ESC European Society of Cardiology

European Journal of Heart Failure (2023) **25**, 773–775
doi:10.1002/ejhf.2954

June 2023 at a glance: focus on worsening heart failure, heart failure with preserved ejection fraction and valvular heart disease

Daniela Tomasoni, Marianna Adamo, and Marco Metra

Cardiology and Cardiac Catheterization Laboratory, Cardio-Thoracic Department, Civil Hospitals; Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy

Worsening heart failure

Episodes of worsening heart failure (HF) are landmark events in the clinical course, followed by an increased risk of hospitalizations and death.[1–5] The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) provided a new definition of worsening chronic HF: worsening symptoms and signs of HF in patients with pre-existing HF, requiring intensification of treatment, most often diuretic therapy. Of note, intensification of treatment also includes escalation of oral diuretics and/or admission to ambulatory or emergency department.[6]

A secondary analysis of the REPORT-HF (prospective international REgistry to assess medical Practice with lOngitudinal obseRvation for Treatment of Heart Failure) registry sought to examine the utilization of healthcare resources for hospitalized patients with HF across the spectrum of left ventricular ejection fraction (LVEF). HF with reduced ejection fraction (HFrEF) was the most prevalent. The length of hospitalization was similar irrespective of LVEF. Prescription of neurohormonal antagonists was suboptimal in HFrEF at discharge, similar to what shown in other registries.[7] The risk of 12-month all-cause and cardiovascular mortality were lower for HF with mildly reduced ejection fraction and HF with preserved ejection fraction (HFpEF), compared to HFrEF.[8,9]

Changes in plasma concentrations of biomarkers may predict the development of HF or worsening HF events.[10–12] Oyama *et al.*[13] investigated the role of three biomarkers – high-sensitivity troponin T (hsTnT), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and growth differentiation factor-15 (GDF-15) – measured at baseline and at 12 months in predicting HF outcome among patients with atrial fibrillation enrolled in the ENGAGE AF-TIMI 48 trial. Serial measurement of hsTnT, NT-proBNP, and GDF-15 revealed that higher baseline values, and increasing or persistently elevated values over 1 year are associated with higher risk of HF outcomes in patients with atrial fibrillation regardless of HF history or HF phenotype based on LVEF.

Heart failure with preserved ejection fraction

Abnormal pulmonary haemodynamic response to exercise is common in patients with HFpEF.[14] A total of 345 patients (166 HFpEF and 179 controls) underwent ergometry exercise stress echocardiography with simultaneous expired gas analysis. Patients with HFpEF and disproportionate exercise-induced pulmonary hypertension in relation to cardiac output (CO) displayed distinct pathophysiologic features only during exercise. Specifically, they had lower peak oxygen consumption, depressed right ventricular (RV) systolic function, impaired RV–pulmonary artery coupling, limitation in CO augmentation, more right-sided congestion, and worse ventilatory efficiency.[15]

Left atrial (LA) enlargement and dysfunction is a pathophysiologic hallmark of HFpEF and often contributes to an increase in pulmonary pressures.[16] Gard *et al.*[17] investigated the association between LA volume and pulmonary arterial haemodynamics in patients with HFpEF. Overall, 85 patients who underwent exercise right heart catheterization and echocardiography were retrospectively included. LA enlargement was associated with blunted increases in CO during exercise, higher resting mean pulmonary artery pressure, similar wedge pressure and an abnormal pulmonary vascular resistance–compliance relationship.

Cardiac amyloidosis (CA) may be a cause of HFpEF.[18] Its prevalence remains uncertain due to frequent misdiagnosis.[19–21] An Italian multicentre study investigated the different pathways leading to the diagnosis of wild-type transthyretin (ATTR-wt) CA. The HF pathway was the one most frequently observed (i.e. about a half of ATTR-wt CA), and associated with older age and more advanced New York Heart Association (NYHA) class. Additional diagnostic pathways were a previous diagnosis of hypertrophic cardiomyopathy (7%), incidental imaging (23%) and incidental clinical assessment (19%). The prognosis was associated with age, NYHA class and comorbidities, rather than the diagnostic pathway.[22]

Valvular heart disease

Mitral regurgitation (MR) has a negative prognostic impact in patients with chronic HF.[23] Mitral transcatheter edge-to-edge repair (M-TEER) is a well-established therapeutic option for these patients[10] and many clinical and echocardiographic parameters have been found to be prognostically relevant in these patients undergoing M-TEER.[24–27] However, the impact of cardio-hepatic syndrome (CHS) in this setting is unknown, differently from patients with HF and/or tricuspid regurgitation (TR).[28,29] Stolz *et al.*[30] investigated the impact of both types of CHS: (1) ischaemic type I CHS (elevation of both transaminases) and (2) cholestatic type II CHS (elevation of two out of three parameters of hepatic cholestasis), among 1083 patients who underwent M-TEER for primary or secondary MR. Ischaemic type I and cholestatic type II CHS were observed in 11.1% and 23.0% of patients, respectively. CHS was associated with a significant increase in 2-year mortality.

Transcatheter mitral valve replacement (TMVR) may represent an alternative option for MR correction in patients at prohibitive surgical risk and unfavourable anatomy for M-TEER.[31,32] However, haemodynamic complications (i.e. left ventricular outflow tract obstruction and afterload mismatch) pose new intriguing challenges towards these new devices. Hungerford *et al.*[33] proposed a review about peri-procedural management of patients undergoing TMVR.

The prognostic impact of secondary TR was investigated in a large database including 13 469 patients with HF. Severe secondary TR was found in 11% of these patients and was most common in patients with HFrEF. Moderate and severe TR were associated with excess mortality independent of HF subtype.[34] These findings may have important clinical implications because of a growing interest in new percutaneous devices for TR treatment.[35]

Left atrial pressure monitoring

The VECTOR-HF study was the first in-human, single-arm, prospective trial enrolling 30 HF patients to examine a wireless, remote monitoring of LA pressure. An interatrial miniaturized device was positioned and after 3 months a right heart catheterization was performed to correlate mean pulmonary capillary wedge pressure with simultaneous mean LA pressure obtained from the device. The system proved to be safe and well-tolerated. Moreover, significant improvements in NYHA class and 6-min walking test distance were reported in the patients with this device.[36]

Clinical trials

The impact of sex differences in the generalizability of randomized clinical trials (RCTs) in HFrEF was assessed in a study including data from two HF registries and five HF RCTs. Three subpopulations were obtained: one RCT population ($n = 16\,917$; 21.7% female), registry patients eligible for RCT inclusion ($n = 26\,104$; 31.8% female), and registry patients ineligible for RCT inclusion ($n = 20\,810$; 30.2% female). Females enrolled in trials displayed a lower mortality compared to similar females in registries, while males in RCTs showed a greater than expected mortality in trials compared to similar males in registries. Overall, female participants in RCTs were fewer than males,[37] consistent with previous analyses and despite the impact of sex on the response to therapy.[38,39]

References

1. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, *et al.* Universal definition and classification of heart failure: A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail* 2021;**23**:352–380. doi: 10.1002/ejhf.2115
2. Kimmoun A, Takagi K, Gall E, Ishihara S, Hammoum P, El Beze N, *et al.*; METAHF Team. Temporal trends in mortality and readmission after acute heart failure: A systematic review and meta-regression in the past four decades. *Eur J Heart Fail* 2021;**23**:420–431. doi: 10.1002/ejhf.2103
3. Labrosciano C, Horton D, Air T, Tavella R, Beltrame JF, Zeitz CJ, *et al.* Frequency, trends and institutional variation in 30-day all-cause mortality and unplanned readmissions following hospitalisation for heart failure in Australia and New Zealand. *Eur J Heart Fail* 2021;**23**:31–40. doi: 10.1002/ejhf.2030
4. Hariharaputhiran S, Peng Y, Ngo L, Ali A, Hossain S, Visvanathan R, *et al.* Long-term survival and life expectancy following an acute heart failure hospitalization in Australia and New Zealand. *Eur J Heart Fail* 2022;**24**:1519–1528. doi: 10.1002/ejhf.2595
5. Girerd N, Mewton N, Tartiere JM, Guijarro D, Jourdain P, Damy T, *et al.* Practical outpatient management of worsening chronic heart failure. *Eur J Heart Fail* 2022;**24**:750–761. doi: 10.1002/ejhf.2503
6. Metra M, Tomasoni D, Adamo M, Bayes-Genis A, Filippatos G, Abdelhamid M, *et al.* Worsening of chronic heart failure: Definition, epidemiology, management and prevention. A clinical consensus statement by the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2023;**25**:776–791. doi: 10.1002/ejhf.2874
7. Tomasoni D, Fonarow GC, Adamo M, Anker SD, Butler J, Coats AJS, *et al.* Sodium-glucose co-transporter 2 inhibitors as an early, first-line therapy in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail* 2022;**24**:431–441. doi: 10.1002/ejhf.2397
8. Farmakis D, Tromp J, Marinaki S, Ouwerkerk W, Angermann CE, Bistola V, *et al.* Impact of left ventricular ejection fraction phenotypes on healthcare resource utilization in hospitalized heart failure: A secondary analysis of REPORT-HF. *Eur J Heart Fail* 2023;**25**:818–828. doi: 10.1002/ejhf.2833
9. Tromp J, Beusekamp JC, Ouwerkerk W, van der Meer P, Cleland JGF, Angermann CE, *et al.* Regional differences in precipitating factors of hospitalization for acute heart failure: Insights from the REPORT-HF registry. *Eur J Heart Fail* 2022;**24**:645–652. doi: 10.1002/ejhf.2431
10. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. doi: 10.1002/ejhf.2333
11. Meijers WC, Bayes-Genis A, Mebazaa A, Bauersachs J, Cleland JGF, Coats AJS, *et al.* Circulating heart failure biomarkers beyond natriuretic peptides: Review from the Biomarker Study Group of the Heart Failure Association (HFA), European Society of Cardiology (ESC). *Eur J Heart Fail* 2021;**23**:1610–1632. doi: 10.1002/ejhf.2346
12. Nunez J, de la Espriella R, Rossignol P, Voors AA, Mullens W, Metra M, *et al.* Congestion in heart failure: A circulating biomarker-based perspective. A review from the Biomarkers Working Group of the Heart Failure Association, European Society of Cardiology. *Eur J Heart Fail* 2022;**24**:1751–1766. doi: 10.1002/ejhf.2664
13. Oyama K, Giugliano RP, Ruff CT, Berg DD, Jarolim P, Tang M, *et al.* Serial assessment of biomarkers and heart failure outcomes in patients with atrial fibrillation. *Eur J Heart Fail* 2023;**25**:832–841. doi: 10.1002/ejhf.2844
14. Guazzi M, Wilhelm M, Halle M, Van Craenenbroeck E, Kemps H, de Boer RA, *et al.* Exercise testing in heart failure with preserved ejection fraction: An appraisal through diagnosis, pathophysiology and therapy – A clinical consensus statement of the Heart Failure Association and European Association of Preventive Cardiology of the European Society of Cardiology. *Eur J Heart Fail* 2022;**24**:1327–1345. doi: 10.1002/ejhf.2601

15. Saito Y, Obokata M, Harada T, Kagami K, Sorimachi H, Yuasa N, *et al.* Disproportionate exercise-induced pulmonary hypertension in relation to cardiac output in heart failure with preserved ejection fraction: A non-invasive echocardiographic study. *Eur J Heart Fail* 2023;**25**:792–802. doi: 10.1002/ejhf.2821
16. Inciardi RM, Bonelli A, Biering-Sorensen T, Cameli M, Pagnesi M, Lombardi CM, *et al.* Left atrial disease and left atrial reverse remodelling across different stages of heart failure development and progression: A new target for prevention and treatment. *Eur J Heart Fail* 2022;**24**:959–975. doi: 10.1002/ejhf.2562
17. Gard EK, Beale AL, Telles F, Silvestry FE, Hanff T, Hummel SL, *et al.* Left atrial enlargement is associated with pulmonary vascular disease in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2023;**25**:806–814. doi: 10.1002/ejhf.2805
18. Tomasoni D, Aimo A, Merlo M, Nardi M, Adamo M, Bellicini MG, *et al.* Value of the HFA-PEFF and H_2FPEF scores in patients with heart failure and preserved ejection fraction caused by cardiac amyloidosis. *Eur J Heart Fail* 2022;**24**:2374–2386. doi: 10.1002/ejhf.2616
19. Merlo M, Pagura L, Porcari A, Cameli M, Vergaro G, Musumeci B, *et al.* Unmasking the prevalence of amyloid cardiomyopathy in the real world: Results from Phase 2 of the AC-TIVE study, an Italian nationwide survey. *Eur J Heart Fail* 2022;**24**:1377–1386. doi: 10.1002/ejhf.2504
20. Aimo A, Merlo M, Porcari A, Georgiopoulos G, Pagura L, Vergaro G, *et al.* Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. *Eur J Heart Fail* 2022;**24**:2342–2351. doi: 10.1002/ejhf.2532
21. Antonopoulos AS, Panagiotopoulos I, Kouroutzoglou A, Koutsis G, Toskas P, Lazaros G, *et al.* Prevalence and clinical outcomes of transthyretin amyloidosis: A systematic review and meta-analysis. *Eur J Heart Fail* 2022;**24**:1677–1696. doi: 10.1002/ejhf.2589
22. Tini G, Milani P, Zampieri M, Caponetti AG, Fabris F, Foli A, *et al.* Diagnostic pathways to wild-type transthyretin amyloid cardiomyopathy: A multicentre network study. *Eur J Heart Fail* 2023;**25**:845–853. doi: 10.1002/ejhf.2823
23. Pagnesi M, Adamo M, Sama IE, Anker SD, Cleland JG, Dickstein K, *et al.* Impact of mitral regurgitation in patients with worsening heart failure: Insights from BIOSTAT-CHF. *Eur J Heart Fail* 2021;**23**:1750–1758. doi: 10.1002/ejhf.2276
24. Bedogni F, Popolo Rubbio A, Grasso C, Adamo M, Denti P, Giordano A, *et al.* Italian Society of Interventional Cardiology (GIse) registry Of Transcatheter treatment of mitral valve regurgitaTiOn (GIOTTO): Impact of valve disease aetiology and residual mitral regurgitation after MitraClip implantation. *Eur J Heart Fail* 2021;**23**:1364–1376. doi: 10.1002/ejhf.2159
25. Adamo M, Pagnesi M, Ghizzoni G, Estevez-Loureiro R, Raposeiras-Roubin S, Tomasoni D, *et al.* Evolution of tricuspid regurgitation after transcatheter edge-to-edge mitral valve repair for secondary mitral regurgitation and its impact on mortality. *Eur J Heart Fail* 2022;**24**:2175–2184. doi: 10.1002/ejhf.2637
26. Caiffa T, De Luca A, Biagini E, Lupi L, Bedogni F, Castrichini M, *et al.* Impact on clinical outcomes of right ventricular response to percutaneous correction of secondary mitral regurgitation. *Eur J Heart Fail* 2021;**23**:1765–1774. doi: 10.1002/ejhf.2316
27. Adamo M, Cani DS, Gavazzoni M, Taramasso M, Lupi L, Fiorelli F, *et al.* Impact of disproportionate secondary mitral regurgitation in patients undergoing edge-to-edge percutaneous mitral valve repair. *EuroIntervention* 2020;**16**:413–420. doi: 10.4244/EIJ-D-19-01114
28. Adamson C, Cowan LM, de Boer RA, Diez M, Drozdz J, Dukat A, *et al.* Liver tests and outcomes in heart failure with reduced ejection fraction: Findings from DAPA-HF. *Eur J Heart Fail* 2022;**24**:1856–1868. doi: 10.1002/ejhf.2649
29. Unterhuber M, Kresoja KP, Besler C, Rommel KP, Orban M, von Roeder M, *et al.* Cardiac output states in patients with severe functional tricuspid regurgitation: Impact on treatment success and prognosis. *Eur J Heart Fail* 2021;**23**:1784–1794. doi: 10.1002/ejhf.2307
30. Stolz L, Orban M, Karam N, Lubos E, Wild M, Weckbach L, *et al.* Cardio-hepatic syndrome in patients undergoing mitral valve transcatheter edge-to-edge repair. *Eur J Heart Fail* 2023;**25**:872–884. doi: 10.1002/ejhf.2842
31. Ben Ali W, Ludwig S, Duncan A, Weimann J, Nickenig G, Tanaka T, *et al.*; CHOICE-MI Investigators. Characteristics and outcomes of patients screened for transcatheter mitral valve implantation: 1-year results from the CHOICE-MI registry. *Eur J Heart Fail* 2022;**24**:887–898. doi: 10.1002/ejhf.2492
32. Wild MG, Kreidel F, Hell MM, Praz F, Mach M, Adam M, *et al.*; TENDER Investigators. Transapical mitral valve implantation for treatment of symptomatic mitral valve disease: A real-world multicentre experience. *Eur J Heart Fail* 2022;**24**:899–907. doi: 10.1002/ejhf.2434
33. Hungerford SL, Dahle G, Duncan A, Hayward CS, Muller DWM. Peri-procedural management of transcatheter mitral valve replacement in patients with heart failure. *Eur J Heart Fail* 2023;**25**:890–901. doi: 10.1002/ejhf.2758
34. Heitzinger G, Pavo N, Koschatko S, Jantsch C, Winter MP, Spinka G, *et al.* Contemporary insights into the epidemiology, impact and treatment of secondary tricuspid regurgitation across the heart failure spectrum. *Eur J Heart Fail* 2023;**25**:857–867. doi: 10.1002/ejhf.2858
35. Russo G, Taramasso M, Pedicino D, Gennari M, Gavazzoni M, Pozzoli A, *et al.* Challenges and future perspectives of transcatheter tricuspid valve interventions: adopt old strategies or adapt to new opportunities? *Eur J Heart Fail* 2022;**24**:442–454. doi: 10.1002/ejhf.2398
36. D'Amario D, Meerkin D, Restivo A, Ince H, Sievert H, Wiese A, *et al.*; VECTOR-HF Trial Investigators. Safety, usability, and performance of a wireless left atrial pressure monitoring system in patients with heart failure: The VECTOR-HF trial. *Eur J Heart Fail* 2023;**25**:902–911. doi: 10.1002/ejhf.2869
37. Schroeder M, Lim YMF, Savarese G, Suzart-Woischnik K, Baudier C, Dyszynski T, *et al.* Sex differences in the generalizability of randomized clinical trials in heart failure with reduced ejection fraction. *Eur J Heart Fail* 2023;**25**:912–921. doi: 10.1002/ejhf.2868
38. Ravera A, Santema BT, Sama IE, Meyer S, Lombardi CM, Carubelli V, *et al.* Quality of life in men and women with heart failure: Association with outcome, and comparison between the Kansas City Cardiomyopathy Questionnaire and the EuroQol 5 dimensions questionnaire. *Eur J Heart Fail* 2021;**23**:567–577. doi: 10.1002/ejhf.2154
39. Whitelaw S, Sullivan K, Eliya Y, Alruwayeh M, Thabane L, Yancy CW, *et al.* Trial characteristics associated with under-enrolment of females in randomized controlled trials of heart failure with reduced ejection fraction: A systematic review. *Eur J Heart Fail* 2021;**23**:15–24. doi: 10.1002/ejhf.2034