Review

The 'diamond' approach to personalized drug treatment of heart failure with reduced ejection fraction

Hongbo Gan[1,†], Heng Tang[1,†], Yujie Huang[2], Dan Wang[3], Peng Pu[1,*], Zhong Zuo[1,*]

[1] *Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, 400016 Chongqing, China*

[2] *Department of Cardiology, The First Affiliated Hospital of Chongqing Medical and Pharmaceutical College, 400060 Chongqing, China*

[3] *Department of Cardiology, Chongqing Red Cross Hospital, 400020 Chongqing, China*

*Correspondence: pp841103@sina.com (Peng Pu); zzuo-cq@hotmail.com (Zhong Zuo)
† These authors contributed equally.

DOI:10.31083/j.rcm2203069

Submitted: 14 July 2021 Revised: 3 August 2021 Accepted: 20 August 2021 Published: 24 September 2021

Heart failure (HF) is a complex clinical syndrome with symptoms and signs due to cardiac dysfunction, leading to high hospitalization and morbidity. HF treatment has rapidly developed in recent decades, and breakthroughs have been made. Although conventional neurohormonal blockade therapies, including β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs), significantly improve the prognosis of patients with heart failure with reduced ejection fraction (HFrEF), mortality and rehospitalization remain high. Therefore, new therapies are needed. Previous studies demonstrated that ivabradine, angiotensin receptor-neprilysin inhibitor (ARNI), sodium-glucose cotransporter 2 (SGLT2) inhibitor, vericiguat, and omecamtiv mecarbil (OM) are beneficial for HFrEF. However, there is a lack of systematic review of the most optimal manner to use under various clinical conditions. This review summarizes the current knowledge regarding these therapies to give suggestions regarding clinical use timing, application scope, and optimal therapies under various conditions. Most importantly, we propose the HF diamond approach to express the necessity of conjunction of therapies. Different from the current guidelines, we suggest to use the diamond approach in an early and comprehensive manner at the beginning of ventricular remodeling in HFrEF to prevent further deterioration of HF and maximize the prognosis of patients.

Keywords

Heart failure; Diamond approach; New therapies; Individualized treatment

1. Introduction

Heart failure (HF) is the biggest challenge to cardiovascular disease treatment in the 21st century, with substantial morbidity, rehospitalization, and mortality, which affected estimated 23 million people worldwide [1]. The incidence of HF in American adults increased from 5.7 million to 6.2 million in the past few years [2]. The data from GWTG®-HF (Get With The Guidelines–Heart Failure, Dallas, Texas, USA) showed that the rates for 5-year mortality and readmission in patients hospitalized for HF exceeded 80% and 75%, respectively [3]. According to the 2021 ESC (European society of cardiology, Brussels, Belgium) heart failure guideline, HF is now subdivided as either reduced ejection fraction (rEF) (HFrEF: left ventricular ejection fraction (LVEF) $\leq$40%), mildly reduced EF (HFmrEF: LVEF of 41–49%), or preserved EF (HFpEF: LVEF $\geq$50%) [4].

Although conventional neurohormonal blockade therapies significantly improve the prognosis of patients with HFrEF, mortality and rehospitalization remain high. A study enrolled 11,064 HFrEF patients showed that under neurohormonal blockade therapies, the 2-year mortality for patients with worsening HF events was as high as 22.5%, and the hospitalization for recurring malignant HF within 30 days was 56% [5].

A large amount of data showed that conventional therapies cannot meet the current needs, and HF treatment urgently needs to be updated. New therapy for HFrEF has been rapidly developing in recent years. Therapies such as ivabradine, angiotensin receptor-neprilysin inhibitor (ARNI), sodium-glucose cotransporter 2 (SGLT2) inhibitor, vericiguat, and omecamtiv mecarbil, etc., which have been proved to improve the prognosis of HFrEF patients. This article mainly clarified the timing, scope of application, contraindications for the clinical use of each agent, and optimal therapies under various clinical conditions.

Multiple factors are involved in the occurrence of HF and progressive treatment, and therefore, it is necessary to combine drugs with different mechanisms for the most successful treatment of HFrEF. The effective combination of angiotensin-converting enzyme (ACE) inhibitors (ACEI)/angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and β-blockers is widely recognized.

We proposed the diamond approach and it included new drugs and provided possible combinations based on the mechanism and clinical trials so that the most suitable drug regimen was used for an individual patient, and most importantly, to propose the necessity of the conjunction of medicines (Fig. 1). Different from the current guidelines, we

proposed to use the diamond approach in an early and comprehensive manner at the beginning of ventricular remodeling in HFrEF to prevent further deterioration of HF and maximize the prognosis of patients (Fig. 2).

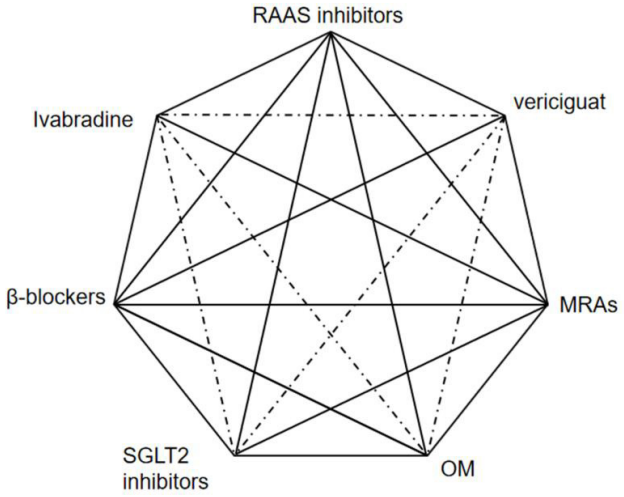

Fig. 1. Possible combinations of different heart failure drugs based on latest clinical research. The diagram shows useful combinations (thick lines), possible combinations (dotted lines). RAAS inhibitors, renin-angiotensin-aldosterone inhibitors; MRAs, mineralocorticoid receptor antagonists; SGLT2 inhibitors, sodium-glucose cotransporter 2 inhibitors; OM, omecamtiv mecarbil.

2. Drug therapy

2.1 β-blockers

Dysregulation of cardiac β1-adrenergic receptor signaling and transduction are key features of HF progression [6]. By blocking the GS protein-cyclic adenosine monophosphate-protein kinase A (Gs-cAMP-PKA) pathway, β-blockers reversed ventricular remodeling or reduced the risk of death [7]. β-blockers (metoprolol, carvedilol, or bisoprolol) have been proven to significantly reduced mortality, HF hospitalization, and sudden death in HFrEF (LVEF ≤35%) [8–12]. A prospective study enrolled 1518 HFrEF patients also yielded similar results in a real world setting [13]. Patients diagnosed with HFrEF should take β-blockers unless contraindicated (e.g., cardiogenic shock, sick sinus syndrome, high-grade atrioventricular block, heart rate <50 beats/min, acute bronchial asthma attack) or not tolerated (e.g., exacerbation of HF, bradycardia, hypotension, fatigue) [14–17].

Bronchospasm was one of the adverse reactions caused by β-blockers, but the use of β-blocker therapy was not contraindicated by chronic obstructive pulmonary disease (COPD) [18, 19] or bronchial asthma [20]. The use of cardioselective β-blockers was relatively safe in asthma patients [20]. β-blockers should be gradually titrated to the maximum tolerated dose or the target dose recommended by guidelines [14–17]. Study found that patients who reached the target dose and target heart rate had the lowest mortality, and those who only met the target dose attained higher survival if they achieved the target heart rate [21].

2.2 ACEIs and ARBs

ACEIs and ARBs reversed ventricular remodeling by blocking the renin-angiotensin-aldosterone system (RAAS). ACEIs competitively inhibited ACE and reduce angiotensin II (A-II), and they were important mediators of cardiac remodeling because A-II caused myocardial hypertrophy [22] and promoted cardiac fibrosis [23]. Same as β-blockers, evidence-based ACEIs (enalapril, ramipril, or lisinopril) should be guaranted to all HFrEF unless contraindicated (e.g., previous angioedema, pregnancy, bilateral renal stenosis, hyperkalemia (>6.0 mmol/L)), as these agents reduced morbidity and mortality [24–26]. ARBs blocked the activation of A-II type 1 receptors and were considered as an alternative to ACEIs as first-line drugs in patients with HFrEF [27–29].

Contraindications to ACEIs also applied to ARBs [14–17]. Several trials found that greater cardiovascular benefits were obtained by the combination of ACEIs and ARBs [27, 29]. However, there was no recommendation for this combination because of the increased possibility of adverse reactions such as hypotension, hyperkalemia, and worsening of renal function [14, 30]. There should be concern for patients on ACEIs or ARBs if any of the following occurs: symptomatic hypotension (systolic blood pressure (SBP) <90 mmHg), chronic kidney disease (CKD) (creatinine >3.0 mg/dL), or hyperkalemia (potassium >5.5 mEq/L) [14–17, 30].

2.3 MRAs

Aldosterone was the terminal hormone of the RAAS and played a role in myocardial remodeling. In addition to diuresis and potassium preservation, aldosterone caused myocardial interstitial fibrosis [6]. MRAs blocked the action of aldosterone on mineralocorticoid receptors and reversed cardiac remodeling. Spironolactone [31] and eplerenone [32] significantly reduced the mortality and hospitalization of HFrEF (LVEF <35%). The 'escape phenomenon' of aldosterone occured after long-term use of ACEIs/ARBs. ACEIs/ARBs alone was not ideal for reducing aldosterone in this setting, and MRA therapy was necessary. For patients who still has symptoms of HF even under the treatment of ACEIs/ARBs and β-blockers, MRAs were recommended according to guidelines [14–17]. MRA should be avoided in the following situations: patients with kidney failure (estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2), hyperkalemia (>5.0 mmol/L), or patients who are pregnant [14–17].

2.4 Ivabradine

The correlation between adverse cardiovascular events and rapid heart rhythm has been confirmed in patients with cardiovascular disease, and lowering the heart rate reduced cardiovascular risk [33–35]. A retrospective cohort study found that high resting heart rates often occured in HFrEF and were always associated with adverse outcomes [36]. Ivabradine slowed down the heart rate by selectively inhibit-

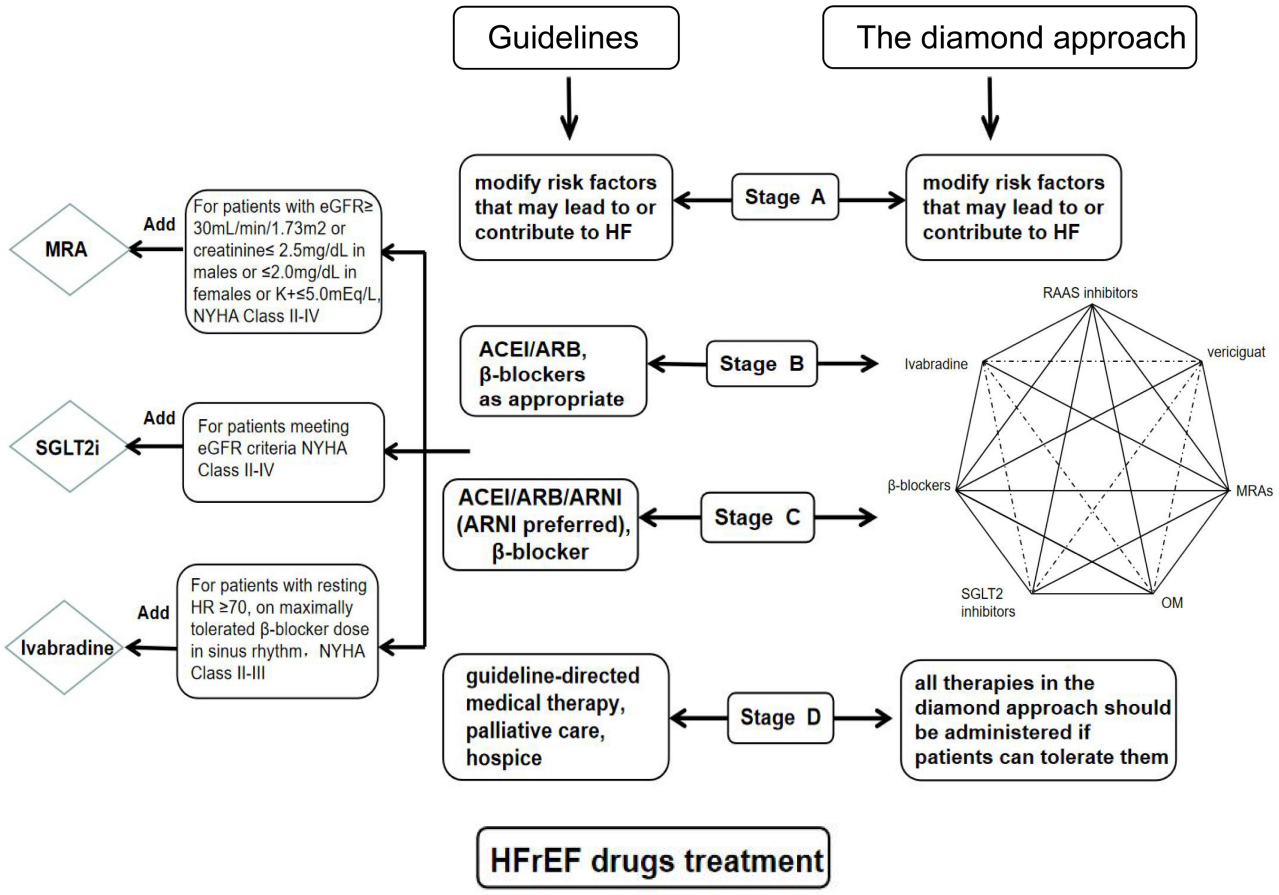

Fig. 2. Drug treatment algorithm for heart failure according to guidelines and diamond approach. Comparison of drug treatments between guidelines and the diamond approach in the four stages of heart failure. MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter 2 inhibitor; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; HF, heart failure.

ing the funny ion current (I_f) channel of the sinoatrial node cells. It dose-dependently reduced heart rate and became more effective when the heart rate was faster [37]. Ivabradine also significantly reversed left ventricular remodeling [38].

In the SHIFT trial, ivabradine significantly reduced HF hospitalization but not cardiovascular or all-cause mortality compared with placebo [34]. A prospective study showed that ivabradine is beneficial for HFrEF by effectively improving the symptoms and quality of life [39]. Ivabradine was added to therapy when patients have received the maximum dose of β-blockers but still had a resting sinus heart rate $\geq$70 beats/min, or if symptoms remained after optimized treatment [14, 16, 17].

Ivabradine should be avoided in patients with sinus bradycardia, sinoatrial block, or second degree or above atrioventricular block [14, 16, 17]. Due to its mechanism of action, it had no effect on cardiac inotropy or systemic vascular resistance [33]. However, cornerstone research did not include patients with hypotension (blood pressure (BP) $<$90/50 mmHg), and therefore, the specific impact of ivabradine on blood pressure is still unclear [34]. Ivabradine might increase atrial fibrillation by blocking the I_f channel in sinus node tissue [40, 41]. However, several individual cases [42, 43] and a small sample study [44] indicated that ivabradine slowed the ventricular rate and improved heart function in patients with atrial fibrillation. It is necessary to perform further clinical trials to confirm whether ivabradine is an effective agent in this condition.

2.5 ARNI

As a multi-compound drug composed of the ARB valsartan and the neprilysin inhibitor sacubitril, ARNI showed an extraordinary effect on the reversal of cardiac remodeling. The PARADIGM-HF trial demonstrated that ARNI exceeded enalapril in reducing cardiovascular mortality (hazard ratio (HR), 0.80 [95% CI, 0.71–0.89]) and hospitalization for HFrEF (HR, 0.79 [95% CI, 0.71–0.89]) patients [45]. The superiority of ARNI compared with enalapril in improving the quality of life has also been proven [46].

In the EVALUATE-HF trial, a significant reversal in cardiac remodeling was observed after 3 months of ARNI treatment for HFrEF patients [47]. The PROVE-HF study further explored the association between improvement of ven-

tricular remodeling and the reduced level of N-terminal-pro-brain natriuretic peptide (NT-ProBNP) [48]. For patients hospitalized with acute HF, the TRANSITION study demonstrated the safety and efficacy of early in-hospital initiation of ARNI after hemodynamic stability [49], and the PIONEER-HF trial confirmed the superiority of initial treatment with ARNI compared to enalapril through the 8 weeks of follow-up [50]. Similar conclusions were made in several studies where ARNI exceeded ACE inhibitors/ARBs in reducing hospitalization [51] and improving the quality of life for HFrEF patients during the 12 months of follow-up in real world practice [52]. The cardio-renal benefit provided by natriuretic peptides indicates that ARNI was superior to other traditional RAAS inhibitors for the treatment of HF and CKD.

Despite causing a modest increase in the urine albumin-to-creatinine ratio (UACR), ARNI was found to slow the rate of decrease in the eGFR more effectively compared to enalapril [53]. Prospective researches have proved that patients with HFrEF and CKD can benefit from ARNI [54, 55]. ARNI has become a new cornerstone and first-line therapy for HFrEF in guidelines [14, 16, 30]. Common side effects of ARNI were related to hypotension, renal insufficiency, and rare angioedema. It should be further noted that the contraindications to ACE inhibitors/ARBs also apply to ARNI.

2.6 SGLT2 inhibitors

By inhibiting sodium-glucose cotransporter 2 (SGLT2) which presented at the early proximal tubule, SGLT2 inhibitors prevented the reabsorption of the majority of filtered urinary glucose, and lowered blood glucose levels. Except as glucose-lowering agents [56], SGLT2 inhibitors showed beneficial effects on hospitalization for HF, and cardiovascular and total mortality in patients with diabetes [57–61]. The specific mechanisms of SGLT2 inhibitors that confer cardiac benefits remained unknown, and might be related to lowering of blood pressure, diuresis, weight loss, amelioration of myocardial metabolism and fibrosis, and reduction of the excessive activation of the sympathetic nervous system (SNS) and RAAS [62–64].

In the DAPA-HF trial, dapagliflozin reduced the primary endpoint for cardiovascular death or worsening of HF (HR, 0.74 [95% CI, 0.65–0.85]; $P < 0.001$), cardiovascular mortality (HR, 0.82 [95% CI, 0.69–0.98]), and all-cause mortality (HR, 0.83 [95% CI, 0.71–0.97]) in HFrEF, and benefits for the primary endpoint of HFrEF were comparable irrespective of diabetes [65]. A subsequent analyses from the DAPA-HF trial was performed, and it was found that dapagliflozin reduced the outpatient episodes of HF ($P < 0.0001$) [66], improved the Kansas City Cardiomyopathy Questionnaire (KCCQ) score ($P < 0.0001$) [67] in HFrEF, and its efficacy and safety in elderly individuals was also confirmed [68].

The EMPEROR-Reduced trial enrolled HFrEF patients with more severe HF (73% of patients with LVEF $\leq$30%, 79% with NT-proBNP $\geq$1000 pg/mL) than those included in the DAPA-HF trial [69]. Empagliflozin reduced hospitalization for HF (HR, 0.70 [95% CI, 0.58–0.85]; $P < 0.001$) but failed to reduce cardiovascular death. Heart failure guidelines, including the 2021 ESC guideline, recommend the SGLT2 inhibitors as the cornerstone medication for all HFrEF, whether the patient has diabetes or not [16, 70].

A subgroup analysis of the DAPA-HF trial [71] showed that the combination of SGLT2 inhibitors and ARNI was efficacious and safe. Caution was advised in patients with genital and urinary tract infections [72, 73], ketoacidosis [74], hypovolemia (e.g., hypotension, dehydration, and cerebral infarction), or hypoglycemia (when combined with insulin or an insulin secretagogue) [75]. Ketoacidosis was a serious but extremely rare clinical condition in patients on SGLT2 inhibitors. The rate reportedly was less than 0.76/1000 patient-years in patients receiving canagliflozin [76] and 1/1000 for empagliflozin [57]. How SGLT2 inhibitors might be contributing to ketoacidosis has not been fully understood, but major illness, prolonged starvation, heavy alcohol use, and lower insulin doses were potential ketoacidosis triggers.

2.7 Vericiguat

The nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate (NO-sGC-cGMP) pathway was the main regulator in myocardial metabolism and endothelial function, and it was a potential target for the treatment of chronic HF [77]. As a new oral sGC stimulator, vericiguat was cardioprotective by increasing the activity of cyclic guanosine monophosphate (cGMP) [78, 79].

In the SOCRATES-REDUCED trial [80], vericiguat was proven to be well-tolerated and safe in HFrEF during the 12 weeks of follow-up. The VICTORIA trial [81] enrolled HFrEF patients with more severe heart failre than those in other contemporary clinical trials, and found that even under guideline-directed medical therapy (GDMT), vericiguat still reduced the composite primary outcome of cardiovascular death or first HF hospitalization ($P = 0.02$) over a median follow-up of 10.8 months. This result was mostly driven by reduced HF hospitalization, with a statistically nonsignificant reduction in cardiovascular death. A secondary analysis of the vericiguat trial showed that there were time-dependent risks of events according to index hospitalization subgroups, in which the worsening outpatient subgroup had the lowest risk compared to those at <3 months or 3 to 6 months after HF hospitalization, no significant difference was found in the risk reduction between these subgroups [82]. Based on those positive clinical results, vericiguat is considered for symptomatic HFrEF (even under GDMT) according to the 2021 ESC heart failure guideline [4].

2.8 Omecamtiv mecarbil

HFrEF was characterized by decreased ejection fraction and cardiac contractility. Current available inotropic agents, including adrenergic receptor agonists (i.e., dobutamine), phosphodiesterase inhibitors (i.e., milrinone), and calcium sensitizer (i.e., levosimendan), effectively increased cardiac contractility. However, due to their specific mechanisms of

action, these agents were associated with increased myocardial oxygen consumption, intracellular calcium, increased heart rate, hypotension, arrhythmias, and mortality [83–85].

OM was a selective, small-molecule cardiac myosin activator (also referred to as a cardiac myotrope) that binded to the catalytic domain of myosin and increased cardiac contractility without affecting cardiac myocyte intracellular calcium concentrations or myocardial oxygen consumption [86, 87]. Different from conventional inotropic agents, OM was a potential treatment for HFrEF patients due to its properties [88].

The recent large randomized controlled trial GALACTIC-HF was conducted to demonstrate this hypothesis [89]. This trial enrolled HFrEF patients with EF $\leq$35%, and most of these patients were under standard HF therapy. The results showed that OM still reduced the composite primary outcome of the time to cardiovascular death or first HF event (P = 0.03). However, no statistical differences were found for secondary endpoint events including cardiovascular death and the first HF hospitalization. The benefit of OM for patients with HF was moderate compared to neurohormonal blockade therapies. However, OM remained safe and effective even under standard medical care for HF, which maked it a promising treatment. However, it is worth noting that OM can induce ischemia if plasma concentrations that prevent complete relaxation of the heart are achieved [90].

3. 'Diamond' approach to treatment

Many patients with heart failure have not received the optimal treatment due to clinicians' insufficient awareness of the importance of drug combinations and excessive caution of adverse reactions it brings. Therefore, we proposed the diamond approach in this review to express the necessity of conjunction of therapies and exhibit possible combinations based on the latest clinical researches.

HF frequently have comorbidities such as hypotension, arrhythmias, and kidney disfunction. Considering that it may take months to prescribe all therapies recommended in the diamond approach, we believe the choice of optimal agents should vary along with different conditions and is worthy of attention. The following summarize the related studies and give some suggestions about personalized treatment in this regard.

Unless contraindicated or not tolerated, usage of the diamond approach in an early and comprehensive manner is crucial. In clinical practice, commonly step-up therapy of HF may reduce the benefit in patients with heart failure. Therefore, we combined the diamond approach and proposed a more aggressive treatment for HF (Fig. 2).

3.1 Special considerations

3.1.1 Hypotension

Patients with HF often had low BP. HF therapies such as ACEIs/ARBs, MRAs, and β-blockers lowered BP. ARNI had a stronger antihypertensive effect [91]. SGLT2 inhibitors also lowered BP through significant diuresis. In recent studies, it was found that SGLT2 inhibitors had a direct natriuretic effect rather than promoting osmotic diuresis [92] and urine volume increased without an increase in urinary sodium over time [93]. A post-mortem analysis from the EMPA-REG OUTCOME trial found that empagliflozin reduced SBP ($\geq$5 mmHg) in the fourth week of use [94]. Although ivabradine had little effect on hemodynamics, related studies did not included patients with hypotension. The use of ivabradine was not recommended in this setting [14].

The VICTORIA trial found that patients receiving vericiguat therapy had a higher incidence of hypotension and syncope, which was related to the drug's mechanism [81]. The GALACTIC-HF trial excluded patients with low blood pressure (SBP $<$85 mmHg), and found no deleterious effects of OM on BP [89]. In patients with HFrEF and hypotension, it was necessary to distinguish whether low perfusion exists. It should be noted whether patients are tolerant of the above HF drugs before initiating therapy if there is the pre-existing condition of low perfusion (e.g., dizziness, fatigue, cold limbs, oliguria).

For patients with hypotension but lack of evidence of low perfusion, usage of these disease-modifying drugs should be considered. For these patients, it is necessary to titrate from a small dose and strictly monitor BP and heart rate. There are often improvements in heart function and hypotension for HFrEF patients after a period of treatment. When hypotension occurs, the most important action to be taken is reducing unnecessary vasodilators and diuretics and then adjusting the above medications.

3.1.2 HF after acute myocardial infarction (AMI)

Myocardial ischemia, infarction, and scar formation caused by coronary heart disease were the most common causes of HF. A randomized controlled retrospective (PARADISE-SWEDEHEART) study performed in Sweden found that the incidence of HF in patients after MI was as high as 13–32%, and these HF patients were associated with higher morbidity and rehospitalization. Early, comprehensive, and standardized drug treatment largely determined the prognosis for these patients. ACEIs [95, 96]/ARBs [28], MRAs [97], and β-blockers [98] reduced the mortality and hospitalization in patients after AMI. Unless contraindicated or not tolerated, the early use of ACEIs/ARBs [99] and MRAs [97, 99] were universally recognized. Because the early use of β-blockers ($<$24 hours) increased cardiogenic shock and/or death, they should be initiated after hemodynamic stability in these patients [14, 16, 100]. A short-acting plain tablet of a β-blocker was preferred in this setting. By antagonizing the RAAS and strengthening the natriuretic peptides, ARNI had a stronger effect on the reversal of cardiac remodeling compared with the use of ACEIs/ARBs [47, 48].

In the recent PARADISE-MI trial, it was found that when compared with an ACEI, ARNI reduced the primary endpoints (cardiovascular death, HF hospitalization, or outpatient development of HF) by 10% in patients with AMI, although statistical difference was not reached (P = 0.17). This

study also observed that ARNI improved heart function more effectively because of its gradual action. Whether OM is benefical for AMI was not clear, since the GALACTIC-HF trial did not include relevant patients [89]. Because OM effectively increased cardiac contractility without increasing myocardial oxygen consumption and arrhythmia, it benefited patients after AMI. The specific effects of early use of ivabradine, SGLT2 inhibitors, and vericiguat on AMI remained unknown due to a lack of data.

3.1.3 CKD

CKD and HF often coexist, with CKD being present in 40–50% of chronic HF patients [101]. In addition to hemodynamic disturbances, the continuous activation of the SNS and RAAS also played a crucial role in CKD [102, 103]. The key to treatment lied in breaking the vicious cycle between the neuroendocrine system and hemodynamic disorder. ACEIs/ARBs [26, 104–107]/ARNI [53, 108] and MRAs [32, 109] improved the prognosis of HFrEF with CKD. ARNI was a more optimal choice than ACEIs/ARBs for CKD because its superior cardiorenal effect has been proven. In the Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference, it was suggested that ARNI is an essential medicine for patients with HFrEF and CKD [110].

A meta-analysis including several randomized trials [111] found that β-blockers offer consistent benefits for patients with HFrEF and moderate CKD (eGFR: 30–60 mL/min/1.73 m^2). Although a study on ivabradine in CKD patients was lacking, ivabradine is considered safe in moderate CKD as a result of low renal clearance rate of 20% [112]. SGLT2 inhibitors caused a mild, short-term decrease in eGFR in the early stage, but it did not affect the long-term renal protective effect [57, 60, 61, 113, 114]. Vericiguat was beneficial for CKD because it promoted the production of cGMP. After a post-hoc analysis of the VICTORIA trial was performed, it was found that the beneficial effects of vericiguat on the primary endpoint were consistent across the full range of eGFR ($>$15 mL/min/1.73 m^2), irrespective of worsening renal function [115].

Out of consideration for renal insufficiency, disease-modifying drugs including ACE inhibitors, ARBs, ARNI, and MRAs are usually underused. Stopping these drugs or administering a low-dose of these drugs always leads to poor outcomes. Unless contraindicated or not tolerated, all patients with HFrEF and CKD should be routinely and comprehensively receiving these therapies, and drugs need to be titrated to the maximum dosage under strict monitoring.

3.1.4 End-stage renal disease (ESRD)

Due to most clinical trials excluding patients with advanced CKD (eGFR $<$30 mL/min/1.73 m^2), there was a lack of strong evidence of safety and effectiveness for medical therapies that were used with these patients. However, some small non-randomized controlled studies have been conducted with these patients, and we can learn from them. β-blockers were found to be associated with lower morbidity and mortality in HFrEF patients with advanced CKD [116], and among β-blockers, carvedilol was the first recommendation for dialysis patients with HFrEF [117, 118].

A study showed that ARNI increased the LVEF and was well tolerated in HFrEF with ESRD on dialysis [119]. It was found that in the DAPA-CKD [120] trial, dapagliflozin can delay the deterioration of renal function and reduce cardiovascular death in patients with CKD (eGFR: 25–75 mL/min/1.73 m^2). It is important to note the dialysis rate of drugs in patients with advanced CKD. Additional clinical studies are needed to guide the medical treatment of these patients.

3.1.5 Arrhythmia-induced cardiomyopathy (AiCM)

Known as reversible non-ischemic dilated cardiomyopathy, AiCM was caused by tachycardias, atrial fibrillation (AF), and premature ventricular contractions. The elimination of arrhythmia was the optimal treatment for AiCM, and it reversed cardiomyopathy. Because AiCM often occured with HF, therapies for HF should also be considered for AiCM [121]. Thus far, guidelines only recommend HF treatments for tachycardia-induced cardiomyopathy (T-CM). We suggested that the same therapy should be used for atrial fibrillation-induced cardiomyopathy (AF-CM) and premature ventricular contraction-induced cardiomyopathy (PVC-CM), because these patients were very likely to benefit from these disease-modifying drugs.

There were double benefits from the use of β-blockers because they prevented arrhythmia and antagonize the sympathetic (beta adrenergic) nervous system, and their use should be placed first in the medical treatment of HF. ARNI further reduced the occurrence of arrhythmias compared with ACEIs/ARBs [122]. In addition to decreasing cardiac remodeling, the extra anti-arrhythmic effect of ARNI might be derived from enkephalinase inhibitors [123]. Dapagliflozin was found to effectively reduced the incidence of atrial fibrillation/atrial flutter events by up to 19%, which may have resulted due to the improvement of cardiomyocyte metabolism by SGLT2 inhibitors [124]. The use of ivabradine should be avoided in non-sinus tachyarrhythmia. Although a few case reports and small studies found that ivabradine may be useful for treatment for AF, the associated clinical data are still lacking.

3.2 HF in different stages

The two HF classification schemes that are widely used are the American College of Cardiology Foundation/American Heart Association (ACCF, West End, Washington, D.C., USA/AHA, Dallas, Texas, USA) staging system and the New York Heart Association (NYHA, Dallas, Texas, USA) functional classification. The stage system mentioned by ACCF/AHA considers the development and progression of HF, whereas the NYHA classes focused on exercise capacity and the severity of symptoms of HF. According to the different classifications, the treatments for HF were also dynamic

and subject to change. Different from the current guidelines [16, 125, 126], we proposed a much more aggressive treatment for HF.

Stage A HF exhibited no structural heart disease or HF symptoms. However, due to combined risk factors, these patients are vulnerable to heart failure. Thus, we held the same point of view as the guidelines in terms of stage A treatment, that was, risk factors that may lead to or contribute to HF should be modified [15].

Stage B HF was characterized by asymptomatic cardiac dysfunction, and the neuroendocrine system was activated at this stage [127]. It was previously demonstrated that ACEIs [128] and β-blockers [129] reduce the risk of HF and reverse ventricular remodeling in asymptomatic patients with reduced EF. The 2013 ACCF/AHA guidelines recommended the use of ACEIs/ARBs and β-blockers in stage B HF [15]. Although other disease-modifying drugs mentioned for use in the diamond program were not recommended in guideline [15], we believe that the early and comprehensive use of these drugs is reasonable and necessary to prevent ventricular remodeling and improve outcomes.

Patients in stage C have symptoms of heart failure based on structural heart disease. In this stage, recommended therapies include ACEIs/ARBs/ARNI, β-blockers, MRAs, SGLT2 inhibitors, and ivabradine [17]. It is more important to use disease-modifying drugs for these patients to prevent further deterioration of heart function, and therefore, increasingly aggressive use of vericiguat and OM is warranted.

Stage D patients were associated with worsening heart function and often required inotrope or device therapy. However, therapies that improve prognosis should be considered if patients can tolerate them, or even tolerate only a small dose. Drugs should be initiated at very low doses, and patients should be closely monitored for signs or symptoms of intolerance. Vericiguat and OM may exert a satisfactory effect on these patients due to their mechanisms of action.

4. Conclusions

The continuous update of HF drugs enables the use of numerous effective targeted therapies for patients with HFrEF, and brings hopes to further improve the outcome of these patients. How to use these drugs to maximize the benefits in these patients is what clinicians must consider. Based on evidence-based clinical data, the diamond approach tries to give the suggestions on most appropriate drugs for individual HF patient. Furthermore, we believe the key of HF treatment is to effectively prevent deterioration of HF. The 'diamond' approach proposed in this review did not focus only on the derivation of individualized and optimized treatments, but also conveyed the perspective of aggressive treatment for HFrEF.

Abbreviations

DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DECLARE-TIMI 58, Dapagliflozin Effect on the Incidence of Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR-REDUCED, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure with Reduced Ejection Fraction; EVALUATE-HF, Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients with Mild to Moderate Heart Failure and Reduced Ejection Fraction; GALACTIC-HF, Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure; PARADIGM-HF, Prospective Comparison of LCZ696 Compared to Enalapril to Determine the Impact on Global Morbidity and Mortality in Heart Failure; PARADISE-MI, Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After Myocardial Infarction; PARADISE-SWEDEHEART, Trial with the use of a nationwide myocardial infarction registry from Sweden (SWEDEHEART); PIONEER-HF, Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode; PROVE-HF, Effects of Sacubitril/Valsartan Therapy on Biomarkers, Symptom Improvement, and Ventricular Remodeling for Heart Failure; SHIFT, Systolic Heart Failure Treatment with the I_f inhibitor Ivabradine Trial; SOCRATES-REDUCED, Phase IIb Safety and Efficacy Study of Four Dose Regimens of BAY1021189 in Patients with Heart Failure with Reduced Ejection Fraction Suffering from Worsening Chronic Heart Failure; TRANSITION, Comparison of Pre-discharge and Post-discharge Treatment Initiation with Sacubitril/Valsartan in Heart Failure Patients with Reduced Ejection-Fraction Hospitalised for an Acute Decompensation Event; VICTORIA, Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction.

Author contributions

HBG and HT wrote the manuscript with support from PP and ZZ. HBG, HT, YJH and DW revised the manuscript under PP and ZZ guidance. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Not applicable.

Funding

Supported by the Science and Health Joint Medical Research Project of Chongqing (2018ZDXM010) (2020FYYX101) and the Fundamental Science and Advanced Technology Research of Chongqing (cstc2019jcyj-msxmX0433).

Conflict of interest

The authors declare no conflict of interest.

References

[1] Roger VL. Epidemiology of Heart Failure. Circulation Research. 2013; 113: 646–659.

[2] Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, *et al.* Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020; 141: e139–e596.

[3] Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, *et al.* Heart Failure with Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. Journal of the American College of Cardiology. 2017; 70: 2476–2486.

[4] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European heart journal. 2021; 1522–9645.

[5] Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, *et al.* Clinical Course of Patients with Worsening Heart Failure with Reduced Ejection Fraction. Journal of the American College of Cardiology. 2019; 73: 935–944.

[6] Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. Journal of the American College of Cardiology. 2009; 54: 1747–1762.

[7] Prijic S, Buchhorn R. Mechanisms of Beta-Blockers Action in Patients with Heart Failure. Reviews on Recent Clinical Trials. 2014; 9: 58–60.

[8] Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, *et al.* The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. The New England Journal of Medicine. 1996; 334: 1349–1355.

[9] Tepper D. Frontiers in congestive heart failure: Effect of Metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Congestive Heart Failure. 2019; 5: 184–185.

[10] Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, *et al.* Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. Journal of the American Medical Association. 2000; 283: 1295–1302.

[11] Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, *et al.* Effect of carvedilol on survival in severe chronic heart failure. The New England Journal of Medicine. 2001; 344: 1651–1658.

[12] Simon T. Bisoprolol dose–response relationship in patients with congestive heart failure: a subgroup analysis in the cardiac insufficiency bisoprolol study (CIBIS II). European Heart Journal. 2003; 24: 552–559.

[13] Opasich C, Boccanelli A, Cafiero M, Cirrincione V, Sindaco DD, Lenarda AD, *et al.* Programme to improve the use of beta-blockers for heart failure in the elderly and in those with severe symptoms: results of the BRING-up 2 Study. European Journal of Heart Failure. 2006; 8: 649–657.

[14] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2016; 37: 2129–2200.

[15] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, *et al.* 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013; 62: e147–e239.

[16] McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, *et al.* CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure with Reduced Ejection Fraction. Canadian Journal of Cardiology. 2021; 37: 531–546.

[17] Maddox TM, Januzzi JL, Allen LA, Breathett K, Butler J, Davis LL, *et al.* 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues about Heart Failure with Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. Journal of the American College of Cardiology. 2021; 77: 772–810.

[18] Hawkins NM, Petrie MC, Macdonald MR, Jhund PS, Fabbri LM, Wikstrand J, *et al.* Heart failure and chronic obstructive pulmonary disease the quandary of Beta-blockers and Beta-agonists. Journal of the American College of Cardiology. 2011; 57: 2127–2138.

[19] Malerba M, Montuschi P, Radaeli A, Pirisi M. Role of beta-blockers in patients with COPD: current perspective. Drug Discovery Today. 2015; 20: 129–135.

[20] Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. BMC Medicine. 2017; 15: 18.

[21] Corletto A, Fröhlich H, Täger T, Hochadel M, Zahn R, Kilkowski C, *et al.* Beta blockers and chronic heart failure patients: prognostic impact of a dose targeted beta blocker therapy vs. heart rate targeted strategy. Clinical Research in Cardiology. 2018; 107: 1040–1049.

[22] Sadoshima J, Izumo S. Molecular characterization of angiotensin II–induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the at1 receptor subtype. Circulation Research. 1993; 73: 413–423.

[23] Schmidt-Ott KM, Kagiyama S, Phillips MI. The multiple actions of angiotensin II in atherosclerosis. Regulatory Peptides. 2000; 93: 65–77.

[24] Fröhlich H, Henning F, Täger T, Schellberg D, Grundtvig M, Goode K, *et al.* Comparative effectiveness of enalapril, lisinopril, and ramipril in the treatment of patients with chronic heart failure: a propensity score-matched cohort study. European Heart Journal. Cardiovascular Pharmacotherapy. 2018; 4: 82–92.

[25] Swedberg K, Kjekshus J. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The American Journal of Cardiology. 1988; 62: 60A–66A.

[26] Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The New England Journal of Medicine. 1991; 325: 293–302.

[27] Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. The New England Journal of Medicine. 2001; 345: 1667–1675.

[28] Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau J, Køber L, Maggioni AP, *et al.* Valsartan, Captopril, or both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or both. New England Journal of Medicine. 2003; 349: 1893–1906.

[29] Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003; 362: 772–776.

[30] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, *et al.* 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a Report of the American College of Cardiology/American Heart

Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Journal of Cardiac Failure. 2017; 23: 628–651.
[31] Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. The New England Journal of Medicine. 1999; 341: 709–717.
[32] Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, *et al.* Eplerenone in patients with systolic heart failure and mild symptoms. The New England Journal of Medicine. 2011; 364: 11–21.
[33] Canet E, Lerebours G, Vilaine J. Innovation in coronary artery disease and heart failure: clinical benefits of pure heart rate reduction with ivabradine. Annals of the New York Academy of Sciences. 2011; 1222: 90–99.
[34] Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, *et al.* Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010; 376: 875–885.
[35] Fox K, Ford I, Steg PG, Tardif J, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. The New England Journal of Medicine. 2014; 371: 1091–1099.
[36] Ibrahim NE, Gaggin HK, Turchin A, Patel HK, Song Y, Trebnick A, *et al.* Heart rate, beta-blocker use, and outcomes of heart failure with reduced ejection fraction. European Heart Journal - Cardiovascular Pharmacotherapy. 2019; 5: 3–11.
[37] Koruth JS, Lala A, Pinney S, Reddy VY, Dukkipati SR. The Clinical Use of Ivabradine. Journal of the American College of Cardiology. 2017; 70: 1777–1784.
[38] Tardif J, O'Meara E, Komajda M, Böhm M, Borer JS, Ford I, *et al.* Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. European Heart Journal. 2011; 32: 2507–2515.
[39] Zugck C, Störk S, Stöckl G. Long-term treatment with ivabradine over 12months in patients with chronic heart failure in clinical practice: Effect on symptoms, quality of life and hospitalizations. International Journal of Cardiology. 2017; 240: 258–264.
[40] Fox K, Ford I, Steg PG, Tardif J, Tendera M, Ferrari R. Bradycardia and atrial fibrillation in patients with stable coronary artery disease treated with ivabradine: an analysis from the SIGNIFY study. European Heart Journal. 2015; 36: 3291–3296.
[41] Martin RIR, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial fibrillation associated with ivabradine treatment: meta-analysis of randomised controlled trials. Heart. 2014; 100: 1506–1510.
[42] Moubarak G, Logeart D, Cazeau S, Cohen Solal A. Might ivabradine be useful in permanent atrial fibrillation? International Journal of Cardiology. 2014; 175: 187–188.
[43] Kosiuk J, Oebel S, John S, Hilbert S, Hindricks G, Bollmann A. Ivabradine for rate control in atrial fibrillation. International Journal of Cardiology. 2015; 179: 27–28.
[44] Wongcharoen W, Ruttanaphol A, Gunaparn S, Phrommintikul A. Ivabradine reduced ventricular rate in patients with non-paroxysmal atrial fibrillation. International Journal of Cardiology. 2016; 224: 252–255.
[45] McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, *et al.* Angiotensin-neprilysin inhibition versus enalapril in heart failure. The New England Journal of Medicine. 2014; 371: 993–1004.
[46] Lewis EF, Claggett BL, McMurray JJV, Packer M, Lefkowitz MP, Rouleau JL, *et al.* Health-Related Quality of Life Outcomes in PARADIGM-HF. Circulation: Heart Failure. 2017; 10: e003430.
[47] Desai AS, Solomon SD, Shah AM, Claggett BL, Fang JC, Izzo J, *et al.* Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients with Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. Journal of the American Medical Association. 2019; 322: 1077–1084.
[48] Januzzi JL, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, *et al.* Association of Change in N-Terminal Pro–B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment with Cardiac Structure and Function in Patients with Heart Failure with Reduced Ejection Fraction. Journal of the American Medical Association. 2019; 322: 1085–1095.
[49] Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, *et al.* Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. European Journal of Heart Failure. 2019; 21: 998–1007.
[50] Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, *et al.* Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure. New England Journal of Medicine. 2019; 380: 539–548.
[51] Albert NM, Swindle JP, Buysman EK, Chang C. Lower Hospitalization and Healthcare Costs with Sacubitril/Valsartan Versus Angiotensin-Converting Enzyme Inhibitor or Angiotensin-Receptor Blocker in a Retrospective Analysis of Patients with Heart Failure. Journal of the American Heart Association. 2019; 8: e011089.
[52] Haddad H, Bergeron S, Ignaszewski A, Searles G, Rochdi D, Dhage P, *et al.* Canadian Real-World Experience of Using Sacubitril/Valsartan in Patients with Heart Failure with Reduced Ejection Fraction: Insight from the PARASAIL Study. CJC Open. 2020; 2: 344–353.
[53] Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, *et al.* Renal Effects and Associated Outcomes during Angiotensin-Neprilysin Inhibition in Heart Failure. JACC: Heart Failure. 2018; 6: 489–498.
[54] Chang H, Feng A, Fong M, Hsueh C, Lai W, Huang K, *et al.* Sacubitril/valsartan in heart failure with reduced ejection fraction patients: Real world experience on advanced chronic kidney disease, hypotension, and dose escalation. Journal of Cardiology. 2019; 74: 372–380.
[55] Spannella F, Marini M, Giulietti F, Rosettani G, Francioni M, Perna GP, *et al.* Renal effects of Sacubitril/Valsartan in heart failure with reduced ejection fraction: a real life 1-year follow-up study. Internal and Emergency Medicine. 2019; 14: 1287–1297.
[56] de Leeuw AE, de Boer RA. Sodium-glucose cotransporter 2 inhibition: cardioprotection by treating diabetes-a translational viewpoint explaining its potential salutary effects. European Heart Journal. Cardiovascular Pharmacotherapy. 2016; 2: 244–255.
[57] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England Journal of Medicine. 2015; 373: 2117–2128.
[58] Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, *et al.* Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. European Heart Journal. 2016; 37: 1526–1534.
[59] Neal B, Perkovic V, Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England Journal of Medicine. 2017; 377: 2099.
[60] Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, *et al.* Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. New England Journal of Medicine. 2019; 380: 2295–2306.
[61] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, *et al.* Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2019; 380: 347–357.
[62] Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, *et al.* Empagliflozin in Patients with Heart Failure, Reduced Ejection Fraction, and Volume Overload: EMPEROR-Reduced Trial. Journal of the American College of Cardiology. 2021; 77: 1381–1392.
[63] Lin B, Koibuchi N, Hasegawa Y, Sueta D, Toyama K, Uekawa K, *et al.* Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive

dysfunction in obese and type 2 diabetic mice. Cardiovascular Diabetology. 2014; 13: 148.
[64] Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2020; 75: 422–434.
[65] McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, *et al.* Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine. 2019; 381: 1995–2008.
[66] Docherty KF, Jhund PS, Anand I, Bengtsson O, Böhm M, de Boer RA, *et al.* Effect of Dapagliflozin on Outpatient Worsening of Patients with Heart Failure and Reduced Ejection Fraction. Circulation. 2020; 142: 1623–1632.
[67] Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, *et al.* Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients with Heart Failure and Reduced Ejection Fraction: Results From the DAPA-HF Trial. Circulation. 2020; 141: 90–99.
[68] Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang C, Tereshchenko S, *et al.* Efficacy and Safety of Dapagliflozin in Heart Failure with Reduced Ejection Fraction According to Age: Insights From DAPA-HF. Circulation. 2020; 141: 100–111.
[69] Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, *et al.* Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. New England Journal of Medicine. 2020; 383: 1413–1424.
[70] O'Meara E, McDonald M, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, *et al.* CCS/CHFS Heart Failure Guidelines: Clinical Trial Update on Functional Mitral Regurgitation, SGLT2 Inhibitors, ARNI in HFpEF, and Tafamidis in Amyloidosis. Canadian Journal of Cardiology. 2020; 36: 159–169.
[71] Solomon SD, Jhund PS, Claggett BL, Dewan P, Køber L, Kosiborod MN, *et al.* Effect of Dapagliflozin in Patients with HFrEF Treated with Sacubitril/Valsartan: The DAPA-HF Trial. JACC: Heart Failure. 2020; 8: 811–818.
[72] Arakaki RF. Sodium-glucose cotransporter-2 inhibitors and genital and urinary tract infections in type 2 diabetes. Postgraduate Medicine. 2016; 128: 409–417.
[73] Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium–Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. Annals of Internal Medicine. 2019; 171: 248–256.
[74] Fralick M, Schneeweiss S, Patorno E. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. The New England Journal of Medicine. 2017; 376: 2300–2302.
[75] Sheu WH, Chan SP, Matawaran BJ, Deerochanawong C, Mithal A, Chan J, *et al.* Use of SGLT-2 Inhibitors in Patients with Type 2 Diabetes Mellitus and Abdominal Obesity: an Asian Perspective and Expert Recommendations. Diabetes & Metabolism Journal. 2020; 44: 11–32.
[76] Erondu N, Desai M, Ways K, Meininger G. Diabetic Ketoacidosis and Related Events in the Canagliflozin Type 2 Diabetes Clinical Program. Diabetes Care. 2015; 38: 1680–1686.
[77] Gheorghiade M, Marti CN, Sabbah HN, Roessig L, Greene SJ, Böhm M, *et al.* Soluble guanylate cyclase: a potential therapeutic target for heart failure. Heart Failure Reviews. 2013; 18: 123–134.
[78] Breitenstein S, Roessig L, Sandner P, Lewis KS. Novel sGC Stimulators and sGC Activators for the Treatment of Heart Failure. Handbook of Experimental Pharmacology. 2017; 243: 225–247.
[79] Armstrong PW, Roessig L, Patel MJ, Anstrom KJ, Butler J, Voors AA, *et al.* A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of the Oral Soluble Guanylate Cyclase Stimulator: the VICTORIA Trial. JACC: Heart Failure. 2018; 6: 96–104.
[80] Gheorghiade M, Greene SJ, Butler J, Filippatos G, Lam CSP, Maggioni AP, *et al.* Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients with Worsening Chronic Heart Failure and Reduced Ejection Fraction: the SOCRATES-REDUCED Randomized Trial. Journal of the American Medical Association. 2015; 314: 2251–2262.
[81] Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, *et al.* Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine. 2020; 382: 1883–1893.
[82] Lam CSP, Giczewska A, Sliwa K, Edelmann F, Refsgaard J, Bocchi E, *et al.* Clinical Outcomes and Response to Vericiguat According to Index Heart Failure Event: Insights From the VICTORIA Trial. JAMA Cardiology. 2021; 6: 706–712.
[83] O'Connor CM, Gattis WA, Uretsky BF, Adams KF, McNulty SE, Grossman SH, *et al.* Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (first). American Heart Journal. 1999; 138: 78–86.
[84] Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, *et al.* Effect of oral milrinone on mortality in severe chronic heart failure. the PROMISE Study Research Group. The New England Journal of Medicine. 1991; 325: 1468–1475.
[85] Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, *et al.* Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC: Heart Failure. 2013; 1: 103–111.
[86] Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, *et al.* Omecamtiv Mecarbil in Chronic Heart Failure with Reduced Ejection Fraction: Rationale and Design of GALACTIC-HF. JACC: Heart Failure. 2020; 8: 329–340.
[87] Planelles-Herrero VJ, Hartman JJ, Robert-Paganin J, Malik FI, Houdusse A. Mechanistic and structural basis for activation of cardiac myosin force production by omecamtiv mecarbil. Nature Communications. 2017; 8: 190.
[88] Teerlink JR, Felker GM, McMurray JJV, Solomon SD, Adams KF, Cleland JGF, *et al.* Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial. Lancet. 2016; 388: 2895–2903.
[89] Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, e*t al.* Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure. New England Journal of Medicine. 2021; 384: 105–116.
[90] Cleland JGF, Teerlink JR, Senior R, Nifontov EM, Mc Murray JJV, Lang CC, *et al.* The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. Lancet. 2011; 378: 676–683.
[91] Zhang H, Huang T, Shen W, Xu X, Yang P, Zhu D, *et al.* Efficacy and safety of sacubitril-valsartan in heart failure: a meta-analysis of randomized controlled trials. ESC Heart Failure. 2020; 7: 3841–3850.
[92] Griffin M, Rao VS, Ivey-Miranda J, Fleming J, Mahoney D, Maulion C, *et al.* Empagliflozin in Heart Failure: Diuretic and Cardiorenal Effects. Circulation. 2020; 142: 1028–1039.
[93] Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC. Renal and Cardiovascular Effects of SGLT2 Inhibition in Combination with Loop Diuretics in Patients with Type 2 Diabetes and Chronic Heart Failure: The RECEDE-CHF Trial. Circulation. 2020; 142: 1713–1724.
[94] Böhm M, Fitchett D, Ofstad AP, Brueckmann M, Kaspers S, George JT, *et al.* Heart failure and renal outcomes according to baseline and achieved blood pressure in patients with type 2 diabetes: results from EMPA-REG OUTCOME. Journal of Hypertension. 2020; 38: 1829–1840.
[95] Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. the SAVE Investigators. The New England Journal of Medicine. 1992; 327: 669–677.

[96] Cleland JG, Erhardt L, Murray G, Hall AS, Ball SG. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. a report from the AIRE Study Investigators. European Heart Journal. 1997; 18: 41–51.
[97] Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, *et al.* Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. The New England Journal of Medicine. 2003; 348: 1309–1321.
[98] Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta Blockade after myocardial infarction: systematic review and meta regression analysis. British Medical Journal. 1999; 318: 1730–1737.
[99] O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013; 127: e362–e425.
[100] Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, *et al.* Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005; 366: 1622–1632.
[101] Carubelli V, Metra M, Lund LH. Negotiating renal dysfunction when treating patients with heart failure. Expert Review of Cardiovascular Therapy. 2018; 16: 113–122.
[102] Faul C, Amaral AP, Oskouei B, Hu M, Sloan A, Isakova T, *et al.* FGF23 induces left ventricular hypertrophy. The Journal of Clinical Investigation. 2011; 121: 4393–4408.
[103] Braam B, Joles JA, Danishwar AH, Gaillard CA. Cardiorenal syndrome–current understanding and future perspectives. Nature Reviews Nephrology. 2014; 10: 48–55.
[104] Desai AS, Swedberg K, McMurray JJV, Granger CB, Yusuf S, Young JB, *et al.* Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. Journal of the American College of Cardiology. 2007; 50: 1959–1966.
[105] Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, Chronic Kidney Disease, and the Effect of an Angiotensin Receptor Blocker in Addition to an Angiotensin-Converting Enzyme Inhibitor in Patients with Moderate to Severe Heart Failure. Circulation. 2009; 120: 1577–1584.
[106] Ahmed A, Fonarow GC, Zhang Y, Sanders PW, Allman RM, Arnett DK, *et al.* Renin-Angiotensin Inhibition in Systolic Heart Failure and Chronic Kidney Disease. The American Journal of Medicine. 2012; 125: 399–410.
[107] Bowling CB, Sanders PW, Allman RM, Rogers WJ, Patel K, Aban IB, *et al.* Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: insights from the SOLVD Treatment trial. International Journal of Cardiology. 2013; 167: 151–156.
[108] Packer M, Claggett B, Lefkowitz MP, McMurray JJV, Rouleau JL, Solomon SD, *et al.* Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. The Lancet Diabetes & Endocrinology. 2018; 6: 547–554.
[109] Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, *et al.* Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). Journal of the American College of Cardiology. 2012; 60: 2082–2089.
[110] House A, Wanner C, Sarnak M, Piña I, McIntyre C, Komenda P, *et al.* Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney International. 2019; 95: 1304–1317.
[111] Kotecha D, Gill SK, Flather MD, Holmes J, Packer M, Rosano G, *et al.* Impact of Renal Impairment on Beta-Blocker Efficacy in Patients with Heart Failure. Journal of the American College of Cardiology. 2019; 74: 2893–2904.
[112] Damman K, Tang WH, Felker GM, Lassus J, Zannad F, Krum H, *et al.* Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. Journal of the American College of Cardiology. 2014; 63: 853–871.
[113] Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, *et al.* Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. The Lancet Diabetes & Endocrinology. 2017; 5: 610–621.
[114] Pareek A, Chandurkar N, Naidu K. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. The New England Journal of Medicine. 2016; 375: 1800.
[115] Voors AA, Mulder H, Reyes E, Cowie MR, Lassus J, Hernandez AF, *et al.* Renal function and the effects of vericiguat in patients with worsening heart failure with reduced ejection fraction: insights from the VICTORIA (Vericiguat Global Study in Subjects with HFrEF) trial. European Journal of Heart Failure. 2021; 23: 1313–1321.
[116] Fu EL, Uijl A, Dekker FW, Lund LH, Savarese G, Carrero JJ. Association between β-Blocker Use and Mortality/Morbidity in Patients with Heart Failure with Reduced, Midrange, and Preserved Ejection Fraction and Advanced Chronic Kidney Disease. Circulation: Heart Failure. 2020; 13: e007180.
[117] Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, *et al.* Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. Journal of the American College of Cardiology. 2003; 41: 1438–1444.
[118] Roberts MA, Pilmore HL, Ierino FL, Badve SV, Cass A, Garg AX, *et al.* The β-Blocker to Lower Cardiovascular Dialysis Events (BLOCADE) Feasibility Study: a Randomized Controlled Trial. American Journal of Kidney Diseases. 2016; 67: 902–911.
[119] Lee S, Oh J, Kim H, Ha J, Chun K, Lee CJ, *et al.* Sacubitril/valsartan in patients with heart failure with reduced ejection fraction with end-stage of renal disease. ESC Heart Failure. 2020; 7: 1125–1129.
[120] Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F, *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. New England Journal of Medicine. 2020; 383: 1436–1446.
[121] Huizar JF, Ellenbogen KA, Tan AY, Kaszala K. Arrhythmia-Induced Cardiomyopathy: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2019; 73: 2328–2344.
[122] Sarrias A, Bayes-Genis A. Is Sacubitril/Valsartan (also) an Antiarrhythmic Drug? Circulation. 2018; 138: 551–553.
[123] de Diego C, González-Torres L, Núñez JM, Centurión Inda R, Martin-Langerwerf DA, Sangio AD, *et al.* Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Heart Rhythm. 2018; 15: 395–402.
[124] Zelniker TA, Bonaca MP, Furtado RHM, Mosenzon O, Kuder JF, Murphy SA, *et al.* Effect of Dapagliflozin on Atrial Fibrillation in Patients with Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial. Circulation. 2020; 141: 1227–1234.
[125] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, *et al.* 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: an Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2016; 134: e282–e293.
[126] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, *et al.* 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a

Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017; 136: e137–e161.

[127] Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, *et al*. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. a substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation. 1990; 82: 1724–1729.

[128] Yusuf S, Pitt B, Davis CE, Hood WB Jr., Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. New England Journal of Medicine. 1992; 327: 685–691.

[129] Colucci WS, Kolias TJ, Adams KF, Armstrong WF, Ghali JK, Gottlieb SS, *et al*. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction: the reversal of ventricular Remodeling with Toprol-XL (REVERT) trial. Circulation. 2007; 116: 49–56.