SPECIAL FOCUS ISSUE | Cardiovascular Outcomes Trials

Review

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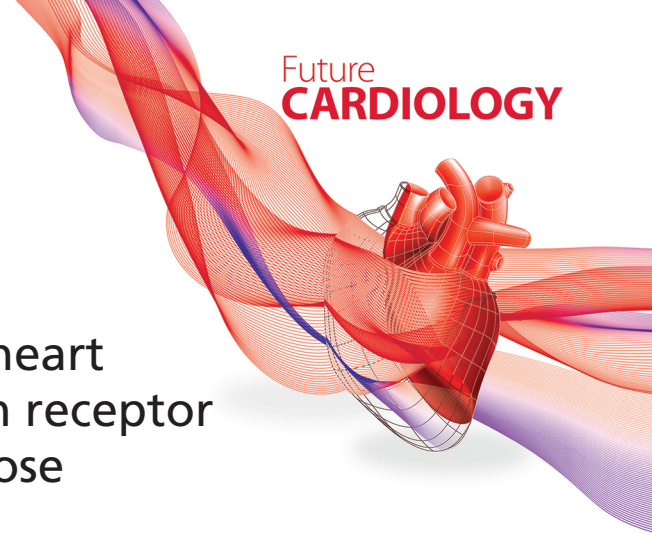

Shift of conventional paradigm of heart failure treatment: from angiotensin receptor neprilysin inhibitor to sodium–glucose co-transporter 2 inhibitors?

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Current clinical guidelines for heart failure (HF) contain a brand new therapeutic strategy for HF with reduced ejection fraction (HFrEF), which is based on neurohumoral modulation through the use of angiotensin receptor neprilysin inhibitors. There is a large body of evidence for the fact that sodium-glucose co-transporter 2 inhibitors may significantly improve all-cause mortality, cardiovascular mortality and hospitalization for HF in patients with HFrEF who received renin–angiotensin system blockers including angiotensin receptor neprilysin inhibitors, β-blockers and mineralocorticoid receptor antagonists. The review discusses that sodium-glucose co-transporter 2 inhibitors have a wide spectrum of favorable molecular effects and contribute to tissue protection, improving survival in HFrEF patients.

Lay abstract: Current clinical guidelines for heart failure (HF) contain a new therapeutic strategy for a certain type of HF. There is a large body of evidence for the fact that certain types of drugs called sodium-glucose co-transporter 2 inhibitors may significantly improve outcomes in patients with this type of HF who received a different group of drugs. The review discusses the features of sodium-glucose co-transporter 2 inhibitors that make them successful in improving the outcomes in patients with HF.

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Keywords: angiotensin receptor neprilysin inhibitor • clinical outcomes • heart failure • prognosis • sodium-glucose co-transporter 2 inhibitors

Heart failure (HF) affects 37.7 million individuals worldwide. It remains a leading cause of hospitalization among people with established cardiovascular (CV) disease [1]. In the USA, the direct medical costs for patients having HF are expected to have dramatic growth up to 60% by 2030 (from US$20.9 billion in 2012 to US$53.1 billion in 2030) [1]. Moreover, the total costs including direct and indirect expenditures for HF are estimated to have a markedly rise from US$31 billion in 2012 to US$70 billion in 2030 [2]. In fact, the prevalence of HF in both developed and developing countries continues to rise predominantly due to HF with preserved ejection fraction (HFpEF), whereas the total occurrence of HF with reduced election fraction (HFrEF) tends to slightly decrease in developed countries, but not in developing countries [3]. Although multimorbidity is common for both HF phenotypes, HFpEF is much more frequently associated with additional CV risk factors (hypertension, diabetes mellitus, abdominal obesity and chronic coronary syndromes), older age and female sex than HFrEF [4,5]. In addition, the majority of deaths in HFpEF patients occurred due to CV reasons, while the proportion of non-CV deaths in HFpEF was higher than HFrEF individuals [6,7].

The most reputed cardiology associations, such as American College of Cardiology/American Heart Association and European Society of Cardiology reported evidence-based clinical guidelines for the diagnosis and treatment of HF with a brand new strategy for HFrEF care, which is based on neurohumoral modulation through the use of angiotensin receptor neprilysin inhibitors (ARNIs) [8]. The management of HF-related comorbidities, such as Type

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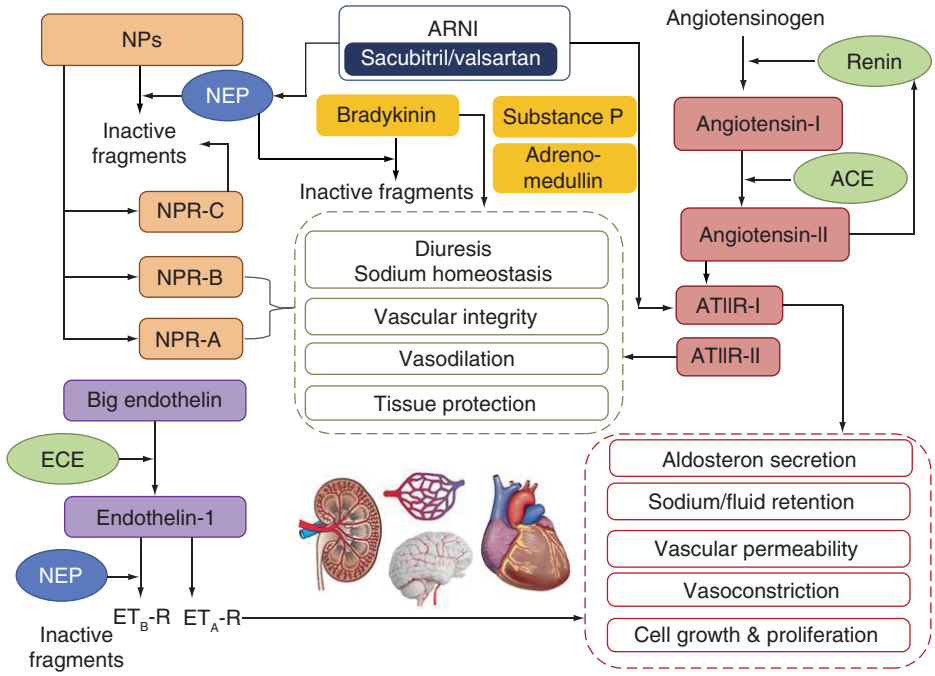

Figure 1. Multiple impacts of sacubitril/valsartan on neurohumoral homeostasis and tissue remodeling.
ACE: Angiotensin-converting enzyme; ARNI: Angiotensin receptor neprilysin inhibitor; ATII-R: Angiotensin-II receptor; ECE: Endothelin-converting enzyme; NEP: Neutral endopeptidase; NP: Natriuretic peptide; NPR: NP receptor.

2 diabetes mellitus (T2DM), closely relates to both HF phenotypes in these guidelines [9,10]. Indeed, sodium-glucose co-transporter 2 (SGLT2) inhibitors along with metformin and glucagon-like peptide-1 receptor agonists are considered as the therapy of T2DM in HF [9,10]. The European Society of Cardiology expert consensus meeting report has recently published with extensive indications of SGLT2 inhibitors in non-T2DM patients with HFrEF, but not those who had HFpEF, because there was limiting evidence for SGLT2 inhibitors received in specially designed randomized clinical trials that supported the possibility of these drugs to improve mortality and decrease in hospitalization among HFpEF patients [11]. Finally, SGLT2 inhibitors became the next add-on strategy in addition to renin–angiotensin system blockers including ARNI, β-blockers and mineralocorticoid receptor antagonists (MRAs) to successfully treat HFrEF and probably HFpEF. Whether the molecular mechanisms by which SGLT2 inhibitors improve cardiac and renal outcomes in HF overlap with those in ARNI are not completely understood. The aim of the review is: to discuss whether SGLT2 inhibitors are add-on drugs to ARNI or they should be prescribed regardless of ARNI used, and what cardiac and renal protective mechanisms contribute to clinical benefits for both drug classes.

Angiotensin receptor neprilysin inhibitors

ARNI & neurohumoral modulation

Sacubitril/valsartan is a first-in-class ARNI that simultaneously inhibits angiotensin-II receptors and neprilysin and thereby suppresses activity of renin–angiotensin–aldosterone system (RAAS) and enhances circulating vasoactive peptides [12]. This approach called neurohumoral modulation is reported in Figure 1. Although sacubitril/valsartan augments natriuretic peptides (NPs) activity and counteracts with RAAS, there are large pleiotropic abilities of this drug that are beyond primary pharmacological effects. Indeed, the development of HF is associated with the overwhelming effects of some components of RAAS predominantly angiotensin-II on the tissue expression of NP receptors and their sensitization that consequently lead to absolute NP deficiency [13]. Thus, the suppression of RAAS activity contributes to upregulation in NP receptor expression and diminishes a degradation of circulating NPs resulting to elevation of circulating levels of NPs (brain NP [BNP] and N-terminal fragment of BNP [NT-proBNP]). Finally, endogenous NPs decrease in preload, peripheral artery resistance, induce diuresis, improve the perfusion of kidney, myocardium, liver, skeletal muscle and lungs, attenuate skeletal muscle energy homeostasis, free fatty acids and glucose metabolism, and decrease in insulin resistance [14]. In addition, sacubitril/valsartan through

the inhibition of neutral endopeptidase mediates increasing circulating levels of large spectrum of vasoactive peptides, such as bradykinin, substance P and adrenomedullin, which are able to potentiate vasodilation, water and sodium homeostasis, and vascular integrity, and thereby meaningfully influence tissue protection predominantly via concomitantly blocking pro-fibrotic/pro-hypertrophic mechanism [15]. Therefore, sacubitril/valsartan can interfere with amyloid-β, while there are major concerns of its potential implications on the occurrence of chronic kidney disease, Alzheimer's disease and macular degeneration [14,15].

ARNI in HFrEF/HFpEF

During last decade the efficacy and safety of ARNIs in HFrEF and HFpEF have been widely investigated in large clinical trials [15]. The PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial has shown superiority of sacubitril/valsartan to enalapril in reduction of CV morbidity and mortality, renal and HF-related outcomes in HFrEF patients notwithstanding glycemic status, chronic kidney disease, previous coronary revascularization or background therapy [16–18]. In addition, sacubitril/valsartan resulted in greater reductions in NT-proBNP levels and less increased in soluble suppressor tumorigenisity-2 levels than enalapril [19]. Even though an adjustment of HFrEF intensive therapy (increasing oral therapy or temporary intravenous treatment in the community or emergency department), sacubitril/valsartan was better than enalapril in reduction of a risk of death and HF hospitalization [20]. Subsequent network meta-analysis of 57 randomized controlled trials among HFrEF patients has consciously yielded that the treatment with angiotensin-converting enzyme (ACE) inhibitors (ACEIs), angiotensin-II receptor blockers (ARBs), β-blockers, MRAs and ARNI and their combinations had much more better impact on all-cause mortality and CV mortality when compared with placebo [21]. Moreover, the combination of ARNI with β-blockers and MRA led to the greatest reduction in CV mortality among HFrEF patients [21].

The effect of ARNI on hard clinical end points in patients with HFpEF was not so dramatic and impressive as it was expected [22,23]. The PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction) trial did not result in a significantly lower total rate of HF-related hospitalizations and CV mortality in HFpEF individuals, especially when left ventricular ejection fraction (LFEF) was >45%, but reduced the risk of HF hospitalization in women [23]. Nevertheless, a few options of disease-modifying therapies of HFrEF with ARNI can be available for patients having the range of LVEF >40% [24]. Indeed, the pooled analysis of the combined data received from PARADIGM-HF (LVEF eligibility ≤40%; n = 8399) and PARAGON-HF (LVEF eligibility ≥45%; n = 4796) trials have revealed that sacubitril/valsartan exceeded ACE inhibitors and ARBs in improvement of all-cause mortality, CV death or HF-related hospitalization [24]. These findings have been explained by beneficial capability of sacubitril/valsartan to tissue protection and thereby abrogation of pro-fibrotic signaling, attenuation of CV remodeling and improvement of vascular integrity. Indeed, it has found significantly decrease of circulating levels of numerous pro-fibrotic biomarkers, including aldosterone, soluble suppressor tumorigenisity-2, galectin-3, N-terminal pro-peptide of collagen I, N-terminal pro-peptide of collagen III, matrix metalloproteinase-2, matrix metalloproteinase-9 and their tissue inhibitors in patients treated with sacubitril/valsartan [25,26]. Nowadays ARNI, specifically sacubitril/valsartan, is recommended instead of ACEIs or ARB for patients with HFrEF who remained symptomatic despite optimal treatment with ACEIs/ARBs, β-blockers and MRAs [27].

ARNI in combined therapy of HF in routine & large clinical trials

The CHAMP-HF (Change the Management of Patients with Heart Failure) registry, which included the data about 3518 patients with established HFrEF from 150 primary care and cardiology practices in the USA, has unveiled significant gaps in prescription of the drugs and their dosing [28]. Unlike the guideline-directed medical therapy the only 1% of patients with HFrEF were simultaneously receiving target doses of ACEIs/ARBs/ARNI, β-blockers and MRAs. This was more than surprising because the Swedish Heart Failure Registry, which consisted of 12,866 outpatients with HFrEF in New York Heart Association functional class II–IV with LVEF ≤40%, has shown that from 34 to 76% of symptomatic HFrEF patients could have been eligible for treatment with sacubitril/valsartan in a routine [29]. Notably, the results received in the TITRATION trial [30] and PIONEER-HF trial [31] have shown that there was a great possibility to shorten a titration period of sacubitril/valsartan up to 1 week and even less without a loss of well tolerability. The network meta-analysis of 58 relevant randomized clinical trials that were performed in pre-SGLT2 inhibitor era (from 1987 to 2017) among HFrEF patients has shown an incremental benefit of the combinations of ARNI + β-blocker + MRA and ACEI + β-blocker + MRA + ivabradine in reductions in all-cause mortality (versus placebo) of 62 and 59%, respectively; and in all-cause hospitalizations with reductions

of 42% for both [32]. Thus, there is a new paradigm of HFrEF therapy based on the neurohumoral modulation, but it remains on demand in real clinical practice and the optimal timing for the initiation of valsartan/valsartan has to be determined [33].

Sodium-glucose co-transporter 2 inhibitors

Biological role of Na^+/H^+ exchanger

SGLT2 inhibitors were designed to selectively decrease in the resorption of glucose in the proximal renal tubules is result of inhibition of Na^+/H^+ exchanger (NHE) isoform 3. NHE is a widely expressed plasma membrane transport protein having N-terminal (membrane) and C-terminal (cytosolic) domains. The C-terminal domain is engaged in the regulation of the N-terminal membrane domain by its binding and ATP-related phosphorylation with extracellular signal-regulated kinase (ERK) and serine/threonine kinase B-Raf [34]. Finally, ERK pathway mediates activity, structure and function of N-terminal membrane NHE protein [35]. There are at least ten isoforms of NHE, which are constitutively expressed in numerous tissues, such as kidney, myocardium, intestitum, lung, liver, muscles, placenta, testis and ovaries. NHE isoform 1 is mostly expressed in heart, vasculature; NHE isoforms 1, 2 and 4 are noticed in intestinum, whereas NHE isoform 3 is represented in renal proximal tubule [36,37].

Animal studies have shown that main biological function of NHE isoform 3 is prevention of metabolic acidosis via pH regulation, regulation of intracellular Na^+ concentration, volume depletion and reduction of blood pressure [38,39]. Indeed, inhibition of NHE isoform 3 with dipeptidyl-peptidase-4 was closely associated with natriuresis. Therefore, carbohydrate homeostasis by reabsorption of the filtered glucose was regulated by ERK-mediated NHE isoform 3 activity in the proximal tubule [40].

NHE is activated in results of elevation of pH and intracellular sodium concentration, as well as in response to other stimuli, such as hormones (epinephrine, aldosterone and parathormone), regulatory peptides (heat shock proteins), biomechanical stress, inflammation and ischemia/hypoxia [41–43]. Physiologically renal sympathetic nervous system is the main regulator of expression of both NHE isoforms 1 and 3 in the kidney [44].

Molecular mechanisms underlying beneficial effects with SGLT2 inhibitors

SGLT2 inhibitors ensure decrease in fasting glucose, glycated hemoglobin and weight loss, as well as enhance ketone metabolism, fasting mimicry, reduce intraglomerular pressure, and thereby lead to favorable CV and renal effects [45]. The underlying molecular and pathophysiological mechanisms for CV and renal protection by SGLT2 inhibitors in HF are complex, multifactorial and not fully clear. Initially, it has been postulated that SGLT2 inhibitors directly inducing diuresis and natriuresis and regulating NHE at the level of the myocardium and kidney, are able to decrease in fluid retention, peripheral resistance, preload and postload [46]. Probably, other systemic and local effects of SGLT2 inhibitors, such as increase in the production of erythropoietin, promoting growth and differentiation of proangiogenic progenitor cells, suppression of apoptosis, and prevention of arrhythmogenic activity, can be ensured by Ca^{++}/calmodulin-dependent protein kinase/NHE-signaling mechanism [47,48]. Then it has been determined evidence regarding their pivotal role in an attenuation of myocardial energy metabolism and substrate utilization, improving vascular structure and function, suppression of myocardial fibrosis, oxidative stress, inflammation and a modulation of adipocytokine production [49–51]. Nevertheless, SGLT2 inhibitors can increase of circulating levels of ketones in result of suppression of aerobic glycolysis and declining ketone kidney clearance and thereby indirectly influence cardiac metabolism through activation of free fatty acids oxidation. Indeed, ketones are excellent alternative source for mitochondrial fatty substrate utilization in myocardium, especially in failing heart [50,51]. Primary impact of SGLT2 inhibitors on cardiac metabolism remains uncertain, while there is convincing suggestions that these drugs have hypoglycemic and pleiotropic effects that are corresponded by different mechanisms and that these underlying molecular pathways can be mediated by several NHE isoforms. Yet, SGLT2 inhibitors can induce increase in hematocrit, which promotes favorably effect in patients having ischemic cardiomyopathy, but this assumption was not supported by the results of recent clinical trials [52–54]. Therefore, accumulating evidence supported SGLT2 inhibitors shifted the ACE/ACE2 balance in favor of ACE2 [55,56]. It protected target organs against damage by modulating of the RAAS activity through decreasing angiotensin II levels, anti-inflammatory effects due to ADAM17-mediated ectodomain shedding, and attenuation of glucose homeostasis via several mechanisms, such as enhancing islet function, increasing β-cell proliferation and insulin content, and decreasing insulin resistance by expression of GLUT-4 [57,58].

The Figure 2 summarizes knowledge and hypothetical assumption regarding the underlying mechanism for tissue protection with SGLT2 inhibitors. These several possible mechanisms explain beneficial impact of SGLT2 inhibitors

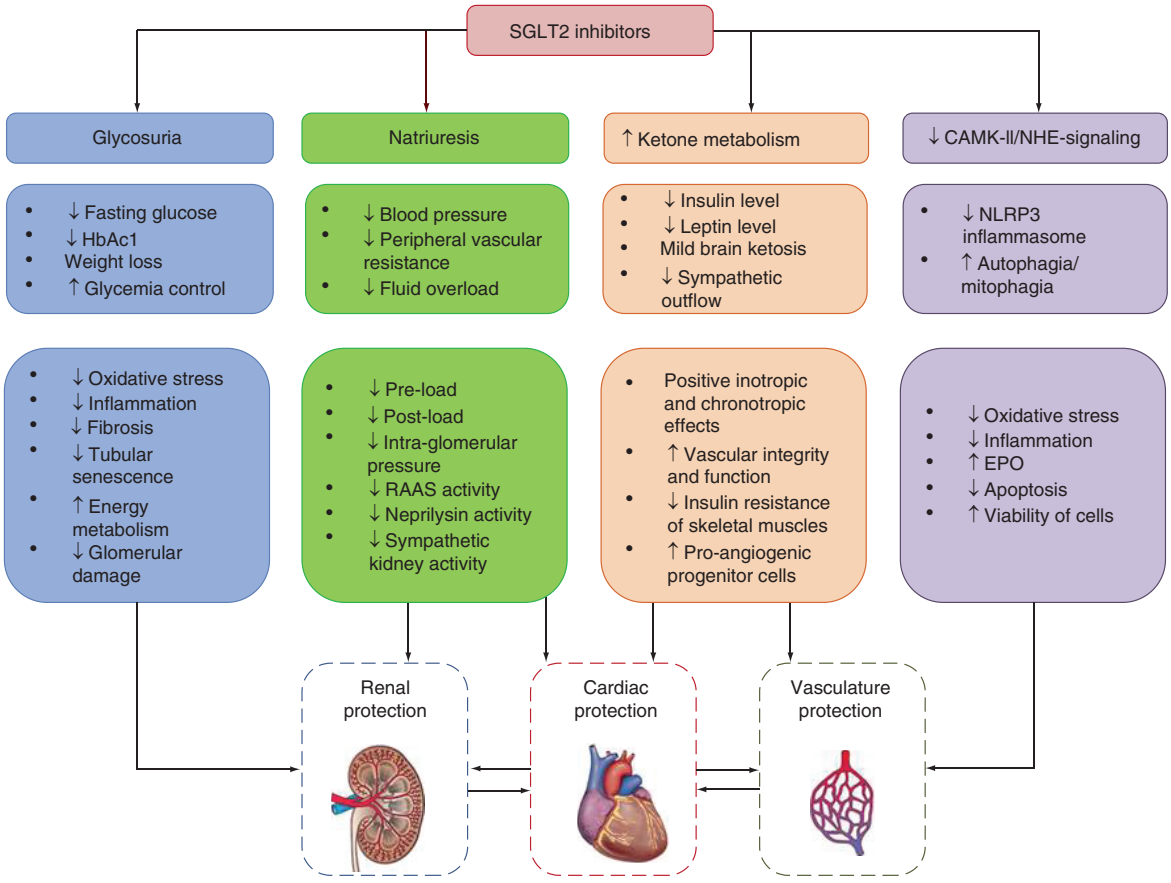

Figure 2. Potent mechanisms that are engaged in the tissue protection and attenuation of the clinical outcomes in heart failure patients receiving sodium-glucose co-transporter 2 inhibitors.
CAMK-II: Ca^{++}/calmodulin-dependent protein kinase; EPO: Erythropoietin; HbAc1: Glycated hemoglobin; NHE: Na^{+}/H^{+} exchanger; RAAS: Renin–angiotensin–aldosterone system.

on substantial improvement in hemodynamics, prevention of CV remodeling and renal injury, and inhibition of neurohormonal and inflammatory activation, which is crucial for HF development and progression in patients with T2DM [59,60].

SGLT2 inhibitors in large clinical trials for HFrEF/HFpEF

The cardiac and renal protective effects of SGLT2 inhibitors in connection with unprecedented improvement in survival and HF-related outcomes are proven in several large randomized clinical trials. Indeed, the remarkable results from the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcomes Event Trial in Type 2 Diabetes Mellitus Patients – Removing Excess Glucose) exhibited that patients at higher risk of CV disease having T2DM who received SGLT2 inhibitor empagliflozin had the superiority in both early and substantial reduction in major CV events (death from CV causes, nonfatal myocardial infarction or nonfatal stroke), hospitalization for HF and renal clinical outcomes when compared with those who were treated with placebo [61]. The ability of other SGLT2 inhibitors (canagliflozin, dapagliflozin and ertugliflozin) to reduce CV risk in diabetics was confirmed in several clinical trials [62–65]. In fact, dapagliflozin, empagliflozin, canagliflozin and ertugliflozin have obviously powerful class effects on cardiorenal outcomes [66,67].

Later two SGLT2 inhibitors – dapagliflozin and empagliflozin – have unveiled their ability to sufficiently reduce combined risk of CV death or HF hospitalization in patient population with HFrEF regardless of T2DM presence. The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, which enrolled 4744 patients with HFrEF (LVEF <40%) with and without T2DM, has demonstrated a significant decrease in a risk of worsening HF or death from CV causes among those who received dapagliflozin in comparison with HFrEF patients who were treated with placebo [54]. The EMPEROR-Reduced (Evaluation of the effect of sodium-glucose

co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction) trial has shown the beneficial effect of empagliflozin on combined CV death or HF hospitalization when compared with placebo (hazard ratio [HR] = 0.75; 95% CI: 0.65–0.86; $p < 0.001$) [68]. The total number of hospitalizations due to HF was also lower in the empagliflozin group in comparison with the placebo group (HR = 0.70; 95% CI: 0.58–0.85; $p < 0.001$), whereas CV mortality did not differ in both groups [52]. The meta-analysis of the data received from both the DAPA-HF trial and the EMPEROR-Reduced trial has revealed 13% reduction in all-cause mortality, 14% reduction in CV death. Therefore, the risk of the composite renal end point was also substantially reduced (HR = 0.62; 95% CI: 0.43–0.90; $p = 0.013$) [69]. Whether SGLT2 inhibitors exert favorable effects in HFpEF is not clearly understood, because the large clinical trials, such as the EMPEROR-preserved and the DELIVER (Dapagliflozin for Heart Failure with Preserved Ejection Fraction), which were specially designed for this matter, are still ongoing [70,71].

Comprehensive disease-modifying therapy versus conventional therapy of HFrEF

The most impressive clinical trials for SGLT2 inhibitors, which were recently completed, the DAPA-HF and the EMPEROR-Reduced, have enrolled patients with HFrEF who were treated according to modern clinical recommendations. The majority of the patients in the DAPA-HF trial and the EMPEROR-Reduced trial received ACEIs or ARBs, β-blockers and MRA, and even up to 14 and 17% of them, respectively, were treated with ARNI at the baseline. On the one hand, the impact of SGLT2 inhibitors on clinical outcomes in these trials did not relate to the concomitant medicine and was found in patients receiving loop diuretics to maintain euvolemic status and circulating levels of NT-proBNP <1500 pg/ml. On the other hand, the optimization of the fluid management and the support of LVEF with ARNI may influence the prognosis independently from SGLT2 inhibitor use. Do SGLT2 inhibitors exert sustainable positive effects on the natural evolution of HFrEF regardless of the use of the most powerful combination of ARNI + β-blockers +MRA called HF-modifying therapy? The cross-trial analysis, which is based on the data from HFrEF patients enrolled in three pivotal trials, EMPHASIS-HF (n = 2737), PARADIGM-HF (n = 8399) and DAPA-HF (n = 4744), has unveiled meaningful benefit of comprehensive disease-modifying therapy (ARNI, β-blocker, MRA and SGLT2 inhibitor) versus conventional (conservative) therapy (ACEI or ARB and β-blocker) [72]. Authors established that the cumulative treatment effect of new therapy on the primary end point of CV death or HF-related hospitalization was substantially higher than that was in conservative therapy (HR = 0.38; 95% CI: 0.30–0.47) [72]. Therefore, new strategy was more effective than conservative approach to reduce all-cause mortality (HR = 0.53; 95% CI: 0.40–0.70), CV mortality (HR = 0.50; 95% CI: 0.37–0.67) and hospital admission for HF (HR = 0.32; 95% CI: 0.24–0.43) [72]. Thus, these findings support the use of the combination of ARNI, β-blocker, MRA and SGLT2 inhibitor as a new therapeutic standard in the therapy of HFrEF.

Future perspective

Whether SGLT2 inhibitors will be able to potentiate the impact of RAAS antagonists and β-blockers on CV remodeling, as well as CV mortality and HF-related outcomes among HFpEF is not fully clear, but the results of recently completed large clinical trials allow us to expect that it would be. However, specially designed large clinical trials (the EMPEROR-preserved and the DELIVER) will definitely shed a light on the ability of the SGLT2 inhibitors to modify the development and progression of HFpEF. Although currently available SGLT2 inhibitors have a strict similarity in their pharmacokinetic characteristics and the effects on glycemic control, there is promising evidence that dual SGLT1/SGLT2 inhibition, which exerts multiple effects on glucose reabsorption inhibition in proximal renal tubule and intestinum, as well as acute and sustained release of glucagon-like peptide-1, can be more effective in HF patients than isolated either SGLT1 or SGLT2 inhibition [73,74]. Moreover, based on the data received recently in large clinical trials it seems to be obvious that SGLT1/SGLT2 inhibitors and ARMI might have at least close resemblance in clinical efficacy among patients with HFrEF regardless of T2DM. In addition, there is no possibility to define which of the SGLT inhibitors are superior to others due to lack of direct face-to-face comparisons, and it requires conducting large clinical trials in the future.

Conclusion

Both ARNI and SGLT2 inhibitors have an overlap in the spectrum of favorable molecular effects that contribute to tissue protection in HF. It has been suggested that neurohumoral modulation of NP system/RAAS by ARNIs and regulation of NHE activity by SGLT2 inhibitors well correspond to the reduction in blood pressure, water/sodium

homeostasis, energy metabolism attenuation, vasodilation and activity of endogenous repair system. Add-on HF therapy with SGLT2 inhibitor to ARNI will probably have serious synergic effect on cardiac and vascular remodeling and improving clinical outcomes.

Executive summary

Angiotensin receptor neprilysin inhibitors & sodium-glucose co-transporter 2 inhibitors in neurohumoral modulation

- The review has discussed that angiotensin receptor neprilysin inhibitors (ARNIs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors having strong overlap in the spectrum of molecular effects can demonstrate a synergy in contributing tissue protection and improving prognosis in heart failure (HF) patients.

Underlying molecular mechanisms of beneficial effects of ARNIs & SGLT2 inhibitors

- It has widely disputed the modulation of natriuretic peptides' system/renin–angiotensin–aldosterone system by ARNI and regulation of Na^+/H^+ exchanger activity by SGLT2 inhibitor in water/sodium homeostasis, energy metabolism attenuation, vasodilation, and activity of endogenous repair system.

ARNIs & SGLT2 inhibitors in large clinical trials for HF

- Being added to ARNI-based HF therapy SGLT2 inhibitor is able to give substantial positive impact on cardiac and vascular remodeling and consequently improve clinical outcomes in HF.

Author contributions

AE Berezin contributed to the conception and design of the manuscript. Both the authors participated in selection of articles, evaluation of their quality and writing of the final article. AE Berezin contributed to the critical revision of the article.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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