

The treatment of dyslipidemia in type 2 diabetes

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In 2014 close to 30 million Americans, or 10% of the population, had either type 1 or type 2 diabetes. Diabetes is estimated to affect over 410 million individuals worldwide, and the prevalence is growing with the number of affected individuals projected to increase to over 640 million by 2040. Not only does diabetes increase the risk of developing atherosclerotic cardiovascular disease, but in patients with atherosclerotic cardiovascular disease concomitant diabetes is associated with worse outcomes. Not surprisingly, cardiovascular disease is the greatest cause of morbidity and mortality in patients with diabetes. Consequently, patients with diabetes need intensive management of their cardiovascular risk factors. To that end, low-density lipoprotein (LDL) cholesterol lowering with a high-intensity statin is recommended in patients with diabetes, both in those with and without atherosclerotic cardiovascular disease. Yet despite such therapy, patients with diabetes remain at high risk of recurrent cardiovascular events.

Dyslipidemia in patients with diabetes is characterized by the specific phenotype of increased triglycerides (TG), low levels of high-density lipoprotein cholesterol (HDL-C) and LDL-C levels often within the normal range (increased LDL-C levels are seen in 25% of patients). Diabetes is accompanied by increased levels of small dense LDL-C particles which are more proatherogenic than the larger ones. Except for diet and lifestyle changes there are six-pharmacological agents to treat diabetic dyslipidemia with and which are going to be discussed below.

Life style: diet, exercise and weight loss

More than 3 out of 4 patients with diabetes are at least overweight and nearly 50% are obese. A weight reduction of at least 5% is necessary to see any, and only modest improvements in the lipid profile. Various diets have a wide-range of effects on plasma lipids. For example a diet low in carbohydrates increases HDL-C by 10% with no changes in LDL-C or TG levels, a Mediterranean diet decreases TG by 9% and increases HDL-C by 5% with no changes in LDL-C levels, while a high-protein diet, which require 20% to 30% or more of the total daily caloric intake to come from protein, have

no effect on lipid parameters. The Look-AHEAD study examined overweight patients with diabetes that were randomised to an intensive lifestyle intervention (weight loss and regular physical activity) and were followed for a median of 9.6 years. While there was an improvement in blood pressure, HbA1c and lipid profile, this did not translate to reduced cardiovascular events and thus the trial was stopped early. Compared with counselling alone, there was modest overall benefits including 6% more weight loss, a 5.8 mg/dl reduction in TG an 1.7 mg/dl increase in HDL-C and no significant change in LDL-C when adjusted for medication use. Despite the unimpressive effect on lipid profile, weight loss via any means remains very important for the overweight patient with diabetes since it is associated with improved glycemic control and insulin sensitivity. Regarding exercise there dot seem to be any significant, reproducible and independent effect of exercise on LDL-C, HDL-C or TG in patients with diabetes.

Statins

The 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-CoA) reductase inhibitors or statins are the cornerstone of the treatment of dyslipidemia. The role of statins for the management of dyslipidemia among patients with diabetes has been established. The Heart Protection Study randomised 5963 patients with type 2 diabetes to either simvastatin or placebo, which resulted in a 39 mg/dl reduction in LDL-C compared with placebo and a reduction in Major Adverse Cardiac Events (MACE) of 22%. The Collaborative Atorvastatin Diabetes Study (CARDS) randomized 2838 patients with type 2 diabetes and an LDL-C of less than 160 mg/dl to low-dose atorvastatin over a median follow-up of 4 years. There was a significant 37% reduction in MACE but no effect significant on mortality even though it was decreased by -27% ($p=0.0569$). A large meta-analysis that included more than 18.000 patients with diabetes treated with statin monotherapy showed a 95 reduction in all-cause mortality and a 215 reduction in the incidence of MACE per 38 mg/dl decrease in LDL-C, a finding similar to that observed in patients without diabetes. Therefore, the established relationship between LDL-c reduction and cardiovascular risk reduction is true also for patients with diabetes. Despite a small effect on glucose metabolism raising HbA1c on average by

0.12% the safety and efficacy of statin treatment justifies the position of statins as the first -line choice for the treatment of dyslipidemia in patients with diabetes. Still recent randomized controlled trials show that up to 1 in 5 patients with diabetes and established CVD are not on statin therapy.

Ezetimibe

Ezetimibe is a cholesterol absorption inhibitor targeting the Niemann-Pick C1-like 1 (NPC1L1) protein in the intestine. The decrease in absorbed cholesterol causes the liver to use more circulating cholesterol and as a consequence decreases LDL-C plasma levels by 15-25%. The IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a randomised controlled trial comparing ezetimibe and simvastatin with placebo and simvastatin among 18.144 patients post acute coronary syndrome. Ezetimibe was associated with a 24% additional decrease in LDL-C (70 mg/dl vs 53 mg/dl) and a small 2% reduction in cardiovascular events. Approximately 25% of all subjects in each arm had also diabetes. When stratified into those with and without diabetes, it was those with diabetes (40% vs 45.5%; HR 0.86, 95% CI 0.78-0.94) that benefited significantly more than those without diabetes (30.2% vs. 30.8%, HR 0.98 CI 0.91-1.04).

Fibrates

Fibrates are peroxisome proliferator receptor agonists and have been shown to reduce TG by up to 30% and increase HDL-C by 10%. The FIELD (Fenofibrate Intervention and Event Lowering in diabetes) trial compared fenofibrate therapy with placebo in 9795 patients and found a significant reduction in non-fatal MI and coronary revascularisation among individuals with diabetes taking fenofibrate. Statin use was variable and ultimately higher in the placebo arm. At mean follow-up of 5 years there was no difference between the two groups in the composite primary endpoint of CV death, MI, stroke and need for coronary or carotid revascularisation. In a prespecified analysis of the group of patients with elevated TG (>204 mg/dl) and low HDL-C (<40 mg/dl) there was a significant relative risk reduction of 27% ($p=0.005$) in the composite endpoint.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial compared 5518 patients who in addition to statin therapy received either fenofibrate or placebo. Overall the trial failed to show any benefit in the composite of fatal CV events, nonfatal MI or nonfatal stroke. However, as observed in the FIELD trial, a subgroup of patients with the highest TG (≥ 204 mg/dl) and lowest HDL-C (≤ 34 mg/dl) had a 29% relative risk reduction (17.3% vs. 12.4%). A large metaanalysis further evaluated the effects of fenofibrate in this subgroup and found that fibrates reduce vascular events by 25% in patients with both elevated TG alone (N=7389), by 29% in those with both elevated TG and low HDL-C (N=5068) and by 16% in those with low HDL-C only (N=15.303).

Bile acid sequestrants

The administration of bile acid sequestrants depletes the endogenous bile acid pool and as a consequence stimulates an increase in bile acid synthesis from cholesterol, which in turn upregulates the LDL receptor expression, thus reducing circulating LDL-C concentrations. At the maximum dose of cholestyramine, colestipol or colesevelam a decrease in LDL-C of 18% to 25% has been observed. There are no effects on the HDL-C levels and a tendency to increase TG levels. Furthermore, use of these drugs is associated with significant gastrointestinal side effects such as nausea, flatulence, dyspepsia and drug interactions. Without CV outcomes trials, bile acid sequestrants remain an option for the statin-intolerant patient either as monotherapy or in combination with ezetimibe.

Omega-3 fatty acids

Omega-3 fatty acids can be used at pharmacologic doses (2-4 gr/day) to lower TG by up to 45%. The exact mechanism of action remains unclear. One potential mechanism is via the activation of the peroxisome proliferator receptor α and decrease the secretion of apolipoprotein B. There has been conflicting outcome data on omega-3 fatty acid supplementation. The most recent and largest meta-analysis included more than 63.000 subjects from 20 primary and secondary prevention studies and found no overall effect of omega-3 fatty acids on a composite endpoint of CV events or mortality. Two very

important randomized placebo-controlled trials each with ≥ 8.000 subjects (REDUction of Cardiovascular Events with EPA-Intervention Trial [REDUCE-IT] and Outcomes Study to Assess STatin residual Risk REDuction with EpaNova in hiGh CV risk PatienTs with Hypertriglyceridemia [STRENGTH]) are studying the potential benefits of these drugs on CVD outcomes in patients with elevated triglycerides. Of particular interest for the diabetic patient is the ASCEND Study (A Study of Cardiovascular Events in Diabetes) which is evaluating if aspirin 100 mg/day and/or omega-3 fatty acids 1g/day reduce the risk of CV events in this population in a primary prevention setting (N=15.480).

PCSK9 antibodies

Proprotein convertase subtilisin kexin type 9 (PCSK9) is a serine protease that is mainly synthesized and secreted from the liver which binds to the LDL receptor and triggers its degradation. Fully human monoclonal antibodies against PCSK9 have been developed, like evolocumab and alirocumab, that prevent this binding thus allowing for more LDL receptors on the liver surface and subsequently lower LDL-C levels. We recently published a pre-specified analysis of the FOURIER trial examining the efficacy and safety of evolocumab by diabetes status and the effect of evolocumab on glycemia and risk of developing diabetes. FOURIER was a randomized trial of evolocumab (140 mg every 2 weeks or 420 mg once a month) versus placebo in 27,564 patients with atherosclerotic disease who were on statin therapy, followed up for a median of 2.2 years. We investigated the effect of evolocumab on cardiovascular events by diabetes status at baseline. The primary endpoint of FOURIER was a composite of cardiovascular death, myocardial infarction (MI), stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary endpoint was cardiovascular death, MI, or stroke. We also assessed the effect of evolocumab on glycemia, and on the risk of new-onset diabetes among patients without diabetes at baseline.

At study baseline, 11,031 patients (40%) had diabetes and 16533 (60%) did not, of whom 10.344 had prediabetes and 6189 had normoglycemia). The median baseline LDL-C levels were 89 mg/dl and 93 mg/dl in patients with and without diabetes, respectively. Compared with placebo evolocumab lowered

LDL-C by 57% in the diabetes subgroup and by 60% in the non-diabetes subgroup at 48 weeks down to 31 mg/dl. Evolocumab similarly lowered related atherogenic lipid measures. Compared with placebo, at 48 weeks, evolocumab reduced non-HDL cholesterol levels by 50 and 53%, apolipoprotein B by 48 and 50% and TG by 16% and 17% in patients with and without diabetes at baseline, respectively ($p < 0.001$ for evolocumab vs. placebo for all lipid measures in both subgroups). Evolocumab significantly reduced cardiovascular outcomes consistently in patients with and without diabetes at baseline. For the primary endpoint the hazard ratios (HRs) were 0.83 (95% CI 0.75-0.93; $p = 0.0008$) for patients with diabetes and 0.87 (0.79-0.96; $p = 0.0052$) for those without diabetes. For the key secondary endpoint the HRs were 0.82 (0.79-0.96; $p = 0.0021$) for those with diabetes and 0.78 (0.69-0.89; $p = 0.0002$) for those without diabetes. Evolocumab did not increase the risk of new-onset diabetes in patients without diabetes at baseline (HR 1.05, 0.94-1.17), including in those with prediabetes (HR 1.00, 0.89-1.13). Levels of HbA1c and fasting plasma glucose (FPG) were similar between the evolocumab and placebo groups over time in patients with diabetes, prediabetes or normoglycemia. Among patients with diabetes at baseline, the proportions of patients with adverse events were 78.5% in the evolocumab group and 78.3% in the placebo group. Among patients without diabetes at baseline the proportions with adverse events were 76.8% in the evolocumab group and 76.8% in the placebo group.

In summary our analyses yielded three main findings. First, among patients with atherosclerotic cardiovascular disease, the presence of diabetes, was independently associated with a substantially increased risk of cardiovascular morbidity and mortality. Second, evolocumab lowered LDL-C and significantly reduced cardiovascular risk with similar efficacy in patients with and without diabetes. However, due to their heightened baseline risk of cardiovascular events, patients with diabetes tended to have a greater absolute risk reduction with evolocumab therapy. Third, evolocumab did not increase the risk of new-onset diabetes, even in patients with prediabetes, nor did it worsen glycemia over a median of 2.2 years of follow-up.

The similar relative risk reductions in cardiovascular outcomes seen with LDL-C lowering with

evolocumab in patients with and without diabetes is supported by analogous observations for LDL-C lowering with statin therapy. However, the rate of cardiovascular events was approximately 50% higher in patients with diabetes in this modern trial of patients with atherosclerotic cardiovascular disease. Recent guidelines have recommended identifying people with diabetes and established atherosclerotic cardiovascular disease as having an extreme risk requiring more intensive treatment to achieve lower LDL-C goals (< 55 mg/dl). The number needed to treat over 3 years to prevent one primary endpoint was 63 in patients without diabetes, but only 37 in patients with diabetes.

The ESC/EAS Guidelines for Dyslipidemia use the same LDL-C target (LDL-C < 70 mg/dl) for patients with diabetes without atherosclerotic cardiovascular disease (but over the age of 40 and with cardiovascular risk factors or markers of target organ damage) as they do for patients with atherosclerotic cardiovascular disease because of their high risk for cardiovascular events. Given the FOURIER inclusion criteria, our data do not inform on the potential benefits of PCSK9 inhibition in patients with diabetes without atherosclerotic cardiovascular disease, which would require a separate study. However, the data suggest this population may be a high-yield primary prevention population to investigate.

Equally important is the safety profile of evolocumab. In addition to providing reassurance that the overall safety profile was similar in patients with and without diabetes, the risk of new-onset diabetes (which was adjudicated using a centralized clinical events committee) appeared to be similar in the two treatment arms. However, we have to point out that the trial has a median follow-up of 2.2 years.

In conclusion, evolocumab lowers LDL-C and significantly reduced cardiovascular risk with similar efficacy in patients with and without diabetes. Due to their heightened baseline risk of cardiovascular events, patients with diabetes tended to have a greater absolute risk reduction with evolocumab therapy. Evolocumab did not increase the risk of new-onset diabetes, even in patients with prediabetes, nor did it worsen glycemia over several years. These data suggest evolocumab use in patients with atherosclerotic disease and diabetes is particularly efficacious and is safe.

Alirocumab has been shown to significantly de-

crease cardiovascular events in patients cardiovascular disease in the Odyssey Outcomes trial. Twenty nine percent of the patients had also type 2 diabetes. An analysis of the effects of alirocumab in this subgroup of the Odyssey Outcomes patients

with diabetes has not been published yet.

Considering the many existing therapeutic options it is disappointing to see that ~50% of patients with diabetes do not achieve their LDL-C prespecified treatment goals.