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SGLT2 inhibitors: Providing cardiovascular protection in type 2 diabetes?

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Commentary

New glucose lowering agents for type 2 diabetes are expensive compared to older drugs, so it is important for patients, those treating them and payers that information used to guide treatment decisions is based on a clear analysis of the benefits and risks of each drug. Whilst the benefit of glucose lowering to reduce microvascular complications was established in the UKPDS trial (1), there remains uncertainty in relation to the risk of cardiovascular disease, highlighted by the controversy about thiazolidinediones, particularly rosiglitazone, and the adverse effects on cardiovascular death observed in the ACCORD trial of intensive glucose lowering in patients with longstanding diabetes (2). As a result, regulatory agencies now require evidence (based on adjudicated outcomes from phase 3 trials) that the risk of cardiovascular harm is low for all new glucose lowering therapies before a drug is made available, and usually also require a post-marketing cardiovascular safety trial. The results of most recent trials with the DPP-IV inhibitor class of drugs and of one trial with a GLP-1 receptor agonist have largely confirmed the safety of these treatments, with the exception of a signal for increased heart failure hospitalisation with saxagliptin, but not demonstrated cardiovascular benefit (3-6). The latest class of glucose-lowering therapies, the sodium-glucose co-transporter 2 (SGLT2) inhibitors, inhibit glucose reabsorption from the proximal renal tubules resulting in glycosuria. This results in lowering of blood glucose, weight loss and (partly as a result of a transient natriuresis) blood pressure reduction; they do however modestly increase LDL cholesterol and increase the risk of genital fungal infections. Several other safety concerns have also been raised, including the risk of bacterial urinary tract infections, bone fractures, hypotension, ketoacidosis and bladder and breast cancers. The regulatory assessment of benefit / risk, including cardiovascular safety meta-analyses based on phase 3 data, allowed marketing of these drugs, but the first of the cardiovascular outcome trials, the EMPA-REG trial, which studied 7020 patients with type 2 diabetes and pre-existing cardiovascular disease treated for 3.1 years, found a reduction (hazard ratio, HR 0.86) in a composite of myocardial infarction, non-fat stroke and cardiovascular death with empagliflozin treatment compared with placebo. Interestingly there was no significant reduction of myocardial infarction and a trend for increased risk of stroke, so the overall benefit was largely due to a reduction in cardiovascular death (HR 0.62). There was also a striking reduction in heart failure hospitalisation compared to placebo (HR 0.65). (7). These results raise several questions about mechanisms, especially as there did not seem to be a reduction in atherosclerotic disease, and also as to whether this is a class effect and if beneficial effects might extend to patients without pre-existing cardiovascular disease. In this issue of the journal, Wu and colleagues present a meta-analysis using all available data from published clinical trials and regulatory submissions to provide the most comprehensive analysis of the benefit / risk of the SGLT2 inhibitor class available to date (8). Despite being strongly influenced by the EMPA-REG data (which contributed three-quarters of the CV events to the analysis), the study suggests these benefits extend to other drugs in the class, and largely confirms a null effect for most of the other safety concerns with the exception of genital infections. There are some limitations to this approach, as the analysis does not distinguish between studies that included special populations such as those with renal impairment that are currently excluded from the license and also includes some studies that used doses above those that are currently recommended; nevertheless this should, if anything exaggerate harms, so again provides some reassurance. Should we now embrace the use of SGLT2 inhibitors as glucose-lowering drugs that provide cardiovascular benefit for all patients with type 2 diabetes? Probably not yet. Much of the benefit seems to relate to heart failure, and as the effects seen are too rapid to be due to a reduction in atherosclerotic disease mechanistic studies to fully understand the effects of SGLT2 inhibitors on the heart are essential. Ongoing trials include the DECLARE TIMI-58 trial with dapagliflozin which includes over 17,000 patients, and the CANVAS and CANVAS-R studies with

canagliflozin together include over 6000 patients, of which a significant proportion have CV risk factors but not pre-existing cardiovascular disease. These studies will provide essential additional information about the risks and benefits of SGLT2 inhibitors in these lower risk patients, where the risk of heart failure is likely to be much lower. There is also the intriguing potential for renoprotection, brought into sharp focus by the EMPA-REG results which show a reduction in the composite of time to doubling of serum creatinine, the development of end stage renal failure or death in patients with an eGFR < 60 ml/min (HR 0.54) (9). The results of the CREDENCE and CANVAS-R studies with canagliflozin that have primary renal outcomes should be informative in this respect. The SGLT2 inhibitors may represent the start of a new era for diabetes treatment, but we should await the results of these ongoing trials before adopting widespread use in the expectation of cardiovascular benefit, despite the encouraging data from this latest meta-analysis.

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Conflict of Interest Statement

I have provided consultancy (both via my institution and personal) for AstraZeneca (manufacturers of dapagliflozin), Janssen (canagliflozin); Boehringer Ingleheim (empagliflozin and Astellas (ipragliflozin). Lecture fees (personal and institutional)- AstraZeneca, Boehringer, Astellas, Janssen

I have been / am an investigator for clinical trials of dapagliflozin, canagliflozin, empagliflozin and ipragliflozin (this includes the ongoing CV outcomes trials with dapagliflozin and canagliflozin) [Institutional]

Current grant support for an investigator-initiated trial of dapagliflozin [Institutional]

I have also undertaken consultancy and given lectures on behalf of companies producing other glucose-lowering drugs: Lilly, NovoNordisk, Sanofi, Merck [Personal and Institutional].