Editorial

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition with evolocumab: powerful low-density lipoprotein cholesterol (LDL-C) lowering and improved cardiovascular outcomes without an increase in the risk of diabetes mellitus

Constantine E. Kosmas¹, Andreas Sourlas², Kyriaki V. Bouza³, Eddy DeJesus⁴, Delia Silverio⁵, Peter D. Montan⁶, Eliscer Guzman⁶

¹Department of Medicine, Division of Cardiology, Mount Sinai Hospital, New York, NY, USA; ²School of Medicine, University of Crete, Heraklion, Greece; ³Iatriki Diagnosi Group, PC, Athens, Greece; ⁴Department of Medicine, Bronx-Lebanon Hospital Center, Bronx, NY, USA; ⁵Cardiology Clinic, Cardiology Unlimited, PC, New York, NY, USA; ⁶Department of Medicine, Division of Cardiology, Montefiore Medical Center, Bronx, NY, USA

Correspondence to: Constantine E. Kosmas, MD, PhD. 168-24 Powells Cove Blvd., Beechhurst, NY 11357, USA. Email: cekosmas1@gmail.com.

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Cardiovascular disease (CVD) is the leading global cause of death and accounts for approximately 30% of the total annual deaths worldwide (1). In the United States, CVD is very common and affects over one third of the population (2). It is well established that low-density lipoprotein cholesterol (LDL-C) is involved in the pathogenesis of atherosclerosis, and treatment with LDL-C-lowering medications has elicited a marked reduction in cardiovascular risk in both primary (3) and secondary (4) prevention.

Statins remain the standard of care (SOC). Extensive clinical trial evidence has proved their effectiveness for LDL-C lowering and reduction of cardiovascular risk (5,6). However, there are still cases in which patients fail to attain the desired LDL-C goals or demonstrate intolerance to statins due to side effects (mostly myalgias).

Furthermore, the use of statins has been linked to an increased incidence of diabetes. In a randomized, double-blind, placebo-controlled, multicenter trial ["Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin" (JUPITER)], treatment with rosuvastatin led to a 25% increase in the incidence of physician-reported newly diagnosed diabetes (7). In a meta-analysis, which included 57,593 patients with a mean follow-up of 3.9 years, statin use was associated with a 13% increase in diabetes risk (8). In another large meta-analysis, which included 91,140 participants from 13 incorporated statin trials, treatment with statins led to a 9% increased risk of incident diabetes (9). A very large network meta-analysis, which included 29 trials with 163,039 participants, revealed that statins, as a class, led to a 12% increase in the likelihood of developing diabetes. Atorvastatin 80 mg was the main offender, as it increased the risk of diabetes by 34%, followed by rosuvastatin, which increased the risk of diabetes by 17% (10). Finally, an analysis conducted to evaluate the statin-diabetes association using data from the Diabetes Prevention Program (DPP), which studied a cohort of overweight and obese individuals at high risk for diabetes, followed specifically for incident diabetes, showed that statin therapy raised the risk of incident diabetes by 36% (11).

Thus, extensive research is being carried out for the
development of new drugs with a favorable side effect profile, which (used alone or in combination with statins) would be able to significantly reduce LDL-C and decrease cardiovascular risk (12,13).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease, which is highly expressed in the liver, small intestine and kidneys. In humans, the PCSK9 gene resides on chromosome 1p32.3 and encodes a 692-amino acid inactive glycoprotein, which undergoes an intramolecular self-catalytic processing in the endoplasmic reticulum (14). PCSK9 induces the degradation of LDL receptors by targeting the receptors for lysosomal destruction. Thus, recycling of the LDL receptors is reduced and the removal rate of LDL-C from circulation is decreased (15-17).

Several new drug therapies with different mechanisms of action have been developed or are in development in order to decrease circulating levels of PCSK9, including inhibition of its self-cleavage to an active form, enhancement of its cleavage by furin, and impedence of its binding with the LDL receptor (18). However, up to date, the human monoclonal antibodies evolocumab and alirocumab are the only approved PCSK9 inhibitors associated with a remarkable reduction in the levels of LDL-C and other apoB-containing lipoproteins, such as lipoprotein(a) (19).

Several studies have evaluated the lipid-lowering effects of PCSK9 inhibitors. The Open-Label Study of Long-Term Evaluation against LDL Cholesterol 1 (OSLER-1) and 2 (OSLER-2) revealed that after 12 weeks of therapy evolocumab, compared to standard therapy, reduced the LDL-C level by 61%, and this effect remained consistent over time (20). In the Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial, alirocumab, administered on top of maximally tolerated dose of statin, alone or in combination with other LDL-C-lowering drugs, induced an additional 61.9% LDL-C reduction, as compared with placebo (21).

Given the remarkable LDL-C lowering conferred by PCSK9 inhibitors, outcome studies were eagerly awaited to establish their true clinical benefits in decreasing the risk for CVD. Recently, in the Further cardiovascular OUcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) trial, inhibition of PCSK9 with evolocumab, administered on a background of statin therapy over an average follow-up period of 2.2 years, reduced the primary outcome (composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospital admission for unstable angina) by 15% and the key secondary outcome (composite of cardiovascular death, myocardial infarction, or stroke) by 20%. The effect appeared also to increase over time. There was no significant difference in the incidence of adverse events (including neurocognitive events) between the study groups, but for injection-site reactions, which were somewhat more frequent with evolocumab (22).

As it was mentioned earlier, statin therapy has been linked to an increased risk of incident diabetes. On the other hand, there is evidence that certain genetic PCSK9 variants linked to lower LDL-C levels are also associated with higher fasting plasma glucose (FPG) levels, bodyweight, and waist-to-hip ratio, as well as a 29% increased risk of type 2 diabetes (23).

Thus, a prespecified analysis of the FOURIER trial was conducted to investigate the efficacy and safety of evolocumab by diabetes status at baseline and the effect of evolocumab on glycemia and risk of developing diabetes. The primary endpoint was a composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularisation and the key secondary endpoint was a composite of cardiovascular death, myocardial infarction, or stroke. At baseline, there were 11,031 patients (40%) with diabetes and 16,533 patients (60%) without diabetes (of whom 10,344 were prediabetic and 6,189 had normoglycemia). It was shown that evolocumab significantly reduced cardiovascular risk in patients with and without diabetes at baseline. More specifically, for the primary endpoint, the hazard ratios (HR) with evolocumab were 0.83 and 0.87 for patients with and without diabetes, respectively. For the key secondary endpoint, the HR with evolocumab were 0.82 and 0.78 for patients with and without diabetes, respectively. Furthermore, evolocumab did not increase the risk of new-onset diabetes in patients without diabetes at baseline (HR, 1.05; 95% CI, 0.94–1.17), including those with prediabetes (HR, 1.00; 95% CI, 0.89–1.13). Levels of glycosylated hemoglobin (HbA1c) and FPG did not differ significantly over time between the evolocumab and placebo groups in patients with diabetes, prediabetes, or normoglycemia (24).

This analysis clearly establishes the favorable clinical effects of evolocumab in the reduction of cardiovascular risk in patients with and without diabetes. Furthermore, it was clearly shown that these beneficial effects of evolocumab occurred without an increased risk of incident diabetes. Although, the median duration of follow-up in
the FOURIER trial was only 2.2 years, there is evidence that even longer use of evolocumab, up to 4 years, does not lead to an increase in the risk of diabetes. More specifically, results up to 4 years from the Open-Label Study of Long-term Evaluation Against LDL-C (OSLER-1) Extension Study revealed an annualized incidence of new-onset diabetes of 4% in the SOC therapy alone group versus an annualized incidence of 2.8% in the evolocumab plus SOC therapy group after adjusting for duration of evolocumab exposure (25).

Thus, PCSK9 inhibition with evolocumab provides powerful LDL-C lowering and improved cardiovascular outcomes without an increase in the risk of diabetes mellitus. Further studies with other PCSK9 inhibitors (alirocumab), as well as other PCSK9 targeting agents, such as inclisiran, are eagerly awaited in order to confirm (or disprove) that any drug-induced reduction of PCSK9 levels does not lead to an increase in the risk of incident diabetes.

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Footnote

Conflicts of Interest: CE Kosmas has received personal fees from Amgen, Inc. (Member of the Speaker Bureau) and Sanofi US (Consultant). The other authors have no conflicts of interest to declare.

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