Randomised, pragmatic, "real-world" trials – a useful way to assess benefits of glucose-lowering drugs

Four-way comparison of DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors and sulfonylureas in this randomised, pragmatic trial supports potential cardiovascular benefits of the newer diabetes drugs compared to older classes, with no significant difference between GLP-1 RAs and SGLT2 inhibitors. To emulate a randomised controlled trial, the study used the US Department of Veterans Affairs databases to identify people with type 2 diabetes, with or without cardiovascular disease, who were prescribed metformin monotherapy at study baseline and who were initiated on one of the four drug classes between October 2016 and September 2021. The cohort was followed for an average of 3.85 years. Rates of major adverse cardiovascular events (MACE: myocardial infarction, stroke and all-cause mortality) were similar between those initiated on a GLP-1 RA or an SGLT2 inhibitor, and those receiving either of these drug classes had a lower risk than those receiving DPP-4 inhibitors or sulfonylureas. Additionally, those receiving DPP-4 inhibitors had a lower MACE risk than those receiving sulfonylureas. Although randomised controlled trials are useful in demonstrating safety and efficacy of drug therapies, they recruit restricted populations of people with type 2 diabetes, and their results can therefore be difficult to generalise to our "real-world" populations. Pragmatic real-world trials such as this better represent the likely results in day-to-day clinical practice, although confounding cannot be ruled out with this type of study. These findings provide real-world evidence of the comparative effectiveness of the four most commonly used second-line glucose-lowering classes on MACE and could help guide our choice of glucose-lowering agent. This is particularly useful now, when a shortage of GLP-1 RAs is requiring us to switch people at high cardiovascular risk to other glucose-lowering therapies.

Pam Brown
GP in Swansea

Most cardiovascular outcome trials (CVOTs) have studied the cardiovascular effects of glucose-lowering drugs in comparison with placebo and in narrowly defined groups of people who are not representative of the people we see in day-to-day practice. Studies show that only 8–58% of the people we see in practice would meet the criteria for inclusion in randomised clinical trials. To date, only the CAROLINA study (Rosenstock et al, 2019) and TOSCA.IT (Vaccaro et al, 2017) have provided head-to-head comparisons between glucose-lowering classes, in this case between glimepiride and linagliptin, and sulfonylureas and pioglitazone, respectively. The GRADE study compared cardiovascular effects of GLP-1 receptor agonists, DPP-4 inhibitors, sulfonylureas and insulin glargine, but did not include SGLT2 inhibitors and may have been underpowered to fully demonstrate the comparative benefits of GLP-1 RAs (GRADE study research group, 2022).

In the current randomised, pragmatic, real-world study published in *Lancet Diabetes & Endocrinology*, Xie and colleagues aimed to evaluate the comparative effectiveness of the four groups of commonly used second-line drugs on major adverse cardiovascular events (MACE). MACE was defined as stroke, myocardial infarction and all-cause mortality (rather than

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cardiovascular mortality, as studied in CVOTs). Secondary outcomes were the individual components of MACE, hospitalisations for heart failure, and adverse events such as amputation, hypoglycaemia, genital infections and diabetic ketoacidosis.

The investigators used the US Department of Veterans Affairs databases to build a cohort of 284 000 metformin users who were started on only one of the four drug classes (DPP-4 inhibitors, GLP-1 RAs, SGLT2 inhibitors or sulfonylureas) between 1 October 2016 and 30 September 2021. Groups were carefully balanced for a large number of variables, and the study undertook both intention-to-treat (everyone started on one of the four drugs) and per-protocol (those who had remained on the drugs at study end) evaluations of the estimated rate of MACE. Drugs included in the evaluation were the SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin; the DPP-4 inhibitors alogliptin, saxagliptin, sitagliptin and linagliptin; the GLP-1 RAs liraglutide, exenatide, semaglutide, dulaglutide and albiglutide; and the sulfonylureas glyburide, glipizide and glimepiride. Insulins were not included in this pragmatic trial.

In the intention-to-treat analyses, compared with sulfonylureas, SGLT2 inhibitors (hazard ratio [HR] 0.77), GLP-1 RAs (HR 0.78) and DPP-4 inhibitors (HR 0.90) were all associated with reduced MACE. Compared to DPP-4 inhibitors, both SGLT2 inhibitors (HR 0.86) and GLP-1 RAs (HR 0.86) were associated with the same, significant, lower risk of MACE. There was no significant difference in risk of MACE between SGLT2 inhibitors and GLP-1 RAs.

Absolute risk reductions per 1000 person-years compared to sulfonylureas were 12.34 for SGLT2 inhibitors, 12.07 for GLP-1 RAs and 5.34 for DPP-4 inhibitors.

Findings from the per-protocol evaluations were similar to those from the intention-to-treat analyses and, in addition, demonstrated that around 50% of those in the SGLT2 inhibitor and GLP-1 RA groups, and 39% and 36% of those initiated on DPP-4 inhibitors and sulfonylureas, respectively, were still adhering to protocol medication at the end of follow-up.

The results were robust when challenged in multiple sensitivity analyses. Analyses of the individual components of MACE and of hospitalisation for heart failure gave similar results to the primary outcome.

The authors highlight the key limitations of their study. US veterans are mostly older, white and male and, despite efforts to reduce confounding, this cannot be completely ruled out in this type of study. Cause of death was not examined and only differences between drug classes, rather than within classes, were explored.

An accompanying commentary describes such pragmatic trials as a "step forward to assess cardiovascular efficacy of new glucose-lowering agents", and highlights that, although these results support evidence from network meta-analyses of the CVOTs for SGLT2 inhibitors and GLP-1 RAs, they differ in their conclusions for sulfonylureas, since other studies have shown no difference in MACE and all-cause mortality between sulfonylureas and DPP-4 inhibitors (Scheen, 2023).

As we cope with the effects of the national GLP-1 RA shortage and are forced to switch people with type 2 diabetes at high risk of cardiovascular disease onto other drugs, real-world studies such as this can aid our decision-making. ■

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