Once-weekly Dulaglutide and Major Cardiovascular Events—Results of the REWIND Trial

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The REWIND study investigated the effect of the glucagon-like peptide 1 (GLP-1) receptor agonist dulaglutide on major adverse cardiovascular events (MACE) in individuals with type 2 diabetes (T2D) with and without previous cardiovascular disease and with a wide range of glycemic control. At a median follow-up of 5.4 years, the longest to date for a cardiovascular outcome trial for a GLP-1 receptor agonist, the first occurrence of MACE (including non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes) occurred in 12.0% of dulaglutide-treated patients compared with 13.4% in the placebo group. Dulaglutide is therefore a useful option in the management of glycemic control in middle-aged and older people with T2D with either previous cardiovascular disease or cardiovascular risk factors.

Cardiovascular outcome trials (CVOTs) have become mandatory for glucose-lowering drugs in the treatment of patients with type 2 diabetes (T2D) since 2008, following the withdrawal of rosiglitazone from the market because of its association with increased risk of cardiovascular disease (CVD). In subsequent years, results have emerged from several CVOTs, with many more underway, all demonstrating the noninferiority of glucose-lowering agents to placebo in terms of CV outcomes. In 2015, the EMPA-REG trial demonstrated that the sodium–glucose cotransporter-2 (SGLT2) inhibitor empagliflozin (JARDIANCE®, Boehringer Ingelheim, Ridgefield, CT, USA) significantly reduced the rate of CV events compared with placebo. Since then, other studies, including CANVAS with the SGLT1 inhibitor canagliflozin (INVOKANA®, Janssen, Beerse, Belgium); LEADER, with the injectable once-weekly glucagon-like peptide 1 (GLP-1) agonist, liraglutide (Victozza®, Novo Nordisk, Bagsværd, Denmark); SUSTAIN-6 with semaglutide (Ozempic®, Novo Nordisk, Bagsværd, Denmark); and DECLARE-TIMI 58 with the SGLT inhibitor, dapagliflozin (FARXIGA®, AstraZeneca, Cambridge, UK) and have also shown clinically meaningful CV benefits.

However, CVOTs to date have a number of important limitations. They all involved patients either with established CVD or chronic renal failure at baseline, or at high risk of CVD. In addition, a subgroup analysis of the LEADER trial suggested that liraglutide effectively lowered CV risk only in people with established CVD. It is, therefore, difficult to extrapolate the study findings to the entire population of people with T2D. In addition, CVOTs to date have only addressed short-term outcomes, although many complications of T2D—including blindness, renal failure, amputation, CV death—do not usually appear within the first 5 years. There is a need for CVOTs involving lower-risk patients who have not yet developed CVD to determine whether their risk of developing CVD can be reduced. Such studies would need a large sample size and long follow-up to achieve a statistically significant number of major adverse CV events (MACE) events, but would provide valuable information about CVD prevention.

The most recent CVOT, the REWIND study (ClinicalTrials.gov identifier: NCT01394952), evaluated the CV safety of the once-weekly injectable GLP-1 receptor agonist dulaglutide (Trulicity®, Lilly, Indianapolis, IN, USA). This is the first CVOT with a GLP-1 receptor agonist to include a majority of patients who did not have established CVD (defined as prior myocardial infarction [MI], ischemic stroke, unstable angina, revascularization, hospitalization for ischemia-related events, or documented myocardial ischemia) at baseline—only 31% of the participants had established CVD. Compared to other CVOTs, this better reflects the broader T2D patient population seen in routine clinical practice. However, participants were still at high risk of CV events: the study included patients aged ≥50 with established CVD, and patients ≥60 years old with risk factors. The 9,901 participants from 371 sites across 24 countries were aged ≥50 years, had a mean duration of T2D of 10 years and a mean baseline glycated

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In an accompanying editorial, Subodh Verma, David Mazer, and Vlado Perkovic, all from the University of Toronto, Ontario, Canada, commented that the magnitude of benefit in terms of the composite CV outcome (12%) that the DECLARE-TIMI 58 study showed was modest and numerically lower than that seen in the other GLP-1 receptor agonists. Dulaglutide was well-tolerated among the study population. The safety profile of dulaglutide was consistent with that of other GLP-1 receptor agonists. Dulaglutide was well-tolerated among the study population.

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was consistent with the overall effect size from a meta-analysis of all previous GLP-1 receptor agonist trials. Additionally, they highlighted the fact that participants in the REWIND trial were at lower risk of CV events than participants in the previous studies.11

The stroke reduction seen with dulaglutide is not a typical finding of CVOTs. Interestingly, the only other CVOT, to date, to show a substantial and significant reduction of stroke was SUSTAIN-6, with the GLP-1 receptor agonist semaglutide (Table 1).6 A recent systematic review and meta-analysis found that GLP-1 receptor agonists showed a significant reduction, by 13%, in the risk of total stroke, suggesting possible neuroprotective effects.12

The fact that the primary outcome of the REWIND study seemed to be driven largely by a reduction in stroke rather than a reduction in MI may need further investigation. Nevertheless, these are valuable clinical findings. This international study’s broad patient population, including a high proportion of women (46%), people without established CVD and inclusion of participants with a lower mean baseline HbA1c (7.2%) suggest that the findings will be directly applicable to patients with T2D seen in everyday clinical practice worldwide. The study authors concluded that dulaglutide could be considered for the management of glycemic control in middle-aged and older people with T2D with either previous CVD or CV risk factors.9