Cardioprotective glucose-lowering medications: evidence and uncertainties in a new therapeutic era

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Cardiovascular disease is the principal cause of death in patients with type 2 diabetes. However, while hyperglycemia is the major risk factor for microvascular complications in type 2 diabetes, lowering hemoglobin A_{1c} has only modest effects on reducing cardiovascular disease risk and mortality. The EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial was a breakthrough for clinical trials in diabetes with the demonstration of cardiovascular protection from empagliflozin – a member of the sodium–glucose cotransporter (SGLT)-2 inhibitor class [1]. Empagliflozin reduced the primary major adverse cardiac event (MACE) endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) by 14%. This beneficial effect was driven by a 38% reduction in cardiovascular mortality with no significant decrease in nonfatal myocardial infarction or stroke. Empagliflozin reduced hospitalization for heart failure by 35% without affecting hospitalization for unstable angina.

In CANVAS (Canagliflozin Cardiovascular Assessment Study), canagliflozin provided additional support for a class effect of SGLT-2 inhibitors on cardiovascular disease – that is, a reduction in three-point MACE and heart failure hospitalization risk, although tempered by an increase in amputations [2]. Furthermore, the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) trials demonstrated that, in patients with type 2 diabetes at high risk of cardiovascular disease, the glucagon-like peptide (GLP)-1 receptor agonists liraglutide and semaglutide reduced the primary MACE endpoint [3, 4]. All of these trials also showed renoprotective effects.

It is apparent that the cardiovascular benefits observed in these trials are not primarily attributable to glucose control or improvements in other major risk factors for cardiovascular events. Moreover, the pattern of cardiovascular protection in these trials differed according to the class of glucose-lowering medication: the SGLT-2 inhibitors were effective in reducing heart failure, while the GLP-1 receptor agonists appeared to attenuate the atherosclerotic process [5,6]. Major questions remain

concerning the mechanism of benefits observed in these practice-changing cardiovascular outcome trials (CVOTs) [7,8]. The clinical impact of combinations of glucose-lowering drugs on cardiovascular disease is another area of research activity [9].

Timely revisions to recommendations for antihyperglycemic therapy for adults with type 2 diabetes have recently been added to the latest version of the American Diabetes Association's Standards of Medical Care. These revisions, which reflect the recent CVOT data, recommends that patients with atherosclerotic cardiovascular disease should begin with lifestyle management and metformin with subsequent incorporation of an agent proven to reduce MACE and/or cardiovascular mortality – currently empagliflozin and liraglutide – after considering drug-specific and patient factors [10]. Following the recent approval of semaglutide in December 2017 further revisions of this guidance may be anticipated. However, semaglutide does not currently have an indication for cardiovascular protection. SUSTAIN-6 was powered to demonstrate noninferiority of semaglutide to placebo when it came to cardiovascular safety. The cardioprotection observed in SUSTAIN-6 – which showing an overall 26% reduction in the MACE compared with placebo – was not sufficient. The cardiovascular benefits in SUSTAIN-6 were driven largely by a 39% decrease in nonfatal stroke with a nonsignificant (26%) decrease in nonfatal myocardial infarction and no significant difference in the rate of cardiovascular death. However, the small number of events necessitates a larger sample size to inform regulators and prescribers about the cardiovascular benefits of semaglutide. A further definitive semaglutide CVOT is to be performed. Incidentally, the American Diabetes Association has signaled its intention to update clinical practice recommendations more frequently than annually in response to new data.

With these considerations in mind, we are pleased to present a special issue of the journal that examines the mechanisms, benefits, and clinical implications of these trials. The complex pathophysiology of cardiovascular disease in diabetes is reviewed by Dr Gerardo Rodriguez and Dr Hironori Nakagami. The concept of heart failure as a therapeutic target in diabetes is delineated by Dr Nicolaus Marx. Dr Angelo Avogaro and colleagues review the impact of glucose-lowering medications of cardiovascular disease. Dr Joshua Reed and

colleagues explore the mechanism of cardiovascular benefit of GLP-1 agonists. Dr Sunder Mudaliar considers the integration of cardioprotective glucose-lowering medications into clinical practice.

It seems appropriate to believe that a new therapeutic era in the treatment of diabetes-associated cardiovascular disease has been entered. We hope that these articles will help to equip clinicians and researchers in both specialties with the information they require to apply best practice – albeit with residual uncertainties about patient selection and stratification – and formulate new hypotheses that can be tested in future clinical trials.

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Conflicts of interest

There are no conflicts of interest.

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