Diabetes medications with cardiovascular protection: the likelihood of benefit from combination therapy increases further following new evidence during 2020

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In every recent year, new cardiovascular outcome studies are published, illumining our understanding regarding diabetes medications with cardiovascular protection, and we have discussed these in our previous editorials.1–6 In 2020 two new studies from the sodium glucose transporter 2 (SGLT2) inhibitor class and one from the glucagon-like peptide-1 receptor agonist (GLP-1RA) class of antidiabetic medications are worth highlighting. Each provided new information to help our understanding about the cardioprotective benefits of these classes so that we can further improve patient care. On 16 June 2020, during the 80th Scientific Sessions of the American Diabetes Association virtual meeting, the results of the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) study were presented and have since been published in the New England Journal of Medicine.7,8 On 29 August 2020, during the European Society of Cardiology – The Digital Experience Congress 2020, the results of the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) were presented and published simultaneously in the New England Journal of Medicine.9,10 The study was then presented in detail on 24 September 2020 during the European Association for the Study of Diabetes Virtual Congress (EASD) 2020.11 With regard to the GLP-1RA class, some further cardiovascular outcome data were presented at the EASD 2020 in the form of a post hoc analysis of pooled data from the LEADER, SUSTAIN 6 and PIONEER 6 cardiovascular outcome studies.12

SGLT2 inhibitors

VERTIS CV was a randomised controlled trial of the SGLT2 inhibitor ertugliflozin versus placebo in 8,246 people with type 2 diabetes all of whom had prior cardiovascular disease.7,8 After a follow-up period of 6.1 years, the primary endpoint of 3-point major adverse cardiovascular events (MACE: cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) achieved statistical significance for non-inferiority (HR=0.97, 95.6% CI 0.85 to 1.11; p<0.001 for non-inferiority).7,8 However, it did not achieve statistical significance for superiority with regard to 3-point MACE or the combined endpoint of death from cardiovascular causes or hospitalisation for heart failure (HHF). There was a 30% reduction in HHF (HR=0.70, 95% CI 0.54 to 0.90).7,8

EMPEROR-Reduced was a randomised controlled trial of empagliflozin 10 mg daily versus placebo in 3,730 patients with class II, III or IV heart failure and an ejection fraction of 40% or less (HFrEF).9–11 50% of the study population had type 2 diabetes and 50% did not have diabetes. Over a median follow-up of 16 months there was a 25% reduction in the primary composite endpoint of cardiovascular death or hospitalisation for worsening heart failure (HR=0.75, 95% CI 0.65 to 0.86). The results were similar whether the patient had diabetes (HR=0.72, 95% CI 0.60 to 0.87) or did not have diabetes (HR=0.78, 95% CI 0.64 to 0.97). There was a 30% reduction in HHF (HR=0.70, 95% CI 0.58 to 0.85).9–11

Building on the experience gained from their predecessor trials with SGLT2 inhibitors,1,3,5,6,13,14 we have learned further from VERTIS-CV and EMPORER-Reduced about the extent to which the cardiovascular benefits of SGLT2 inhibitors are mediated through the protection from heart failure. Figure 1A shows a meta-analysis of time to first HHF from the five cardiovascular outcome studies with SGLT2 inhibitors showing this universal benefit for the class with no heterogeneity. In keeping with this, a recent meta-analysis of the association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes concluded that the largest benefit across the class was for an associated reduction in risk for HHF and kidney outcomes, with benefits for HHF risk being the most consistent observation across the trials.15 Whilst the time to first MACE concludes a positive benefit for the class in meta-analysis (Figure 1B), there is nevertheless heterogeneity3,5 with VERTIS-CV7,8 and DECLARE-TIMI 5815 being outliers. Figure 2 shows a meta-analysis of the two trials of patients with HFrEF (DAPA-HF6,14 and EMPEROR-Reduced6,11) which studied SGLT2 inhibitors in patients with and without diabetes. Using the primary outcome of first HHF or cardiovascular death, the same benefit is seen for dapagliflozin and empagliflozin in patients with and without diabetes.11,16 This suggests the benefit of SGLT2 inhibitors on heart failure does not depend upon the presence of diabetes or reduction in plasma glucose concentration, because SGLT2 inhibitors do not

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Figure 1. (A) Time to first hospitalisation for heart failure (HHF) and (B) time to first major adverse cardiovascular events (MACE) results from the five cardiovascular outcome trials with SGLT2 inhibitors shown side by side with result of meta-analysis also shown. The agents studied were empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS and CREDENCE), dapagliflozin (DECLARE-TIMI 58) and ertugliflozin (VERTIS-CV). Adapted from reference 34

Table 1. Mortality outcomes in cardiovascular outcome trials with SGLT2 inhibitors and cardiovascular mortality outcomes in the cardiovascular outcome trials in comparable patients with type 2 diabetes – i.e. empagliflozin in EMPA-REG OUTCOME (HR=0.59, 95% CI 0.44 to 0.79) and dapagliflozin in DECLARE-TIMI 58 (HR=0.92, 95% CI 0.69 to 1.23). In contrast, the effects of these drugs to prevent HHF (and serious renal events – see below) seems to be a very consistent finding with this class of drugs.

Table 2. Mortality outcomes in cardiovascular outcome trials with SGLT2 inhibitors and cardiovascular mortality outcomes in the cardiovascular outcome trials in comparable patients with type 2 diabetes – i.e. empagliflozin in EMPA-REG OUTCOME (HR=0.59, 95% CI 0.44 to 0.79) and dapagliflozin in DECLARE-TIMI 58 (HR=0.92, 95% CI 0.69 to 1.23). In contrast, the effects of these drugs to prevent HHF (and serious renal events – see below) seems to be a very consistent finding with this class of drugs. Several possible mechanisms by which SGLT2 inhibitors lead to this cardiac benefit in patients with HFrEF have been proposed, and these are summarised in Figure 3.

Whilst detailed consideration of the impact of SGLT2 inhibitors on renal disease is beyond the scope of this editorial, it is notewor-
Figure 3. Possible mechanisms by which SGLT2 inhibitors exert their cardio-renal benefits. (A) Heart (B) Kidney. Adapted from references 20 and 21.

GLP-1 receptor agonists
It was noteworthy that the MACE cardiovascular benefit of the long-acting GLP-1 RA, dulaglutide, in REWIND was primarily driven by a benefit on stroke reduction (by 24%; HR=0.76, 95% CI 0.62 to 0.94). In all the other trials of long-acting GLP1-RAs, LEADER (li- raglutilide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide QW), Harmony Outcomes (albiglutide) and PIONEER 6 (oral semaglutide) the number of strokes was less in the treatment group than in the placebo group, although in the individual studies this did not achieve statistical significance. Meta-analysis of the seven cardiovascular outcome trials with GLP-1RAs showed a 16% reduction in stroke for the class as a whole (HR=0.84, 95% CI 0.76 to 0.93; Figure 4). Against this background, in the post hoc analysis from the LEADER, SUSTAIN 6 and PIONEER 6 trials, data were pooled to examine the effect of liрагlutilide and semaglutide on stroke and its subtypes. Across the three trials, 2167/907 (2.7%) in the GLP-1RA group and 2627/913 (3.3%) in the placebo group had a history of stroke. There was an 18% reduction in the time to first occurrence of stroke in the GLP-1RA group compared with the placebo group (HR=0.82, 95% CI 0.68 to 0.98; Figure 5A). Treatment effects were consistent across all stroke subtypes. However,
the greatest benefit was seen regarding small vessel occlusion strokes (HR=0.78, 95% CI 0.59 to 1.02, p=0.07). The impact of semaglutide seemed to be greater than liraglutide, with a significant reduction in outcomes despite smaller and shorter trials (Figure 5B). It is noteworthy that separation of the Kaplan–Meier curves occurred very early (Figures 5A and 5B) and hence it seems likely that at least some of the benefit is via mechanisms other than reducing atherosclerosis.12

The case for combination therapy now stronger than ever

In previous editorials we proposed that SGLT2 inhibitors, long-acting GLP-1RAs, pioglitazone and metformin in combination could complement each other to prevent cardiovascular events and save lives in patients with type 2 diabetes at high cardiovascular risk.1–6 With regard to stroke, we came to this conclusion because of the accumulated evidence from multiple studies suggesting that pioglitazone is very effective in reducing stroke risk by slowing down – or even reversing – the atherosclerotic process1–3,26–28 whereas, as discussed above, the cardiovascular benefit of SGLT2 inhibitors is primarily due to a reduction in cardiac risk with little benefit on stroke risk and seems not to be mediated via slowing/reduction of atherosclerosis.11,20,21 On the other hand, although both GLP-1RAs and pioglitazone significantly reduce the risk of stroke, the cellular/molecular mechanisms of GLP-1RAs and pioglitazone are distinct (GLP-1 receptor activation versus PPAR gamma activation).5 Further, as previously noted, SGLT2 inhibitors mitigate the fluid retention associated with pioglitazone use,29 suggesting that pioglitazone and SGLT2 inhibitors would complement each other not only in reducing cardiovascular risk but also in reducing side effects related to fluid retention. We pointed to the evidence that the early use of triple combination therapy with metformin, pioglitazone and a GLP-1RA achieved lower HbA1C, weight loss and much less hypoglycaemia compared with the traditional approach of sequential escalation through metformin, sulfonylurea and insulin, which was associated with significant weight gain.30

From the new evidence gained in 2020 we can now expand these previous editorials:

- Multiple mechanisms have been suggested regarding the cardiovascular benefit of GLP-1RAs.5 Because of the early separation of the curves by GLP-1RAs, it is likely that mechanisms additional to atherosclerosis are activated by GLP-1RAs and benefit stroke (Figures 5A and 5B).12 Further, because of the distinct cellular/molecular mechanism of GLP-1RA and pioglitazone action, it is possible that a combination of both agents will exert an additive benefit to slow atherosclerosis and reduce stroke risk.1–3,26–28 It is noteworthy that the benefit of stroke in both the IRIS study32 and the PROactive study33 was relatively rapid and the difference between the two curves continued to widen thereafter. Thus, it is likely that GLP-1RAs and pioglitazone exert an additive cardiovascular benefit, particularly for stroke reduction. A cardiovascular outcome trial looking particularly at stroke, comparing the combination of dulaglutide or semaglutide with pioglitazone versus either medication alone, especially with regard to stroke, would be of great interest.


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