatic HFrEF (17, 21, 30).

4. Restoration of corin-ANP-cGMP biological activity protects against cardiac fibrosis and HFrEF development

In experimental DCM, ANP was a critical protective modulator of aldosterone-Ang II-induced interstitial/perivascular fibrosis in the left atrium and ventricle (38). ANP also protected against systolic dysfunction, symptomatic HF, and survival in mice with normal renal function (38). Cardiac pro-ANP deficiency in mice with DCM was associated with significant reduction of cGMP levels in circulation. In these mice, cardiac pro-ANP deficiency was not compensated by cardiac expression of pro-BNP, but was associated with a decline in cardiac transcripts for pro-C-type NP (38), a potent anti-fibrotic modulator that inhibits cardiac fibroblast proliferation and collagen synthesis (34, 38). Consistent with these findings, the survival benefits of neprilysin inhibitors within ARNI therapy (combined Ang II receptor, AT1 and neprilysin inhibitors sacubitril/valsartan) have been attributed in part to its effect on blunting cardiac ventricular remodeling and fibrosis (a risk factor for sudden cardiac death), by preserving biologically active levels of ANP. Thus, ANP circulating levels were elevated after treatment with ARNI therapy, the difference in BNP levels was inconsistent, NT-pro-BNP levels decreased and CNP levels were not affected by treatment (34, 52–54). Increases in ANP plasma levels in patients with ARNI therapy for chronic HFrEF were associated with increased urinary cGMP levels (55). Another study demonstrated that in patients with acute decompensated HFrEF, ARNI therapy was associated with higher urinary cGMP levels (56). However, in both these studies (55, 56), corin levels were not analyzed.

Similar to ANP, genetic restoration of both proteolytically active or inactive cardiac corin in mice with DCM improved systolic function, delayed symptomatic HFrEF progression and prolonged survival (17, 18, 41). However, only proteolytically active (ANP-cleaving) cardiac corin has protective anti-fibrotic action (17, 41). Cardiac restoration of proteolytically active corin led to a significant reduction in cardiac collagen I/III transcripts and a trend towards reduction of TGFβ transcripts, and overall suppression of interstitial and perivascular ventricular fibrosis (17). Restoration of cardiac corin significantly increased pro-ANP cleavage to ANP and cGMP production, both of which are potent inhibitors of cardiac fibroblast proliferation and collagen synthesis (17). Cardiac-specific overexpression of proteolytically active corin reduced myocardial infarct size 24 h post-experimental myocardial infarction (MI) induced by left coronary artery ligation in mice. Corin overexpression prevented these mice from development of severe systolic dysfunction, cardiac remodeling and edema 4 weeks post-MI (57). However, this study did not assess the impact of cardiac corin overexpression on the pro-ANP-cGMP axis and cardiac fibrosis. In mouse HF models induced by left coronary artery ligation and transverse aortic constriction, intraperitoneal injection of a recombinant extracellular fragment of human corin with an engineered activation site lowered Ang II and aldosterone plasma levels, boosted cGMP levels, improved cardiac function and attenuated cardiac remodeling and fibrosis (22). The analysis of pro-ANP metabolism in the plasma of patients with stable chronic HFrEF, indicated that ARNI therapy increased pro-ANP cleavage, which was linked to an increase in corin activity (58).

Considering the above knowledge, we hypothesize that enhancing cardiac corin expression by ARNI therapy might contribute to improved cardiac remodeling in HFrEF. Thus,

ARNI therapy could provide beneficial antifibrotic outcomes by suppressing the profibrotic action of angiotensin II and boosting antifibrotic ANP activity. Increased ANP activity may be achieved not only through reduced degradation of biologically active ANP by neprilysin, but also through a feedback mechanism of improved systolic function stimulating cardiac corin expression, which in turn improves pro-ANP cleavage and increases biologically active ANP levels. It is worth testing the hypothesis that in HFrEF patients, ARNI therapy is associated with increased corin levels in circulation and cardiac left ventricle and reduced impairment of pro-ANP cleavage, which contribute to reverse cardiac remodeling.

5. Conclusions and translational value

Available experimental and clinical evidence suggests that in DCM, dysregulation of the biological effects of ANP, at least in part by insufficient corin expression and/or activity, promotes cardiac fibrosis associated with relative cGMP deficiency and contributes to the progression of systolic dysfunction and symptomatic HFrEF. These insights may suggest a new therapeutic paradigm to prevent DCM from becoming a relentless, progressive and fatal form of HFrEF. Preserving or boosting the biological activity of the corin-ANP-cGMP axis by corin targeted interventions may offer potential therapeutic strategies for preventing or blocking progressive cardiac fibrosis in DCM-HFrEF.

Author contributions

IPG: contributed to the conceptualization, writing original draft, illustration and editing. RDS: contributed to editing and Figure generation. GLR: contributed to the conceptualization, editing and illustration of the manuscript. All authors contributed to the article and approved the submitted version.

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The Scheme presented as a **Figure 1** was created using BioRender.com.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Alexander H. Maass,
University Medical Center Groningen,
Netherlands

REVIEWED BY
David Zizek,
University Medical Centre Ljubljana, Slovenia
Erberto Carluccio,
Heart Failure Unit, Italy

*CORRESPONDENCE
Matteo Beltrami
✉ beltrami.matteo1@gmail.com

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The role of fibrosis, inflammation, and congestion biomarkers for outcome prediction in candidates to cardiac resynchronization therapy: is "response" the right answer?

Matteo Beltrami[1]*, Alessandro Galluzzo[2], Riccardo Tappa Brocci[3], Alessandro Paoletti Perini[4], Paolo Pieragnoli[5], Manuel Garofalo[6], Geza Halasz[7], Massimo Milli[1], Maria Barilli[8] and Alberto Palazzuoli[9]

[1]Cardiology Unit, San Giovanni di Dio Hospital, Azienda USL Toscana Centro, Florence, Italy, [2]Cardiology Unit, Santa Croce Hospital, Moncalieri, Italy, [3]Department of Clinical Trial, Le Scotte Hospital, University of Siena, Siena, Italy, [4]Department of Internal Medicine, Cardiology and Electrophysiology Unit, Azienda USL Toscana Centro, Florence, Italy, [5]Arrhythmia and Electrophysiology Unit, Careggi University Hospital, Florence, Italy, [6]Department of Clinical and Experimental Medicine, Careggi University Hospital, Florence, Italy, [7]Department of Cardiosciences, Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy, [8]Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Le Scotte Hospital, Siena, Italy, [9]Cardiovascular Diseases Unit, Cardio Thoracic and Vascular Department, Le Scotte Hospital, University of Siena, Siena, Italy

Background: Cardiac resynchronization therapy (CRT) is an established treatment in selected patients suffering from heart failure with reduced ejection fraction (HFrEF). It has been proposed that myocardial fibrosis and inflammation could influence CRT "response" and outcome. Our study investigated the long-term prognostic significance of cardiac biomarkers in HFrEF patients with an indication for CRT.

Methods: Consecutive patients referred for CRT implantation were retrospectively evaluated. The soluble suppression of tumorigenicity 2 (sST2), galectin-3 (Gal-3), N-terminal portion of the B-type natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate (eGFR) were measured at baseline and after 1 year of follow-up. Multivariate analyses were performed to evaluate their correlation with the primary composite outcome of cardiovascular mortality and heart failure hospitalizations at a mean follow-up of 9 ± 2 years.

Results: Among the 86 patients enrolled, 44% experienced the primary outcome. In this group, the mean baseline values of NT-proBNP, Gal-3, and sST2 were significantly higher compared with the patients without cardiovascular events. At the multivariate analyses, baseline Gal-3 [cut-off: 16.6 ng/ml, AUC: 0.91, $p < 0.001$, HR 8.33 (1.88–33.33), $p = 0.005$] and sST2 [cut-off: 35.6 ng/ml AUC: 0.91, $p < 0.001$, HR 333 (250–1,000), $p = 0.003$] significantly correlated with the composite outcome in the prediction models with high likelihood. Among the parameters evaluated at 1-year follow-up, sST2, eGFR, and the variation from baseline to 1-year of Gal-3 levels showed a strong association with the primary outcome [HR 1.15 (1.08–1.22), $p < 0.001$; HR: 0.84 (0.74–0.91), $p = 0.04$; HR: 1.26 (1.10–1.43), $p \leq 0.001$, respectively]. Conversely, the echocardiographic definition of CRT response did not correlate with any outcome.

Conclusion: In HFrEF patients with CRT, sST2, Gal-3, and renal function were associated with the combined endpoint of cardiovascular death and HF hospitalizations at long-term follow-up, while the echocardiographic CRT response did not seem to influence the outcome of the patients.

KEYWORDS

galectin-3, sST2, eGFR, biomarkers, heart failure, outcome, HF hospitalization, cardiovascular death

1. Introduction

Despite the significant advances in medical treatment, the prognosis in heart failure with reduced ejection fraction (HFrEF) remains poor, and the use of markers for outcome prediction remains scarce. Cardiac resynchronization therapy (CRT) proved to reduce mortality and heart failure (HF) hospitalizations in patients with left bundle branch block (LBBB) and left ventricular ejection fraction (LVEF) ≤35%, still symptomatic on top of optimal medial therapy (1). However, given that not all patients seem to equally benefit from CRT, the concept of "response" has been developed: various definitions, mainly based on clinical or echocardiographic modifications following CRT implantation, have tried to identify the subgroup of HF patients that gains the greatest advantage from resynchronization therapy. The aim is to optimize the candidates' selection and the cost/benefit ratio of a relatively expensive tool (2). The degree of myocardial inflammation and fibrosis can impair the efficiency of resynchronization by affecting left ventricle (LV) adverse remodeling and outcome, becoming the main determinant of the so-called "CRT response" (3). Clinical and imaging assessments alone, performed before CRT implantation, are not able to fully evaluate the state of cardiomyocytes and myocardial extracellular matrix. Conversely, some biomarkers, such as the soluble suppression of tumorigenicity 2 (sST2), galectin-3 (Gal-3), and N-terminal portion of the B-type natriuretic peptide (NT-proBNP), have been related with myocardial fibrosis, inflammation, and congestion, which are affecting the prognosis in HF patients (4–6). Chronic kidney disease and HF may amplify pathophysiologic mechanisms that lead to a dangerous vicious cycle. It is still unclear whether the dynamic change of renal function after CRT implantation directly contributes to a poor outcome or whether eGFR only marks the advances of cardiac and renal dysfunction (7).

The associations between the variations of the mentioned biomarkers, renal function, CRT response, and cardiovascular (CV) outcome have not been systematically evaluated in contemporary cohorts. Thus, the aim of our study is to investigate the potential relationship of cardiac biomarkers, CRT response, and long-term outcome in a cohort of patients with HFrEF undergoing CRT implantation.

2. Materials and methods

2.1. Study design and participants

We retrospectively evaluated consecutive patients undergoing implantation of CRT pacing (CRT-P) or CRT and defibrillation (CRT-D) in our institution "Azienda Ospedaliera-Universitaria Careggi" from November 2010 to January 2012. According to current guidelines, the patients were addressed for implantation when affected by symptomatic HFrEF (New York Heart Association class II to ambulatory class IV) despite optimal medical therapy, LV systolic dysfunction with ejection fraction ≤35%, and QRS width ≥130 ms together with LBBB morphology (8). The presence of a LBBB was defined in case of QRS ≥ 130 ms; QS or rS complex in V1 to V2; monophasic and notched or slurred R waves in I, aVL, V5, or V6; and absent Q waves in leads V5 and V6 (9). A three pacing-lead device was implanted in each patient and was programmed to obtain the highest percentage of biventricular stimulation (≥90% of total beats). This study excluded patients with a QRS morphology different from LBBB or already carriers of a right-sided pacing system, either pacemaker or implantable defibrillator. The implantation of transvenous CRT systems was performed according to standard techniques, preferring the basal position of the lateral veins for LV lead placement avoiding the apical segment (10), and placing the right atrial and ventricular leads preferably at the atrial appendage and at the apex (11). No quadripolar LV leads were implanted since they were not available at that time in our institution. The CRTs were programmed by senior electrophysiology specialists according to current guidelines and manufacturer specifications (12). Our study is in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by our local institutional review board. Informed consents were obtained from all the patients.

2.2. Laboratory assessment

Gal-3, sST2, NT-proBNP, creatinine, and estimated glomerular filtration rate (eGFR calculated with the CKD-EPI formula) were measured at baseline and at 12 months after CRT implantation. The delta (Δ) was considered as the difference between the biomarkers at baseline and 1-year follow-up.

All blood samples obtained from the patients were collected with a sterile disposable syringe containing EDTA. They were analyzed using the Alere Triage BNP Test. This test is an immunoassay in a single-use plastic cartridge containing a monoclonal antibody for BNP, labeled with a fluorescent dye and BNP. Plasma BNP was measured with Triage BNP Test (Biosite Inc., San Diego, CA, United States). The human galectin-3 ELISA is an enzyme-linked immunosorbent assay for the quantitative detection of human galectin-3 (Platinum Elisa,

eBioscience, San Diego, CA, United States). The assay was performed measuring the protein in EDTA plasma. Aliquots of serum samples were stored at temperature ranging from 2° to 8°, and the human galectin-3 level were determined after 24 h. Each sample was manually measured, and it has been assayed in duplicate; a calibration curve was built making serial dilution, starting from a value of 25,000 ng/ml to a value of 0.39 ng/ml. The final reading was realized using a specific scanner (DV 990 BV 4/6, N.T. laboratory Rome, Italy). The Presage sST2 assay is a quantitative sandwich monoclonal ELISA in a 96-well microtiter plate format for the measurement of sST2 in serum, EDTA plasma, or heparin plasma. The Presage sST2 assay utilizes two mAbs against ST2. A mouse monoclonal antihuman sST2 antibody is coated onto the surface of the microtiter plate wells and acts as the capture antibody to bind sST2 molecules in the solution. A second mouse monoclonal antihuman sST2 antibody is provided in the solution and functions as the tracer antibody for detecting ST2 molecules that bounded to the capture antibody (Critical Diagnostics, San Diego, CA, United States).

2.3. Echocardiography

All patients underwent a cardiologic evaluation and echocardiographic study at baseline, before CRT implantation, and at 1-year follow-up. The responders were defined by the reduction of LV end-systolic volume ≥15% at 1-year follow-up. The echocardiographic evaluation was interpreted and independently reviewed by three senior cardiologists according to the instructions provided by the American Society of Echocardiography (13). The LV volumes and LVEF were calculated using the apical two- and four-chamber views by the Simpson biplane formula. The pulsed-Doppler transmitral flow velocity was used to obtain the early diastolic velocity (E wave), late diastolic velocity (A wave), and their ratio (E/A), and the deceleration time of E wave. The tissue Doppler imaging (TDI) was used to collect the early diastolic myocardial velocity (e') at the septal and lateral level and the average E/e' ratio. The M-mode was then used to obtain the values of tricuspid annular plane systolic excursion (TAPSE). The delta (Δ) was defined as the difference between the echocardiographic data (LV volumes, LVEF) at baseline and 1-year follow-up.

2.4. Outcome definition

The primary clinical outcome was assessed using a composite clinical endpoint consisting of CV mortality and HF hospitalization. CV decease includes death that result from an acute myocardial infarction, sudden cardiac death, HF, stroke, CV procedures, CV hemorrhage, and other CV causes. The secondary outcomes were cardiovascular mortality, HF hospitalizations, and the first episode of sustained rapid ventricular tachyarrhythmias > 180 beats/min detected and terminated or recorded by the CRT device. All such events are routinely registered in our database at each outpatient visit and following consultations in the emergency room of hospital wards. The mean follow-up was 9 ± 2 years.

2.5. Statistical analysis

The continuous variables reported as mean ± standard deviation (SD) or as median were compared between patients with CV events and patients without CV events using the Student's *t*-test or non-parametric tests, as appropriate. The χ^2 or Fisher exact test was used to compare non-continuous variables expressed as proportions. The categorical variables reported as percentages were compared between groups using the chi-squared test (or a Fisher exact test when any expected cell count was <5). The predictive parameters of the outcomes were determined by analyzing the receiver operating characteristic (ROC) curves to obtain the best cut-off values. The survival analyses and curves were performed using the Kaplan–Meier method. A Cox regression modeling was performed to assess the factors associated with the composite outcome, CV death or HF hospitalization: multivariate analyses included covariates in a rate of 1:10 with the events recorded. Given the relative low numbers of events at follow-up, we built different prognostic models including at least one clinical, one echocardiographic, and one laboratory parameter. The ones with the highest log-likelihood were then selected. *P*-values are two-sided and considered significant when <0.05. All analyses were performed using IBM SPSS Statistics for Macintosh, Version 26.0 (IBM Corp., Armonk, NY, United States).

3. Results

3.1. Baseline characteristics, biomarkers, and primary outcome

A total of 86 patients fulfilled the inclusion criteria and were enrolled in the current study. The mean age was 70 ± 9 years, mean QRS duration 165 ± 21 ms, and LVEF 26 ± 6%, and 43% of them had ischemic cardiomyopathy (**Table 1**). The biomarker levels according to HF etiology (non-ischemic vs. ischemic) are shown in **Supplementary Table S1**. The patients with non-ischemic etiology showed lower levels of sST2 and better renal function both at baseline and during follow-up compared with patients with ischemic etiology.

At a median follow-up of 9 ± 2 years, 38 patients (44%) experienced any component of the primary outcome: considering the single outcomes, 33 (38%) were hospitalized for HF and 20 (23%) died. Moreover, 15 (17%) experienced an episode of ventricular arrhythmia. **Table 2** shows the differences of the baseline characteristics of the study groups in relation to the composite primary outcome.

In the group with clinical events, the concentrations of all the biomarkers analyzed were significantly higher, as shown by the mean values of creatinine (1.44 ± 0.48 vs. 1.30 ± 0.43 mg/dl,

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TABLE 1 Baseline and follow-up clinical, biomarkers, and echocardiographic characteristics of the population enrolled.

	Total patients, $N = 86$
Baseline	
Age (years)	70 ± 9
Sex female	27 (31)
NYHA functional class	
II	25 (28)
III	56 (66)
IV	5 (6)
Ischemic etiology	37 (43)
Diabetes	26 (30)
Smoke	36 (42)
Dyslipidemia	43 (50)
Hypertension	53 (62)
COPD	13 (15)
AF	21 (24)
QRS duration	165 ± 21
Left ventricular pacing site	
Lateral	59 (68)
Posterolateral	16 (19)
Anterolateral	11 (13)
Biomarkers	
Creatinine (mg/dl)	1.40 ± 0.75
eGFR (ml/min/1.73 m^2)	55.6 ± 20.0
NT-proBNP (pg/ml)	2,510 ± 4,445
Gal-3 (ng/ml)	27.2 ± 12.4
sST2 (ng/ml)	30.7 ± 11.0
Echocardiographic data	
LVEDV (ml)	210 ± 67
LVESV (ml)	154 ± 54
LVEF (%)	26 ± 6
LVDD (mm)	67 ± 9
LVDS (mm)	54 ± 10
E/A	1.3 ± 0.7
E/e'	16 ± 6
LA area (cm^2)	24 ± 6
TAPSE (mm)	18.2 ± 4.0
Treatment	
B-blockers	80 (93)
ACEi/ARB	75 (87)
MRA	71 (83)
Loop diuretics	82 (95)
Follow-up	
QRS duration	114 ± 20
Biomarkers	
Creatinine (mg/dl)	1.38 ± 0.55
eGFR (ml/min/1.73 m^2)	55.5 ± 21.0
NT-proBNP (pg/ml)	2,194 ± 3,856
Gal-3 (ng/ml)	24.2 ± 11.5
sST2 (ng/ml)	26.7 ± 12.2
Echocardiographic data	
LVEDV (ml)	181 ± 77
ΔLVEDV (ml)	−33 ± 34
LVESV (ml)	118 ± 50
ΔLVESV (ml)	−36 ± 41
LVEF (%)	37 ± 11
ΔLVEF (%)	11 ± 11
LVDD (mm)	64 ± 11
LVDS (mm)	51 ± 12
E/e'	14.8 ± 6.4
LA area (cm^2)	25 ± 6
TAPSE (mm)	18.4 ± 4.0
Treatment	
B-blockers	82 (95)
ACEi/ARB	56 (65)
Sacubitril/valsartan	22 (25)
MRA	73 (85)
Loop diuretics	77 (90)

AF, atrial fibrillation; CV, cardiovascular; HF, heart failure; VA, ventricular arrhythmias; BSA, body surface area; COPD, chronic obstructive pulmonary disease; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic diameter; LVDS, left ventricular systolic diameter; LA, left atrium; TAPSE, tricuspid annular plane systolic excursion; ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralcorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal portion of the B-type natriuretic peptide; Gal-3, galectin-3; sST2, soluble suppression of tumorigenicity 2.

All values are expressed as absolute number (*n*) and (%) for categorical variables or mean ± standard deviation for continuous variables.

TABLE 2 Baseline and follow-up clinical, biomarkers, and echocardiographic characteristics of the patients with CV mortality and HF hospitalization vs. patients without CV events.

	Patients with CV mortality, HF hospitalization $N = 38$	Patients without events $N = 48$	*p*-value
Baseline			
Age (years)	71 ± 8	69 ± 9	0.5
Sex female	10 (26)	17 (35)	0.01
BSA (mq)	1.7 ± 0.14	1.6 ± 0.10	0.09
Ischemic etiology	20 (52)	17 (35)	<0.001
Diabetes	16 (42)	10 (21)	<0.001
Biomarkers			
Creatinine (mg/dl)	1.44 ± 0.48	1.30 ± 0.43	0.007
eGFR (ml/min/1.73 m^2)	51.5 ± 19	56.7 ± 19	<0.001
NT-proBNP (pg/ml)	2,820 ± 4,778	1,036 ± 928	<0.001
Gal-3 (ng/ml)	34.4 ± 8.2	19.4 ± 8.3	<0.001
sST2 (ng/ml)	37.9 ± 11	23.5 ± 6.9	<0.001
Echocardiographic data			
LVEDV (ml)	238 ± 75	194 ± 58	<0.001
LVESV (ml)	175 ± 60	141 ± 51	<0.001
LVEDV/BSA (ml/mq)	134 ± 31	125 ± 41	<0.001
LVESV/BSA (ml/mq)	127 ± 39	110 ± 33	<0.001
LVEF (%)	26 ± 6	28 ± 5	0.01
LVDD (mm)	71 ± 9	64 ± 8	<0.001
LVDS (mm)	58 ± 9	52 ± 8	<0.001
E wave (cm/s)	86 ± 28	68 ± 23	<0.001
E/A	1.45 ± 0.9	1.04 ± 0.6	<0.001
E/e'	18.8 ± 5	13.4 ± 5	<0.001
LA area (cm^2)	24 ± 6	23 ± 4	0.01
TAPSE (mm)	16.7 ± 4.1	19.3 ± 3.9	<0.001
Treatment			
B-blockers	35 (92)	45 (93)	0.6
ACEi/ARB	32 (84)	43 (89)	0.9

(*Continued*)

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TABLE 2 Continued

	Patients with CV mortality, HF hospitalization $N = 38$	Patients without events $N = 48$	*p*-value
MRA	31 (82)	40 (83)	0.6
Loop diuretics	36 (94)	46 (95)	0.4
Follow-up			
Biomarkers			
Creatinine (mg/dl)	1.64 ± 0.71	1.17 ± 0.39	<0.001
eGFR (ml/min/1,73 m2)	48.5 ± 24	62.7 ± 21	<0.001
NT-proBNP (pg/ml)	2,858 ± 4,741	963 ± 1,158	<0.001
Gal-3 (ng/ml)	35.3 ± 12.1	18.2 ± 8.1	<0.001
sST2 (ng/ml)	33.4 ± 12	20 ± 9.9	<0.001
Echocardiographic data			
LVEDV (ml)	205 ± 77	158 ± 75	<0.001
ΔLVEDV (ml)	−24 ± 14	−42 ± 53	<0.001
LVESV (ml)	140 ± 55	95 ± 45	<0.001
ΔLVESV (ml)	−25 ± 45	−46 ± 36	<0.001
LVEF (%)	32 ± 10	41 ± 10	<0.001
ΔLVEF (%)	6 ± 11	14 ± 10	<0.001
LVDD (mm)	68 ± 10	62 ± 10	<0.001
LVDS (mm)	56 ± 11	49 ± 11	<0.001
E/e'	17.3 ± 6	12.3 ± 6	<0.001
LA area (cm^2)	26 ± 6	23 ± 6	<0.001
TAPSE (mm)	16.8 ± 3.7	20.7 ± 3.4	<0.001

CV, cardiovascular; HF, heart failure; VA, ventricular arrhythmias; BSA, body surface area; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic diameter; LVDS, left ventricular systolic diameter; LA, left atrium; TAPSE, tricuspid annular plane systolic excursion; ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralcorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal portion of the B-type natriuretic peptide; Gal-3, galectin-3; sST2, soluble suppression of tumorigenicity 2.
All values are expressed as absolute number (*n*) and (%) for categorical variables or mean ± standard deviation for continuous variables.

TABLE 3 Prediction models with multivariable risk analyses for CV death and HF hospitalization (primary outcome).

Model 1					
Parameter	*p*-value	HR	CI min	CI max	log-likelihood = 88.75
Baseline Gal-3[a]	0.005	8.33	1.88	33.33	
E/e'	0.001	1.22	1.09	1.37	
ΔLVESV	0.095				
Sex	0.068				
Model 2					
Parameter	*p*-value	HR	CI min	CI max	log-likelihood = 51.33
Baseline sST2[b]	0.003	333	250	1,000	
E/e'	0.001	0.72	0.59	0.88	
ΔLVESV	0.130				
Sex	0.276				
Model 3					
Parameter	*p*-value	HR	CI min	CI max	log-likelihood = 93.02
eGFR FU	0.040	0.84	0.74	0.91	
E/e'	0.001	1.20	1.08	1.33	
ΔLVESV	0.497				
Sex	0.088				
Model 4					
Parameter	*p*-value	HR	CI min	CI max	log-likelihood = 78.88
ΔGal-3	0.001	1.25	1.09	1.43	
E/e'	0.006	1.18	1.05	1.33	
ΔLVESV	0.595				
Sex	0.226				

eGFR, estimated glomerular filtration rate; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; Gal-3, galectin-3; sST2, soluble suppression of tumorigenicity 2; FU, follow-up.
[a]Gal-3 ≥ 16.6 pg/ml.
[b]sST2 ≥ 35.6 ng/ml.

$p < 0.001$), NT-proBNP (2,820 ± 4,778 vs. 1,036 ± 928 pg/ml, $p < 0.001$), Gal-3 (34.4 ± 8.2 vs. 19.4 ± 8.3 mg/ml $p < 0.001$), and sST2 (37.9 ± 11 vs. 23.5 ± 6.9 ng/ml, $p < 0.001$).

Considering the relative low numbers of events at follow-up, several multivariate analyses including at least one clinical, one echocardiographic, and one laboratory parameter were considered. Table 3 includes some of the multivariate analyses among those showing the highest log-likelihood. Baseline Gal-3 and sST2 cut-off values with the highest AUC at the ROC curve analysis were identified (Gal-3 cut-off: 16.6 ng/ml, AUC: 0.91, $p < 0.001$; sST2 cut-off: 35.6 ng/ml AUC: 0.91, $p < 0.001$) and maintained a strong correlation with the outcome at the multivariate analyses [HR 8.33 (1.88–33.33), $p = 0.005$ and HR 333 (250–1,000), $p = 0.003$, respectively]. In these "prediction models", E/e' was also statistically significant; conversely, no clinical variable maintained its correlation with the outcome, including ischemic etiology, as shown in Supplementary Table S2.

The Kaplan–Meier curve built with the same cut-off values of sST2 is shown in Figure 1. The survival curves were then created using the combination of the cut-off values of sST2 and Gal-3 found in our analysis. As displayed in Figure 2, the patients with both high baseline sST2 and Gal-3 had the lowest survival probability.

NT-proBNP was not significantly related with the composite outcome when considered singularly in various prediction models, but the parameter obtained by its combination with sST2 (both considered as categorical variables) proved to be significant [HR 7.69 (3.13–20), $p < 0.001$, log-likelihood = 56.16] and showed a high prediction performance (AUC 0.85).

The laboratory values obtained at 12 months confirmed the same trend presented at baseline, with higher levels of all cardiac biomarkers in the patients with CV events. At the multivariate analyses, sST2 [HR 1.15 (1.08–1.22), $p < 0.001$] and the ΔGal-3 [HR 1.26 (1.10–1.43), $p \leq 0.001$] maintained their prognostic value at follow-up (Table 3). Interestingly, the baseline eGFR values did not significantly correlate with the composite outcome, as opposed to the values obtained at 1-year follow-up [HR: 0.84 (0.74–0.91), $p = 0.04$].

3.2. Predictive role of biomarkers and secondary outcomes

Concerning the secondary endpoints, baseline Gal-3 and sST2 maintained their significant association with both HF

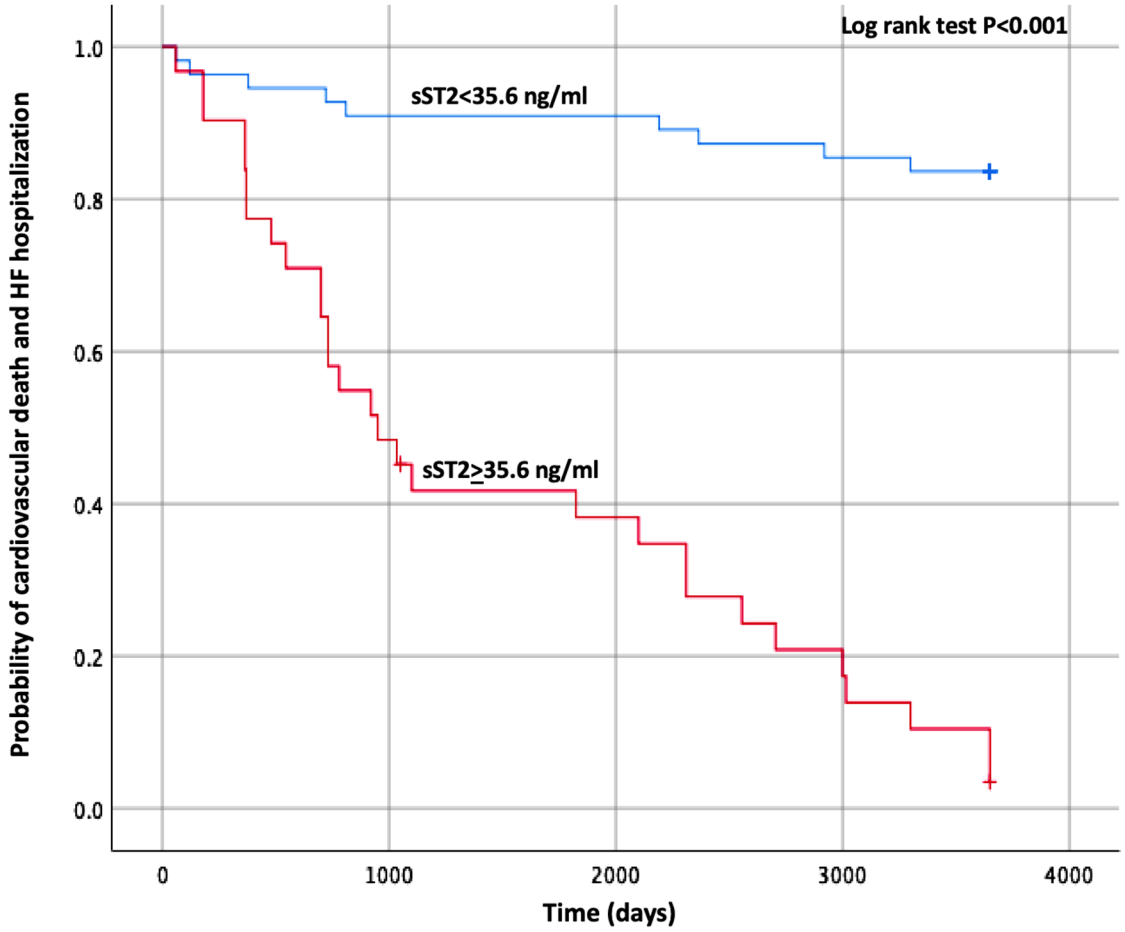

FIGURE 1
Kaplan–Meier estimates of the cumulative probability of CV death and HF hospitalization by ST2 cut-off. CV, cardiovascular; HF, heart failure; ST2, suppression of tumorigenicity 2.

hospitalizations and CV mortality alone at the multivariate analyses, as shown in **Supplementary Table S3**, **S4**. The best predictor of CV mortality was Gal-3 with a cut-off value of 33.6 pg/ml (AUC 0.91 $p < 0.001$), and the relative Kaplan–Meier curve is shown in **Figure 3**.

As for the composite outcome, even if NT-proBNP alone was not significant, the parameter obtained by its combination with baseline sST2 (AUC 0.88, $p < 0.001$) showed good outcome prediction at the multivariate analysis [HR for HF hospitalizations 3.23 (1.89–4.35), $p < 0.001$, log-likelihood = 58.26; HR for CV mortality 3.33 (1.39–5.88), $p = 0.010$, log-likelihood = 59.37].

When biomarkers were evaluated at 1 year, the prediction model built with ΔGal-3 was predictive for the single components of secondary outcomes [HR for HF hospitalizations 1.19 (1.07–1.33), $p = 0.001$; HR for CV mortality 1.14 (1.04–1.26), $p = 0.005$]. The eGFR at follow-up maintained its prognostic role for cardiovascular mortality [HR 0.84 (0.80–0–90), $p = 0.002$].

Finally, no single predictor for the outcome of ventricular arrhythmias was significant at the multivariate analysis.

3.3. LV dimensions, CRT response, and outcomes

The difference between the left ventricular end-systolic volume (LVESV) at baseline and follow-up (ΔLVESV) did not correlate with primary and secondary outcome in all prognostic models when including biomarkers at the multivariate analyses, as shown in **Table 3** and **Supplementary Tables S2–S4**. Accordingly, the echocardiographic definition of CRT response did not relate with the single components of the composite outcome in various prediction models and, among the total of 52 (62%) patients who showed LV reverse remodeling and were considered responders to CRT, no difference in terms of events rate was recorded.

4. Discussion

4.1. Biomarkers and outcome

In this paper concerning HFrEF patients undergoing CRT implantation, a significant correlation between biomarkers of

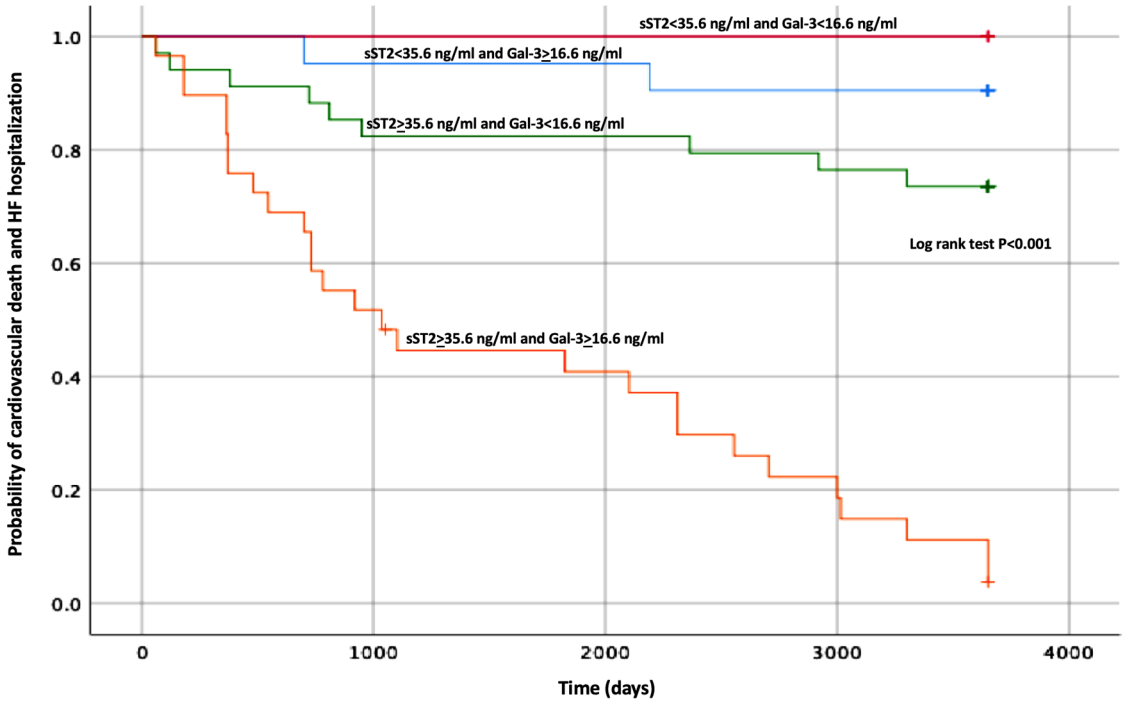

FIGURE 2
Kaplan–Meier estimates of the cumulative probability of CV death and HF hospitalization by Gal-3 and ST2 levels. CV, cardiovascular; HF, heart failure; ST2, suppression of tumorigenicity 2; Gal-3, galectin-3.

myocardial inflammation, congestion, and fibrosis, together with renal function and the composite long-term outcome of HF hospitalization and CV mortality was found. Gal-3 and sST2 showed the highest power in the prediction models for CV death and HF hospitalization, also when analyzed as single endpoints. This finding supports the theory that inflammation and fibrosis can contribute to the course of the disease even when HF reaches advanced stages, indicating an ongoing myocardial damage and portending poor prognosis (14).

Although NT-proBNP, sST2, Gal-3, and eGFR, when considered individually, have already been demonstrated to have a prognostic role in HF (15–17), to the best of our knowledge, a combination of these parameters and its variations during the course of the disease were not tested in the candidates to CRT implantation in the long-term follow-up.

The sST2 was included in the Biomarker CRT score, developed in a sub-analysis of the SMART-AV trial, due to its additive predictive value of CRT response when considered against a composite of clinical variables (18). Its concentrations have been shown to predict sudden cardiac death in patients with HFrEF and provided complementary information to NT-proBNP (19). Moreover, serial measurements of sST2 provided incremental information to baseline levels, reflecting changes in myocardial remodeling over time and an increased risk of CV death (20).

Similarly, Gal-3 is a soluble beta-galactoside-binding lectin that has been related to inflammation and fibroblast activation; its effect on myocardial fibrosis, CV stiffness, and immune response modulation seems to determine pathological myocardial remodeling (21). High Gal-3 values have been related with CRT response at 6 months and with CV outcome at 48 months. Serial measurements have shown a prognostic role in acute HF, independently from BNP values (22). In a sub-analysis of CARE-HF, Gal-3 was an independent predictor of death from any cause or an unplanned hospitalization for a major CV event, even if it did not predict the response to CRT if considered as a separated outcome (23). Interestingly, in our population, the patients who met the primary outcome also showed higher Gal-3 levels at 1-year follow-up, and the ΔGal-3 was a prognostic marker at the prediction model, in line with the previous findings by Van Vark et al. (24).

When it comes to HF, heart and kidney functions are strictly intertwined. A renal dysfunction is very common in HFrEF, and it is acknowledged as a powerful predictor of survival (25). From a pathophysiological point of view, several mechanisms explain renal involvement in cardiac diseases, mainly attributable to renal congestion due to elevated venous pressure, decreased cardiac output, and activation of neurohormonal system (26). It has been described that the slight improvement in cardiac output after CRT may be associated with a concurrent improvement in renal function (27, 28). In our analysis, we confirm that the patients with adverse CV outcome show a significant decline of eGFR at follow-up compared with the patients without CV events. Moreover, eGFR is able to predict the absolute risk for adverse cardiac events. Maaten et al. demonstrated that the patients with chronic kidney disease undergoing CRT implantation, while experiencing a reverse remodeling in a lesser extent than those

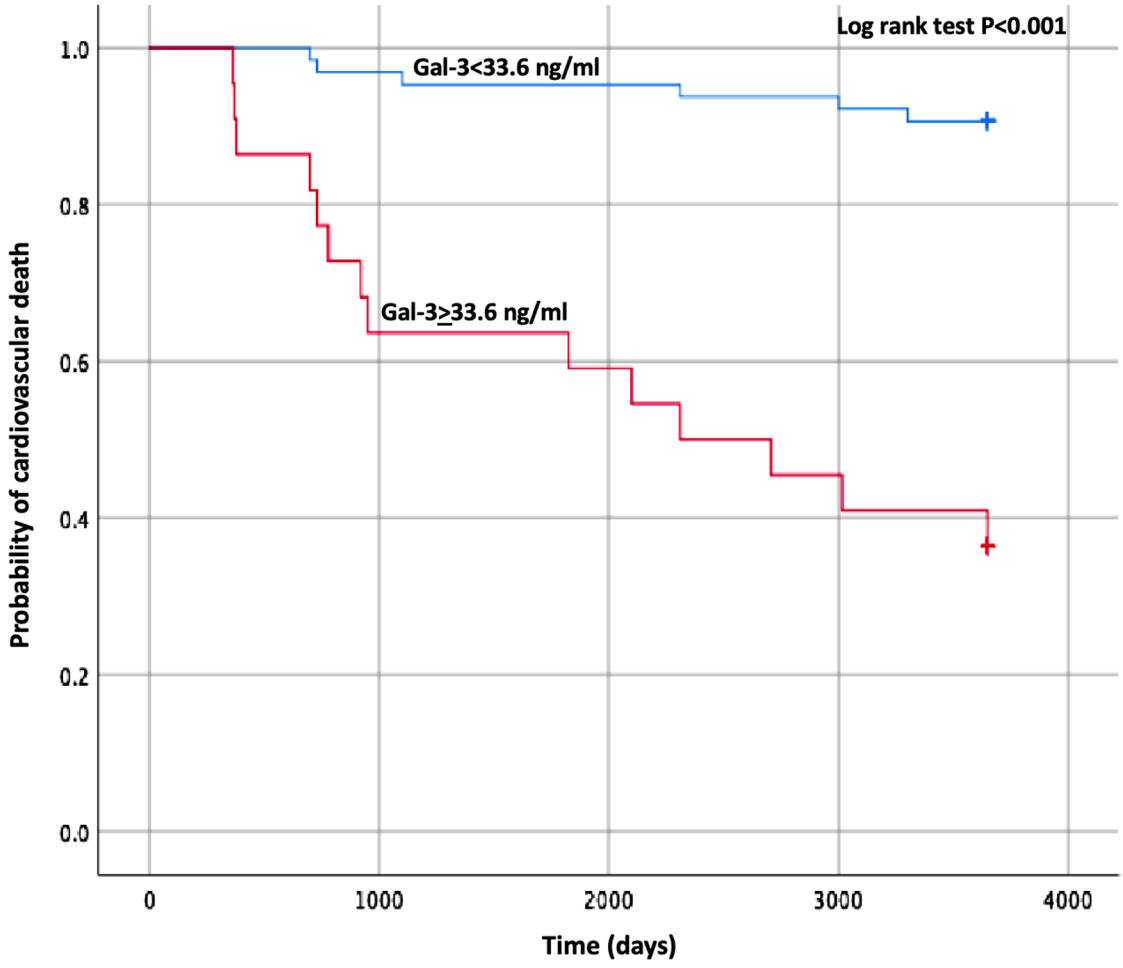

FIGURE 3
Kaplan–Meier estimates of the cumulative probability of cardiovascular death by Gal-3 cut-off. Gal-3, galectin-3.

patients without renal dysfunction, also derive benefit on outcome at a lesser degree of remodeling. This could be related to the underlying pathogenesis of the renal dysfunction, such as nephrosclerosis, which is unlikely to respond to hemodynamic improvement (29).

4.2. Response to CRT and outcome

At follow-up, ΔLVESV and the reduction of more than 15% of LVESV did not show a significant relation with the outcome in our population. This finding seems to contrast with the large actual attention for the so-called CRT "response," but lines up with a recent ESC position statement, which questions this arbitrary definition (30). Historically, the interest in literature for the research of variables to identify the patients who are less likely to benefit from CRT has always been alive. Also, a uniform way to define the desirable echocardiographic "response" to CRT is lacking, and echo improvement has been shown to be variable among different etiologies of HF. In fact, it has been argued that a binary definition of response underestimates the true benefits of CRT and that similar attention has not been posed to select patients for drug therapy. We challenge the idea that the selection of CRT candidates should be limited in base of the underlying etiology: while it is true that the patients with an ischemic etiology manifest less reverse remodeling, it should also be noticed that they have an equal relative risk reduction after CRT for HF admission and death as the non-ischemic group. Moreover, such a simple and cautious approach has resulted in a well-known undertreatment of dyssynchrony, preventing the patients to take advantage of a device that demonstrated to reduce morbidity and mortality (31). A lack of improvement in LVEF or in the symptoms of the patients (also considering the limitations of this evaluation) is not considered a good reason to withdraw one of the "drugs pillars" and accordingly should not be interpreted as a failure of CRT. The term "disease modification" (that may even imply a mere stabilization) should therefore replace the term "response" (32). Accordingly, our results corroborate the role of the laboratory values in CRT recipients, beyond the technical parameters used to define the efficacy of resynchronization. Importantly, the levels of these biomarkers, namely, sST2 and Gal-3, together with renal

function, maintained their prognostic power also at 1-year follow-up. This should encourage clinicians to serially assess those values, especially when considering that many other parameters do not hold the same significance in advanced HF stages.

In our cohort, the risk stratification models incorporating one biomarker and E/e' identified the patients at risk for CV outcome, confirming that the patients with higher left ventricular filling pressure (LVFP) at baseline before the device implantation show a worse prognosis. E/e' is the most robust echocardiographic surrogate of an elevated LVFP, and several validation studies have confirmed the prediction of normal and abnormal LVFP when E/e' ratio was <8 or >15 (33, 34). Elevated values of E/e' ratio related to HF progression and worse prognosis as a consequence of an increased myocardial stiffness (35). Our data reproduce the findings of the REVERSE trial, where E/e' ratio was associated with the endpoints of mortality and a new or recurrent HF in CRT recipients (36).

In summary, our results suggest that the laboratory parameters related to fibrosis production and extracellular matrix deposition, together with the concordant increase in echocardiographic surrogates of wall rigidity and chamber stiffness, are linked to an unfavorable outcome in CRT patients.

Our study comes with several limitations. All data were collected retrospectively from our single center, allowing the achievement of a small sample size with low cardiovascular events. However, we included an accurately screened population undergoing CRT implantation, following the indication of the latest guidelines. Gal-3 often increases in renal failure and chronic inflammatory diseases. Moreover, the so-called "response" to CRT depends on many different parameters: a role of underlying etiology, percentage of biventricular pacing, loss of LV capture, and compliance to medical therapy cannot be ruled out. In addition, notwithstanding that efforts should be made to optimize the efficacy of CRT capture after implantation, this does not affect the main finding of our study concerning the correlation between the biomarkers and the outcomes in these patients.

A total of four patients experienced the primary endpoint in the first year after the implantation, hence the correlation between echocardiographic and laboratory parameters at 1-year follow-up, and the outcome do not apply for them.

In conclusion, our study showed how, in a population of HFrEF patients implanted with CRT, a combined evaluation of biomarkers of cardiac inflammation, fibrosis, and renal function correlated with the combined outcome of CV death and HF hospitalization, as opposite to the echocardiographic definition of CRT response. The current findings cannot be extended to all HF patients with different etiologies and need to be confirmed in larger multi-center studies. However, despite the potential confounders, our results encourage clinicians to serially assess the levels of cardiac biomarkers to add significant prognostic implication.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Author contributions

MB, APao, AG, MG, and MM performed the literature search and the data extraction. RB did the statistical analysis. MB, AG, and APal wrote the manuscript. MB and APal conceptualized and coordinated the study. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1180960/full#supplementary-material

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EDITED BY
Matteo Cameli,
University of Siena, Italy

REVIEWED BY
Qingui Chen,
The First Affiliated Hospital of Sun Yat-sen University, China
Vyacheslav Ryabov,
Russian Academy of Sciences, Russia

*CORRESPONDENCE
Kye Hun Kim
✉ christiankyehun@hanmail.net

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Timing of heart failure development and clinical outcomes in patients with acute myocardial infarction

Hyung Yoon Kim, Kye Hun Kim*, Nuri Lee, Hyukjin Park, Jae Yeong Cho, Hyun Ju Yoon, Youngkeun Ahn, Myung Ho Jeong and Jeong Gwan Cho

Department of Cardiology, Chonnam National University Medical School/Hospital, Gwangju, Republic of Korea

Background and objectives: To investigate the clinical relevance of the timing of heart failure (HF) development on long-term outcome in patients with acute myocardial infarction (AMI).
Materials and methods: A total of 1,925 consecutive AMI patients were divided into 4 groups according to the timing of HF development; HF at admission (group I, $n = 627$), *de novo* HF during hospitalization (group II, $n = 162$), *de novo* HF after discharge (group III, $n = 98$), no HF (group IV, $n = 1{,}038$). Major adverse cardiac events (MACE) defined as the development of death, re-hospitalization, recurrent MI or revascularization were evaluated.
Results: HF was developed in 887 patients (46.1%) after an index AMI. HF was most common at the time of admission for AMI, but the development of *de novo* HF during hospitalization or after discharge was not uncommon. MACE was developed in 619 out of 1,925 AMI patients (31.7%). MACE was highest in group I, lowest in group IV, and significantly different among groups; 275 out of 627 patients (43.9%) in group I, 64 out of 192 patients (39.5%) in group II, 36 out of 98 patients (36.7%) in group III, and 235 out of 1,038 patients (22.6%) in group IV ($P < 0.001$). MACE free survival rates at 3 years were 56% in group I, 62% in group II, 64% in group III, and 77% in group IV ($P < 0.001$).
Conclusions: HF was not uncommon and can develop at any time after an index AMI, and the development of HF was associated with poor prognosis. The earlier the HF has occurred after AMI, the poorer the clinical outcome was. To initiate the guideline directed optimal medical therapy, therefore, the development of HF should be carefully monitored even after the discharge from an index AMI.

KEYWORDS
heart failure, myocardial infarction, prognosis, acute myocardal infarct, death

Introduction

Heart failure (HF) is a major public health problem with over 37.7 million cases reported worldwide, and its prevalence is increasing rapidly (1). The most common cause of HF is ischemic heart disease including acute myocardial infarction (AMI), which is also growing constantly. With the advances in both optimal revascularization and medical therapy, the survival rate after AMI have improved, on the other hand, the incidence of HF associated with MI also has been increased (2, 3). The development of HF after an index MI is known to be associated with poor clinical outcomes (4, 5).

After an index AMI, HF may develop at the time of hospitalization in association with the degree of myocardial injury with a varying incidence of 14%–36% (2). As a maladaptive process for myocardial injury, so called adverse left ventricular (LV) remodeling, HF may also develop at any time of post-discharge period (6). Conflicting evidences on the incidence and temporal trend of HF after MI arises from the different definition of HF and the timing and population of HF differ among the previous reports (2, 7–9). Regardless of the type of infarct-related artery (IRA), the size of the infarcted or ischemic myocardium supplied by the IRA is a critical determinant for favorable clinical outcomes including HF prevention. In patients with chronic coronary artery diseases, routine invasive therapy for the lesions with significant myocardial ischemia failed to reduce the overall cardiovascular mortality compared to optimal medical treatment in the recent ISCHEMIA trial. However, the rapid restoration of IRA patency by percutaneous coronary intervention (PCI) and subsequent optimal medical therapy would be essential to prevent or minimize the risk of progression to HF through myocardial damage in patients with AMI. Therefore, it is important to understand the natural course of HF development or progression after MI to introduce optimal management, thereby to provide better long-term prognosis.

Contrary to the HF at the time of hospitalization for AMI, the risk of development or clinical course of *de novo* HF during post-discharge period for AMI has been poorly studied. Therefore, we investigated the post-MI clinical course for HF development and the impacts of the clinical relevance of HF development on long-term prognosis in patients with AMI.

Materials and methods

Study subjects and design

This is a single center retrospective and observational study, and the study protocol was approved by the institutional review board (IRB) of Chonnam National University Hospital (IRB file No. CNUH-2011-172).

We evaluated patients with clinically diagnosed for AMI at Chonnam National University Hospital (Gwangju, Korea) between November 2011 and June 2015. The diagnosis of MI was based on the criteria for a universal definition of MI: (1) when there was a rise and/or fall in cardiac biomarker values (troponin I/T or creatine kinase-MB with at least one value above the 99th percentile upper reference limit) and (2) with at least one of the following (a) symptoms of myocardial ischemia, (b) changes on the electrocardiogram (ECG) including new or presumed new significant ST-segment-T wave changes, new left bundle branch block, or pathologic Q waves in 2 contiguous leads, and (c) imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality (10). Exclusion criteria included subjects with complex structural or congenital heart disease, and any clinical instability or life-threatening disease.

The diagnosis of HF was based on the following conditions, which were predominantly established from the European Society of Cardiology (ESC) guideline for AMI-associated HF: (1) cardinal manifestations of HF (such as dyspnea or fatigue), (2) rales (Killip class II or higher), (3) pulmonary edema on chest x-ray, (4) elevated level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (11).

Patients were categorized into 4 groups according to their development of HF and their onset time of HF after an index AMI: (1) HF development at the time of admission (group I), (2) *de novo* HF during hospitalization (group II), (3) *de novo* HF after discharge (group III), and (4) no HF development during follow-up (group IV).

Data collection

Baseline clinical, angiographic, and echocardiographic data were obtained retrospectively from medical record. Demographic and clinical data included age at diagnosis, sex, associated cardiovascular risk factors such as presence of diabetes mellitus, hypertension or smoking history, and initial presentations. Pulmonary edema on initial chest x-ray were used in the assessment of Killip class (12). Coronary angiography (CAG) and percutaneous coronary intervention (PCI) were performed according to the standard protocol (13). Decision of revascularization was made by the agreement of attending physician and interventional cardiologist. Findings of CAG were analyzed based on the ACC/AHA (American College of Cardiology/American Heart Association) classification system (14). All echocardiographic parameters including left ventricular ejection fraction (LVEF) and chamber sizes were measured according to the current recommendations for cardiac chamber quantification of American Society of Echocardiography (15, 16).

Primary endpoint

The primary outcome of this study was a composite of major adverse cardiac events (MACE) defined as all-cause death, re-hospitalization, recurrent MI, or any revascularization.

Statistical analysis

Data were analyzed using SPSS statistical software (version 25.0 for windows, SPSS, Inc., Chicago, IL). Categorical variables were presented as frequencies and percentages. The chi-square test or Fisher's exact test was performed appropriately to test the difference of categorical variables among groups. In order to determine any statistical difference of continuous variables among groups, analysis of variances (ANOVA) or Kruskal-Wallis test was performed. A *post hoc* Bonferroni test for multiple comparisons was applied in order to further determine any significant differences between means among the individual groups, if any statistical differences were observed from the ANOVA or Kruskal-Wallis test. Continuous variables were presented as mean ± standard deviations. The probability of

freedom from MACE of each group and survival rate were estimated by the Kaplan-Meier method and log-rank test. *P*-values <0.05 were considered as significant. Multivariable Cox proportional hazard regression analysis was performed for the adjustment of baseline characteristics.

Results

Baseline clinical characteristics

From November 2011 to June 2015, a total of 1,925 consecutive patients with AMI were included in this study (1,323 males, 65.7 ± 12.5 years), and HF was developed in 887 patients (46.1%) after an index AMI. HF was noted at the time of admission in 627 patients (group I: 32.6%), and *de novo* HF during hospitalization was developed in 162 patients (group II: 8.4%). Among 1,136 AMI patients who had no HF development during hospitalization, post-discharge *de novo* HF was developed in additional 98 patients (group III: 5.1%). HF was not developed in the remaining 1,038 AMI patients (group IV: 53.9%).

The clinical characteristics among the groups were statistically different in most variables, and the differences between group I and group IV were statistically significant, whereas the differences between group II and group III were not statistically significant in most variables in the post-hoc analysis.

Majority of clinical indicators, except the conventional cardiovascular risk factors, were most severe in group I and most favorable in group IV, and the values of group II and group III are allocated between the values in group I and group IV. Notably, the presence of past medical history of heart failure was not different among groups. The baseline characteristics of each group were described in detail in Table 1.

Laboratory, echocardiography, and CAG findings

The level of CK-MB (creatine kinase MB isoenzyme), troponin I and hsCRP (high sensitivity C-reactive protein) are greatest in group I and decreased in order of later onset of HF, and lowest in group IV.

Diminished LVEF at initial echocardiography were severe in group I and II and lesser severe in order of group III, and group IV ($P < 0.001$). In addition, there was a significant difference regarding the presence of multi-vessel disease on CAG, with the higher prevalence in group I, group II, and group III, while the lowest prevalence in group IV ($P = 0.012$). Laboratory, echocardiography, and CAG findings were summarized in Table 2.

Clinical outcomes

Clinical outcomes of the patients were summarized in Table 3. During the median 60 months (range, 0.03–93.4 months) of

TABLE 1 Baseline clinical characteristics.

	Group I ($n = 627$)	Group II ($n = 162$)	Group III ($n = 98$)	Group IV ($n = 1,038$)	*P*-value
	Mean ± SD or *n* (%)				
Age (years)	69.7 ± 11.4	67.6 ± 12.4	67.6 ± 11.3	62.5 ± 12.4	<0.001$^{‡§\#}$
Sex, male	379 (60.4)	111 (68.5)	68 (69.4)	765 (73.7)	<0.001§¶
Dyspnea	163 (26.0)	22 (13.6)	7 (7.1)	50 (4.8)	<0.001$^{*§¶\#}$
Diagnosis					<0.001*§¶
STEMI	328 (52.3)	58 (35.8)	34 (34.7)	351 (33.8)	
NSTEMI	299 (47.7)	104 (64.2)	64 (65.3)	687 (66.2)	
CV Risk factors					
HTN	378 (60.3)	90 (55.6)	62 (63.3)	509 (49.0)	<0.001‡§
DM	226 (38.6)	63 (38.9)	34 (34.7)	262 (25.2)	<0.001$^{‡§\#}$
Dyslipidemia	40 (6.4)	12 (7.4)	8 (8.2)	82 (7.9)	0.702
Current smoking	180 (27.3)	44 (27.2)	27 (27.6)	408 (39.3)	<0.001$^{‡§\#}$
Previous MI	50 (8.0)	25 (15.4)	10 (10.2)	107 (10.3)	0.040*
Previous PCI	38 (6.1)	11 (6.8)	7 (7.1)	49 (4.7)	0.452
Previous CVA	60 (9.6)	11 (6.8)	8 (8.2)	52 (5.0)	0.004§
Previous HF	10 (1.6)	0 (0)	1 (1.0)	20 (1.9)	0.319
Killip class					<0.001$^{*†§¶\#}$
1	289 (46.1)	114 (70.4)	84 (85.7)	930 (89.6)	
2	113 (18.0)	26 (16.0)	11 (11.2)	85 (8.2)	
3	121 (19.3)	11 (6.8)	1 (1.0)	11 (1.1)	
4	104 (16.6)	11 (6.8)	2 (2.0)	12 (1.2)	

The *P*-value denotes statistical significance comparing each group. Data are listed as numbers (percentage of group), mean value. ANOVA or χ^2-test for group 1 vs. group 2 vs. group 3 vs. group 4; *P*-value was calculated by one way ANOVA test and Bonferroni multiple comparisons tests for continuous variables. *$P < 0.05$ between group I vs. group II; †group II vs. group III; ‡group III vs. group IV; §group I vs. group IV; ¶group I vs. group III; $^{\#}$group II vs. group IV. CV, cardiovascular; CVA, cerebrovascular accident; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; MI, myocardial infarction; NSTEMI, non-ST-elevation MI, PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-elevation MI. Group I, HF at admission; Group II, *de novo* HF during hospitalization; Group III, *de novo* HF after discharge; Group IV, no HF during follow-up.

TABLE 2 Comparison of laboratory, echocardiography, angiography findings, and prescribed medications among groups.

	Group I ($n = 627$)	Group II ($n = 162$)	Group III ($n = 98$)	Group IV ($n = 1,038$)	*P*-value
	Mean ± SD or *n* (%)				
Laboratory findings					
WBC	11.95 ± 5.4	10.84 ± 3.6	9.81 ± 4.3	10.18 ± 8.3	<0.001[¶§]
Creatinine	1.29 ± 1.2	1.41 ± 1.7	1.29 ± 1.8	0.97 ± 0.9	<0.001[§#]
CK-MB	110.2 ± 165.8	97.96 ± 141.6	90.87 ± 104.7	76.76 ± 188.8	0.002[§]
Troponin I	58.98 ± 96.4	48.20 ± 69.1	52.51 ± 74.1	32.48 ± 49.1[‡]	<0.001[§]
hsCRP	2.84 ± 4.67	2.54 ± 4.82	1.37 ± 3.69	0.97 ± 2.14	<0.001[§¶#]
NT-proBNP (pg/dl)	7,806.1 ± 22,180.9	7,547.9 ± 10,785.5	2,234.9 ± 5,263.8	1,873.5 ± 6,736.5	<0.001[§¶#]
Echocardiographic parameters					
LA dimension	39.7 ± 8.0	40.1 ± 6.9	39.7 ± 5.6	37.6 ± 6.3	<0.001[‡§#]
LAVI (ml/m^2)	43.5 ± 12.4	42.0 ± 22.0	30.3 ± 1.13	31.3 ± 9.37	0.008[§]
LVMI (g/m^2)	116.6 ± 32.9	114.6 ± 28.5	102.9 ± 21.1	101.2 ± 24.8	0.013[§]
LVEDD (mm)	50.6 ± 6.7	52.4 ± 6.6	49.7 ± 7.0	49.2 ± 5.8	<0.001[*†§#]
LVESD (mm)	36.5 ± 7.5	38.3 ± 8.8	34.7 ± 6.2	33.0 ± 6.1	<0.001[*†§#]
IVS (mm)	9.64 ± 2.0	9.47 ± 1.7	9.82 ± 1.3	9.32 ± 1.7	0.002[§]
LVPW (mm)	9.72 ± 1.8	9.56 ± 1.6	10.0 ± 1.4	9.52 ± 1.5	0.011[‡]
LVEF (%)	47.2 ± 10.1	45.5 ± 11.7	50.1 ± 7.9	54.0 ± 8.1	<0.001[†‡§#]
LVEDV (ml)	93.2 ± 31.8	98.9 ± 36.9	86.0 ± 26.6	84.9 ± 26.5	<0.001[§#]
LVESV (ml)	50.3 ± 24.4	57.2 ± 31.4	43.4 ± 15.4	39.7 ± 17.7	<0.001[*†§#]
RVSP (mmHg)	40.4 ± 12.8	31.8 ± 9.6	30.8 ± 8.7	30.4 ± 6.7.	<0.001[*§¶]
Angiographic parameters					
Culprit vessel					0.043[§]
LM	28 (5.0)	3 (2.1)	4 (4.6)	20 (2.2)	
LAD	256 (45.3)	71 (49.0)	37 (42.5)	413 (45.8)	
LCX	81 (14.3)	21 (14.5)	14 (16.1)	177 (19.6)	
RCA	200 (35.4)	50 (34.5)	32 (36.8)	292 (32.4)	
Multi-vessel disease	219 (35.7)	55 (34.6)	62 (36.1)	293 (28.5)	0.012[§]
Medications					
Beta-blocker	451 (71.9)	125 (77.2)	80 (81.6)	816 (78.6)	0.010[§¶]
Calcium channel blocker	26 (4.1)	10 (6.2)	12 (12.2)	102 (9.8)	<0.001[§¶]
ACEi/ARB	456 (72.7)	128 (79.0)	82 (83.7)	857 (82.6)	<0.001[§¶]
Statin	481 (76.7)	132 (81.5)	87 (88.8)	935 (90.1)	<0.001[§¶#]
Warfarin	33 (5.3)	6 (3.7)	3 (3.1)	24 (2.3)	0.016[§]
Aspirin	624 (99.5)	161.1 (98.8)	98 (100)	1,032 (99.4)	0.591

The *P*-value denotes statistical significance comparing each groups. Data are listed as numbers (percentage of group), mean value. ANOVA or χ^2-test for group 1 vs. group2 vs. group 3 vs. group 4; *P*-value was calculated by one way ANOVA test and Bonferroni multiple comparisons tests for continuous variables. *$P < 0.05$ between group I vs. group II; [†]group II vs. group III; [‡]group III vs. group IV; [§]group I vs. group IV; [¶]group I vs. group III; [#]group II vs. group IV. ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; EDD, end diastolic dimension; EDV, end diastolic volume; EF, ejection fraction; ESD, end systolic dimension; ESV, end systolic volume; hsCRP, high sensitivity C-reactive protein; IVS, interventricular septum; MACE, major adverse cardiac events; LA, left atrium; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; LV, left ventricular; LVMI, left ventricular mass index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PW, posterior wall; RCA, right coronary artery; RVSP, right ventricular systolic pressure; SD, standard deviation; WBC, white blood cell. Group I, HF at admission; Group II, *de novo* HF during hospitalization; Group III, *de novo* HF after discharge; Group IV, no HF during follow-up.

clinical follow-up, MACE occurred in 275 (43.9%) patients in group I, 64 (39.5%) patients in group II, 36 (36.7%) in group III, and 235 (22.6%) in group IV. MACE was significantly common in HF groups than in no HF group.

Overall MACE free survival was 80.8%, 73.7%, and 68.6% at 1, 2, and 3 years, respectively. Cumulative MACE free survival at 3 years were 56.2% in group I, 61.5% in group II, 63.7% in group III, and 77.5% in group IV. Cumulative MACE free survival was statistically lower in HF groups than in no HF group ($P < 0.001$) (**Figure 1**). However, no statistical difference in MACE free survival was demonstrated between group I and group II ($P = 0.247$), and between group II and group III ($P = 0.375$).

All-cause mortality and cardiac death were occurred in 214 (34.1%) and 135 (21.5%) patients in group I, 45 (27.8%) and 33 (20.4%) in group II, 15 (15.3%) and 8 (8.2%) in group III, and 125 (12.0%) and 72 (6.9%) in group IV, with showing significant difference among groups ($P < 0.001$).

Overall cumulative survival for all-cause death and cardiac death were 86.0% and 90.1 at 1 year, 82.3% and 88.5% at 2 years, and 79.3% and 86.8% at 3 years of follow-up. Kaplan-Meier survival curves for all-cause mortality and cardiac death showed statistical differences among groups ($P < 0.001$, for all). However in the subgroup analysis, Kaplan-Meier survival curves for all-cause mortality demonstrated no statistical differences between group I and group II ($P = 0.100$) and between group III and group IV ($P = 0.426$) (**Figure 2**).

TABLE 3 Comparisons of clinical outcomes among groups.

	Group I ($n = 627$)	Group II ($n = 162$)	Group III ($n = 98$)	Group IV ($n = 1,038$)	*P*-value
	Mean ± SD or *n* (%)				
MACE	275 (43.9)	64 (39.5)	36 (36.7)	235 (22.6)	<0.001$^{\ddagger\S\#}$
All-cause death	214 (34.1)	45 (27.8)	15 (15.3)	125 (12.0)	<0.001$^{\dagger\S\P\#}$
Cardiac death	135 (21.5)	33 (20.4)	8 (8.2)	72 (6.9)	<0.001$^{*\S\P\#}$
Re-hospitalization	47 (7.5)	13 (8.0)	10 (10.2)	42 (4.0)	0.003$^{\ddagger\S\#}$
Recurrent MI	28 (4.5)	6 (3.7)	9 (9.2)	47 (4.5)	0.177
Any revascularization	33 (5.3)	8 (4.9)	12 (12.2)	71 (6.8)	0.050¶

The *P*-value denotes statistical significance comparing each group. Data are listed as numbers (percentage of group), mean value. ANOVA or χ^2-test for group 1 vs. group2 vs. group 3 vs. group 4; *P*-value was calculated by one way ANOVA test and Bonferroni multiple comparisons tests for continuous variables. *$P < 0.05$ between group I vs. group II; †group II vs. group III; ‡group III vs. group IV; §group I vs. group IV; ¶group I vs. group III; $^{\#}$group II vs. group IV. MACE, major adverse cardiac events; MI, myocardial infarction; SD, standard deviation. Group I, HF at admission; Group II, *de novo* HF during hospitalization; Group III, *de novo* HF after discharge; Group IV, no HF during follow-up.

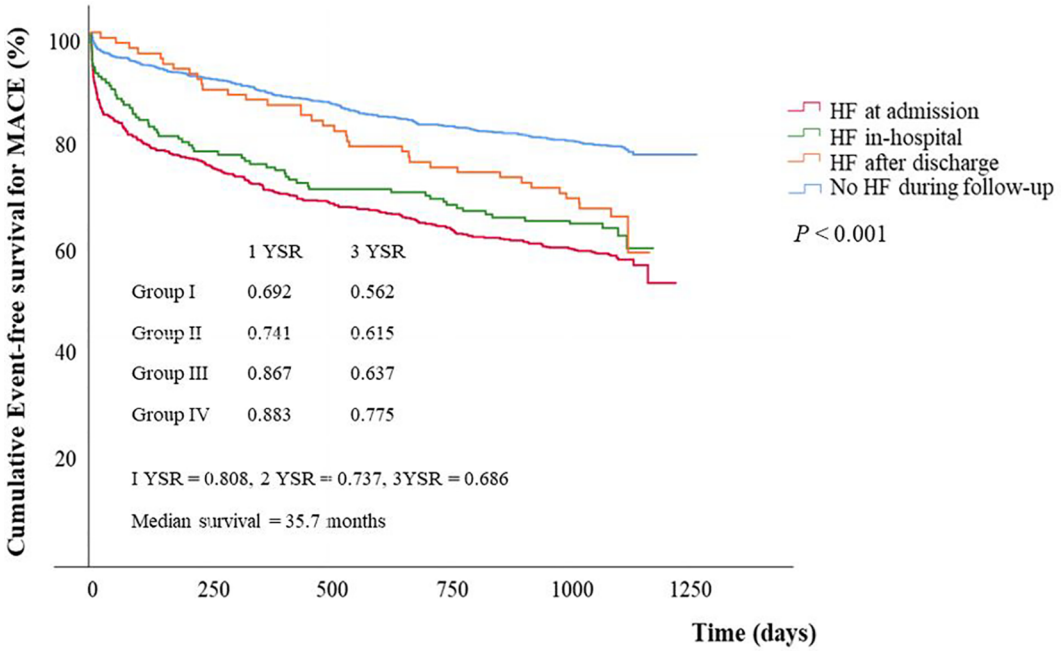

FIGURE 1
Event free survival curves for major adverse cardiac events stratified by groups. Event free survival for MACE was significantly different between group IV and any other groups (group I vs. group IV, $P < 0.001$; group II vs. group IV, $P < 0.001$; group III vs. group IV, $P = 0.003$) and between group III and group IV ($P = 0.003$), but it showed no significant difference between group I and group II ($P = 0.247$), and between group II and group III ($P = 0.375$). MACE, major adverse cardiac events; HF, heart failure; YSR, year survival rate.

Predictors of MACE

To identify independent predictors of MACE, multiple Cox regression analysis was performed, and the results were summarized in Table 4.

Older age (HR 1.037, 95% CI 1.027–1.046, $P < 0.001$), number of CV risk factors ≥3 (HR 1.438, 95% CI 1.155–1.790, $P = 0.001$), LVEF (HR 0.977, 95% CI 0.970–0.985, $P < 0.001$), multi-vessel disease (HR 1.248, 95% CI 1.023–1.522, $P = 0.029$), and earlier onset of HF development after index MI ($P = 0.017$), beta-blocker use (HR 0.640, 95% CI 0.506–0.808, $P < 0.001$), and ACEi or ARB use (HR 0.620, 95% CI 0.488–0.788, $P < 0.001$) were independent predictors for MACE.

A subgroup analysis on STEMI and NSTEMI

Among 771 STEMI patients, HF was developed in 328 patients at the time of hospitalization (group I, 42.5%), in 58 patients during hospitalization (group II, 7.5%), and in 34 patients after discharge (group III, 4.4%). HF was not developed in the remaining 351 STEMI patients (group IV: 45.5%). Whereas, HF was developed in 299 patients at the time of hospitalization (group I, 25.9%), in 104 patients during hospitalization (group II, 9.0%), and in 64 patients after discharge (group III, 5.5%) and HF was not developed in the remaining 687 patients (group IV: 59.5%) among a total of 1,154 NSTEMI patients. Kaplan-Meier survival curves for MACE showed significant difference among 4

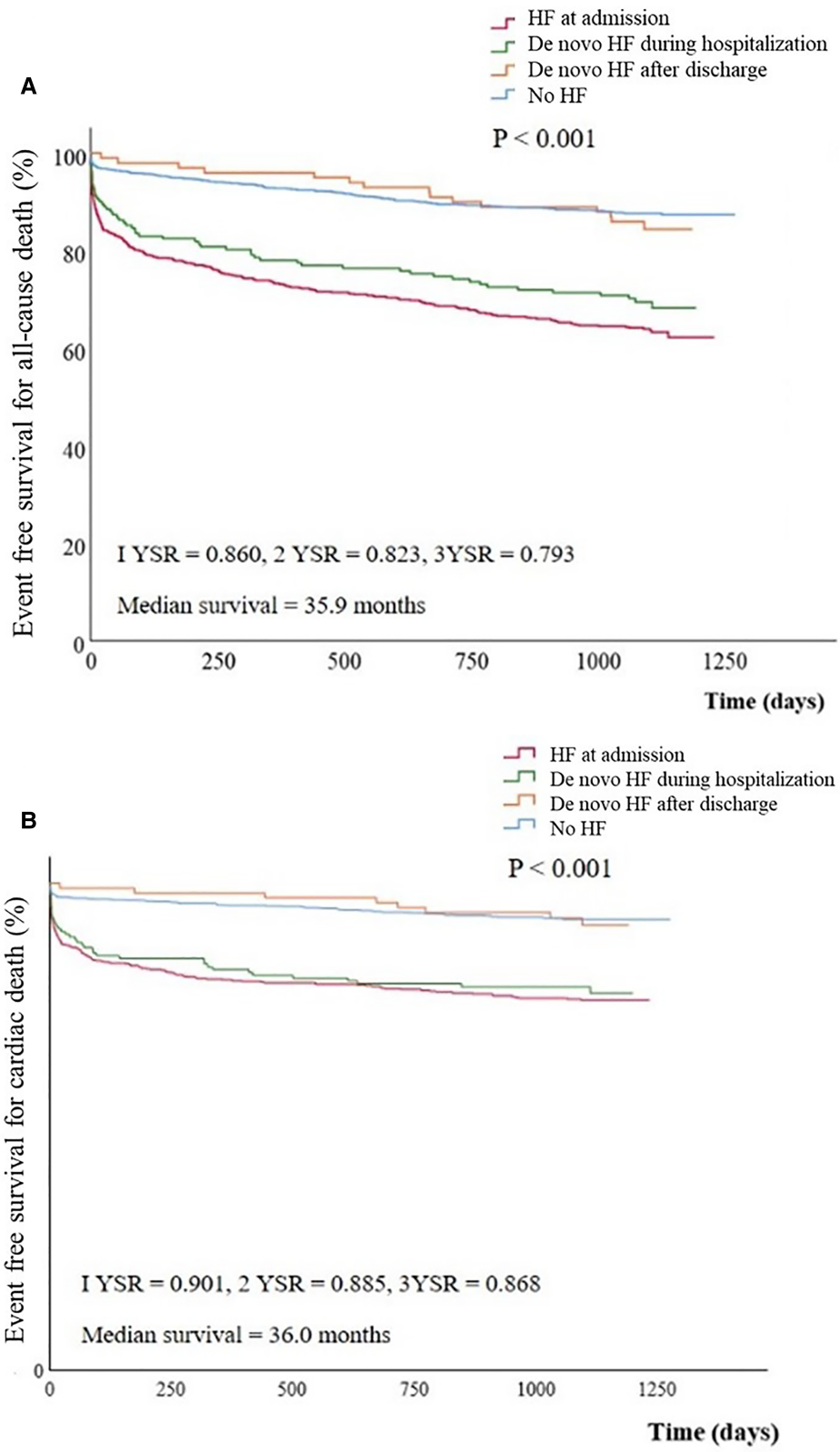

FIGURE 2
Event free survival curves for All-cause death (**A**) and cardiac death (**B**) stratified by groups. Cumulative all-cause (**A**) or cardiac death (**B**) free survival was significantly lower in group I or II than in group III or IV. (**A**) group I vs. group II, $P = 0.100$; group II vs. group III, $P = 0.013$; group III vs. group IV, $P = 0.426$; group I vs. group IV; $P < 0.001$ (**B**) group I vs. group II, $P = 0.100$; group II vs. group III, $P = 0.007$; group III vs. group IV, $P = 0.713$; group I vs. group IV, $P < 0.001$. HF, heart failure; YSR, year survival rate.

TABLE 4 Predictors for major adverse cardiac events.

Variables	HRs (95% CI)	
	Univariate analysis	Multivariate analysis
Age, years	1.044 (1.037–1.052)*	1.037 (1.027–1.046)*
Sex, male	1.433 (1.217–1.689)*	1.037 (0.844–1.273)
CV risk factors, <3 vs. ≥3	1.365 (1.137–1.639)*	1.438 (1.155–1.790)*
LVEF	0.957 (0.948–0.966)*	0.977 (0.970–0.985)*
Multi-vessel disease	1.264 (1.068–1.496)*	1.248 (1.023–1.522)*
Onset of HF Development, late vs. early		
Group IV	1	1
Group I	2.349 (1.973–2.796)*	1.400 (1.123–1.744)*
Group II	1.997 (1.515–2.633)*	1.332 (0.960–1.847)
Group III	1.670 (1.176–2.373)*	1.415 (0.973–2.059)
Beta-blocker Use	0.400 (0.339–0.472)*	0.640 (0.506–0.808)*
ACEi or ARB Use	0.345 (0.292–0.408)*	0.620 (0.488–0.788)*

*P-values <0.05. ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; LVEF, left ventricular ejection fraction. Group I, HF at admission; Group II, *de novo* HF during hospitalization; Group III, *de novo* HF after discharge; Group IV, no HF during follow-up.

groups in STEMI and NSTEMI patients ($P < 0.001$). However, in the results of z-test at 360, 720, and 1,080 days of STEMI patients, there were no statistical differences among the 4 groups at 1,080 days ($P = 0.123$). These findings are added in the **Supplementary Figure S4**. Multivariate analysis showed different results in several variables when STEMI and NSTEMI were analyzed separately. This finding is also added as a **Supplementary Table S1**.

Discussion

The present study investigated the timing of HF development and its relevance to clinical outcomes in patients with AMI and demonstrated several clinically important findings. First, HF was not uncommon and can develop at any time after an index AMI including post-discharge periods. Second, regardless of the timing, the development of HF in patients with AMI was significantly associated with poor clinical outcomes. Third, the pre-discharge development of HF (at admission or during hospitalization) was associated with poorer clinical outcomes including all-cause or cardiac death in patients with AMI as compared to those with the post-discharge or no HF development. Fourth, age, LV function, number of CV risk factors, multi-vessel disease, and earlier onset of HF development were significant predictors of MACE. To initiate optimal guideline directed medical therapy for HF and improve clinical outcomes, therefore, the development of acute *de novo* HF in AMI patients who had no HF at the time of admission should be carefully monitored not only in the initial hospitalized period, but also in post-discharge period, especially in AMI patients with older age, higher level of cardiac troponin, and lower LV EF (**Supplementary File**).

The current universal definition of myocardial infarction and heart failure were released in 2018 and 2021, respectively (10, 17). The current definition of myocardial infarction indicates the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia. The current universal definition represents HF as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. In this study, we included patients enrolled before the release of the current guidelines, however there were no patients who were excluded from enrollment due to the changes of the definition.

HF can develop in any time after an index AMI, it occurred simultaneously with AMI in one-third of all cases, while it did not occur at all in a half of all cases in the present study. Among the baseline characteristics, it is demonstrated to be most favorable in the group IV and worst in the group I, in regards to the important clinical indicators such as older age, higher CV risk, diminished LVEF, multivessel disease. This means that patients with poor clinical indicators are more susceptible to HF development after MI. Meanwhile, previous history of HF was not significantly associated with the presence of HF or the onset of HF development after AMI.

There have been several studies reporting the outcomes and natural history of HF after AMI. A. Torabi et al. demonstrated that HF occurred in 62.7% of all subjects with MI, which was higher than our study results (18). In addition, almost one-third of patients who did not have HF at the time of discharge developed HF after discharge, which was also much higher than the result of our study. In the study, authors categorized HF groups according to early mortality, timing of onset, and persistence. Long-term prognosis of patients without HF at any time demonstrated most favorable, which is similar to our result. Another study demonstrated the increasing trend of HF development after MI over time; 5-year incidence of HF after MI was 27.6% in 1970s and rose up to 31.9% in 1990s (19). However in the recent study by Desta et al., the incidence of HF after MI declined from 46% to 28%, regardless of the onset of HF, between 1996 and 2008 (7). Limited and conflicting data may have contributed to the inconsistent results on the incidence and prognosis of HF after MI.

In the present study, event-free survival rates for MACE were significantly different according to the timing of HF occurrence. It is perceptible when considering that the baseline characteristics of groups were statistically different. Obviously, group I demonstrated the worst, and group IV demonstrated the most favorable prognosis. MACE is more likely to occur in patients who develop HF at least once, even after the discharge, compared to those who never develop HF during follow-up period. Unlikely, survival rates for all-cause mortality and cardiac death were favorable in patients who did not develop HF until discharge compared to those who developed during hospitalization. All-cause death and cardiac death were similar in patients who did not develop HF until discharge, whether HF developed or not after the index discharge. There were two different timing of delayed onset of HF after MI, in-hospitalization (group II) vs. after discharge (group III). Critical risk factors of HF including presence of pulmonary edema,

higher Killip class, enlarged LV cavity size and diminished LV EF were significantly different between those two groups. The event-free survival for MACE was similar, and the overall survival for all-cause mortality and cardiac death were different between those two groups. This also supports that the earlier development of HF could be one of major risk factors of poor prognosis after MI. For better outcome, it is necessary to provide proper guideline-directed medical therapy for patients who have already experienced HF after MI, and to give close monitoring for patients who did not develop HF before their discharge as well.

There are several potential limitations in this study. First, the present study has inevitable limitations of retrospective study such as selection bias, inhomogeneity of the use of medications or percutaneous coronary intervention related parameters including reperfusion status, etc. These limitations of retrospective should be carefully considered in the interpretation of the results of this study. Second, number of group II and III were small and even unequal although relatively large number of study population, which could result in limited statistical power. Third, the diagnosis of HF was based on the symptoms and signs, which could be subjective and inaccurate indicators. However, criteria for the definition of HF also included chest x-ray and level of serum BNP to improve specificity. Fourth, the time interval of AMI onset to admission may differ for each patient, there remains a possibility of confounding bias on clinical outcomes. Further in this study, there is a possibility of immortal time bias on clinical outcomes of our study because of its retrospective design. Lastly in this study, not the timing of HF resolution but the timing of HF development was highlighted. It is likely that the temporal trends in HF after MI are associated with prognosis, not only with the development but also with its progression or improvement. In the future, the prognostic value of the temporal trends in HF after MI will be established more precisely in multicenter, prospective, larger population studies.

Conclusions

HF development after MI is a major cause of CV morbidity and mortality. The earlier development of HF after MI is one of the independent prognostic predictors in patients with MI. To provide better outcome, careful monitoring and the guideline-directed optimal medical therapy for HF should be provided earlier in patients with MI.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

HK and KK contributed to conception and design of the study. NL and HP organized the database. JC and HY performed the statistical analysis. HK wrote the first draft of the manuscript. YA, MJ and JGC wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1193973/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Cumulative major adverse cardiac events free survival curves, No HF vs HF during hospitalization ($P < 0.001$).

SUPPLEMENTARY FIGURE S2
Cumulative major adverse cardiac events free survival curves, HF never vs HF ever ($P < 0.001$).

SUPPLEMENTARY FIGURE S3
A 30-day landmark analysis for event free survival curves for major adverse cardiac events (**A**) and all-cause death (**B**) stratified by groups. The MACE showed a difference between the 4 groups after 150 days. All-cause death was analyzed to have a difference between the 4 groups after 180 days. The prognostic analysis between the 4 groups showed no differences at 30 days.

SUPPLEMENTARY FIGURE S4
Event free survival curves for major adverse cardiac events (**A**) and all-cause death (**B**) stratified by groups in STEMI (**A**) and NSTEMI (**B**).

SUPPLEMENTARY TABLE S1
Predictors for major adverse cardiac events in STEMI and NSTEMI.

SUPPLEMENTARY TABLE S2
Analysis for proportional hazards for acute de novo HF in AMI patients without HF at the time of admission.

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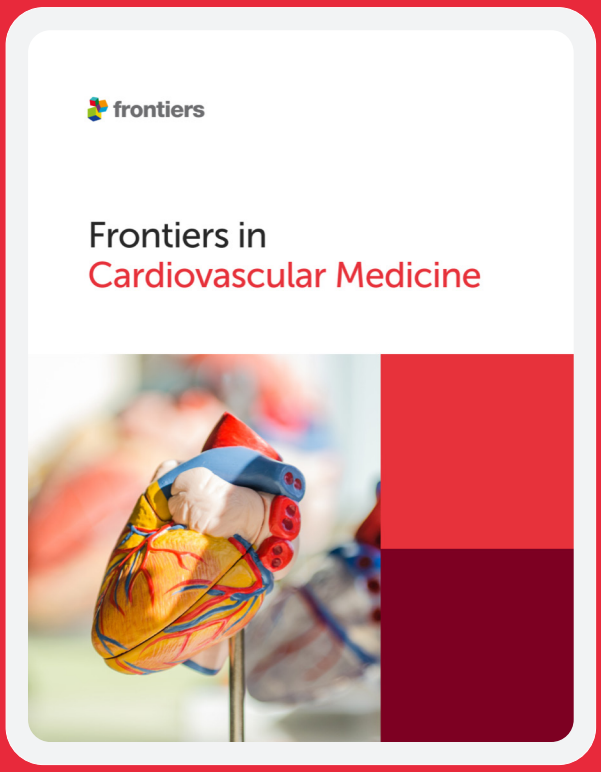

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