UPDATES ON DIABETES FROM THE 2018 ESC CONGRESS

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Diabetes was a key player at the 2018 ESC congress (Munich, Germany – August 25-29, 2018). Several sessions highlighted the importance of diabetes in the overall field of cardiovascular disease and discussed its interaction with other co-morbidities and aging, current treatments, and future perspectives.

ASCEND TRIAL

A major study presented during the late-breaking trial session by Jane Armitage and Louise Bowman (UK) was the ASCEND trial, which was simultaneously published in two articles in the *New England Journal of Medicine*.[1,2] The aim of this study was to test aspirin and n–3 fatty acid supplements in patients with diabetes mellitus without a previous cardiovascular event. Thus, between 2005 and 2011, the ASCEND investigators randomized 7740 patients to aspirin 100 mg once daily and 7740 to placebo. Participants were also randomized 1:1 to receive 1-g capsules of n–3 fatty acid (840 mg of marine n-3 fatty acids [460 mg of eicosapentaenoic acid and 380 mg of docosahexaenoic acid]) once daily or matching placebo.

Every 6 months after randomization, patients received, by mail, tablets and questionnaires assessing the occurrence of outcomes, adverse events, adherence to trial treatments, use of concomitant antiplatelet or anticoagulant therapy. Blood and urine samples and data on blood pressure and weight were collected from 1800 randomly selected participants after a mean follow-up of 2.5 years. Major inclusion criteria of the trial were a previous diagnosis of diabetes mellitus (any type) and the lack of known cardiovascular disease. During a mean follow-up of 7.4 years, 8.5% of patients randomized to aspirin vs 9.6% of those randomized to placebo experienced the occurrence of a cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, or transient ischemic attack, or death from any cause). Thus, the risk of the primary efficacy outcomes was significantly reduced by 12% in patients taking aspirin vs placebo (absolute risk reduction, 1.1%).

In exploratory analyses, the difference in risk was seen mainly in the first 5 years. Aspirin was also shown to reduce the risk of the secondary outcomes (nonfatal myocardial infarction, nonfatal stroke, or transient ischemic attack, or death from any vascular cause or revascularization) by 12% (absolute risk reduction, 1.3%). However, patients receiving aspirin showed a 29% higher risk of major bleeding vs those randomized to placebo (4.1% vs 3.2%; absolute risk reduction, 0.9%), without any signal for attenuation of the effect over time and with an increasing incidence of major bleeding events and an increasing baseline vascular risk. Notably, there was no difference in the occurrence of fatal bleeding (0.2% vs 0.2%) and of fatal/nonfatal cancer across the study groups. A substantial proportion of the major bleeding events was in the upper GI tract, which might have been pharmacologically avoidable/preventable with a proton-pump inhibitor. In this regard, it should be emphasized that only one out of four ASCEND patients were being treated with a proton-pump inhibitor at the end of the study. Analyses on n–3 fatty acids reported neutral results.

In summary, the findings of the ASCEND trial provided direct evidence for the balance of the benefits and hazards of using aspirin for prevention purposes (and thus on top of other cardioprotective treatments, such as statins and blood pressure–lowering therapy) in contemporary patients with diabetes, but without a history of cardiovascular disease.

ADVANCES FROM PREVENTION TO INTERVENTION

In the *European Heart Journal*'s advances from prevention to intervention scientific session, the most important studies published on diabetes were reported. A systematic review of randomized controlled trials and genetic studies by Mach F et al focused on the perception vs the evidence of statin-related adverse effects.[3] The main results were as follows:

1. Statin therapy is associated with a modest increase in the risk of new-onset diabetes (1/1000 patient-years), particularly in patients with metabolic syndrome or prediabetes.
2. Statins do not adversely affect cognitive function and are not associated with clinically significant deterioration of renal function or development of cataracts.
3. Of the patients treated with statins, 0.5% to 2.0% reported a nonclinically relevant transient increase in liver enzymes.
4. There is no evidence of an increased risk of hemorrhagic stroke in patients without cerebrovascular disease, whereas the small increase in risk suggested by the Stroke Prevention by Aggressive Reduction of Cholesterol Levels study in subjects with a prior stroke has not been confirmed in randomized controlled trials and observational studies.

In the same session, the findings of a post-hoc analysis of the EMPA-REG OUTCOME trial that focused on the effects of empagliflozin on the risk of cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk were discussed.[4] This study considered diabetic patients without heart failure at baseline (90% of the overall EMPA-REG OUTCOME population) and reported that 67% of them had a low-to-average (<10%), 24% a high (10% to 20%) and 5% a very high (>20%) 5-year risk of heart failure. Empagliflozin was effective regardless of the risk of heart failure in terms of reducing cardiovascular death and heart failure hospitalization.

Another topic of discussion was an analysis of the Get With The Guidelines-Stroke registry investigating the impact of diabetes on outcomes in patients with a history of ischemic stroke.[5] The results of this study that enrolled 409 060 patients with a previous stroke were that concomitant diabetes was associated with a higher risk of all-cause death, all-cause readmission, risk of the composite of mortality and all-cause readmission, risk of readmission for ischemic stroke/transient ischemic attack, heart failure readmission, noncardiovascular readmission, and nonischemic stroke/transient ischemic attack readmission.

Another study published in the *European Heart Journal* and discussed during the same session was a post hoc analysis of the SAVOR-TIMI 53 trial that assessed the optimal blood pressure for prevention of cardiovascular outcomes in high-risk patients with diabetes.[6] The main result was the evidence of a U-shaped relationship between the risk of the composite of cardiovascular death, myocardial infarction, or ischemic stroke and baseline systolic and diastolic blood pressure, with nadirs at a systolic blood pressure of 130 to 140 mm Hg or a diastolic blood pressure of 80 to 90 mm Hg. Diastolic blood pressure <60 mm Hg was associated with an increased risk of myocardial infarction compared with diastolic blood pressure between 80 and 90 mm Hg.

Two lectures, one from Petar Seferovic (Serbia) and one from John McMurray (UK), focused on the tight relationship between diabetes and heart failure. Indeed, since patients with type 2 diabetes are at a high risk of developing heart failure, the prevention of heart failure has become a major emerging treatment goal in this setting. Previous studies showed an increased risk of heart failure in diabetic patients receiving peroxisome proliferator-activated receptor agonists, whereas metformin appears to have a favorable effect on outcomes in patients with diabetes mellitus and concomitant heart failure, and thus it is currently the first-line treatment option. Major attention has been dedicated to SGLT2 inhibitors, which are particularly promising for preventing heart failure in patients with diabetes mellitus (EMPA-REG and CANVAS trials). The mechanisms for SGLT2 inhibitor–related cardiovascular protection may be hemodynamic (diuretic/natriuretic effect, blood pressure reduction, arterial stiffness reduction) and metabolic

(improved myocardial metabolism, direct myocardial action, improved renal function) actions. Currently, SGLT2 inhibitors have been demonstrated to be beneficial for the prevention of heart failure in patients with type 2 diabetes, but there is a paradigm shift toward the use of these treatments in patients without diabetes. The DAPA-HF and EMPEROR-Reduced trials are currently testing the hypothesis of whether SGLT2 inhibitors will demonstrate an improvement in outcomes in these patients.

LATE-BREAKING SCIENCE

At the late-breaking science session, Peter Ueda (SE) presented the results of propensity-score matched analysis comparing the occurrence of adverse events in 17 213 patients with diabetes receiving SGLT2 inhibitors vs 17 213 treated with GLP-1 receptor agonists enrolled in Swedish and Danish registers. This study showed that GLP-1 receptor agonist use was associated with a higher incidence of lower limb amputation and diabetic ketoacidosis vs SGLT2 inhibitors, whereas there were no differences between the treatments regarding the occurrence of bone fracture, acute kidney injury, serious urinary tract infection, venous thromboembolism, and acute pancreatitis.

ADVANCES IN SCIENCE

At the advances in science session, Rasmus Roerth (DK) discussed a post-hoc analysis of the DANISH trial that assessed the association between implantable cardioverter defibrillator treatment and outcomes in heart failure patients with vs without diabetes. Overall, this study showed that, compared with patients without diabetes, patients with diabetes had a higher risk of all-cause mortality, primarily driven by increased cardiovascular mortality, including sudden cardiac death. Implantable cardioverter defibrillator treatment was associated with a reduced risk of sudden cardiac death in patients without diabetes, but not in those with diabetes, although there was no statistically significant interaction between diabetes and treatment. Patients with diabetes did not have a significantly increased risk of device complications.

SUMMARY

Overall, the presentation of the important trials' findings and lectures from key opinion leaders in cardiovascular medicine made the 2018 ESC congress a unique opportunity to widen the most recent knowledge on the burdensome relationship between type 2 diabetes and cardiovascular disease. ■

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