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Chronic heart failure: advances in pharmacological treatment and future perspectives

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Summary

Besides noticeable progress in device therapy during the past decade, more recent advances in the management of chronic heart failure have led to exciting new pharmacological options. Among these, the combined angiotensin II receptor/neprilysin inhibitor (ARNI) valsartan/sacubitril has already proven highly effective in heart failure with reduced ejection fraction (HFrEF), and convincing data are available regarding the cardioprotective effects of sodium-glucose-co-transporter 2 (SGLT2) inhibitors. These two treatments have earned a class I and a class II recommendation, respectively, in the European Society of Cardiology guidelines for the diagnosis and treatment of heart failure. Whereas progress with respect to heart failure with preserved ejection fraction (HFpEF) is still slow, both ARNIs and SGLT2 inhibitors hold great promise for this condition as well, and large clinical trials are currently ongoing. In addition, new diagnostic algorithms have recently been developed to improve the diagnostic accuracy for HFpEF, which will ultimately aid the search for effective therapies in future clinical trials. In this review article, these most recent advances in the diagnosis and pharmacological management of HFrEF and HFpEF are highlighted, and setbacks as well as opportunities for future developments (e.g., tafamidis for the treatment of transthyretin amyloid cardiomyopathy) are discussed.

Keywords: heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, angiotensin II receptor/neprilysin inhibitor, sodium-glucose-co-transporter 2 inhibitors, amyloid cardiomyopathy, diagnostic algorithms

Introduction

After almost two decades without ground-breaking changes in the pharmacological management of heart failure (HF), a set of promising new drugs has successfully entered the clinical arena of HF treatment. Moreover, the classification of HF phenotypes based on the left ventricular ejection fraction (LVEF) has recently been refined by defining the following three entities: HF with preserved ejection fraction (HFpEF) if the LVEF is ≥50%; HF with mid-range ejection fraction (HFmrEF) if the LVEF is 40–49%; and HF with reduced ejection fraction (HFrEF) if the LVEF is <40% [1]. Whereas diagnosis and treatment are best defined for HFrEF, diagnosis of HFpEF still remains a matter of debate. Similarly, and despite considerable progress in the mechanistic understanding of HFpEF based on more recent data from preclinical and clinical studies, disease-modifying therapies with a prognostic impact are still lacking. In this review we focus on the latest advances in the pharmacological treatment of HF and discuss the newly proposed diagnostic algorithms for HFpEF.

Paradigm shift in HF therapy: from neurohormonal inhibition to neurohormonal modulation

The overshooting and sustained activation of the sympathetic nervous system (SNS) and the renin angiotensin aldosterone system (RAAS) constitutes the basis of the HF syndrome. Although initially adaptive to increase cardiac performance in response to a variety of short-lasting physiological and pathophysiological stressors, these systems remain chronically activated and thus become maladaptive in HF [2]. The notion of the central role of neurohormonal activation in the perpetuation of the HF syndrome has paved the way for the successful use of neurohormonal antagonists such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs) and beta-blockers. Their striking benefit in reducing morbidity and mortality in HFrEF has been demonstrated in a multitude of large, randomized, controlled landmark trials during the last three decades [3–8]. Therefore, complete SNS and RAAS inhibition by using the maximum tolerated doses of a beta-blocker, an ACE inhibitor (or an ARB in the case of ACE-inhibitor intolerability) and an MRA has become the international standard to treat HFrEF for many years. Only in 2014, with the publication of the PARADIGM-HF trial [9], did this long-lasting paradigm of isolated neurohormonal inhibition change with the introduction of a new class of medication, the angiotensin receptor-neprilysin in-

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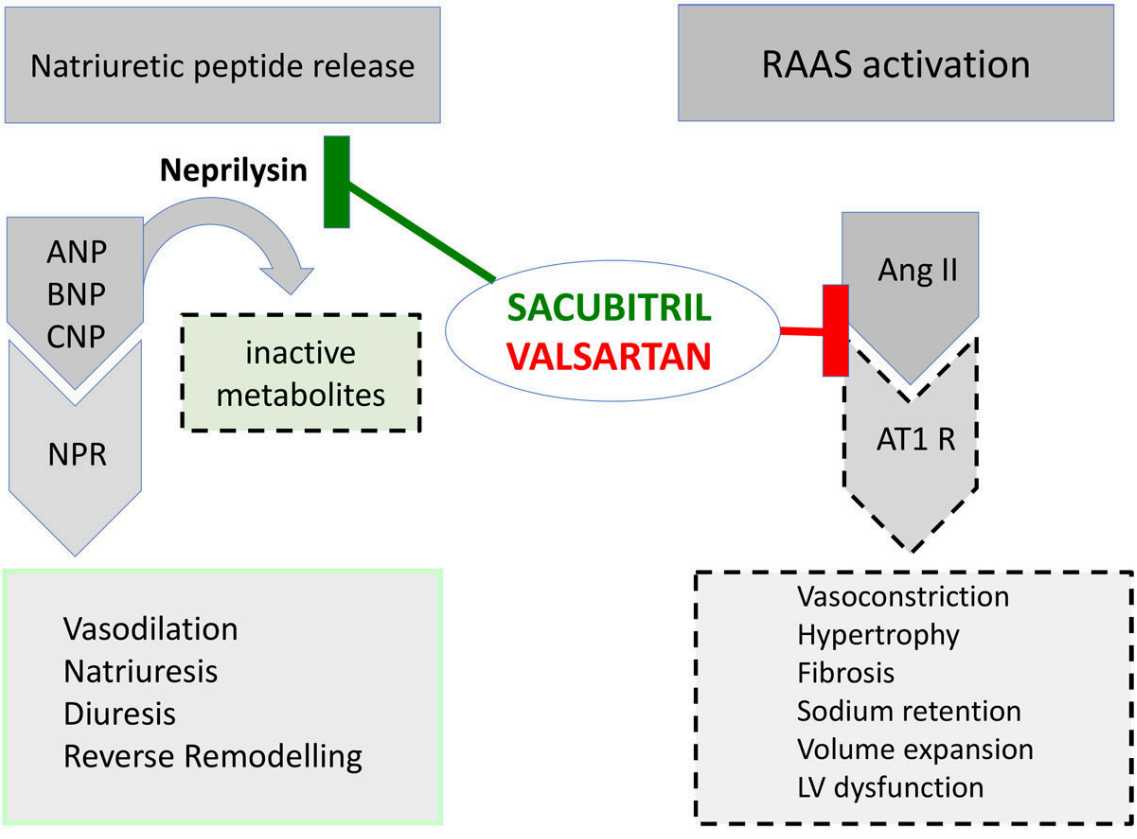
hibitor (ARNI), which combines the inhibition of RAAS neurohormones with the activation of beneficial neurohormones, the natriuretic peptides (fig. 1).

Natriuretic peptides are vasoactive peptides that are released in response to distension of the myocardial wall (B-type natriuretic peptide, BNP, and atrial natriuretic peptide, ANP) or by the vascular endothelium (C-type natriuretic peptide, CNP). Natriuretic peptides have various beneficial haemodynamic and cardioprotective effects, including vasodilation, natriuresis and diuresis, as well as anti-fibrotic and anti-hypertrophic properties [10]. This beneficial cardiovascular profile counteracts the deleterious cardiovascular effects of sustained SNS and RAAS activation. Endogenous augmentation of natriuretic peptides has become, therefore, a main focus of novel HF therapies. Because natriuretic peptides are degraded enzymatically by neprilysin, one way to increase endogenous natriuretic peptide levels is to inhibit neprilysin, which is predominantly expressed in the kidneys [11]. In the early 1980s, the first neprilysin-inhibitors were studied as a monotherapy in the setting of arterial hypertension, but proved ineffective at lowering blood pressure. Because angiotensin II and endothelin-1 are also degraded by neprilysin, neprilysin inhibition resulted in a consecutive increase in these potent vasoconstrictors [12]. As a result, subsequent studies combined neprilysin-inhibitors with ACE inhibitors. Omapatrilat was the most prominent combined neprilysin- and ACE-inhibitor. It was tested in a series of HF and hypertension trials, but was later retracted because of a high incidence of life-threatening angioedema due to a marked reduction in the breakdown of bradykinin [13–15]. Eventually, the goal of safe combined RAAS-neprilysin inhibition was achieved with the use of an ARB instead of an ACE-inhibitor. This change circumvents the issue of bradykinin accumulation whilst preserving the benefits of combined RAAS-neprilysin inhibition. This led to the advent of a new class of medications: ARNIs.

The first-in-class ARNI is sacubitril/valsartan. This drug combines the well-known ARB valsartan with sacubitril, a neprilysin-inhibitor prodrug. After ingestion, sacubitril is rapidly metabolized into the active neprilysin-inhibitor sacubitrilat [16]. In the PARADIGM-HF study, sacubitril/valsartan at a target dose of 97/103 mg twice daily (bid) was compared to the actual gold standard, enalapril (target dose 10 mg bid) in over 8,000 stable, ambulatory HFrEF patients (LVEF <40%) [9]. Due to the overwhelming benefit in the sacubitril/valsartan group, the data-safety monitoring board stopped the trial prematurely after a median follow-up of 27 months. In the PARADIGM-HF study, sacubitril/valsartan reduced the primary composite endpoint of cardiovascular (CV) death or HF hospitalization by 20% with overwhelming statistical evidence ($p < 0.0000004$), resulting in a number needed to treat of 21. Importantly, both components of the composite endpoint were significantly reduced (CV death by 20%, HF hospitalization by 21%) [9]. Sacubitril/valsartan was well tolerated and no cases of angioedema with critical airway compromise were reported, although numerically, simple

Figure 1: Actions of ARNI in the neurohormonal cascade. The angiotensin II receptor/neprilysin inhibitor valsartan/sacubitril combines traditional neurohormonal inhibition targeting the renin-angiotensin-aldosterone system with an enhancement of the natriuretic peptide system through inhibition of natriuretic peptide degradation, thereby promoting their beneficial effects. ANP: atrial natriuretic peptide; BNP: brain (or B-type) natriuretic peptide; CNP: C-type natriuretic peptide; NPR: natriuretic peptide receptor; RAAS: renin-angiotensin-aldosterone system; Ang II: angiotensin II; AT1R: angiotensin II type 1 receptor; LV: left ventricular.



angioedema was more common in the ARNI group than in the enalapril group (19 versus 10 cases). Symptomatic hypotension was slightly more prevalent in the ARNI group (14% vs. 9%), whereas elevation of serum potassium and creatinine was more frequent in the enalapril group. Subsequent subgroup analyses of PARADIGM-HF revealed the following important benefits of sacubitril/valsartan over enalapril:

− Reduction in sudden cardiac death risk [17]

− *Better tolerance of MRA treatment due to a reduced risk of severe hyperkalemia* [18]

− *Improvement in quality of life and sexuality* [19]

− *Beneficial metabolic profile in diabetes:* patients with diabetes showed a significant decrease in HbA1c and a lower incidence of nw onset insulin treatment during follow-up [20]

− *Renal protection:* slower decline in renal function, particularly in the group of HF patients with diabetes [21, 22]

− *Reduction in repetitive hospitalization due to HF* [23]

− *Reduction in serum uric acid concentration* [24]

− *Cost-effectiveness* [25]

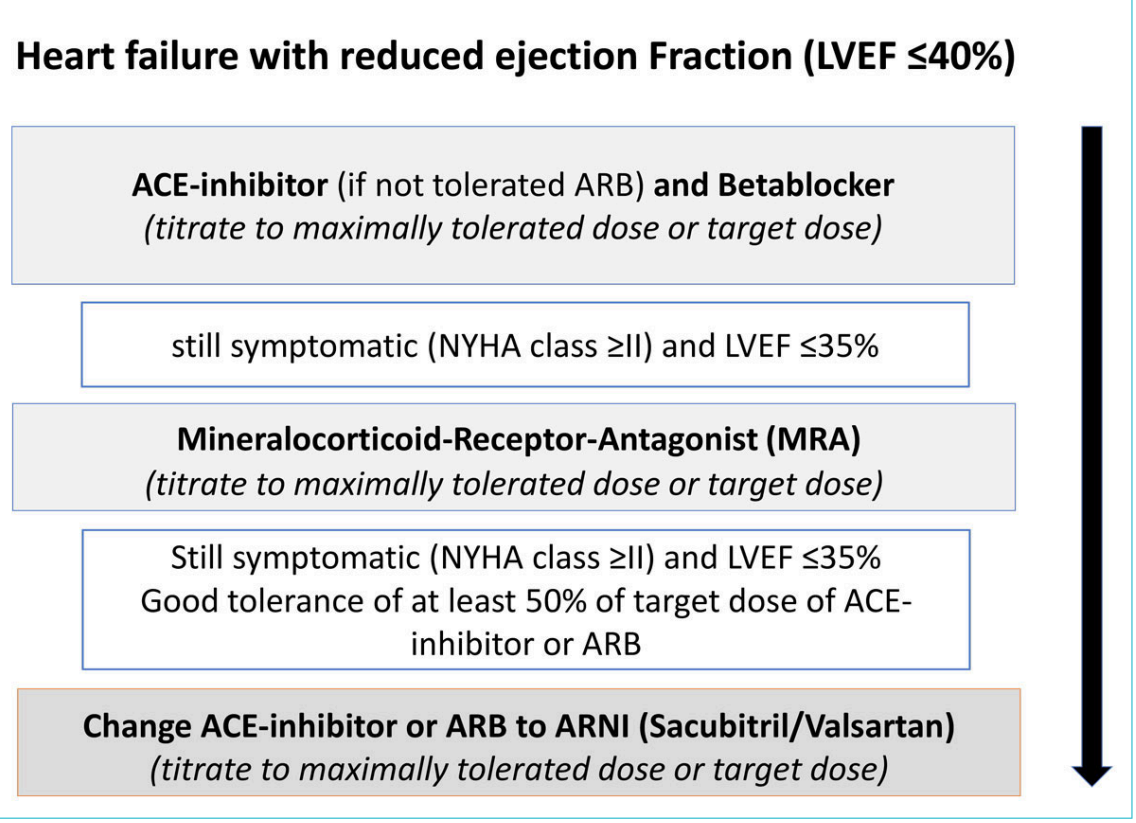
The guideline committees of the European Society of Cardiology (ESC) and the American Heart Association (AHA) strongly support the use of ARNI in HFrEF patients with LVEF ≤35% who remain symptomatic (≥NYHA II), despite optimal medical therapy including maximum tolerated doses of an ACE-inhibitor or ARB, a betablocker and a MRA, to reduce the risk of death and HF hospitalization (Class 1b indication) [1]. Practical guidance on the introduction of an ARNI is shown in figure 2.

Sodium-glucose-co-transporter 2 inhibitors: anti-diabetic drugs with a significant impact on HF

Diabetes and HF are vicious twins. Patients with diabetes have a 4-fold increase in the incidence of HF hospitalizations compared to the general population [26], and 30% of diabetic patients have unrecognized HF and ventricular dysfunction [27]. In turn, HF leads to insulin resistance and thereby promotes the development of diabetes [28, 29]. Also, a series of antidiabetic drugs such as sulfonylureas, glitazones and some dipeptidyl peptidase-4 inhibitors have been shown to promote the development of HF in patients with diabetes [30, 31]. Importantly, patients with both conditions, HF and diabetes, have an almost 10-fold increase in mortality compared to patients suffering solely from diabetes [32].

The pivotal role of the kidneys in regulating glucose homeostasis has been known for decades. Only recently has the main glucose regulatory system in the kidney, the sodium-glucose co-transporters (SGLTs), become a therapeutic target in patients with type 2 diabetes. There are two isoforms of SGLTs, SGLT1 and SGLT2, that are expressed in the proximal tubule and absorb glucose coupled to sodium across the Na+ gradient generated by the sodium/potassium pump. The high capacity, low affinity transporter SGLT2 accounts for 90% of glucose reabsorption, whereas SGLT1 reabsorbs the remaining glucose with high affinity [33]. The introduction of SGLT2-inhibitors as antidiabetic

Figure 2: Guidance on the introduction of an ARNI in clinical practice. Criteria for the commencement of treatment with a combined angiotensin II receptor/neprilysin inhibitor (ARNI) based on the 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure [1] are depicted. LVEF: left-ventricular ejection fraction; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.



drugs brought unexpected cardiovascular outcome results. In two large trials, the SGLT2 inhibitors empagliflozin and canagliflozin consistently reduced the primary composite endpoint of myocardial infarction, stroke and cardiovascular death in patients with type 2 diabetes and established cardiovascular disease or cardiovascular risk factors [34, 35]. It is of note that the observed endpoint reduction was mainly driven by a reduction in cardiovascular death. Importantly, the relative risk of HF hospitalization was reduced by ≥33% in both studies. Although information about the precise HF phenotype, i.e., with reduced versus preserved ejection fraction, is lacking, this consistent reduction in HF events puts SGLT2 inhibitors at the forefront of efforts to prevent HF in patients with type 2 diabetes. Taking into account the results from EMPA-REG OUTCOME, the latest ESC guidelines for the diagnosis and treatment of HF awarded empagliflozin a class IIa indication to reduce the risk of HF in patients with type 2 diabetes [1]. The mechanisms by which SGLT2 inhibitors prevent HF are manifold and not completely understood. Besides haemodynamic effects driven by lowering of blood pressure and natriuresis, effects on the RAAS and changes in myocardial metabolism may play a significant role (**table 1**). A series of upcoming clinical trials in various HF populations (HFrEF, HFpEF, with or without type 2 diabetes) will hopefully clarify the role of SGLT2 inhibitors in the treatment and prevention of HF.

Increasing the diagnostic accuracy of HFpEF through new algorithms

Difficulties in correctly diagnosing HFpEF pose a major obstacle to real progress regarding its treatment, and a lack of diagnostic accuracy has at best jeopardized, if not hampered, the outcome of large clinical trials. The current diagnostic criteria for HFpEF are based on an expert consensus outlined in the 2016 ESC guidelines for the diagnosis and treatment of HF [1]. Although a major refinement of the previous, 2007 consensus [36], the sensitivity of the 2016 algorithm is still limited, and the absence of exercise testing has been criticized [37].

Recently, Borlaug and colleagues derived and validated a new diagnostic score that allows for the non-invasive prescreening of euvolemic patients presenting with exertional dyspnea and having an EF ≥50% in order to identify those who would benefit the most from haemodynamic assessment and exercise testing [38]. The 0-9 point **H_2FPEF** score (which stands for **h**eavy, **h**ypertensive, atrial **f**ibrillation, **p**ulmonary hypertension, **e**lder, **f**illing pressure) is based on the presence/absence of the following key contributors and predictors of the disease: atrial fibrillation (3 points), obesity as defined by a BMI>30 kg/m^2 (2 points), age>60 years, ≥2 antihypertensive drugs, E/e'>9, and estimated systolic pulmonary arterial pressure by echocardiography >35 mmHg (1 point each) (table 2). This score provided a higher diagnostic accuracy (AUC 0.841) than the algorithm based on the 2016 ESC guidelines [1] when using invasive haemodynamic exercise testing as the gold standard. HFpEF could be refuted with a score of 0-1 and established with a score of 6-9, whereas an intermediate score of 2-5 identified patients who should be further evaluated with invasive exercise testing.

The new ESC Heart Failure Association (HFA) consensus on the diagnosis of HFpEF presented by Burkert Pieske at the 2018 ESC Heart Failure Meeting in Vienna is currently awaiting publication [39]. It follows a similar approach, using a score to identify patients that should be further evaluated with invasive or non-invasive (stress echocardiography) exercise testing. The HF-**PEF_2** score encompasses a four-step work-up including a **p**retest assessment (step 1), an **e**chocardiography and natriuretic peptide score (step 2), a **f**unctional exercise echocardiography and haemodynamic work-up (step 3), and strategies to **f**ind the etiology

Table 1: Proposed mechanisms of the beneficial cardiovascular effects of SGLT2 inhibitors.

Mechanism	Clinical outcome
Diuretic effect	Reduction of pre-load Reduction of blood pressure Weight loss
Less arterial stiffness	Reduction of after-load Reduction of blood pressure
Metabolic shift: Less fatty acid oxidation More ketone body oxidation	Improvement in mitochondrial efficiency Improvement in cardiac efficiency
Other metabolic effects	Improvement in glycemia Reduction of uric acid Reduction of epicardial adipose tissue
Renal effects	Delay in micro- and macroalbuminuria Delay in decline in GFR

Table 2: Score to non-invasively pre-screen patients with exertional dyspnea as proposed by Reddy et al. [38]

Criterion	Points
Atrial fibrillation	3
BMI >30 kg/m^2	2
Age >60 years	1
≥2 antihypertensive drugs	1
E/e' >9	1
Estimated systolic pulmonary arterial pressure >35 mmHg	1
HFpEF likely	**6–9**
HFpEF unlikely	**0–1**
Requiring exercise testing	**2–5**

(step 4). Similarly to the H_2FPEF score, the most crucial step is step 2, a 0-6 point score, on the basis of which patients are confirmed (5-6 points) or refuted to have HFpEF (<2 points), or identified as needing additional stress testing to corroborate the diagnosis (2-4 points). In contrast to the H_2FPEF score, however, which does not include natriuretic peptide levels, step 2 of the HF-PEF_2 score is exclusively based on comprehensive echocardiography and BNP or NT-BNP levels, whereas age and co-morbidities are included in the pretest assessment of step 1. As a final step, the new HFA consensus proposes advanced imaging (magnetic resonance imaging, myocardial scintigraphy), laboratory testing and/or myocardial biopsy to establish the underlying etiology and to further identify the HFpEF phenotype in order to guide therapy.

Although in many points different from each other, both scores have the potential to significantly increase the number of patients that are correctly diagnosed as having HFpEF, and to allow for better characterization of the individual phenotype of the disease. Furthermore, the exclusion of patients not fulfilling the diagnostic criteria is a prerequisite for clinical trials to be able to generate reliable results, and increases the likelihood that novel therapeutics which benefit real HFpEF patients can be identified in the future.

Current and future treatment concepts of HFpEF

HFpEF is a heterogenous entity driven by various co-morbidities which shape the phenotype of the disease. Similar to the case for HFrEF of ischemic versus non-ischemic origin, etiology and phenotype may determine the treatability of HFpEF. Several therapeutic targets of HFpEF have been identified based on haemodynamic abnormalities, including congestion, diastolic dysfunction, pulmonary hypertension and volume overload; on cellular and structural abnormalities, including systemic microvascular inflammation, cardiomyocyte hypertrophy, stiffening and matrix remodelling; or on metabolic alterations. Nevertheless, a reduction in hospitalizations, symptom relief and/or improved quality of life could only be shown for diuretic use [40, 41] and spironolactone when considering the in-depth analyses, which sorted out the regional discrepancies between Russia and Georgia as opposed to the Americas in the TOPCAT trial [42–44]. In contrast, ACE-inhibitors and ARBs, although beneficial in some studies [45, 46], are mainly recommended for the treatment of concomitant hypertension.

Recently, numerous new agents have raised hope for the long-awaited therapeutic break-through, but most of them have either failed to improve outcomes in mostly small clinical trials, or their efficacy is still uncertain [47]. This is particularly the case for direct or indirect activators of the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP)-protein kinase (PK) axis (fig. 3), which include organic [48] or inorganic nitrates [49], phosphodiesterase-5 inhibitors [50] and stimulators of soluble guanylate cyclase (sGC) [51]. These all aim to maintain intracellular cGMP levels. Depletion of intracellular cGMP unleashes intracellular pro-hypertrophic pathways and depresses PKG-mediated phosphorylation of titin, which are associated with cardiomyocyte hypertrophy and stiffening. In this respect, ARNIs may represent a promising new option currently under investigation in larger clinical trials. Because natriuretic peptides signal through cGMP, inhibition of their degradation may help preserve cGMP-mediated intracellular signalling and prevent hypertrophy and stiffening on the cardiomyocyte level. Natriuretic peptides also exert natriuretic and diuretic effects, thus counteracting volume overload, and inhibit fibrosis [10], another key pathogenetic feature of HFpEF which contributes to ventricular stiffness and impaired compliance on the organ level. In addition, neprilysin degrades numerous other targets besides natriuretic peptides, including glucagon-like peptide 1 (GLP-1) [52]. Inhibition of neprilysin-mediated GLP-1 degradation by sacubitril may improve glycaemic control and benefit diabetic patients with HFpEF [20]. In the recently completed PARAMOUNT trial, a phase II trial involving 301 patients, sacubitril/valsartan lowered NT-proBNP levels after 12 weeks and decreased atrial volumes and NYHA functional class after 26 weeks in patients with HFpEF [53]. Whether these early beneficial effects translate into improvements of "hard endpoints" such as mortality is currently being tested in the ongoing PARAGON-HF trial.

Similarly, SGLT2 inhibitors have the potential to add to the therapeutic repertoire of treatments for HFpEF in the future. There are several properties which make them interesting drug candidates, especially in patients presenting with the obesity-associated phenotype. Through the inhibition of glucose reabsorption, they act as osmotic diuretics and contribute to the correction of plasma volume expansion [54, 55], which is of particular importance in obese HFpEF patients [56]. SGLT2 inhibitors also exert anti-inflammatory and anti-fibrotic properties. Through the reduction of visceral – and epicardial – fat, they lower the secreted load of adipocytokines such as leptin. This mitigates their paracrine pro-inflammatory and pro-fibrotic actions in neighbouring organs, including the heart [57–59]. The EMPEROR-Preserved trial (NCT03057951) is a phase III randomized, double-blind and placebo-controlled trial currently testing the safety and efficacy of empagliflozin on top of guideline-directed therapy to delay cardiovascular death or HF hospitalization in HFpEF patients irrespective of concomitant diabetes. While awaiting the results of these and other currently ongoing pharmacological trials, optimal risk factor management and control of contributing factors, which include atrial fibrillation (rhythm control), obesity (exercise training, weight loss), hypertension (blood pressure control) and coronary artery disease (revascularization), remain the cornerstones of the treatment of patients with HFpEF.

Transthyretin amyloid cardiomyopathy

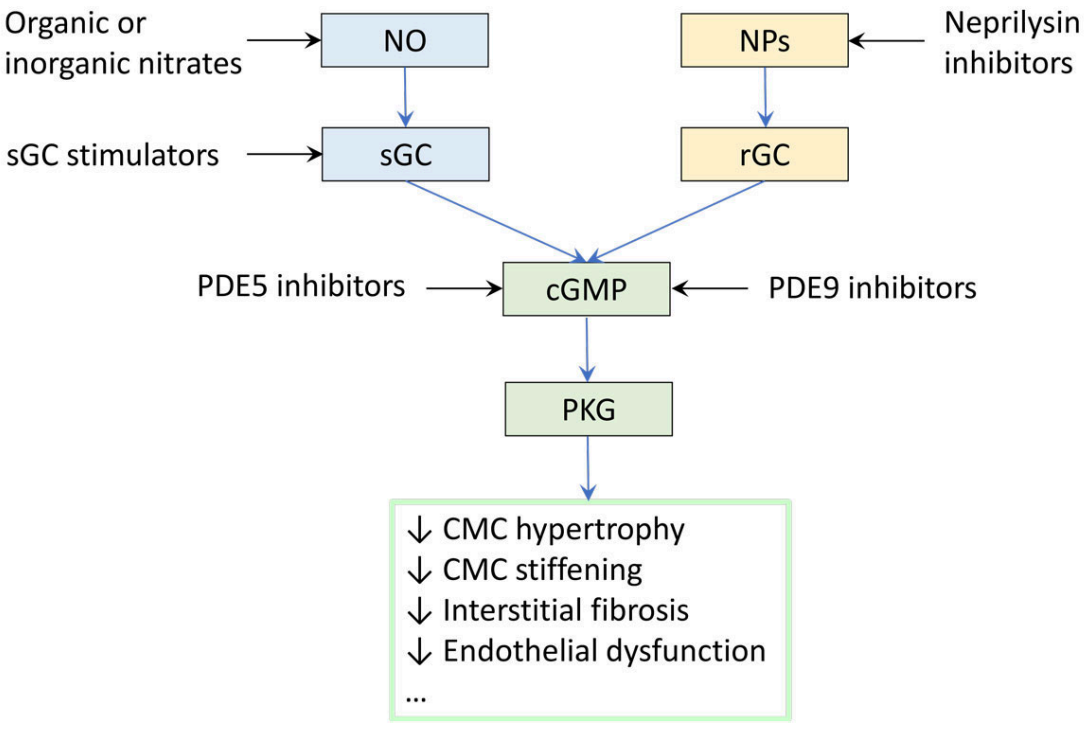
Senile systemic amyloidosis is a condition caused by the deposition of wild-type transthyretin (ATTRwt) and a common cause of cardiomyopathy associated with HFpEF in the elderly. Its prevalence is estimated at roughly 13% of HFpEF patients [60], but this is likely to be an underestimate due to the limited availability and/or application of specific non-invasive diagnostic options such as scintigraphy. Transthyretin is a protein synthesized in the liver. It is involved in the binding and transportation of thyroxine and retinol-binding protein-retinol complex (vitamin A) [61]. Originally secreted as a more or less stable tetramer,

transthyretin can dissociate into less stable monomers that may undergo misfolding and polymerize to form amyloid fibrils [62] (fig. 4). Whereas dissociation and denaturation of monomers occurs more frequently in the elderly (i.e., >60 years-old), with a predominance in men [63], there is also a hereditary, autosomal dominant form. There are so far more than 120 known mutations in the transthyretin gene (ATTRm) which cause this hereditary form. Survival is limited in patients with transthyretin amyloid cardiomyopathy, ranging from 2–6 years after diagnosis [64, 65]. Recently, several strategies have been designed to either inhibit transthyretin secretion, stabilize the transthyretin tetramer or inhibit amyloid deposition. Among those strategies, tafamidis has now emerged as a promising new therapy to treat ATTR cardiomyopathy. Tafamidis is a benzoxazole derivative binding to the thyroxine-binding sites of transthyretin, thereby stabilizing its tetramer formation. In the double-blind and placebo-controlled ATTR-ACT trial, 441 patients with ATTR cardiomyopathy (both ATTRwt and ATTRm) were randomly assigned to receive tafamidis or placebo with a treatment duration of 30 months. The first results now show that tafamidis significantly decreased all-cause mortality and cardiovascular hospitalizations and reduced the decline in functional capacity and quality of life when compared to placebo [66]. Identification and consecutive treatment of patients presenting with HFpEF that exhibit ATTR cardiomyopathy may help to lower the HFpEF disease burden in elderly patients in the future.

HFmrEF: more in common with HFrEF than HFpEF

HFmrEF was introduced as a third category in the 2016 ESC HF guidelines [1]. HFmrEF includes a heterogenous population of patients, who may exhibit an early decline in EF with or without progression to HFrEF, recovery or partial recovery from previous HFrEF, or predominantly diastolic dysfunction with mild compromise of EF. Therefore, the clinical significance of HFmrEF remains poorly defined. Because patients with near-to-normal EF were mostly included in HFpEF trials, the 2016 ESC guidelines primarily recommended a “HFpEF-like approach” for the treatment of HFmrEF [1]. However, recent subgroup analyses of TOPCAT [67] and CHARM [68] suggested that patients with an EF in the lower normal or below-normal EF range were the ones benefitting the most from treatment with spironolactone [67] or candesartan [68] regarding the primary outcome of cardiovascular death and HF rehospitalization. In a very recent study, Cleland et al. re-examined the data from all major double-blind, randomized and placebo-controlled trials on the effect of beta-blocker therapy in HF patients on a single-patient basis stratified by EF [69]. They found that, similar to patients with EF<40%, patients with mrEF, i.e., EF between 40 and 49%, and a sinus rhythm showed a significant reduction in all-cause and cardiovascular mortality when treated with a beta-blocker (on top of ACE inhibitor / ARB) compared to placebo. In contrast, patients with EF≥50% showed no difference in mortality. Taken together, these findings suggest that standard HFrEF therapy is beneficial in patients with HFmrEF, not only by decreasing morbidity, but also by improving prognosis. They therefore support the use of ACE

Figure 3: The NO-cGMP-PK axis as a potential therapeutic target in HFpEF. Intracellular cGMP may be maintained through the action of nitric oxide (NO)-mediated activation of soluble guanylate cyclase (sGC), through direct stimulation of sGC or through inhibition of the phosphodiesterase-(PDE) mediated degradation. Alternatively, natriuretic peptides (NPs) induce cGMP through activation of the receptor guanylate cyclase (rGC). PKG: protein kinase G; CMC: cardiomyocyte.



inhibitors or ARBs, betablockers and aldosterone antagonists in all patients with EF<50%.

Conclusions and outlook

Recent years have shown that progress in HF therapy may not necessarily come from obvious sources (e.g., the recently discovered role of the NO-cGMP-PK axis in HFpEF, which has not yet materialized into new clinical therapies), but rather from the unexpected (e.g., SGLT2 inhibitors) or through perseverance (e.g., ARNI). New approaches may include a stronger focus on inflammation and metabolic aspects that were not covered in the present article, or may just as likely come from completely different or even surprising approaches. In the long run, it will pay to stay curious and keep an open mind for the exploration of potential new avenues in the future.

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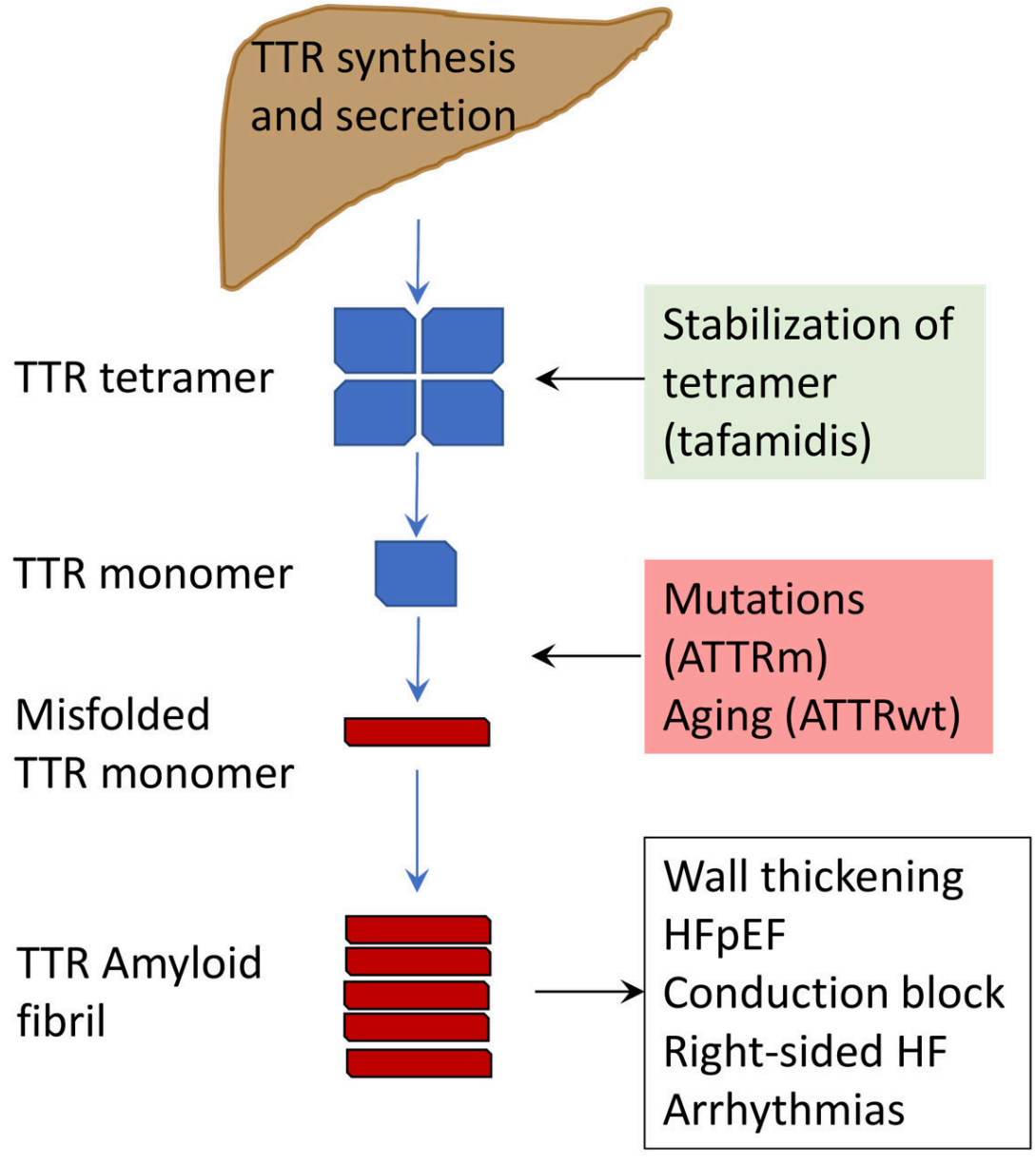
Figure 4: Secretion and metabolism of transthyretin. Transthyretin (TTR) is synthesized and secreted by the liver and assembles to tetramers. Dissociation of the TTR tetramer leads to the occurrence of monomers, which are prone to denaturalization and misfolding either through mutations (ATTRm, hereditary forms) or during aging (ATTRwt). Misfolded TTR polymerizes to form amyloid fibrils that are deposited in various organs including the heart. Tafamidis (and other compounds, e.g., diflunisal) can stabilize TTR in its tetramer formation, thus preventing misfolding and amyloid formation.



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