Milestone 24

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Getting to the heart of the matter

In 2008, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issued draft guidance to the pharmaceutical industry to address the need for more thorough evaluation of cardiovascular safety in diabetes drug development. They did so as several trials suggested intensive reduction of glucose may not necessarily lessen cardiovascular events and may even cause harm. This was worrying because diabetes is associated with increased risk of cardiovascular events. The FDA and EMA recommended that new trials for anti-diabetes drugs be designed to demonstrate, at minimum, no increased risk of cardiovascular disease in individuals with type 2 diabetes (T2D).

HbA_{1c} levels, the gold standard for assessing glycaemic control, remained the recommended primary outcome for new trials. However, sponsors were recommended to involve an independent cardiovascular endpoints committee in new trials, as well as designing phase II and phase III studies in such a way that cardiovascular endpoints could be readily compared in meta-analyses.

Clinical trials of dipeptidyl peptidase 4 inhibitors were among the first to measure cardiovascular outcomes. These studies were largely successful in demonstrating non-inferiority for risk of cardiovascular events compared with placebo, but there was no evidence of benefit. In 2015, the EMPA-REG study, assessing the effects of empagliflozin (a sodium–glucose co-transporter 2 inhibitor (SGLT2i) in people with T2D, over 60 years of age and with known cardiovascular disease, took the world by storm. The study demonstrated not only no increased risk of cardiovascular disease but that empagliflozin treatment resulted in a significant beneficial reduction in a composite cardiovascular outcome (fatal and non-fatal myocardial infarction and stroke), plus substantial reductions in heart failure and chronic kidney disease, over a median time of 3.1 years.

"The unexpected yet overwhelming clinical benefits conferred by new-generation glucose-lowering therapies have brought about a veritable revolution in T2D management"

In 2019, Zelniker et al. reported findings from a meta-analysis of three major trials of SGLT2is that included 34,322 patients, 60% of whom had established atherosclerotic disease. They found that treatment with SGLT2is across the trials reduced incidence of major adverse cardiovascular events (MACE) by 11%, suggesting a moderate class-effect cardiovascular benefit for SGLT2is. However, this benefit was only seen in patients with existing atherosclerotic disease. The analysis also showed substantial reductions in cardiovascular death and hospitalizations for heart failure, regardless of whether patients had a history of atherosclerotic disease or heart failure. Other secondary outcomes, including chronic kidney disease (CKD), were also found to be positively affected by treatment with SGLT2is. Subsequent trials of SGLT2is in patients with heart failure and CKD, with and without T2D, also showed clinical benefit.

Another meta-analysis from 2019 reported cardiovascular outcomes of seven trials testing glucagon-like peptide 1 receptor agonists, with data from 56,004 participants. Kristensen et al. reported a 12% overall reduction in MACE, as well as reductions in all-cause mortality, hospitalizations due to heart failure and a composite kidney disease outcome.

The question of whether the beneficial effects on cardiovascular and renal disease observed are attributable to improved glycaemic control or whether they are mediated by independent mechanisms are subject to debate and ongoing research. However, the mixed results for cardiovascular outcomes in individual trials, as well as heart failure and kidney benefits extending to patients without diabetes, suggest that these effects cannot be due to improved glycaemic control alone.

The unexpected yet overwhelming clinical benefits conferred by new-generation glucose-lowering therapies have brought about a veritable revolution in T2D management, providing patients and physicians with more options to reduce the burden of chronic complications associated with the disease.

Jennifer Sargent Senior Editor, *Nature Medicine*

Milestone studies

Zelniker, T. A. et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* **393**, 31–39 (2019) | Kristensen, S. L. et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol.* **10**, 776–785 (2019)

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