The serendipitous story of SGLT2 inhibitors in heart failure: New insights from DECLARE-TIMI 58 [Editorial]

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10.1161/CIRCULATIONAHA.119.040514

The Serendipitous Story of SGLT2 Inhibitors in Heart Failure: New Insights from DECLARE-TIMI 58

Running Title: *Verma et al.; SGLT2 Inhibitors in Heart Failure*

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Diabetes intersects with cardiovascular disease at every level. While there has been much focus on understanding atherosclerotic complications, less well appreciated is the relationship between diabetes and heart failure. In addition to being a key and independent risk factor for the development of heart failure,[1] diabetes is also one of the most important adverse prognostic factors in those with established heart failure with either reduced or preserved ejection fraction.[1,2] Diabetes is associated with a high prevalence of unrecognized left ventricular diastolic and systolic dysfunction, and accelerates the development of overt heart failure compared to similar patients without diabetes.[3] In addition to cardiac predictors such as left ventricular dysfunction, hypertrophy, and coronary artery disease, features of diabetes associated with the development of heart failure include poor glycemic control, longer duration of diabetes, insulin treatment, and the presence of microvascular complications, such as retinopathy or nephropathy.[2, 4] Finally, data from randomized trials and registries remind us that heart failure is numerically nearly as common as ischemic complications in patients with type 2 diabetes, and remains one of the leading causes of hospitalizations in this population.[1, 2] While conventional risk factor control can reduce ischemic complications, heart failure risk remains a recalcitrant problem in diabetes for which intensive glycemic control has had little benefit.

The serendipitous story of SGLT2 inhibitors and heart failure stems from the EMPA-REG OUTCOME trial,[5] which unexpectedly demonstrated a profound 35% relative risk reduction in hospitalization for heart failure in patients with type 2 diabetes and established atherosclerotic vascular disease (ASCVD) who were treated with empagliflozin. Two additional SGLT2 inhibitors, canagliflozin and dapagliflozin, have been studied in large cardiovascular outcome trials (the CANVAS Program[6] and DECLARE-TIMI 58,[7] respectively). Both confirmed the benefit of SGLT2 inhibitors on hospitalization for heart failure (HHF), the composite of HHF

or cardiovascular death (HHF/CV death), and renal composite outcomes. Importantly, these latter studies included people with type 2 diabetes with and without established ASCVD.

By contrast to the clear benefit on HHF, none of the three trials showed a convincing effect of SGLT2 inhibition on atherothrombotic events. A recent meta-analysis of the three trials confirmed the robust effect of SGLT2 inhibitors in reducing HHF/CV death by 23% with similar benefits across primary and secondary prevention patients and in those with and without a history of heart failure.[8] Worse initial renal function was associated with a higher HHF/CV death event rate, and SGLT2 inhibition appeared to offer greater risk reduction in heart failure in the setting of reduced eGFR.[8] The traditional atherosclerotic composite outcome of major adverse cardiovascular events (MACE) was reduced, but only modestly, by 11%, with this benefit only clearly apparent in patients with ASCVD.[8]

Two analyses from the DECLARE-TIMI 58 trial are published in this issue of the *Journal* and extend our understanding of dapagliflozin in individuals with and without a prior MI,[9] and the according heart failure status and baseline ejection fraction.[10] Among the 17,160 patients with type 2 diabetes randomized to receive dapagliflozin or placebo in DECLARE-TIMI 58, 6,974 had known ASCVD, of which 3,584 had a history of MI, with a median duration from their last event of 5.4 years.[9] As observed in the other trials, patients with a prior MI were at ~2-fold higher risk for both MACE and HHF/CV death.[11] Dapagliflozin significantly reduced MACE by 16% (HR 0.84, 95% CI 0.72-0.99, P=0.039) in those with a history of prior MI, but not among those with no prior MI but with established ASCVD (HR 0.98, .0.81-1.19; p=0.85;) The effect in patients with prior MI translated into an absolute risk reduction of 2.6% and a number needed to treat (NNT) of 38 over a 4-year period (Figure 1A). These benefits were driven by reductions in recurrent MI with numerical trends towards fewer coronary heart disease

(CHD) death (HR 0.84), all-cause mortality (HR 0.83), and the composite of CHD death, non-fatal recurrent MI or sudden death (HR 0.81). The MACE benefits appeared greater in those who had had a recent MI (< 2 years ago) with statistical evidence supporting the observation that this benefit seemed to be time-dependent. Given that the number of patients in this subgroup were small, this finding should be considered hypothesis-generating. In patients without a history of a prior MI, or in those with ASCVD but without a prior MI, there were no MACE benefits observed. In contrast, the benefit on HHF/CV death was observed across all subgroups (and was largest in absolute terms in patients with prior MI). Overall, these findings are consistent with the suggestion from the metanalysis that SGLT2 inhibitors can reduce coronary events in patients at high risk of such outcomes, the best example of which may be patients particularly those with recent acute MI.

In the second analysis, Kato and colleagues address another important and previously unanswered question about the heart failure phenotype in patients included in the SGLT2 inhibitor trials and whether baseline ejection fraction (EF) modifies the effect of therapy. Data on baseline heart failure status were available for all 17,160 participants DECLARE-TIMI 58 and EF data were collected in ~5,000 patients. The authors defined heart failure and a reduced ejection fraction ("HFrEF") as the presence of a reduced EF (<45%), whether the patient had a history of heart failure or not. In total, 671 patients (3.9%) met this definition although only 408 had a history of heart failure. The median EF of the HF patients was 38% and most were in either New York Heart Association class I or II (patients in NYHA IV were not eligible). A further 1,316 patients (7.7% of the total) had a history of HF without a reduced EF (808 with a documented EF≥45% and 508 without a documented EF) and were classified as HF without known reduced EF. The remaining 15,173 patients had no history of HF and no documented

reduced EF. The rate of HHF/CV death in patients assigned to placebo in each of these three patient groups was 27.1%, 14.8% and 3.9%, respectively (and was highest in the "HFrEF" patients with a history of heart failure).

Dapagliflozin led to a greater reduction in HHF/CV death in patients with "HFrEF" compared to patients without "HFrEF" (HR 0.62 vs. 0.88; $P_{interaction}$=0.046). Among the patients without "HFrEF", there was no heterogeneity of treatment-effect between patients with HF without known reduced EF and those with no history of heart failure. The larger treatment-effect in patients with "HFrEF" seemed to be driven by a greater reduction in CV death (HR 0.55 "HFrEF" vs. 1.08 in those without "HFrEF"). The NNT over 4 years in patients with "HFrEF" was 11, 19 and 16 for HHF/CV death, CV death and all-cause mortality respectively (Figure 1B). Conversely, when heart failure hospitalization alone was examined, the benefit of dapagliflozin was more consistent across all patient groups. These findings must be treated with caution given that they reflect subgroup analyses, and because there are many data on EF missing. However, several of the observations are notable. Firstly, the prevalence of reduced EF was perhaps higher than might be expected. Of the 1724 patients with a history of heart failure, 408 (24%) had heart failure with reduced EF, 808 heart failure with preserved EF (45%) and 508 heart failure with unknown EF (29%); a further 263 patients without a history of heart failure had a documented reduced EF. Often the focus in diabetes has been on heart failure with preserved EF, which although more common, is not the sole heart failure phenotype and carries considerably less risk of adverse outcomes than heart failure with reduced EF. More surprising, perhaps, is the suggestion that it is patients with heart failure and reduced EF who benefit most from SGLT2 inhibitors, through reduction in cardiovascular death. This preliminary observation is intriguing but based on small numbers (<100 cardiovascular deaths in each heart failure subgroup) and is

thus purely hypothesis generating. Fortunately, however, the hypothesis that SGLT2 inhibitors might reduce HHF/CV death is being tested prospectively in heart failure with reduced and preserved ejection fraction.

Several mechanism(s) have been suggested to mediate the cardiorenal benefits of SGLT2i.[12] Briefly, these include improvement in filling conditions (through a reduction in preload and afterload), changes in left ventricular wall stress, and improved myocardial energetics .[12, 13] In a recent randomized study, empagliflozin was demonstrated to promote a reduction in left ventricular mass index as assessed by cardiac magnetic resonance imaging over a 6-month period in patients with type 2 diabetes and coronary disease (EMPA-HEART Cardiolink-6 Trial – ClinicalTrials.gov Identifier: NCT02998970[14]). These data suggest that SGLT2i may promote reverse cardiac remodeling, and reduce left ventricular wall stress, which provide translational clues to the heart failure benefit noted in clinical trials.

What are the key learnings from these two analyses? In general, physicians should be aware that diabetes adversely affects the pump (heart failure), pipes (atherosclerosis) and filter (renal disease), and that these effects can occur independently.[15] In patients with diabetes who have had a prior MI, the use of an SGLT2 inhibitor should be strongly considered as part of routine secondary prevention. In these individuals, SGLT2 inhibitors will reduce ischemic, heart failure and renal events, benefits which appear to be mediated largely via glucose-independent mechanisms. The absolute risk reduction for MACE in post-MI patients are similar and additive to what are observed with antiplatelet therapies and intensive LDL-C lowering in recent trials. Whether patients with a *recent* acute coronary syndrome can also be treated safely and effectively with a SGLT2 inhibitor has not been studied, and a definitive recommendation cannot be given. This may be a useful area for further investigation.

For patients with diabetes and without a history of a prior MI or ASCVD, but with multiple risk factors, SGLT2 inhibitors have still been shown to reduce incident heart failure and worsening renal function. In these individuals at much lower risk of atherothrombotic events, SGLT2 inhibitors have not been shown to reduce MACE.

As for patients with heart failure, especially heart failure with preserved EF, we suggest waiting for the results of the dedicated studies with SGLT2i which are ongoing in people with heart failure (and CKD). Combining SGLT2 inhibitors with other diuretics and other drugs which reduce blood pressure may not be straightforward and the initial small decrease in eGFR with SGLT2 inhibition may also be potentially problematic in patients who often have markedly impaired renal function and who are receiving renin-angiotensin-aldosterone blocking agents. The ongoing trials will also answer the two remaining questions about the potential use of these drugs in patients with heart failure – can they be used in patients without diabetes and can they be used in patients hospitalized with acute decompensation?

Acknowledgments

The authors thank H. Teoh, (St. Michael's Hospital, Toronto, ON, Canada) for editorial assistance.

Disclosures

Dr. Verma holds a Tier 1 Canada Research Chair in Cardiovascular Surgery; and reports receiving research grants and/or speaking honoraria from Amgen, AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Servier and Valeant. He is a member of the scientific excellence committee of the EMPEROR-

Preserved and EMPEROR-Reduced trials; a member of the scientific committee of the DETERMINE-A and DETERMINE-B trials; a member of the global expert panel of the SELECT study; and a national lead investigator of the Dapa-HF, DELIVER, DETERMINE-A, DETERMINE-B, EMPEROR-Preserved, EMPEROR-Reduced, SELECT and SOLOIST studies. Dr. McMurray's reports that his employer, the University of Glasgow, paid for his participation in clinical trial committees by AbbVie, AstraZeneca, Amgen, Bayer, Bristol-Myers Squibb, Dalcor, GlaxoSmithKline, Merck, Novartis, Resverlogix, Stealth and Theracos. In addition, his travel and accommodation costs for attendance at meetings related to some of the clinical trials have been funded by these sponsors. Dr McMurray's employer has also paid for his attendance at advisory boards organized by Novartis and Sanofi-Aventis.

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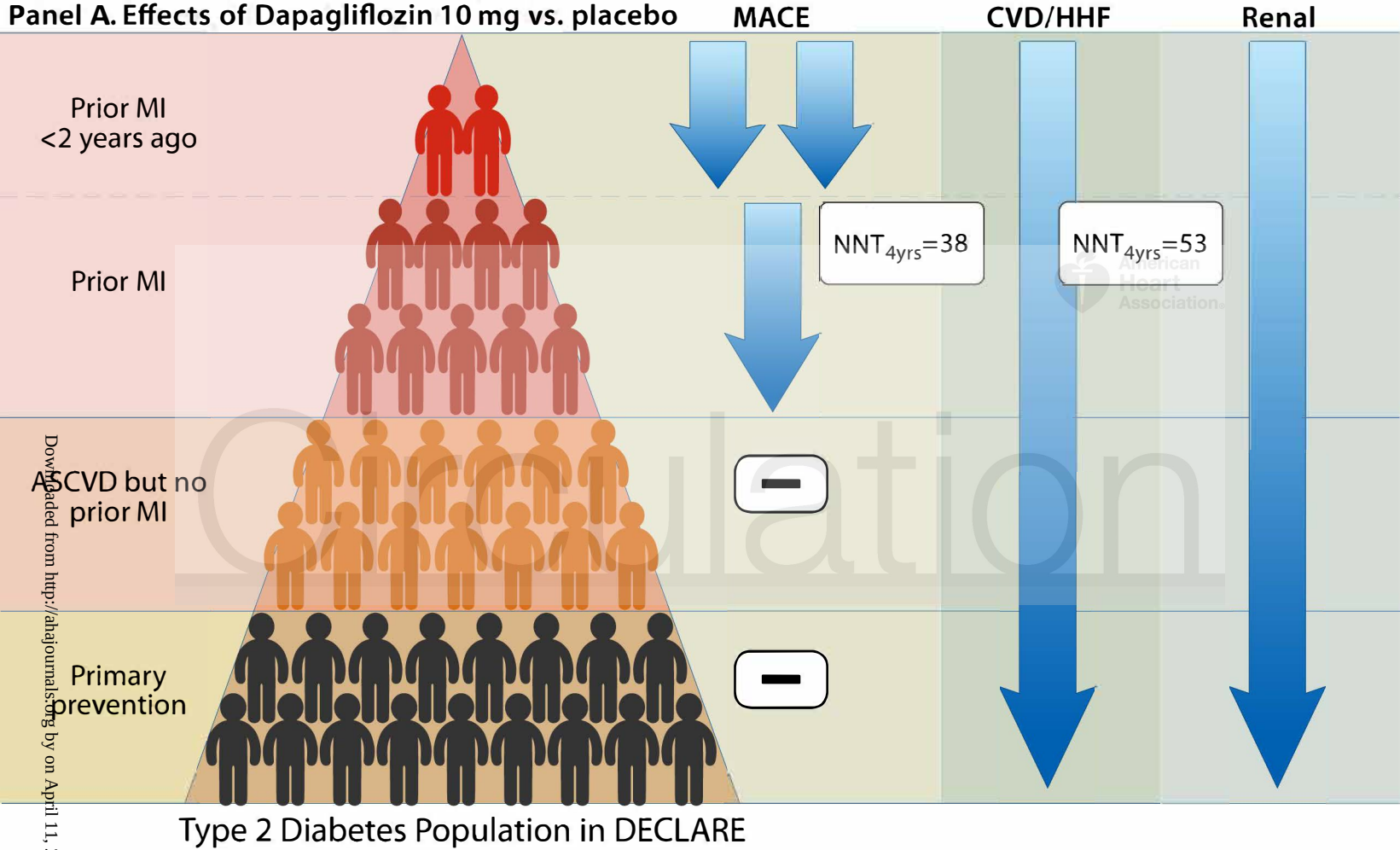
Figure Legend

Schematic representation of the effects of dapagliflozin vs. placebo in the DECLARE-TIMI 58 study based on clinical history and heart function. **Panel A:** Schematic representation of the effects of dapagliflozin vs. placebo in the DECLARE-TIMI 58 study as a function of a history of prior MI, those without MI but ASCVD and those with multiple risk factors only. There was a significant reduction in MACE in patients with a history of prior MI (but not in the other 2 groups), with an NNT=38 in this cohort. There appeared to be a greater benefit in those patients with type 2 diabetes who had had a recent MI (<2 years ago). The heart failure and renal benefits were observed across all groups. **Panel B:** Schematic representation of the effects of dapagliflozin vs. placebo in the DECLARE-TIMI 58 study based on baseline ejection fraction and history of heart failure. In patients who had an ejection fraction of less than 45% with or without a known history of heart failure (defined as the "HFrEF" group), there appeared to be reductions in CV and all-cause mortality. Both groups derived consistent benefits on reduction in heart failure hospitalizations.

ASCVD, atherosclerotic vascular disease; CV, cardiovascular; CVD, cardiovascular disease; EF: ejection fraction; HF: heart failure; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; NNT, number needed to treat.



Panel B. Efficacy of Dapagliflozin Based on Ejection Fraction