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MINI REVIEW

Sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors and vericiguat for congestive heart failure therapy

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Abstract

Heart failure is associated with notable morbidity and mortality, and therefore, novel therapies are needed. This minireview focused on the effects and mechanisms of action of sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors and vericiguat in heart failure patients. A systematic review of the current literature was conducted. Seventeen randomised clinical trials regarding the effects of these drug classes were included. The mechanism of action of each treatment could improve pathophysiological imbalances present in heart failure. All three drug classes revealed a reduction in hospitalisations for heart failure or death from cardiovascular causes in patients with reduced ejection fraction. Sacubitril/valsartan also reduced hospitalisations and death from cardiovascular causes in patients with mid-range ejection fraction, but not in patients with preserved ejection fraction. The sodium-glucose cotransporter 2 inhibitors, sotagliflozin and empagliflozin, reduced hospitalisations and death from cardiovascular causes in heart failure patients with preserved ejection fraction. None of the three drug classes was associated with a higher prevalence of treatment discontinuation due to increases in adverse effects in large-scale randomised clinical trials compared with placebo. Further studies are required to clarify the extent of effects of these medications in different subpopulations—especially in patients with mid-range and preserved ejection fraction.

KEYWORDS
clinical trials, heart failure, sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors, vericiguat

1 | INTRODUCTION

Congestive heart failure is a clinical syndrome characterised by fatigue, dyspnoea and symptoms of stasis caused by dysfunction of the left ventricle. Traditionally, congestive heart failure is classified into two categories—heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Patients with HFrEF have a reduced left ventricular ejection fraction (LVEF) $\leq 40\%$ and

patients with HFpEF have LVEF ≥ 50%. A third group, heart failure with mid-range ejection fraction (HFmrEF) with LVEF 41%–49%, has been introduced in recent years.[1]

In HFrEF, angiotensin-converting enzyme inhibitors (ACEi),[2,3] angiotensin II type 1 (AT_1) receptor antagonists,[4,5] beta-adrenergic antagonists (BAAs)[6–8] and mineralocorticoid receptor antagonists (MRAs)[9,10] had shown to reduce mortality and morbidity and had been the mainstay of treatment for symptomatic HFrEF. In recent years, sacubitril/valsartan[11] and sodium-glucose cotransporter 2 inhibitors (SGLT2i)[12,13] demonstrated to reduce mortality and morbidity, and they are now new recommended treatment options for symptomatic HFrEF according to the recommendations from the American College of Cardiology (ACC), the European Society of Cardiology (ESC) and the Danish Society of Cardiology (DCS).[1,14,15]

At the time of ESC guideline publication, no pharmacological treatment had demonstrated to reduce mortality and morbidity in HFpEF. Clinical trials have investigated the effect of ACEi,[16] BAAs,[17] AT_1 receptor antagonists,[18,19] MRAs[20] and calcium-channel blockers[21] without showing any significant effect. This reflects the recommendations from ACC, ESC and DCS. They recommend treating comorbidities such as hypertension and symptoms of stasis but do not include any mortality-reducing drugs.[1,15,22]

HFrEF and HFpEF are associated with notable morbidity and mortality. Consequently, it is essential to find novel therapies for these patients.[23,24] Three novel treatment modalities including sacubitril/valsartan, SGLT2i and vericiguat are currently under investigation in clinical trials for the treatment of heart failure.

Sacubitril/valsartan is a neprilysin inhibitor prodrug combined with an AT_1 receptor antagonist (see Figure 1). The prodrug sacubitril is metabolised to the active neprilysin inhibitor.[25] Neprilysin inactivates with varying relative affinities among different substrates: Its highest affinity is for atrial natriuretic peptide, C-type natriuretic peptide and angiotensin I and II, whereas its lowest affinity is for B-type natriuretic peptide, endothelin-1 and bradykinin.[26] Hence, the inhibition of neprilysin causes levels of natriuretic peptides to rise.[27] Natriuretic peptides stimulate myocardial relaxation and reduce myocardial fibrosis. In the kidneys, they have a diuretic and natriuretic effect. In blood vessels, natriuretic peptides cause vasodilation.[28,29] The inhibitory effect on neprilysin combined with the angiotensin receptor II antagonism by valsartan results in a more pronounced reduction in blood pressure compared with valsartan alone.[30]

According to the US Food and Drug Administration (FDA), adverse effects (AEs) of sacubitril/valsartan include hypotension, hyperkalaemia, cough, impaired renal function, angioedema and foetal toxicity.[31] Sacubitril/valsartan has not been associated with a higher risk of treatment discontinuation due to AEs compared with placebo in heart failure therapy.[11,32]

SGLT2i have been developed for glycaemic control in diabetes mellitus. SGLT2i inhibit the reabsorption of

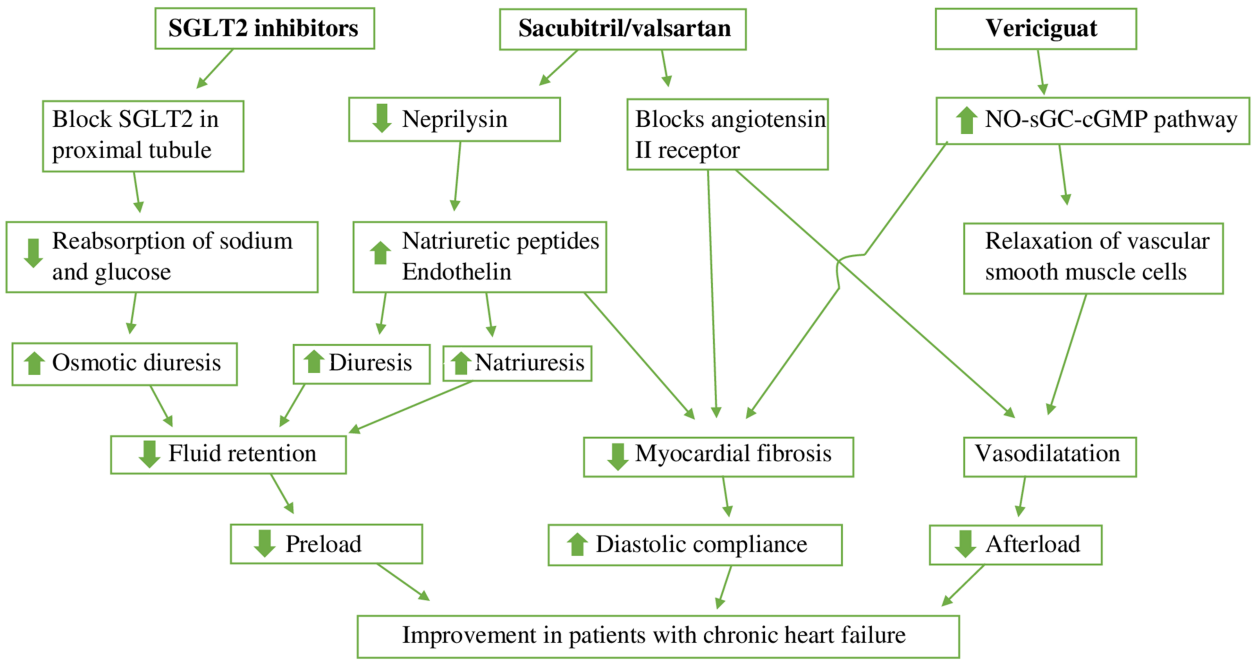

FIGURE 1 Mechanism of action of SGLT2 inhibitors, sacubitril/valsartan and vericiguat in congestive heart failure. cGMP, cyclic guanosine monophosphate; NO, nitric oxide; sGC, soluble guanylate cyclase; SGLT2, sodium-glucose cotransporter 2

sodium and glucose in the proximal tubule of the kidney (see Figure 1). SGLT2i exert a significant effect on the risk of heart failure in patients with type 2 diabetes.[33] Besides lowering blood glucose levels, SGLT2i have a diuretic effect caused by osmotic diuresis.[34] This diuretic effect leads to a decrease in systolic blood pressure.[35] The combination of osmotic diuresis by glucose and sodium may cause a higher degree of loss of interstitial fluid compared with conventional diuretics, which diuretic effect primarily relies on sodium.[36,37] SGLT2i resulted in lowering of the lung fluid volumes and lowering of left ventricle end-diastolic and end-systolic volumes compared with placebo.[38,39] The SGLT2i class includes the drugs canagliflozin, dapagliflozin, empagliflozin, ertugliflozin and sotagliflozin.

According to the FDA, AEs include genital mycotic infections, urinary tract infections, hypotension, impaired renal function, necrotising fasciitis, hypoglycaemia (in diabetes mellitus) and ketoacidosis (in diabetes mellitus).[40–42] SGLT2i have not been associated with a higher risk of treatment discontinuation due to AEs compared with placebo in heart failure therapy.[12,13,43]

Vericiguat is a soluble guanylate cyclase (sGC) stimulator (see Figure 1). It stimulates the sGC to produce cyclic guanosine monophosphate (cGMP) both directly and by sensitising the sGC to nitric oxide (NO).[44] This NO–sGC–cGMP pathway is dysregulated in heart failure.[45] The NO–sGC–cGMP pathway is thought to play a role in vascular smooth muscles and myocardium.[46] In vascular smooth muscles, this pathway results in relaxation, which can reduce afterload and increase the blood flow to the myocardium and the kidneys to prevent the cardiorenal syndrome.[47,48]

According to the FDA, AEs include hypotension and anaemia.[49] Vericiguat has not been associated with a higher risk of treatment discontinuation due to AEs compared with placebo in heart failure therapy.[50]

The three drug classes have recently been reviewed.[51–53] They exert different mechanisms of action. In order to discuss the effects of the three drug classes, we performed a systematic minireview of randomised controlled trials (RCTs) where sacubitril/valsartan, SGLT2i or vericiguat was applied as treatment.

2 | MATERIALS AND METHODS

The RCTs were found through searches in the databases PubMed, Embase and ClinicalTrials.gov (see Figure 2).

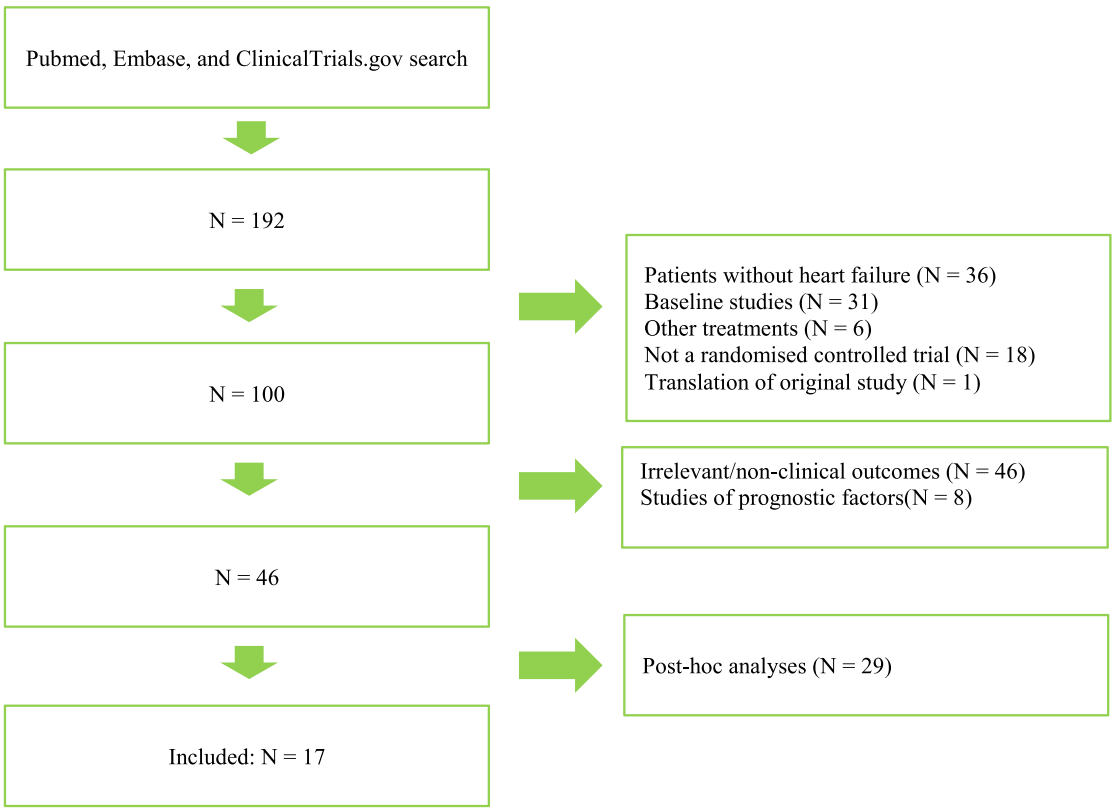

FIGURE 2 The search for randomised controlled trials. The first exclusion was based on a read-through of the titles. The second exclusion was based on a read-through of the abstracts. The third exclusion was based on a read-through of the full articles

Three searches were performed in PubMed (27 December 2021), Embase (27 December 2021) and ClinicalTrials.gov (27 December 2021). The following inclusion filters were used: 'Clinical Trial' and 'Randomized Controlled Trial'. Search terms were '(vericiguat) AND (heart failure)', '(sodium-glucose cotransporter 2 inhibitors) AND (heart failure)' and '(sacubitril/valsartan) AND (heart failure)'.

In total, the search found 11 results, 64 results and 117 results, respectively. Inclusion criteria were randomised controlled studies, patients with heart failure, original studies, clinical outcomes and treatment with sacubitril/valsartan, SGLT2i or vericiguat. Seventeen randomised clinical trials regarding the effects of these drugs were included. The exclusion criteria comprised languages other than English, or studies on cell culture experiments or animals. In addition, systematic reviews, meta-analyses and case reports were not included. Only published articles were reviewed.

Status and NCT numbers of the trials were recruited from ClinicalTrials.gov. Completed studies on vericiguat are as follows: VICTORIA (NCT02861534) and VITALITY-HFpEF (NCT03547583). Completed studies on SGLT2i are as follows: DAPA-HF (NCT03036124), EMPEROR-Reduced (NCT03057977), EMPEROR-Preserved (NCT03057951), DECLARE-TIMI 58 (NCT01730534) and VERTIS CV (NCT1986881). Completed studies on sacubitril/valsartan are as follows: PARAGON-HF (NCT01920711), PARADIGM-HF (NCT01035255) and PIONEER-HF (NCT02554890).

Terminated studies on SGLT2i are as follows: SOLOIST-WHF (NCT03521934).

3 | RESULTS

3.1 | Effects on heart failure with reduced ejection fraction

The results from selected RCTs investigating the clinical effect of sacubitril/valsartan, SGLT2i and vericiguat in HFrEF were included (see Table 1) in this minireview. The effects of the three different drug classes will be presented separately.

3.1.1 | Sacubitril/valsartan

The effects of sacubitril/valsartan in HFrEF are known since the PARADIGM-HF trial in 2014. The PARADIGM-HF trial randomised patients to treatment with 200 mg sacubitril/valsartan twice daily or 10 mg enalapril twice daily. The sacubitril/valsartan group experienced fewer hospitalisations for heart failure (HHF) or deaths from cardiovascular causes.[11]

This effect was significant for the two outcomes separately—HHF (relative risk, RR: 0.79 [95% confidence interval, CI: 0.71–0.89]) and death from cardiovascular causes (RR: 0.80 [95% CI: 0.71–0.89]). Furthermore, the sacubitril/valsartan group revealed a lower risk of death from any cause (RR: 0.84 [95% CI: 0.76–0.93]).[11] With respect to AEs, the sacubitril/valsartan group revealed higher proportions of patients with hypotension and non-serious angioedema but lower proportions with renal impairment, hyperkalaemia and cough than the enalapril group.[11]

3.1.2 | Sodium-glucose cotransporter 2 inhibitors

The effects of SGLT2i in HFrEF were studied intensively in recent years. The EMPEROR-Reduced trial randomised patients to treatment with 10 mg empagliflozin once daily or placebo. The DAPA-HF trial treated patients with HFrEF with 10 mg dapagliflozin once daily or placebo. In both studies, the SGLT2i group experienced fewer HHF or deaths from cardiovascular causes.[12,13]

In the DAPA-HF trial, this effect was significant for the two outcomes separately—HHF (RR: 0.70 [95% CI: 0.59–0.83]) and death from cardiovascular causes (RR: 0.82 [95% CI: 0.69–0.98]). Furthermore, the dapagliflozin group was at a lower risk of death from any cause (RR: 0.83 [95% CI: 0.71–0.97]).[13]

In the EMPEROR-Reduced trial, this effect was significant for HHF only (RR: 0.69 [95% CI: 0.59–0.81]), but not for death from cardiovascular causes (RR: 0.92 [95% CI: 0.75–1.12]) or death from any cause (RR: 0.92 [95% CI: 0.77–1.10]).[12]

The effect on HHF or death from cardiovascular causes was independent of type 2 diabetes. In the DAPA-HF trial, the RRs were 0.75 (95% CI: 0.63–0.90) and 0.73 (95% CI: 0.60–0.88) with and without type 2 diabetes, respectively. In the EMPEROR-Reduced trial, the RRs were 0.72 (95% CI: 0.60–0.87) and 0.78 (95% CI: 0.64–0.97) with and without type 2 diabetes, respectively.[12,13]

In the EMPEROR-Reduced trial, the subpopulation with LVEF $\geq$ 30% did not show a lower risk of HHF or death from cardiovascular causes (RR: 0.99 [95% CI: 0.76–1.31]).[12]

The DECLARE-TIMI 58 trial randomised patients with type 2 diabetes to treatment with 10 mg dapagliflozin or placebo. A subgroup of these patients had HFrEF. The patients with HFrEF treated with

TABLE 1 Randomised controlled trials investigating the effect of sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors and vericiguat therapy in HFrEF

Trial and drug	Inclusion criteria and number of participants	Intervention	Median duration	RR for HHF or death from cardiovascular causes
PARADIGM-HF[11] Sacubitril/valsartan	1. LVEF ≤ 40% 2. NYHA II–IV 3. NT-proBNP > 600 pg/ml or hospitalised within 12 months and NT-proBNP > 400 pg/ml $N = 8442$	97/103 mg twice daily or enalapril of 10 mg twice daily in addition to recommended therapy	27 months	RR: 0.80 (95% CI: 0.73–0.87)
EMPEROR-Reduced[12] Empagliflozin	1. LVEF ≤ 40% 2. NYHA II–IV 3. HHF within 12 months, NT-proBNP > 1000 pg/ml if LVEF 31%–35%, or >2500 pg/ml if LVEF 36%–40% $N = 3730$	10 mg once daily or placebo in addition to recommended therapy	16 months	RR: 0.70 (95% CI: 0.65–0.86)
DAPA-HF[13] Dapagliflozin	1. LVEF ≤ 40% 2. NYHA II–IV 3. NT-proBNP > 600 pg/ml or hospitalised within 12 months and NT-proBNP > 400 pg/ml $N = 4744$	10 mg once daily or placebo in addition to recommended therapy	18.2 months	RR: 0.75 (95% CI: 0.65–0.85)
DECLARE-TIMI 58[54] Dapagliflozin	1. Type 2 diabetes 2. HFrEF (LVEF < 45%) $N = 671$	10 mg once daily or placebo in addition to recommended therapy	4.2 years	RR: 0.62 (95% CI: 0.45–0.86)
VICTORIA[50] Vericiguat	1. LVEF < 45% 2. NYHA II–IV 3. NT-proBNP > 1000 pg/ml 4. HHF within 6 months or receiving intravenous diuretic therapy within 3 months $N = 5055$	10 mg once daily or placebo in addition to recommended therapy	10.8 months	RR: 0.90 (95% CI: 0.82–0.98)

Abbreviations: CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisations for heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RR, relative risk.

dapagliflozin had a lower incidence of HHF or deaths from cardiovascular causes. This effect was significant for the two outcomes separately—HHF (RR: 0.64 [95% CI: 0.43–0.95]) and death from cardiovascular causes (RR: 0.55 [95% CI: 0.34–0.90]). Furthermore, the dapagliflozin group was at a lower risk of dying from any cause (RR: 0.59 [95% CI: 0.40–0.88]).[54]

The VERTIS CV trial investigated the effect of 5 or 15 mg ertugliflozin compared with placebo in patients with type 2 diabetes and atherosclerotic cardiovascular disease. A subgroup of these patients had heart failure. In the heart failure subgroup, the ertugliflozin group had a lower incidence of HHF or death from cardiovascular causes (RR: 0.63 [95% CI: 0.44–0.90]).[55]

Focusing on the side effects of empagliflozin in the EMPEROR-Reduced trial, the annual rate of decline in the estimated glomerular filtration rate was lower in the empagliflozin group than in the placebo group. Furthermore, empagliflozin-treated patients showed a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.[12]

Dapagliflozin (DAPA-HF trial) did not show a higher amount of AEs related to volume depletion, renal dysfunction and hypoglycaemia in comparison with the placebo groups.[13]

In the DECLARE-TIMI 58 trial, fewer patients in the dapagliflozin group compared with the placebo

group discontinued the assigned regimen during the course of the trial (8.1% vs. 6.9%), and fewer patients in the dapagliflozin group reported serious AEs (34.1% vs. 36.2%) or had major hypoglycaemia (0.7% vs. 1%), acute kidney injury (1.5% vs. 2%) or bladder cancer (0.3 vs. 0.5%). Diabetic ketoacidosis was more common in the dapagliflozin group (0.3 vs. 0.1%). Genital infections leading to discontinuation and serious AEs were more frequent in the dapagliflozin group, both in men and in women, although genital infections reported as serious adverse events were rare (0.9% vs. 0.1%).

3.1.3 | Vericiguat

The effect of vericiguat in HFrEF was investigated in the VICTORIA trial. The VICTORIA trial randomised patients to treatment with 10 mg vericiguat once daily or placebo. The vericiguat group experienced fewer HHF or deaths from cardiovascular causes.[50]

The effects for the two outcomes separately were HHF (RR: 0.90 [95% CI: 0.81–1.00]) and death from cardiovascular causes (RR: 0.93 [95% CI: 0.81–1.06]). The vericiguat group did not show a significantly lower death risk from any cause (RR: 0.95 [95% CI: 0.84–1.07]). The subpopulation with LVEF ≥ 40% did not show a lower risk of HHF or death from cardiovascular causes (RR: 1.05 [95% CI: 0.81–1.36]).[50]

With respect to AEs, symptomatic hypotension was reported in 9.1% of the patients in the vericiguat group and in 7.9% of the patients in the placebo group ($p = 0.12$). Furthermore, syncope was found in 4.0% of the patients in the vericiguat group and in 3.5% of the patients in the placebo group ($p = 0.30$).[51]

3.2 | Effects on heart failure with preserved ejection fraction

The results from the most important RCTs investigating the clinical effects of sacubitril/valsartan, SGLT2i and vericiguat in HFpEF were included (see Table 2). The effects of the three drug classes will be presented separately.

3.2.1 | Sacubitril/valsartan

The effect of sacubitril/valsartan in HFpEF was studied in 2012 in the PARAMOUNT trial. The PARAMOUNT trial randomised patients to treatment with 200 mg sacubitril/valsartan twice daily or 160 mg valsartan twice daily. The sacubitril/valsartan group showed a higher reduction in levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) after 12 weeks.[56]

The large-scale PARAGON-HF trial investigated the clinical outcome by randomising patients to treatment with 200 mg sacubitril/valsartan twice daily or 160 mg valsartan twice daily. The incidence of death from cardiovascular causes was 8.5% in the sacubitril–valsartan group and 8.9% in the valsartan group (RR: 0.95 [95% CI: 0.79–1.16]). The sacubitril/valsartan group did not experience significantly fewer HHF from cardiovascular causes compared with the valsartan group (RR: 0.85 [95% CI: 0.72–1.00]).[32]

In the PARAGON-HF trial, the subpopulation with LVEF ≤ 57% (lower median) had a lower risk of HHF or death from cardiovascular causes (RR: 0.78 [95% CI: 0.64–0.95]). This was not the case for the subpopulation with LVEF > 57% (upper median) (RR: 1.00 [95% CI: 0.81–1.21]).[32]

With respect to safety, patients in the sacubitril–valsartan group showed a higher incidence of hypotension and angioedema and a lower incidence of hyperkalaemia.[32]

3.2.2 | Sodium-glucose cotransporter 2 inhibitors

The DECLARE-TIMI 58 trial randomised patients with type 2 diabetes to treatment with 10 mg dapagliflozin once daily or placebo. A subgroup of these patients had HFpEF. The patients with HFpEF treated with dapagliflozin did not show a significantly lower incidence of HHF or deaths from cardiovascular causes. There was no significant effect for the two outcomes separately—HHF (RR: 0.72 [95% CI: 0.50–1.04]) and death from cardiovascular causes (RR: 1.41 [95% CI: 0.93–2.13]).[54]

The SOLOIST-WHF trial randomised patients with type 2 diabetes and heart failure to treatment with 200 mg sotagliflozin once daily or placebo. The patients with HFpEF receiving sotagliflozin did reveal a significantly lower incidence of HHF or death from cardiovascular causes (RR: 0.48 [95% CI: 0.27–0.86]).[43]

The EMPEROR-Preserved trial randomised patients to treatment with 10 mg empagliflozin once daily or placebo. The empagliflozin group experienced fewer HHF (407 with empagliflozin and 541 with placebo; RR: 0.73 [95% CI: 0.61–0.88]; $p < 0.001$) or deaths from cardiovascular causes (RR: 0.79 [95% CI: 0.69–0.90]). This effect was independent of the diabetic status. Reported AEs in the empagliflozin group were uncomplicated genital and urinary tract infections and hypotension.[57]

TABLE 2 Randomised controlled trials investigating the effect of sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors and vericiguat therapy in HFpEF

Trial and drug	Inclusion criteria and number of participants	Intervention	Median duration	Outcome and result
PARAMOUNT[56] Sacubitril/valsartan	1. LVEF ≥ 45% 2. NYHA II–III 3. NT-proBNP > 400 pg/ml *N* = 290	97/103 mg twice daily or valsartan of 160 mg twice daily	12 weeks	The ratio between changes in NT-proBNP from baseline RR: 0.77 (95% CI: 0.64–0.92)
PARAGON-HF[32] Sacubitril/valsartan	1. LVEF ≥ 45% 2. NYHA II–IV 3. HHF within 9 months and NT-proBNP > 200 pg/ml or NT-proBNP > 900 pg/ml *N* = 4822	97/103 mg twice daily or valsartan of 160 mg twice daily	35 months	Death from cardiovascular causes or HHF RR: 0.87 (95% CI: 0.75–1.01)
DECLARE-TIMI 58[54] Dapagliflozin	1. Type 2 diabetes 2. HFpEF (LVEF ≥ 45%) *N* = 1316	10 mg once daily or placebo in addition to recommended therapy	4.2 years	Death from cardiovascular causes or HHF RR: 0.88 (95% CI: 0.66–1.17)
SOLOIST-WHF[43] Sotagliflozin	1. Type 2 diabetes 2. HFpEF (LVEF ≥ 50%) and recent acute decompensation *N* = 256	200 mg once daily or placebo in addition to recommended therapy	9 months	Death from cardiovascular causes or HHF RR: 0.48 (95% CI: 0.27–0.86)
EMPEROR-Preserved[57] Empagliflozin	1. LVEF > 40% 2. NYHA II–IV 3. HHF within 12 months or NT-proBNP > 300 pg/ml and structural heart changes *N* = 5988	10 mg once daily or placebo in addition to recommended therapy	26 months	Death from cardiovascular causes or HHF RR: 0.79 (95% CI: 0.69–0.90)
VITALITY-HFpEF[58] Vericiguat	1. LVEF ≥ 45% 2. NYHA II–III 3. HHF or intravenous diuretics for heart failure within the previous 6 months 4. NT-proBNP ≥ 600 pg/ml *N* = 789	15 mg once daily, 10 mg once daily or placebo	24 weeks	Change in KCCQ PLS score from baseline 15 mg versus placebo: −1.5 points (95% CI: −5.5 to +2.5) 10 mg versus placebo: −0.5 points (95% CI: −4.6 to +3.5)

Abbreviations: CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalisations for heart failure; KCCQ PLS, Kansas City Cardiomyopathy Questionnaire—Physical Life Status; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RR, relative risk.

3.2.3 | Vericiguat

There are only few studies examining the effect of vericiguat on HFpEF. The VITALITY-HFpEF trial randomised patients to treatment with 15 mg vericiguat once daily, 10 mg vericiguat once daily or placebo. The outcome was a change in points according to KCCQ PLS (Kansas City Cardiomyopathy Questionnaire—Physical Life Status) between baseline and after 24 weeks. Both the 15 mg/day vericiguat group and the 10 mg/day vericiguat group did not show a better score compared with the placebo group.[58] The percentage of patients with AEs was 65.2% in the 15 mg/day vericiguat group, 62.2% in the 10 mg/day vericiguat group and 65.6% in the placebo group. Reported AEs were symptomatic hypotension and syncope.[58]

3.3 | Adverse effects

None of the three drug classes was associated with a higher prevalence of treatment discontinuation due to AEs in large-scale RCTs compared with placebo (see Table 3).

TABLE 3 Adverse effects in randomised controlled trials of sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors and vericiguat in heart failure

Trial and drug	Outcome	Result
PARADIGM-HF[11] Sacubitril/valsartan	Stopped medication prematurely due to adverse effects	Sacubitril/valsartan group: 10.7% Enalapril group: 12.3%
PARAGON-HF[32] Sacubitril/valsartan	Stopped medication prematurely due to adverse effects	Sacubitril/valsartan group: 25.3% Valsartan group: 26.7%
EMPEROR-Reduced[12] Empagliflozin	Stopped medication prematurely due to adverse effects	Empagliflozin group: 16.3% Placebo group: 18.0%
DAPA-HF[13] Dapagliflozin	Stopped medication prematurely due to adverse effects	Dapagliflozin group: 4.7% Placebo group: 4.9%
VICTORIA[50] Vericiguat	Serious adverse effects	Vericiguat group: 32.8% Placebo group: 34.8%

4 | DISCUSSION

The effect, recommendations and future studies regarding the three novel therapies are discussed for HFrEF, HFpEF and HFmrEF separately.

4.1 | Heart failure with reduced ejection fraction

4.1.1 | Sacubitril/valsartan

In the PARADIGM-HF trial, sacubitril/valsartan was more effective than enalapril in HFrEF with regard to HHF, death from cardiovascular causes and death from any cause.[11] The effect was also significant in health-related quality of life outcomes.[59] Post hoc analyses of the PARADIGM-HF trial demonstrated that this superiority to enalapril was independent of age, risk status, reaching target doses, background therapy, blood pressure and aetiology of heart failure.[60–65] In the PIONEER-HF trial, the superior effect of sacubitril/valsartan to enalapril was also present following acute decompensation.[66] The LIFE trial did not find a better effect of sacubitril/valsartan compared with valsartan in patients with LVEF ≤ 35% and New York Heart Association (NYHA) IV.[67]

The ESC and DCS recommend sacubitril/valsartan to replace ACEi in HFrEF after initiation of ACEi, BAA and MRA, if the patient is still symptomatic (NYHA II–IV).[1,15] The ACC recommends the initiation of sacubitril/valsartan as first treatment without prior treatment with ACEi.[14]

These recommendations reflect the evidence from the PARADIGM-HF trial (see Table 1). In the TITRATION study, initiation of sacubitril/valsartan without prior ACEi treatment was tolerated as well as the initiation of ACEi.[68]

Future trials should investigate the effects in stable patients with lower levels of natriuretic peptides and should be tested as initiation therapy instead of ACEi.

At the moment, the PARALLEL-HF trial examines the effect shown in the PARADIGM-HF trial in a Japanese population.[69] Currently, sacubitril/valsartan is investigated in other subpopulations of HFrEF patients such as paediatric patients and patients with sleep apnoea.[70,71]

4.1.2 | Sodium-glucose cotransporter 2 inhibitors

In both the DAPA-HF trial and the EMPEROR-Reduced trial, SGLT2i showed a better effect than placebo in addition to recommended therapy in HFrEF when it comes to HHF or death from cardiovascular causes.[12,13] The effect was also significant in health-related quality of life outcomes.[72,73] Post hoc analyses revealed that the effect was independent of diabetic status, age and sacubitril/valsartan or enalapril treatment.[74,75] In the EMPEROR-Reduced trial, the subpopulation with LVEF ≥ 30% did not show this effect, but this could be a result of underpoweredness. The DAPA-HF trial showed a significant effect on death from any cause, but the EMPEROR-Reduced trial did not have this effect.[12,13] Ertugliflozin has also a beneficial effect in heart failure in the VERTIS CV trial, thus indicating a class effect of SGLT2i.[55]

The ACC and ESC recommend SGLT2i for HFrEF patients with symptoms after initiating an ACEi or sacubitril/valsartan, a BAA and an MRA.[1,14] The DSC recommends considering SGLT2i treatment in patients with HFrEF after initiation of ACEi or sacubitril/valsartan and BAA when the patient is with (1) NYHA II–IV and (2) LVEF ≤ 40%.[15]

The results from the DAPA-HF and EMPEROR-Reduced studies suggest that SGLT2i should be a part of

the recommended therapy for symptomatic patients with HFrEF.[12,13] The recommendations for SGLT2i treatment in HFrEF reflect the evidence from DAPA-HF and EMPEROR-Reduced.

EMPIRE-HF is investigating the effect on NT-proBNP levels of empagliflozin in HFrEF.[76] The effects of SGLT2i should be investigated in stable patients with lower levels of natriuretic peptides.

4.1.3 | Vericiguat

In the VICTORIA trial, vericiguat showed a better effect than placebo in addition to recommended therapy in HFrEF when it comes to HHF or death from cardiovascular causes. The effect was independent of sacubitril/valsartan or enalapril treatment. The subpopulation with LVEF of 40%–44% did not reveal this effect. Moreover, there was no effect of vericiguat on death from any cause.[50] A post hoc analysis of the VICTORIA trial investigated the effect of vericiguat in subgroups according to NT-proBNP levels. Vericiguat showed an effect in patients with NT-proBNP $\leq$ 8000 pg/ml but showed no effect in patients with NT-proBNP > 8000 pg/ml.[77]

The ACC and DSC do not recommend vericiguat for HFrEF patients.[14,15] The ESC recommends to consider vericiguat in patients with worsening heart failure when treated with an ACEi or sacubitril/valsartan, a BAA and an MRA.[1] The VICTORIA trial showed a significant effect of vericiguat in HFrEF.[50] Inclusion of vericiguat should be considered in future recommendations reflecting the results from the VICTORIA trial.

Future studies should investigate the optimal dosage of vericiguat. At the present time, the highest dosage given in HFrEF is 10 mg once daily.[50,78]

4.1.4 | Sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors and vericiguat: A comparison

The study populations in the PARADIGM-HF, DAPA-HF and EMPEROR-Reduced trials are comparable.[11–13] The fact that the EMPEROR-Reduced trial did not show a significant effect on death from any cause could be attributable to less statistical power as the PARADIGM-HF trial had more participants and longer duration. The results suggested that sacubitril/valsartan had a more pronounced effect than SGLT2i in patients with LVEF $\geq$ 30%, but the effect of SGLT2i may be stronger than sacubitril/valsartan in the subpopulation with LVEF < 30%. The comparison is arbitrary in the sense that sacubitril/valsartan involved the discontinuation of enalapril, whereas SGLT2i were given in addition to recommended treatment.

In the VICTORIA trial, vericiguat showed an effect in HFrEF.[50] Unlike the studies on sacubitril/valsartan and SGLT2i, the VICTORIA trial included patients with LVEF of 40%–44%. The VICTORIA trial differed in other inclusion criteria as well and the duration was shorter. Generally, this makes it difficult to compare the effect of vericiguat to SGLT2i and sacubitril/valsartan. Current evidence suggests that sacubitril/valsartan and SGLT2i are beneficial in HFrEF compared with vericiguat.

It should be mentioned that both SGLT2i and vericiguat were effective in combination with sacubitril/valsartan in HFrEF.[50,79]

4.2 | Heart failure with preserved ejection fraction

4.2.1 | Sacubitril/valsartan

In the PARAGON-HF trial, sacubitril/valsartan did not show a better effect than valsartan on HHF or death from cardiovascular causes in patients with LVEF $\geq$ 45%. However, sacubitril/valsartan exerted a significant effect on the subpopulation with LVEF < 57% (lower median).[32]

The ACC, ESC and DSC do not recommend sacubitril/valsartan for HFpEF patients.[1,15,22] The recommendations reflect the results from the PARAGON-HF trial.[32] Future studies and post hoc analyses from the PARAGON-HF trial should investigate the effect in certain subpopulations such as LVEF of 50%–55%.

4.2.2 | Sodium-glucose cotransporter 2 inhibitors

The DECLARE-TIMI 58 trial did not show a significantly better effect of dapagliflozin than placebo on HHF or death from cardiovascular causes in patients with LVEF $\geq$ 45% and type 2 diabetes.[54] The SOLOIST-WHF trial demonstrated a significantly better effect of sotagliflozin than placebo on the primary endpoint, which was total number of deaths from cardiovascular causes and hospitalisations and urgent visits for heart failure in patients with LVEF $\geq$ 50% and type 2 diabetes, but the rate of death from cardiovascular causes was not different.[43] This can probably be ascribed to lack of power as the SOLOIST-WHF trial was terminated early due to lack of funding. These studies only included patients with type 2 diabetes. The EMPEROR-Preserved trial showed a better effect of empagliflozin than placebo

on HHF or death from cardiovascular causes independent of the diabetic status.[57]

The ACC, ESC and DSC do not recommend SGLT2i for HFpEF patients.[1,14,15] Evidence from the EMPEROR-Preserved trial suggests that empagliflozin should be initiated in patients with HFpEF.[57] Currently, the DELIVER trial is focusing on the effect of dapagliflozin in HFpEF.[80] The effect of SGLT2i is varying. This could be due to variation in diagnostic criteria, varying dosages or that the effect is only seen with specific SGLT2i and is not a drug class effect. Future studies should investigate these questions.

4.2.3 | Vericiguat

The VITALITY-HFpEF did not show a better effect of vericiguat than placebo on KCCQ PLS in patients with LVEF ≥ 45%.[58]

Furthermore, the ACC, ESC and DCS do not recommend vericiguat for HFpEF treatment.[1,15,22] This reflects current evidence and does not indicate an effect of vericiguat in HFpEF.

4.2.4 | Sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors and vericiguat: A comparison

Generally, the effects of sacubitril/valsartan, SGLT2i and vericiguat were not as well studied in HFpEF as in HFrEF. The PARAGON-HF trial showed that sacubitril/valsartan might be effective in patients with LVEF of 50%–55%.[32] The DECLARE-TIMI 58 was difficult to compare with the PARAGON-HF trial due to different and less precise inclusion criteria and a smaller population.[54] Moreover, the VITALITY-HFpEF was difficult to compare with the PARAGON-HF trial because of different outcome measures.[58] Vericiguat did not have a positive effect in HFpEF. In the EMPEROR-Preserved trial, empagliflozin showed a significant effect on HHF or death from cardiovascular causes independent of diabetic status.[57] In the SOLOIST-WHF, sotagliflozin had a positive effect on urgent visits and HHF.[43] SGLT2i is the drug class with compelling effect on HFpEF. Generally, the three drug classes need to be evaluated in further RCTs with focus on HFpEF.

4.3 | Heart failure with mid-range ejection fraction

Traditionally, HFmrEF has been studied as a part of HFpEF. Recent studies suggest that HFmrEF should be treated differently than HFpEF, and evidence-based treatment guidelines for HFmrEF are needed. As a result of lacking research, the ACC and DSC do not have separate guidelines for HFmrEF.[15,22] The ESC has developed separate guidelines.[1] They all recognise the need for such specific guidelines for HFmrEF.

4.3.1 | Sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors and vericiguat: A comparison

The PARAGON-HF trial demonstrated a better effect of sacubitril/valsartan than valsartan on HHF or death from cardiovascular causes in patients with LVEF of 45%–57% (lower median).[32] Therefore, an RCT investigating the effect of sacubitril/valsartan in patients with LVEF of 40%–49% (HFmrEF) would be interesting.

Vericiguat is not well studied in patients with HFmrEF. In the VICTORIA trial, the subgroup of patients with LVEF of 40%–44% did not reveal a lower risk of HHF or death from cardiovascular causes.[50]

In the EMPEROR-Preserved trial, empagliflozin showed a significant effect on HHF or death from cardiovascular causes and empagliflozin is the only drug with compelling effect on HFmrEF.[57] Currently, the DELIVER trial is investigating the effect of dapagliflozin in HFmrEF.[80]

5 | LIMITATIONS

The clinical trials reviewed in this minireview are all listed in ClinicalTrials.gov and a major part of them are published in highly ranked journals. An important limit is the difficulty to generalise the results because the enrolled study patients are different from the patient population entering the health care system. In addition, being part of a clinical trial might influence the patients' well-being and quality of life and thus influence the data. The current COVID-19 pandemic is a factor that have influenced enrolment and willingness of the patients to participate in studies running from February 2020. Another factor might be the compliance of the patients. Moreover, further analysis and clinical trials will be required to address whether sex, age and ethnicity play a role for the outcome of these drug classes.

The LIFE trial reported a smaller sample size and a relatively short duration compared with other phase 3 trials investigating NYHA class II to III heart failure patients. Moreover, the reasons for premature discontinuation of the study drug were not given. In addition, interpreting the findings of LIFE results needs a

discussion of how the COVID-19 mitigation strategy affected the results. The reduced number of enrolled patients from 400 to 335 can decrease the statistical power of the trial.[67]

Finally, it should be taken into account that the majority of the international clinical studies are financed by pharmaceutical companies. The industry sponsorship of clinical trials can lead to important therapeutic advances, but the potential for bias in these studies may exist at multiple levels. Therefore, it is of high importance to recognise bias in clinical trials and to ensure objectivity in clinical research and that only drugs supported by unbiased, scientific evidence reach the market, clinic and finally the practicing doctors and patients.

6 | CONCLUSIONS

All three reviewed drug classes have mechanisms of action that could improve some of the pathophysiological imbalances presented in heart failure.

The three drug classes showed a positive effect in HFrEF. Current evidence suggests that sacubitril/valsartan and SGLT2i are more beneficial in HFrEF compared with vericiguat. The results suggested that sacubitril/valsartan had a more pronounced effect than SGLT2i in patients with LVEF $\geq$ 30%, but the effect of SGLT2i may be more pronounced than sacubitril/valsartan in the subpopulation with LVEF < 30%. However, lack of sufficient statistical power could be the reason for these differences. The comparison is arbitrary in the sense that sacubitril/valsartan involved discontinuation of enalapril, whereas SGLT2i and vericiguat were given in addition to recommended treatment. Both SGLT2i and vericiguat are shown to be effective in combination with sacubitril/valsartan in HFrEF.

Sacubitril/valsartan might be effective in HFpEF with LVEF of 50%–55%. The SGLT2i, empagliflozin, showed a compelling effect in HFpEF independent of the diabetic status. Vericiguat did not prove to be effective in HFpEF. It has to be taken into account that these treatments were not well studied. The comparison of the three drug classes in HFpEF was complicated by different inclusion criteria, population sizes and outcome measures.

Sacubitril/valsartan and SGLT2i, empagliflozin specifically, showed promising results in HFmrEF. Vericiguat is not well studied in HFmrEF. The ACC and DSC do not have separate guidelines for HFmrEF.

The three drug classes could be a part of the therapy regimen in patients with congestive heart failure and should already be a part of the treatment among patients with reduced ejection fraction. Empagliflozin treatment should be considered for both HFmrEF and HFpEF. The effects vary between subpopulations.

Further studies need to be conducted to clarify the extent of effects in different subpopulations of patients with heart failure—especially in HFmrEF and HFpEF.

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CONFLICT OF INTEREST

Ulf Simonsen is consultant and owner of shares in Initiator Pharma A/S (https://www.initiatorpharma.com/en/). This article is not related to the profile or pipeline of this company. The authors report no conflicts of interest.

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