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PCSK9 Inhibitors in Lipid Management of Patients With Diabetes Mellitus and High Cardiovascular Risk: A Review

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Elevated levels of low-density lipoprotein cholesterol (LDL-C) are well established to be associated with the development of atherosclerotic cardiovascular disease (ASCVD), defined as acute coronary syndrome, a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, ischemic stroke, transient ischemic attack, or peripheral artery disease (all presumed to be of atherosclerotic origin).[1] ASCVD is the leading cause of morbidity and mortality in individuals with diabetes mellitus.[2] Individuals with diabetes mellitus and elevated levels of LDL-C are at higher absolute risk of cardiovascular disease compared with those with high LDL-C without diabetes mellitus.[3] Statin therapy is recommended as the first-line lipid-lowering drug therapy for the management of dyslipidemia in individuals with diabetes mellitus (unless contraindicated) in current major US guidelines and recommendations (summarized in Table S1).[1,2,4,5] However, some patients with high cardiovascular risk either do not achieve adequate LDL-C reductions on statins, or are intolerant to statins and therefore receive suboptimal statin doses or discontinue statin therapy, and thus remain at increased risk of cardiovascular events. For such patients, additional and/or alternative nonstatin lipid-lowering treatment options should be considered.[4,6–12]

Several nonstatin therapies are currently available, including the cholesterol absorption inhibitors (ezetimibe), bile acid sequestrants, nicotinic acid (niacin), and fibrates.[4] Previous studies with statins and ezetimibe have shown that patients with diabetes mellitus benefit from tight lipid control at least in the same way (if not more) as patients with other risk factors, as well as those without diabetes mellitus.[11,13] The Cholesterol Treatment Trialists' Collaboration meta-analysis of 14 randomized statin trials found that the cardiovascular benefits of LDL-C lowering with statin therapy were similar in those with (n=18 686) and without diabetes mellitus (n=71 370).[13] In the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trial evaluating the addition of ezetimibe concomitant with statin therapy, which lowered LDL-C levels below previous targets to a median level of 53 mg/dL in 18 144 patients with recent acute coronary syndromes (27% of whom had diabetes mellitus),[11] individuals with diabetes mellitus had significantly greater relative and absolute benefit in improved cardiovascular outcomes than those without diabetes mellitus.[14] Clinical outcomes studies for niacin (AIM-HIGH [Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes] and HPS2-THRIVE [Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events]) and fenofibrate (ACCORD [Action to Control Cardiovascular Risk in Diabetes] and FIELD [Fenofibrate Intervention and Event Lowering in Diabetes]) did not demonstrate significant cardiovascular benefits in individuals with diabetes mellitus, although there was a suggestion of benefit in subgroups with very high triglyceride levels in the fenofibrate studies.[15–18] Because of increased risk of adverse events (AEs) and lack of evidence of meaningful benefits as seen in cardiovascular outcomes trials,[15–17] the US Food and Drug Administration (FDA) has recently rescinded its approval of the combined use of statins with niacin extended-release tablets or fenofibric acid delayed-release capsules.[19] These nonstatin therapies only produce moderate LDL-C-lowering effects and have side effects that limit their use.[11,15–17]

Recently, monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) have received considerable attention as promising nonstatin therapeutic options for the management of lipid disorders in patients with persistent cardiovascular risk, including in patients with diabetes mellitus. In this review, we discuss the results of studies investigating lipid-lowering efficacy, safety, and

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cardiovascular outcomes in patients with diabetes mellitus and elevated LDL-C, and recently released data and forthcoming clinical trials with a focus on 2 FDA-approved monoclonal antibodies that inhibit PCSK9: alirocumab (Praluent®, Sanofi-Aventis US LLC, Bridgewater, NJ, and Regeneron Pharmaceuticals, Inc, Tarrytown, NY)[20] and evolocumab (Repatha®, Amgen Inc, Thousand Oaks, CA).[21]

Mechanism of Action of PCSK9 Inhibitors

The PCSK9 protein is an important regulator of circulating LDL-C levels, through its inhibitory action on recycling of the LDL receptor (LDLR). LDLR on the liver cell surface binds to LDL and the LDLR–LDL complex is then internalized, after which the LDLR is normally recycled back to the cell surface up to 150 times.[22] Secreted PCSK9 binds to the LDLR on the surface of the hepatocyte, leading to the internalization and degradation of the LDLR in the lysosomes, and reducing the number of LDLRs on the cell surface. Inhibition of secreted PCSK9 should therefore increase the number of available LDLRs on the cell surface and increase uptake of LDL-C into the cell. PCSK9 inhibition thus offers a novel therapeutic mechanism for the lowering of LDL-C levels.[23]

The relevance of PCSK9 to coronary heart disease was determined from human genetic studies that identified gain-of-function mutations in the *PCSK9* gene associated with elevated serum LDL-C levels and premature coronary heart disease.[24–26] Conversely, loss-of-function *PCSK9* mutations are associated with lower serum LDL-C levels, lower lifelong exposure of vascular structures to LDL, and marked reduction of risk of coronary heart disease.[27–29] Moreover, healthy subjects with severe loss of *PCSK9* function have been shown to have serum LDL-C concentrations as low as 14 mg/dL without apparent adverse health effects.[28,30]

In addition to the well-established role of PCSK9 in LDL metabolism, a recent study suggested that it could play a significant role in the metabolism of triglyceride-rich lipoproteins also through interaction with the LDLR.[31] This has important implications for individuals with type 2 diabetes mellitus (T2D), and for those with type 1 diabetes mellitus (T1D) with poor glycemic control, who typically have a pattern of lipid abnormalities related to insulin resistance that is characterized by reduced hepatic clearance of triglyceride-rich lipoproteins, increased hepatic production of very-low-density lipoproteins, and enhanced intestinal production of chylomicrons.[32] These lipid abnormalities, termed diabetic (or mixed) dyslipidemia (Figure), account for their elevated levels of non-high-density lipoprotein cholesterol, triglycerides, and small dense LDLs.[32,33] Remnants of triglyceride-rich lipoproteins, which include chylomicrons and very-low-density lipoproteins, have enhanced atherogenic potential since they contain more cholesterol per particle than LDL,[34] and have been shown to have a substantial and independent causal association with cardiovascular risk.[35] Whereas the LDLR binds to LDLs via apolipoprotein-B100 (apoB100),[36] LDLR binds triglyceride-rich lipoprotein remnants through interactions with apolipoprotein-E (apoE), and clearance of these particles occurs along with other receptors such as LDLR-related protein 1 and Syndecan-1.[37,38] The recent study showed lower levels of fasting and postprandial triglycerides, apoB48 (an indicator of remnant lipoprotein metabolism), and total apoB (a surrogate of apoB100) in individuals carrying loss-of-function *PCSK9* genetic variants, supporting a role of PCSK9 in the reduction of uptake of apoE-containing remnant particles as well as LDL.[31] Recent kinetic studies in healthy subjects showed that PCSK9 inhibitors decreased fractional production rate of LDL and intermediate-density lipoprotein, and increased fractional clearance rates of very-low-density lipoprotein, intermediate-density lipoprotein, and LDL particles, which may reflect a much higher expression of hepatic LDLRs than with statin treatment.[39,40] Similarly, lipoprotein (a) levels were also decreased with PCSK9 inhibitors, which was previously not seen with statins.[40,41] Thus, PCSK9 inhibitors could be especially potent in the treatment of dyslipidemia in those with diabetes mellitus.

PCSK9 Inhibitors and Their Effects in Patients With Diabetes Mellitus and High LDL-C Levels

Currently, the only FDA-approved PCSK9 inhibitors are 2 fully human monoclonal antibodies that bind extracellular PCSK9: alirocumab[20] and evolocumab,[21] administered via subcutaneous injections every 2 weeks (Q2W) or once monthly. Several other approaches to inhibit PCSK9 are in the early stages of clinical development, including small interfering ribonucleic acids, antisense oligonucleotides, small molecule inhibitors, and vaccines; these nonmonoclonal antibody approaches, which utilize alternative strategies to inhibit intracellular or extracellular PCSK9, could potentially provide greater convenience than use of monoclonal antibodies through oral administration, and less frequent dosing.[42]

Both alirocumab and evolocumab received FDA approval in 2015 as adjunct therapy to diet and maximally tolerated statin therapy to treat adults with heterozygous familial hypercholesterolemia or clinical ASCVD who need greater LDL-C reduction.[20,21] Evolocumab is also indicated as adjunct therapy to diet and other lipid-lowering therapies (eg, statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia who need additional LDL-C reduction; additionally, as of 2017, evolocumab is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease.[21] Both antibodies are approved by the FDA to be administered subcutaneously Q2W or once monthly. The recommended starting dose

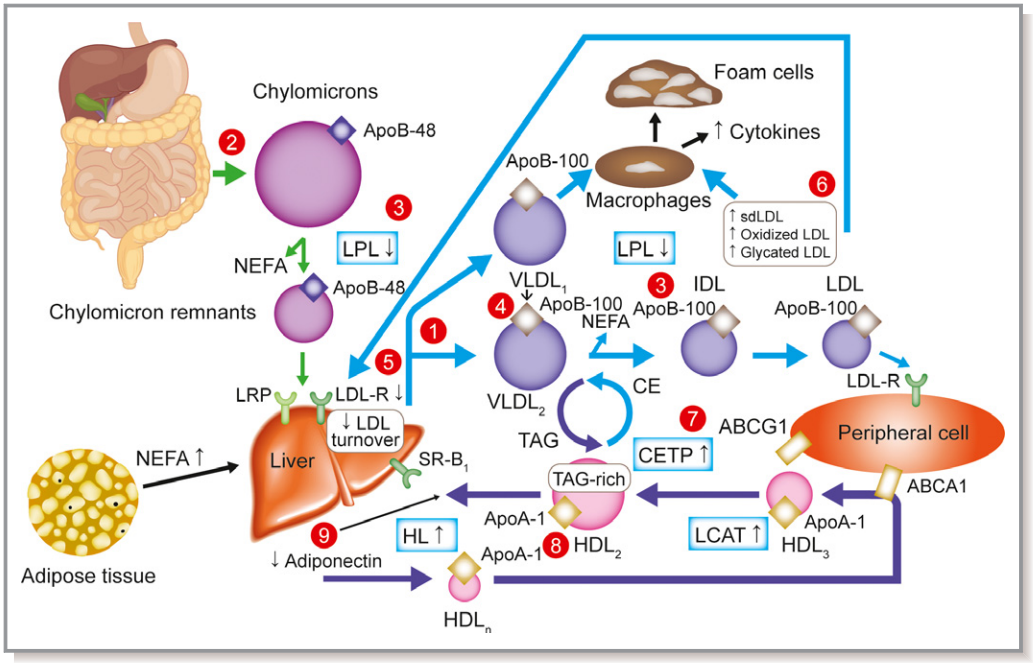

Figure. Overview of lipid abnormalities in T2DM.[32] Triacylglycerols (hypertriglyceridemia, qualitative and kinetic abnormalities): (1) increased VLDL production (mostly VLDL1); (2) increased chylomicron production; (3) reduced catabolism of both chylomicrons and VLDLs (diminished LPL activity); (4) increased production of large VLDL (VLDL1), preferentially taken up by macrophages; LDL (qualitative and kinetic abnormalities); (5) reduced LDL turnover (decreased LDL B/E receptors); (6) increased number of glycated LDLs, small, dense LDLs (TAG-rich) and oxidized LDLs, which are preferentially taken up by macrophages; HDL (low HDL-C, qualitative and kinetic abnormalities); (7) increased CETP activity (increased transfer of triacylglycerols from TAG-rich lipoproteins to LDLs and HDLs); (8) increased TAG content of HDLs, promoting HL activity and HDL catabolism; (9) low plasma adiponectin favoring the increase in HDL catabolism. ABCA1 indicates ATP-binding cassette A1; ABCG1, ATP-binding cassette G1; Apo, apolipoprotein; CE, cholesterol ester; CETP, CE transfer protein; HDL, high-density lipoprotein; HDL-C, HDL cholesterol; HDL_n, nascent HDL; HL, hepatic lipase; LCAT, lecithin–cholesterol acyltransferase; LDL, low-density lipoprotein; LDL-R, LDL receptor; LPL, lipoprotein lipase; LRP, LDL receptor-related protein; NEFA, nonesterified fatty acid; sdLDL, small, dense LDL; SR-B1, scavenger receptor B1; T2DM, type 2 diabetes mellitus; TAG, triacylglycerol; VLDL, very low-density lipoprotein.

for alirocumab is 75 mg Q2W, or 300 mg every 4 weeks for patients who prefer less frequent dosing; with either starting dose, the alirocumab dose can be increased to 150 mg Q2W if patients did not have sufficient LDL-C lowering within 4 to 8 weeks of initiating treatment. The FDA-approved doses for evolocumab are 140 mg Q2W or 420 mg once monthly.[20,21] Currently, individuals with diabetes mellitus who have established ASCVD and need to reduce LDL-C levels can receive treatment with PCSK9 inhibitors.

Alirocumab and evolocumab, either alone or in combination with statins and/or other lipid-lowering therapies, have been shown in their respective phase 3 clinical trial programs (ODYSSEY and PROFICIO [Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations]) to significantly reduce LDL-C levels by up to 60% from baseline (depending on dosing regimen; Table) in patients with hypercholesterolemia, including those with familial hypercholesterolemia, moderate to very high cardiovascular risk, and statin intolerance.[43–62] The inclusion/exclusion criteria and other details of each phase 3 ODYSSEY and PROFICIO trial are shown in Table S2. LDL-C reductions in the placebo-controlled phase 3 trials were consistent with those found in the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) cardiovascular outcomes trial (Table), studying evolocumab versus placebo in 27 564 patients with clinically evident ASCVD and on a moderate-to-high-intensity statin regimen over a median follow-up duration of 2.2 years.[63] The GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) study (which included 968 statin-treated patients with angiographic coronary disease to evaluate the effect of evolocumab versus placebo on the progression of coronary atherosclerosis) also showed comparable reductions in LDL-C levels over 76 weeks of evolocumab treatment (from 93 mg/dL at baseline to

Table. Alirocumab ODYSSEY and Evolocumab PROFICIO Phase 3 Studies Show Similar Reductions in Calculated LDL-C Levels From Baseline to Primary End Point in Individuals With vs Without DM, Pre-DM, and Metabolic Syndrome (ITT Analysis)

		% Change From Baseline (LDL-C) to Primary End Point				Difference vs Control, LS Mean % Change From Baseline (SE or 95% CI If Published), Unless Otherwise Specified	Interaction *P* Value
		ALI or EVO		Control (PBO or EZE)			
		n	LS Mean (SE), Unless Otherwise Specified	n	LS Mean (SE), Unless Otherwise Specified		
ALIROCUMAB 150 mg Q2W vs PBO (with statin), 24 wks							
LONG TERM, ALI 150 vs PBO[62]							
Overall	All (n=2310)	1530	−61.0 (0.7)	780	0.8 (1.0)	−61.9 (1.3)	–
DM subanalysis	DM (n=818)	545	−60.0 (1.3)	273	−1.0 (1.8)	−59.0	0.0957
	Non-DM (n=1492)	985	−61.6 (0.9)	507	1.8 (1.3)	−63.4	
Pooled analysis of HIGH FH, LONG TERM, ALI 150 vs PBO							
Overall[59,60]	All (n=2416)	1601	−60.4 (0.7)	815	0.5 (1.0)	−60.9 (−63.3 to −58.5)	–
DM subanalysis[69]	DM (n=833)	554	−59.7 (1.2)	279	−1.4 (1.7)	−58.3 (2.1)	0.13
	Non-DM (n=1583)	1047	−60.7 (0.9)	536	1.5 (1.2)	−62.3 (1.5)	
Pre-DM subanalysis[72]	Pre-DM (n=876)	–	−61.8 (1.2)	–	2.1 (1.6)	−63.9	0.1431
	NG (n=656)	–	−59.5 (1.4)	–	−0.1 (1.9)	−59.4	
DM+ASCVD subanalysis[68]	DM+ASCVD (n=512)	340	−61.5 (1.6)	172	−1.0 (2.2)	−60.5 (−65.9 to −55.2)	–
ALIROCUMAB 75/150 mg Q2W vs PBO (with statins), 24 wks							
Pool of FH I & II, ALI 75/150 vs PBO[46]							
Overall	All (n=732)	–	−48.8 (1.2)	–	7.1 (1.7)	−55.9	–
DM subanalysis	DM (n=66)	–	−51.4 (4.5)	–	2.4 (5.5)	−53.8	0.7912
	Non-DM (n=666)	–	−48.5 (1.3)	–	7.6 (1.8)	−56.1	
COMBO I, ALI 75/150 vs PBO[47]							
Overall	All (n=311), estimated mean (95% CI)	205	−48.2 (−52.0 to −44.4)	106	−2.3 (−7.6 to 3.1)	−45.9 (−52.5 to −39.3)	–
DM subanalysis	DM (n=135), estimated mean (95% CI)	94	−42.2 (−47.8 to −36.6)	41	−2.6 (−11.1 to 5.8)	−39.6	0.0841
	Non-DM (n=176), estimated mean (95% CI)	111	−53.2 (−58.4 to −48.1)	65	−2.0 (−8.8 to 4.8)	−51.2	
Pooled analysis of FH I & II, COMBO I, ALI 75/150 vs PBO							
Overall[59,60]	All (n=1043)	693	−48.6 (1.0)	350	4.2 (1.5)	−52.7 (−56.3 to −49.2)	–
DM subanalysis[69]	DM (n=201)	131	−43.4 (2.6)	70	0.3 (3.4)	−43.7 (4.1)	0.02[†]
	Non-DM (n=842)	562	−49.8 (1.2)	280	5.1 (1.6)	−54.8 (2.0)	
Pre-DM subanalysis[72]	Pre-DM (n=396)	–	−52.4 (1.7)	–	3.3 (2.4)	−55.7	0.8451
	NG (n=422)	–	−46.1 (1.6)	–	8.9 (2.3)	−55.0	
DM+ASCVD subanalysis[68]	DM+ASCVD (n=137)	92	−46.4 (3.0)	45	6.3 (4.5)	−52.7 (−63.5 to −41.9)	–

Continued

Table. Continued

		% Change From Baseline (LDL-C) to Primary End Point				Difference vs Control, LS Mean % Change From Baseline (SE or 95% CI If Published), Unless Otherwise Specified	Interaction *P* Value
		ALI or EVO		Control (PBO or EZE)			
		n	LS Mean (SE), Unless Otherwise Specified	n	LS Mean (SE), Unless Otherwise Specified		
DM-INSULIN[75]							
DM+insulin	T2DM (n=429)	287	−48.2 (1.6)	142	0.8 (2.2)	−49.0 (2.7)	–
	T1DM (n=74)	49	−51.8 (3.7)	25	−3.9 (5.3)	−47.8 (6.5)	–
ALIROCUMAB 75/150 mg Q2W vs EZE, 24 wks							
COMBO II DM subanalysis, ALI 75/150 vs EZE (with statin)							
Overall[45]	All (n=707)	467	−50.6 (1.4)	240	−20.7 (1.9)	−29.8 (2.3)	–
DM subanalysis[67]	DM (n=225*)	148†	−49.1	77†	−18.4	−30.7	0.8025
	Non-DM (n=495*)	331†	−51.2	164†	−21.8	−29.5	
Pooled analysis of COMBO II, OPTIONS I & II, ALI 75/150 vs EZE (with statin)							
Overall[59,60]	All (n=1105)	669	−48.9 (1.4)	436	−19.3 (1.7)	−29.6 (−33.8 to −25.3)	–
Pre-DM subanalysis[72]	Pre-DM (n=432)	–	−51.7 (2.2)	–	−16.1 (2.6)	−35.6	0.0428
	NG (n=244)	–	−45.8 (2.8)	–	−21.8 (3.6)	−24.0	
DM+ASCVD subanalysis[68]	DM+ASCVD (n=283)	173	−48.7 (2.6)	110	−20.6 (3.3)	−28.1 (−36.6 to −19.6)	–
ALTERNATIVE, ALI 75/150 vs EZE (without statin)							
Overall[48]	All (n=168)	90	−54.8 (1.4)	78	−20.1 (2.4)	−34.7	
DM+ASCVD subanalysis[68]	DM+ASCVD (n=34)	23	−54.9 (6.0)	11	4.0 (8.8)	−58.9 (−80.9 to −36.8)	–
Pooled analysis of ALTERNATIVE & MONO, ALI 75/150 vs EZE (without statin)							
Overall[59,60]	All (n=351)	178	−45.6 (1.8)	173	−14.8 (1.8)	−30.9 (−35.9 to −25.9)	–
Pre-DM subanalysis[72]	Pre-DM (n=135)	–	−44.0 (2.9)	–	−16.0 (2.7)	−28.0	0.4073
	NG (n=147)	–	−46.3 (2.7)	–	−13.7 (2.6)	−32.6	
DM-DYSLIPIDEMIA§[77]							
T2DM+mixed dyslipidemia§	All (n=409)§	273§	−43.3§	136§	−0.3§	−43.0§	–
EVOLOCUMAB 140 mg Q2W or 420 mg QM vs PBO							
Pool of LAPLACE-2 & RUTHERFORD-2, EVO 140 or 420 vs PBO, 12 wks[66]							
T2DM subanalysis	T2DM (n=304)	210	–	94	–	−60 (−69 to −51)‡	0.27
	Non-T2DM (n=1700)	1127	–	573	–	−66 (−70 to −62)‡	
DESCARTES, EVO 420 vs PBO, 52 wks							
Overall[61]	All (n=901)	599	–	302	–	−57.0 (2.1)	–
Subanalysis by glycemic status and MetS[73]	T2DM (n=120)	77	–	43	–	−50.8 (6.0)	–
	IFG (n=293)	194	–	99	–	−59.4 (3.4)	–
	MetS (n=289)	182	–	107	–	−55.0 (3.5)	–
	No dysglycemia or MetS (n=393)	274	–	119	–	−58.1 (3.5)	–

Continued

Table. Continued

		% Change From Baseline (LDL-C) to Primary End Point				Difference vs Control, LS Mean % Change From Baseline (SE or 95% CI If Published), Unless Otherwise Specified	Interaction *P* Value
		ALI or EVO		Control (PBO or EZE)			
		n	LS Mean (SE), Unless Otherwise Specified	n	LS Mean (SE), Unless Otherwise Specified		
FOURIER, EVO 140 or 420 vs PBO, 48 wks							
Overall[63]	All (n=27 563)	13 784	–	13 779	–	−59 (58 to 60)	–
DM subanalysis[71]	DM (n=11 031)	5515	–	5516	–	−57 (56 to 58)	–
	Non-DM (n=16 533)	8269	–	8264	–	−60 (60 to 61)	
EVOLOCUMAB 140 mg Q2W or 420 mg QM vs EZE							
Pool of LAPLACE-2 (atorvastatin cohorts only) & GAUSS-2, EVO 140 or 420 vs EZE, 12 wks[66]							
T2DM subanalysis	T2DM (n=187)	114	–	73	–	−39 (−47 to −32)‡	0.79
	Non-T2DM (n=780)	530	–	250	–	−40 (−45 to −36)‡	

LS means and SEs taken from mixed-effect model with repeated measures analysis. All values shown are as published in the respective referenced articles; if the values for difference vs control were not published, values were estimated based on the respective percent changes with alirocumab/evolocumab and controls. ALI indicates alirocumab; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; DM, diabetes mellitus; DESCARTES, Durable Effect of PCSK9 Antibody Compared with Placebo Study; EVO, evolocumab; EZE, ezetimibe; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; GAUSS-2, Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; ITT, intention-to-treat; LAPLACE-2, LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy; LDL-C, low-density lipoprotein cholesterol; LS, least squares; MetS, metabolic syndrome; NG, normoglycemia; PBO, placebo; Q2W, every 2 weeks; QM, once monthly; RUTHERFORD-2, Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder-2; SE, standard error; T1, type 1; T2, type 2.

*Randomized population.

†Because of a higher proportion of participants without DM receiving an alirocumab dose increase at wk 12 (36.5% vs 25.6%).

‡Random-effects treatment difference (95% CI) between evolocumab and control (placebo or ezetimibe), generated by use of the DerSimonian and Laird random-effect estimator.

§The comparator in the DM-DYSLIPIDEMIA trial was usual care, which included the option to continue on maximally tolerated statin therapy without adding another lipid-lowering therapy at randomization, or with the addition of one of the following at randomization: ezetimibe, fenofibrate, omega-3 fatty acids, or nicotinic acid. Mixed dyslipidemia was defined as non-HDL-C ≥100 mg/dL (2.59 mmol/L), and triglycerides ≥150 mg/dL (1.70 mmol/L) and <500 mg/dL (5.65 mmol/L) at the screening visit. The primary efficacy end point in this trial was non-HDL-C: at week 24, mean non-HDL-C changes were superior with alirocumab (−37.3%) vs usual care (−4.7%). The LDL-C reduction (secondary end point) values shown for DM-DYSLIPIDEMIA in this table are measured LDL-C values, not calculated LDL-C.[76,77]

37 mg/dL at week 76).[64] Moreover, in a 4-year assessment of an ongoing open-label extension of the phase 2 OSLER-1 (Open-Label Study of Long-Term Evaluation against LDL Cholesterol 1) trial (the longest clinical trial exposure to date with a PCSK9 inhibitor), monthly doses of evolocumab treatment produced sustained LDL-C reductions over 4 years of follow-up without increased incidence of AEs.[65]

Lipid-Lowering Efficacy of PCSK9 Inhibitors in Patients With Diabetes Mellitus

Subanalyses of the diabetes mellitus subpopulations in the alirocumab and evolocumab phase 3 trials (Table) showed significant reductions in LDL-C that were generally similar between individuals with and without diabetes mellitus.[46,47,62,66–70] Findings were consistent in the prespecified diabetes mellitus subanalysis of FOURIER, which analyzed 11 031 patients with diabetes mellitus versus 16 533 patients without diabetes mellitus; compared with placebo, median LDL-C levels were reduced by 57% in those with diabetes mellitus and by 60% in those without diabetes mellitus.[71] Other subanalyses of ODYSSEY and PROFICIO phase 3 trials showed that LDL-C reductions were also similar in those with and without prediabetes,[72] impaired fasting glucose, and metabolic syndrome (Table).[73] Similarly, a recent post-hoc subanalysis of 9 ODYSSEY phase 3 trials (24–104 weeks' treatment duration) showed significant LDL-C reductions with alirocumab in patients with both diabetes mellitus and ASCVD (Table).[68] Moreover, LDL-C reductions in these subpopulations with alirocumab and evolocumab were comparable to those seen in the overall phase 3 patient populations (Table).

Further information on the impact of alirocumab in patients with diabetes mellitus is available from the ODYSSEY DM-INSULIN[74,75] and DM-DYSLIPIDEMIA[76,77] trials, which were dedicated phase 3b and phase 4 studies, respectively, investigating alirocumab in individuals with diabetes mellitus. The placebo-controlled DM-INSULIN trial assessed the efficacy and safety of concomitant administration of 2 injectable biological agents (alirocumab and insulin) in insulin-treated individuals with hypercholesterolemia and T1D or T2D at high cardiovascular risk, on background stable maximally tolerated statin therapy with or without other lipid-lowering therapy (Table).[74,75] The DM-DYSLIPIDEMIA trial assessed the efficacy and safety of alirocumab versus lipid-lowering usual care

(ezetimibe, fenofibrate, omega-3 fatty acids, or nicotinic acid) in individuals with T2D and mixed dyslipidemia at high cardiovascular risk, on background stable maximally tolerated statin therapy without other lipid-lowering therapies; this trial was the first trial of a PCSK9 inhibitor to evaluate non-high-density lipoprotein cholesterol as a primary efficacy end point (Table).[76,77] Two evolocumab phase 3 trials study individuals with T2D and hypercholesterolemia or mixed dyslipidemia (NCT02739984, NCT02662569).

Safety of PCSK9 Inhibitors in Patients With Diabetes Mellitus, and Impact On Risk of Diabetes Mellitus Development

In the overall phase 3 patient populations, pooled safety analyses of 14 alirocumab ODYSSEY trials (including 5234 patients with 8–104 weeks' treatment duration),[78] 12 evolocumab PROFICIO parent trials (including 6026 patients with 6–52 weeks' treatment duration), and the first year of 2 open-label extension trials (which included 4465 of the 6026 patients who were included in this analysis in the parent trials),[79] and the FOURIER trial[63] showed that the incidence of overall treatment-emergent AEs, serious treatment-emergent AEs, discontinuations because of treatment-emergent AEs, and deaths was similar with the PCSK9 inhibitors versus controls. Among alirocumab- or evolocumab-treated patients, nasopharyngitis, injection-site reactions, and upper respiratory tract infections were the most commonly occurring AEs.[78,79] Generally, a higher incidence of local injection-site reactions (the majority of which were mild in nature) was seen with alirocumab/evolocumab versus controls.[63,78]

Consistent with the overall patient populations mentioned above,[63,78] subanalyses by diabetes mellitus status demonstrated that overall alirocumab/evolocumab safety was comparable to that of control in those with and without diabetes mellitus.[66,67,69,71,80] Overall safety was also comparable versus control between patients with diabetes mellitus and ASCVD,[68] insulin-treated patients with diabetes mellitus in the DM-INSULIN study,[75] patients with T2D and mixed dyslipidemia in the DM-DYSLIPIDEMIA study,[77] individuals with prediabetes and normoglycemia,[72] and those with and without dysglycemia or metabolic syndrome.[73] As shown in prior studies in the overall patient population,[63,78] higher rates of local injection-site reactions (also generally mild) were typically seen with alirocumab/evolocumab compared with control for patients both with and without diabetes mellitus.[69,71,80] However, in those with diabetes mellitus, several analyses showed lower rates of local injection-site reactions with alirocumab/evolocumab versus control.[66,67,75] Furthermore, alirocumab/evolocumab-treated individuals with diabetes mellitus showed a lower incidence of local injection-site reactions compared with alirocumab/evolocumab-treated individuals without diabetes mellitus.[66,67,69,71,80]

Statin therapy and recent genetic epidemiology studies of *PCSK9* loss-of-function genetic variants associated with LDL-C reductions have suggested a small but statistically significant increased risk of the development of new-onset diabetes mellitus.[4,81–84] However, current clinical trial data for alirocumab and evolocumab do not suggest an association between PCSK9 inhibitors and loss of glycemic control. Analyses of ODYSSEY phase 3 trials with alirocumab with duration of 78 to 104 weeks of follow-up showed no changes in fasting plasma glucose or hemoglobin A1c levels over time with alirocumab or control in patients with and without diabetes mellitus [67,68,75,77,80,85] or in individuals with prediabetes or normoglycemia at baseline.[72] Analyses of PROFICIO trials of 48 to 52 weeks of follow-up and the diabetes mellitus subanalysis of the FOURIER trial of 168 weeks of follow-up also did not show changes in fasting plasma glucose or hemoglobin A1c levels with evolocumab in patients with and without diabetes mellitus,[71] high risk of diabetes mellitus,[70] impaired fasting glucose, metabolic syndrome, or normoglycemia,[73] although a small but statistically significant increase in fasting plasma glucose with evolocumab (but no change in hemoglobin A1c) at 78 weeks of treatment was found in the GLAGOV study.[64] Furthermore, in contrast to the results seen in the statin and *PCSK9* genetic variant studies mentioned above,[4,81–84] no evidence of increased transition from normoglycemia to new-onset diabetes mellitus following alirocumab or evolocumab treatment was found in pooled analyses.[70,73,85] Findings from the FOURIER trial showed no significant differences in rates of adjudicated new-onset diabetes mellitus cases between evolocumab and placebo over a median follow-up of 2.2 years.[63,71] The lack of increased risk of developing new-onset diabetes mellitus on a PCSK9 inhibitor was further confirmed in the longest-running PCSK9 inhibitor trial to date (the 4-year assessment of the ongoing open-label extension of the phase 2 OSLER-1 trial), which indicated an annualized incidence of new-onset diabetes mellitus of 2.8% for the evolocumab group over up to 4 years of continued exposure (versus 4.0% for the control group).[65] The lack of effect of PCSK9 inhibitors on new-onset diabetes mellitus in contrast to the increased risk of new-onset diabetes mellitus in those with *PCSK9* loss-of-function genetic variants could be attributed to differences in biological effects of LDL-C lowering associated with treatment with a PCSK9 inhibitor (ie, inhibiting circulating, extracellular PCSK9) versus the lifelong exposure to decreased LDL-C levels because of *PCSK9* loss-of-function genetic variants.[81,83] Indeed, PCSK9 monoclonal antibodies have been shown to affect the PCSK9 extracellular pathway without altering the PCSK9 intracellular pathway, which remains poorly characterized, especially in beta cells.[86]

Impact of PCSK9 Inhibitors on Atherosclerosis and Cardiovascular Outcomes in Patients With Diabetes Mellitus

The cardiovascular benefits of LDL-C reductions with a PCSK9 inhibitor were first suggested by the post-hoc analyses of the phase 3 LONG TERM and OSLER trials.[58,62] Recently, the GLAGOV study found that the addition of evolocumab to statin therapy in patients with angiographic coronary artery disease could lead to regression of atherosclerotic plaques after 76 weeks of treatment in those patients with LDL-C reductions.[64] In the subgroup analysis of GLAGOV by diabetes mellitus status, patients with diabetes mellitus had the same benefits as those without diabetes mellitus in the change in percent atheroma volume from baseline to week 78.[64] Evidence of cardiovascular outcome benefits with a PCSK9 inhibitor was recently provided by the FOURIER trial, the first clinical outcomes trial to be reported for a PCSK9 inhibitor (evolocumab), which included 27 564 patients with clinically evident ASCVD and on a moderate-to-high-intensity statin regimen over a median follow-up duration of 2.2 years.[63] FOURIER showed a statistically significant 15% reduction in occurrence of the primary composite end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization with evolocumab treatment relative to placebo (9.8% versus 11.3%; hazard ratio, 0.85; 95% confidence interval [CI], 0.79–0.92; $P<0.001$).[63] The benefit was driven by a reduction of ischemic stroke, myocardial infarction, and revascularization. The magnitude of cardiovascular benefit of evolocumab in FOURIER (with a reduction in LDL-C from 92 to 30 mg/dL) over 2.2 years[63] was close to the range expected based on the Cholesterol Treatment Trialists' meta-analysis of statin trials, which reported a 22% relative risk reduction over 5 years per 1 mmol/L (39 mg/dL) LDL-C reduction.[87] Improved cardiovascular outcomes were observed down to LDL-C levels as low as 8 mg/dL, with no significant associations between such very low LDL-C levels and AEs.[88] Together with the GLAGOV findings, these results show that patients with ASCVD benefit from LDL-C lowering below current targets.[63] As a result, the FDA indicated evolocumab to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease.[21]

Previous studies with other lipid-lowering therapies have shown that patients with diabetes mellitus benefit from tight lipid control at least in the same way as patients with other risk factors,[11,13] or can often benefit significantly more than those without diabetes mellitus as shown in the recent IMPROVE-IT analysis.[14] The prespecified diabetes mellitus subanalysis of FOURIER (which, as previously mentioned, included 11 031 patients with diabetes mellitus versus 16 533 patients without diabetes mellitus, of whom 10 344 had prediabetes and 6189 had normoglycemia) found that evolocumab significantly reduced cardiovascular risk consistently in patients with and without diabetes mellitus at baseline[71]: the hazard ratios for the primary composite end point (defined as above) for patients with diabetes mellitus and without diabetes mellitus were 0.83 (95% CI , 0.75–0.93; $P=0.0008$) and 0.87 (95% CI , 0.79–0.96; $P=0.0052$), respectively (P-interaction=0.60).[71] However, attributed to their elevated cardiovascular risk at baseline, patients with diabetes mellitus tended to have a greater absolute risk reduction over time with evolocumab compared with those without diabetes mellitus (2.7% [95% CI , 0.7–4.8] versus 1.6% [95% CI, 0.1–3.2] reduction in the primary end point over 3 years).[71]

The long-term cardiovascular outcomes trial for alirocumab (ODYSSEY OUTCOMES; NCT01663402), the primary results for which are now available (presentation by Dr Philippe Steg at the American College of Cardiology Annual Scientific Session 2018, Orlando, FL, March 10, 2018; unpublished data), enrolled 18 924 patients (≈29% of whom had diabetes mellitus) randomized 1 to 12 months after acute coronary syndrome, with a median follow-up of 2.8 years. Data on diabetes mellitus and prediabetes parameters (reported by investigators and determined by serial hemoglobin A1c and fasting plasma glucose measurements) from OUTCOMES in this high and very high-risk patient cohort are expected to be reported at a later date. Findings could provide further valuable information on the efficacy and safety of PCSK9 inhibitors in individuals with diabetes mellitus and high to very-high cardiovascular risk, which will ultimately help to guide clinical decision-making beyond statin therapy in this high-risk patient population.

Conclusion

Overall, clinical evidence shows that PCSK9 inhibitors are well tolerated and provide significant LDL-C lowering in individuals with hyperlipidemia and diabetes mellitus on top of maximally tolerated statin therapy, without loss of glycemic control or increased risk of developing diabetes mellitus in those without pre-existing diabetes mellitus, and can prevent or reduce further cardiovascular events.

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Key Words: alirocumab • cardiovascular outcomes • diabetes mellitus • evolocumab • proprotein convertase subtilisin/kexin type 9 inhibitors

SUPPLEMENTAL MATERIAL

Table S1. Summary of Major US Guidelines/Consensus Statements for Individuals with DM

Recommendation source	Recommendations
ADA 2017 guidelines[1]	High-intensity statin therapy in addition to lifestyle therapy is recommended for: • Patients of all ages with DM and ASCVD • Patients 40–75 years of age with DM and ASCVD risk factors* Moderate-intensity statin therapy is recommended in patients ≥40 years of age without cardiovascular risk factors. Moderate- or high-intensity statin therapy is recommended for adults with DM who are <40 or >75 years of age with ASCVD risk factors* The addition of ezetimibe to moderate-intensity statin therapy is recommended in: • Patients ≥40 years of age with DM with acute coronary syndrome and LDL-C ≥50 mg/dL (1.3 mmol/L) • Patients with a history of ASCVD who cannot tolerate high-dose statins.
ACC/AHA 2013 guidelines[2]	Primary prevention of ASCVD in individuals with DM is one of the major risk groups identified by the ACC/AHA Expert Panel. Moderate-intensity statins are recommended for the primary prevention of ASCVD in individuals with DM and LDL-C 70–189 mg/dL aged 40–75 years. High-intensity statin therapy is reasonable for adults 40–75 years of age with DM with a ≥7.5% estimated 10-year ASCVD risk,† unless contraindicated. In adults with DM, who are <40 or >75 years of age, or with LDL-C <70 mg/dL, the ACC/AHA Expert Panel indicated that it is reasonable to evaluate the potential for ASCVD benefits, and for adverse effects and drug–drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.

AACE/ACE consensus statement[3]	Treatment targets: • LDL-C goal of <55 mg/dL, non-HDL-C goal of <80 mg/dL, and Apo B goal of <70 mg/dL in individuals at extreme ASCVD risk, including those with T2DM and a prior ASCVD event (ie, recognized “clinical ASCVD”) or CKD Stage 3 or 4 • LDL-C goal of <70 mg/dL, non-HDL-C goal of <100 mg/dL, and Apo B goal of <80 mg/dL in individuals at very high ASCVD risk, including those with DM plus one or more additional risk factors • LDL-C goal of <100 mg/dL, non-HDL-C goal of <130 mg/dL, and Apo B goal of <90 mg/dL in individuals at high ASCVD risk, including those with DM with no other risk factors.
NLA 2016 annual summary[4]	Co-primary treatment target: • LDL-C goal of <70 mg/dL and non-HDL-C goal of <100 mg/dL in individuals at very high ASCVD risk, including those with clinical evidence of ASCVD and/or DM plus ≥2 major ASCVD risk factors or evidence of end-organ damage (eg, retinopathy, microalbuminuria [ACR >30 mg/g], or CKD [eGFR <60 mL/min/1.73 m^2]) • LDL-C goal of <100 mg/dL and non-HDL-C goal of <130 mg/dL in individuals at high ASCVD risk, including patients with ≥3 major ASCVD risk factors; DM with 0 to 1 additional major ASCVD risk factors and no evidence of end-organ damage; CKD Stage 3B or 4; or LDL-C ≥190 mg/dL.

*ASCVD risk factors included LDL-C ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, CKD, albuminuria, and family history of premature ASCVD.

[†]≥7.5% estimated 10-year ASCVD risk included first occurrence of nonfatal myocardial infarction, coronary heart disease death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations.

AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; ACR, albumin-to-creatinine ratio; ADA, American Diabetes Association; AHA, American Heart Association; Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NLA, National Lipid Association; T2, type 2.

Table S2. Summary of Phase 3 Alirocumab ODYSSEY and Evolocumab PROFICIO Studies

	Study acronym, treatment duration, N	Eligibility criteria	Treatment arms	Background statin
ALIROCUMAB Phase 3 ODYSSEY trials				
1	FH I[5] • 78 weeks • N=486	Patients with HeFH, and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or LDL-C ≥100 mg/dL (for patients with no documented ASCVD) Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded	• ALI 75/150 mg Q2W • PBO	Stable maximally tolerated statin* for ≥4 weeks prior to screening ± other LLT
2	FH II[5] • 78 weeks • N=249	Patients with HeFH, and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or LDL-C ≥100 mg/dL (for patients with no documented ASCVD)	• ALI 75/150 mg Q2W • PBO	Stable maximally tolerated statin* for ≥4 weeks prior to screening ± other LLT

		Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded		
3	HIGH FH[6] • 78 weeks • N=107	Patients with HeFH, and LDL-C ≥160 mg/dL Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded	• ALI 150 mg Q2W • PBO	Stable maximally tolerated statin* for ≥4 weeks prior to screening ± other LLT
4	COMBO I[7, 8] • 52 weeks • N=316	Patients with hypercholesterolemia (non-FH), and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or LDL-C ≥100 mg/dL (for patients with no documented ASCVD) Patients with newly diagnosed DM (within 3 calendar months prior to	• ALI 75/150 mg Q2W • PBO	Stable maximally tolerated statin* for ≥4 weeks prior to screening ± other LLT

		randomization) or poorly controlled DM (HbA1c >8.5% at screening) were excluded		
5	COMBO II[8, 9] • 104 weeks • N=720	Patients with hypercholesterolemia (non-FH), and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or LDL-C ≥100 mg/dL (for patients with no documented ASCVD) Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded	• ALI 75/150 mg Q2W • EZE	Stable maximally tolerated statin* for ≥4 weeks prior to screening without other LLT
6	LONG TERM[10] • 78 weeks • N=2341	Patients with HeFH or non-FH, and LDL-C ≥70 mg/dL No specified DM exclusion criteria	• ALI 150 mg Q2W • PBO	Stable maximally tolerated statin* for ≥4 weeks prior to screening ± other LLT
7	OPTIONS I[11, 12] • 24 weeks	Patients with HeFH or non-FH, and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or	• ALI 75/150 mg Q2W • EZE	Atorvastatin 20 or 40 mg ± other LLT (except EZE as it was used as a comparator)

	• N=355	LDL-C ≥100 mg/dL (for patients with no documented ASCVD) Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded		
8	OPTIONS II[12, 13] • 24 weeks • N=305	Patients with HeFH or non-FH, and LDL-C ≥70 mg/dL (for patients with documented clinical ASCVD) or LDL-C ≥100 mg/dL (for patients with no documented ASCVD) Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded	• ALI 75/150 mg Q2W • EZE	Rosuvastatin 10 or 20 mg ± other LLT (except EZE as it was used as a comparator)
9	ALTERNATIVE[14, 15] • 24 weeks	Statin-intolerant patients with HeFH or non-FH and moderate to very high CV risk,† with LDL-C ≥70 mg/dL (for	• ALI 75/150 mg Q2W • EZE	No statin, but other LLTs (except EZE) were allowed

	• N=361	patients with very high risk) or LDL-C ≥100 mg/dL (for patients with moderate or high risk) Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded		
10	MONO[16] • 24 weeks • N=103	Subjects with 10-year risk of fatal CV events of ≥1% and <5% based on SCORE, and LDL-C ≥70 and <190 mg/dL Patients with history of CHD, HeFH, DM associated with a risk SCORE ≥5% or any additional risk factor, or newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >8.5% at screening) were excluded	• ALI 75/150 mg Q2W • EZE	No statin or other LLT

11	CHOICE I[17] • 48 weeks • N=803	Patients with hypercholesterolemia at moderate to very high CV risk Patients with newly diagnosed DM (within 3 months prior to the screening visit) or poorly controlled DM (HbA1c >9% at the screening visit) were excluded	• ALI 300 mg Q4W/150 mg Q2W • ALI 75/150 mg Q2W • PBO	Maximally tolerated statin or no statin, both ± other LLT
12	CHOICE II[18] • 24 weeks • N=233	Patients with hypercholesterolemia at moderate to very high CV risk, and LDL-C ≥100 and <160 mg/dL for patients on diet therapy alone Patients with newly diagnosed DM (within 3 calendar months prior to randomization) or poorly controlled DM (HbA1c >9% at screening) were excluded	• ALI 150 mg Q4W/150 mg Q2W • ALI 75/150 mg Q2W • PBO	No statin, but receiving fenofibrate or EZE, or diet alone
13	OUTCOMES[19] • Median follow-up 2.8 years	Patients with recent acute coronary syndrome (within 1 year) and inadequate control of atherogenic lipoproteins (defined by at least one	• ALI 75/150 mg Q2W • PBO	Atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg daily, or the maximum tolerated or advisable dose

	• N=18,924	of the following: LDL-C ≥70 mg/dL, non-HDL-C≥ 100 mg/dL, or Apo B ≥80 mg/dL) on specified statin therapy No specified DM exclusion criteria		of one of these statins
14	DM-INSULIN[20, 21] • 24 weeks • N=517	Patients at high CV risk with T2DM or T1DM and LDL-C ≥70 mg/dL	• ALI 75/150 mg Q2W • PBO	Maximally tolerated statin or no statin, both ± other LLT
15	DM-DYSLIPIDEMIA[22, 23] • 24 weeks • N=413	Patients with T2DM and mixed dyslipidemia (defined as non-HDL-C ≥100 mg/dL, and triglycerides ≥150 and <500 mg/dL) with documented ASCVD or ≥1 additional CV risk factor	• ALI 75/150 mg Q2W • Usual care (EZE, fenofibrate, omega-3 fatty acids or nicotinic acid)	Maximally tolerated statin or no statin, without other LLT

EVOLOCUMAB Phase 3 PROFICIO trials				
1	DESCARTES[24] • 52 weeks • N=901	Patients with LDL-C ≥75 mg/dL (1.9 mmol/L) Excluded: • LDL-C ≤99 mg/dL (2.6 mmol/L) with CHD or CHD risk equivalent and not receiving a statin • T1DM or newly diagnosed T2DM (within 6 months of randomization or new screening FPG ≥126 mg/dL [7.0 mmol/L] or HbA1c ≥6.5%), or poorly controlled T2DM (HbA1c >8.5%)	Background LLT stabilized, then patients were randomized to receive EVO 420 mg Q4W OR PBO SC Q4W; 8 treatment groups: • Diet alone + EVO 420 mg Q4W • Diet alone + PBO SC Q4W • Diet + atorvastatin 10 mg QD + EVO 420 mg Q4W • Diet + atorvastatin 10 mg QD + PBO SC Q4W • Diet + atorvastatin 80 mg QD + EVO 420 mg Q4W • Diet + atorvastatin 80 mg QD + PBO SC Q4W • Diet + atorvastatin 80 mg QD + EZE 10 mg QD + EVO 420 mg Q4W • Diet + atorvastatin 80 mg QD + EZE 10 mg QD + PBO SC Q4W	LLT, ranging from diet alone to atorvastatin 80 mg plus EZE, was optimized to reach NCEP ATP III LDL-C treatment goals
2	MENDEL-2[25] • 12 weeks • N=614	Patients with LDL-C ≥100 and <190 mg/dL (≥2.6 and <4.9 mmol/L) Patients with DM were excluded	Six treatment groups: • EVO 140 mg Q2W + PBO PO QD • PBO SC Q2W + EZE PO QD • PBO SC Q2W + PBO PO QD • EVO 420 mg QM + PBO PO QD • PBO SC QM + EZE PO QD • PBO SC QM + PBO PO QD	None

3	LAPLACE-2[26, 27] • 12 weeks • N=1896	Patients with LDL-C ≥150 mg/dL (4.0 mmol/L) on no statin, ≥100 mg/dL (2.6 mmol/L) on nonintensive statin, or ≥80 mg/dL (2.1 mmol/L) on intensive statin Patients with T1DM or newly diagnosed or poorly controlled T2DM (HbA1c >8.5%) were excluded	24 treatment groups: Background atorvastatin 80 mg QD OR atorvastatin 10 mg QD, PLUS one of the following: • EVO 140 mg Q2W + PBO PO QD • PBO SC Q2W + EZE PO QD • PBO SC Q2W + PBO PO QD • EVO 420 mg QM + PBO PO QD • PBO SC QM + EZE PO QD • PBO SC QM + PBO PO QD OR Background rosuvastatin 40 mg QD OR rosuvastatin 5 mg QD OR simvastatin 40 mg QD, PLUS one of the following: • EVO 140 mg Q2W • PBO SC Q2W • EVO 420 mg QM • PBO SC QM	Five background statin regimens: atorvastatin 80 mg, atorvastatin 10 mg, rosuvastatin 40 mg, rosuvastatin 5 mg, or simvastatin 40 mg
4	GAUSS-2[28, 29]	Statin-intolerant patients not at LDL-C goal per NCEP ATP III risk	Four treatment groups: • EVO 140 mg Q2W + PBO PO QD	None, or on a low-dose statin defined as a

	• 12 weeks • N=307	categories for fasting LDL-C Patients with T1DM or newly diagnosed T2DM (within 6 months of randomization or new screening FPG ≥126 mg/dL [7.0 mmol/L] or HbA1c ≥6.5%), or poorly controlled T2DM (HbA1c >8.5%) were excluded	• EVO 420 mg QM + PBO PO QD • PBO SC Q2W + EZE PO QD • PBO SC QM + EZE PO QD	maximum weekly dose of ≤70 mg atorvastatin, ≤140 mg simvastatin/pravastatin/lovastatin, ≤35 mg rosuvastatin, or ≤280 mg fluvastatin
5	GAUSS-3[30] • 24 weeks (Phase A) + 2 weeks (washout) + 24 weeks (Phase B) • N=491 (Phase A), N=218 (Phase B)	Statin-intolerant patients with muscle-related adverse effects, not at LDL-C goal per NCEP ATP III risk categories for fasting LDL-C Patients with T1DM or newly diagnosed T2DM (within 6 months of randomization or new screening FPG ≥126 mg/dL [7.0 mmol/L] or HbA1c ≥6.5%), or poorly controlled T2DM (HbA1c >8.5%) were excluded	Phase A (24 weeks): atorvastatin 20 mg QD or PBO to identify patients having muscle-related symptoms only with atorvastatin but not PBO. These patients entered Phase B (24 weeks after a 2-week washout), and were randomized to EVO 420 mg QM or EZE 10 mg QD	Atorvastatin 20 mg QD
6	RUTHERFORD-2[31] • 12 weeks	Patients with HeFH and LDL-C ≥100 mg/dL (2.6 mmol/L)	Four treatment groups: • EVO 140 mg Q2W • PBO Q2W	On stable background statin with or without other approved LLT for ≥4 weeks

	• N=329	Patients with T1DM or newly diagnosed or poorly controlled T2DM (HbA1c >8.5%) were excluded	• EVO 420 mg QM • PBO QM	
7	THOMAS-1[32] • 6 weeks • N=149	Patients with LDL-C ≥85 mg/dL (2.2 mmol/L) Patients with T1DM, or uncontrolled or recently diagnosed T2DM, were excluded	EVO 140 mg SC Q2W with autoinjector versus prefilled syringe	On stable statin (with or without EZE) for ≥4 weeks before LDL-C screening
8	THOMAS-2[32] • 12 weeks • N=164	Patients with LDL-C ≥85 mg/dL (2.2 mmol/L) Patients with T1DM, or uncontrolled or recently diagnosed T2DM, were excluded	EVO 420 mg SC QM with autoinjector versus automated minidoser	On stable statin (with or without EZE) for ≥4 weeks before LDL-C screening
9	GLAGOV[33, 34] • 76 weeks • N=968	Patients with angiographic coronary disease, and LDL-C ≥80 mg/dL or 60−80 mg/dL with 1 major or 3 minor CV risk factors Patients with T1DM or poorly controlled T2DM (HbA1c >9%) at	• EVO 420 mg QM • PBO QM	On stable statin for ≥4 weeks before LDL-C screening

		screening were excluded		
10	FOURIER[35] • Median follow-up 2.2 years • N=27,564	Patients with ASCVD and LDL-C ≥70 mg/dL No specified DM exclusion criteria	Four treatment groups: • EVO 140 mg Q2W • PBO Q2W • EVO 420 mg QM • PBO QM	Optimized regimen of LLT, defined as preferably a high-intensity statin but must have been at least atorvastatin 20 mg daily or its equivalent, with or without EZE
11	NCT02739984 • 12 weeks • N=424	Patients with T2DM on stable DM therapy, LDL-C or non-HDL-C levels and fasting triglycerides ≤600 mg/dL, with HbA1c <10%	• EVO 420 mg QM • PBO QM	Maximally tolerated dose of statin of at least moderate intensity
12	NCT02662569 • 12 weeks • N=986	Patients with T2DM on stable DM therapy, and fasting LDL-C ≥100 mg/dL for those on statin or ≥130 mg/dL for those not on statin Patients with T1DM or poorly controlled T2DM were excluded	Four treatment groups: • EVO 140 mg Q2W • PBO Q2W • EVO 420 mg QM • PBO QM	Atorvastatin 20 mg PO QD

Clinicaltrials.gov identifiers: FH I, NCT01623115; FH II, NCT01709500; HIGH FH, NCT01617655; COMBO I, NCT01644175; COMBO II,

NCT01644188; LONG TERM, NCT01507831; OPTIONS I, NCT01730040; OPTIONS II, NCT01730053; ALTERNATIVE, NCT01709513; MONO, NCT01644474; CHOICE I, NCT01926782; CHOICE II, NCT02023879; OUTCOMES, NCT01663402; DM-INSULIN, NCT02585778; DM-DYSLIPIDEMIA, NCT02642159; DESCARTES, NCT01516879; MENDEL-2, NCT01763827; LAPLACE-2, NCT01763866; GAUSS-2, NCT01763905; GAUSS-3, NCT01984424; RUTHERFORD-2, NCT01763918; THOMAS-1, NCT01849497; THOMAS-2, NCT01879319; GLAGOV, NCT01813422; FOURIER, NCT01764633.

*Maximally tolerated statin dose = the highest tolerable registered dose of daily statin currently administered to the patient, i.e. rosuvastatin 20 or 40 mg, atorvastatin 40 or 80 mg, or simvastatin 80 mg. Lower doses could be used, e.g. in the case of intolerance or local practice, according to the investigator's judgment.

†Moderate risk = 10-year risk of fatal CV events of ≥1% and <5% (SCORE). High risk = SCORE ≥5%, eGFR 30 to <60 mL/min/1.73 m^2, T1DM or T2DM without target organ damage or HeFH. Very high risk = CHD, ischemic stroke, peripheral artery disease, transient ischemic attack, abdominal aortic aneurysm, or carotid artery occlusion >50% without symptoms; carotid endarterectomy or carotid artery stent procedure; renal artery stenosis or renal artery stent procedure; or T1DM or T2DM with target organ damage.

NCEP ATP III risk category LDL-C goals:[36] <100 mg/dL (2.6 mmol/L) for those with diagnosed CHD or risk equivalent, <130 mg/dL (3.4 mmol/L) for those without CHD or risk equivalent and ≥2 risk factors, <160 mg/dL (4.1 mmol/L) for those without CHD or risk equivalent and 1 risk factor, or <190 mg/dL (4.9 mmol/L) for those without CHD or risk equivalent and no risk factors.

ALI, alirocumab; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EVO, evolocumab; EZE, ezetimibe; FH, familial hypercholesterolemia; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; NCEP ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; PBO, placebo; PO, oral; Q2W, every two weeks; Q4W, every 4 weeks; QD, once daily; QM, monthly; SC, subcutaneous; SCORE, European Systematic Coronary Risk Evaluation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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