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STATE OF THE ART REVIEW
Heart failure and cardiomyopathies

Genetic causes of heart failure with preserved ejection fraction: emerging pharmacological treatments

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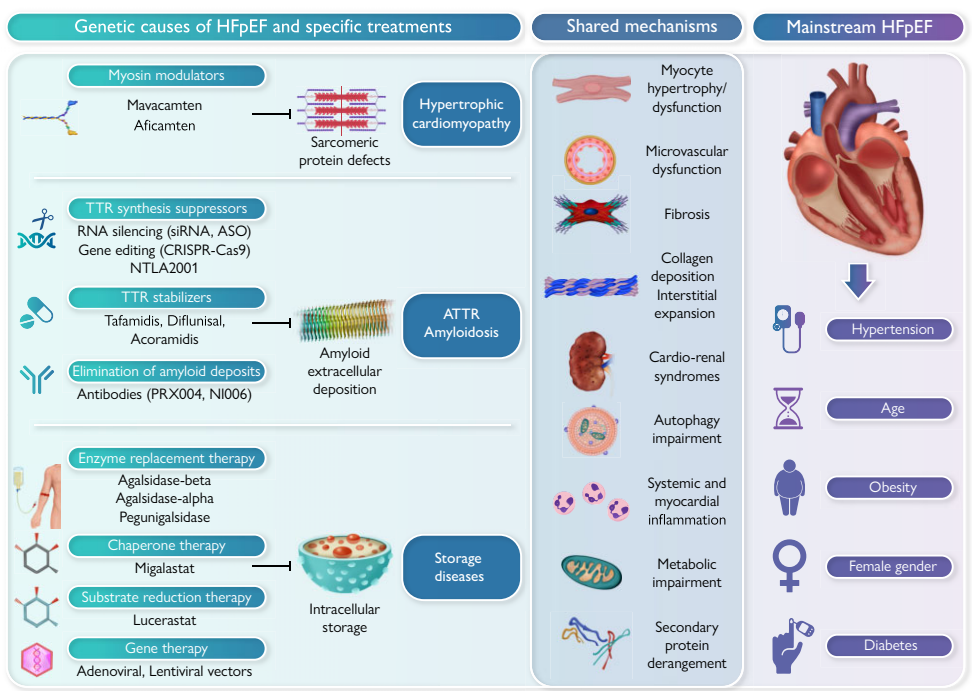
Graphical Abstract



Genetic causes of HFpEF: distinct vs. shared mechanisms with 'mainstream' HFpEF, and specific treatments. While the pathophysiology and phenotypes of specific aetiologies are unique, several disease features overlap with mainstream HFpEF. Therefore, each of these conditions may offer important insights and identify potential therapeutic targets which may translate from rare to more prevalent forms of disease. ASO, antisense oligonucleotide; ATTR, transthyretin amyloidosis; siRNA, small-interfering RNA; TTR, transthyretin.

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† C.R. sadly passed away in October 2022. This work is dedicating to his lasting scientific, academic, and human legacy.

Abstract

Heart failure with preserved ejection fraction (HFpEF) is a major driver of cardiac morbidity and mortality in developed countries, due to ageing populations and the increasing prevalence of comorbidities. While heart failure with reduced ejection fraction is dominated by left ventricular impairment, HFpEF results from a complex interplay of cardiac remodelling, peripheral circulation, and concomitant features including age, hypertension, obesity, and diabetes. In an important subset, however, HFpEF is subtended by specific diseases of the myocardium that are genetically determined, have distinct pathophysiology, and are increasingly amenable to targeted, innovative treatments. While each of these conditions is rare, they collectively represent a relevant subset within HFpEF cohorts, and their prompt recognition has major consequences for clinical practice, as access to dedicated, disease-specific treatments may radically change the quality of life and outcome. Furthermore, response to standard heart failure treatment will generally be modest for these individuals, whose inclusion in registries and trials may dilute the perceived efficacy of treatments targeting mainstream HFpEF. Finally, a better understanding of the molecular underpinnings of monogenic myocardial disease may help identify therapeutic targets and develop innovative treatments for selected HFpEF phenotypes of broader epidemiological relevance. The field of genetic cardiomyopathies is undergoing rapid transformation due to recent, groundbreaking advances in drug development, and deserves greater awareness within the heart failure community. The present review addressed existing and developing therapies for genetic causes of HFpEF, including hypertrophic cardiomyopathy, cardiac amyloidosis, and storage diseases, discussing their potential impact on management and their broader implications for our understanding of HFpEF at large.

Keywords Heart failure with preserved ejection fraction (HFpEF) • Hypertrophic cardiomyopathy • Fabry disease • Danon disease • Cardiac amyloidosis • Gene therapy • Myosin inhibitors • Tafamidis • Drug development

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a broad term encompassing a spectrum of conditions with diverse pathophysiology, currently defined as heart failure (HF) with left ventricular ejection fraction (LVEF) > 50%, in the absence of prior evidence of systolic dysfunction.[1–4] The complementary definition of HF with normal LVEF and elevated left ventricular (LV) filling pressure at rest or during exercise is possibly more useful conceptually.[5,6] In addition, based on the haemodynamic response to exercise, HFpEF can be diagnosed in the presence of an end-expiratory pulmonary artery wedge pressure (PAWP) ≥ 25 mmHg at peak exercise, a PAWP/cardiac output slope >2 mmHg/L/min, or a respiratory-averaged mean pulmonary artery pressure (PAP) > 30 mmHg at peak exercise with a total pulmonary resistance >3 Wood Units and PAWP ≥20 mmHg.[5]

The evolving understanding of HFpEF has led to the identification of different clinical phenotypes with only partially overlapping pathophysiology. While the classic model of heart failure with reduced ejection fraction (HFrEF) is largely a *cardiocentric* condition dominated by functional LV impairment, 'mainstream' HFpEF results from a complex interaction of the heart, the peripheral circulation, and the environment, with major roles played by age, female gender, and comorbidities such as obesity, diabetes, hypertension, and inflammation.[3,4] These differences are reflected in outcomes: HFrEF patients die predominantly of worsening HF and sudden cardiac death, while in HFpEF, non-cardiac mortality due to dysfunction of multiple organ systems plays an important role.[7]

In a peculiar subset of patients, however, HFpEF is subtended by genetic conditions that have distinct pathophysiology and are increasingly amenable to targeted treatments[3,4] (*Graphical Abstract* and *Table 1*). These conditions belong to the realm of primary myocardial disease—i.e. cardiomyopathies—with clinical profiles and outcomes that are largely independent of extra-cardiac factors: as such, they rather follow the *cardiocentric* paradigm of HF generally associated with systolic dysfunction. Despite sharing several features of mainstream HFpEF, such as hypertrophy, interstitial fibrosis, myocardial inflammation, microvascular dysfunction, and disordered autophagy and mitochondria, their phenotypes are unique.[3,6,8–10] These aetiologies present in individuals that are generally younger (with the exception of cardiac amyloidosis), have little or none of the classic co-morbidities associated with HFpEF, and show no predilection for the female gender. Rather, a male preponderance is observed, particularly in X-linked conditions such as Fabry disease (FD).[8] A long history of neglected complaints and a suggestive pedigree are common. Importantly, these patients exhibit peculiar electrocardiogram (ECG) and multimodality imaging phenotypes (*Figure 1*) and may present with distinct extra-cardiac red flags such as carpal tunnel syndrome in cardiac amyloidosis or angiokeratomas and proteinuria in FD. For all, diastolic dysfunction represents the main cause of HF symptoms, with systolic dysfunction occurring only in selected subsets following progressive myocardial replacement fibrosis and myocyte loss.[8] Marked atrial remodelling and dysfunction are frequent complications, triggering and perpetuating atrial fibrillation, further worsening HF symptoms. Cardioembolic risk is generally high irrespective of CHA_2DS_2-VASc score, and ischaemic events may occur even in patients who are in sinus rhythm and adequately treated with anticoagulants.[10] Systemic manifestations can exacerbate HF symptoms, such as involvement of the peripheral nervous system with chronotropic incompetence in FD, or muscular involvement in glycogenosis, and mortality is largely due to refractory HF or arrhythmic events.[10,11]

While each of these conditions may be uncommon, they collectively represent a relevant subset of HFpEF cohorts, in whom prompt recognition has major consequences for the clinical practice: while the response to standard treatment will generally be modest for these individuals, access to dedicated therapies may radically change their quality of life and outcome.[8,11,12] On the other hand, by enhancing our understanding of cardiac pathophysiology, genetic cardiomyopathies are shedding light on novel therapeutic targets that may be relevant to the broader HFpEF world.[3,4] Once considered a niche of limited epidemiological interest, the field of genetic cardiomyopathies is undergoing rapid transformation due to recent, groundbreaking advances in drug development.[12] We here review the existing and developing

Table 1 **Functional profile of genetic cardiomyopathies associated with heart failure with preserved ejection fraction**

	HCM	ATTRv amyloidosis	Fabry	Danon
Prevalence of heart failure	35%	50%–80%	20%	20%
LVEF at presentation	75%	40%–50%	70%	70%
Progressive LVEF dysfunction	↓ in 10% with end-stage evolution	↓ in advanced phases	↓ in a small subgroup in advanced disease	No
Left ventricular volumes	↓=	↓	=	↓↓
Longitudinal systolic function	↓	↓↓	↓	↓
Longitudinal strain	↓ (no apical sparing)	↓ (with apical sparing)	↓ (inferolateral impairment)	↓ (possible apical sparing)
Chamber stiffness	↑	↑↑	↑	↑↑
Parietal stiffness	↑		↑	↑↑
Myocardial relaxation	=	↓	↓	?
Stroke volume	=	↓↓ and fixed	=	↓
Inotropic reserve	=	↓↓	?	?
NT-proBNP	↑	↑↑↑	↑	?
LVH pattern and ancillary features	Asymmetric LVH, LVOTO, elongated mitral leaflets, abnormal morphology and insertion of papillary muscles	Thickening of AV valves, interatrial septum and RV free wall. Granular-sparkling appearance of myocardial tissue	Disproportionate hypertrophy of papillary muscles, 'Binary sign'	Massive concentric LVH
Cardiac magnetic resonance findings	Midwall/transmural LGE in the most hypertrophic segments. Mildly increased native T1 and ECV	Diffuse subendocardial or transmural LGE, increased native T1 and ECV	Midwall LGE in basal inferolateral segment. Reduced native T1, normal ECV	Extensive LGE with mid-septum sparing. Reduced native T1, normal ECV
Typical ECG features	High QRS voltages, q waves	Normal–low* QRS voltages, AV blocks, q waves	High QRS voltages, short PQ interval	High QRS voltages, pre-excitation, AV blocks

LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; AV, atrioventricular; RV, right ventricle; LGE, late gadolinium enhancement; ECV, extra-cellular volume.

therapies for the principal genetic causes of HFpEF and discuss their potential implications for a deeper understanding of mechanisms leading to cardiac dysfunction and HF.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy, with a prevalence of 1:500 in the general population, often caused by sarcomere protein gene mutations.[10,13,14] The phenotype is a complex blend including asymmetric LV hypertrophy not explained by abnormal loading conditions, mitral valve abnormalities, microvascular remodelling, and myocardial disarray. At the molecular level, sarcomere gene mutations directly or indirectly cause a hypercontractile phenotype resulting in downstream consequences ranging from cardiomyocyte calcium overload and electrophysiological remodelling to mitochondrial dysfunction, energy depletion, myocardial ischaemia, and replacement fibrosis.[15,16] Clinically, the disease is characterized by arrhythmic propensity and limiting symptoms of varying severity, either in the context of hyperdynamic LV contraction promoting dynamic outflow obstruction or—in advanced disease—of LV dysfunction associated with extensive myocardial fibrosis.[10,13,14] Notably, the natural history of HCM may be influenced by environmental factors such as obesity, partly mediated by secondary worsening of the intrinsic microvascular abnormalities typical of the disease, as well as obesity-related inflammation.[17] The role of the environment on phenotypic expression and the course of HCM, however, remains largely unresolved.[18]

To date, treatment of obstructive HCM rests on beta-blocker or verapamil, with the addition of disopyramide as a negative inotrope.[16] Patients with persistent symptoms require invasive options including surgical myectomy and alcohol septal ablation.[10,13] When HF develops due to LV fibrosis and dysfunction, culminating in the so-called end-stage phase, standard HF therapy including cardiac resynchronization shows modest efficacy.[13] To date, none of the classic HF treatments, including renin–angiotensin–aldosterone system inhibitors and spironolactone, have been shown to alter disease progression or improve outcome. Until recently, HCM was an orphan condition in urgent need of drugs targeting its core pathophysiological mechanisms.[16]

Our current understanding of HCM pathogenesis originates from patients and experimental animals carrying cardiac beta myosin heavy chain gene (MHY7) mutations. These are gain-of-function variants leading to enhanced myosin activation and an increase in the number of heads involved in cardiac contraction at any given cycle.[15,19] All pathophysiological and clinical manifestations of HCM are now believed to derive from this molecular 'original sin', or along similar pathways in HCM patients with variants in other sarcomeric genes, such as MYBPC, which also result, albeit indirectly, in myosin over-activation.[15] Following seminal work from James Spudich's group, this realization led to the concept of myosin inhibition as a potential therapeutic strategy for HCM, representing the mirror image of myosin stimulation with omecamtiv mecarbil in HFrEF.[20,21] The first-in-class cardiac myosin inhibitor, mavacamten, showed promising results in a mouse model of MHY7-associated HCM, in which the drug markedly attenuated the functional and structural phenotype, including disarray and interstitial fibrosis[22] (*Figure 2*). The drug, therefore, entered human experimentation, focusing on patients with symptomatic obstructive HCM. This choice was based on the well-established relation between LV hypercontractility, dynamic obstruction, and limiting symptoms, as well as on the consistent and measurable symptomatic improvement following gradient relief.[13]

The landmark Phase 3 EXPLORER-HCM trial was successfully completed in 2020,[23] and led to Food and Drug Administration (FDA) approval of mavacamten in April 2022. The study randomized 251 patients with symptomatic obstructive HCM to mavacamten or placebo, on a background therapy including beta-blockers or calcium antagonists.[23] The primary endpoint was a composite assessing variation in oxygen consumption at cardiopulmonary exercise testing and perceived symptom burden. After a 30-week treatment period, patients were considered to have achieved the endpoint if their peak oxygen consumption (pVO_2) increased ≥1.5 mL/kg/min (compared with baseline) with an improvement of at least one New York Heart Association (NYHA) class or ≥3.0 mL/kg/min with no worsening of NYHA class. Overall, 37% of patients in the mavacamten arm reached the primary endpoint compared with 17% in the placebo arm ($P = 0.0005$). In addition, there was a consistent benefit of mavacamten across all secondary endpoints, including pVO_2 increase vs. baseline (1.4 vs. −0.1 mL/kg/min), NYHA functional class (≥1 NYHA class improvement in 65% vs. 31% in the placebo arm), relief of post-exercise LV outflow gradient (an almost 50 mmHg reduction, compared with no change in the placebo arm), symptomatic status and quality of life (13.6 point improvement in Kansas City Cardiomyopathy Questionnaire, compared with 4.2 in the placebo arm; $P < 0.001$ for all comparisons).[23]

Clinical and haemodynamic improvement with mavacamten was independent of age, gender, and genetic status, and was associated with favourable biomarker profile, as shown by a marked reduction in serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin I. Mavacamten was generally well tolerated, and its safety profile was not different from placebo. Notably, the average reduction in LVEF in the mavacamten arm was only 4%, and most patients remained well above a normal threshold of systolic function. Only seven patients experienced a temporary reduction in LVEF to values <50%; three had protocol-driven temporary treatment discontinuation during the 30-week treatment, while in four, the event occurred at end-of-treatment visit. In all patients, LVEF recovered to normal values following washout, except one who experienced only partial recovery (LVEF 50%) due to a procedural complication following atrial fibrillation ablation.[23] A recent interim analysis based on the patients enrolled in the EXPLORER-HCM Long-Term Extension study has shown sustained benefit and safety of mavacamten beyond 1 year.[24] In the recently presented VALOR-HCM trial (A study to evaluate mavacamten in adults with symptomatic obstructive HCM who are eligible for septal reduction therapy, NCT04349072), mavacamten was effective in reducing the need for invasive septal reduction therapies in obstructive patients referred to surgical centres due to severe symptoms.[25]

Another myosin inhibitor, aficamten, is currently undergoing Phase 3 experimentation in the international, multicentre, randomized Sequoia HCM trial, also focusing on symptomatic obstructive HCM patients. The study has been designed on the wake of the successful Phase II randomized placebo-controlled sequential cohort REDWOOD-HCM trial, showing excellent symptomatic gradient relief and symptomatic improvement in patients with obstructive HCM.[21] Aficamten has a similar mechanism of action to mavacamten, although the binding site and half-life are different.[26]

As myosin inhibitors start to penetrate clinical practice, relevant gaps in knowledge remain, calling for prudent use in the real world. Such caution is well reflected in the titration algorithm recommended in the mavacamten prescription label (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214998s000lbl.pdf). Despite their excellent safety

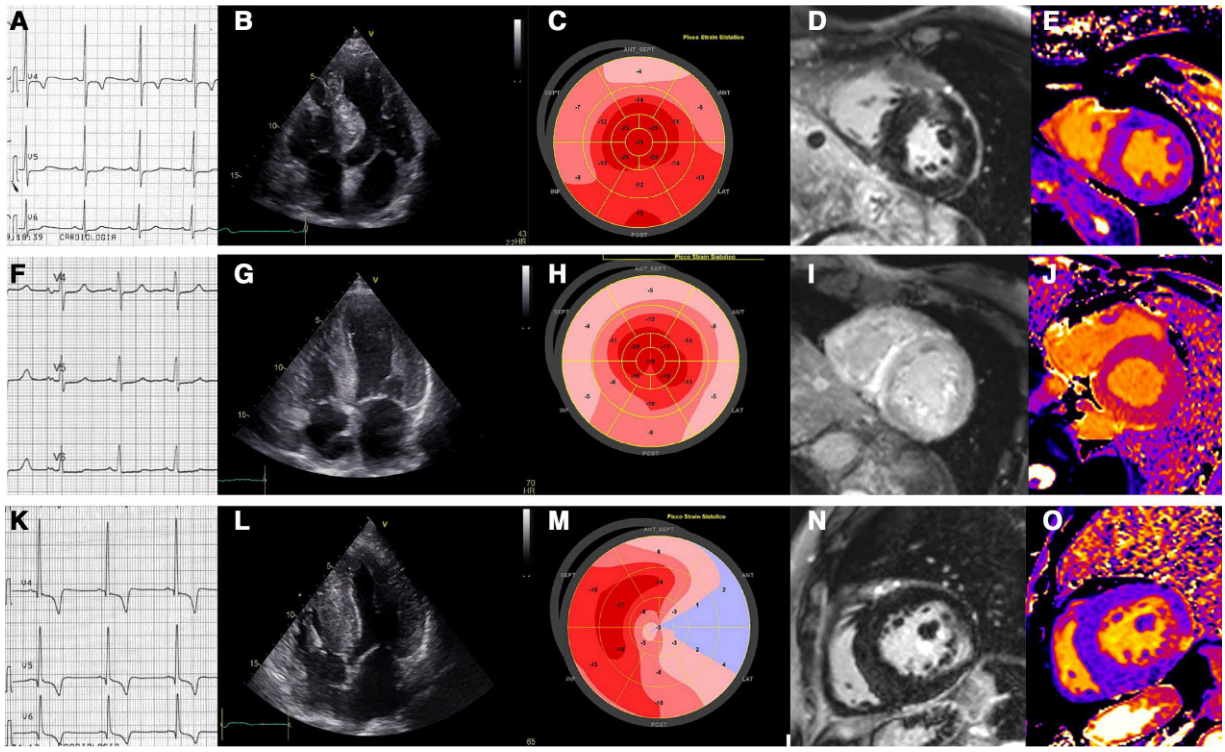

Figure 1 Electrocardiogram and imaging features of specific causes of heart failure with preserved ejection fraction. (*A–E*) Sarcomeric obstructive hypertrophic cardiomyopathy in a 45-year-old female. (*A*) Electrocardiogram presents high QRS voltages and diffuse repolarization abnormalities with diphasic-negative T waves in precordial leads V4–V6. (*B*) Echocardiography shows significant hypertrophy of basal and mid-septum favouring left ventricular outflow tract obstruction (not shown). (*C*) Strain imaging shows reduced longitudinal strain velocities in the basal-medium segments of the interventricular septum and anterior wall. (*D*) At cardiac magnetic resonance, a transmural area of late gadolinium enhancement of the mid-anterior interventricular septum is present; septal native T1 mapping values are within the normal range in (*E*) (1000 ms; normal values 960–1040 ms). (*F–J*) Transthyretin amyloidosis cardiac amyloidosis in a 79-year-old male. (*F*) Electrocardiogram shows sinus rhythm with left atrial enlargement and low-normal QRS voltages in V4–V6. (*G*) Echocardiography shows concentric left ventricular hypertrophy with granular-sparkling appearance of the myocardium, thickening of interatrial septum and atrioventricular valves, and left atrial enlargement. (*H*) Strain rate imaging is characterized by a significant diffuse reduction of longitudinal strain velocities with apical sparing. (*I*) At cardiac magnetic resonance diffuse LGE more evident in subendocardial myocardial layers is evident, with significantly increased septal T1 mapping values (*J*) (1100 ms; normal values 960–1040 ms). (*K–O*) Fabry disease in a 51-year-old male. (*K*) ECG shows sinus rhythm with a short PQ interval (118 ms), high QRS voltages, and diffuse repolarization abnormalities with negative T waves in V4–V6 leads. (*L*) Echocardiography shows concentric hypertrophy with thickening of right ventricular free wall and septal endocardium. (*M*) At strain rate, imaging significantly reduced longitudinal strain velocities in inferolateral and anterolateral mid-basal segments are present. (*N*) Cardiac magnetic resonance shows midwall LGE in the lateral basal segments with reduced septal native T1 mapping values (890 ms; normal values 960–1040 ms). Pseudo-normalized native T1 mapping values (980 ms; normal values 960–1040 ms) are present in the lateral segment corresponding to LGE area (O).

record so far, there are no data regarding the long-term safety and efficacy of myosin inhibitors, and particular caution is required in the identification of slow metabolizers, at risk of excessing reduction in LVEF during titration or in the presence of intervening modifiers such as atrial fibrillation. Furthermore, whether myosin inhibitors may benefit symptomatic patients with non-obstructive HCM remains unresolved.[27] The most important question, however, is whether myosin inhibitors may fulfil the promise of exerting in patients the disease-modifying impact shown in experimental HCM models,[22,28] and thus prevent long-term myocardial energy depletion, fibrosis, and LV remodelling, ultimately impacting outcome (*Figure 2*). Because of the slow progression and low event rates typical of HCM, answers to this question will require long exposure times. However, based on the solid scientific rationale and encouraging initial results, hopes are justified for the first class of drugs specifically addressing the core disease mechanism of HCM.

Hereditary transthyretin amyloidosis

Cardiac amyloidosis is characterized by extra-cellular deposition of misfolded proteins in the heart with the pathognomonic histological property of green birefringence when a tissue specimen is examined under cross-polarized light after staining with Congo red.[29–33] While more than 30 known proteins are capable of aggregating as amyloid *in vivo*, only nine accumulate in the myocardium producing significant cardiac disease, and more than 98% of currently diagnosed cardiac amyloidosis result from fibrils composed of either monoclonal immunoglobulin light chains (AL) or transthyretin (ATTR), either in its genetically altered (i.e. hereditary—ATTRv) or wild-type (ATTRwt) form.[32] Two main mechanisms of tissue and organ damage occur in amyloidosis: chronic infiltration and acute proteotoxic effect of circulating precursors and

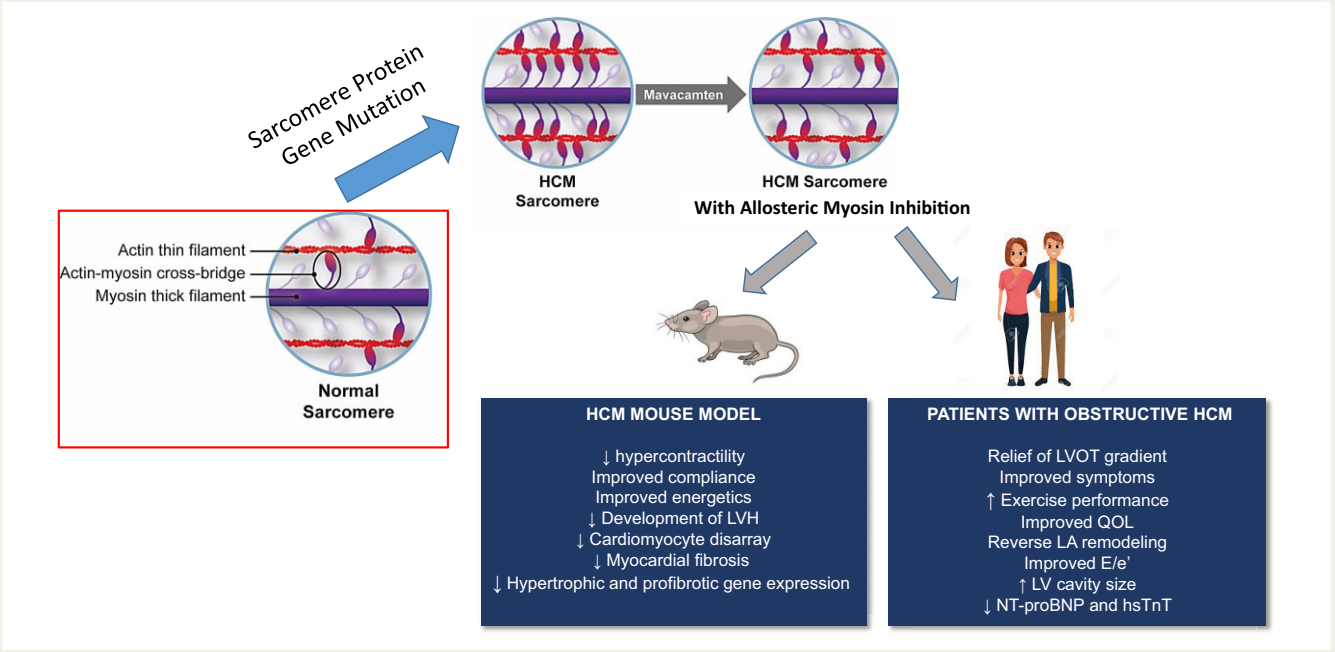

Figure 2 Myosin inhibitors: mechanism of action and clinical benefits. Molecular mechanism of action of myosin inhibitors, with demonstrated structural effects in animal models and clinical benefits in clinical trials.

non-amyloid aggregates. The latter is particularly evident in AL but also occurs in ATTRv and ATTRwt.[30] Myocardial infiltration by rigid, space-occupying amyloid fibrils leads to increased stiffness and dysfunction of atrial and ventricular myocardium. Infiltration is generally diffuse but can be mainly subendocardial or with patchy areas of transmural involvement; involvement of the valves, pericardium, and conduction system is common.[30] Cardiac amyloidosis is classically considered a form of restrictive cardiomyopathy. However, a restrictive haemodynamic profile is limited to the advanced phases of the disease, in which a progressive increase in parietal and chamber stiffness leads to an upward and leftward shift in the end-diastolic pressure–volume relationship with concomitant declines in stroke volume, cardiac output, and, frequently, arterial blood pressure.[29] Very high NT-proBNP values result, which represent an important clinical red flag.[32] Parallel declines in stroke volume and end-diastolic volume explain why LVEF is often preserved during the course of the disease, despite the fact that myocardial contraction is reduced—as shown by reduced LV longitudinal function and strain.[29] When a restrictive physiology has fully developed, the duration of diastole and increased filling pressures have a limited impact on ventricular filling. As a result, stroke volume is virtually fixed and cardiac output becomes crucially dependent on heart rate.[29,33]

Previously considered a rare disease, cardiac amyloidosis is considered today rather underdiagnosed than rare. In systematic screening studies on HFpEF, up to 12% of patients are found to have ATTR amyloidosis.[30,31] The clinical manifestations are heterogeneous and range from an exclusive or dominant neurological phenotype, with motor sensory polyneuropathy and autonomic disturbances, to a pure cardiologic phenotype, with HFpEF as the most frequent manifestation.[30,33] Organ involvement is strictly driven by the underlying genetic variant: I122L, T60A, and I68L are classic examples of 'cardiac' mutations.[31] Notably, between 3% and 4% of the African-American population in the USA harbour I122L, albeit penetrance is low.[34]

Treatment of cardiac amyloidosis has long been limited to the treatment and prevention of complications including HF, arrhythmias, conduction disturbances, and thromboembolism. Recent advances, however, have shifted the focus towards halting or delaying amyloid deposition by specific disease-modifying drugs,[31,33,35] which are becoming increasingly available for ATTRv (as well as ATTRwt) amyloidosis. Conversely, treatment of AL amyloidosis largely rests on therapies addressing the underlying haematological condition.[33,36]

Novel therapies act at different steps of the ATTR amyloidogenic process: some have proven effective in stabilizing circulating TTR molecules by preventing its dissociation or cleavage into amyloidogenic fragments, others in reducing the production of mutated TTR (an approach previously treated by liver transplantation) with gene silencers. Other investigational compounds include agents directed at removing amyloid fibrils, potentially reverting tissue infiltration[33] (*Figure 3*). Tafamidis, a kinetic TTR stabilizer, binds to the unoccupied thyroxine-binding sites of tetrameric TTR and prevents the amyloidogenic cascade.[37,38] Tafamidis was the first drug tested in a randomized, controlled trial, and is now approved by European Medicines Agency (EMA) and FDA for ATTR cardiac amyloidosis patients who have reasonably expected survival. The ATTR-ACT study demonstrated a 30% reduction in all-cause mortality and in cardiovascular-related hospitalization and a slower decline in quality of life after 30 months of treatment in ATTRv or ATTRwt cardiomyopathy patients, compared with placebo.[39] ATTR-ACT can be considered the 'three first times' trial: (i) the first time a medical treatment has been shown to reduce mortality and HF hospitalization in HFpEF; (ii) the first time a medical treatment has been shown to reduce mortality and morbidity in TTR-related amyloidosis; (iii) the first time an HF drug has proven effective on a hard endpoint by acting centrally on the myocardium, rather than peripherally or by neurohormonal modulation.[39] Focusing on a similar therapeutic aim, AG10 is a highly selective, small-molecule TTR stabilizer. Phase I and II studies showed a good toxicity profile and stabilization of both mutant and wild-type TTR.[40] A Phase 3 efficacy and safety study to evaluate AG10 compared with placebo in subjects with symptomatic ATTR cardiomyopathy is ongoing (ClinicalTrials.gov Identifier: NCT03860935).

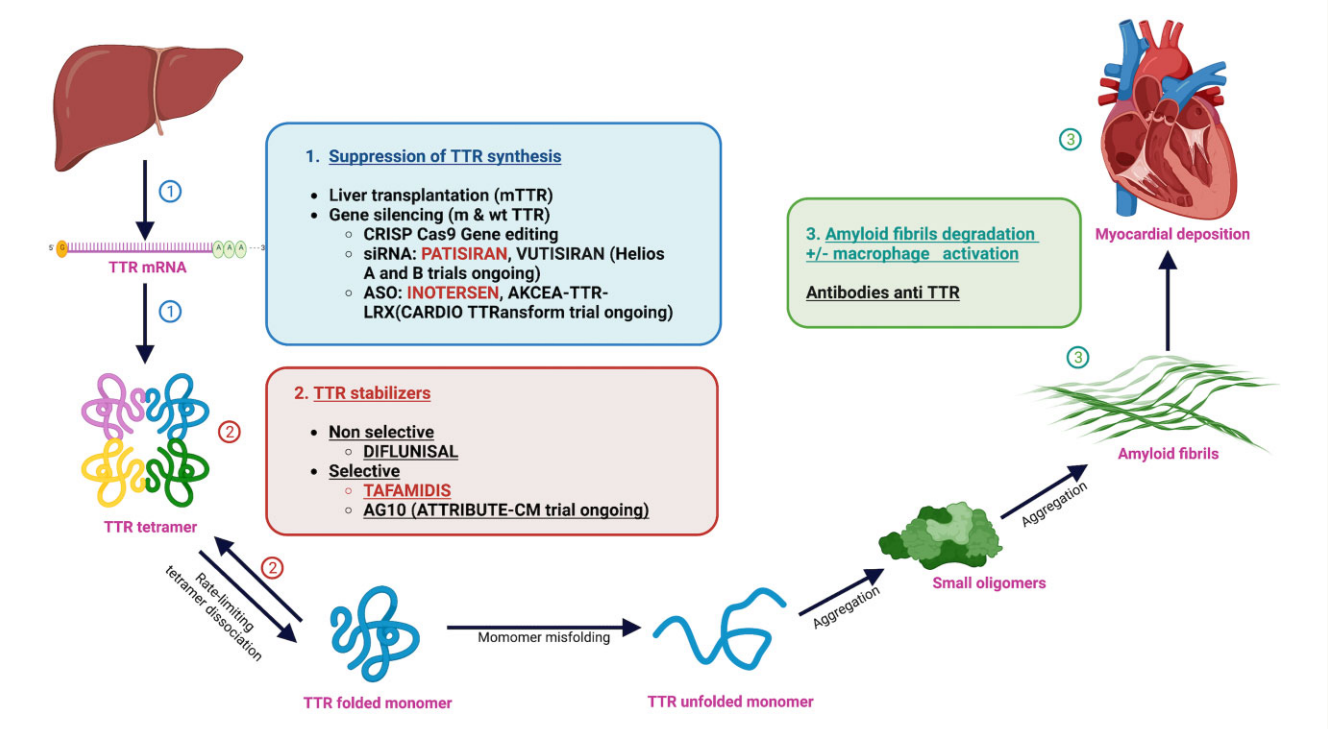

Figure 3 Novel treatments for transthyretin amyloidosis cardiac amyloidosis. Currently approved and forthcoming treatments for transthyretin cardiac amyloidosis represented according to their targets in the pathogenetic process of amyloidosis from transthyretin synthesis to cardiac infiltration.

Gene silencing by small-interfering RNA (siRNA) and antisense oligonucleotide (ASO) technologies causes a drastic reduction of TTR production by the liver. The siRNA patisiran and the ASO inotersen have been approved for the treatment of patients with ATTRv-related polyneuropathy, irrespective of cardiac involvement.[35,41] Patisiran, currently undergoing Phase 3 experimentation (APOLLO-B; NCT03997383), is administered by intravenous infusion once every 3 weeks and is generally well tolerated. Other gene silencers for ATTR cardiac amyloidosis currently under investigation in Phase 3 trials include vutrisiran (HELIOS B; NCT04153149) and eplontersen (CARDIO-TTRansform; NCT04136171). Finally, the most recently devised strategy is the blockade of TTR production by genome editing by CRISPR–Cas9 technology: preliminary findings of a Phase 1 study (NCT04601051) are encouraging.[41]

Storage diseases

Storage diseases represent a group of inherited errors of metabolism characterized by the accumulation of intracellular material in various organs and tissues, including the myocardium. Those presenting with cardiomyopathy include Fabry, Danon, and PRKAG2-related disease,[42–44] often referred to as HCM phenocopies, due to overlapping morphological and functional features such as cardiac wall thickening, diastolic dysfunction, left atrial enlargement, microvascular ischaemia, and myocardial fibrosis. However, they only exceptionally develop LV outflow tract obstruction and often show distinct cardiac and extra-cardiac red flags that may help suspect a rare disease and exclude sarcomeric HCM.[8,42]

Fabry disease

Fabry disease is an X-linked disorder caused by pathogenic variants in the GLA gene, leading to deficient activity of the enzyme α-galactosidase A. Such deficit leads to progressive intralysosomal storage of globotriaosylceramide (Gb3) in affected tissues, including heart, vessels, kidneys, and peripheral nervous system.[11,45] Systemic manifestations, mainly occurring in males, include small fibres neuropathic pain, hypo-anhidrosis with heat and cold intolerance, angiokeratomas, gastrointestinal disturbances, and cornea verticillata. Renal involvement with albuminuria occurs early in young male patients while cardiomyopathy and premature cerebrovascular accidents usually manifest in the third or fourth decade.[45] Some missense variants, including p.N215S and p.F113L, are associated with residual α-galactosidase A activity, leading to a late-onset phenotype predominantly affecting the heart.[11] Heterozygous female patients usually present at an older age and with milder clinical manifestations compared with males. However, in the case of skewed X chromosome inactivation, female patients may also develop severe phenotypes and present a severe clinical course.[46] Cardiac involvement in FD is characterized by progressive thickening of cardiac walls mimicking sarcomeric disease (*Figure 1*): in consecutive cohorts, FD accounts for up to 1% of patients with an initial diagnosis of HCM.[11,47] Mitral and aortic valve regurgitation are common due to leaflet infiltration; LV dysfunction may ensue due to progressive fibrosis and myocyte loss. Atrioventricular block, atrial fibrillation, and ventricular arrhythmias manifest late during the course of the cardiomyopathy.[11]

Available treatments for FD include enzyme-replacement therapies (ERTs) (agalsidase-alfa and agalsidase-beta) and the oral pharmacological chaperone (migalastat) (*Graphical Abstract*).[11,45] Collectively, these therapies have radically improved the outcome of FD patients, largely due to their positive effects on the progression of renal disease. However, early start of treatment is critical in order to obtain satisfactory results.[45,48,49] Furthermore, long-term studies and registry data demonstrate that ERT may halt or slow the progression of cardiac

disease, reducing the rate of cardiovascular events.[50] Regression of mild LV hypertrophy has been occasionally reported, with some evidence that LV hypertrophy may be prevented by early treatment.[49] In ERT-naïve patients with initial signs of cardiomyopathy, 1 year of ERT stabilized LV mass index and attenuated reduction in T1, an early magnetic resonance imaging (MRI) marker of disease.[51]

Chaperone molecules such as migalastat are iminosugars that bind to the catalytic domain of α-Gal A promoting its proper folding and trafficking to the lysosome thus increasing enzymatic activity.[52] While ERT is indicated in all patients with FD, migalastat can be administered only to patients with amenable variants (i.e. mutations that are responsive to the drug in a dedicated *in vitro* assay, as listed in https://galafold.com/hcp/amenability). In clinical trials and open-label extension studies, the efficacy of migalastat is comparable with ERT in reducing the overall progression of the disease. In addition, migalastat treatment is associated with a sustained decrease of LV mass index, suggesting distinct disease-modification properties at the myocardial level.[11,52]

New therapies for FD include second-generation ERTs, substrate reduction therapies, and gene and mRNA therapies. Pegunigalsidase-alpha is a pegylated form of α-Gal A produced in a PlantCell Ex system, characterized by a much longer circulatory half-life and increased heart and kidney uptake compared with currently available ERTs.[53] In the Phase III BRIDGE trial (NCT03018730), patients switched from agalsidase-alfa to pegunigalsidase-alfa showed slower progression of renal failure (estimated glomerular filtration rate slope improved from −5.1 to 0.23 mL/min/1.73 m^2/year in both males and females).[53] Other Phase III clinical trials (NCT02795676; NCT03018730, NCT03180840) evaluating pegunigalsidase-alfa treatment are ongoing. Substrate reduction therapy is also being pursued, by oral iminosugars inhibiting glycosphingolipid synthesis and lowering the cellular content of Gb3. Two agents, venglustat and lucerastat, are currently under investigation in Phase II and III clinical trials, respectively.[54] In addition, cardiotropic vectors specifically targeting myocardial tissue have been developed for gene therapy of FD. Results from the Phase I/II STAAR trial with the adenoviral vector isaralgagene-civaparvovec were promising, leading to increased α-Gal A activity in four patients, ranging from 2- to 15-fold above normal mean values. In one patient, with sustained 15-fold enzymatic activity at Week 52, ERT was withdrawn (https://clinicaltrials.gov/ct2/show/NCT04046224). Adult male patients with classic FD enrolled in the 4D-310 trial presented a sustained increase of α-Gal A activity and significant decrease in lyso-Gb3 levels, together with promising cardiac improvement in terms of T1 mapping increase at MRI (https://ir.4dmoleculartherapeutics.com/static-files/bb460939-74bf-44bb-a0e0-caf85c0ac58c). Finally, initial experience with human α-Gal A mRNA encapsulated with lipid nanoparticles, administered to mice and non-human primates, has led to a significant increase in α-Gal A levels in the liver, heart, and kidney.[55]

Cardiac glycogenoses

Danon disease is an X-linked dominant lysosomal storage disorder, caused by a deficiency of the lysosome-associated membrane protein-2 (LAMP2), a crucial promoter of lysosomal biogenesis. Such deficit leads to the accumulation of autophagic vacuoles containing amorphic material and glycogen deposition in cardiac and skeletal myocytes.[42,56,57] The prevalence of Danon disease among patients with HCM phenotype is 4%–6% in paediatric cohorts and 0.7%–4.0% in adults.[56–58] Males present during childhood with severe systemic involvement including ocular, hepatic, cognitive, and musculoskeletal manifestations.[42,56] Danon cardiomyopathy is severe, characterized by rapidly progressive, massive biventricular hypertrophy, leading to early death or transplant.[42,56] In females, conversely, cardiac involvement is milder, due to the lyonization process, and may present in the absence of systemic manifestations around the third or fourth decade of life, often indistinguishable from sarcomeric HCM. The ECG classically shows a short PR interval, pre-excitation, and high QRS voltages with deep T-wave inversion.[59,60] Atrioventricular conduction abnormalities have been observed in up to 15% of patients.[60,61] A gene therapy programme is currently being developed for Danon disease using a recombinant adeno-associated virus serotype 9 (AAV9) containing the human lysosome-associated membrane protein 2 isoform B (LAMP2B) transgene (RP-A501). In a Phase I trial, a single intravenous dose was generally well tolerated and led to cardiac LAMP2B gene expression associated with preliminary evidence of cardiac and extracardiac benefits.[62]

Finally, PRKAG2-related cardiomyopathy is a rare disease accounting for 0.23%–1% of consecutive patients with an initial diagnosis of HCM.[43,63] Pathogenic variants in the gamma-2 regulatory subunit of AMP-activated protein kinase (PRKAG2) cause cardiomyopathy through an anomalous activation of adenosine monophosphate (AMP) kinase, leading to increased glucose uptake and cytosolic accumulation of glycogen metabolism by-products (polyglucan and amylopectin).[63] The disease, transmitted with autosomal dominant inheritance pattern, is characterized by severe HCM with LV pre-excitation and a high prevalence of atrioventricular blocks and ventricular tachyarrhythmias.[43] Although specific pharmacological treatments are lacking, a correct diagnosis is essential for management, as these patients often present with syncope due to atrioventricular block, but may also develop life-threatening ventricular tachyarrhythmias. Aggressive monitoring of arrhythmias and timely device implantation is warranted even at an early age. Conversely, ablation of accessory pathways should be considered only in selected, symptomatic patients, due to frequent recurrences and the risk of advanced atrioventricular block.[43,64]

Implications for the broader heart failure with preserved ejection fraction scenario

Randomized trials involving HFpEF patients have been notoriously challenging, particularly when LVEF exceeds 60%–65%,[65] and only recently have large randomized outcome studies advanced the field, as spironolactone and sacubitril/valsartan have shown benefit for patients in the lower end of the HFpEF LVEF spectrum, and sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown definite improvement on survival.[66,67] One explanation for the disappointing outcome of many HFpEF trials includes the lack of clear therapeutic rationale for using drugs such as angiotensin receptor blockers, in contrast to their use in HFrEF, where neurohormonal activation is a clear driver of prognosis.[67] Furthermore, the HFpEF syndrome seems to represent a far more heterogeneous group than HFrEF, due to the 'contamination' by subsets of patients not likely to respond to the interventions. It has been estimated that up to 15%–20% of patients enrolled in HFpEF outcome trials may have a more specific disease causing the syndrome.[68] In trials enrolling thousands of patients at hundreds of multinational sites, little attention had been paid over the years to identifying such patients prior to enrollment. However, the availability of specific therapies has now created a highly compelling rationale to identify potential outliers, not only during clinical practice but also during the screening period of clinical trials. In the near future, artificial intelligence and machine

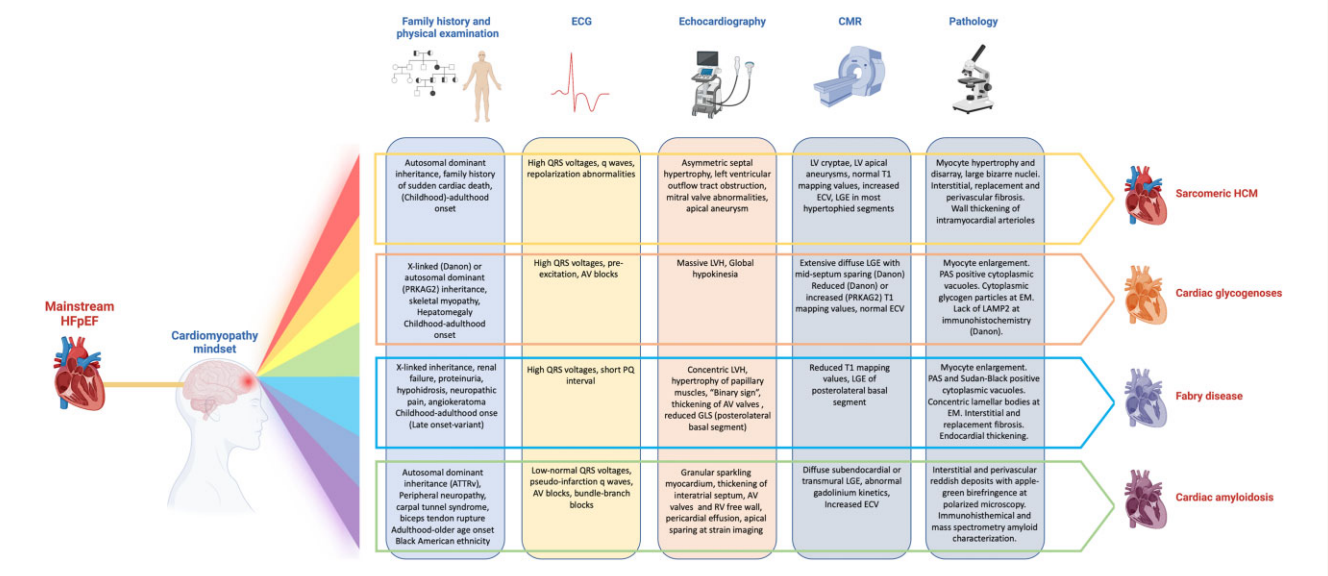

Figure 4 Dissecting the complexities of the heart failure with preserved ejection fraction spectrum: the cardiomyopathy mindset. Flowchart illustrating the approach to the differential diagnosis of potentially treatable Heart failure with preserved ejection fraction causes, through a cardiomyopathic mindset. For each diagnostic step (in vertical), red flags suggesting a specific cardiomyopathy (in horizontal) underlying the initial heart failure with preserved ejection fraction presentation are reported. LV, left ventricle; ECV, extra-cellular volume; LGE, late gadolinium enhancement; CK, creatine kinase; AST, aspartate transaminase; ALT, alanine transaminase; AV, atrioventricular; LVH, left ventricular hypertrophy; GLS, global longitudinal strain; ATTRv, hereditary transthyretin amyloidosis; LAMP2, lysosomal-associated membrane protein 2.

learning techniques may provide the best solution to define HFpEF subsets and differentiate monogenic diseases within a number of broader phenotypes,[69] as well as highlight common mechanisms across subsets.[70] In contemporary practice, the 'red flag' concept continues to represent the most effective approach alerting clinicians to certain clinical signs requiring further evaluation with targeted imaging, biomarkers, and genetic tests.[8] Often referred to as the *cardiomyopathy mindset* (*Figure 4*), such an approach can be extended to the evaluation of HFpEF, in order to reach a timely suspicion of specific aetiologies based on dedicated algorithms.[71] As the general awareness for rare cardiac diseases increases in the medical community, earlier recognition, and improvements in the management of these patients will inevitably follow.[8]

Notably, the emergence of treatments targeted at genetic causes of HFpEF has other, far-reaching implications, by providing a unique insight into cardiac pathophysiology and identifying novel targets of potential relevance for the HF community. Treatments that have been developed for a well-defined niche of HFpEF may turn out to be beneficial to wider groups of patients sharing similar mechanisms of disease—as witnessed in the last two decades in the field of oncology.[72] A case in point is represented by HFpEF with hypercontractile phenotype. Recent evidence shows that, among adults without cardiovascular disease, LVEF in the supranormal range is associated with a higher risk of adverse cardiovascular outcomes. In a large MRI-based study, participants with LVEF above the 75th percentile had an increased risk of adverse events independent of their baseline risk profile and other potential confounders.[73] Consistently, a combined analysis of the UK Biobank cohort and the BioMe cohort (using MRI and echocardiography-based assessment of LVEF, respectively) demonstrated an increased risk of mortality and higher burden of HF symptoms and natriuretic peptide elevation among individuals with LVEF >70%.[74] Intriguingly, higher LVEF was associated with a greater risk of events only among those with low stroke volume index—a combination reminiscent of initial/mild HCM phenotypes.[75] Because sarcomere genetic variants are present in 1:200 in the general population, it is tempting to postulate that a number of these individuals may harbour unrecognized HCM.[76] In the remainder, late-onset, hypertrophic/hypercontractile phenotypes are now thought to result from the interplay of ageing, polygenic predisposition, and acquired modifications occurring both in cardiomyocytes (e.g. titin hypophosphorylation) and the extra-cellular matrix.[77] Although cardiomyocytes are known to exhibit a number of age-related modifications, including hypertrophy and changes in contraction and relaxation,[78] there is still limited understanding of how ageing may promote HF. Among other insults, ageing cardiomyocytes are exposed to somatic mutations, i.e. genomic changes that escape DNA repair mechanisms over time. Very recent evidence suggests that cardiomyocytes accumulate age-related single nucleotide variants at rates higher than neurons and lymphocytes, but similar to hepatocytes.[79] In organs characterized by active metabolism, such as the heart, cells more often tend to develop somatic mutations and become polyploid, possibly in order to endure oxidative stress by increasing cell size and metabolic production. However, polyploidization may also promote alterations in the transcriptome and metabolome and might ultimately result in dysfunction, with HFpEF as the final result.[79]

Rosch *et al.*[80] recently provided a thorough characterization of HFpEF phenotypes including haemodynamic and histological features. Intriguingly, they found that patients with LVEF in the low-normal range (50%–60%) showed features overlapping with HFrEF, including larger cardiac dimensions and higher levels of myocardial fibrosis. Conversely, patients with supranormal LVEF (>60%) had smaller but thicker ventricles, less fibrosis, and increased preload and afterload sensitivity in the context of enhanced diastolic and systolic stiffness. Such behaviour is consistent with the observation that drugs that are successful in HFrEF, fail to show benefit in HFpEF with supranormal LVEF,[81] suggesting that this is a

different patient subset altogether. In such individuals, it is tempting to speculate that myosin inhibitors may play a role by countering the core pathophysiological and clinical abnormalities, irrespective of their cause (genetic vs. acquired). Many gaps in knowledge remain. Promisingly, however, just as many years ago the empiric treatment recommendations for 'diastolic HF' were informed by the approach to HCM, today a favourable Phase 2 trial signal in non-obstructive HCM[27] has led to a pilot trial of mavacamtem in patients with HFpEF.[82]

Storage diseases are providing invaluable insight regarding the role of deranged autophagy and myocardial inflammation in inherited and acquired cardiac diseases. Autophagy regulation is central in normal and diseased myocardium, and changes in autophagy activation are implicated in several cardiac conditions including cardiomyopathies and HF.[83,84] Lysosomal storage disorders represent a unique model to improve our knowledge of lysosomal function and develop new therapeutic strategies targeting autophagy regulation.[85] In addition to well-established autophagy inducers like rapamycin and other agents regulating the mTOR signalling pathways, there is increasing evidence that drugs effective in the management of HFpEF, such as SGLT2 inhibitors, and other cardiovascular drugs including beta-adrenergic blockers, calcium channel blockers, and amiodarone, exert part of their therapeutic actions by influencing myocyte autophagy.[86,87] Interestingly, while small non-coding RNAs are among the main regulators of autophagic processes, autophagy itself may represent a key step in the mechanism of action of therapeutic ASO.[88,89] Furthermore, autophagy is interlinked with unfolded protein response, an intracellular process triggered by the accumulation and aggregation of unfolded proteins in the endoplasmic reticulum lumen.[90,91] A persistent activation of this process may lead to secondary protein metabolism alterations, perturbation of autophagy, and tissue inflammation, ultimately promoting cell dysfunction and death.[90] While the accumulation of misfolded or abnormally degraded proteic material is a common feature in genetic disorders specifically associated with abnormal contractile or cytoskeletal protein synthesis, unfolded protein response has been increasingly associated with the most prevalent acquired cardiovascular conditions, including hypertensive heart disease, ischaemic heart disease, and HF.[91] In a recent experimental HFpEF model,[92] nitric oxide synthase induction was shown to cause deficient activity of unfolded protein response effectors potentially associated with further interstitial accumulation of proteins. Today, targeting the unfolded protein response represents a promising therapeutic approach for a broad spectrum of conditions including cancer and neurodegenerative disorders, as well as cardiac disease.[93]

Conclusions

A conceptually important subset of HFpEF is due to genetic causes amenable to treatment. While their epidemiological relevance may seem small compared with mainstream HFpEF, the clinical implications of a timely diagnosis for individual patients and their families cannot be overemphasized. Furthermore, the theoretical implications of such disease paradigms for broader sections of the HFpEF population are just beginning to emerge. As the field rapidly evolves, the concept that deep phenotyping of HFpEF patients will enable personalized therapies targeting different underlying mechanisms is emerging powerfully. It is hoped that from the privileged observation site of monogenic disease, novel solutions will surface for the whole HF community. The concept of treating mechanisms, rather than clinical diagnosis, is already a reality in the world of oncology and may represent the near future for cardiologists.

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Data availability

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