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REVIEW

A year in heart failure: updates of clinical and preclinical findings

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Abstract

We witnessed major advances in the management of heart failure (HF) in 2022. Results of recent clinical and preclinical investigations aid preventive strategies, diagnostic efforts, and therapeutic interventions, and collectively, they hold promises for a more effective HF care for the near future. Accordingly, currently available information extends the 2021 European Society of Cardiology guidelines and provides a solid background for the introduction of improved clinical approaches in the number of HF-related cases. Elaboration on the relationships between epidemiological data and risk factors lead to better understanding of the pathophysiology of HF with reduced ejection fraction and HF with preserved ejection fraction. The clinical consequences of valvular dysfunctions are increasingly interpreted not only in their haemodynamic consequences but also in association with their pathogenetic factors and modern corrective treatment possibilities. The influence of coronavirus disease 2019 pandemic on the clinical care of HF appeared to be less intense in 2022 than before; hence, this period allowed to refine coronavirus disease 2019 management options for HF patients. Moreover, cardio-oncology emerges as a new subdiscipline providing significant improvements in clinical outcomes for oncology patients. Furthermore, the introduction of state-of-the-art molecular biologic methods, multi-omic approaches forecast improved phenotyping and precision medicine for HF. All above aspects are addressed in this article that highlights a selection of papers published in ESC Heart Failure in 2022.

Keywords Heart failure; HFpEF; HFrEF; Risk factors; valvular heart disease; therapy; preclinical research

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Introduction

Despite major advances in present time cardiology, heart failure (HF) most probably remains a major health problem in the coming decades worldwide. Results of randomized controlled trials form the backbone of the management of this syndrome. Nevertheless, with the advent of novel diagnostic/therapeutic approaches and better understanding of the pathophysiology of HF, a number of new questions arise. Finding the proper responses for these questions paves the way for better HF management in the years to come. In this review article, the editorial team of ESC Heart Failure proudly offers a selection of papers that impressively advanced our knowledge on HF both at the clinical and preclinical levels in 2022.

Risk factors and prevention

Guidelines have called for a greater focus on prevention of HF to curtail its growing burden,[1] but there is lack of studies able to differentially examine the risk of developing for HF with preserved (HFpEF) and reduced ejection fraction (HFrEF). The first race-specific and sex-specific risk prediction model, based on easily obtainable clinical variables, was recently presented as potentially useful tool to implement preventive strategies. The risk prediction model for HFpEF included age, diabetes, higher body mass index, chronic obstructive pulmonary disease, previous myocardial infarction (MI), antihypertensive treatment, systolic pressure, smoking status, atrial fibrillation, and estimated glomerular filtration rate

(eGFR), while the HFrEF model additionally included previous coronary artery disease.[2]

Although HF is common in both men and women, yet disease pathophysiology, presentation and progression differ between sexes. Studies addressing whether biomarkers predict new onset HF sex specifically are scarce. In a study aiming to test the sex specificity of 252 protein biomarkers for new onset HF, no differences between women and men were shown, despite clear differences in biomarkers at baseline, as women had a biomarker profile reflecting activated metabolism and immune responses.[3]

Epidemiological data, that is, prevalence, incidence, mortality, and morbidity, showed geographical variations across the European countries, depending on differences in aetiology, clinical characteristics, and treatment. However, data on the prevalence of the disease are scarce, as are those on quality of life. For these reasons, the HFA of ESC has developed a position paper to comprehensively assess our understanding of the burden of HF in Europe, in order to guide future policies for this syndrome.[4] The burden of HF mortality in China is presented, where HFrEF accounts for less than a fourth of HF patients. One-sixth individuals with HF died in 5 years. HFrEF was associated with a nearly two-fold increased risk of 5 year mortality than HFpEF.[5]

The prevention of cardiac complication in patients after adjuvant breast cancer treatments is discussed by Bikiewicz *et al*.[6] The patho-mechanisms of different chemotherapy and radiotherapy interventions are reviewed, with predictors of cardiovascular damage. The contributions of the new cardio-specific biomarkers in serum and of modern imaging techniques (global longitudinal strain and three-dimensional left ventricular ejection fraction) and genotyping, and especially their combined use in risk prediction are presented. The benefit of a cardio-oncology unit on prevention of cardiovascular events in cancer patients is discussed.[7]

An effective fluid management programme is associated with improving readmission and mortality in HF according to a systemic review.[8] The results encourage attainment of optimal volume status at discharge and prescription of optimal diuretic dose. Ongoing support to maintain euvolaemia and effective collaboration between healthcare teams, along with effective patient education and engagement, may help to reduce adverse outcomes in HF patients.

Risk stratification models of sudden cardiac death (SCD) assume that risk factors of SCD affect risk to a similar extent in both sexes. This assumption has been recently challenged by a cohort study where it is observed that male implantable cardioverter-defibrillator (ICD) patients were at higher risk of SCD compared with female ICD patients, irrespective of an ischaemic or non-ischaemic underlying cardiomyopathy.[9]

While the efficacy of the ICD for primary prevention is not disputed, the relevant studies were carried out more than 20 years ago. Since then, improved therapeutic modalities have lowered present-day rates of mortality and of SDC. Thus, nowadays, ICD therapy may be less effective than previously reported and not as beneficial as many people currently believe. Deckers *et al*. discussed and presented some rational criteria to assist the clinician in improving risk stratification for preventive ICD implantation.[10]

Takotsubo cardiomyopathy (TCM), characterized by reversible ventricular dysfunction, has similar mortality to acute coronary syndrome. With the growing interest in the diagnosis of and interventions for TCM, many risk factors had been found to affect the prognosis of TCM patients, such as age, sex, and pre-existing diseases. A review found that male sex, physical triggers, and certain co-morbidities such as chronic kidney disease, malignant disease, higher body mass index, sepsis, chronic obstructive pulmonary disease, and anaemia were associated with poor TCM prognosis. There is limited evidence that any commonly used medications confer a survival benefit.[11]

Improvement in exercise capacity and quality of life is among the primary goal for HF patients. Exercise training plays a major role in this topic, but not every patient benefit from such an intervention. Jaarsma *et al*.[12] observed that individuals with lower baseline physical activity and cognitive impairment were less able to benefit from exercise training programme. In fact, patients with very limited exercise tolerance ($<$300 m at the 6 min walk test) were often frail and gained less in exercise capacity.[12] These patients may need a more comprehensive approach to improve exercise capacity, including an individually tailored exercise programme with aerobic exercise (if tolerated) and strength exercises. Two secondary analyses of the OptimEx-Clin (Optimizing Exercise Training in Prevention and Treatment of Diastolic Heart Failure) have shown that in patients with HFpEF, the easily measurable peak O_2 pulse seems to be a good indicator of the potential for improving peak $\dot{V}O_2$ through exercise training[13] and that high intensity interval training only exerts beneficial effect on lipid metabolism.[14]

A consensus document from the ESC Digital Health Committee and the ESC Working Group on e-Cardiology discusses the potential implementation of digital health technology in older adults, suggesting a practical approach to general cardiologists working in an ambulatory outpatient clinic, highlighting the potential benefit and challenges of digital health in older patients with, or at risk of, cardiovascular disease.[15] The benefit of home-based cardiac rehabilitation using information and communication technology for HF patients with frailty was demonstrated in a controlled trial.[16]

Valvular heart disease

The relation between HF and valvular disease (VHD) is complex with difficulties to distinguish primary/organic VHD as an underlying aetiology of HF from secondary/functional

VHD as consequences of myocardial remodelling. Coronary artery disease (53%) and VHD (28%) were the most common HF aetiologies in a retrospective European single-centre study of patients admitted for acute HF during a period of 1 year.[17] A larger cohort from the Indian National Heart Failure Registry determined the cause of the full spectrum of HF being mainly coronary artery disease (71%) and dilated cardiomyopathy (DCM; 18%), whereas VHD represented only 8% of HF causes.[18] It is however notable that rheumatic VHD was the second most common aetiology for HFpEF in India (24%).[18] The Japanese community-based, prospective, observational KUNIUMI registry cohort with a mean age of 79 years found that VHD was the most common cause of chronic symptomatic HF (50%).[19] The VHD prevalence increased in higher age groups for tricuspid and mitral regurgitation as well as aortic stenosis (AS), whereas mitral stenosis was less common in older chronic HF cases.[19] These studies illustrate the close link between HF and VHD, with major geographical and age-related differences. It should also be considered that delays in VHD interventions during the COVID-19 pandemic may have aggravated HF in VHD patients, which was suggested from a systematic review of the relationships between HF and COVID-19 pandemic with respect to epidemiology, pathogenetic mechanisms, and differential diagnoses.[20]

The haemodynamic consequences of AS, which exhibited the most pronounced increase over the age of 85 years in the KUNIUMI cohort,[19] may be decisive for a trajectory towards HF. Right and left heart catheterization in 477 patients undergoing aortic valve replacement (AVR) because of severe AS identified that the lowest mean arterial pressure quartile exhibited lower systemic vascular resistance and lower valvulo-arterial impedance, which may facilitate preserved stroke volume and filling pressures despite reduced left ventricular performance.[21] Nevertheless, low mean arterial pressure was associated with a worse prognosis after AVR,[21] suggesting insufficient left ventricular reserve for a beneficial response to AVR. Left heart catheterization before and after transcatheter aortic valve implantation (TAVI) demonstrated that haemodynamic changes and improved ventricular function were immediate.[22] The latter findings were in line with an echocardiographic improvement of left ventricular strain within 7 days of AVR.[23] However, the left ventricular function changes after AS treatment were not predictive for long-term survival.[22,23] Studies of vascular stiffness have raised the notion of an unmasking of maladaptive ventricular-arterial coupling when left ventricular obstruction is relieved by AS treatment,[24,25] although its prognostic value remains to be established. In a study of AS patients with preserved ejection fraction undergoing TAVI, the HFA-PEFF score[26] was associated with all-cause mortality and HF rehospitalization post-TAVI.[27] These findings point to HFpEF evaluation using the HFA-PEFF score being applicable to AS with a potential to be incorporated into risk stratification algorithms for severe AS. Another potential would be to apply HF evaluation to moderate VHD to predict the disease progression and optimize intervention timing. The latter is supported by a study of 81 patients with moderate and mixed aortic valve disease, in which age and B-type natriuretic peptide levels were associated with adverse events.[28]

In patients with HFrEF, functional mitral regurgitation (MR) is frequently observed and associated with poor prognosis. A recent meta-analysis of edge-to-edge transcatheter mitral repair revealed a lower mortality of patients with functional MR of non-ischaemic compared with ischaemic origin.[29] The novel PASCAL system for transcatheter mitral valve repair showed comparable outcomes in terms of clinical improvement after 1 year compared with MitraClip in a 1:2 propensity-matched cohort of 123 MR cases.[30] Importantly, also medical therapy of HFrEF can improve functional MR, as demonstrated in a retrospective analysis of 159 patients, which showed a reduced MR severity in 57% of the proportion receiving only medical therapy.[31] An echocardiographic MR grading $\leq$2 after either medical therapy optimization or mitral valve intervention was associated improved survival, independently of medical or interventional treatment,[31] suggesting MR reduction as a treatment goal in HFrEF. The latter notion opens an avenue for the discovery of targeted therapies for MR as part of the HFrEF therapeutic strategies. In this direction, a plasma metabolomic and lipidomic analysis in HFrEF patients found that eicosanoids were increased in those with a concomitant functional MR.[32] Eicosanoids are bioactive lipids and comprises enzymatically derived mediators from the lipoxygenase (e.g. leukotrienes), cyclooxygenase (e.g. prostaglandins, thromboxane, and leukotrienes), and cytochrome p450 (e.g. HETE and EET) pathways as well as non-enzymatic oxidative fatty acid metabolites (e.g. isoprostanes).[33] These mediators ligate with specific receptors to not only transduce proinflammatory and prothrombotic responses but also act to be anti-aggregatory and stimulate a resolution of inflammation.[34] Interestingly, increased plasma levels of the eicosanoid 8,9-DiHETrE derived from arachidonic acid through cytochrome p450 was independently associated with all-cause mortality in HFrEF patients with, but not without, functional MR.[32] Although the causal relation of 8,9-DiHETrE with MR and HFrHF outcomes remains to be established, these observations evoke a first suggestion for ASA-independent arachidonic acid metabolism as a novel therapeutic target to be explored in HF. In this context, omega-3 fatty acid treatment alters arachidonic acid bioavailability, although its effects on 8,9-DiHETrE are not consistent in previous reports.[35,36]

The tricuspid valve may have been considered as the forgotten valve for a long time. However, tricuspid regurgitation (TR) is a common VHD aetiology of HF,[19] for which risk scores are emerging for determining prognosis and guiding therapeutic decisions.[37,38] As part of the HF treatment options, Volz *et al*. highlight the novel percutaneous interventions to treat TR. In their single-centre retrospective analysis of 11

patients undergoing transcatheter tricuspid valve leaflet repair, using the PASCAL system reduced TR severity and improved cardiopulmonary exercise capacity.[39]

Treatment

The ESC guidelines for the management of HF published in 2021 have introduced new algorithms into the treatment of HF.[1] Much emphasis is on the individualization of therapy and on the need for fast initiation of the four main treatment pillars consisting of an angiotensin-converting enzyme inhibitor or an angiotensin receptor-neprilysin inhibitor, a beta-blocker, a mineralocorticoid receptor antagonist and—as the latest addition to the portfolio—a sodium-glucose cotransporter 2 inhibitor (SGLT2i). Indeed, the two SGLT2is, dapagliflozin and empagliflozin, have shown beneficial effects on morbidity and mortality in both HFrEF and HFpEF. Pandey *et al*. recently confirmed the beneficial effects of SGLT2i using data from four randomized controlled trials (DAPA-HF, EMPEROR-Preserved, EMPEROR-Reduced, and SOLOIST-WHF) including 15 684 patients. They found that the use of SGLT2i reduces cardiovascular death and HF hospitalization rates among patients with HF, regardless of left ventricular ejection fraction (LVEF) status.[40] More recent data suggest that the reduction in hard endpoints is irrespective of the cause of HF, baseline use of MRA, and NT-proBNP level.[41] The underlying mechanisms are, however, only partly understood and embrace certainly much more than mere diuresis. Using data from the EMPA-REG OUTCOME trial, Fitchett *et al*. performed a sub-analysis in order to identify mediators of improvement in HF outcomes. A mediator in this study had to fulfil the following criteria: (i) affected by active treatment, (ii) associated with the outcome, and (iii) adjustment for it results in a reduced treatment effect compared with the unadjusted analysis. In essence, this analysis suggested that changes in haematocrit and haemoglobin levels were the most important mediators of the reduction in HF hospitalizations and death from HF in patients with type 2 diabetes and established CV disease treated with empagliflozin. Levels of albumin, uric acid, and logarithmic urine albumin-to-creatinine ratio had smaller mediating effects in this population.[42] In addition, a recent meta-analysis of randomized cardiac magnetic resonance imaging trials has shown that SGLT2i treatment in patients with HFrEF is associated with larger regression in left ventricular mass than in those treated with placebo.[43]

Kolwelter *et al*. performed a double-blind, randomized, placebo-controlled, parallel-group study in 74 patients with symptomatic HF in New York Heart Association class II-III and a left ventricular ejection fraction of $\leq$49% who were randomized 2:1 to receive 10 mg empagliflozin or placebo for 3 months. Vascular function improved as assessed using central systolic blood pressure, central pulse pressure, forward and reflected pressure pulse height as these parameters decreased under resting conditions after 1 and 3 months in patients treated with empagliflozin. Therefore, the authors concluded that decreased afterload of the left ventricle may contribute to the beneficial effects of SGLT2i in HF.[44] Using isolated myocardial fibroblasts from patients with HFrEF, it was found that dapagliflozin, the angiotensin receptor-neprilysin inhibitor sacubitril-valsartan, and the MRA spironolactone modulate their function through the activation of different signalling pathways. Dapagliflozin, in particular, slowed the migration rate of HFrEF fibroblasts in a dose-dependent manner and markedly decreased the expression of interleukins (IL) IL-6 and IL-1β, matrixmetalloproteinase-3 (MMP3), -9 (MMP9), galectin 3 (GAL3), and fibronectin (FN1). The combination of SGLT2i + LCZ696 showed an additive effect on migration, while spironolactone modifies the signalling pathways activated by SGLT2i and its beneficial effects of biomarkers of HF.[45]

With regard to the individualization of treatment, the treatment of iron deficiency has recently received increasing attention. In patients with HFrEF, it is well established that iron deficiency is associated with reduced quality of life and exercise capacity as well as increased morbidity and mortality.[46] A similar pattern has been described for HFpEF, even though iron deficiency remained independently associated with survival only after multivariable adjustment, but not so for exercise capacity.[47] Another study by Fitzsimons *et al*. found contrasting results. Using data from 1563 patients with HF participating in a prospective international cohort study comparing HFpEF with HFrEF, the prevalence of iron deficiency was similar in patients with HFpEF and in those with HFrEF (58%). Interestingly, patients with iron deficiency were more likely to be female, diabetic, and to have a higher co-morbidity burden. The presence of iron deficiency was negatively prognostic only in HFrEF but not in HFpEF. Over 6 months of follow-up persistence of iron deficiency was strongly associated with mortality, whereas resolution was not.[48] In clinical practice, however, iron deficiency remains underdiagnosed and undertreated.[49] Several intravenous (IV) iron products have been used in HF trials; however, the ESC guidelines currently only recommend ferric carboxymaltose.[50] This recommendation may change after the IRONMAN trial has been published recently that demonstrated beneficial effects of the use of ferric derisomaltose in patients with HFrEF.[51] Indeed, a meta-analysis has recently shown that IV iron-carbohydrate therapy significantly reduces hospitalization for worsening HF [hazard ration with 95% confidence intervals 0.53 (0.42–0.65); $P < 0.0001$] and first hospitalization for worsening HF or death [0.75 (0.59–0.95); $P = 0.016$], but it did not significantly impact all-cause mortality. No significant differences in adverse events were observed between the treatment groups.[50] A retrospective

database analysis has shown that IV iron administration appears to improve ejection fraction and cardiac functional status in outpatients with iron deficiency, HFpEF, and HFrEF.[52]

Another important aspect in the individualization of HF therapy is the use of vericiguat in patients with a recent episode of worsening HF requiring IV diuretic treatment. Using data from the VICTORIA trial, Senni *et al*. found that plasma NT-proBNP may help to identify patients with worsening HFrEF, in whom the beneficial effects of vericiguat may be highest. They concluded that patients with the highest NT-proBNP (values >5314 pg/mL) may be too far advanced, suffering more co-morbidities, or still clinically unstable after decompensation to derive benefit from vericiguat.[53] Oh *et al*. analysed real-world data from the Korean Acute Heart Failure (KorAHF) registry, a multicentre prospective cohort study, that enrolled 5625 patients who were admitted for HF decompensation. Patients were stratified according to VICTORIA enrolment criteria and evaluated whether they would be candidates for treatment with vericiguat. Therefore, the authors excluded patients without LVEF quantification, patients with LVEF >45%, patients with in-hospital death or urgent heart transplantation, and patients without natriuretic peptide measurement. Among a total of 3014 enrolled patients, there were 21.9% patients with lower systolic blood pressure (<100 mmHg) and 20.1% patients without elevated natriuretic peptides. Regarding chronic kidney disease (CKD) status, 5.1% patients had CKD stage V [eGFR $<$ 15 mL/min/1.73 m^2] and 11.8% patients had CKD stage IV ($15 \leq$ eGFR $<$ 30 mL/min/1.73 m^2). In summary, 94.9% met the label criteria, while 58% met the inclusion criteria of the VICTORIA trial.[54]

Preclinical and translational investigations

Extrapolation of experimental results from animal models to human pathologies is often complicated by species differences. Hence, the inclusion of human tissue materials in preclinical studies is highly recommended. In their review article, Zhu *et al*. aimed at the facilitation of translational research and precision medicine through analysing current methods and considerations of cardiovascular tissue biobanking and databasing. The techniques shared also holds promises for personalized medical care.[55]

Normalization of left ventricular structure and function, referred to as reverse remodelling, is a desired aim by therapeutic interventions in HF patients. Nevertheless, despite effective neurohumoral inhibition, a number of HF associated abnormalities may persist at the molecular, cellular, and interstitial levels rendering the myocardium susceptible for dysfunction redevelopment in most patients. In their comprehensive review, Hnat *et al*. elaborated the distinctions between reverse remodelling and true myocardial recovery and also addressed current evidence on left ventricular reverse remodelling and its prognosis, giving an emphasis on HF patients with non-ischaemic cardiomyopathy, and on novel cardiac medications.[56]

Using a systems biology approach Zhang *et al*. aimed at uncovering the genetic links of SARS-CoV-2 infections with HF co-morbidities. Gene expression profiles of HF and COVID-19 were retrieved from a large database. Authors identified 10–12 genes from a protein–protein interaction study and as a shared transcriptional signature. Interestingly, the importance of the unhealthy microbiota status and a gut–heart axis were emphasized as bridging pathogenic mechanisms between HF and COVID-19.[57]

Dubé *et al*. conducted a pharmacogenomic study of HF and the angiotensin-II receptor blocker, candesartan response from the CHARM programme where their objective was to identify genetic predictors of HF progression and of the efficacy and safety of treatment with candesartan. In short, in their genome-wide association studies, including 2727 patients, they have identified a candidate genetic variant potentially predictive of the progression of HF in patients with preserved ejection fraction. Nevertheless, as also acknowledged by the authors, their findings require further verifications.[58]

Cancer therapies can evoke cardiac dysfunction; nevertheless, the underlying pathophysiological mechanisms and contributing risk factors are only partially understood. Terada *et al*. explored histopathological and epigenetic changes of the myocardium in association with cancer therapy-related cardiac dysfunctions. To these ends, endomyocardial biopsies of autopsied cancer cases and of controls without cancer were compared. Their results indicated distinct morphological characteristics in myocardial histopathology for cancer therapies-related cardiac dysfunctions, and they proposed the mechanistic involvement of epigenetic changes and identified sensitive markers for cardiotoxicity.[59]

Congenital heart disease-associated pulmonary hypertension is a severe condition with unknown mechanism. Relying on a number of complimentary preclinical approaches and animal models, Zhou tested whether synemin, an intermediate filament protein, is involved in the above clinical situation. Importantly, the expression level of synemin was tightly coupled to indices of pulmonary arteriole remodelling, suggestive for a promising therapeutic target in the treatment of congenital heart disease-associated pulmonary hypertension.[60]

The molecular links between MI and subsequent long-term HF development are obscure. Rincón *et al*. aimed at the hypothetical role of circulating miRNAs as prognostic biomarkers in patients presenting with MI. In their prospective study involving 311 consecutive patients hospitalized with MI, 14 candidate miRNAs were analysed. The primary outcome was the composite of hospital admission for HF or cardiovascular death. Based on the results obtained following a

mean follow-up of 2.1 years, miR-21-5p, miR-23a-3p, miR27b-3p, miR-122-5p, miR210-3p, and miR-221-3p reliably predicted the primary outcome, implicating prognostic values of circulating miRNAs for HF-related events among patients with MI.[61]

Factors determining the progression of DCM are also unclear. In their study, Fujita *et al*. tested whether phosphorylation of mixed lineage kinase domain-like protein (MLKL) is associated with the progression of DCM. The results suggest that increased localization of nuclear phosphorylated MLKL in cardiomyocytes is associated with left ventricular diastolic dysfunction and future adverse events in DCM.[62]

Although the nitric oxide (NO) signalling pathway has been implicated in HFpEF, the involvement of this pathway in the pathophysiology of HFpEF is not entirely clear. Piatek *et al*. conducted a clinical study on 73 prospectively enrolled patients. Their results were compatible with impaired NO metabolism in at least a subgroup of patients with HFpEF, and hence, these authors argued for further evaluation of NO-based therapies in HFpEF.[63]

Insulin-like growth factor binding protein 7 (IGFBP7) is a marker of senescence secretome and a novel biomarker in patients with HF. Bracun *et al*. evaluated the prognostic value of insulin-like growth factor binding protein 7 (IGFBP7) in patients with HF. According to the results of this clinical study, IGFPB7 presents as an independent and robust prognostic biomarker in patients with HFpEF and HFrEF. Shortly, IGFBP7 pathways are supposedly involved in different stages of immune system regulation, linking HF to senescence pathways.[64]

The acute phase of a coxsackievirus 3 (CVB3)-induced myocarditis involves direct toxic cardiac effects and the systemic activation of the immune system, including the cardiosplenic axis. In their model study in mice, Pappritz *et al*. tested whether the anti-inflammatory drug colchicine can improve experimental CVB3-induced myocarditis. They found that colchicine improved LV function in CVB3-induced myocarditis, involving a decrease in cardiac and splenic nucleotide-binding oligomerization domain-like receptor pyrin domain-containing-3 (NLRP3) inflammasome activity, without exacerbation of CVB3 load.[65]

Wei *et al*. aimed at determining the proteomic signature for cardiac allograft vasculopathy (CAV), a major long-term complication after heart transplantation. To this end, they measured urinary proteome by capillary electrophoresis coupled with mass spectrometry in 217 heart transplantation recipients. Results of this pilot study not only identified but also validated a urinary proteomic signature implicating a potential approach for the surveillance of CAV.[66]

Nunez-Toldra *et al*. tested the hypothesis whether altered mechanical load in response to injury is a main driver of myocardial interstitial fibrosis. A novel approach, where living myocardial slices (LMS) of human and rodent hearts were included, served as experimental preparations to answer this question. Importantly, LMS responded with fibrotic remodelling to pathological load, which could be modulated by a transforming growth factor beta-blocker.[67]

Taken together, here, we illuminated papers published in ESC Heart Failure during 2022 in selected themes of HF. We are confident that these studies (and others not referenced in this review article) of ESC Heart Failure faithfully illustrate preclinical and clinical efforts around the globe for an improved HF management.

Conflicts of interest

All authors have nothing to declare for this contribution.

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