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MACROVASCULAR COMPLICATIONS IN DIABETES (VR ARODA AND A GETANEH, SECTION EDITORS)

Comparison of Lipid-Lowering Medications and Risk for Cardiovascular Disease in Diabetes

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Abstract

Purpose of the Review To summarize available evidence regarding lipid-lowering interventions for the prevention of cardiovascular disease in patients with diabetes.

Recent Findings Statins and non-statin therapies that act through upregulation of LDL receptor expression are associated with similar cardiovascular risk reduction per decrease in LDL cholesterol.

Summary In subjects with diabetes, with or without established cardiovascular disease, each 39 mg/dl reduction in LDL cholesterol observed with statins is associated with a 21% relative reduction in the risk of major coronary events at 5 years. Statins remain the first-line lipid-lowering agents for the management of dyslipidemia in individuals with diabetes; however, the addition of non-statin therapies to lower LDL cholesterol, such as ezetimibe and PCSK-9 inhibitors, to maximally tolerated statin therapy is recommended in patients with atherosclerotic cardiovascular disease and baseline LDL cholesterol over 70 mg/dl. Recent data support even lower LDL cholesterol targets (< 55 mg/dl) to further reduce the risk of cardiovascular events especially in subjects with diabetes and documented cardiovascular disease.

Keywords Diabetes · Lipid-lowering interventions · Cardiovascular disease

Introduction

Recent estimates indicate that 425 million people worldwide are affected by diabetes mellitus and exposed to its complications which are major causes of premature death [1]. Diabetes is known to be a potent risk factor for the occurrence of a first cardiovascular event [2]; in patients with established cardiovascular disease, the presence of diabetes is associated with worse outcomes [3]. Therefore, in patients with diabetes, intensive management of cardiovascular risk factors is crucial [4, 5].

The UK Prospective Diabetes Study (UKPDS) including 3055 patients with type 2 diabetes showed that elevated low-density lipoprotein (LDL)–cholesterol was the primary risk

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factor for cardiovascular events within 10 years of follow-up; of note, for each increment of 39 mg/dl in LDL-cholesterol concentration there was a 1.57-fold increased risk of coronary artery disease [6].

Statins are recommended as the first-line lipid-lowering drug therapy for the management of dyslipidemia in individuals with diabetes [7–9]. However, several non-statin therapies are currently available including ezetimibe, a cholesterol absorption inhibitor, fibrates, and the more recent proprotein convertase subtilisin kexin-9 (PCSK-9) inhibitors.

The aim of this review was to summarize available evidence regarding lipid-lowering interventions for the prevention of cardiovascular disease and to provide a practical guide for their use focusing on the subgroup of patients with diabetes.

LDL Cholesterol: The Lower The better Also in Diabetes

LDL cholesterol is a well-established risk factor for cardiovascular disease and is the primary target of lipid-lowering therapy in current practice guidelines.

The Cholesterol Treatment Trialists' meta-analysis of > 18,000 patients with diabetes reported that each 39 mg/dl reduction in LDL cholesterol observed with statins was associated with a 21% relative reduction in the risk of major vascular events at 5 years [10]. The proportional effects of statin therapy in diabetes were similar irrespective of whether there was a prior history of vascular disease.

Table 1 summarizes current recommendations for the management of hypercholesterolemia in patients with diabetes. The American Diabetes Association and the American College of Cardiology/American Heart Association propose a clinically defined risk-based approach in primary prevention recommending moderate- to high-intensity statins based on age and/or baseline LDL cholesterol values; in secondary prevention, the LDL cholesterol goal is less than 70 mg/dl [7, 11]. The European Society of Cardiology maintains a cardiovascular risk equivalence status for diabetes suggesting LDL cholesterol targets less than 70 mg/dl for all patients with diabetes with or without established cardiovascular disease [9].

Although there is consensus on the value of lowering LDL cholesterol, recommendations about how to do so have shifted over time. Statins are widely prescribed due to their cost-effectiveness; however, only ~ 67% of subjects with diabetes take optimal statin doses, only 30% of those with diabetes and cardiovascular disease reach the LDL goal of less than 70 mg/dl in the USA, and some patients discontinue therapy due to intolerance, thus remaining at increased risk of cardiovascular events [12•, 14]. A recent American College of Cardiology expert consensus document recommended adding certain non-statin therapies to lower LDL cholesterol, such as ezetimibe and PCSK-9 inhibitors to maximally tolerated statin therapy in patients with atherosclerotic cardiovascular disease and baseline LDL cholesterol over 70 mg/dl [12•]. However, the clinical benefit of non-statin therapies to lower LDL cholesterol has been questioned by some. To address this issue, Silverman et al. performed a meta-regression analysis to evaluate the association between lowering LDL cholesterol and cardiovascular risk reduction across different therapeutic interventions [15•]. This analysis, including 49 clinical trials with 312,175 participants, indicates that each 39 mg/dl reduction in LDL cholesterol level was associated with a relative risk of major vascular events of 0.77 for statins ($p < 0.001$) and 0.75 for non-statin interventions that act via upregulation of LDL receptor expression ($p = 0.002$) [15•]. These data suggest statins and non-statin therapies that act through upregulation of LDL receptor expression are associated with similar cardiovascular risk reduction per decrease in LDL cholesterol.

Lifestyle Modifications to Improve the Lipid Profile

Dietary and other lifestyle factors are known to have an effect on lipids. A large meta-analysis of 70 studies indicated that even a modest weight reduction through dieting was able to improve lipid abnormalities [16]. Indeed, the long-term effectiveness of weight loss on the lipid profile is particularly evident in patients undergoing bariatric surgery with remission rates from hyperlipidemia of 23 to 60% depending on the type of surgery [17]. Weight reduction can be achieved inducing a caloric deficit of 300–500 Kcal per day, and physical activity should be performed for at least 30 min every day [18].

The Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts (PREDIMED) trial demonstrated that a Mediterranean diet with consumption of fruit, vegetables, legumes, extra-virgin oil, nuts, and fish reduces the incidence of major cardiovascular events compared to a reduced fat diet (3.8% with extra-virgin oil vs. 3.4% with nuts vs. 4.4% with a reduced fat diet) [19]. Therefore, dietary choices inspired by this model with a limited intake of trans or saturated fat are recommended for both primary and secondary prevention of cardiovascular disease.

Lipid-Lowering Medications

Statins

Statins reduce hepatic cholesterol synthesis through the competitive inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity. The reduction of

Table 1 Recommendations for management of hypercholesterolemia in adults with diabetes (Please note that updated ACC/AHA guidelines are due to be reported soon)

	Type of prevention	Sub-group categories		Suggested lipid-lowering drug regimen
ADA, 2018 [7]	Primary prevention	Age < 40 years		• Consider moderate-intensity statin if LDL ≥ 100 mg/dl or other CV risk factor (high blood pressure, smoking, chronic kidney disease, albuminuria, or family history of premature atherosclerotic cardiovascular disease)
		Age > 40 years		• Moderate-intensity statin recommended • Consider high-intensity if other CV risk factor
	Secondary prevention	All subjects		• High-intensity statin recommended. • If LDL ≥ 70 mg/dl after high-intensity statin, consider addition of Ezetimibe or PCSK9i[§]
ACC/AHA, 2013 and focused update, 2017 [11, 12•]	Primary prevention	LDL ≥ 190 mg/dl	All ages	• Search for secondary causes • High-intensity statin recommended - If LDL reduction < 50% (or LDL-c levels > 100 mg/dl) consider addition of ezetimibe or PCSK9i[#]
		LDL 70–190 mg/dl	Age 40–75 years	• Moderate-intensity statin recommended - If LDL reduction < 50% (or LDL-c levels > 100 mg/dl) consider addition of ezetimibe • High-intensity statin therapy is reasonable for with a ≥ 7.5% estimated 10-year ASCVD risk* unless contraindicated.
			Age < 40 or > 75 years	• Individualize treatment based on risk/benefit ratio
		LDL < 70 mg/dl	All ages	• No specific recommendations
	Secondary prevention	Age ≤ 75 years		• High-intensity statin recommended - If LDL reduction <50% (or LDL-c levels >70 mg/dl) consider addition of ezetimibe or PCSK9i[#]
		Age > 75 years		• Moderate intensity statin recommended - If LDL reduction < 50% (or LDL-c levels > 70 mg/dl) increase to high-intensity statin. - Consider addition of ezetimibe or PCSK9i[#] if LDL reduction target still not achieved • Personalize treatment based on risk/benefit ratio, drug interactions, and patients' preference
ESC/EAS, 2016 [9]	No differences between primary and secondary prevention	All diabetic patients (very high-risk group)		• Set LDL target at < 70 mg/dl (or at a reduction of at least 50% from baseline) • Prescribe statin at the highest recommended/tolerable dose to reach the target - If goal not reached (or statin intolerance) consider combination (or substitution) with ezetimibe. - If goal not reached after statin + ezetimibe (or statin intolerance) consider PCSK9i.
AACE/ACE consensus statement, 2017 [13]	Primary prevention	No additional risk factors		• LDL goal of < 100 mg/dl
		≥ 1 additional risk factor*		• LDL goal of < 70 mg/dl
	Secondary prevention or with chronic kidney disease stage 3 or 4			• LDL goal of < 55 mg/dl

Moderate-intensity statin regimens: atorvastatin 10–20 mg/day, rosuvastatin 5–10 mg/day, simvastatin 20–40 mg/day, pravastatin 40–80 mg/day, lovastatin 40 mg/day, fluvastatin extended release 80 mg/day, pitavastatin 2–4 mg/day; high-intensity statin therapy regimens: atorvastatin 40–80 mg/day, rosuvastatin 20–40 mg/day

[§] Ezetimibe may be preferred due to lower cost

[#] After maximization of adherence to lifestyle recommendation and to statin therapy and after evaluation of risk/benefit ratio, drug interactions, and patients' preferences

*Polycystic ovary syndrome, cigarette smoking, hypertension, HDL < 40 mg/dl, family history of coronary artery disease, chronic kidney disease stage 3–4, evidence of coronary artery calcification, or age ≥ 45 years for males and ≥ 55 years for females (1 risk factor should be subtracted in case of high HDL)

intracellular cholesterol concentration raises the expression of LDL receptors on the surface of the hepatocytes resulting in increased uptake of LDL cholesterol from the blood and decreased plasma concentration of LDL cholesterol and other apoB-containing lipoproteins, including triglyceride-rich particles [9].

Statins are among the most prescribed drugs for cardiovascular disease prevention. The first statin trial focusing on subjects with diabetes without documented history of cardiovascular disease was the Collaborative Atorvastatin Diabetes (CARDS) study [20]. This study randomized 2838 patients with diabetes to atorvastatin 10 mg daily or placebo. The trial was stopped early after 4 years of follow-up due to overwhelming benefit. In fact, patients treated with atorvastatin experienced a 37% relative risk reduction of major cardiovascular events. Assessed separately, there was a 36% reduction in acute coronary heart disease events, 31% reduction in coronary revascularizations, 48% reduction in stroke, and a numerical, although not statistically significant, 27% reduction of mortality. The treatment effect did not vary by pretreatment cholesterol amount, and no excess of adverse events was reported in the atorvastatin group. These results were replicated in multiple studies in the setting of primary prevention including the Heart Protection Study (HPS) showing a significant 33% reduction of major vascular events in 2912 patients with diabetes, but no previous occlusive vascular disease randomized to simvastatin 40 mg daily [21]. The proportional reduction in risk appeared to be largely independent of the type of diabetes although only 615 participants were classified as having type 1 diabetes [21]. Similarly, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA), there was a consistent reduction in major cardiovascular events with atorvastatin 10 mg without significant heterogeneity among prespecified subgroups including those with diabetes [22]. On the other hand, the results of the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) trial did not confirm the cardiovascular benefit of atorvastatin in subjects with diabetes both in those with prior myocardial infarction or coronary revascularization and in those without [23].

Regarding secondary prevention, as seen in the Cholesterol Treatment Trialists' meta-analysis focusing on the subgroup of patients with diabetes, the proportional reduction of about a fifth in major vascular events per each 39 mg/dl LDL cholesterol decrease was nearly the same irrespective of whether vascular disease (i.e., coronary, cerebrovascular, or peripheral arterial) was present (rate ratios 0.80, 95% confidence interval [CI] 0.74–0.88 with vascular disease; 0.73, 95% CI 0.66–0.82 without vascular disease) [10]. However, the group of those with known vascular disease at baseline experienced a larger absolute benefit compared to those without such disease (57 vs 36 fewer major vascular events per 1000 per 39 mg/dl LDL cholesterol reduction). The 20% proportional reduction in major vascular events per 39 mg/dl LDL cholesterol was confirmed in every subcategory of LDL cholesterol, total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL/HDL ratio, and triglycerides. The same can be said for other subcategories analyzed based on individual characteristics such as sex, age, body mass index, blood pressure, smoking history, and estimated glomerular filtration rate. Moreover, among the 6956 individuals with diabetes and previous evidence of cardiovascular disease, the benefit of statins was replicated in those with coronary heart disease (rate ratio 0.82, 99% CI 0.73–0.92; $p < 0.0001$) and in those with other types of vascular disease (rate ratio 0.80, 99% CI 0.61–1.03; $p = 0.02$) [10]. The benefit seemed to be linearly related to the absolute decrease in LDL cholesterol blood levels offered by statin therapy, without any lower threshold below which that benefit was nonexistent. In patients with diabetes and known cardiovascular disease, intensive-dose statin treatment has been shown to provide an additional 9% relative risk reduction of cardiovascular events when compared to standard-dose statins [24]. As a result, more intensive statin treatment should be recommended for diabetes patients at high cardiovascular risk.

On the other hand, it seems meaningful to mention that in patients without diabetes, statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio 1.09; 95% CI 1.02–1.17), but the risk is low both in absolute terms and when compared with the reduction in coronary events [25]. Treatment of 255 patients with statins for 4 years resulted in one extra case of diabetes [25]. The risk of development of diabetes with statins was highest in trials with older participants but neither baseline body mass index nor change in LDL cholesterol concentrations accounted for residual variation in risk. Despite this evidence, clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change, and statins should be widely prescribed in patients with and without diabetes [9, 25].

Bile Acid Sequestrants

Bile acid sequestrants bind the bile acids preventing their entry into the blood; as a result, the decrease in bile acid leads to the upregulation of enzymes promoting cholesterol catabolism. These drugs reduce LDL cholesterol of 18–25% [9]. In historical clinical trials, before the introduction of modern treatment options, these agents resulted in a cardiovascular benefit proportional to the degree of LDL lowering [26–28]. However, their use is limited by common adverse gastrointestinal effects such as flatulence, constipation, dyspepsia, and nausea and by major drug interactions.

Nicotinic Acid

Nicotinic acid decreases fatty acid influx to the liver and the secretion of VLDL resulting in a 15–18% reduction of LDL

cholesterol and a 20–40% reduction of triglycerides [9]. However, two large randomized studies testing the addition of nicotinic acid to simvastatin compared to placebo have failed to demonstrate any benefit but rather showed an increased frequency of serious adverse effects [29, 30]. As a result, this therapeutic option is not available.

Ezetimibe

The target of ezetimibe is the Niemann–Pick C1–like 1 (NPC1L1) protein, which is involved in the absorption of cholesterol from the intestine, thereby resulting in a reduction of the amount of cholesterol delivered to the liver without affecting the absorption of fat-soluble nutrients [31, 32]. In particular, ezetimibe inhibits the interaction between NPC1L1/cholesterol complex and clathrin/adaptor protein 2, thereby preventing endocytosis of the NPC1L1/cholesterol complex into the enterocytes of the small intestine [31]. By reducing enterocyte cholesterol absorption, ezetimibe depletes hepatic pools of cholesterol and increases the expression of the LDL receptor on the surface of hepatocytes leading to an increased clearance of LDL cholesterol from the blood [33].

In clinical studies, ezetimibe in monotherapy was shown to reduce LDL cholesterol by 15–22% [34]. When added to statins, LDL cholesterol reduction increases by an additional 23 to 24% on average [23, 35]. In patients with diabetes, ezetimibe, beyond reducing LDL cholesterol, also has a more consistent beneficial impact than statins alone on the levels of other atherogenic particles, such as remnant-like particle cholesterol, small dense LDL cholesterol, malondialdehyde-modified LDL, apoliprotein B-48, and ratios of total cholesterol/HDL cholesterol and apolipoprotein B/apolipoprotein A-I [34, 36–38]. This beneficial impact on lipid profile more than on sole LDL cholesterol was suggested by the specific subgroup analysis of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [39]. This study included 18,144 patients stabilized after an acute coronary syndrome with LDL cholesterol values between 50 and 125 mg/dl randomized to the addition of ezetimibe 10 mg daily or placebo on top of simvastatin [39]. The median time-weighted average LDL cholesterol level during the study was 53.7 mg/dl in the simvastatin-ezetimibe group as compared with 69.5 mg/dl in the simvastatin-monotherapy group ($p < 0.001$) [39]. Overall, the addition of ezetimibe was associated with a significant reduction in the incidence of major adverse cardiovascular events at 7 years (32.7 vs. 34.7% in the simvastatin-monotherapy group; HR 0.936; 95% CI 0.89–0.99; $p = 0.016$). Among 4933 patients with diabetes, the benefit of adding ezetimibe to simvastatin was particularly evident as shown by a 5.5% absolute reduction of the primary endpoint event rate at 7 years compared to simvastatin (HR 0.85; 95% CI 0.78–0.94); in patients without diabetes, the absolute difference between the two treatment arms was only 0.7% (HR 0.98; 95% CI 0.91–1.04; p for interaction = 0.02) [40]. This enhanced benefit in diabetes was driven by reductions of acute ischemic events, including myocardial infarction and ischemic stroke [40]. The explanation for these findings is far from being clear: even if there was a greater incremental reduction in the median time-averaged LDL cholesterol in individuals with diabetes compared to those without randomized to ezetimibe, the same cannot be said for triglycerides, HDL cholesterol, or C-reactive protein (CRP). It appears clear that the sole difference in LDL cholesterol reduction (3 mg/dl) is too modest to entirely justify the significant reduction of strong endpoints such as acute ischemic events. Furthermore, the probability of obtaining the reduction of both targets (LDL cholesterol < 70 mg/dl and CRP < 2 mg/l) in patients randomized to ezetimibe was greater among those without diabetes than in those with diabetes. Therefore, other elements could be responsible for the enhanced benefit of the combination therapy ezetimibe/simvastatin in patients with diabetes seen in the IMPROVE-IT trial; perhaps its beneficial effects on glucose metabolism, ranging from reductions in fasting plasma glucose to insulin levels and insulin resistance or its potential effects on other atherogenic lipid particles [34, 41]. As for now, practice guidelines recommend the use of ezetimibe for the treatment of hypercholesterolemia in cases of statin intolerance or if the target level of LDL cholesterol is not reached with the highest recommended or tolerable statin dose without any particular distinction for patients with diabetes [9, 12•]. Data from the IMPROVE-IT study support the 2017 American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease treatment goal of a LDL cholesterol less than 55 mg/dl in patients with extreme risk, including patients with diabetes mellitus with established clinical cardiovascular disease (Table 1) [13]; in the latter, the addition of ezetimibe to simvastatin resulted in a greater clinical benefit than simvastatin alone. Therefore, in patients with extreme risk, such as those with diabetes mellitus admitted with an acute coronary syndrome and low-density lipoprotein cholesterol ≥ 50 mg/dl, healthcare providers should consider adding ezetimibe to statin to reduce the risk of cardiovascular events.

Fibrates

Fibrates lower hepatic apoC-III production and increase lipoprotein lipase-mediated lipolysis via peroxisome proliferator-activated receptors (PPARs) [42]. In addition, fibrates stimulate cellular fatty acid uptake, conversion to acyl-CoA derivatives, and catabolism by the β-oxidation pathways, which combined with a reduction in fatty acid and triglyceride synthesis results in a decrease in very low-density lipoprotein production [42]. Treatment with fibrates substantially

decreases plasma triglycerides and is usually associated with a moderate decrease in LDL cholesterol and an increase in HDL cholesterol [43].

Different historical studies have shown the beneficial effects of fibrates in patients with diabetes or metabolic syndrome. In particular, the Helsinki Heart Study testing gemfibrozil in subjects with hypercholesterolemia without previous coronary artery disease reported a significant 34% relative reduction in coronary events; the treatment effect was consistent in patients with diabetes [44]. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial (VA-HIT) enrolling patients with coronary heart disease, gemfibrozil lowered the recurrence of coronary events compared to placebo, with greater relative benefits seen in those with diabetes or insulin resistance [45].

Lately, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial assessing the effects of long-term treatment with fenofibrate on coronary morbidity and mortality specifically in patients with type 2 diabetes was the first trial to question previous findings [43]. Of note, as per study protocol, other lipid-lowering therapies including statins were permitted in the placebo arm. In this study, although fenofibrate reduced total cardiovascular disease events, particularly nonfatal myocardial infarction and coronary revascularization at 5 years, the primary endpoint of major coronary events was not significantly reduced by fenofibrate compared with placebo. Finally, the more contemporary Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid trial evaluated the combination therapy statin/fibrate in over 5000 patients randomized to simvastatin plus fenofibrate versus simvastatin alone [46]. The combination therapy with fenofibrate/statin showed a mild but significant increase in HDL cholesterol and a considerable reduction in plasma triglycerides; however, the occurrence of major cardiovascular events was similar in the two treatment arms when the entire cohort was taken into consideration.

Fibrates may be considered in patients with diabetes in case of significant hypertriglyceridemia (> 200 mg/dl in the European guidelines) despite statin treatment [9]. On the contrary, according to the American Diabetes Association guidelines combination therapy statin/fibrate is generally not recommended because it has not been shown to improve atherosclerotic cardiovascular disease outcomes; for patients with fasting triglyceride levels, ≥ 500 mg/dl medical therapy may be considered to reduce the risk of pancreatitis [7].

PCSK-9 Inhibitors

The physiological function of PCSK-9 is to promote the degradation of the LDL receptor. Therefore, inhibition of PCSK-9 favors LDL catabolism and reduces plasma LDL-cholesterol levels [47].

Since 2015, two fully human monoclonal antibodies to PCSK-9, alirocumab and evolocumab, have been approved as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with familial hypercholesterolemia or atherosclerotic cardiovascular disease (coronary heart disease, cerebrovascular, or peripheral artery disease), when additional LDL-cholesterol lowering is required [48]. In patients treated with an optimized lipid-lowering regimen including a high- or moderate-intensity statin, these agents, administered via subcutaneous injections every 2 weeks or once monthly, cause large reductions in LDL cholesterol levels as compared with placebo (39 to 62% reduction for alirocumab and 47 to 56% for evolocumab) [48]. This further LDL reduction achieved with PCSK-9 inhibitors was translated in a significant clinical benefit.

In the Further Cardiovascular Outcomes Research with PCSK-9 Inhibition in Subjects with Elevated Risk (FOURIER) study including 27,564 patients with clinically evident atherosclerotic cardiovascular disease, evolocumab treatment was shown to significantly reduce the risk of the primary endpoint, a composite of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina by 15% relative to placebo during a median follow-up of 2.2 years (9.8% vs. 11.3%; HR 0.85; 95% CI 0.79–0.92; $p < 0.001$) [49]. The benefit of evolocumab in reducing cardiovascular event risk was evident even in patients starting with LDL-cholesterol levels below 70 mg/dl and in patients already on maximum-intensity statin therapy [50]. There was no significant difference between the study groups with regard to adverse events; the incidence of neurocognitive events was comparable also in patients achieving very low LDL-cholesterol values [49]; injection-site reactions were more common with evolocumab (2.1% vs. 1.6%).

A subsequent post hoc analysis of the trial demonstrated that evolocumab lowered LDL cholesterol and significantly reduced cardiovascular risk with similar efficacy in patients with (approximately 40%, $n = 11{,}031$) and without diabetes with HRs of 0.83 and 0.87 respectively for the primary endpoint (p for interaction = 0.60) [51]. However, due to higher baseline risk, the absolute risk reductions in the primary endpoint with evolocumab tended to be greater in patients with diabetes (2.7% over 3 years, number needed to treat 37) than in patients without diabetes (1.6%, number needed to treat 62), largely driven by a greater absolute risk reduction in coronary revascularization [51]. Finally, the safety of evolocumab was confirmed also in the subgroup of patients with diabetes; in addition, in subjects without diabetes at baseline it did not increase the risk of new onset diabetes compared with placebo (8.0% vs. 7.6%, HR 1.05, 95% CI 0.94–1.17) and did not worsen glycemia over a median of 2.2 years of follow-up [51].

The preliminary results of the Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome During

Treatment with Alirocumab (ODYSSEY-Outcomes) study testing alirocumab in 18,924 patients with a recent acute coronary syndrome have been recently presented during the Annual Congress of the American College of Cardiology 2018. The trial met its primary endpoint, reducing the incidence of the composite outcome of coronary heart disease death, myocardial infarction, stroke, or unstable angina requiring hospitalization by 15% (HR 0.85, 95% CI 0.78–0.93, $p = 0.0003$) during a median follow-up of 2.8 years. The investigators also reported a reduction in overall mortality, from 4.1% in the placebo group to 3.5% in the alirocumab group (HR 0.85; 95% CI 0.73–0.98, $p = 0.026$). However, the reduction in overall mortality was considered an observational finding because, in accordance with the predetermined statistical analysis plan, it did not achieve statistical significance. No new safety issues emerged in the trial. A subsequent analysis of ODYSSEY-Outcomes presented during the Annual Congress of the American Diabetes Association 2018 confirmed the efficacy and safety of alirocumab in the subgroup of patients with diabetes with higher absolute risk reductions of the primary endpoint (2.3% in diabetes vs. 1.2% in the prediabetes and normoglycemia groups). In the phase IIIb ODISSEY DM-INSULIN trial alirocumab produced significant LDL cholesterol reductions in participants with insulin-treated diabetes regardless of diabetes type without safety concerns related to concomitant administration with insulin [52].

Conclusions

Given the elevated risk of a first or recurrent cardiovascular event in diabetes, aggressive management of dyslipidemia in such patients is crucial. Statins remain the first-line lipid-lowering agents in individuals with diabetes; however, other non-statin therapies that lower LDL cholesterol, such as ezetimibe and PCSK-9 inhibitors can be added to maximally tolerated statin therapy to further reduce cardiovascular risk in diabetes. Although the cardiovascular clinical benefit of fibrates has been questioned, these agents may be considered in patients with diabetes in case of significant hypertriglyceridemia despite statin treatment.

Compliance with Ethical Standards

Conflict of Interest Ilaria Cavallari, Alessia Delli Veneri, Rosetta Melfi, Nicola Napoli, and Germano Di Sciascio declare that they have no conflict of interest.

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