Evaluation of large-scale clinical trials on cardiovascular disease risk in patients with type 2 diabetes mellitus treated with dipeptidyl peptidase 4 inhibitors and a new class of drugs

INTRODUCTION
Recent major progress in the clinical management of type 2 diabetes mellitus has been accomplished with the introduction of several new classes of drugs, some of which might also improve cardiovascular outcomes. Most of these studies are supported by pharmaceutical companies and claim cardiovascular (CV) benefits. However, whether or not these benefits hold in clinical settings is dubious.

EVALUATION OF DIPEPTIDYL PEPTIDASE 4 INHIBITORS WITH REGARD TO CARDIOVASCULAR EVENTS
The US Food and Drug Administration states that cardiovascular safety of all new drugs for diabetes should be shown through pooled analyses of phase III studies or specifically designed trials. Under this rigorous standard, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trials were published. These trials were carried out with the dipeptidyl peptidase 4 (DPP-4) inhibitors, saxagliptin and alogliptin, respectively, in 2013. In addition, in 2015 the results of Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) using the DPP-4 inhibitor, sitagliptin, were published. Indeed, all three trials were carried out to show non-inferiority, but not superiority, of the drugs. The US Food and Drug Administration guidance, for establishing that a new therapy is not associated with an unacceptable increase in cardiovascular risk, requires recruitment of patients with high CV risk whose benefit from interventions regarding CV risk factors is minimal. Remarkably, most of the patients involved in these studies also received multiple treatments for the prevention of development of cardiovascular diseases. In SAVOR-TIMI 53, EXAMINE and TECOS, 78–80% of patients received statins, angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor and aspirin. Thus, superiority for CV risk including residual and/or minimal risk cannot be detected. In addition, US Food and Drug Administration guidance requires drug companies to plan a protocol to last more than the typical 3–6 months’ duration to obtain enough events, and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years) for these chronically used therapies. Accordingly, the studies mentioned were carried out for only a short duration, and were designed to prove non-inferiority to reduce costs. The EXAMINE study was carried out for 3 years, but claimed only non-inferiority compared with a placebo. Accordingly, it is not convincing to conclude the non-superiority of DPP-4 inhibitors for its cardiovascular benefit, until it fails to prove its superiority compared with the conventional therapy in the clinical trials.

REDUCED RISK OF CV WITH SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITOR AND GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST
Important reports regarding CV risk reduction by drugs used for diabetes mellitus are the Randomized, Placebo-Controlled Cardiovascular Outcome Trial of Empagliflozin (EMPA-REG) and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial. These two trials surprisingly report superiority of primary CV end-points including death. The primary end-points in the EMPA-REG trial are death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke; a lower rate of composite cardiovascular outcome and death from any cause for the study drug added to standard care is claimed. However, these events occurred in 243 of 2,345 patients (10.4%) in the 10-mg empagliflozin group, and in 247 of 2,342 patients (10.5%) in the 25-mg empagliflozin group, compared with 282 of 2,333 patients (12.1%) in the placebo group (hazard ratio [HR] in the 10-mg empagliflozin group 0.85, 95% confidence interval 0.72–1.01, P = 0.07; and HR in the 25-mg empagliflozin group 0.86, 95% CI: 0.73–1.02, P = 0.09 non-superiority, respectively). The authors showed the combined data from the 10-mg and 25-mg empagliflozin groups: the primary end-point occurred in 490 of 4,687 patients (10.5%) in the pooled empagliflozin group (HR in the pooled empagliflozin group 0.86, 95.02% confidence interval 0.74–0.99, P = 0.04 for superiority). Nevertheless, in a clinical setting, the drugs are used in only one dose for one person. CV death was significantly reduced in the empagliflozin group compared with that in the placebo group (HR 0.62, 95% CI: 0.49–0.77, P < 0.001). However, the incidence rate in the placebo group was rapidly increased during the last 6 months, and significance was observed only in those aged >65 years.
Although the difference in CV deaths is significant, glycemic control differed. The possibility that the difference in glycemic control affected the results should be considered.

In the LEADER trial, the primary composite outcome was the first occurrence of death from CV causes, non-fatal myocardial infarction or non-fatal stroke. The absolute risk for primary outcome in the liraglutide group was 0.1302 (608/4,668) and absolute risk in the placebo group was 0.1485 (694/4,672). The absolute risk reduction was 0.0183, and patient number to treat was 54.6 for 3.8 years. This diabetes drug has significant efficacy on glycemic control, and it may well provide additional protection against cardiovascular events. However, a question has been raised for the LEADER trial regarding the significant and important differences in baseline medications between the liraglutide group and the placebo group involved, such as the rate of use of β-blockers (56.8 vs 54.1%, \( P = 0.009 \)), statins (72.9 vs 71.4%, \( P = 0.10 \)) and platelet-aggregation inhibitors (68.7 vs 66.8%, \( P = 0.05 \)).

CONCLUSION
Major trials to establish cardiovascular safety in clinical situations for treatment of diabetes mellitus have been carried out. However, whether or not these newer drugs for diabetes reduce cardiovascular risk remains to be decided.

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