Type 2 diabetes is a major risk factor for cardiovascular disease\textsuperscript{1,2} and the coexistence of cardiovascular disease and type 2 diabetes increases the risk of death\textsuperscript{3}. Although a modest cardiovascular benefit may be observed after a prolonged follow up, evidence that glucose lowering reduces the rates of cardiovascular events and more important death has not been convincingly shown\textsuperscript{4-6}. Moreover, the use of specific glucose lowering drugs as well as intensive glucose lowering may be associated with adverse cardiovascular outcomes\textsuperscript{7,8}. Therefore, the cardiovascular safety benefits of glucose-lowering agents should be established\textsuperscript{9}.

Inhibitors of sodium-glucose cotransporter 2 reduce rates of hyperglycemia in patients with type 2 diabetes by decreasing renal glucose absorption, thereby increasing urinary glucose excretion\textsuperscript{10}. Empagliflozin is a selective inhibitor of sodium glucose cotransporter 2\textsuperscript{11} that has been approved for type 2 diabetes\textsuperscript{12}. The drug reduces glycated hemoglobin levels in patients with type 2 diabetes, including those with stage 2 or 3a chronic kidney disease\textsuperscript{13-20}, given as either monotherapy or as add on therapy. Moreover, it is reported to reduce blood pressure without increases in heart rate\textsuperscript{13-20} and has favorable effects on markers of arterial stiffness and vascular resistance\textsuperscript{21}, albuminuria\textsuperscript{20} and plasma urate\textsuperscript{13-19}. Empagliflozin is also associated with weight loss and reduction of visceral adiposity\textsuperscript{22}. The most common side effects of empagliflozin are urinary tract infection and genital infection\textsuperscript{12}.

In the EMPA-REG OUTCOME trial, the effects of empagliflozin, as compared with placebo, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care, were examined.

The EMPA-REG OUTCOME trial was a randomized, double-blind, placebo-controlled trial to assess the effect of once daily empagliflozin (at a dose of either 10 mg or 25 mg) versus placebo on cardiovascular events in adults with type 2 diabetes at high cardiovascular risk against a background standard of care. Patients were treated at 590 sites in 42 countries. The trial continued until an adjudicated primary outcome event had occurred in at least 691 patients.

Eligible patients with type 2 diabetes were adults with a body mass index of 45 or less and an estimated glomerular filtration rate (eGFR) of at least 30ml per minute per 1.73m\textsuperscript{2} of body-surface area,
according to MDR criteria. All the patients had established cardiovascular disease and had received no glucose-lowering agents for at least 12 weeks before randomization and had a glycated hemoglobin level of at least 7.0% and no more of 9.0% or had received stable glucose lowering therapy for at least 12 weeks before randomization and had a glycated hemoglobin level of at least 7.0% and no more than 10.0%.

Eligible patients underwent a 2-week open-label, placebo run-in period in which background glucose lowering therapy was unchanged. Patients meeting the inclusion criteria were then randomly assigned in a 1:1:1 ratio to receive either 10 mg or 25 mg of empagliflozin or placebo once daily.

Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomization, although intensification was permitted if the patient had a confirmed fasting glucose level of more than 240 mg/dl. In cases of medical necessity, dose reduction or discontinuation of background medication could occur. After week 12, investigators were encouraged to adjust glucose-lowering therapy at their discretion to achieve glycemic control according to local guidelines. Throughout the trial, investigators were encouraged to treat other cardiovascular risk factors (including dyslipidemia and hypertension) to achieve best available standard of care according to local guidelines. Patients were instructed to attend the clinic at prespecified times, which included a follow-up visit 30 days after the end of treatment.

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina.

Safety was assessed on the basis of adverse events that occurred during treatment or within 7 days after the last dose of a study drug. Adverse events of special interest included confirmed hyperglycemic adverse events, and adverse events reflecting urinary tract infection, genital infection, volume depletion, acute renal failure, bone fracture, diabetic ketoacidosis, and thromboembolic events.

A total of 7,028 patients underwent randomization from September 2010 through April 2013. Of these patients, 7,020 were treated and included in the primary analysis.

At baseline, demographic and clinical characteristics were well balanced between the placebo group and the empagliflozin group. According to the inclusion criteria, more than 99% of patients had established cardiovascular disease, and patients were well treated with respect to the use of lipid-lowering therapy and antihypertensive medications at baseline. The median duration of treatment was 2.6 years, and the median observation time was 3.1 years; both durations were similar in the pooled empagliflozin group the placebo group.

The primary outcome occurred in a significantly lower percentage of patients in the empagliflozin group [490 of 4,687 (10.5%)] than in the placebo group [282 of 2,333 (12.1%)] (hazard ratio in the empagliflozin group, 0.86: 95% confidence interval, 0.74 to 0.99; P<0.001) for non-inferiority and P= 0.04 for superiority.

The key secondary outcome occurred in 599 of 4,687 patients (12.8%) in the empagliflozin group and 333 of 2,333 patients (14.3%) in the placebo group (hazard ratio, 0.89: 95% confidence interval, 0.78 to 1.01; P< 0.001) for noninferiority and P=0.08 for superiority.

As compared with placebo, empagliflozin resulted in a significant lower risk of death from cardiovascular causes (hazard ratio, 0.62; 95% confidence interval, 0.49 to 0.77; P<0.001), death from any cause (hazard ratio, 0.68; 95% confidence interval, 0.57 to 0.82, P<0.001) and hospitalization for heart failure (hazard ratio, 0.65; 95% confidence interval, 0.50 to 0.85; P=0.002). All categories of death from cardiovascular causes contributed to the reduction in cardiovascular death in the empagliflozin group. There were no significant between-group differences in the occurrence of myocardial infarction or stroke. Myocardial infarction was reported in 4.8% of patients in the empagliflozin group and 5.4% of those in the placebo group, and stroke in 3.5% and 3.0% of patients, respectively.

For the primary and key secondary outcomes, hazard ratios for the comparison between the 10 mg dose of empagliflozin versus placebo and the 25 mg dose versus placebo were virtually identical to those in the pooled analysis, but in the individual dose effects were not significant, owing to the smaller number of outcome events in the individual groups.

In prespecified sensitivity analyses based on events that occurred within 30 days after last dose of a study drug, results for the primary outcome, car-
diovascular death, myocardial infarction and stroke were consistent with the primary analyses, and the point estimate for the hazard ratio for stroke was closer to 1.00.

After 12 weeks, during which glucose-lowering therapy was to remain unchanged, the adjusted mean differences in the glycated hemoglobin level between patients receiving empagliflozin and those receiving placebo were -0.54 percentage points (95% confidence interval, -0.58 to -0.49) in the 10 mg group and -0.60 percentage points (95% confidence interval, -0.64 to -0.55) in the 25 mg group.

At week 94, the adjusted mean differences in the glycated level between patients receiving empagliflozin and those receiving placebo were -0.42 percentage points (95% confidence interval, -0.48 to -0.36) and -0.47 percentage points (95% confidence interval, -0.54 to -0.41), respectively. At week 206, the differences were -0.24 percentage points (95% confidence interval, -0.40 to -0.08) and -0.36 percentage points (95% confidence interval, -0.51 to -0.20).

Over the course of the study, empagliflozin, as compared with placebo, was associated with small reductions in weight, waist circumference, uric acid level, and systolic and diastolic blood pressure with no increase in heart rate and small increases in both LDL and HDL cholesterol. A higher percentage of patients in the placebo group received additional glucose-lowering medications (including sulfonylurea and insulin), antihypertensive medications (including diuretics), and anticoagulants during the trial, with no between-group difference in the receipt of lipid-lowering drugs.

The proportion of patients who had adverse events, serious adverse events, and adverse events leading to the discontinuation of a study drug were similar in the empagliflozin group and the placebo group. Genital infection was reported in a higher percentage of patients in the placebo group than in the pooled empagliflozin group. The proportions of patients with confirmed hypoglycemic adverse events, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fracture, and events consistent with volume depletion were similar in the two study groups.

There were no relevant changes in electrolytes in the two study groups. Hematocrit values were higher in the empagliflozin groups than in the placebo group (mean[SD±] changes from baseline, 4.8%±5.5% in the group receiving 10 mg of empagliflozin, 5.05 (3%) in the group receiving 25 mg of empagliflozin, and 0.9±4.7% in the placebo group).

Benefits of empagliflozin were observed in a population with established cardiovascular disease in whom cardiovascular risk factors, including blood pressure and dyslipidemia, were well treated with the use of renin-angiotensin-aldosterone system inhibitors, statins, and acetylsalicylic acid. The reductions in the risk of cardiovascular death in the empagliflozin group were consistent across subgroups according to baseline characteristics.

Notably, reductions in the risks of death from cardiovascular causes and from any cause occurred early in the trial, and these benefits continued throughout the study. The relative reduction of 32% in the risk of death from any cause in the pooled empagliflozin group means that 39 patients (41 in the 10 mg group and 38 in the 25 mg group) would need to be treated during a 3-year period to prevent one death, but these numbers cannot be extrapolated to patient populations with other clinical characteristics.

Even though investigators were encouraged to adjust glucose-lowering therapy according to local guidelines, many patients did not reach their glycemic target, with an adjusted mean glycated hemoglobin level at week 206 of 7.81% in the pooled empagliflozin group and 8.16% in the placebo group. EMPA-REG OUTCOME trial was designed to assess the specific effects of empagliflozin on clinical outcomes, and the mechanisms behind the observed benefits are speculative. It is speculated that the mechanisms behind the cardiovascular benefits of empagliflozin are multidimensional and possibly involve changes in arterial stiffness, cardiac function, and cardiac oxygen demand (in the absence of sympathetic nerve activation), as well as cardiorenal effects, reduction in albuminuria, reduction in uric acid, and established effects on hyperglycemia, weight, visceral adiposity and blood pressure.

This trial provides data to support the long term use of empagliflozin, as well as strong evidence for a reduction in cardiovascular risk. As observed in previous trials, genital infection was more common in patients treated with empagliflozin.

Concern has been expressed about the renal safety of inhibitors of sodium-glucose cotransporter 2 over time. However, the percentage of patients with acute renal failure was lower in the empagliflozin groups than in the placebo group, and
renal function was maintained with empagliflozin.

In conclusion, patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin had significantly lower rates of the primary composite cardiovascular outcome and of death from any cause than did those in the placebo group when the study drugs were added to standard care.

References