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SGLT2 inhibition in heart failure with reduced or preserved ejection fraction: Finding the right patients to treat

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Abstract. Girerd N, Zannad F. SGLT2 inhibition in heart failure with reduced or preserved ejection fraction: Finding the right patients to treat. *J Intern Med.* 2023;**00**:1–9.

Sodium–glucose transport inhibitors (SGLT2i) are effective in heart failure (HF) with ejection fraction (EF) <40% (referred to as HF with reduced EF – HFrEF) and left ventricular EF (LVEF) >40%. Current evidence suggests that SGLT2i should be initiated across a large spectrum of EFs and renal function in patients with HF and with and without diabetes. We reviewed the benefits of SGLT2i in the entire spectrum of HF and provided some clues that may guide physicians in their strategy of initiating and maintaining SGLT2i (with or without SGLT1i effect) therapy. Taken together, the evidence thus far arises from an array of trials

Sodium–glucose transport inhibitors (SGLT2i) have been shown to be effective in heart failure (HF) with ejection fraction (EF) <40% (referred to as HF with reduced EF – HFrEF) and left ventricular EF (LVEF) >40%. Recent guidelines have divided the latter category of patients with HF into mild EF fraction (when EF is 40%–50%; HFmrEF) and preserved EF (when EF is greater than 50%; HFpEF). Although some moderately sized trials enrolled patients with acute HF, most of which are enrolled with chronic stable HF. Current evidence suggests that SGLT2i should be initiated across a large spectrum of EFs and renal function in patients with HF and with and without diabetes.

Here, we reviewed the benefits of SGLT2i in the entire spectrum of HF and provide a few clues that may guide physicians in their strategy of initiating

performed in different settings (acute/chronic), risk categories, and phenotypes of HF (HFrEF/HFpEF), and in addition to the most common HF therapies, supports the homogenous effect of SGLT2i across a large spectrum of patients with HF. SGLT2i appear to be effective and well-tolerated drugs in the majority of clinical HF scenarios, regardless of LVEF, estimated glomerular filtration rate, diabetic status or the level of the acuteness of the clinical setting. Therefore, most patients with HF should be treated with SGLT2i. However, in the face of the therapeutic inertia that has been observed in HF over the past decades, the actual implementation of SGLT2i in routine practice remains the most significant challenge.

Keywords: cardiovascular diseases, heart failure, SGLT2i, sodium–glucose transport inhibitors

and maintaining SGLT2i (with or without SGLT1i effect) therapy.

Evidence of benefits of SGLT2i on cardiovascular outcomes in various settings of HF

Large outcome trials performed in patients with type 2 diabetes (T2D) showed that SGLT2i are associated with better cardiovascular outcomes in patients with diabetes [1–3], mainly with no prevalent HF. These initial findings, which were particularly convincing when considering the prevention of HF hospitalization, prompted trials testing SGLT2i in patients with prevalent HF, irrespective of the diabetes status.

In chronic HFrEF

Two large pivotal clinical trials performed in patients with HFrEF, DAPA-HF and

EMPEROR-Reduced provided key evidence supporting the major benefits related to SGLT2i use in chronic HFrEF [4, 5]. Both DAPA-HF and EMPEROR-Reduced included patients with HFrEF, regardless of diabetes status. The risk profile of patients enrolled in these trials was slightly different (with a higher risk profile in EMPEROR-Reduced) with age, LVEF and estimated glomerular filtration rate (eGFR) of approximately 65 years, approximately 30%, and 65 mL/min/1.73 m². Despite slight differences in population characteristics, the benefit of the primary outcome (cardiovascular mortality and hospitalization for HF and urgent visit resulting in intravenous therapy for HF in DAPA-HF) was almost identical (DAPA-HF: hazard ratio [HR] 0.74, 95% confidence interval 0.65–0.85, EMPEROR-Reduced: HR 0.75, 0.65–0.86). In DAPA-HF, all components of the primary composite outcome were significantly reduced, whereas in EMPEROR-Reduced, the benefit of the primary outcome was primarily driven by a reduction in hospitalization for HF. However, a meta-analysis of the two trials did not show any significant heterogeneity [6]. Taken together, these two trials served as the basis for IA recommendations in the most recent international HFrEF guidelines.

In chronic HFmrEF and HFpEF

The EMPEROR-Preserved trial specifically evaluated the effect of SGLT2i in patients with LVEF of 40% or more [7]. The effect of empagliflozin on the composite of CV death or hospitalization for HF was assessed in 5988 patients with classes II–IV HF and LVEF 40%. The reduction in the primary outcome was almost identical to that observed in HFrEF (HR 0.79, 0.69–0.90, $p < 0.001$) and was mainly related to a lower risk of hospitalization for HF in the empagliflozin group (similar to that observed in the EMPEROR-Reduced trial). It should be highlighted that this was the first trial performed in patients with HFpEF that indisputably showed positive results. In addition, the DELIVER trial (NCT03619213) [8], which tested the effect of dapagliflozin on the risk of the first occurrence of the composite or CV death, HF hospitalization and urgent HF visit in patients with LVEF of 40% or more similarly, reduced the primary outcome of worsening HF (which was defined as either an unplanned hospitalization for HF or an urgent visit for HF) or cardiovascular death (HR 0.82, 0.73–0.92, $p < 0.001$) [9]. This result further

strengthens evidence supporting the homogeneous effect of SGLT2i across the LVEF strata.

Taken together, the results of the aforementioned HFrEF and HFpEF trials indicate that SGLT2i (and certainly empagliflozin) are beneficial regardless of LVEF. To further investigate this aspect, Butler et al. evaluated the effect of empagliflozin in the meta-analysis of EMPEROR-Reduced and EMPEROR-Preserved. The HRs for first HF hospitalization were very similar up to an LVEF of 64% (HR 0.73, 0.55–0.96 in LVEF <25%, HR 0.63, 0.50–0.78 in LVEF 25%–34%, HR 0.72, 0.52–0.98 in LVEF 35%–44%, HR 0.66, 0.50–0.86 in LVEF 45%–54%, HR 0.70, 0.53–0.92 in LVEF 55%–64%, whereas it was close to 1 in LVEF > 65% (HR 1.05, 0.70–1.58) [10]. These results strongly suggest that the effect of SGLT2i is surprisingly homogeneous (HR approximately 0.70) in the vast majority of patients with HF, as patients with LVEF greater than 65% are rather scarce and may have different pathophysiologies.

The SCORED trial randomized patients with T2D, chronic kidney disease (CKD) (eGFR 25–60 mL/min/1.73 m²) and risks for cardiovascular disease to receive either sotagliflozin or placebo. Approximately 30% of the included patients had HF, most of which (15%) had HFpEF. Sotagliflozin was associated with a 25% reduction (HR 0.74, 0.63–0.88, $p < 0.001$) in the rate of the primary composite end-point events of the total number of deaths from cardiovascular causes, hospitalizations for HF, and urgent visits for HF [11]. These additional results further strengthen the evidence of the benefits of SGLT2i in a variety of CV settings, with or without HF, regardless of the HF phenotype.

In acute settings

The EMPA-RESPONSE-AHF trial evaluated the effect of empagliflozin in patients with acute HF (mean LVEF, 36%) on symptoms, diuretic response and change in NT-pro-BNP levels from baseline to day 4, as well as on the combined endpoint of in-hospital worsening of HF, all-cause mortality and HF hospitalization at day 60 ($n = 80$) [12]. Despite the limited size of this pilot trial, empagliflozin increased urinary output and reduced the combined clinical endpoint compared with the placebo.

The SOLOIST-WHF trial evaluated the effect of SGLT2i initiated either during or soon after

a hospital stay for worsening HF in patients with reduced or preserved LVEF (although most patients had HFrEF, and the median LVEF in the trial was 35%) [13]. Sotagliflozin reduced (by approximately 30%) the number of deaths from cardiovascular causes, hospitalizations and urgent visits for HF as compared to placebo (HR 0.67, 0.52–0.85). The effects of sotagliflozin on cardiovascular death and first hospitalization for worsening HF were similar (HR 0.71, 0.56–0.89). Although the results of this trial are consistent with those of other HF SGLT2i trials, it must be noted that only patients with T2D were enrolled. Furthermore, sotagliflozin is a dual SGLT inhibitor with a potentially pharmacological profile different from that of SGLT2i [14].

The EMPULSE trial evaluated the effect of early initiation of SGLT2i in acute HF (mean LVEF, 31%). The analysis used the Win Ratio, hierarchically considering four events as follows: (1) death, (2) the number of hospitalizations for HF and/or urgent HF visits and/or unplanned outpatient visits, (3) time to first HF event and (4) change from baseline in Kansas City Cardiomyopathy Questionnaire Score. Empagliflozin significantly improved the conditions listed above by approximately 30% (Win Ratio 1.36, 1.09–1.68, $p = 0.005$) [15]. Taken together, the results of the EMPA-RESPONSE-AHF, SOLOIST and EMPULSE trials suggest that SGLT inhibitors may be safely initiated in patients hospitalized for worsening HF and are associated with clinically meaningful benefits, consistent with the benefits observed in the chronic stable setting.

In the presence/absence of diabetes

Although SGLT2i were initially developed as glucose-lowering agents in T2D, no significant interaction with diabetes was identified in HF trials that enrolled patients with and without diabetes (p for interaction = 0.81 in the meta-analysis of EMPEROR-Reduced and DAPA-HF [6]). Further, estimates of the SGLT2i effect have been reported to be very similar in patients with or without diabetes [4, 5, 7], firmly establishing that SGLT2i are independent of the underlying diabetic status.

In the presence/absence of CKD

SGLT2i provide a major benefit in CKD, as exemplified by the results of the DAPA-CKD trial; patients with an eGFR of 25–75 mL/min/1.73 m² and a urinary albumin-to-creatinine ratio of 200–5000 mg/g randomized to dapagliflozin expe-

rienced a markedly reduced risk of death from cardiovascular causes or hospitalization for HF (HR 0.71, 0.55–0.92, $p = 0.009$) [16]. These results will soon be amplified by the results of the EMPA-Kidney trial which was recently terminated prematurely for an excess of benefits [17].

More specifically, in patients with HF, the SGLT2i effect has repeatedly been reported to be unaffected by CKD and/or impaired eGFR. This was specifically assessed in the meta-analysis of EMPEROR-Reduced and DAPA-HF, where a p -value for the interaction of 0.44 was reported with an eGFR of <60 mL/min/1.73 m² [6]. In an analysis dedicated to cardiorenal interactions in reduced EMPEROR, the risk of the composite kidney outcome was reduced similarly in patients with and without CKD, and the effect of empagliflozin on the primary composite outcome was consistent across a broad range of baseline eGFR and albuminuria [18]. Likewise, a similar pattern of association was observed in patients with eGFR of <60 mL/min/1.73 m² and >60 mL/min/1.73 m² (HR for the primary endpoint 0.78, 0.66–0.91 and 0.81, 0.65–1.00, respectively) in the EMPEROR-Preserved trial [7]. Similarly, the benefit of SGLT2i was unaffected by eGFR status in acute settings, as emphasized by the EMPULSE trial [15].

On top of background guideline therapy

SGLT2i are well-tolerated and provide clinical benefit in patients treated with other HF drugs, such as renin-angiotensin inhibitors, β -blockers and MRAs [19–21]. Of note, ARNi and SGLT2i have different mechanisms of action in HFrEF [19, 22]. SGLT2i are effective regardless of background ARNi treatment [6]. The use of SGLT2i may favour the initiation of other drugs. Indeed, in the EMPEROR-Reduced trial, empagliflozin use was associated with a lower frequency of discontinuation of MRAs [HR 0.78, 0.64–0.96] in users during follow-up [21] and was also associated with a lower risk of severe hyperkalaemia, suggesting that SGLT2i may enable better use of MRAs.

The intrinsic risk of patients

DAPA-HF identified a significant benefit of SGLT2i in relatively low-risk patients with HFrEF, whereas the EMPULSE and SOLOIST trials reported similarly important benefits in much higher risk populations. In addition, the efficacy of empagliflozin is homogeneous across risk levels

derived from biomarker-driven prognostic models in the EMPEROR-Reduced trial [23]. The efficacy of SGLT2i is consistent across a wide spectrum of risk categories.

Overall assessment. Taken together, the evidence from an array of trials performed in different settings (acute/chronic), risk categories and phenotypes of HF (HFrEF/HFpEF), and on top of the most common HF therapies, supports a homogenous effect of SGLT2i across a large spectrum of patients with HF (Fig. 1). This consistent effect might arise from its underlying mechanisms of action. Current evidence [24], including proteomics data in the EMPEROR trials, suggested that SGLT2i therapy effectively enhances autophagic flux, nutrient deprivation signalling and transmembrane sodium transport [25]. These very broad biological mechanisms are understandably not highly related to specific conditions (such as diabetic status), which may explain why SGLT2i effects are remarkably stable across clinical trials performed in various settings.

Safety profile of SGLT2i and consequences on therapy initiation, titration and maintenance

An 'eGFR dip' is expected in the first few weeks following SGLT2i initiation [26, 27]. However, this initial change is reversible and is not associated with a lower SGLT2i benefit or later adverse outcomes. Specifically, in patients randomized to empagliflozin in the EMPEROR-Reduced trial, the risk of cardiovascular and renal outcomes did not differ between patients with decreased or increased early post-treatment eGFR, whereas patients in the placebo group with decreased early post-treatment eGFR had a higher risk of those events [28]. This differential association between renal function changes and subsequent outcomes highlights the innocuity of the early eGFR dip following SGLT2i initiation. Therefore, an initial drop in eGFR of less than 30% should not lead to the discontinuation of therapy. A similar early change in eGFR is a hurdle when introducing renin-angiotensin inhibitors [29] and MRAs and is, unfortunately, a pretext for frequent early discontinuation of therapy. Importantly, the effect of SGLT2i is not altered by poorer initial renal function (considering that patients included in HF trials had eGFR of >20 mL/min per inclusion criteria) [7, 9, 30].

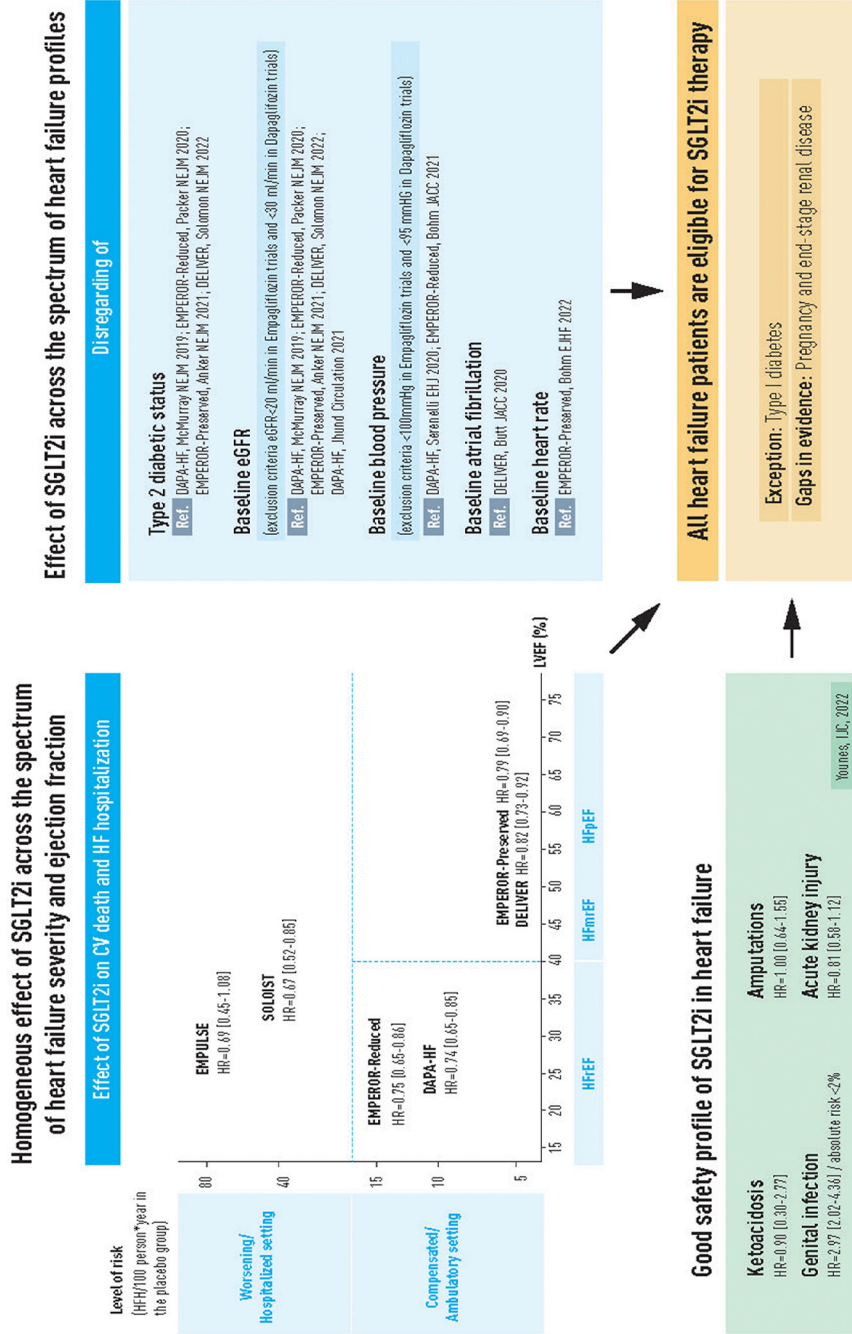
The incidence of the main adverse effects of concern with the other foundational treatments of HF

[29, 31], such as hypotension, significantly worsening renal function and volume depletion, was similar in patients treated with SGLT2i and placebo in several trials. The main adverse event related to SGLT2i is genital tract infection [32, 33], which is very uncommon in patients without diabetes [3, 4]. In addition, in patients with diabetes, an increased risk for ketoacidosis has been reported; however, the additional absolute risk of this complication is as low as 0.3% per year [34].

Of particular interest is the fact that SGLT2i have a relatively weak effect on blood pressure (BP) [35]; BP was modestly decreased only in patients with the highest BP and was not associated with hypotension symptoms in most patients. Interestingly, in the SCORED trial, dual SGLT1i/SGLT2i treatment was associated with a moderate increase in SBP when BP was below 110 mmHg [35], where sotagliflozin could consequently be continued in patients with persistently low BP [36]. In any case, the favourable effects and safety of SGLT2i in HFrEF are not dependent on baseline BP, as shown in both the EMPEROR-Reduced and DAPA-HF trials [35, 37]. Likewise, baseline heart rate [38] and the presence/absence of atrial fibrillation [39] did not seem to affect the SGLT2i effect and safety profile.

Because of the favourable safety profile, SGLT2i persistence is likely to be easier to achieve in the context of frequent safety-related discontinuation of other HF drugs.

As it has been suggested that providing a low dose of all four pillars of HFrEF treatment appears more reasonable and efficient than trying to obtain a maximal dose of one or a limited number of HF treatments, [31] it is recommended that RAASi, ARNi, MRA and beta-blocker therapies are started at low doses and gradually up-titrated to maximally tolerated doses. This 'start low – go slow' strategy is challenging to achieve, requiring frequent visits and monitoring of serum potassium, renal function, heart and BP. As a result, most patients remain underdosed, as emphasized in international studies. Of note, Greene et al. showed in the CHAMP-HF registry [40] that among eligible patients, approximately one third of patients were not prescribed ACEi/ARB/ARNi and beta-blockers, and two thirds were not prescribed MRAs. In addition, when medications were prescribed, few patients were receiving target doses of ACEi/ARB, ARNi and beta-blockers (all <30%). In contrast, one



single upfront dose of SGLT2is was recommended, with no requirement for titration.

The situation in HFpEF is significantly different. SGLT2i is the only treatment that provides undisputed benefits for HFpEF. Consequently, its use should be favoured over any other medical treatments in this population. However, it should be noted that the HFrEF/HFpEF classification has some limitations. First, the benefit from most HF drugs only fades away above a 55% LVEF threshold [41]. Most importantly, the segmentation of HF-based LVEF has recently been challenged, mainly because LVEF mostly reflects the volume rather than the contractility of the heart [41]. HF might represent a continuous entity rather than a segmented entity.

Patients with HF eligible for SGLT2i therapy

All patients with HF should be treated with SGLT2i. It would be easier to identify patients who may not be suitable for SGLT2i initiation because they represent a much smaller or limited group of patients.

When are SGLT2i contraindicated?

SGLT2i are currently not indicated in type 1 diabetes. Although reassuring results have been reported from the SGLT2i experience in patients with type 1 diabetes [42], the available level of evidence is insufficient to permit the use of SGLT2i in this population.

Sotagliflozin and dapagliflozin can be initiated only in patients with eGFR of >25 mL/min/1.73 m², whereas empagliflozin can be initiated to 20 mL/min/1.73 m². However, there are no data on the use of SGLT2is in patients with end-stage renal disease and/or on haemodialysis.

SGLT2i are associated with an increased risk of ketoacidosis. Rather than contraindicating patients at risk of ketoacidosis, the Canadian Diabetes Association Clinical Practice recommended that insulin should be stabilized in patients with insulin deficiency before starting an SGLT2i, and SGLT2i should be withheld only when a precipitating factor of ketoacidosis occurs (acute illness, surgery, dehydration or excessive alcohol intake). This pragmatic approach makes the vast majority of patients with T2D eligible for SGLT2i treatment. However, in the setting of HF trials, the absolute risk of ketoacidosis remains less than 2% [33].

Other conditions that were listed as exclusion criteria in most HF trials may be perceived as conditions where evidence is lacking rather than true contraindications (for instance, restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic [obstructive] cardiomyopathy or uncorrected primary valvular disease). In fact, in most of the above-mentioned heart conditions, no classical pharmacological treatment for HF has been proven to be beneficial.

Most common situation facing a patient with HF

In most instances, when facing a patient with HF, regardless of LVEF, setting, BP, and eGFR (if >20 mL/min), the most likely scenario is that SGLT2i is one of the (if not the best) therapeutic options to be considered. In most patients, introducing SGLT2i is probably easier or more likely to be retained than other pharmacological choices. This makes SGLT2i initiation a suitable optimization option for HF in the majority of patients.

This is especially true for patients with HFpEF, in whom no other unquestionably effective treatment exists.

Initiating SGLT2i therapy before or after achieving the maximally tolerated dose of guideline-directed medical therapy before?

In HFrEF, SGLT2i were tested before RAASi/ARNi, β -blockers and MRAs. Initiating the effect of SGLT2i in patients naïve to any one of these therapies would not be evidence-based. Therefore, sooner than later, all patients with HFrEF should receive foundational therapies. It is expected that the cumulative benefit will be substantial [43, 44]. The use of SGLT2i along with ARNi, β -blocker and MRAs versus a more conservative ACEi/ β -blocker approach resulted in a more than 60% reduction (HR = 0.38, 0.30–0.47) in the risk of cardiovascular death or hospital admission for HF [43] and 8.3 additional years free of events in patients aged 55 years [43].

Although challenging to apply, polypharmacy is likely to be the most reasonable approach to the treatment of patients with HF, and the use of SGLT2i is expected to be the easiest to implement. Yet, to favour the implementation of all four drugs and fight therapeutic inertia, it seems reasonable to empower dedicated healthcare organizations' strategies to develop a global response to

fight therapeutic inertia, which has been reviewed elsewhere [45]. Briefly, disease management programmes, usually heavily relying on HF nurses, HF clinics and multidisciplinary HF team management for hospitalized patients, are among the solutions that could strongly favour the implementation of HF drugs, including SGLT2i [45].

Conclusion

SGLT2i are a major addition to HF treatment, regardless of LVEF, eGFR, diabetic status or the level of the acuteness of the clinical setting. SGLT2i appear to be effective and well-tolerated drugs in the majority of clinical HF scenarios (Fig. 1). Therefore, most patients with HF should be treated with SGLT2i. However, considering the therapeutic inertia observed in HF over the past decades [45], the issue of the actual implementation of SGLT2i in routine practice remains a source of concern. Given the multiplicity of currently available HF drugs, the best healthcare organization to achieve effective HF treatment is of paramount importance. The challenge of how to implement SGLT2i in routine practice appears as much more challenging than the identification of good candidates for SGLT2i implementation.

Author Contributions

Nicolas Girerd: Conceptualization-equal; writing – original draft. Faiez Zannad: Conceptualization-equal, writing – review.

Conflict of interest statement

F.Z. reports personal fees from Boehringer Ingelheim, Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, Bayer and Cellprothera outside of the submitted work, and others support from cardiovascular clinical trialists and cardiorenal outside of the submitted work. He has served on the advisory board, steering committee or executive committee for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardior, Cereno Scientific, Cellprothera, CEVA, CVRx, KBP Biosciences, Novartis, Novo Nordisk, Merck, Roche and Vifor Fresenius and is the co-founder of CardioRenal, CVCT and Eshmoun.

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