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Sudden death in heart failure with preserved ejection fraction and beyond: an elusive target

Antonis S. Manolis[1] · Antonis A. Manolis[2] · Theodora A. Manolis[3] · Helen Melita[4]

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Abstract

Heart failure (HF) with preserved ejection fraction (HFpEF) represents half of HF patients, who are more likely older, women, and hypertensive. Mortality rates in HFpEF are higher compared with age- and comorbidity-matched non-HF controls and lower than in HF with reduced ejection fraction (HFrEF); the majority (50–70%) are cardiovascular (CV) deaths. Among CV deaths, sudden death (SD) (~ 35%) and HF-death (~ 20%) are the leading cardiac modes of death; however, proportionally, CV deaths, SD, and HF-deaths are lower in HFpEF, while non-CV deaths constitute a higher proportion of deaths in HFpEF (30–40%) than in HFrEF (~ 15%). Importantly, the underlying mechanism of SD has not been clearly elucidated and non-arrhythmic SD may be more prominent in HFpEF than in HFrEF. Furthermore, there is no specific strategy for identifying high-risk patients, probably due to wide heterogeneity in presentation and pathophysiology of HFpEF and a plethora of comorbidities in this population. Thus, the management of HFpEF remains problematic due to paucity of data on the clinical benefits of current therapies, which focus on symptom relief and reduction of HF-hospitalization by controlling fluid retention and managing risk-factors and comorbidities. Matching a specific pathophysiology or mode of death with available and novel therapies may improve outcomes in HFpEF. However, this still remains an elusive target, as we need more information on determinants of SD. Implantable cardioverter-defibrillators (ICDs) have changed the landscape of SD prevention in HFrEF; if ICDs are to be applied to HFpEF, there must be a coordinated effort to identify and select high-risk patients.

Keywords Heart failure · Heart failure with preserved ejection fraction · Sudden death · Sudden cardiac death · Non-cardiac sudden death · Cardiovascular death · Non-cardiovascular death · Left ventricular dysfunction · Ventricular tachycardia · Ventricular fibrillation · Cardiac arrest

Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CKD	Chronic kidney disease
CMR	Cardiac magnetic resonance (imaging)
CV	Cardiovascular
DM	Diabetes mellitus
ECG	Electrocardiogram
EP	Electrophysiology
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICD	Implantable cardioverter defibrillator
LGE	Late gadolinium enhancement
LV	Left ventricle(−ular)
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NICM	Non-ischemic cardiomyopathy
PCI	Percutaneous coronary intervention
RCT	Randomized controlled trial
RV	Right ventricular
SCD	Sudden cardiac death

✉ Antonis S. Manolis
asm@otenet.gr

[1] Third Department of Cardiology, Athens University School of Medicine, Vas. Sofias 114, 115 27 Athens, Greece

[2] Patras University School of Medicine, Patras, Greece

[3] Red Cross Hospital, Athens, Greece

[4] Onassis Cardiac Surgery Center, Athens, Greece

SD	Sudden death
STEMI	ST elevation myocardial infarction
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VTA	Ventricular tachyarrhythmia

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) represents ~ 50% (31–84%) of HF patients [1–5]. These patients are more likely to be older, women, and hypertensive [3]. Mortality rates in patients with HFpEF are clearly elevated compared with age- and comorbidity-matched controls without HF [6]. The majority of deaths in HFpEF are cardiovascular (CV) deaths, comprising 50–70% of deaths in epidemiological and clinical studies; CV mortality rates are a bit lower than in those with HF with reduced ejection fraction (HFrEF) [5, 7]. Among CV deaths, sudden death (SD) (~ 35%) and HF death (~ 20%) are the leading cardiac modes of death in this HF population. Compared with HFrEF, the proportions of CV deaths, SD, and HF deaths are lower in HFpEF. On the other hand, non-CV deaths constitute a higher proportion of deaths in HFpEF (30–40%) than in HFrEF (~ 15%), a result of older age and higher comorbidity rates in HFpEF [6]. Significant mortality risk factors include, among others, age, gender, body mass index, burden of comorbidities, and coronary artery disease (CAD) (Table 1). Importantly, the contribution of ventricular tachyarrhythmias (VTAs) to SD has not been clearly demonstrated in patients with HFpEF [9], as it has been in patients with HFrEF [10], and thus, the underlying mechanism of SD may be different in these patients. Hence, SD could be sudden cardiac death (SCD), either arrhythmic SCD (most commonly attributable to ventricular tachycardia (VT) or ventricular fibrillation (VF) and less commonly to bradyarrhythmias or pulseless electrical activity), or non-arrhythmic SCD (attributable to cardiac or vascular catastrophe, such as pulmonary embolus, stroke, or cardiac or vascular rupture) [11] (Fig. 1). However, SD could also be due to non-cardiac causes, such as pulmonary disease and acute hemorrhage [15].

Although SD has been estimated to be a frequent cause of death in HFpEF (≥ 1/4–1/3 of all deaths), a specific strategy for identifying high-risk patients is unknown. In TOPCAT (2018), SD constituted ~ 21–24% of deaths in HFpEF [16]. Male sex and diabetes mellitus (DM) identified patients at higher risk for SD [12]. Sudden death and all-cause mortality were lower in patients with HFpEF than in patients with HFrEF [17]. In the CHARM-preserved trial, among 3022 patients with HFpEF, defined as left ventricular (LV) ejection fraction (LVEF) > 40%, the SD rate was 4.4% compared with a 9.4–12.5% SD rate in the other CHARM component trials with HFrEF [18].

Table 1 Risk factors and comorbidities for sudden death in HFpEF

Age
Males
Hypertension
CAD
Prior MI
No recovery of initially reduced LVEF after MI
DM
Obesity
Atrial fibrillation
CKD
Anemia
PHTN
SDB
HCM
Infiltrative CM
LBBB
Electrical risk score *
Heart rate, LVH, QRS transition zone, QRS-T angle, QTc, and T-peak-to-T-end interval
Biomarkers
NT-pro-BNP
? Soluble ST2 protein/? Galectin-3
Imaging
Mid-wall LGE on CMR
RV dysfunction on echo
Genetics
Underlying genetic predisposition to electrical instability

BNP type B natriuretic peptide, *CAD* coronary artery disease, *CM* cardiomyopathy, *CMR* cardiac magnetic resonance (imaging), *QTc* corrected QT interval, *DM* diabetes mellitus, *HCM* hypertrophic cardiomyopathy, *LGE* late gadolinium enhancement, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *MI* myocardial infarction, *PHTN* pulmonary hypertension, *RV* right ventricular, *SDB* sleep disordered breathing

*subjects with ≥ 4 ECG abnormalities had an odds ratio (OR) of 26.1 for SCD ($p < 0.001$) in the LVEF > 35% subgroup [8]

In the I-PRESERVE trial, the annual mortality rate was 5.2%. The cause of death was cardiovascular in 60% (including 26% sudden, 14% heart failure, 5% myocardial infarction, and 9% stroke), non-CV in 30%, and unknown in 10% [19]. Treatment with irbesartan did not affect overall mortality or the distribution of mode-specific mortality rates.

As mentioned, according to the I-PRESERVE trial, among 4128 patients with HFpEF, the incidence of SD was 26% [20]. Multivariate analysis in 3480 patients identified a subgroup of 837 (24%) patients with 11% cumulative incidence of SD over 5 years, compared with a 4% incidence of SD in the lower risk group; 32% of all deaths were SD in the higher risk group compared with 26% in the entire I-PRESERVE cohort.

For all these issues and for the compilation of presented data on SD in HFpEF and beyond (including all types of SD

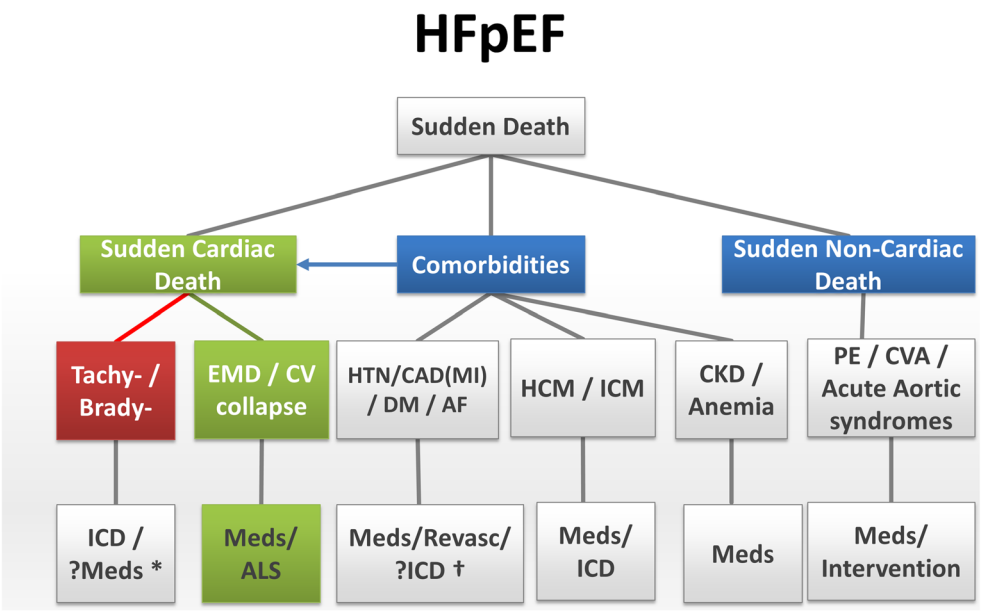

Fig. 1 The schema illustrates the various causes of sudden death in patients with heart failure with preserved ejection fraction (HFpEF) and the contributing comorbidities, as well as the possible therapies available. AF, atrial fibrillation; ALS, advanced life support; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; CVA, cerebrovascular accident; DM, diabetes mellitus; EMD, electromechanical dissociation; HCM, hypertrophic cardiomyopathy; HTN, hypertension; ICD, implantable cardioverter defibrillator; ICM, infiltrative cardiomyopathy; Meds, medications; MI, myocardial infarction; PE, pulmonary embolism; Revasc, revascularization. *Sudden death was numerically, but not statistically, lower in HFpEF patients treated with spironolactone compared with placebo in the TOPCAT trial [12]; according to the Swedish Heart Failure Registry, the use of ACE inhibitors/ARBs in HFpEF patients was associated with lower all-cause mortality [13]. †the MADIT S-ICD trial will evaluate subcutaneous ICD therapy in patients with diabetes mellitus, prior myocardial infarction, and LVEF of 36–50% [14] (recently halted due to poor enrollment)

and all patients with LVEF > 35%), an extensive literature review was conducted on the topics of SD, SCD, arrhythmic- and non-arrhythmic death, CV death in HFpEF, HFpEF, diastolic HF, mild-moderate LV dysfunction, VTAs, VT and VF in HFpEF, implantable cardioverter defibrillators (ICDs) in HFpEF, and relevant similar subjects with a focus on SD, carried out in PubMed, Scopus, and Google Scholar.

Definitions

HFpEF (LVEF ≥ 50%) remains the main focus of our discussion, which though may extend beyond HFpEF and include all patients with LVEF > 35%, such as patients with HF with mid-range LVEF (HFmrEF) (40–49%) and patients with mild (LVEF 41–49%) and moderate (LVEF 36–40%) LV dysfunction [21].

With regard to the definitions of sudden death (SD), there is great heterogeneity [22]. As mentioned, sudden death could be SCD, either arrhythmic SCD (tachy- or brady-arrhythmic) or pulseless electrical activity; or non-arrhythmic cardiac or vascular SD (e.g., coronary occlusion, pulmonary embolus, stroke, or cardiac or vascular rupture) [11, 22] (**Fig. 1**). Finally, SD could also be non-cardiac (e.g., from pulmonary disease, acute hemorrhage) [15]. A recent postmortem ICD interrogation analysis reviewing 22 studies with 23,600 participants assessed the proportion of SCDs in patients with an ICD who had a confirmed arrhythmia and indicated that VTAs were present at the time of death in 76% of "sudden" deaths, while 24% of such deaths were identified as nonarrhythmic [23].

Causes and modes of death

Cause of death relates to the mechanisms by which death occurs, such as arrhythmia, acute myocardial infarction (MI), or progressive HF [22]. Mode of death indicates the way patients die and is described as sudden or non-sudden [24]. Although mode and cause of death are not the same, they are often used interchangeably. Sudden death has various underlying causes, such as VTAs, acute MI, pulmonary embolism, myocardial rupture, aortic dissection, and stroke (Fig. 1).

According to randomized controlled trials (RCTs), in ~ 60–70%, the causes of death are of CV origin in patients with HFpEF, attributed to SD in the majority (~ 25–30%) of cases, to LV dysfunction in ~ 20–30%, and to MI and stroke in a smaller percentage (~ 5–15%) [7]. In ~ 20–30%, the causes are non-CV and ~ 5–20% unknown. According to epidemiological studies, CV causes of death account for ~ 60%, attributed to SD in ~ 20–30%, HF in ~ 17–60%, MI and stroke in ~ 15–20%; again, non-CV causes account for 20–30% of cases [7].

In a prospective study of 1203 patients with HFpEF and LVEF ≥ 50% grouped into very young (< 55 years of age; n = 157), young (55–64 years of age; n = 284), older (65–74 years of age; n = 355), and elderly (≥ 75 years of age; n = 407), younger age was associated with male preponderance and a higher prevalence of obesity (body mass index ≥ 30 kg/m^2; 36% in very young HFpEF vs 16% in elderly) together with less renal impairment, atrial fibrillation (AF), and hypertension (all $p < 0.001$) [25]. Left ventricular filling pressures and prevalence of LV hypertrophy (LVH) were similar in very young and elderly HFpEF. Quality of life was better, and death and HF hospitalization at 1 year occurred less frequently ($p < 0.001$) in the very young (7%) compared with elderly (21%) HFpEF patients. Compared with control subjects, very young HFpEF patients had a 3-fold higher death rate and 3-fold higher prevalence of LVH.

The mode of death was investigated among 323 patients in whom information was available on both the mode of death and LVEF on echocardiography in a prospective registry (JCARE-CARD) of 2675 patients hospitalized with worsening HF [26]. Over a mean of 2.1 years, the mode of death was CV in 63% (including 17% sudden, 36% HF, 3% MI, and 3% stroke), non-CV in 23%, and unknown in 14%. The prevalence of CV death including SD was higher in patients with HFrEF compared with HFpEF (68% vs 58%, $p = 0.020$). Heart failure death, the most common mode of death, was similar between groups (37% vs 35%, $p = 0.694$). In contrast, non-CV mortality was significantly higher in HFpEF than those with HFrEF (28% vs 18%, $p = 0.021$).

According to another more recent prospective registry of 230 patients with a diagnosis of HFpEF, over a mean of 2 ½ years, the overall mortality rate was 16.5%; 60.5% of deaths were classified as CV, 34.2% as non-CV, and 5.3% as unknown [27]. Of the CV cases (n = 23), 91.4% of deaths were attributed to right HF, 4.3% died from stroke, and 4.3% from SD. Of the non-CV deaths (n = 13), 46.2% were attributed to major infections, 38.4% of deaths were related to cancer, 7.7% to ileus, and 7.7% to major bleeding.

In *summary*, despite some differences noted between RCTs and epidemiological studies, death in HFpEF is of CV origin in ~ 60–70%, with the majority being SD (~ 20–40%), followed by HF-death (~ 20–30%), and other CV death (MI and stroke in ~ 5–20%). In ~ 20–30%, the causes are non-CV and ~ 5–20% unknown.

Role of right ventricular (RV) dysfunction

A control study of 96 HFpEF patients and 46 controls showed that right ventricular (RV) dysfunction (defined by RV fractional area change < 35%) was common, found in 33% of HFpEF patients and was associated with more severe symptoms and greater comorbidity burden [28]. Over a median follow-up of 529 days, 31% of HFpEF patients died. In Cox analysis, RV dysfunction was the strongest predictor of death (hazard ratio-HR 2.4, $p < 0.0001$).

Among 314 patients with ischemic cardiomyopathy or non-ischemic cardiomyopathy (NICM), RV dysfunction was independently predictive of the primary outcome of SD or appropriate ICD therapy (hazard ratio = 2.98; $p = 0.002$) [29]. Among those with a LVEF > 35% (N = 121; mean LVEF, 45 ± 6%), RV dysfunction provided an adjusted hazard ratio of 4.2 ($p = 0.02$). The authors concluded that RV dysfunction is a strong, independent predictor of arrhythmic events; among patients with mild to moderate LV dysfunction, this marker provides robust discrimination of high- versus low-risk subjects.

As mentioned, in another study, among 230 patients with HFpEF, of the 60.5% deaths classified as CV deaths (n = 23), 91.4% of deaths were attributed to right heart failure [27]. The authors concluded that over half of all deaths in patients with HFpEF could directly be attributed to right heart failure, rendering the right ventricle a potential therapeutic target in a subset of HFpEF patients.

A recent observational study including 5463 consecutive patients admitted to the coronary care unit, of whom ~ 15% had mild and 17% had moderate-severe RV dysfunction, indicated that over a median of 14 months, the incidence of SCD was highest in patients with moderate-severe RV dysfunction (7.4% vs 4.4% in mild RV dysfunction vs 1.6% in normal RV function; $p < 0.001$) [30]. After adjustment for baseline characteristics, mild RV dysfunction (hazard ratio-HR, 1.57; p = 0.046) and moderate-severe RV dysfunction (HR, 1.91; p = 0.006) were independently associated with an increased risk of SCD. Moderate-severe RV dysfunction remained an independent predictor of SCD for patients with LVEF > 35% without or with preexisting ICD (HR, 4.12–5.04; $p < 0.001$).

In *summary*, RV dysfunction appears to be an independent predictor of arrhythmic events and SCD in patients with LVEF > 35%.

Mechanisms of sudden death in HFpEF or LVEF > 35%

Mechanisms involved in the SD pathogenesis in HFrEF may also increase the risk in patients with HFpEF or those with an LVEF > 35% [9, 11]. Worsening congestion, myocardial stretch, and neurohormonal activation due to the failing myocardium influence the risk of SD [31]. Imbalances in the autonomic nervous system, namely excess adrenergic tone, in HFpEF likely are involved in the pathogenesis of SD. The amount of denervated myocardium noted on nuclear imaging has been predictive of arrhythmic death in patients with ischemic cardiomyopathy [32]. Ischemia is an under-recognized contributor to progressive diastolic impairment and increased

VTAs in HFpEF [33]. Noninvasive tests lack sensitivity in detecting significant ischemia in this patient group and CAD often needs to be angiographically proven [34]. Left ventricular hypertrophy (LVH), one of the structural features of HFpEF, is associated with increased fibrosis, collagen deposition, and risk of SD [35]. Areas of fibrosis alter regional conduction patterns and serve as islands of reentry, which is the commonest underlying mechanism of sustained VTAs. A multifold increase in the risk of SCD has been observed among patients with ECG evidence of LVH and intraventricular conduction delay, and this risk has been reported as comparable with those with established symptomatic CAD [36].

Mineralocorticoid receptor activation has been shown to promote arrhythmia, both by increasing tissue remodeling and fibrosis and through electrophysiological (EP) alterations that lead to the formation of the arrhythmogenic substrate of reentry which is the underlying mechanism of monomorphic VT; or the substrate of triggered activity resulting from the premature activation of cardiac tissue by early and delayed after-depolarizations, which is the underlying mechanism of polymorphic VT, all potentially degenerating into VF leading to SCD [37]. Aldosterone is clearly involved in these pathophysiological effects, as a physiological ligand of the mineralocorticoid receptor, hence the anticipation that mineralocorticoid receptor antagonists (MRAs) might prevent these life-threatening arrhythmias and thus offer protection from SD. The latter has been shown in HFrEF [38–40], but remains to be confirmed in HFpEF [16].

On a molecular level, calcium overload in cardiomyocytes occurs in HFpEF and may result in cell-to-cell regional repolarization heterogeneity, establishing a substrate for fatal arrhythmias. Downregulation of certain enzymes involved in calcium reuptake into the sarcoplasmic reticulum (governed by the SERCA2a gene) may be responsible for cytoplasmic calcium overload, leading to delayed action potential durations, a known trigger for reentry [41]. On a microstructural basis, T-tubule disorganization and disruption of intracellular calcium cycling have been further implicated in early development of cardiac fibrosis and dysfunction in HFpEF. Altered calcium handling and increased oxidative stress in mitochondria may be central to development of HF and SCD [9]. Electrolyte deficits and proarrhythmic drugs may also play a role in SD in HF patients [42]. Finally, an important determinant of SD in HF could be an underlying genetic predisposition to electrical instability [11]. Autopsy studies characterizing the pathological myocardial correlates of SCD may better refine these mechanisms in HFpEF [9].

In *summary*, a variety of mechanisms including worsening congestion, myocardial stretch, neurohormonal activation, ischemia, electrolyte abnormalities, proarrhythmic drugs, calcium overload, myocardial fibrosis, and/or genetic susceptibility may be implicated in the pathogenesis of SD in patients with HFpEF or LVEF > 35%.

Risk factors/predictors for SCD in HFpEF

Validated prognostic scores/models have been suggested in the setting of HFpEF for all-cause mortality and hospitalizations. However, few data exist regarding the prediction of SCD. In an early study of 1941 HFpEF patients (LVEF > 50%), of whom 548 (28%) died (40 SD), 5 variables were found to be independently associated with a significant increase in the risk of SD; DM ($p < 0.01$), the presence of mild mitral regurgitation ($p < 0.01$), severity of HF ($p < 0.01$), the occurrence of a MI within 3 days prior to the date of the index cardiac catheterization ($p = 0.01$), and severity of CAD ($p = 0.02$) [43].

In the I-PRESERVE study, in a post hoc analysis of 4128 HFpEF patients, key risk predictors of SCD were characterized during a mean follow-up period of ~ 4 years [20]. Six variables were found independently associated with SCD risk: age (hazard ratio-HR 1.03), male sex (HR 1.79), history of DM (HR 1.80), history of prior MI (HR 1.60), the presence of left bundle branch block (LBBB) on the electrocardiogram (ECG) (HR 1.65), and natriuretic peptide (NP) levels (HR 1.63). These variables were predictive of increased all-cause mortality and a SCD risk at 5 years of > 10%.

According to the JCARE-CARD registry of a mixed-LVEF population, where independent predictors of SCD in patients were separately sought for patients with LVEF < 40% and LVEF ≥ 40%, estimated glomerular filtration rate (eGFR) was associated with SCD in the HFpEF cohort, but not in patients with HFrEF [26]. Furthermore, eGFR was not predictive of HF mortality in HFpEF; however, there were few SCD events in HFpEF ($n = 18$ over ~ 2 years).

According to a multivariate analysis of a prospective observational (KaRen) study of the long-term outcomes of 538 patients presenting with HFpEF, only the echocardiographic parameter of E/e' remained as a predictor of adverse clinical outcomes (death, HF hospitalization), with a hazard ratio of 1.49 ($p = 0.0012$) [44].

In a prospective registry study (CHART) of 357 stable HFpEF patients (mean LVEF 63%), of whom 39% had anemia (hemoglobin < 12 g/dl in women and < 13 g/dl in men), over a mean period of 3.6 ± 1.7 years, 30 (8.4%) patients died suddenly [45]. Multivariate analysis showed that lower hemoglobin level was significantly associated with the development of SD ($p < 0.001$). The authors concluded that anemia may be an important therapeutic target to reduce SD in HFpEF patients.

Finally, in the Maastricht circulatory arrest registry (2003) reporting on 492 SCD victims, the authors analyzed the subgroup of 101 SCD cases with high LVEF (> 50%); as was the case for the whole group, CAD was found to be the most important culprit (71%) in this subgroup as well, followed by valvular disease (10%) and hypertensive heart disease

(8%) [46]. However, within the SCD group with an LVEF > 50%, overt HF episodes had occurred in only 9% of cases.

In *summary*, several clinical, echocardiographic, ECG, and laboratory variables have been suggested as associated with a significant increase in the risk of SD in HFpEF, among which CAD and DM play a most important role (Table 1).

Comorbidities

Patients with HFpEF are more likely to be elderly, more often women and a significant proportion of these patients have several important comorbidities [4]. Clinical outcomes in these patients seem to be driven by these comorbidities that are more common in patients with HFpEF than patients with HFrEF [47–49]. Comorbidities include, among others, hypertension (~ 50–85%), CAD (30–60%), atrial fibrillation (AF) (~ 30%), DM (~ 30%), chronic kidney disease (CKD) (~25%), cerebrovascular disease (~ 15%), obesity, and anemia (Table 1) [3–5, 45, 49].

Hypertension Hypertension is considered as the most important cause of or risk factor for HFpEF development, with a prevalence of 50–85% in large RCTs, epidemiological studies, and HF registries [50]. The most important mechanisms that associate arterial hypertension and HFpEF are neuro-humoral-induced myocardial fibrosis and consequently LVH and LV diastolic dysfunction [51]. However, control of blood pressure in these patients has not sufficed to improve outcome. Large prospective studies are needed to define an adequate diagnostic and therapeutic approach to this expanding group of patients.

Coronary artery disease (CAD) CAD is present in up to 60% of HFpEF patients with distinct prognostic significance [1]. A Mayo Clinic experience exploring 376 HFpEF patients found that about 2/3 had evidence of obstructive CAD (> 50% stenosis) on coronary angiography, which tracked with adverse clinical course with declines in LVEF and excess mortality at follow-up. Interestingly, the subgroup of HFpEF patients with CAD had improved outcomes after any form of revascularization. As such, CAD represents a prevalent and potentially modifiable comorbidity in HFpEF, mechanistically associated with SCD.

In a prospective analysis of 591 HF patients (320 HFpEF and 271 HFrEF), CAD was less common (25%) in patients with HFpEF compared with patients with HFrEF (39%) ($p < 0.001$) [52]. Overall, over 10 years, CAD was independently predictive of all-cause and CV death. However, in HFpEF, the association between CAD and CV death was no longer observed after adjustment for covariates, while HFpEF patients with CAD appeared at greater risk of SD (adjusted HR 2.22).

The frequency of CAD was 36% among 4128 patients with HFpEF included in the I-PRESERVE study [53]. In presence of CAD, SD was the leading cause of death in HFpEF, while most patients with CAD and HFrEF died of refractory HF. After adjustment for other important variables, CAD remained independently predictive of SD in HFpEF. The authors concluded that patients with HFpEF and CAD are at higher risk of all-cause mortality and SD when compared with those without CAD.

In the era of early reperfusion therapy via fibrinolysis and/or primary percutaneous coronary intervention (PCI) of ST-elevation myocardial infarction (STEMI), preserved LV function is common [54]. However, despite preservation of LV systolic function, there remains a considerable risk for VTAs and SCD. The size of the infarcted myocardium seems to determine this risk as scar formation underlies the arrhythmogenic substrate. In the CLARITY-TIMI 28 study comprising 3491 patients with STEMI who underwent fibrinolytic therapy, 1436 patients underwent assessments of LV function, of whom 1133 had adequate CK-MB for analysis [55]. The median LVEF in this group was 55%, and most patients (87.1%) had LVEF $\geq$ 40%. Among patients with LVEF $\geq$ 40%, the ratio of peak CK-MB to the upper limit of normal was significantly associated with the incidence of VT/VF through 30 days (2.2%, 3.7%, and 5.5% across tertiles, respectively, $p = 0.041$ for trend) and the incidence of the composite of CV death, HF, shock, and VT/VF through 30 days (3.7%, 6.0%, 8.5%, respectively, $p = 0.018$ for trend). The authors concluded that, in patients with STEMI with preserved LV function after reperfusion therapy, larger infarct size, as estimated by peak serum CK-MB concentration, is significantly associated with VT/VF as well as other adverse clinical outcomes [55]. It should be noted, however, that it remains unclear whether this study is about bona fide HFpEF, but rather about patients with LVEF $\geq$ 40% possibly in New York Heart Association (NYHA) functional class I.

Change in LVEF between the early (2 to 7 days) and later (2 to 12 weeks) post-MI periods in patients with a first MI was assessed in 3 independent cohorts (REFINE, median baseline LVEF 40%; CARISMA, median LVEF $\leq$ 35%; ISAR, median LVEF 41–44%) [56]. In REFINE, the overall median LVEF of 40% measured 2 to 7 days post-MI increased to 49% by 8 to 10 weeks after MI; patients with no LVEF recovery had a higher risk of sudden cardiac arrest (SCA) (hazard ratio-HR 5.8, $p = 0.001$) and death (HR 3.9, $p < 0.001$), independent of revascularization, baseline LVEF, and medical therapy compared with patients with recovery. Similar findings were observed in the other cohorts. LVEF reassessments beyond 6 weeks post-MI were more predictive of outcome than were earlier reassessments. The authors concluded that the degree of LVEF recovery after a first MI provides important prognostic information. Patients with no recovery in LVEF after MI are at high risk of SCA events and death. It should be noted

that the majority of patients in these studies had NYHA class I symptoms of HF.

Although HFpEF patients with CAD are at increased risk of SD, the absolute rate is low (≈ 2% per year), and the potential role of ICD therapy is unclear, especially as coronary revascularization might also ameliorate this risk [53].

Diabetes mellitus (DM) DM is reported to be present in 30–40% of patients with HFpEF, [57, 58] associated with decreased exercise tolerance and increased hospitalization burden and may represent a target for therapy. In HFpEF, patients with DM have a worse clinical picture and a poorer prognosis [59]. Data are emerging which link diabetes and SCD in these patients [20].

According to the ARTEMIS study comprising 834 DM patients and 1112 nondiabetic patients with CAD and preserved ejection fraction, over a mean of ~ 6 years, SCDs/SCAs occurred in 50 patients [60]. The prevalence of SCD/SCA was higher in DM patients (4.1%) than in nondiabetic patients (1.4%) (adjusted hazard ratio 2.6; $p < 0.01$). The authors concluded that DM is an independent risk factor for SCD/SCA in CAD patients with preserved LVEF.

In the subset of the TOPCAT trial of the Americas comprising 1767 patients with HFpEF (EF ≥ 45%), over a median follow-up of 3 years, 77 patients experienced SD/aborted cardiac arrest (ACA) (1.4 events/100 patient-years), and 312 experienced non-SD/ACA (5.8 events/100 patient-years); SD accounted for ~ 20% of deaths [12]. After accounting for competing risks of non-SD/ACA, male sex and insulin-treated DM were independently predictive of composite SD/ACA (C-statistic = 0.65). The authors concluded that male sex and insulin-treated DM identified patients at higher risk for SD/ACA with modest discrimination.

Atrial fibrillation In a large Swedish registry cohort study (SwedeHF) comprising 41,446 patients, (23% HFpEF, 22% HFmrEF, and 55% HFrEF), the prevalence of AF was highest in HFpEF (65%) compared with HFmrEF (60%) and HFrEF (53%) [61]. In all 3 LVEF groups the prevalence of AF was higher in men, and increased with age. The prevalence ranged from a minimum of 21% in women < 60 years of age with HFrEF and HFmrEF to a maximum of 77% in men > 90 years of age with HFpEF. AF (vs sinus rhythm) was associated with similarly increased mortality risk in all LVEF groups (adjusted hazard ratios 1.11 in HFpEF, 1.22 in HFmrEF, and 1.17 in HFrEF).

Anemia Recent data from the Swedish Heart Failure Registry comprising 24,856 HFrEF patients and 6488 HFpEF patients indicated that anemia was more prevalent in the group of HFpEF patients (43.7% vs 33.8%, $p < 0.0001$), while it was an independent predictor of mortality in both groups (hazard ratio 1.70 vs 1.65) [62]. Results of the Japanese HFpEF registry, reported recently for 535 HFpEF patients, indicated that the prevalence rate of anemia on admission was ~ 70% in both male and female HFpEF patients [63]. Anemic patients had poor prognosis compared with non-anemic patients; blood hemoglobin level at discharge (< 9.4 g/dL for male and < 12.3 g/dL for female) was an independent predictor of all-cause mortality in HFpEF patients.

As mentioned, according to a prospective study of 357 HFpEF patients, whereby anemia was present in 39%, lower hemoglobin level was significantly associated with the development of SD in the multivariate model ($P < 0.001$) [45]. The authors concluded that anemia may be an important therapeutic target to reduce SD in HFpEF patients. However, anemia was not confirmed a major contributor in identifying patients with HFpEF at a high risk of SCD as evaluated in the I-PRESERVE trial in a multivariable prediction model [20]. On the other hand, in a recent nationwide cohort study in South Korea, anemia was identified as a risk factor for SCD even in the general population with the association persisting after accounting for comorbidities such as hypertension, DM, and MI [64]. QTc prolongation and LVH, which are associated with SCD, increased with the severity of anemia.

Chronic kidney disease In a recent analysis of patients with HFpEF enrolled in the Americas region of the TOPCAT trial, it was found that moderately severe renal dysfunction at baseline (eGFR < 45 ml/min/1.73 m^2) was associated with older age, female sex, greater comorbidity burden, and more severe HF [65]. Rates of CV outcomes were nearly doubled in patients with severe renal dysfunction compared with those with lesser degrees of renal dysfunction. The incidence of the primary endpoint (composite of CV death, aborted cardiac arrest, or HF hospitalization) was 9.1 per 100 patient-years in patients with an eGFR of ≥ 60 ml/min/1.73 m^2, 10.6 per 100 patient-years in patients with an eGFR of 45–60 ml/min/1.73 m^2, and 18.4 per 100 patient-years in patients with an eGFR of < 45 ml/min/1.73 m^2. There were similar associations between eGFR and the composite outcome of aborted cardiac arrest or SD (incidence rates 1.1 vs 1.4 vs 2.1, respectively) [65]. According to a prior meta-analysis of 57 studies (1,076,104 HF patients) investigating CKD (prevalence at 32%), the presence of CKD was of greater prognostic importance in patients with more preserved LVEF, with CKD conferring a higher mortality risk in HFPEF, probably attributable to underlying disease, such as hypertension and DM, both of which are associated with impaired eGFR and worse outcome [66].

In *summary*, several risk factors and comorbidities have been identified to predispose to SD in HFpEF patients, including DM, CAD, history of MI, AF, anemia, and CKD (Table 1, Fig. 1). Based on the Maastricht circulatory arrest registry, one might infer that, although hypertension is the most common comorbidity in HFpEF, CAD is likely the underlying

structural heart disease in most SD victims [46]. In the era of reperfusion via fibrinolysis and/or primary PCI in acute MI, more patients with preserved LVEF are encountered and one has to identify those with large-sized infarcts or no recovery in baseline post-MI LVEF who remain at risk for SD.

Biomarkers

In a retrospective analysis of the HF-ACTION trial comprising 813 chronic HFrEF patients, all studied biomarkers (NT-proBNP, soluble ST2, and galectin-3) were independently predictive of both pump failure and SCD; less robustly predictive of SCD compared with pump failure [67]. However, the combination of ST2 and galectin-3 allowed for improved appropriate net reclassification of SCD. Nevertheless, in the case of HFpEF, limited data are available regarding biomarkers and SCD.

Galectin-3 in HFpEF appears to be an emerging marker of cardiac fibrosis and LV remodeling [68–70] and an attractive and pathophysiologically promising marker in SCD risk prediction. In a study of 377 patients with HFpEF, higher galectin-3 levels at baseline were associated with a worse patient status, while an increase in galectin-3 over time was associated with an increased risk of death or hospitalization after adjustment for known prognostic markers, including NT-proBNP [71]. Galectin-3 is, however, closely linked to progression of CKD [72], which, in turn, is a known predictor of SCD [73, 74]. All these surrogates are associated with overall risk, but do not seem to adequately capture and discriminate SCD-specific risk.

In a comparative study of 217 hospitalized patients with HF (172 HFpEF, 45 HFrEF) and 30 controls, the concentrations of galectin-3 and NT-proBNP were higher compared with controls but much higher in HFrEF (both $p = 0.000$) [70]. After adjustment for clinical factors and NT-proBNP, galectin-3 was strongly correlated with an increased risk of the endpoint events (CV death and HF hospitalization) in HFpEF patients, and the hazard ratio per 1 SD increase of the galectin-3 level was 2.33 ($p = 0.009$).

In a retrospective analysis, comprising 2152 patients with HFrEF (LVEF < 40%), of whom 1419 were in sinus rhythm and 733 had AF, and 524 patients with HFpEF (LVEF ≥ 50%), of whom 286 in sinus rhythm and 238 with AF, the biomarker profiles (of 92 CV risk markers measured) were compared between HFrEF and HFpEF. The circulating biomarker pattern observed in HFrEF was different from the pattern in HFpEF; the authors concluded that these findings suggest differences in underlying pathophysiological mechanisms of AF in these two HF phenotypes [75].

In the I-PRESERVE trial, NT-proBNP (measured in 3480 HFpEF patients) above the median of 339 pg/mL was independently associated with an increased risk of the primary end point of all-cause mortality and prespecified CV hospitalizations (adjusted hazard ratio—HR, 1.79; $p < 0.001$); all-cause mortality (HR, 2.04; $p < 0.001$); and a composite of HF events, including HF death or SD or HF hospitalization (adjusted HR, 1.77; $p < 0.001$) [76].

In the TOP-CAT trial, among 687 HFpEF patients with available natriuretic peptides (NPs) (BNP or NT-proBNP) at baseline, higher levels of NPs were independently associated with an increased risk for the primary endpoint of CV mortality, aborted cardiac arrest, or hospitalization for HF [77]. Furthermore, both in the I-PRESERVE and TOP-CAT trials, treatment (irbesartan and spironolactone, respectively) appeared to have greater benefit in patients with lower compared with higher baseline BNP [76, 77], indicating that elevated NPs in HFpEF seem to identify a higher risk patient group that is less responsive to treatment.

In *summary*, limited data are available regarding biomarkers and SCD in HFpEF; galectin-3 appears to be an emerging marker of cardiac fibrosis and LV remodeling and thus a potential marker of an arrhythmogenic substrate (reentry) for malignant VTAs and SCD. Also, higher NP levels in HFpEF are associated with worse outcome, whether this is related to HF risk alone or also implicated in SCD requires further substantiation. Other HF markers under investigation include cardiac troponin, protein ST2, and microRNAs [78, 79].

ECG parameters

The electrocardiogram (ECG) is useful in post-MI and HFrEF cohorts. Depolarization and/or repolarization abnormalities, such as QRS duration, fragmentation of the QRS complex, J-point elevation, late potentials on signal-averaged ECG (SAECG), and T-wave alternans have been variably predictive of SCD risk in these populations [80]. However, their clinical utility has not been proven as their positive predictive value has remained relatively low, and these parameters have not been routinely adopted for risk prediction [81, 82].

The data regarding these ECG-based variables in HFpEF are even more limited. In the I-PRESERVE trial, both prolongation of QRS duration and abnormal QRS morphology (LBBB/non-LBBB) were found to be a predictor of SCD in this sample [20, 83]. QRS duration has also been associated with all-cause mortality in a large series of HFpEF patients in the Swedish HF Registry [84]. Several metrics of ECG analysis, including QRS-T angle, T-peak to T-end interval, and QT interval, have been shown to adversely predict diastolic dysfunction and abnormal cardiac structure/function, but have not been explored or validated for SCD risk prediction [9, 81, 85, 86].

A large cohort study comprising 872 HFpEF patients (LVEF ≥ 50%) showed that prolonged QRS duration

(≥ 120 ms) increased all-cause mortality by univariable (HR 1.71, $P < 0.001$) and multivariable analysis (HR 1.31, $p = 0.04$) over a median follow-up of 660 days [87].

In a post hoc analysis of the TOPCAT trial, the QRS duration of ≥ 120 ms was independently associated with an increased risk of the primary outcome (composite of CV death, aborted cardiac arrest, or HF hospitalization) ($p = 0.009$) and HF hospitalization ($p = 0.003$) [88]. There was a linear relation of QRS duration with risk of the primary outcome and HF hospitalization. No interaction was observed between treatment with spironolactone and QRS duration. The authors concluded that this post hoc analysis demonstrated that prolonged QRS duration identifies HFpEF subjects at a higher risk of adverse clinical outcomes, and that spironolactone had a similar effect on outcomes independent of QRS duration.

In *summary*, although several ECG markers have been suggested to predict prognosis in HFpEF, the QRS duration and morphology (LBBB) seem to predominate as in HFrEF, although this has not been a consistent finding in all studies, particularly in patients with NICM [89].

Cluster-based phenotyping

In a prospective study of 397 patients with HFpEF (mean age 65 ± 12 years; 62% female; 39% black; with common comorbidities), detailed clinical, laboratory, ECG, and echocardiographic phenotyping was performed using machine-learning techniques (67 continuous variables) [90]. Although all patients met published criteria for the diagnosis of HFpEF, phenomapping analysis classified study participants into 3 distinct groups that differed markedly in clinical characteristics, cardiac structure/function, invasive hemodynamics, and outcomes. Phenogroup 3 had an increased risk of HF hospitalization (hazard ratio, 4.2) even after adjustment for traditional risk factors (< 0.001). Patients in this group were older, more frequently male, and had elevated NP levels and higher rates of advanced CKD and AF. Although this group was demonstrated to have independently higher HF hospitalization risk, data were not presented regarding cause-specific event rates including SCD. The HFpEF phenogroup classification, including its ability to stratify risk, was successfully replicated in a prospective validation cohort ($n = 107$) [90].

In *summary*, phenomapping in HFpEF indicated that older patients with significant CKD, electrophysiological and myocardial remodeling, pulmonary hypertension, and RV dysfunction have a high-risk profile.

Risk scores

A multivariable prediction model for sudden cardiac death (SCD) in HFpEF patients was suggested by the investigators of the I-PRESERVE trial able to identify patients with a ≥ 10% risk of SCD over 5 years, similar to the risk of SCD in the SCD-Heft trial [20]. Specifically, among 3480 patients, the proposed risk score comprising 6 variables (age, gender, history of DM and MI, LBBB, and the natural logarithm of NT-proBNP) identified a subgroup of 837 (24%) patients with ≥ 10% cumulative incidence of SCD over 5 years, accounting for other deaths as competing risk. The 5-year cumulative incidence of SCD was 11% in the higher and 4% in the lower risk groups. In the higher risk group, 32% of deaths were SCD compared with 26% in the entire I-PRESERVE cohort.

In a prospective observational cohort (PRE-DETERMINE) study including 5761 participants with CAD, of whom 93% had an LVEF ≥ 40% (aged 64 ± 11 years), over a median of 3.9 years, the cumulative incidence of SD and/or arrhythmic death was 2.1% and of non-SD was 7.7% [91]. CV death accounted for 36% and non-CV death for ~ 55% of deaths (9% unknown). Sudden and/or arrhythmic death was the most common mode of CV death accounting for 56%. Moderately reduced LVEF, age, and NYHA class (III/IV) distinguished SD and non-SD; patients with a moderately reduced LVEF (40–49%) were more likely to die of SD, whereas those with class II HF and advancing age were more likely to die of non-SD.

Electrical risk score In the Oregon Sudden Unexpected Death Study, 522 SCD cases with available 12-lead ECGs (age 65.3 ± 14.5 years, 66% male) were compared with 736 geographical controls to assess the incremental value of multiple ECG parameters in SCD prediction [8]. A novel cumulative ECG risk score, comprising parameters such as heart rate, LVH, QRS transition zone, QRS-T angle, corrected QT (QTc), and T peak-to-T end interval, was independently associated with SCD and was particularly effective for LVEF > 35% where risk stratification is currently unavailable. This model was externally validated in the Atherosclerosis Risk in Communities (ARIC) study. Increasing ECG risk score was associated with progressively greater odds of SCD. Overall, subjects with ≥ 4 ECG abnormalities had an odds ratio (OR) of 21.2 for SCD ($p < 0.001$); in the LVEF > 35% subgroup, the OR was 26.1 ($P < 0.001$).

In *summary*, among the variables employed in proposed risk scores for SCD in patients with HFpEF or LVEF > 35%, younger age, male gender, DM, MI, LBBB, NPs, moderately reduced LVEF, LVH, and certain ECG parameters (e.g., prolonged QRS, increased heart rate and QTc) may predict SCD.

Electrophysiology study

The role of an electrophysiology (EP) study in HF patients has been limited and controversial, particularly in patients with

NICM [92, 93], and is not currently recommended for patients with LVEF < 35%, in whom an ICD is implanted for SD prevention [94]. However, there is some resurgence of interest in this classic test for patients with LVEF > 35%, as it may prove useful in certain patients, such as those with runs of non-sustained VT and/or recurrent syncope, or those experiencing symptoms suggestive of a VTA, especially HFpEF patients with CAD [94–96]. An EP study is also recommended for risk stratification in patients with NICM who experience syncope presumed to be due to ventricular arrhythmias [96].

Cardiac magnetic resonance imaging

Quantifying late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) provides additional prognostic information in early risk-stratification of NICM [97, 98]. In a study of 86 patients (median LVEF 50%; 76% NICM), mainly presenting with ventricular arrhythmias (40%) and congestive HF (44%), there was an event rate (CV death, aborted SD, heart transplant) of 26% (14 of 61) in LGE positive patients compared with 4% (1 of 25) in LGE negative patients ($p = 0.041$, Log rank) [97].

Mid-wall LGE identifies a group of patients with NICM and LVEF≥ 40% at increased risk of SCD and low-risk of non-sudden death who may benefit from ICD implantation [99]. Of 399 patients (median age 50 years, LVEF 50%, 25.3% with LGE) followed for a median of 4.6 years, 18 of 101 (17.8%) patients with LGE reached the prespecified endpoint, compared with 7 of 298 (2.3%) without (HR 9.2; $p < 0.0001$). Nine patients (8.9%) with LGE compared with 6 (2%) without (HR 4.9; $p = 0.002$) died suddenly, whilst 10 patients (9.9%) with LGE compared with 1 patient (0.3%) without (HR 34.8; $p < 0.001$) had aborted SCD [99]. Following adjustment, LGE predicted the composite endpoint (HR 9.3; $p < 0.0001$), SCD (HR 4.8; $p = 0.003$) and aborted SCD (HR 35.9; $p < 0.001$). Estimated HRs for the primary end-point for patients with an LGE extent of 0–2.5%, 2.5–5% and > 5% compared with those without LGE were 10.6, 4.9, and 11.8 respectively.

A systematic review and meta-analysis of 29 studies ($N =$ 2948 patients) covering a wide spectrum of NICM (mean LVEF between 20 and 43%), showed that LGE was significantly associated with the arrhythmic endpoint both (sustained VTAs, appropriate ICD therapy, or SCD) in the overall population (odds ratio 4.3; $p < 0.001$); the association between LGE and the arrhythmic endpoint remained significant among studies with mean LVEF > 35% (odds ratio 5.2; $p < 0.001$) and was maximal in studies that included only patients with primary prevention ICDs (odds ratio 7.8; $p = 0.008$) [98]. The authors concluded that across a wide spectrum of patients with NICM, LGE is strongly and independently associated with ventricular arrhythmia or SCD, suggesting LGE as a powerful tool to improve risk stratification for SCD in patients with NICM. Future studies should address the question whether patients with LGE could benefit from primary prevention ICDs irrespective of their LVEF.

Considering the above evidence, the new guidelines recommend that in patients with suspected NICM, CMR with LGE can be useful for assessing risk of SCA/SCD (class IIa, level of evidence B) [96].

Target(s) for therapy

Data are lacking on effective management strategies for patients with HFpEF [100] (Fig. 1). Nevertheless, priority should be placed at treating and correcting any underlying structural heart disease, including but not limited to reperfusion, revascularization, valve repair or replacement, as needed, together with relevant best optimal medical therapies, prevention or correction of electrolyte abnormalities, avoidance of proarrhythmic drugs, and management of comorbidities (Table 2). Revascularization has been associated with preservation of cardiac function and improved outcomes in HFpEF patients with CAD [34].

Clinical trials evaluating drug therapies to date have shown that drugs have not ameliorated the substantial SCD event rate in the HFpEF population, and no guideline-recommended drug or device therapies are available to alter the disease course [94]. Although SCD has been estimated to account for up to 20–40% of CV deaths in HFpEF, the utility of targeting SCD in the setting of preserved EF is unknown [9].

As mentioned, patients with HFpEF often have important comorbidities which strongly influence outcomes [49] (Table 1, Fig. 1). Hence, it is of paramount importance to identify and treat these comorbid conditions, such as hypertension, CAD, AF, DM, CKD, and anemia, in order to ameliorate clinical outcome, including SD. Guidelines on hypertension management indicate that in patients with HFpEF, blood pressure treatment threshold and target values should be the same as for HFrEF [50, 101]. The American guidelines indicate that in patients with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. Those with persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta blockers and/or MRAs titrated to attain systolic blood pressure of < 130 mmHg [50, 102]. Evidence-based recommendations from respective organizations should also be followed for treatment of the other comorbidities in patients with HFpEF, such as CAD, AF, stroke, DM, anemia, and CKD, which is likely to decrease morbidity and mortality in these patients [49]. Whether these therapies will also affect SD incidence and mortality remains to be seen;

Table 2 Potential therapeutic approaches for sudden death prevention in HFpEF

1. Treat underlying SHD
   Reperfusion (MI) / Revascularization (CAD)
   Valve repair/replacement (VHD)
2. Prevent/correct electrolyte abnormalities, avoid proarrhythmic drugs
3. ICD
   Secondary prevention
      HFpEF patients who have survived a cardiac arrest due to VT or VF or who have spontaneous sustained VT causing syncope or hemodynamic compromise, in the absence of a reversible cause or within 48 h of an acute MI, who have a life expectancy > 1 year
      HFpEF patients with recurrent syncope and inducible monomorphic VT at an electrophysiology study
   Primary prevention
      HFpEF patients with CAD or non-ischemic cardiomyopathy (NICM) and symptoms suggestive of VAs (palpitations, syncope/presyncope) and/or runs of NSVT on ECG/HM who have inducible sustained VT at an EP study
      Patients with NICM due to a *Lamin A/C* mutation and ≥ 2 risk factors (NSVT, LVEF < 45%, nonmissense mutation, and male sex)
      Patients with HCM and ≥ 1 of the following risk factors, if meaningful survival of > 1 year is expected:
         a. *Maximum* LV wall thickness ≥ 30 mm (LOE B-NR);
         b. SCD in ≥ 1 first-degree relatives presumably caused by HCM (LOE C-LD);
         c. ≥ 1 episodes of unexplained syncope within the preceding 6 months (LOE C-LD)
      Patients with HCM who have spontaneous NSVT (LOE: C-LD) or an abnormal blood pressure response with exercise (LOE B-NR), who also have additional SCD risk modifiers or high-risk features, an ICD is reasonable if meaningful survival greater than 1 year is expected.
      Patients with cardiac sarcoidosis and LVEF >35% who have syncope and/ or evidence of myocardial scar by cardiac MRI or PET scan, and/or have an indication for permanent pacing, implantation of an ICD is reasonable, provided that meaningful survival of greater than 1 year is expected (IIa C)
      Patients with cardiac sarcoidosis and LVEF > 35%, with inducible sustained VA at an EP study, provided that meaningful survival of greater than 1 year is expected
4. Drugs
   ? ACEI/ARBs
   ? β-blockers
   ? MRAs
   Statins
5. Treatment of comorbidities

ACEI angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CAD* coronary artery disease, *ECG* electrocardiogram, *EP* electrophysiology, *HCM* hypertrophic cardiomyopathy, *HFpEF* heart failure with preserved ejection fraction, *HM* Holter monitor, *ICD* implantable cardioverter defibrillator, *LOE* level of evidence, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *MRA* mineralocorticoid antagonist, *MRI* magnetic resonance imaging, *NSVT* non-sustained ventricular tachycardia, *PET* positron emission tomography, *SCD* sudden cardiac death, *SHD* structural heart disease, *VAs* ventricular arrhythmias, *VF* ventricular fibrillation, *VHD* valvular heart disease, *VT* ventricular tachycardia

however, some data available from existing studies and meta-analyses seem favorable (see discussion below).

Treatment effects

Several therapies have been demonstrated to effectively prevent SCD in HFrEF, especially in the post-MI setting [31]. A meta-analysis of 30 trials comprising ~25,000 patients showed that β-blockers decreased SCD by ~30%. [103] In the CHARM program, the ARB, candesartan, decreased SCD by ~15% compared with placebo [18]. In patients with post-MI LV dysfunction with HF, eplerenone was associated with a 21–37% relative risk reduction in SCD compared with placebo at 1 month and at a mean of 16 months [39, 40, 104]. In the PARADIGM-HF, sacubitril/valsartan decreased SCD risk by 20% (HR 0.80; $p = 0.008$) [105, 106]. ICDs have an established role in preventing SCD in select patients with HFrEF [107].

Unfortunately, trials evaluating these established therapies in patients with HFpEF have not confirmed favorable outcomes [9]. On the other hand, there is no conclusive evidence for the benefit of attempts to lower the heart rate with use of beta-blockers or calcium antagonists in HFpEF [2]. Similarly, blocking the pro-hypertrophic and pro-fibrotic effects of angiotensin II with ACE inhibitors or ARBs has not consistently yielded any concrete benefit [2], although a prospective cohort study has provided encouraging results of a possible decrease in all-cause mortality [13]. The lack of success is probably multifactorial and/or attributable to the heterogeneity of HFpEF syndrome. Targeting certain subsets within HFpEF, such as hypertrophic, infiltrative, or restrictive cardiomyopathy, with inherent high SD risk, may prove successful with specific therapies, such as ICD therapy [94, 108]. However,

effective approaches to reduce SD in less well-defined subgroups of HFpEF remain to be defined.

It is possible that pharmacotherapies under investigation in HFpEF may demonstrate benefits. Such therapies currently under study in HFpEF comprise SGLT-2 inhibitors (NCT03057951), the combination of sacubitril/valsartan, and MRAs, which have shown promise in SCD reduction in other high-risk CV populations [109]. The effect of angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan on clinical outcomes in patients with HFpEF is being tested in a large randomized trial, PARAGON-HF [110].

Sudden death was numerically lower in patients treated with spironolactone compared with placebo in patients enrolled in the Americas region of the TOPCAT trial, but this difference did not reach statistical significance. Hence, spironolactone might be considered in well-selected patients with HFpEF [12].

Finally, the MADIT S-ICD trial, which embarked to evaluate subcutaneous ICD therapy in patients with DM, prior MI, and LVEF of 36–50% [14], was recently halted due to poor enrollment (NCT02787785).

MRAs Aldosterone/mineralocorticoid receptor-stimulated actions can lead to tissue injury involving complex pathophysiologic mechanisms ranging from oxidative stress to fibrosis and inflammation [111, 112]. Such an activation in the CV system can produce cardiac fibrosis and hypertrophy contributing to decreased LV compliance that characterizes HFpEF [113]. Progressive increases in markers of collagen turnover and inflammation have been demonstrated in HFpEF with diastolic dysfunction. Despite high background utilization of renin-angiotensin-aldosterone modulators, eplerenone therapy prevents a progressive increase in pro-collagen type-III aminoterminal peptide and may have a role in management of this disease. Mineralocorticoid antagonists (MRAs) may therefore ameliorate this derangement. Although eplerenone has been shown in small studies to attenuate collagen turnover in patients with HFpEF [114, 115] and improve echocardiographic indices of diastolic function, this did not correlate with functional improvement [115]. Similarly, in a propensity matched sub-study of the OPTIMIZE-HF trial comparing patients with HFpEF receiving MRAs ($n = 492$) with patients not receiving MRAs ($n = 487$) over 2.4 years, MRAs had no association with clinical outcomes as there was no difference in the primary composite endpoint of all-cause mortality or HF hospitalization (81% in both groups) [116].

Another small study of 80 patients [117] showed that addition of spironolactone to standard angiotensin II inhibition improved myocardial function and reduced markers of collagen turnover at 6 months, compared with placebo, in patients with metabolic syndrome already receiving ACE inhibitors. In the Aldo-DHF trial ($n = 422$), spironolactone conferred an improvement in LV diastolic function, but failed to produce any significant benefit on maximal exercise capacity or quality of life over 1 year of follow-up [118]. A large RCT (TOP-CAT), which randomized 3345 patients with HFpEF to spironolactone or placebo, failed to show any significant effect on the primary composite outcome of CV death, aborted cardiac arrest, and HF hospitalization (HR 0.89, $p = 0.14$) over a 3.3-year follow-up period [16]. Nevertheless, the secondary endpoint of HF hospitalization was significantly reduced by spironolactone (HR 0.83, $p = 0.042$). In subgroup analysis, the potential efficacy of spironolactone was greatest at the lower end of the LVEF spectrum (45–50%) [119]. In another secondary analysis, spironolactone appeared to have greater benefit in patients with lower compared with higher baseline BNP [77]. This result is similar to the effects of irbesartan in the I-PRESERVE trial [76]. Thus, elevated NPs in HFpEF seem to identify patients at higher risk for events but who may be less responsive to treatment. A biochemical phenotype of high collagen cross-linking seems to identify HFpEF patients resistant to the beneficial effects of spironolactone on LV diastolic dysfunction [120]. As mentioned, SD was numerically, but not statistically, lower in patients treated with spironolactone compared with placebo in patients enrolled in the Americas region of the TOPCAT trial, which leaves some room for using spironolactone in well-selected patients with HFpEF [12].

A pooled analysis of 11 RCTs involving 942 participants with HFpEF (6 trials) or asymptomatic LV diastolic dysfunction and/or LVH (5 trials), indicated that MRA use (spironolactone in 8 trials, eplerenone in 2 and canrenone in 1) for a mean duration of ~ 9 months was associated with significant reduction in E/e', a specific echocardiographic measure of diastolic function, ($p < 0.0001$) and deceleration time, another measure of diastolic function, as compared with control ($p = 0.04$), suggesting an improvement in diastolic function [121]. Furthermore, blood pressure and serum levels of amino-terminal peptide of pro-collagen type II (PIIINP) and carboxy-terminal peptide of procollagen type I (PICP) (biomarkers of collagen turnover) were also significantly reduced with MRA therapy with no significant change in LV mass or dimensions. A recent meta-analysis of 9 RCTs (1164 HFpEF patients) showed that MRA treatment improved indices of cardiac structure and function, suggesting a decrease in LV filling pressure and reverse cardiac remodeling with an attendant increase in serum potassium and a decrease in blood pressure; however, only a small clinical improvement was noted [122].

Activation of the mineralocorticoid receptor modulates cardiac electrical activity, causing atrial and ventricular arrhythmias (proarrhythmic effect) by increasing tissue remodeling and fibrosis and through various electrophysiological alterations [37]. Thus, inactivation of this proarrhythmic mineralocorticoid receptor effect explains the antiarrhythmic benefit conferred by MRAs that has been demonstrated in studies of

HFrEF where a decrease in the incidence of SD was observed in RALES and EPHESUS studies [38, 104]. Such a beneficial effect remains to be shown in patients with HFpEF.

Prognostic impact of statin use in patients with HFpEF An early (2005) study suggested that statin therapy may be associated with lower mortality in patients with HFpEF; among 137 HFpEF patients, statin therapy was associated with a significant improvement in survival (relative risk of death 0.22; $p = 0.006$; adjusted relative risk of death 0.20; $p = 0.005$) [123]. A report from the CHART-2 study (2015) comprising 4544 HF patients, 3124 with HFpEF (LVEF ≥ 50%; mean age 69 years; male 65%) and 1420 with HFrEF (LVEF < 50%; mean age 67 years; male 75%), indicated that the 3-year mortality in HFpEF patients was lower in patients receiving statins (8.7% vs 14.5%, adjusted hazard ratio—HR 0.74; $p < 0.001$), which was confirmed in the propensity score-matched cohort (HR, 0.72, $p = 0.044$) [124]. The inverse probability of treatment weighted further confirmed that statin use was associated with reduced incidence of all-cause death (HR, 0.71, $p < 0.001$) and non-CV death (HR, 0.53, $p < 0.001$), specifically reduction of SD (HR, 0.59, $p = 0.041$) and infection death (HR, 0.53, $p = 0.001$) in HFpEF. Finally, there was a lack of statin benefit in HFrEF patients [124], which is in keeping with the findings of a recent meta-analysis of 24 RCTs indicating that statins do not reduce SCD in HFrEF patients [125].

In *summary*, established therapies (β-blockers, ACE inhibitors/ARBs, MRAs) in patients with HFrEF have not yielded any concrete benefits in patients with HFpEF, with the caveat that ACE inhibitors/ARBs and MRAs seem to allow for a glimpse of hope, as suggested by a prospective cohort study for the former (possibly lowering all-cause mortality) [13] and by an RCT for the latter (possibly lowering SD rate numerically, albeit non-significantly) [12]. However, a definite beneficial effect of these therapies remains to be shown in patients with HFpEF. Encouraging results for a reduction of SD by use of statin therapy in HFpEF patients has been reported by one study [124]. Newer pharmacotherapies, such as the antihyperglycemic agents, SGLT-2 inhibitors (gliflozins) (EMPEROR-Preserved: NCT03057951) and the angiotensin receptor-neprilysin inhibitor, sacubitril/valsartan [110], proven beneficial in HFrEF patients, are being investigated in HFpEF patients.

Sudden death definition problems

A major problem in establishing the "true" mechanism of death in HFpEF remains with the definition of sudden death (SD) or sudden cardiac death (SCD) [22, 126, 127]. It is possible that the syndrome of SD in HFpEF may occur in patients who have experienced terminal non-arrhythmic CV events, such as acute MI (with consequent acute heart failure or myocardial rupture and electromechanical association), aortic dissection, cerebrovascular accident; or non-CV events, including pulmonary disease with acute respiratory failure, massive pulmonary embolism, acute hemorrhage, drug abuse/overdose, electrolyte disturbances, or sepsis/circulatory collapse; or terminal mechanism of inevitable death in other end-stage conditions, such as hospice residents and patients with advanced cancer [15, 24, 127]. These events would not be expected to respond to ICD preventative approaches. Indeed, it remains unclear how many true arrhythmic SDs in this population are secondary to ventricular tachyarrhythmias (VTAs), as opposed to electro-mechanical dissociation (EMD) or bradyarrhythmias secondary to cardiac or non-cardiac causes. Furthermore, the accuracy of SCDs was called into question by a recent large prospective (POST SCD) study showing that 40% of deaths attributed to stated cardiac arrest were not sudden or unexpected, and nearly half of presumed SCDs were not arrhythmic [128].

Problems with heart failure classification and LVEF cutoffs

Measuring LVEF and assessing NYHA class for the clinical severity of HF remain the principal contemporary risk stratifiers [129]. LVEF ≤ 35% has been used as the major criterion for implanting an ICD for primary prevention of SCD; this group comprises the majority of patients with HFrEF. However, there are many limitations to the use of LVEF as the single determinant of high risk; among them, the fact that most SCDs (numerically) occur in patients with higher LVEF remains an important and convincing reason why newer markers for SCD need to be identified for patients with LVEF > 35%, including patients with HFpEF [129, 130]. Recently, the European guidelines for HF defined a HF group with mid-range (40–49%) LVEF [21]; however, the American guidelines have not adopted this discrimination [107]; the prognostic significance of this new HF group and its difference from the HFpEF group remains dubious. Furthermore, most out-of-hospital cardiac arrests do not occur in persons with overt HF [131]. Hence, in this review, the discussion of SD extends beyond the HFpEF patient group by encompassing all patients with LVEF > 35% including patients with HFmrEF and generally patients with mild (LVEF 40–49%) and moderate (LVEF 36–40%) LV dysfunction.

It is increasingly being recognized that apart from LVEF and NYHA class, many other factors, herein discussed, appear to be important and show promise in the assessment of the SCD risk, such as age, gender, ethnicity, increased heart rate, blood pressure, presence of ischemia, diabetes, CKD, anemia, fibrosis on CMR, certain ECG indices, autonomic parameters, biochemical markers, genetics, and findings of an EP study

(inducible sustained monomorphic VT) [129]. However, the ability of all these factors to guide ICD therapy for SCD prevention needs to be evaluated in prospective clinical trials before they can be recommended. Nevertheless, some of these factors (e.g., inducible VT at EPS, Lamin A/C mutation, fibrosis on CMR) have already been adopted by current guidelines as important risk stratifiers [94, 96].

Implantable cardioverter defibrillator

Primary prevention of SCD Patients with HFpEF who have symptoms suggestive of a ventricular arrhythmia (palpitations, presyncope, or syncope), particularly those with a history of a remote MI [94], or in whom runs of non-sustained VT (NSVT) have been documented may have an indication to be submitted to an EP study. In case of an inducible sustained monomorphic VT, an ICD is recommended (Table 2) [94, 96].

In patients with NICM due to a *Lamin A/C* mutation who have ≥ 2 risk factors (NSVT, LVEF < 45%, nonmissense mutation, and male sex), an ICD can be beneficial. In patients with hypertrophic cardiomyopathy (HCM) and ≥ 1 of the following risk factors, an ICD is reasonable if meaningful survival of greater than 1 year is expected: (a) *Maximum* LV wall thickness ≥ 30 mm (level of evidence-LOE B-NR); (b) SCD in ≥ 1 first-degree relatives presumably caused by HCM (LOE C-LD); (c) ≥ 1 episodes of unexplained syncope within the preceding 6 months (LOE: C-LD).

In patients with HCM who have spontaneous NSVT (LOE C-LD) or an abnormal blood pressure response with exercise (LOE B-NR), who also have additional SCD risk modifiers or high-risk features, an ICD is reasonable if meaningful survival greater than 1 year is expected.

In patients with cardiac sarcoidosis and LVEF > 35% who have syncope and/or evidence of myocardial scar by cardiac MRI or positron emission tomographic (PET) scan, and/or have an indication for permanent pacing, implantation of an ICD is reasonable, provided that meaningful survival of greater than 1 year is expected (class IIa/LOE C). In patients with cardiac sarcoidosis and LVEF > 35%, it is reasonable to perform an EP study and to implant an ICD, if sustained VTA is inducible, provided that meaningful survival of greater than 1 year is expected.

Interestingly, survival data on ICD efficacy for primary prevention in patients with LVEF > 35% were reported from a retrospective analysis of a subset of 1902 participants of the SCD-HeFT trial (which randomly assigned 2521 patients to placebo, amiodarone, or ICD) who had a repeated assessment of LVEF a mean of 13.5 months after randomization [132]. These patients were stratified by LVEF ≤ 35% and > 35% based on the first repeated LVEF measurement after randomization and all-cause mortality was compared in 649 patients randomized to placebo vs 624 patients randomized to ICD. Repeated LVEF was > 35% in 186 patients (29.8%) randomized to ICD and 185 patients (28.5%) randomized to placebo. During a median follow-up of 30 months, the all-cause mortality rate was lower in the ICD vs placebo group, both in patients whose LVEF remained ≤ 35% (7.7 vs 10.7 per 100 person-year follow-up) and in those whose LVEF improved to > 35% (2.6 vs 4.5 per 100 person-year follow-up). Compared with placebo, the adjusted hazard ratio for the effect of ICD on mortality was 0.64 in patients with a repeated LVEF of ≤ 35% and 0.62 in those with a repeated LVEF > 35%. The authors concluded that among participants in the SCD-HeFT with a repeated LVEF assessment during follow-up, those who had an improvement in LVEF to > 35% accrued a similar relative reduction in mortality with ICD therapy as those whose LVEF remained ≤ 35%. The authors also point out that prospective RCTs are needed to test ICD efficacy in patients with an LVEF > 35%. Currently, these are the only survival data on ICD efficacy in primary prevention of SCD in patients with LVEF > 35%.

Secondary prevention of SD For all patients with HFpEF, regardless of the specific type of underlying structural heart disease, ICD implantation is recommended in those who have survived a cardiac arrest due to VT or VF or who have spontaneous sustained VT causing syncope or hemodynamic compromise, in the absence of a reversible cause or within 48 h of an acute MI, who have a life expectancy > 1 year (Table 2) [94, 96]. Of course, effective management of underlying diseases and comorbidities is of paramount importance for the successful management of ventricular tachyarrhythmias and both primary and secondary prevention of SD. An ICD is also recommended for HFpEF patients with recurrent syncope and inducible monomorphic VT at an EP study [96].

Conclusion

Patients with HFpEF represent a broadly heterogeneous group associated with a multitude of comorbidities [49], with consequent variable SD risk. The mortality burden of HFpEF may be variable but remains substantial at 10–30% annually, and higher in epidemiological studies than in clinical trials. Mortality rates compared with HFrEF appear to be strongly influenced by the type of study, but are clearly elevated compared with age- and comorbidity-matched controls without HF. The majority of deaths in HFpEF are CV deaths, comprising 51–60% of deaths in epidemiological studies and 70% in clinical trials. Among CV deaths, SD and HF death are the leading cardiac modes of death in HFpEF clinical trials. Compared with HFrEF, proportions of CV deaths, SD, and HF deaths are lower in HFpEF. Conversely, non-CV deaths constitute a higher proportion of deaths in HFpEF than in HFrEF, particularly in epidemiological studies, where this

difference may be related to fewer CAD deaths in HFpEF. Other key mortality risk factors include age, gender, BMI, and burden of comorbidities.

Due to the wide heterogeneity in presentation and pathophysiology of HFpEF, its management remains problematic as there is a paucity of data on the clinical benefits of current therapies. Thus, currently, the therapeutic targets focus on symptom relief and reduction of HF hospitalization by controlling fluid retention and managing risk factors and comorbidities.

Perspective

Sudden death accounts for up to 1/4 of all mortal events in HFpEF. Available therapies to date have not successfully altered disease progression. Matching a specific pathophysiology or mode of death with available and novel therapies may be integral to improving outcomes in HFpEF. However, this still remains an elusive target. Thus, it is apparent that we need information regarding the determinants of SD. Mechanisms of SD have been poorly characterized at present. ICDs have changed the landscape of SD prevention in HFrEF, but a significant proportion will not ultimately avail of its benefits. If ICDs are to be applied to the HFpEF population, there must be a coordinated effort to identify and select high-risk patients for SD events. In order to prevent SD beyond SCD alone, predictors of non-arrhythmic SD (e.g., pulmonary embolism, stroke) need to first be better defined. Further research is needed to better classify HFpEF; define clinical course and mode of deaths; and examine clinical phenotypes, novel biomarkers, and imaging modalities to identify high-risk subsets. The mode of death may be a viable target of treatment (Fig. 1), if the mode of death is prevalent without significant competing risks; if it is predictable with readily available markers and modalities; and modifiable with known and available therapies. At present, each of these elements requires further clarification.

Given the broad scope and impact of SD in HFpEF, there has been a recent call for large-scale trials of device therapy for primary prevention. Among the ongoing early phase studies regarding SD in HFpEF, the VIP-HF is exploring the utility of implantable loop recorders in HFpEF in detecting incident VTAs among HFpEF patients with NYHA class II or III symptoms and recent HF hospitalization [109]. I-123 metaiodobenzylguanidine (MIBG) planar and single-photon emission computed tomography (SPECT) imaging have been suggested to predict VTAs in HF patients by assessing the abnormalities of the sympathetic nervous system [133, 134]. The MISTIC (MIBG scintigraphy as a tool for selecting patients requiring ICD) study (NCT01185756) is evaluating whether the presence of autonomic dysfunction as assessed by MIBG better predicts appropriate ICD placement in HFrEF; there has been interest in using a similar approach in the HFpEF population. The PARAPET (Prediction of ARrhythmic Events With Positron Emission Tomography) study showed that regional myocardial sympathetic denervation, as assessed by positron emission tomography (PET), was predictive of arrhythmic death or appropriate ICD discharge in 204 HFrEF patients with ischemic cardiomyopathy; more specifically, denervated myocardium was associated with total cardiac mortality, and denervated and viable denervated myocardium were associated with sudden cardiac arrest [32]. The ongoing ADMIRE-ICD (International Study to Determine if AdreView Heart Function Scan Can be Used to Identify Pts with Mild or Moderate HF that Benefit from Implanted Medical Device) study (NCT02656329) is evaluating the role of AdreView™ (123I meta-iodobenzylguanidine, a novel scintigraphy imaging agent) in appropriately selecting patients with HFrEF for ICD therapy [134]. Again, similar approaches could be considered in HFpEF.

Furthermore, wide-scale, comprehensive autopsy studies are underway to capture incident SCD rates and predictors on a community-level. The PRE-DETERMINE study recently reported rates of SCD among patients with CAD and LVEF > 35%, which were carefully adjudicated using next-of-kin/witnessed accounts of death and medical records [91]. Such approaches may help with the problems of SD definition, as discussed earlier.

Quantification of myocardial focal fibrosis by LGE CMR could be useful for the risk stratification in HFpEF patients for SCD [135]. As mentioned, a meta-analysis of 29 studies comprising a wide spectrum of HF patients with NICM ($N = 2948$) showed that LGE is strongly and independently associated with ventricular arrhythmia or SCD. Hence, a positive LGE could guide the selection of HFpEF patients at risk for SD and in need for implantation of an ICD [95]. In keeping with this evidence, the new ACC/AHA guidelines on SCD recommend that in patients with NICM, CMR with LGE can be useful for assessing the risk of SCD (class IIa, level of evidence B) [96]. Whether such patients should be submitted to ICD implantation with or without the performance of an EP study awaits further investigation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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