ESC HEART FAILURE
ESC Heart Failure (2024)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14727

REVIEW

Editors' highlight picks from 2023 in ESC heart failure

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Abstract

Heart failure is a devastating syndrome affecting an increasingly high number of patients worldwide. Its aetiology and pathogenesis are complex with the involvement of factors ranging from the genetic material through valvular dysfunctions to numerous organs beyond the entire cardiovascular system. Based on continuous efforts of the heart failure scientific community we have witnessed major advances in many related disciplines during the last year. For example, epidemiological aspects—paving the road for improved risk prevention—have been thoroughly analysed for various geographical regions. Additionally, evidence-based approaches now allow the introduction of novel guideline recommended medical therapies (i.e. sodium-glucose transporter 2 inhibitors, and iron supplementation) while basic and translational research aim to explore additional molecular targets for future heart failure diagnostics and medications. All above aspects are addressed in this article, where a selection of articles published in the ESC Heart Failure journal in 2023 are highlighted. The editors are confident that the scientific contributions of ESC Heart Failure effectively served a highly relevant area of cardiovascular research last year.

Keywords Heart failure; HFpEF; HFrEF; Preclinical research; Risk factors; Therapy; Valvular heart disease

Received: 19 January 2024; Accepted: 4 February 2024
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Introduction

The ESC Heart Failure journal was launched by the Heart Failure Association of the European Society of Cardiology (ESC) in 2014, hence it became a teenager in 2024. By recognizing the need for a heart failure specific scientific platform, broader than available back in 2014, ESC Heart Failure has been initiated as the first open access ESC journal to gather contributions from a spectrum of heart failure related research areas. Accordingly, it aimed to embrace not only clinical but also preclinical, social, and economic aspects of heart failure. The inclusive approach of ESC Heart Failure is also well-reflected by the fact that besides heart failure specialists it also offers a forum for nurses, geriatricians, primary care physicians, health economists, and basic researchers.

The 10-year-long history of ESC Heart Failure proves that the initial concepts were appropriate. Soon after its first years the journal entered Scopus and PubMed, and subsequently it received its impact factor from ISI Web of Knowledge/Thomson-Reuters, first for 2018. Of note, ESC Heart Failure was ranked as a Q1 journal in the fields of Cardiology and Cardiovascular Medicine for 2022 in 2023, meaning that the journal has emerged as one of the leading journals in the field of heart failure by now. Thus, the editorial board of ESC Heart Failure, its reviewers and contributing authors deserve recognition for their persistent and generous activities. We also owe an enormous debt of gratitude to the Heart Failure Association of the European Society of Cardiology and the European Journal of Heart Failure for their persistent support that allowed the accession of ESC Heart Failure to the well-respected family of ESC journals.

The editors of ESC Heart Failure of 2023 decided to celebrate the 10-year anniversary of ESC Heart Failure by highlighting a modest collection from the rich content appeared in Volume 10 of the journal in this short review article. In agreement with the central philosophy set for the development of our now 'teenage child', the topics addressed here bring seemingly distant areas of cardiovascular

science together. Nevertheless, we are convinced that for heart failure (affecting many aspects of current medicine), this holistic approach is mandatory.

Risk factors and prevention

Epidemiology of heart failure

The future risk of heart failure (HF), predominantly driven by the rising prevalence of cardiovascular risk factors, is becoming a growing public health concern in several new regions worldwide. For example in Sub-Saharan African, the incidence of previously rare forms of cardiovascular diseases, such as coronary artery disease, is increasing, in concert with historically prevalent forms of disease, such as rheumatic heart disease that are yet to be optimally eradicated.[1]

In Asia, the evidence on the risk factors for incident HF was limited in the past. Now, the Circulatory Risk in Communities Study, involving 5335 Japanese, showed that high body mass index, systolic blood pressure, diastolic blood pressure, diabetes current smokers emerged as important contributors. The accumulation of these risk factors was associated with a graded higher risk of HF.[2] Similarly in Korea, the prevalence and incidence of HF are gradually increasing, especially in men between their 50s and 70s: More concern regarding the management of the risk factors may be needed to prevent HF, particularly in the male group.[3]

In China, data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 observed a steadily decrease in HF prevalence over the past two decades, but an alarming increasing trend in the last few years, especially for women. This trend was attributed to the rise in metabolic risks, and systolic hypertension.[4]

Risk factors in the development of heart failure

The importance of correct management of cardiovascular risk factor in HF prevention has been highlighted by several studies. A prospective population-based Kuopio Ischaemic Heart Disease cohort study comprising men aged 42–60 years and women aged 53–73 years a reported that optimal cardiovascular health (CVH) metrics was associated with lower risk of HF. Thus, by targeting four behavioural [smoking, body mass index (BMI), physical activity, and diet] and three health factors [blood glucose, total cholesterol, and blood pressure (BP)] should be considered also in preventing HF occurrence.[5]

Among potential risk factor favouring the development of HF, frailty and pre-frailty, which are highly common in older age play a major role. While frailty is clinically recognizable by weight loss phenotype, pre-frailty may coexist also with high BMI and worsen the risk of HF incidence.[6]

In maintenance haemodialysis patients, HF is a common complication and the leading cause of mortality. In particular, HF with preserved ejection fraction (HFpEF) is common, and age, diabetes mellitus, coronary artery disease and serum phosphorus are independent risk factors for the incidence of HFpEF while normal urine volume, haemoglobin, serum iron, and serum sodium are protective factors in this setting of patients.[7]

The association of HFpEF with chronic inflammation has been repeatedly recognized. Peri-coronary adipose tissue attenuation on coronary computed tomography angiography is a novel non-invasive marker of peri-coronary inflammation and may be one of the underlying mechanisms of the presence of HFpEF.[8] Furthermore, both mild and moderate kidney dysfunction are independently associated with left ventricular diastolic dysfunction parameters and HFpEF. This association is independent of sex and strongest for moderate kidney dysfunction. Considering mild-to-moderate kidney dysfunction as risk factor for HFpEF may help to identify high-risk groups benefiting most from early intervention.[9]

Cardiac amyloidosis is an under-diagnosed cause of HF and has a worse prognosis than other forms of HF: It is associated with a three-fold greater risk of death and a two-fold greater risk of all-cause hospital readmission 90 days after discharge.[10]

In patients with chronic coronary syndrome (CCS), the incidence of HF is comparable with the incidence of myocardial infarction or stroke, but the mortality risk attributable to new-onset HF is more than 2.5-fold.[11]

Risk prediction in heart failure

Several HF risk scores have been developed; however, there is paucity of study regarding their validation in clinical practice. To overcome this limitation, in a large population of HF patients, the prognostic predictive performance of several risk scores [i.e. Seattle Heart Failure Model (SHFM), Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC-HF) risk score, Get With the Guidelines-Heart Failure programme (GWTG-HF), Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND) risk scores, the Acute Decompensated Heart Failure National Registry (ADHERE) model, Barcelona Bio-Heart Failure (BCN-Bio-HF) risk calculator, and Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure (GISSI-HF)] has been tested: All performed reasonably well in predicting 1 year mortality, with areas under the receiver operating characteristic curve (AUCs) fluctuating between 0.757 and 0.822, but with poor accuracy in assessing patients' risk of readmission.[12] Instead, in patients with advanced HF, both Meta-Analysis Global Group in Chronic HF (MAGGIC-HF) risk score and the model of the Barcelona Bio-HF Risk Calculator

(BCN-Bio-HF) showed suboptimal discrimination and calibration with an underestimation of risk.[13]

In HF, its high readmission rate is a big concern. The identification of potential readmission risk factors may allow to optimize outpatient management to prevent them: older age, home medical care, tolvaptan usage, dosage of loop diuretics, diabetes, and renal disease were all associated with more frequent outpatient visits.[14]

Peak oxygen consumption (VO_2) values measurement obtained by the cardiopulmonary exercise testing is recommended to prioritize patients in the transplant recipient list: Its measurement outperformed Heart Failure Survival Score in predicting 1-year and 2-year major outcomes, with the cut-off value of 10.2 (11.8–7.0) mL/kg min for predicting a 20% risk of a major outcome within 2 years.[15]

In patients with coronary artery disease, admission levels of growth differentiation factor 15 (GDF-15) were associated with an increased 1-year risk of cardiovascular death, HF, and bleeding outcomes, but not with thrombotic events. GDF-15 may be a prognostic biomarker for HF and could be used to refine the risk assessment.[16]

New tools like bioelectrical impedance analysis (BIA) could help to risk prediction and to determine when euvolaemia is reached after an acute event. Among overweight and obese patients with HF, the routine use of BIA reduced NT-proBNP levels at 90 days compared with standard care, with a lower incidence of renal damage.[17]

Valvular heart disease

The importance of valvular heart disease (VHD) in HF was previously pointed out in ESC-HF.[18] The relative importance of concomitant CAD and VHD adds further complexity to VHD-HF link. In particular, for calcific aortic valve disease (CAVD), which shares several pathophysiological components and biomarkers with atherosclerosis.[19] In this years' edition of ESC-HF, tissue plasminogen activator (t-PA), which is associated with CAD, was reported to be further increased in subjects with CAD in at least 1-vessel and concomitant aortic valve sclerosis (AVScl) without significant stenosis (Vmax below 2.0 m/s).[20] The precise mechanisms behind tPA increase and AVScl remain to be established. It is however remarkable that plasminogen has homology in terms of kringle repeats with Lp(a),[19] which is a CAVD risk factor. In addition to tPA valvular effects, higher t-PA levels conferred an increased risk of HF hospitalization or cardiovascular death in the subgroup of CAD patients with AVSc,[20] adding tPA to the possible links between CAVD and HF. CAVD leads to a number of pathophysiological processes affecting cardiac function, including left ventricular hypertrophy (LVH) and fibrosis, impaired LV filling, coronary microvascular dysfunction, and chronic subendocardial ischaemia.[21] Transcatheter aortic valve implantation (TAVI) has been reported to lead to improved cardiac function, but HF readmission is still a clinical problem.[21] Reports published in ESC Heart Failure during 2023 confirmed that myocardial fibrosis[22] and LVH[23] were associated with adverse outcomes after TAVI, and also added novel important pieces of information. First, that the degree of aortic valve calcification was inversely associated with post-TAVI mortality in subjects with high myocardial fibrosis[22] suggests prominence of an underlying cardiomyopathy. Second, the reversed LVH after TAVI was accompanied by an increased scintigraphic heart-to-mediastinum (H/M) ratio,[23] suggesting a link between LVH and sympathetic dysfunction in AS and their reversibility after TAVI. In addition, the presence of systolic coronary flow reversal (SFR), defined as the presence of a reversal coronary flow component in systole, before TAVI was associated with more severe AS, and exhibited an increased systolic coronary flow after TAVI.[24] An ESC-HF review by Matsushita et al. highlights the mechanisms and determinants of HF following TAVI and raised the notion of potential beneficial HF treatments after TAVI.[21]

In addition to TAVI, ESC Heart Failure provided important updates on also transcatheter mitral valve repair (TMVr) in 2023. Reduction of secondary MR in patients with HF with reduced ejection fraction (HFrEF) was associated with improved prognosis and that final MR grade, rather than the MR cause, determined the prognosis.[25] Reports in ESC Heart Failure have also specifically looked at interventional treatment in special MR subpopulations. For example, the multi-centre study EXPAND showed that acutely ill patients in NYHA class IV achieved significant MR reduction as well as improvement in functional capacity and Quality of Life, suggesting that TMVr is a safe and effective strategy to reduce MR in acute HF.[26]

Patients with acute decompensated HFpEF patients have a poor 5-year prognosis with CV causes of half of the mortality cases observed in two thirds after 5 years, for which CAD and tricuspid regurgitation (TR) were predictive factors.[27] In the Japanese Kyoto Congestive Heart Failure (KCHF) registry, increased TR severity was associated with a proportional increase in all-cause mortality and HF hospitalization.[28] Remarkedly, among 993 patients with moderate/severe TR, the number of patients who underwent surgical intervention for TR within 1 year was only 13 (1.3%).[28] To address the optimal timing for tricuspid valve repair, L'Official et al. reported a prognostic model for predicting clinical events in patients with isolated functional TR, including right atrial volume index (RAVI) and the tricuspid annular plane systolic excursion to systolic pulmonary arterial pressure (TAPSE/sPAP) ratio for predicting the risk for event at 2 year follow-up in patients with an isolated functional TR.[29] TR is a common finding in amyloidosis, which may either be functional or due to valvular infiltration by amyloid deposits, causing decreased valvular elasticity and leaflet thickening.[30] Transcatheter tricuspid valve repair (TTVR) is now emerging alternative to surgery. In the specific subgroup of cardiac amyloidosis, the initial experience

with TTVR in a series of 8 amyloidosis patients could achieve a reduction of TR grade in all cases, with a persistent reduction at the 3 months post-implantation follow-up.[31]

Treatment

Guideline recommended medical therapy for heart failure

The recent update of the HF guidelines of the European Society of Cardiology (ESC) has focussed on the introduction of sodium-glucose transporter 2 inhibitors (SGLT2i).[32] The most robust evidence in HF is available for dapagliflozin and empagliflozin that now have class IA recommendations for HF across the entire spectrum of left ventricular ejection fraction (LVEF), that is, HFrEF, HFpEF, and HF with mildly-reduced ejection fraction (HFmrEF). Recently, the cost-effectiveness of the treatment with SGLT2i has been established for empagliflozin and for dapagliflozin in HF patients with LVEF $>$40%[33] in several regions across the globe.[34,35] A recent systematic review that included data of 83,878 patients from 12 randomized controlled trials found that the use of the SGLT2is canagliflozin, empagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin is associated with reduced odds to develop atrial fibrillation (odds ratio [OR] = 0.83, 95% confidence interval [CI]: 0.68–1.01), reduced odds for HF hospitalization (OR = 0.69, 95% CI: 0.60–0.78), for cardiovascular death (OR = 0.82, 95% CI: 0.58–1.15), and for major adverse cardiovascular events (OR = 0.90, 95% CI: 0.77–1.06).[36] In line with recent data from another systematic review, SGLT2 inhibitors significantly improve the quality of life in HF patients. With regard to the susceptibility to atrial fibrillation, a recently published animal model found that dapagliflozin reduces pulmonary vascular damage and right heart dysfunction as well as the susceptibility to atrial fibrillation in rats.[37] A Bayesian approach to a network meta-analysis found no significant difference of the major efficacy outcomes among SGLT2i treatments. Interestingly, whilst sotagliflozin showed a trend towards the lowest risk of the composite of cardiovascular death or hospitalization for HF, dapagliflozin was associated with the lowest risk of all-cause and cardiovascular mortality.[38] With SGLT2is forming the fourth cornerstone of HF treatment, vericiguat is awaiting additional trials in patients with stable HF to potentially become the fifth cornerstone[39] in the near future as it is currently indicated in patients after a worsening HF event only.

Iron deficiency

Another key element of change in the clinical update of the ESC HF guidelines focussed around the treatment of iron deficiency (ID). A class IA recommendation is now available for intravenous iron supplementation to alleviate HF symptoms and improve quality of life. A product name is not any longer given for this indication.[32] A class IIa recommenadation has been provided for ferric carboxymaltose or ferric derisomaltose that should be considered in symptomatic patients with HFrEF and HFmrEF and ID, to reduce the risk of HF hospitalization. Indeed, the beneficial effects of treating iron deficiency in HF have been highlighted by several meta-analyses that demonstrated that intravenous iron infusion in patients with HF reduces the composite risk of first hospitalization for HF and cardiovascular mortality as well as the risk of first and recurrent hospitalizations for HF, with no or negligible effect on all-cause mortality or cardiovascular mortality alone.[40,41] Another recent meta-analysis has shown that oral iron supplementation can increase serum iron levels in patients with HF and ID or mild anaemia but does not improve transferrin saturation and the distance covered in the 6-minute walking test.[42] In addition, oral iron supplementation is relatively safe. The concern that has recently been raised for intravenous ferric carboxymaltose concerning the occurrence of hypophosphataemia remains a matter of ongoing debate and has recently been called into question again.[43]

The importance of treating ID is also highlighted by the high prevalence of ID in patients with HF.[44] In a French registry including 1661 patients with HF, most of whom had decompensated HF, the overall prevalence of iron deficiency was 49.6%. Interestingly, patients with preserved LVEF were more likely to have iron deficiency (57.5%) compared with patients with mildly reduced (47.4%) or reduced LVEF (44.3%) ($P < 0.001$).[45] The presence of ID is directly related to exercise capacity and physical function, even though the presence of diabetes mellitus seems to ameliorate this relation.[46] The correct definition of iron deficiency as ferritin $<$100 ng/L or ferritin 100–299 ng/L together with transferrin saturation $<$20% remains a matter of ongoing debate, even though no better recommendation has been reached in HF so far.[47,48]

Preclinical and translational investigations

Preclinical and translational investigations frequently aim at the molecular drivers of HF pathogenesis. Accordingly, interactions between metabolic, microvascular, inflammatory, and haemodynamic parameters are analysed to reveal fine details of myocardial dysfunction in HF phenotypes with distinct aetiologies ranging from Takotsubo cardiomyopathy[49] through severe functional mitral regurgitation,[50] HF complicated by pulmonary hypertension,[51] and HF patients with coronary artery disease (CAD)[52,53] to peripartum cardiomyopathy.[54]

Recognition of genetic variants co-segregating with congenital heart disease (CHD) is instrumental for early prenatal diagnosis. Yi et al. conducted a translational investigation on a cohort of 398 foetuses with CHD using high level genetic analyses: copy number variant-sequencing (CNV-seq) and exome sequencing (ES). Importantly, CNV-seq and ES revealed genetic abnormalities in almost 1/3 of foetal CHD cases suggesting that these methods can significantly advance diagnostic efforts, and thus, they will probably provide clinically relevant information for pregnancy management in the future.[55]

Besides genetic predispositions, epigenetic factors are considered to be detrimental during the course of HF specific myocardial remodelling via cardiomyocyte loss, interstitial fibrosis, vascular remodelling,[56] and for both the left and the right ventricles.[57] Short non-coding RNA molecules, called microRNAs (miRNAs) have the potential to regulate gene expression at the post-transcriptional level and thereby to contribute to the HF specific phenotype. In a recent review article of ESC Hert Failure, Gargiulo et al. summarized the currently available information on the significance of miRNAs as biomarkers and potential therapeutic targets in patients with HF.[58] Interestingly, by analysing large publicly available genetic datasets and a mouse model of HF, Liu et al. highlighted miR-103-3p as a potential mediator of cardiomyocyte apoptosis and autophagy via hepatic leukaemia factor (Hlf) related signalling.[59] In another study, miR-124-3p was illustrated to interfere with cardiomyocyte survival following myocardial ischaemia/reperfusion (I/R) injury. In this latter study, I/R dependent miR-124-3p downregulation was linked to the activation of the calpain1-caspase-3-Bax pathway leading to a decrease in Bcl-2 expression and consequently to cardiomyocyte apoptosis. Surprisingly, hydrogen-rich saline solution could alleviate the apoptotic response following I/R injury possibly by scavenging free radicals.[60] In a preclinical study conducted in in vivo and in vitro rodent models, transcription factor 4 (ATF4) was identified as a regulator of apoptosis and fibrosis.[61]

Heart failure associated metabolic derangements develop not only in adults but also in children,[62] and these alterations are further aggravated by diabetic cardiomyopathy where metabolic alterations via dyslipidaemia and subsequent lipid-induced toxicity (i.e. lipotoxicity) harm and limit the function of the cardiovascular system.[63]

Of note, circulating miRNAs can also serve as biomarkers and thus—as suggested by Wagh et al.—they can report, for example on the efficacy of mechanotransduction in halting the progression of HF through regenerative signalling in the myocardium.[64] Moreover, by monitoring a set of DCMi specific miRNAs as biomarkers, miRNAs can be also useful in diagnosing virus-negative inflammatory dilated cardiomyopathy (DCMi).[65]

In a preclinical investigation where cardiac tissue samples of patients with hypertrophic cardiomyopathy (HCM) and of those of rodent hearts were studied the extracellular matrix proteoglycan lumican was recognized as a possible promoter of fibrosis in HCM. This finding sheds new light on the coordination of collagen accumulation in the pathogenesis of HCM.[66]

Collectively, newly recognized genetic factors, molecular interactions, signalling cascades and closely related biomarkers are increasingly considered for improving the diagnosis and/or the treatment of HF.

Summary

The editors illuminate a set of papers in this article: (i) to increase the visibility of the ESC Heart Failure journal, (ii) to raise awareness of the readership of its broad content, and (iii) to encourage submissions from future authors. Here, we narrowed our focus for a collection of contributions published in ESC Heart Failure during 2023, and we acknowledge that many more papers could have been cited based on their scientific qualities.

Conflict of interest

All authors have nothing to declare for this contribution.

Funding

This work was supported by a grant from the National Research, Development, and Innovation Office (K147173 to ZP). Project no. K147173 has been implemented with the support provided by the Ministry of Culture and Innovation of Hungary from the National Research, Development and Innovation Fund, financed under the K_23 'OTKA' funding scheme.

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