ESC European Society of Cardiology

European Heart Journal (2019) **40**, 2155–2163
doi:10.1093/eurheartj/ehz158

CLINICAL REVIEW
Controversies in cardiovascular medicine

The continuous heart failure spectrum: moving beyond an ejection fraction classification

**Filippos Triposkiadis[1], Javed Butler[2], Francois M. Abboud[3], Paul W. Armstrong[4], Stamatis Adamopoulos[5], John J. Atherton[6], Johannes Backs[7], Johann Bauersachs[8], Daniel Burkhoff[9], Robert O. Bonow[10], Vijay K. Chopra[11], Rudolf A. de Boer[12], Leon de Windt[13], Nazha Hamdani[14], Gerd Hasenfuss[15], Stephane Heymans[16], Jean-Sébastien Hulot[17,18,19], Marvin Konstam[20], Richard T. Lee[21], Wolfgang A. Linke[22], Ida G. Lunde[23], Alexander R. Lyon[24,25], Christoph Maack[26], Douglas L. Mann[27], Alexandre Mebazaa[28], Robert J. Mentz[29], Petros Nihoyannopoulos[30], Zoltan Papp[31], John Parissis[32], Thierry Pedrazzini[33], Giuseppe Rosano[34], Jean Rouleau[35], Petar M. Seferovic[36], Ajay M. Shah[37], Randall C. Starling[38], Carlo G. Tocchetti[39], Jean-Noel Trochu[40], Thomas Thum[41], Faiez Zannad[42], Dirk L. Brutsaert[43], Vincent F. Segers[44,45], and Gilles W. De Keulenaer[44,46]*

[1]Department of Cardiology, Larissa University Hospital, Larissa, Greece; [2]Department of Medicine-L650, University of Mississippi Medical Center, Jackson, MS, USA; [3]Abboud Cardiovascular Research Center, University of Iowa, Iowa City, IA, USA; [4]Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada; [5]Transplant and Mechanical Circulatory Support Unit, Onassis Cardiac Surgery Center, Athens, Greece; [6]Department of Cardiology, Royal Brisbane and Women's Hospital, University of Queensland School of Medicine, Brisbane, Australia; [7]Department of Molecular Cardiology and Epigenetics, Heidelberg University, Heidelberg, Germany; [8]Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; [9]Cardiovascular Research Foundation, New York, NY, USA; [10]Bluhm Cardiovascular Institute, Northwestern University Feinberg School of Medicine, Northwestern Memorial Hospital, Chicago, IL, USA; [11]Department of Cardiology, Medanta Medicity, Gurugram, Haryana, India; [12]Department of Cardiology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands; [13]Department of Cardiology, Faculty of Health, Medicine and Life Sciences, School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands; [14]Department of Systems Physiology, Ruhr University Bochum, Bochum, Germany; [15]Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover 30625, Germany; [16]Department of Cardiology, CARIM School for Cardiovascular Diseases Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands; [17]Université Paris-Descartes, Sorbonne Paris Cité, Paris, France; [18]Paris Cardiovascular Research Center, INSERM UMR 970, Paris, France; [19]Hôpital Européen Georges Pompidou, AP-HP, Paris, France; [20]The CardioVascular Center of Tufts Medical Center, Boston, MA, USA; [21]Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Harvard University, Cambridge, MA, USA; [22]Institute of Physiology II, University of Münster, Münster, Germany; [23]Institute for Experimental Medical Research, Oslo University Hospital and University of Oslo, Oslo, Norway; [24]Cardiovascular Research Centre, Royal Brompton Hospital, London, UK; [25]National Heart and Lung Institute, Imperial College London, London, UK; [26]Comprehensive Heart Failure Center, University Clinic Würzburg, Würzburg, Germany; [27]Department of Medicine, Center for Cardiovascular Research, Washington University School of Medicine, St. Louis Missouri, MO, USA; [28]Department of Anaesthesiology and Critical Care Medicine, AP-HP, Saint Louis and Lariboisière University Hospitals, Inserm U 942, Paris, France; [29]Duke Clinical Research Institute, Durham, NC, USA; [30]Imperial College London, NHLI, National Heart & Lung Institute, London, UK; [31]Division of Clinical Physiology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [32]Heart Failure Unit, Department of Cardiology, Attikon University Hospital, National and Kapodistrian University of Athens, Athens, Greece; [33]Experimental Cardiology Unit, Department of Cardiovascular Medicine, University of Lausanne Medical School, Lausanne, Switzerland; [34]Department of Medical Sciences, IRCCS San Raffaele, Centre for Clinical and Basic Research, Pisana Rome, Italy; [35]Montreal Heart Institute and University of Montreal, Montreal, Quebec, Canada; [36]School of Medicine, Belgrade University, Belgrade, Serbia; [37]School of Cardiovascular Medicine & Sciences, British Heart Foundation Centre, King's College London, London, UK; [38]Cleveland Clinic, Heart and Vascular Institute, Cleveland, OH, USA; [39]Department of Translational Medical Sciences, Federico II University, Naples, Italy; [40]CIC INSERM 1413, Institut du thorax, UMR INSERM 1087, University Hospital of Nantes, Nantes, France; [41]Institute of Molecular and Translational Therapeutic Strategies, Hannover Medical School, Hanover, Germany; [42]Inserm CIC 1433, Université de Lorrain, CHU de Nancy, Nancy, France; [43]Antwerp University, Antwerp, Belgium; [44]Laboratory of Physiopharmacology, Antwerp University, Universiteitsplein 1, Building T, Wilrijk, Antwerp 2610, Belgium; [45]Division of Cardiology, Antwerp University Hospital, Edegem, Belgium; and [46]ZNA Hartcentrum, Antwerp, Belgium

Received 9 November 2018; revised 5 January 2019; editorial decision 5 March 2019; accepted 8 March 2019; online publish-ahead-of-print 8 April 2019

* Corresponding author. Tel: +3232652338, Fax: +3232652412, Email: gilles.dekeulenaer@uantwerpen.be

Randomized clinical trials initially used heart failure (HF) patients with low left ventricular ejection fraction (LVEF) to select study populations with high risk to enhance statistical power. However, this use of LVEF in clinical trials has led to oversimplification of the scientific view of a complex syndrome. Descriptive terms such as 'HFrEF' (HF with reduced LVEF), 'HFpEF' (HF with preserved LVEF), and more recently 'HFmrEF' (HF with mid-range LVEF), assigned on arbitrary LVEF cut-off points, have gradually arisen as separate diseases, implying distinct pathophysiologies. In this article, based on pathophysiological reasoning, we challenge the paradigm of classifying HF according to LVEF. Instead, we propose that HF is a heterogeneous syndrome in which disease progression is associated with a dynamic evolution of functional and structural changes leading to unique disease trajectories creating a spectrum of phenotypes with overlapping and distinct characteristics. Moreover, we argue that by recognizing the spectral nature of the disease a novel stratification will arise from new technologies and scientific insights that will shape the design of future trials based on deeper understanding beyond the LVEF construct alone.

Keywords Heart failure • Ejection fraction • Pathophysiology • Endothelium

Introduction

Heart failure (HF) is a progressive, multi-factorial, and heterogeneous syndrome, in which important therapeutic progress has been made based on clinical trials.[1] These trials were initially designed predominantly on logistics more than on pathophysiological considerations, aiming to increase the statistical power and to limit trial costs, by enrolling patients with poor prognosis based on low left ventricular (LV) ejection fraction (LVEF).[2] These practical enrolment criteria, however, had a profound impact on how we perceive the complex syndrome of HF. Clinical diagnosis, management and even basic physiological research has been inseparably linked to LVEF, which has become the foundational biomarker to classify HF. Connotations like 'HFrEF' (HF with reduced LVEF), 'HFpEF' (HF with preserved LVEF), and more recently even 'HFmrEF' (HF with mid-range LVEF), have now emerged as distinct 'disease' entities, and have been studied as if unrelated syndromes, separated by arbitrary LVEF cut-offs.[3]

In this article, we challenge the epidemiological, clinical, mechanistic, pathophysiological, and therapeutic basis for classifying HF solely according to LVEF. Left ventricular ejection fraction-based taxonomy of HF and its implications have been criticized.[4–6] Here, we advocate the consideration of HF as a syndrome across a spectrum of phenotypes, in which each patient follows a unique trajectory based on the initial trigger(s), the genetic, clinical, and sociodemographic background, and available treatment. As HF progresses, the heart remodels causing functional and structural 'biomarkers' to evolve in unique patterns with levels differing among patients without specifying HF subpopulations. This creates a spectrum of overlapping HF phenotypes necessitating the design of clinical studies based on deeper pathophysiological reasoning.

In this manuscript, we present a consensus opinion authored by 42 scientists studying HF in diverse ways, both clinically and fundamentally. These scientists interacted with each other on several occasions and shared concerns about current HF taxonomy. A few authors took the initiative to summarize arguments, which resulted in a consensus document after several months of intense interactions and input by all authors.

Left ventricular ejection fraction-based taxonomy of HF is imprecise and incomplete

Left ventricular ejection fraction has imprecise physiological implications

Left ventricular ejection fraction is the stroke volume (SV) expressed as a fraction of the LV end-diastolic volume (LVEDV). A normal LVEF simply indicates that the SV is appropriate for the LVEDV and vice versa.[7] In acute myocardial infarction, the reduction in contractility results in a decreased SV in the presence of relatively normal LVEDV, resulting in reduced LVEF. However, LVEF is also dependent on loading conditions which becomes especially important in conditions such as mitral regurgitation, aortic stenosis, etc., that alter ventricular preload or afterload.[5,8] Furthermore, LVEF may be preserved or even augmented in patients with LV hypertrophy even in the presence of myocardial systolic dysfunction. Although circumferential strain is not always reduced in patients with HFpEF compared with age-matched controls, global longitudinal strain is often reduced.[9] As a result, myocardial strain has been increasingly advocated as a complementary metric to LVEF.[6]

Substantial variability between LVEF measurements modalities

There is substantial variability between imaging modalities for LVEF measurement. In a study including 2032 patients with LVEF $\leq$ 35%, the correlation between modalities was modest.[10] Bland-Altman plots showed moderate agreement in LVEF measurements with no consistent overestimation or underestimation by any modality (*Figure 1*). One might argue that this weakness can be overcomed by establishing one imaging modality for the measurement of LVEF in HF patients. For echocardiography, however, which is the most common imaging modality, intra-observer and inter-observer reliability of LVEF assessment is only reasonable among highly experienced echocardiographers with an intra-class correlation coefficient of only 0.78.[11] In addition, as mentioned by Pelikka *et al.*, even the clinically most accessible method to quantify LVEF in daily practice (biplane Simpson method by echocardiography) is feasible in only 46%.[10]

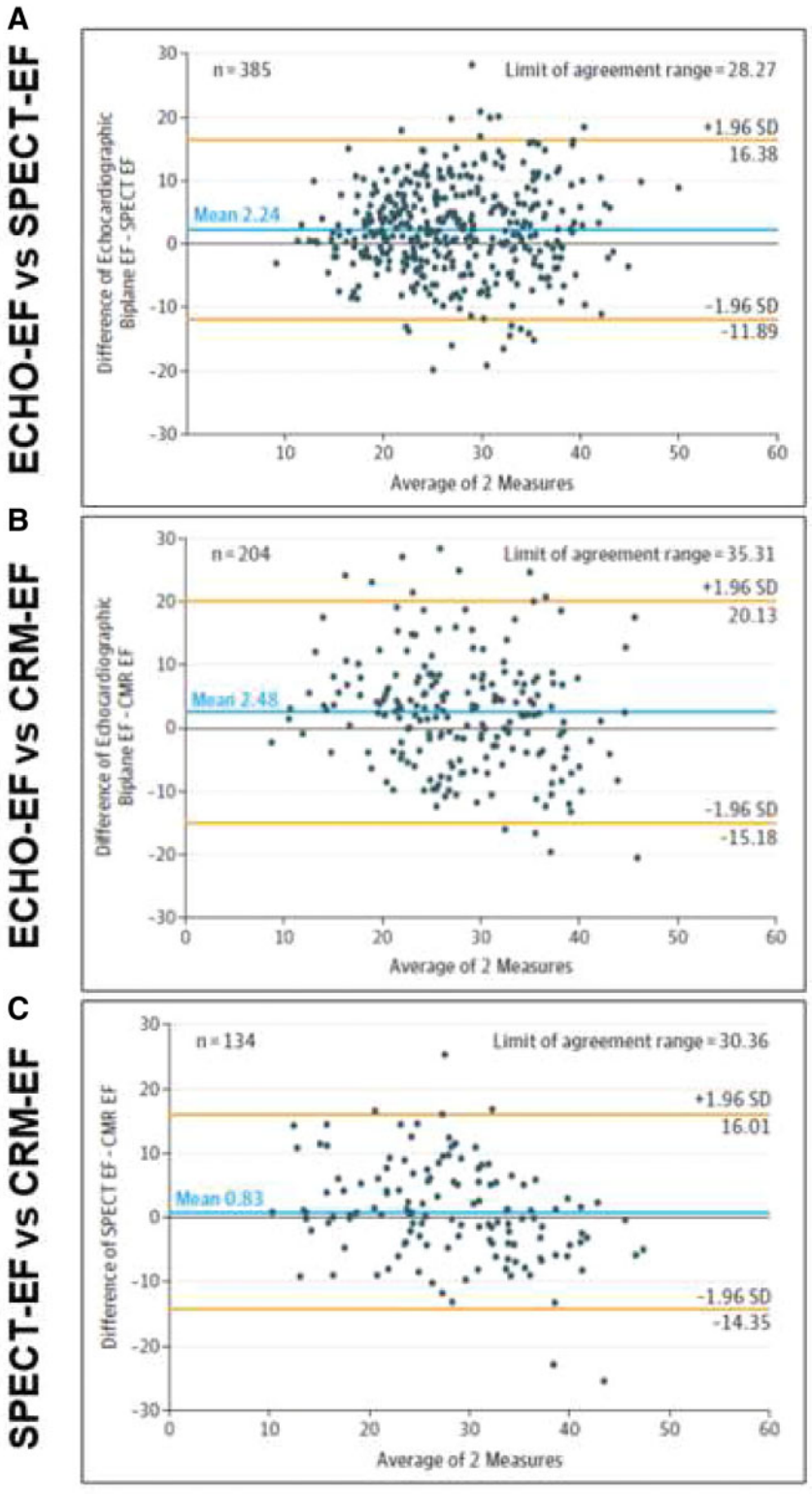

Figure 1 Variability in left ventricular ejection fraction (EF) measurements. Bland-Altman plots for EF compared for biplane Simpson method by echocardiography and gated single-photon emission computed tomography (SPECT) (*A*), biplane Simpson method by echocardiography and cardiovascular magnetic resonance (CRM) (*B*), and SPECT and CRM (*C*). Modified from Ref.[10]

Left ventricular ejection fraction cut-offs are arbitrary

International HF guidelines use varying cut-offs and LVEF-based taxonomy, illustrating the disadvantage of using a continuous variable of vague pathophysiological significance to an ordinal variable in order to describe different HF phenotypes. The American College of Cardiology Foundation/American Heart Association guidelines categorize patients as HFpEF (≥50%) and HFrEF (≤40%). Left ventricular ejection fraction 41–49% is defined as borderline HFpEF, whereas LVEF >40% in patients with previous HFrEF is defined as HFpEF-improved.[12] The European Society of Cardiology guidelines classify patients as HFrEF (<40%), HFmrEF (40–49%), and HFpEF (LVEF ≥50%).[3] Finally, the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand guidelines classify HFrEF as <50% and HFpEF as ≥50% and do not recognize HFmrEF as a distinct entity.[13] Interestingly, none of these guidelines classify acute HF based on LVEF.[3] A plausible explanation is that outcomes following hospitalization for acute HF are poorly related to LVEF.[14]

Left ventricular ejection fraction transitions

Several studies indicate that during the HF disease journey, bidirectional LVEF transitions occur, which may lead to patient misclassification and failure to implement the appropriate treatment.[6] In one community, cohort of incident HF patients LVEFs were assessed by echocardiography from initial HF diagnosis until death or last follow-up.[15] In those with HFpEF, LVEF decreased by 5.8% over 5 years with greater declines in older individuals and those with coronary disease. Conversely, LVEF increased in HFrEF on average by 6.9% over 5 years. Overall, 39% of HFpEF patients had a LVEF <50% and 39% of HFrEF patients had a LVEF ≥50% at some point after diagnosis. Decreases in LVEF were associated with reduced and increases with improved survival.[15] Up to 25% of treated HFrEF patients show LVEF recovery.[16]

In another study, 2413 HF patients had ≥2 LVEF measurements after discharge separated by ≥30 days.[17] In total, 8183 LVEF transitions were observed. Women and patients adherent to β-blockers were more likely to transition from low to normal LVEF. Patients with previous myocardial infarction were more likely to transition from HFpEF to HFrEF.[17] Clinically relevant LVEF transitions were also observed in the Swedish Heart Failure Registry.[18] Finally, in a prospective registry of HF outpatients[19] long-term LVEF trajectories showed a marked rise during the first year, maintained up to a decade, and a slow decline thereafter.

Right ventricular dysfunction/failure

The right ventricle (RV) and LV share common characteristics when they adapt to adverse loading or when they fail. Moreover, through shared myocardial fibres, the interventricular septum and the common pericardium, LV contraction contributes to RV pressure development, and RV loading affects LV function.[20] Thus LVEF may be affected by RV dysfunction.

In conclusion, the above data support the view that classification of HF patients based on LVEF has serious limitations.[4]

Epidemiological, clinical, pathophysiological, and therapeutic features are common across the HF spectrum

In this section, we will outline that despite the differences between HF patients over the LVEF spectrum, patients with HF also share many epidemiological, clinical, and pathophysiological characteristics regardless of LVEF. A disadvantage of LVEF-based HF classification is that it separates overlapping groups of patients as if they would be unrelated.

Left ventricular systolic and diastolic dysfunction and left atrial dysfunction

Both diastolic and systolic dysfunctions are found in HF independent of LVEF. Brucks *et al.*[21] studied 206 patients with HF and 72 age-matched controls. Diastolic dysfunction was present in >90% of patients independent of LVEF. Increased passive stiffness of cardiomyocytes related to hypophosphorylation of the protein titin[22] occurs both in HFpEF and HFrEF.[23,24]

Systolic function may be impaired in patients with LVEF ≤ 40% and those with ≥50%. Tan *et al.*[25] reported reduced ventricular systolic strain, reduced systolic and diastolic longitudinal functional reserve, reduced ventricular systolic twist and delayed ventricular untwisting, and reduced rise in SV on exercise in HFpEF. Kraigher-Krainer *et al.*[26] demonstrated that HFpEF patients had lower longitudinal and circumferential strain compared with normal controls and hypertensive patients. In another HFpEF trial population, LV global longitudinal strain was abnormal in 65% of patients.[27]

Left ventricular dysfunction is associated with left atrial (LA) dilation and mechanical failure, frequently resulting in atrial fibrillation. Left atrial mechanical failure is accompanied by LA endocrine failure, contributing to volume overload.[28] Left atrial mechanical dysfunction is present both in HFpEF and HFrEF and associated with pulmonary hypertension and right-sided HF. Left atrial volume and function predict HF outcomes regardless of LVEF.[28] Increased LA size and dysfunction are associated with impaired exercise capacity both in HFpEF and HFrEF.[29,30]

Thus, systolic and diastolic myocardial dysfunctions frequently coexist in HF regardless of the LVEF and result in atrial dysfunction, present across the HF spectrum. Myocardial strain measurements have endorsed this concept.

Comorbidities

It has been argued that a LVEF-based classification of HF is tracked by the distribution of comorbidities that are directly linked to a pathophysiological framework for HFpEF.[22] The term *comorbidity* is often interchangeably used with the terms *risk factor* and *disease modifier*, and this creates significant misinterpretations.[31] Differences are known regarding the prevalence of risk factors for HFpEF and HFrEF (e.g. hypertension, obesity, and coronary artery disease) and disease modifiers (e.g. sex and age). However, these differences are quantitative and as such there is clearly no risk factor or disease modifier unique for HFpEF or HFrEF.[32] Results of the studies assessing the prevalence of comorbidities (e.g. anaemia, chronic kidney disease,

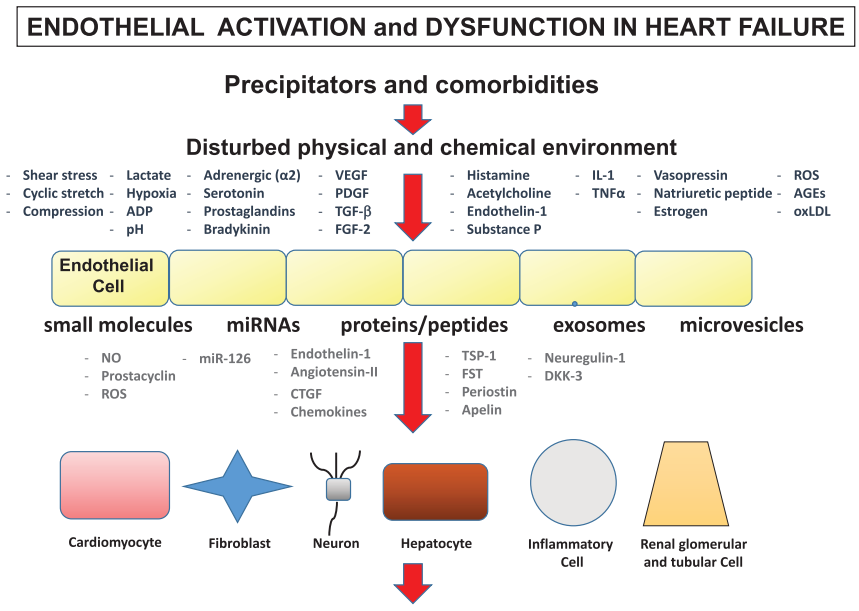

Figure 2 Endothelial physiology: more to say than just NO. Schematic figure illustrating the putative role of endothelial cell activation and dysfunction in heart failure. Albeit too often restricted to an interaction between endothelial cells and adjacent cells through nitric oxide (NO), the physiology of the endothelium and its role in the pathophysiology of heart failure very complex. Endothelial cells have a sensing function to detect changes in the mechanical (shear stress, cyclic stretch, and compression), chemical (lactate, hypoxia, . . .) and neurohormonal (endothelin-1, acetylcholine, . . .) environment, and an effector function by the release of many bioactive factors (prostacyclin, endothelin, neuregulin, . . .) influencing targets cells in many different organs. When endothelial cells become dysfunctional, such as in heart failure, homeostatic balances in virtually each organ system will be affected in a pleiotropic fashion. For more detailed information, we refer the reader to Ref.[40] ADP, adenosine diphosphate; AGE, advanced glycation end products; CTGF, connective tissue growth factor; DKK-3, Dickkopf-related protein 3; FGF, fibroblast growth factor; FST, follistatin; IL-1, interleukin-1; miR, microRNA; NO, nitric oxide; oxLDL; oxidized low density lipoproteins; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; TGF, tissue growth factor; TNF, tumour necrosis factor; TSP-1, thrombospondin-1; VEGF, vascular endothelial growth factor.

chronic obstructive pulmonary disease, etc.) in HF subtypes were inconsistent.[32–34] Comorbidities were highly prevalent both in HFpEF and HFrEF and similarly correlated with symptoms and outcomes.[35] Treating comorbidities may prove beneficial across the LVEF spectrum.

Regarding risk factors there is substantial overlap between incident HFpEF and HFrEF.[36] An example depicting this complexity is visceral adiposity, which is related to three HF phenotypes (HFpEF, HFrEF, and high-output HF), related to activation of the leptin-aldosterone-neprilysin axis.[37]

Endothelial dysfunction and cardiomyocyte injury

HFpEF is proposed to be driven by coronary microvascular endothelial inflammation and oxidative stress, induced by comorbidities, whereas HFrEF by cardiomyocyte loss.[22] Although this may be true at the extremes of the LVEF spectrum, endothelial dysfunction is not a specific pathophysiological characteristic of HFpEF and cardiomyocyte death is not a specific phenomenon for HFrEF. Endothelial dysfunction is common in HF regardless of LVEF,[38,39] and seen in all circulatory beds, involving microvasculature, large conduit, and small resistance vessels.[38,40] This widely proposed HFpEF paradigm couples endothelial dysfunction with diastolic dysfunction related to the disturbed nitric oxide (NO)-cGMP-protein kinase G pathway. Endothelial cells, however, secrete numerous cardio-active proteins besides NO (*Figure 2*) and some of these contribute to LV remodelling over the whole LVEF spectrum. Thus, the role of endothelial dysfunction in HF extends beyond NO.[41,42] It is noteworthy that recent HFpEF trials aiming at improving symptoms targeting the NO/cGMP pathway were negative, suggesting that endothelial dysfunction in HF is more complicated than originally anticipated and to date remains an attractive but still unproven therapeutic target.[43–45]

Similarly, although not all HF patients suffer from cardiomyocyte injury, signs of cardiomyocyte injury can be found in patients with HF throughout the HF spectrum, independent of LVEF. Levels of cardiac troponin (cTn) T may be elevated in both HFrEF and HFpEF.[46] High sensitivity (hs)-cTnI and hs-cTnT[47] are associated with all-cause mortality or HF hospitalization in HFpEF and HFrEF.[48] In a recent study of HFpEF patients,[49] cTn was greater than two-fold higher compared with controls in subjects with HFpEF at rest and during exercise and correlated with LV filling pressures. Finally, hs-cTn levels predicted both incident HFrEF and HFpEF in a pooled analysis of 22 756 subjects at risk for developing HF.[50]

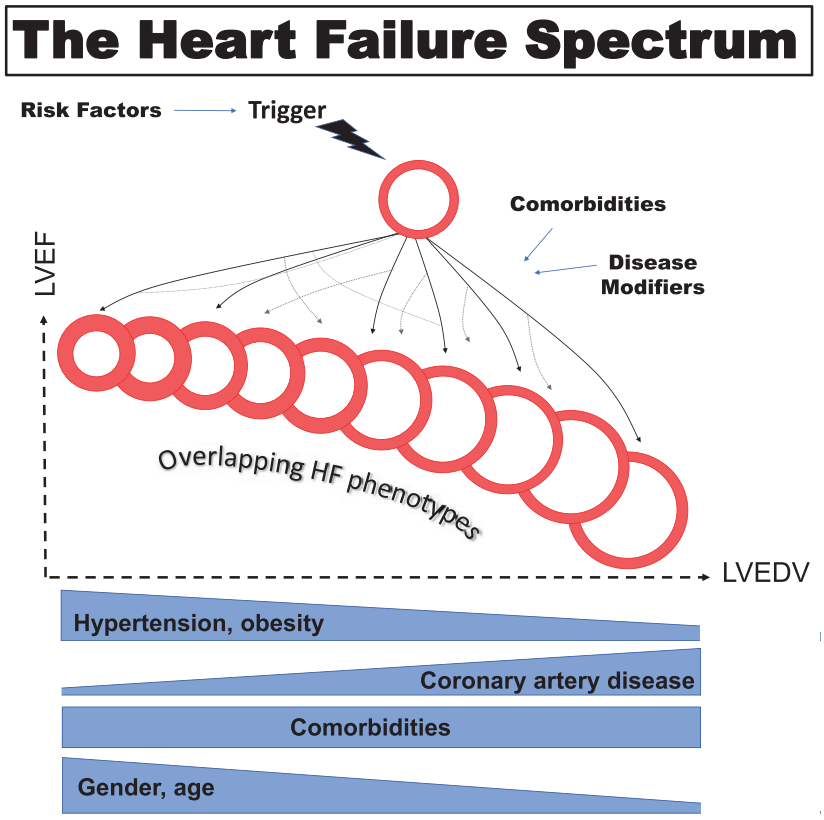

Figure 3 Heart failure a spectrum across phenotypes. Each heart failure phenotype is the result of a patient-specific trajectory wherein the heart remodels towards concentric hypertrophy, eccentric hypertrophy, or a combination of both. The way of entry and the subsequent path of the trajectory depend on the patient's risk factor(s), comorbidity(ies), and disease modifiers. Risk factors are disease entities that always precede the development of heart failure and are associated with an increased heart failure incidence. Comorbidities may precede or develop after heart failure and usually coexist with heart failure in groups of two or more (multi-morbidity). Modifiers are specific patient characteristics that contribute to the development of the entry phenotype and heart failure progression. Across the heart failure spectrum left ventricular ejection fraction variability relates with left ventricular end-diastolic volume in a non-linear relationship. Despite quantitative differences between the extreme left and right sides of the spectrum, there is important overlap between the phenotypes along the entire spectrum. Any subdivision of the spectrum by a single biomarker is artificial. Afib, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM-II, type II diabetes mellitus; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; OSAS, obstructive sleep apnoea syndromes.

Neurohumoral axis activation

Arterial underfilling triggers neurohumoral overactivity in HF. In the Studies of Left Ventricular Dysfunction (SOLVD), baseline plasma norepinephrine (PNE), plasma renin activity (PRA), plasma atrial natriuretic factor (ANF), and plasma arginine vasopressin (AVP) were increased in HFrEF (≤45%), whereas only PRA and AVP were increased in HFpEF (LVEF > 45%).[51] However, PNE values did not differ between HFrEF and HFpEF in another study.[52] Finally, it was recently demonstrated that muscle sympathetic nerve traffic is increased in HFpEF, HFmREF, and HFpEF.[53] Thus, neurohumoral overactivity is present in all HF phenotypes, being highest on the low LVEF side and lowest on the high LVEF side of spectrum.

Myocardial fibrosis

Myocardial fibrosis (MF) plays a major role in LV remodelling independent of LVEF. Accordingly, although the degree of MF varies among HF patients, MF may be present throughout the HF spectrum. The collagen volume fraction in endomyocardial biopsies was similar in HFpEF and HFrEF.[54] Moreover, in both HFrEF and HFpEF, MF estimated on CMR was independently associated with a higher risk of all-cause death and HF hospitalization.[55]

Skeletal myopathy

Skeletal myopathy contributes to the impaired exercise capacity in HF.[56] Both HFpEF and HFrEF patients with exercise intolerance manifest early exercise-induced declines in skeletal muscle high-energy phosphates and reduced oxidative capacity compared with healthier and low-fatigability HF patients.[57,58]

Benefit with neurohumoral inhibition

The success of treatment with neurohumoral inhibitors in HFrEF is not fully reproduced in HFpEF. However, there are undeniable signals for a benefit in HFpEF as well as explained in the following paragraphs and references.

Table 1 Features of heart failure found throughout the full heart failure spectrum

Risk factors, comorbidities, and disease modifiers (quantitative differences depending on LVEF)
Bidirectional transitions of LVEF due to disease treatment and progression
Endothelial dysfunction, cardiomyocyte dysfunction, and cardiomyocyte injury
Systolic and diastolic left ventricular dysfunction
Left atrial dysfunction
Myocardial fibrosis
Skeletal myopathy
Heart failure serum markers (quantitative differences depending on LVEF)
Neurohumoral activation (quantitative differences depending on LVEF)
Effectiveness of neurohumoral inhibitors (quantitative differences depending on LVEF)

LVEF, left ventricular ejection fraction.

Table 2 Possible directions to create a new stratification of heart failure

Hypothesis-driven approach
Stratification based on disease aetiology/mechanism
Ischaemic cardiomyopathy, non-ischaemic dilated cardiomyopathy, light chain amyloid cardiomyopathy, transthyretin amyloid cardiomyopathy, hypertrophic cardiomyopathy, hypertensive cardiomyopathy, diabetic cardiomyopathy, tachy-cardiomyop athy, post-partum cardiomyopathy, doxorubicin- or alcohol-induced cardiomyopathy, myocarditis-induced cardiomyopathy, lamin A/C cardiomyopathy, etc.
Stratification based on activity of pharmaceutical pathway
Endothelin serum levels, cytokine serum levels, vasopressin serum levels + serum sodium levels, endothelial dysfunction + low tissue cGMP, etc.
Data-driven, hypothesis-free approach
Phenotypic characterization based on outcome analysis and stratification by large series of dense phenotypic data.
Identification of signatures to distinguish between groups with different outcomes

cGMP, cyclic guanosine monophosphate.

Perindopril in HF patients with LVEF ≥ 45% improved symptoms and exercise capacity, and lowered hospitalizations.[59] In a recent analysis of the CHARM trial with LVEF as a continuous spline variable, candesartan reduced the primary outcome (cardiovascular death or HF hospitalization) until LVEF well over 50% and recurrent HF hospitalizations until LVEF well over 60%.[60] A meta-analysis of 13 studies concluded that renin-angiotensin system inhibitors may have a role in improving outcomes in HFpEF.[61]

Too few patients have been studied in trials of beta-blockers in HFpEF. However, in a pre-specified sub-analysis of the Study of the Effects of Nebivolol Intervention on OUtcomes and Rehospitalization in Seniors with HF (SENIORS), the benefit with nebivolol in elderly patients with HF was unrelated to LVEF.[62] A meta-analysis involving 21 206 HFpEF patients demonstrated that β-blocker exposure was associated with a 9% reduction in relative risk for all-cause mortality.[63]

Aldosterone receptor blockade is associated with reductions in risk for HF hospitalization in patients with HFpEF and while there was regional heterogeneity, the primary outcome including cardiovascular mortality was reduced by spironolactone in the Americas.[64]

Thus, effectiveness of treatment with neurohumoral inhibitors is highest in the low LVEF side and lowest in the high LVEF side of spectrum, consistent with the degree of neurohumoral overactivity.

QRS duration/ventricular dyssynchrony

Ventricular dyssynchrony based on QRS duration is independent of LVEF. In the Swedish Heart Failure Registry 31% of 25 171 patients had a QRS duration ≥120 ms, with a significant impact on the adjusted risk for all-cause mortality. There was no interaction between QRS width and LVEF.[65] In the TOPCAT study, a QRS duration of ≥120 ms was independently associated with an increased risk of the primary outcome,[66] and this risk was independent of the type of conduction abnormality underlying the prolonged QRS.[66] In the Predictors of Response to CRT (PROSPECT) trial, adjudicated LVEF above the entry criterion of 35%, responded similarly to CRT as those with lower LVEF.[67]

Sudden cardiac death

Therapy with an implantable cardioverter defibrillator (ICD) for the primary prevention of sudden cardiac death (SCD) is recognized when LVEF ≤ 35%.[3] However, data from two large community-based studies suggest that about two-thirds of SCD cases would not be eligible for an ICD before the cardiac arrest based of having an LVEF > 35%.[68] In 1767 HFpEF patients enrolled in the Americas in TOPCAT, SCD accounted for ≈20% of deaths.[69] In a systematic review of 8 randomized trials and 24 epidemiological studies in HFpEF, SCD accounted for 25–30% of deaths.[70] Obviously, it remains to be proven whether SCD can be prevented with ICD therapy in HFpEF.

Future direction

HF is a heterogeneous syndrome in which functional and structural biomarkers change dynamically during disease progression in a patient-specific fashion. This creates a spectrum across overlapping phenotypes (*Figure 3*). The spectrum view challenges a categorical HF classification based solely on LVEF. Epidemiological, clinical, mechanistic, pathophysiological, and therapeutic data reviewed in this article show that LVEF-based HF subgroups are more overlapping than previously appreciated (*Table 1*).

A spectrum view does not imply that all LVEF-based HF phenotypes are totally alike. The extremes of a spectrum exhibit per definition significant differences, for example, a patient with concentric LV hypertrophy and hypertensive HF differs from a HF patient with eccentric hypertrophy awaiting transplant (*Figure 3*). The middle area of a spectrum consists of related and overlapping phenotypes. Any LVEF-based subdivision is artificial. Accepting the extremes as

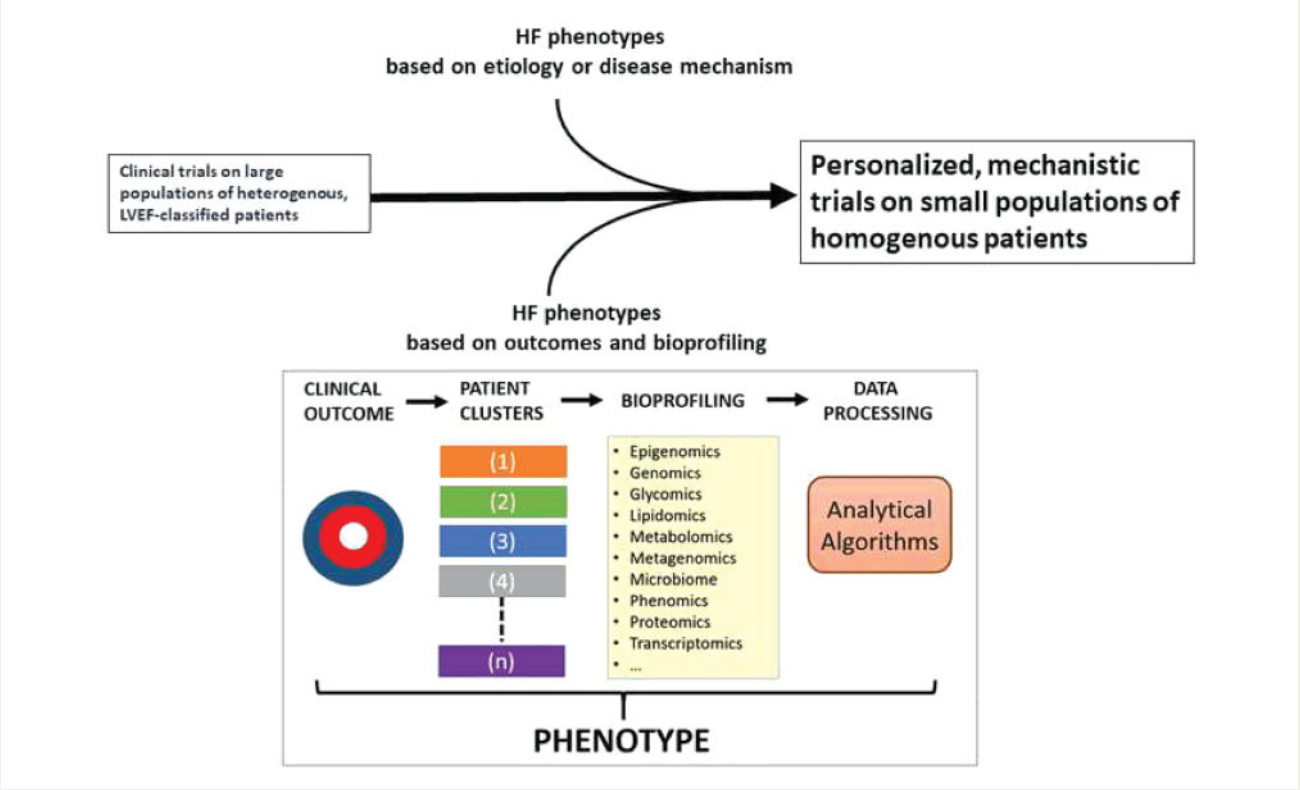

Figure 4 Evolution of heart failure research. Phenotype-oriented research in heart failure will emerge from an updated heart failure classification recognizing phenotypes across the left ventricular ejection fraction spectrum. These may either be based on mechanisms or aetiology of disease, or from unbiased data-driven approaches (see inset). Advances in both technology and computing now provides unprecedented opportunity to understand biologic subgroups of patients to target personalized therapy that maximizes chances of benefit and minimizes chances of risks. One such scheme could be to stratify patients across the risk spectrum and study their biologic, sociologic, demographic, and other determinants in detail to describe not only prediction more accurately (to guide use of existing therapy) but also the relevant biologic pathways involved (to guide development of new therapies).

'prototypes' creates the misleading perception of a categorical nature of HF.

The logic for a more precise characterization of HF phenotypes is supported by the advances in oncology.[71] Introduction of innovative technologies such as next generation sequencing has personalized cancer treatment.

How should we then approach the heterogeneity of HF? One may envision two major directions for progress. The first would be hypothesis-driven, the other data-driven (*Table* 2).

In the hypothesis-driven approach, patients are stratified by a combination of features that are thought to be mechanistically important (e.g. cardiac resynchronization therapy for wide QRS duration or implantable cardioverter defibrillator for ventricular tachycardia/fibrillation). In fact, this approach, which is aetiological and more clinically significant than the current, oversimplified LVEF-based classification, should be incorporated in the current everyday practice, provided that the underlying aetiology is known. When it is not, the disease should be included in a category (e.g. idiopathic dilated cardiomyopathy), a practice that will inevitably shrink in parallel with the increase in knowledge regarding HF. It is reassuring to note that this strategy has already provided some successes with the identification of aetiology-specific therapies, such as transthyretin stabilization with tafamidis for transthyretin amyloid cardiomyopathy.[72] A prerequisite for this approach is better characterization of less established phenotypes (e.g. obesity, uraemic cardiomyopathy, metabolic cardiomyopathy, etc.). Given the spectacular evolution in many fields of medicine, including imaging modalities, machine learning, biomarkers, genotyping, etc., one might expect rapid progress during the characterization of such phenotypes.

A variant of the hypothesis-driven approach is the stratification based on the activity of a drug pathway over the spectrum, for example, studying a vasopressin antagonist in patients with high co-peptin levels or low serum sodium or etanercept in patients with high levels of tumour necrosis factor alfa, etc. This approach would likely result in study populations with a wide range of LVEF, and perhaps lead to better clinical outcomes compared with previous trials on these pathways in patients selected by LVEF.

The data-driven approach is hypothesis free. Patient clusters are generated defined by clinical outcomes. Each patient cluster is identified based on similarities or differences in measured characteristics, with strong associations among members of the same cluster and weak associations among members of other clusters. After this process, data are analysed to identify which variables distinguish clusters with different outcomes ('signatures'). Pairing phenotypes identified

with cluster analyses with an 'omics' approach (genomics, metabolomics, proteomics, etc.) may allow for a more advanced classification scheme founded on the underlying biology. Moreover, artificial intelligence will enable computers to find hidden insights without being explicitly programmed where to look and integrate and interpret complex data in scenarios where traditional statistical methods may not be able to perform.[73] This could set the stage for a more rational clinical trial design for HF, which is likely necessary.

Estimation of LVEF will likely remain temporarily part of the assessment of HF, as a prognosticator, as a rough measure of a patient's sensitivity to neurohormonal inhibitors, and during a transition phase to incorporate current evidence-based medicine into a more personalized evidence-based HF management scheme. For example, when testing a drug in an appropriate HF phenotype (defined without limitations of LVEF), patients will be randomized to receive the active drug or placebo on top of standard therapy, the latter which will require some measure of individual patient's LVEF. However, HF care will be accompanied by a greater awareness of the inaccuracies of LVEF measurement and of its vague pathophysiological significance. By accepting the limitations of LVEF and embracing the spectral nature of HF, the HF field will move from an originally unspecified approach based on statistical analyses of data from large groups of heterogeneous LVEF-clustered populations to a more personalized and mechanistic approach based on smaller studies with homogeneous patient populations (*Figure 4*).

Conflict of interest: J.Bu. reports to be consultant for Amgen, Array, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Mayers Squib, CVRx, G3 Pharmaceutical, Innolife, Janssen, Luitpold, Medtronic, Merck, Novartis, Relypsa, StealthPeptide, SC Pharma, Vifor, ZS Pharma, outside the submitted work. J.Ba. reports personal fees from Novartis, grants and personal fees from Bayer, personal fees from Servier, personal fees from Orion, grants and personal fees from Abiomed, grants and personal fees from CVRx, grants and personal fees from Medtronic, grants from Zoll, grants and personal fees from Vifor, personal fees from Abbott, personal fees from AstraZeneca, outside the submitted work; R.D.B. reports grants from AstraZeneca, grants from Bristol Myers Squibb, grants from Trevena, grants from Novo Nordisk, personal fees from AstraZeneca, personal fees from Novartis, personal fees from Vifor, personal fees from MandalMed, Inc, and other types of support from scPharmaceuticals, Inc, other from ThermoFisher, other from Roche, all outside the submitted work; L.D.W. reports to be co-founder and stockholder of Mirabilis Therapeutics BV, a spin-off Biotech aimed to develop new therapeutics for heart failure; G.H. reports personal fees from Corvia Medical, Servier, Impulse Dynamics, Novartis, AstraZeneca, Vifor Pharma, and Springer all outside the submitted work; J.-S.H. reports personal fees from Servier and Novartis, outside the submitted work; M.K. reports personal fees from Amgen, BMS, Boehringer-Ingelheim, Novartis and grants and personal fees from Ironwood, LivaNova, SCPharma, outside the submitted work; R.L. reports to be a founder of a startup biotechnology company named Elevian, Inc., which has heart failure as one of its target diseases; A.L. reports personal fees from Servier, grants and personal fees from Pfizer, personal fees from Novartis, personal fees from Roche, personal fees from Takeda, personal fees from Boehringer Ingelheim, personal fees from Amgen, personal fees from Clinigen Group, personal fees from Ferring Pharmaceuticals, personal fees from Eli Lily, personal fees from Bristol Myers Squibb, personal fees from Eisai Ltd, outside the submitted work; C.M. reports grants from Deutsche Forschungsgemeinschaft, during the conduct of the study; personal fees from Servier, personal fees from Boehringer Ingelheim, personal fees from Novartis, personal fees from Bayer, personal fees from Bristol Myer Squibb (BMS), personal fees from Berlin Chemie, personal fees from Daiichi Sankyo, outside the submitted work; A.M. reports personal fees from Novartis, personal fees from Orion, personal fees from Roche, personal fees from Servier, grants and personal fees from Adrenomed, grants and personal fees from Abbott, personal fees from Sanofi, outside the submitted work; R.M. reports grants and personal fees from Amgen, grants and personal fees from Bayer, grants and personal fees from Merck, grants and personal fees from AstraZeneca, grants and personal fees from Novartis, grants from Akros, grants from Luitpold, personal fees from Boehringer Ingelheim; J.P. reports horonaria for advisory boards and lectures from Novartis, Servier, Pfizer, Orion Pharma and Roche diagnostics; T.P. has a patent PCT/EP2014/078868 issued; P.M.S. reports grants/research supports from the ministry of education, science and technological development of Republic of Serbia. Receipt of honoraria or consultation fees from Servier, Boehringher Ingelheim, Hemofarm, Novartis, Astra Zeneca. Participation in a company sponsored speaker's bureau: Fondazione Internationale Menarini; R.C.S. reports grants from Novartis, grants from Amgen, other from Abbott, grants from Corvia, other from Novartis, outside the submitted work; C.G.T. reports grants from Federico II University-Ricerca d'Ateneo, personal fees from speaker honoraria from Alere, outside the submitted work; In addition, Dr. Tocchetti has a patent Canadian patent no. 2,613,477: "Thiol Sensitive Positive Inotropes", with royalties paid; J.-N.T. reports personal fees from Amgen, personal fees from Bayer, personal fees from Resmed, grants and personal fees from Abott, grants and personal fees from Novartis, grants and personal fees from Carmat, outside the submitted work; T.T. is the founder and shareholder of Cardior. He also filed and licensed a number of non-coding RNA based patents in the cardiovascular disease era; F.Z. reports personal fees from Janssen, personal fees from Bayer, personal fees from Novartis, personal fees from Boston Scientific, personal fees from Resmed, personal fees from Amgen, personal fees from CVRx, personal fees from Quantum Genomics, personal fees from General Electric, personal fees from Boehringer, other from cardiorenal, other from CVCT, personal fees from AstraZeneca, personal fees from Vifor Fresenius, outside the submitted work.

References

1. Samman Tahhan A, Vaduganathan M, Kelkar A, Georgiopoulou VV, Kalogeropoulos AP, Greene SJ, Fonarow GC, Gheorghiade M, Butler J. Trends in heart failure clinical trials from 2001-2012. *J Card Fail* 2016;**22**:171–179.
2. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. *Circulation* 2011;**123**:1996–2004; discussion 2005.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.

4. Mann DL. Is it time for a new taxonomy for heart failure? *J Card Fail* 2016;**22**: 710–712.
5. Konstam MA, Abboud FM. Ejection fraction: misunderstood and overrated (changing the paradigm in categorizing heart failure). *Circulation* 2017;**135**:717–719.
6. Marwick TH. Ejection fraction pros and cons: JACC state-of-the-art review. *J Am Coll Cardiol* 2018;**72**:2360–2379.
7. Iwano H, Little WC. Heart failure: what does ejection fraction have to do with it? *J Cardiol* 2013;**62**:1–3.
8. Katz AM, Rolett EL. Heart failure: when form fails to follow function. *Eur Heart J* 2016;**37**:449–454.
9. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. *JACC Cardiovasc Imaging* 2018;**11**:260–274.
10. Pellikka PA, She L, Holly TA, Lin G, Varadarajan P, Pai RG, Bonow RO, Pohost GM, Panza JA, Berman DS, Prior DL, Asch FM, Borges-Neto S, Grayburn P, Al-Khalidi HR, Miszalski-Jamka K, Desvigne-Nickens P, Lee KL, Velazquez EJ, Oh JK. Variabilty in ejection fraction measured by echocardiography, gated single-photon emission computed tomography, and cardiac magnetic resonance in patients with coronary artery disease and left ventricular dysfunction. LVEF variablity. *JAMA Network Open* 2018;**1**:e181456.
11. Blondheim DS, Beeri R, Feinberg MS, Vaturi M, Shimoni S, Fehske W, Sagie A, Rosenmann D, Lysyansky P, Deutsch L, Leitman M, Kuperstein R, Hay I, Gilon D, Friedman Z, Agmon Y, Tsadok Y, Liel-Cohen N. Reliability of visual assessment of global and segmental left ventricular function: a multicenter study by the Israeli Echocardiography Research Group. *J Am Soc Echocardiogr* 2010;**23**:258–264.
12. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. American College of Cardiology F and American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**62**:e147–e239.
13. Atherton JJ, Sindone A, De Pasquale CG, Driscoll A, MacDonald PS, Hopper I, Kistler P, Briffa TG, Wong J, Abhayaratna WP, Thomas L, Audehm R, Newton PJ, O'Loughlin J, Connell C, Branagan M. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the management of heart failure 2018. *Med J Aust* 2018;**209**:363–369.
14. Senni M, Gavazzi A, Oliva F, Mortara A, Urso R, Pozzoli M, Metra M, Lucci D, Gonzini L, Cirrincione V, Montagna L, Di Lenarda A, Maggioni AP, Tavazzi L, Investigators I. In-hospital and 1-year outcomes of acute heart failure patients according to presentation (de novo vs. worsening) and ejection fraction. Results from IN-HF Outcome Registry. *Int J Cardiol* 2014;**173**:163–169.
15. Dunlay SM, Roger VL, Weston SA, Jiang R, Redfield MM. Longitudinal changes in ejection fraction in heart failure patients with preserved and reduced ejection fraction. *Circ Heart Fail* 2012;**5**:720–726.
16. Lupon J, Diez-Lopez C, de Antonio M, Domingo M, Zamora E, Moliner P, Gonzalez B, Santesmases J, Troya MI, Bayes GA. Recovered heart failure with reduced ejection fraction and outcomes: a prospective study. *Eur J Heart Fail* 2017;**19**:1615–1623.
17. Clarke CL, Grunwald GK, Allen LA, Baron AE, Peterson PN, Brand DW, Magid DJ, Masoudi FA. Natural history of left ventricular ejection fraction in patients with heart failure. *Circ Cardiovasc Qual Outcomes* 2013;**6**:680–686.
18. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, Braun OO, Savarese G, Dahlstrom U, Lund LH. Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a nationwide cohort study. *Circ Heart Fail* 2017;**10**:e003875.
19. Lupón J, Gavidia-Bovadilla G, Ferrer E, de Antonio M, Perera-Lluna A, López-Ayerbe J, Domingo M, Núñez J, Zamora E, Moliner P, Díaz-Ruata P, Santesmases J, Bayés-Genís A. Dynamic trajectories of left ventricular ejection fraction in heart failure. *J Am Coll Cardiol* 2018;**72**:591–601.
20. Friedberg MK, Redington AN. Right versus left ventricular failure: differences, similarities, and interactions. *Circulation* 2014;**129**:1033–1044.
21. Brucks S, Little WC, Chao T, Kitzman DW, Wesley-Farrington D, Gandhi S, Shihabi ZK. Contribution of left ventricular diastolic dysfunction to heart failure regardless of ejection fraction. *Am J Cardiol* 2005;**95**:603–606.
22. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;**62**:263–271.
23. Linke WA. Titin gene and protein functions in passive and active muscle. *Annu Rev Physiol* 2018;**80**:389–411.
24. Gotzmann M, Grabbe S, Schöne D, von Frieling-Salewsky M, dos Remedios CG, Strauch J, Bechtel M, Dietrich JW, Tannapfel A, Mügge A, Linke WA. Alterations in titin properties and myocardial fibrosis correlate with clinical phenotypes in hemodynamic subgroups of severe aortic stenosis. *JACC Basic Transl Sci* 2018;**3**: 335–346.
25. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. *J Am Coll Cardiol* 2009;**54**:36–46.
26. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, Zile MR, Voors AA, Lefkowitz MP, Packer M, McMurray JJ, Solomon SD, Investigators P. Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2014;**63**:447–456.
27. DeVore AD, McNulty S, Alenezi F, Ersboll M, Vader JM, Oh JK, Lin G, Redfield MM, Lewis G, Semigran MJ, Anstrom KJ, Hernandez AF, Velazquez EJ. Impaired left ventricular global longitudinal strain in patients with heart failure with preserved ejection fraction: insights from the RELAX trial. *Eur J Heart Fail* 2017;**19**: 893–900.
28. Triposkiadis F, Pieske B, Butler J, Parissis J, Giamouzis G, Skoularigis J, Brutsaert D, Boudoulas H. Global left atrial failure in heart failure. *Eur J Heart Fail* 2016;**18**: 1307–1320.
29. von Roeder M, Rommel KP, Kowallick JT, Blazek S, Besler C, Fengler K, Lotz J, Hasenfuss G, Lucke C, Gutberlet M, Schuler G, Schuster A, Lurz P. Influence of left atrial function on exercise capacity and left ventricular function in patients with heart failure and preserved ejection fraction. *Circ Cardiovasc Imaging* 2017;**10**:e005467.
30. Triposkiadis F, Trikas A, Pitsavos C, Papadopoulos P, Toutouzas P. Relation of exercise capacity in dilated cardiomyopathy to left atrial size and systolic function. *Am J Cardiol* 1992;**70**:825–827.
31. Triposkiadis F, Giamouzis G, Parissis J, Starling RC, Boudoulas H, Skoularigis J, Butler J, Filippatos G. Reframing the association and significance of co-morbidities in heart failure. *Eur J Heart Fail* 2016;**18**:744–758.
32. van Deursen VM, Urso R, Laroche C, Damman K, Dahlstrom U, Tavazzi L, Maggioni AP, Voors AA. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2014;**16**:103–111.
33. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC; Get With the Guidelines Scientific Advisory Committee and Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation* 2012;**126**:65–75.
34. Campbell RT, McMurray JJ. Comorbidities and differential diagnosis in heart failure with preserved ejection fraction. *Heart Fail Clin* 2014;**10**:481–501.
35. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, Kjeldsen K, Jankowska EA, Atar D, Butler J, Fiuzat M, Zannad F, Pitt B, O'Connor CM. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 2014;**64**:2281–2293.
36. Ho JE, Enserro D, Brouwers FP, Kizer JR, Shah SJ, Psaty BM, Bartz TM, Santhanakrishnan R, Lee DS, Chan C, Liu K, Blaha MJ, Hillege HL, van der Harst P, van Gilst WH, Kop WJ, Gansevoort RT, Vasan RS, Gardin JM, Levy D, Gottdiener JS, de Boer RA, Larson MG. Predicting heart failure with preserved and reduced ejection fraction: the international collaboration on heart failure subtypes. *Circ Heart Fail* 2016;**9**:e003116.
37. Packer M. Leptin-aldosterone-neprilysin axis: identification of its distinctive role in the pathogenesis of the three phenotypes of heart failure in people with obesity. *Circulation* 2018;**137**:1614–1631.
38. Brutsaert DL. Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance, and rhythmicity. *Physiol Rev* 2003;**83**:59–115.
39. Brutsaert DL. Role of endocardium in cardiac overloading and failure. *Eur Heart J* 1990;**11**(Suppl. G):8–16.
40. De Keulenaer GW, Segers VFM, Zannad F, Brutsaert DL. The future of pleiotropic therapy in heart failure. Lessons from the benefits of exercise training on endothelial function. *Eur J Heart Fail* 2017;**19**:603–614.
41. Vermeulen Z, Hervent AS, Dugaucquier L, Vandekerckhove L, Rombouts M, Beyens M, Schrijvers DM, De Meyer GRY, Maudsley S, De Keulenaer GW, Segers V. Inhibitory actions of the NRG-1/ErbB4 pathway in macrophages during tissue fibrosis in the heart, skin, and lung. *Am J Physiol Heart Circ Physiol* 2017;**313**: H934–H945.
42. Segers VFM, Brutsaert DL, Keulenaer Gw D. Cardiac remodeling: endothelial cells have more to say than just no. *Front Physiol* 2018;**9**:382.
43. Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, LeWinter MM, Joseph SM, Shah SJ, Semigran MJ, Felker GM, Cole RT, Reeves GR, Tedford RJ, Tang WH, McNulty SE, Velazquez EJ, Shah MR, Braunwald E; NHLBI Heart Failure Clinical Research Network. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med* 2015;**373**:2314–2324.
44. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E; RELAX Trial. Effect of phosphodiesterase-5

inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2013;**309**:1268–1277.
45. Borlaug BA, Anstrom KJ, Lewis GD, Shah SJ, Levine JA, Koepp GA, Givertz MM, Felker GM, LeWinter MM, Mann DL, Margulies KB, Smith AL, Tang WHW, Whellan DJ, Chen HH, Davila-Roman VG, McNulty S, Desvigne-Nickens P, Hernandez AF, Braunwald E, Redfield MM, National HL, Blood Institute HF, Clinical Research N. Effect of inorganic nitrite vs placebo on exercise capacity among patients with heart failure with preserved ejection fraction: the INDIE-HFpEF randomized clinical trial. *JAMA* 2018;**320**:1764–1773.
46. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA* 2010;**304**:2503–2512.
47. Gohar A, Chong JPC, Liew OW, den Ruijter H, de Kleijn DPV, Sim D, Yeo DPS, Ong HY, Jaufeerally F, Leong GKT, Ling LH, Lam CSP, Richards AM. The prognostic value of highly sensitive cardiac troponin assays for adverse events in men and women with stable heart failure and a preserved vs. reduced ejection fraction. *Eur J Heart Fail* 2017;**19**:1638–1647.
48. Park KC, Gaze DC, Collinson PO, Marber MS. Cardiac troponins: from myocardial infarction to chronic disease. *Cardiovasc Res* 2017;**113**:1708–1718.
49. Obokata M, Reddy YNV, Melenovsky V, Kane GC, Olson TP, Jarolim P, Borlaug BA. Myocardial injury and cardiac reserve in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2018;**72**:29–40.
50. de Boer RA, Nayor M, deFilippi CR, Enserro D, Bhambhani V, Kizer JR, Blaha MJ, Brouwers FP, Cushman M, Lima JAC, Bahrami H, van der Harst P, Wang TJ, Gansevoort RT, Fox CS, Gaggin HK, Kop WJ, Liu K, Vasan RS, Psaty BM, Lee DS, Hillege HL, Bartz TM, Benjamin EJ, Chan C, Allison M, Gardin JM, Januzzi JL Jr, Shah SJ, Levy D, Herrington DM, Larson MG, van Gilst WH, Gottdiener JS, Bertoni AG, Ho JE. Association of cardiovascular biomarkers with incident heart failure with preserved and reduced ejection fraction. *JAMA Cardiol* 2018;**3**:215–224.
51. Benedict CR, Weiner DH, Johnstone DE, Bourassa MG, Ghali JK, Nicklas J, Kirlin P, Greenberg B, Quinones MA, Yusuf S. Comparative neurohormonal responses in patients with preserved and impaired left ventricular ejection fraction: results of the Studies of Left Ventricular Dysfunction (SOLVD) Registry. The SOLVD Investigators. *J Am Coll Cardiol* 1993;**22**:146A–153A.
52. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002;**288**:2144–2150.
53. Seravalle G, Quarti-Trevano F, Dell'Oro R, Gronda E, Spaziani D, Facchetti R, Cuspidi C, Mancia G, Grassi G. Sympathetic and baroreflex alterations in congestive heart failure with preserved, midrange and reduced ejection fraction. *J Hypertens* 2019;**37**:443–448.
54. Aoki T, Fukumoto Y, Sugimura K, Oikawa M, Satoh K, Nakano M, Nakayama M, Shimokawa H. Prognostic impact of myocardial interstitial fibrosis in non-ischemic heart failure: comparison between preserved and reduced ejection fraction heart failure. *Circ J* 2011;**75**:2605–2613.
55. Roy C, Slimani A, de Meester C, Amzulescu M, Pasquet A, Vancraeynest D, Beauloye C, Vanoverschelde JL, Gerber BL, Pouleur AC. Associations and prognostic significance of diffuse myocardial fibrosis by cardiovascular magnetic resonance in heart failure with preserved ejection fraction. *J Cardiovasc Magn Reson* 2018;**20**:55.
56. Georgiadou P, Adamopoulos S. Skeletal muscle abnormalities in chronic heart failure. *Curr Heart Fail Rep* 2012;**9**:128–132.
57. Kitzman DW, Haykowsky MJ, Tomczak CR. Making the case for skeletal muscle myopathy and its contribution to exercise intolerance in heart failure with preserved ejection fraction. *Circ Heart Fail* 2017;**10**:e004281.
58. Paneroni M, Pasini E, Comini L, Vitacca M, Schena F, Scalvini S, Venturelli M. Skeletal muscle myopathy in heart failure: the role of ejection fraction. *Curr Cardiol Rep* 2018;**20**:116.
59. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006;**27**:2338–2345.
60. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, McMurray JJV, Solomon SD. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail* 2018;**20**:1230–1239.
61. Khan MS, Fonarow GC, Khan H, Greene SJ, Anker SD, Gheorghiade M, Butler J. Renin-angiotensin blockade in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail* 2017;**4**:402–408.
62. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton M, Coats AJ, Poole-Wilson PA, Flather MD; SENIORS Investigators. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol* 2009;**53**:2150–2158.
63. Liu F, Chen Y, Feng X, Teng Z, Yuan Y, Bin J. Effects of beta-blockers on heart failure with preserved ejection fraction: a meta-analysis. *PLoS One* 2014;**9**:e90555.
64. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau J-L, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015;**131**:34–42.
65. Lund LH, Jurga J, Edner M, Benson L, Dahlstrom U, Linde C, Alehagen U. Prevalence, correlates, and prognostic significance of QRS prolongation in heart failure with reduced and preserved ejection fraction. *Eur Heart J* 2013;**34**:529–539.
66. Joseph J, Claggett BC, Anand IS, Fleg JL, Huynh T, Desai AS, Solomon SD, O'Meara E, Mckinlay S, Pitt B, Pfeffer MA, Lewis EF. QRS duration is a predictor of adverse outcomes in heart failure with preserved ejection fraction. *JACC Heart Fail* 2016;**4**:477–486.
67. Chung ES, Katra RP, Ghio S, Bax J, Gerritse B, Hilpisch K, Peterson BJ, Feldman DS, Abraham WT. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. *Eur J Heart Fail* 2010;**12**:581–587.
68. Stecker EC, Vickers C, Waltz J, Socoteanu C, John BT, Mariani R, McAnulty JH, Gunson K, Jui J, Chugh SS. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. *J Am Coll Cardiol* 2006;**47**:1161.
69. Vaduganathan M, Claggett BL, Chatterjee NA, Anand IS, Sweitzer NK, Fang JC, O'Meara E, Shah SJ, Hegde SM, Desai AS, Lewis EF, Rouleau J, Pitt B, Pfeffer MA, Solomon SD. Sudden death in heart failure with preserved ejection fraction: a competing risks analysis from the TOPCAT Trial. *JACC Heart Fail* 2018;**6**:653–661.
70. Vaduganathan M, Patel RB, Michel A, Shah SJ, Senni M, Gheorghiade M, Butler J. Mode of death in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2017;**69**:556–569.
71. Heining C, Horak P, Groschel S, Glimm H, Frohling S. [Personalized oncology]. *Radiologe* 2017;**57**:804–811.
72. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C, Investigators A-A. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016.
73. Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? *Heart* 2018;**104**:1156–1164.