Lowering low-density lipoprotein cholesterol by PCSK9 inhibition in patients with diabetes on insulin therapy: is it efficacious and safe?

Michel Farnier

Department of Cardiology, CHU Dijon Bourgogne, and Lipid Clinic, Point Medical, Dijon, France

Correspondence to: Michel Farnier. Lipid Clinic, Point Medical, 21000 Dijon, France. Email: michelfarnier@nerim.net.

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Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of the excess morbidity and mortality for individuals with diabetes (1). Patients with type 2 diabetes have an atherogenic lipid profile characterized by elevated non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (apoB) and triglycerides (TG), along with low HDL-cholesterol. Often and by comparison to general population, the levels of low-density lipoprotein cholesterol (LDL-C) are normal or only modestly elevated, but with an increased proportion of atherogenic small, dense LDL particles. By contrast, in patients with type 1 diabetes who have good glycaemic control, lipid and lipoproteins concentrations appear similar to those of the background population. However, there are potentially atherogenic changes in the composition of both LDL and HDL particles (2).

In patients with diabetes (mainly type 2 diabetes), several clinical trials and meta-analyses have consistently shown that lowering LDL-C by statins or statin plus ezetimibe is associated with a significant reduction of major vascular events. In the CTT meta-analysis (3), statin therapy reduces the incidence of major vascular events by 21% per mmol/L reduction in LDL-C, with similar reductions of relative risk among people with and without diabetes, and among people with either type 1 or type 2 diabetes (3). The CTT meta-analysis further indicates that the residual absolute risk of major cardiovascular events on statin therapy appears greater for patients with diabetes by comparison with patients without diabetes, and this residual risk is particularly high for patients with ASCVD: despite the effects of statin therapy, the percentage of major vascular events was 31.6% in patients with diabetes and vascular disease, compared with 23.5% for patients with vascular disease, but without diabetes and 11.8% for patients with diabetes and without vascular disease. The potential benefit of more-intensive statin therapy compared with moderate therapy has been tested in several trials in patients with ASCVD: a higher residual risk persists on atorvastatin 80 mg in the TNT trial for patients with diabetes compared with patients without diabetes (4).

It also appears in the CTT meta-analysis that the residual risk on statin therapy was particularly high for patients with type 1 diabetes (3). However, only 1,466 patients with type 1 diabetes are present in this meta-analysis conducted in 18,686 people with diabetes.

In the IMPROVE-IT trial (5), the combination treatment with ezetimibe and simvastatin was compared with simvastatin monotherapy in patients who had a recent acute coronary syndrome. In the large subgroup of patients with diabetes, the addition of ezetimibe was very effective with a 14% reduction in the relative risk and a 5.5% reduction in the absolute risk of major cardiovascular events. Despite the beneficial effect of combination of ezetimibe and simvastatin, major vascular events occurred for 40% of patients with diabetes compared with 30% of

patients without diabetes.

Additional treatments are therefore needed to reduce this residual risk and the most recent guidelines (2,6,7) recommended to consider a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor in individuals with diabetes at very high-risk whose LDL-C levels are not optimally controlled on maximally-tolerated statin and ezetimibe therapies. Indeed, in placebo-controlled trials evaluating the addition of a PCSK9 inhibitor to maximally tolerated doses of statin therapy in participants who were at high risk for ASCVD, the two fully human monoclonal antibodies, alirocumab and evolocumab, administered as subcutaneous injections every 2 or 4 weeks induced significant decreases in LDL-C (from 45% to 70%) (8,9).

In complementary analyses of placebo-controlled phase 3 studies, the efficacy of PCSK9 inhibitors was similar for patients with and without diabetes: in 413 patients with type 2 diabetes (10), evolocumab (140 mg every 2 weeks or 420 mg every 4 weeks) reduced LDL-C by 60% versus placebo and 39% versus ezetimibe. In a subanalysis of ODYSSEY COMBO II trial (11), alirocumab (mainly at the dose of 75 mg every 2 weeks) reduced LDL-C by 49.1% in patients with diabetes. Data on clinically efficacy for patients with diabetes and ASCVD have been recently reported from a prespecified secondary analysis of FOURIER trial (12): in 11,031 patients with diabetes (97% with type 2 diabetes, 25% taking insulin), evolocumab significantly reduced LDL-C by 57% and cardiovascular outcomes with similar relative risk reduction in patients with and without diabetes. Given the higher risk of ASCVD in patients with diabetes, the absolute benefit of evolocumab therapy was expected to be greater in this group than in patients without diabetes. Patients with diabetes tended to have a greater absolute risk reduction with evolocumab for the primary endpoint (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization), but not for the key secondary hard endpoint (composite of cardiovascular death, myocardial infarction or stroke) with an identical 2.0% absolute risk reduction in patients with or without diabetes. No information is available for the subgroup of patients with diabetes on insulin therapy, neither for biological efficacy, nor for cardiovascular risk.

The ODYSSEY DM-INSULIN trial recently published (13,14) is the first trial evaluating specifically the efficacy and safety of a PCSK9 inhibitor, alirocumab, in insulin-treated patients with type 1 or type 2 diabetes and high cardiovascular risk and who had LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) despite stable maximally tolerated dose of statin with or without other lipid lowering drugs. In this double-blind 24-week trial, 517 patients with type 2 diabetes (n=441) or type 1 diabetes (n=76) have been randomized to receive alirocumab 75 mg every 2 weeks or placebo (ratio, 2:1), with an uptitration to 150 mg every 2 weeks if LDL-C level remains ≥70 mg/dL at week 8. Overall, only 22.6% of individuals randomized to alirocumab required an uptitration to 150 mg (20.2% of patients with type 2 diabetes and 36.7% with type 1 diabetes). At week 24, the mean LDL-C decreases were 49.0% and 47.8% versus placebo for patients with type 2 and type 1 diabetes, respectively (P<0.0001). Alirocumab also resulted to significant reductions in non-HDL-C and apoB levels. The magnitude of LDL-C and non-HDL-C reductions was consistent with results observed in previous ODYSSEY phase 3 trials (11,15). The decreases in TG levels were modest and non-significant (–5.7% for type 2 diabetes, –15.5% for type 1 diabetes, versus placebo), suggesting that monoclonal antibodies against PCSK9 have a minor impact on metabolism of TG-rich lipoproteins. In the ODYSSEY DM-INSULIN trial, alirocumab was as well tolerated as in other phase 3 trials (8), with a lower incidence of local injection-site reactions compared to prior studies (8). This study confirms results of previous subgroup analyses showing that individuals with diabetes tend to have fewer injection-site reactions than those without diabetes (11,16). Moreover, the ODYSSEY DM-INSULIN trial provides specific information on the safety and tolerability of the concomitant administration of 2 injectable agents alirocumab and insulin: the overall acceptance of alirocumab was excellent, with the limitation of a relatively short treatment period.

One safety concern related to statin therapy is the increased risk of type 2 diabetes, albeit that the beneficial effect on the risk of cardiovascular disease strongly justifies the use of statin therapy for patients with diabetes (17). In the ODYSSEY DM-INSULIN trial (14), changes in HbA1c and plasma glucose levels were minimal and the total daily insulin dose unchanged for the duration of the study. These results are consistent with other analyses from trials with alirocumab and evolocumab showing no association with an increased risk of new-onset diabetes (12,18). However, findings from Mendelian randomization studies suggest that genetic variants in PCSK9, as well as in HMG-CoA reductase, associated with lower levels of LDL-C are also associated with an increased risk of diabetes (19-21). Moreover, bococizumab treatment was associated with a very small increase in blood glucose at 1 year in

SPIRE-2 trial (22) and in a recent meta-analysis including 68,123 participants with median follow-up of 78 weeks (23), PCSK9 inhibition therapy induces a small but significant increase in plasma glycaemia and HbA1c. Longer follow-up is needed to evaluate more conclusively the effect of PCSK9 inhibitors on glycaemic control, even if it's unlikely that PCSK9 inhibition has a major effect on diabetes risk.

Finally, all these data highly suggest that PCSK9 inhibition with fully human monoclonal antibodies such as alirocumab or evolocumab is efficacious and safe for patients with diabetes and ASCVD, including those on insulin therapy. However, data from FOURIER trial also show that despite evolocumab treatment added to statin therapy, a higher residual risk persists for patients with diabetes: in FOURIER, the incidence of cardiovascular death, myocardial infarction and stroke was higher in the evolocumab group of patients with diabetes (10.2%) than in the placebo group of patients without diabetes (8.4%). It remains to determine if other therapies acting more on TG-rich lipoproteins could be more effective to reduce the cardiovascular risk linked to the specific atherogenic lipid profile usually observed for patients with diabetes.

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Footnote

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