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An update on pharmacotherapies in diabetic dyslipidemia

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ABSTRACT

Hyperlipidemia plays a crucial role in the underlying pathogenesis of multiple cardiovascular diseases (CVD), including coronary artery disease, peripheral arterial disease, carotid stenosis, and heart failure. The risk of developing such diseases in the diabetic population is relatively high. Diabetes mellitus (DM) is an independent risk factor for premature atherosclerosis. The hallmark of DM dyslipidemia is a demonstrably high level of atherogenic triglyceride rich lipids including very low-density lipoprotein, chylomicrons, and small dense low-density lipoprotein (LDL). Moderate to high intensity statins, targeting LDL cholesterol reduction, remain the cornerstone in the management of this unique disorder. Many 'non-statin' drugs have recently been studied in the DM patients who were either on a 'maximally tolerated statin' or 'statin intolerant'. Ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are particularly important and were incorporated in the recent guidelines by the European Society of Cardiology, American College of Cardiology, American Heart Association, and American Diabetes Association. Icosapent Ethyl has garnered huge interest this year following publication of the REDUCE-IT trial. There are several newer hypolipidemic drugs, including Bempedoic acid, Inclisiran and RVX-208, that are in different phases of clinical trials. In this article, we review the underlying pathophysiology of DM dyslipidemia, existing guidelines related to its management, and the potential of newer hypolipidemic and anti-inflammatory drugs being incorporated in the management of DM.

Contents

Abbreviations: ACL, adenosine triphosphate citrate lyase; ARR, absolute risk reduction; ASCVD, atherosclerotic cardiovascular disease; CETP, cholesteryl ester transfer protein; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; GLP-1, glucagon-like peptide-1; HDL-C, high density lipoprotein cholesterol; hs-CRP, highly sensitive C-reactive; IPE, Icosapent Ethyl; LDL-C, low density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; NPC1L1, Niemann-Pick C1-like 1; PCSK9, proprotein convertase subtilisin/kexin type 9; sd-LDL, small dense low-density lipoprotein; TG, triglyceride; VLDL, very low density lipoprotein.

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Diabetes mellitus (DM) is one of the leading causes of premature atherosclerosis in all genders. Consequently, risk of atherosclerotic cardiovascular disease (CVD;ASCVD), like coronary heart disease (CHD), carotid atherosclerosis, and peripheral arterial disease, is high in the DM population and contributes significantly to the morbidity and mortality in this patient subset.[1] A meta-analysis of 102 prospective studies involving 698,782 people showed that CHD occurred in people with DM at twice the rate of non-DM.[2] The characteristics and causation of CVD in patients with DM have been well discussed in the Diabetes Control and Complications Trial (DCCT),[3] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial,[4] Veterans Affairs Diabetes Trial (VADT),[5] and Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial.[6] All of them demonstrated that vascular atherosclerosis in DM patients is contingent not only on glycemic control but also on the duration of illness as well as presence of co-existent risk factors, including dyslipidemia.

Dyslipidemia undeniably contributes to the risk of CVD in DM. Diabetic dyslipidemia is characterized by high levels of lipoproteins that are responsible for atherogenesis: very low-density lipoprotein (VLDL), chylomicrons, and small dense low-density lipoprotein (sdLDL). These are rich in apoprotein B100 and measured in the blood as either apoB or non high-density lipoprotein cholesterol (non-HDL-C). Quantitatively, elevated triglycerides (TG) and low HDL is seen in this patient population.[7]

Presently, several novel therapies for lipid-lowering including ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, RVX-208, Inclisiran, Bempedoic Acid, and Icosapent Ethyl have either been approved or have shown promising outcomes in late phase clinical trials. In 2016, the European Society of Cardiology (ESC) released new guidelines on lipid management, combining some of these results in the routine practice of physicians. Similarly, the American College of Cardiology (ACC) in 2018, and the American Diabetic Association (ADA) in 2019, also released specific guidelines, sections of which are compiled in this review. We also review pathogenetic mechanisms causing DM dyslipidemia and the steps through which these newer drugs could be used, along with maximally tolerated statins, for its management.

Pathophysiology of Dyslipidemia in DM

The underlying mechanisms of 'diabetic dyslipidemia' are complex and only partly understood. It is uniquely characterized by elevated TG, decreased levels of high-density lipoprotein (HDL), and TG-rich lipoproteins (TRL) including remnant chylomicrons, VLDL, and sd-LDL.[8] The disordered lipid profile has its pathogenesis in insulin resistance, hyperinsulinemia, and abnormal adipokine levels, all commonly seen in DM.[9] Hyperglycemia likely plays a smaller direct role in the process since dyslipidemia is frequently observed in normoglycemic patients as well.[10]

Hypertriglyceridemia is possibly central to the development of CVD in DM, attributable to both decreased clearance by hepatic metabolism and lipoprotein lipase and increased production of VLDL.[11] The hyperinsulinemic state of the body enhances hepatic production of VLDL particles which contributes to a high fasting TG level, whereas high postprandial TG levels can be due to the overproduction of intestinal TRLs (chylomicrons). LDL-C in DM, although quantitatively similar to the general population, is highly atherogenic due to compositional differences. This is related to the activation of cholesteryl ester transfer protein (CETP) in response to hypertriglyceridemia, which causes TG enrichment of LDL and HDL,[12] which makes the former more atherogenic and latter less athero-protective. Small dense LDL (sd-LDL) particles undergo glycosylation, even in the euglycemic state, and subsequent oxidation by free radicals. These particles have the unique property of enhanced permeation in the endothelium, and subsequently attracting macrophages thereby promoting atherosclerosis.[7]

Notably, the serum levels of LDL-C can be normal in DM dyslipidemia.The atherogenic lipids in DM are TRLs and sd-LDL, which are rich in apoprotein B100. Thus, apoprotein B levels and non-HDL-C (calculated as total cholesterol-HDL cholesterol) should be used preferentially to estimate the risk and used as targets for lipid-lowering therapy.[13] The complex interplay of diabetic dyslipidemia is outlined in Figure 1.

Pharmacotherapies for diabetic dyslipidemia

Statins

The optimal management of LDL-C with either moderate or high-intensity statin has remained a cornerstone in dyslipidemia treatment, irrespective of the etiology of dyslipidemia. In the following section, we will summarize the existing guidelines from major societies like the AHA/ACC, ADA, ESC, and U.S. Preventive Services Task Force (USPSTF) on the management of blood lipids, with a specific focus on DM.

The 2016 guidelines of ESC specifically outline the treatment strategies for DM dyslipidemia. As per the guidelines, all DM patients should be treated with statins, if tolerated, with different LDL-C goals based on the type of DM, cardiovascular risk factors and complications. In patients with type 1 DM and concurrent renal disease, the target should be lowering LDL-C by 50%. Those with type 2 DM who present with either renal or CVD should have the following targets: LDL-C < 70 mg/dL, non-HDL-C < 100 mg/dL and apoB <80 mg/dL. These targets are also followed in patients without CVD, with age > 40 years, and presence of one or more CVD risk factors. In patients without any CVD or risk factors, the targets are more lenient: LDL-C < 100 mg/dL, non-HDL-C < 130 mg/dL and apoB <100 mg/dL.[14]

The 2018 guideline on hypercholesterolemia management endorsed by the ACC/AHA/ADA, assigns a class I recommendation to use of moderate-intensity statins for primary prevention in the age group of 40 to 75 years in individuals diagnosed with DM. If the LDL-C level is between 70 and 189 in these patients, it is considered reasonable to assess the likelihood of development of ASCVD in the next 10 years using race and gender-adjusted risk calculators. All people with DM with the simultaneous presence of multiple CVD risk factors should be considered for high-intensity statin therapy, with the goal of lowering LDL-C by ≥50%. Patients older than 75 years of age could be continued or started on statins if the physician feels that the risk-benefit ratio warrants treatment.[15]

The guidelines from the ADA released in 2019 have a slightly different perspective- DM patients in the age group of 40–75 years (level of evidence A) or >75 years (level of evidence B) without any other risk factors, should be initiated on a moderate-intensity statin therapy. Adding ezetimibe or a PCSK9 inhibitor to a maximally tolerated dose of statin is recommended (level of evidence A), provided the LDL-C level did not reach the goal of 70 mg/dl with statin therapy alone. The

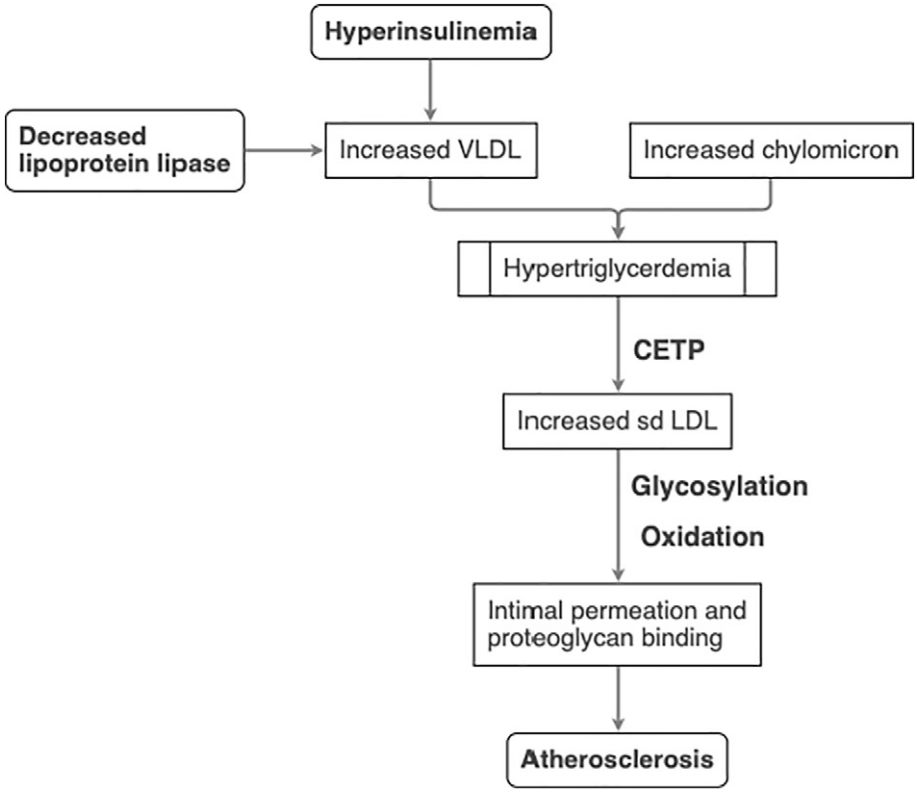

Figure 1. Pathogenesis of diabetic dyslipidemia.

guidelines also recommend prescribing a high-intensity statin in all patients with a 10-year ASCVD risk of >20% (LOE A). In patients < 40 years of age with additional CVD risk factors, initiation of a moderate-intensity statin can be considered (LOE C). Lifestyle modification with changes in diet and exercise should always be recommended before statin initiation in all patient groups.[16]

In contrast to the ADA guidelines, the most recent USPSTF guidelines (published in 2016) follows a more conservative approach. It gives a grade B recommendation to the use of low to moderate-intensity statins in adults of 40–75 years of age with 1 or more CVD risk factors (including DM) and a 10-year ASCVD risk of ≥10%.[17] (Table 1 and Table 2).

Ezetimibe

Ezetimibe acts by inhibiting cholesterol absorption from the intestine, ultimately causing a reduction in LDL-C. This drug is concentrated in the intestinal brush border cells and binds to sterol transporter Niemann-Pick C1-Like 1 (NPC1L1).[18] As per the 2018 ACC guidelines on the management of hypercholesterolemia, it is considered reasonable to add ezetimibe to maximally tolerated statin therapy in patients with 'very high-risk' of ASCVD (defined as history of multiple major CVD events or history of 1 major CVD event with numerous CVD risk factors) if the LDL-C level is ≥70 mg/dL (class of recommendation IIa). Ezetimibe can also be added in patients with maximally titrated dose of statins but baseline LDL-C ≥ 190 mg/dL and post treatment LDL-C ≥ 100 mg/dL.[15]

In the initial trials, designed to study the safety and efficacy of ezetimibe as a lipid-lowering drug, results in patients with DM were unclear.[19] Large scale randomized trials published in years 2005–2006 noted that people with DM who were treated with the combination of statin/ezetimibe had a greater reduction in LDL-C compared to treatment with statin alone.[20,21] Encouraged by these results, a gamut of trials were done to study the progression of atherosclerosis, using carotid intima-media thickness, in patients treated with ezetimibe. As opposed to previous trials, these studies did not find a difference between those receiving statins/ezetimibe or statins monotherapy.[22,23] In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) study, the combination of ezetimibe and a statin produced a superior reduction in LDL-C when compared to statins and extended release niacin (ERN), though it also decreased HDL-C. Interestingly, the trial demonstrated an increase in carotid intimal thickness, which was the primary endpoint, in patients that received ezetimibe.[24]

The landmark 'Improved Reduction of Outcomes: Vytorin Efficacy International Trial', popularly referred to as the IMPROVE-IT trial, was a double-blinded randomized controlled trial of 18,144 patients with a history of recent acute coronary syndrome (ACS) and LDL-C ranging between 50 mg/dl and 125 mg/dl. Out of these, 27% (4933 patients) had DM. The two arms were simvastatin/placebo and simvastatin/ezetimibe, with a composite primary outcome of CVD death, non-fatal myocardial infarction (MI), non-fatal stroke, unstable angina requiring hospitalization, and coronary revascularization in patients at least 30 days after randomization followed up for a median of 6 years. The median LDL-C level was lower in the combination group when analyzed against the statin-only group, which was also reflected in the primary outcome.[25] The main results of this trial showed a significant reduction in MACE after 7 yrs of treatment with the combination of simvastatin and ezetimibe. The IMPROVE-IT trial drew criticism for using moderate intensity statin, instead of higher doses in post-ACS patients. A subgroup analysis of DM patients showed greater absolute risk reduction (ARR) in primary point event rate by 5.5% (hazard ratio, 0.85; 95% confidence interval, 0.78–0.94) compared to a non-significant reduction of only 0.7% (hazard ratio, 0.98; 95% confidence interval, 0.91–1.04; *P*int = 0.02) in patients without DM. The difference was driven mostly by significant reduction in MI (24%) and ischemic stroke (39%) in the DM population.[26]

Subsequently, a comparative meta-analysis using 8 studies with a total of 80,790 DM and 85,555 non-DM demonstrated that patients on the statin-ezetimibe combination had a lower prevalence of CVD compared to patients on statins alone, in both DM and non-DM. Another

Table 1
Summary of Existing Recommendations by Individual Society on Management of Diabetic Dyslipidemia

Society, year	Guideline	Strength of recommendation
ESC, 2016[14]	In all patients with type I diabetes and in the presence of microalbuminuria and/or renal disease, LDL-C lowering (at least 50%) with statins as the first choice is recommended irrespective of the baseline LDL-C concentration.	I
	In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are >40 years of age with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is <1.8 mmol/L (<70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (<100 mg/dL) and for apoB is <80 mg/dL.	I
	In all patients with type 2 diabetes and no additional risk factors and/or evidence of target organ damage, LDL-C <2.6 mmol/L (<100 mg/dL) is the primary goal. Non-HDL-C <3.4 mmol/L (<130 mg/dL) and apoB<100 mg/dL are the secondary goals.	
USPSTF, 2016[17]	Clinicians may choose to offer a low- to moderate-dose statin to certain adults without a history of CVD when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 7.5% to 10%.	C
	Current evidence is insufficient to assess the balance of benefits and harms of initiating statin use for the primary prevention of CVD events and mortality in adults 76 years and older without a history of heart attack or stroke.	I
ACC/AHA/ADA, 2018[15]	In patients who are 75 years of age or younger with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels. T2DM and age 40-75 years, use moderate-intensity statin and risk estimate to consider high-intensity statins.	I (A)
	In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe	I (B)
	In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL, it is reasonable to add a PCSK9 inhibitor following a clinician–patient discussion about the net benefit, safety, and cost	II (A)
	In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level ≥ 70 mg/dL, it may be reasonable to add ezetimibe	II (B-R)
ADA, 2019[16]	For patients of all ages with diabetes and atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >20%, high-intensity statin therapy should be added to lifestyle therapy	A
	For patients with diabetes aged <40 years with additional atherosclerotic cardiovascular disease risk factors, the patient and provider should consider using moderate-intensity statin in addition to lifestyle therapy.	C
	For patients with diabetes aged 40–75 years and >75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin in addition to lifestyle therapy.	A - for 40-75 years B - for>75 years
	In patients with diabetes who have multiple atherosclerotic cardiovascular disease risk factors, it is reasonable to consider high-intensity statin therapy	E
	For patients with diabetes and atherosclerotic cardiovascular disease, if LDL cholesterol is ≥70 mg/dL on maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor). A Ezetimibe may be preferred due to lower cost.	A

network meta-analysis using 35 trials showed the LDL-C responded more with the supplementation of statins with ezetimibe than doubling the initial statin dose.[19] These results eventually consolidated into guidelines placing the status of ezetimibe second to a statin in lipid lowering therapy.

When compared to evolocumab (a PCSK9 inhibitor), ezetimibe also has the advantage of cost-effectiveness and ease of administration. The annual cost of ezetimibe to prevent one major adverse CVD event (MACE) is markedly less than evolocumab in DM patients with ASCVD.[27] In light of these new data on efficacy, safety and cost of ezetimibe, it is now considered as the first line non-statin therapy to achieve optimum cholesterol goals in DM dyslipidemia after high-intensity or maximally tolerated statin therapy.

PCSK9 Inhibitors

The PCSK9 inhibitors are a recently approved class of lipid-lowering therapy that contains 2 prominent drugs: evolocumab and alirocumab; both of which are fully humanized monoclonal antibodies that can bind to free PCSK9 enzyme.[28] This enzyme is responsible for promoting the breakdown of hepatic LDL receptors, and inhibition of the same leads to enhanced clearing of LDL-C by the liver and consequently lower plasma LDL-C levels.[29] Both drugs have comparative pharmacology, as highlighted in Table 3, and a safety profile suitable for DM patients. As per the 2018 ACC guidelines, PCSK9 inhibitors can be added for secondary prevention in patients with very high risk ASCVD and LDL-C ≥ 70 mg/dL on maximally tolerated statin and ezetimibe, baseline LDL-C of 190 mg/dL or higher and current LDL-C level of more than equal to 100 mg/dL on statins. The guidelines do not specify the role of PCSK9 inhibitors in DM dyslipidemia.[15] The drugs have additionally shown benefit in the reduction of major adverse CVD events (MACE).

Although ample data existed proving the efficacy and safety of evolocumab in LDL-C lowering,[36–39] the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial[40] was the first large scale randomized controlled trial to demonstrate clear benefit in CVD outcomes with the addition of evolocumab in patients with pre-existing CVD maintained on statins. The LDL-C levels were found to be reduced by 60% from baseline to a median value of 30 mg/dL with a corresponding 15% relative reduction in the primary endpoint (a composite of MI, CVD death, stroke, and coronary revascularization or unstable angina requiring hospitalization). These results are complimented by the recently published findings of the ODYSSEY Outcomes trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) testing alirocumab for similar endpoints. Enrolling 18,924 patients on statins who had an ACS in the preceding year and a deranged lipid profile at baseline, the trial established significant reduction (15%) in the primary endpoint of major CVD events. Similar to evolocumab, alirocumab has a slightly lower risk of worsening DM and complications as compared to the placebo group.[41] Following concerns about theorized inhibitory action of the drugs on the pancreas, Monami and colleagues from Italy further analyzed the CVD outcomes of PCSK9 inhibitors in the DM population and concluded that unlike statins' association with increased risk of new onset DM, the treatment with PCSK9 inhibitors had no adverse effect on glucose metabolism.[42] These findings open up the possibility of the study of PCSK9 inhibitors in more extensive, long term randomized controlled trials the DM population.

With the safety of PCSK9 inhibitors established in the DM population, these drugs can now be used in patients who fail to attain optimal LDL-C goal with a highest tolerated dose of lipid-lowering therapies with statins and ezetimibe. Neither of the two PCSK9 inhibitors appears to worsen glycemic control in people with DM or increases the

Table 2
Statins with doses as per the American College of Cardiology (ACC) 2018 Guidelines on the Management of Blood Cholesterol.[15]

	High intensity statins	Moderate intensity statins
LDL-C lowering by	≥50%	30–49%
Dose	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 20-40 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40–80 mg Lovastatin 40–80 mg Fluvastatin XL 80 mg Fluvastatin 40 mg twice daily Pitavastatin 1–4 mg

incidence of any other adverse effects in DM as compared to non-DM. The recent decrease in the price of evolocumab and alirocumab will hopefully further expand the scope of this class of drugs.

Icosapent Ethyl

Icosapent Ethyl (IPE) is a highly purified eicosapentaenoic ethyl ester, a long chain omega 3 polyunsaturated fatty acid derived typically from fish oil. The molecule acts on peroxisome proliferator-activated receptor (PPAR) expressed on adipocytes and inflammatory cells to reduce levels of fasting TGs, increase insulin sensitivity, and regulate the inflammatory cascade. Recently, several large-scale randomized trials have been published to examine the exact role of IPE in patients with hypertriglyceridemia.[34]

In the pivotal trial REDUCE-IT, 8179 patients with diagnosed CVD and age ≥ 45 years or DM with at least 1 risk factor and age ≥ 50 years were randomly assigned to IPE 2 g twice daily or placebo, with a median follow up of 4.9 years. Patients were also required to have TG levels between 135 and 499 mg/dL and LDL-C levels 41–100 mg/dL on a stable dose of statin for at least 4 weeks. The primary composite endpoint of major adverse CVD events (MACE) was significantly lower in the group treated with IPE (17.2% vs 22.0%) with an ARR of CVD death of 0.9%.[43]

The REDUCE-IT trial paved the way for the currently ongoing STRENGTH trial, expected to be completed in 2020, that will examine the effect of Epanova 4 g (a combination of 75% eicosapentaenoic acid and 25% docosahexaenoic acid) on CVD outcomes, such as MI, stroke, CVD death, coronary revascularization and unstable angina requiring hospitalization over a median duration of therapy of 3 years.[44]

The REDUCE-IT trial also demonstrated that patients with higher TG levels, in spite of being on a maximally tolerated statin, responded well to the addition of 2 g twice daily IPE. This could indicate a remarkable change in DM dyslipidemia treatment as hypertriglyceridemia lies at the crux of its pathophysiology and 58.5% of the trial patients had DM. The ADA updated its guidelines in 2019 and included recommendations that IPE be considered for individuals with DM and ASCVD or other CHD risk factors who are on a statin with controlled LDL-C, but have elevated TG (135–499 mg/dL).[16]

GLP-1 Analogue Peptide/anti-PCSK9 Antibody Fusion (MEDI4166)

MEDI4166 is a newly developed drug that fuses a glucagon-like peptide (GLP-1) receptor agonist and PCSK9 neutralizing antibody. This drug has dual properties of glycemic control and LDL-C lowering.[45] GLP-1 is a peptide hormone produced in the body from intestinal enteroendocrine cells in response to glucose ingestion. It acts by increasing insulin secretion from the pancreatic cells, decreasing gastric emptying, and promoting early satiety. This mechanism of action makes it useful in the treatment of type II DM and obesity.[46] The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results or the LEADER trial, published in 2016, proved the superiority of GLP-1 agonist liraglutide over placebo in reduction of death from CVD events, non-fatal MI and non-fatal stroke in patients diagnosed with type II DM with a high CVD risk.[47] The MEDI4166 molecule had initial success in lowering LDL-C in cynomolgus monkeys and effectively achieving glycemic control in type 2 DM mouse models.[45] A randomized phase 1 trial in 40 overweight and DM patients was conducted that divided the sample population into a 3:1 ratio of MEDI4166 to placebo. The drug was tolerated well at all doses. Notably, no significant reduction in postprandial glucose and GLP-1 activity were observed as was expected during drug development.[48] However, there was a significant dose-dependent reduction in the LDL-C level in type 2 DM patients with obesity, which is promising for future late phase trials.

Inclisiran

As the potential of small interfering RNA (siRNA) molecules, which critical regulators in genomic expression, grows, it opens up more possibilities for targeted therapy. The siRNA molecules are about 20–30 nucleotide RNA sequences which interfere with specific gene expression and affect the breakdown of mRNA post-transcription, preventing translation.[49] Inclisiran is an example of such a molecule directed against the PCSK9 enzyme genomic expression. It is a long-acting agent requiring infrequent administration (1–2 times annually) and decreases the production of PCSK9 in hepatocytes.[50]

Inclisiran differs from the current PCSK9 inhibitors in multiple ways: it has a longer duration of action, requires biannual administration in contrast to the bi-monthly or monthly, and acts at an intracellular level within the hepatocytes as opposed to the plasma level.

In the phase-2 ORION-1 trial on inclisiran, subjects had a history of either atherosclerosis or CVD risk equivalents and had high LDL-C level. They were randomized to placebo or inclisiran and followed up for 180 days to study the primary endpoint of change in LDL-C from baseline.[51] A post hoc analysis of these subjects showed that there was a significant fall in the atherogenic lipoproteins (apo B protein, non-HDL-C, and lipoprotein (a)) regardless of the DM status at recruitment.

These results align with the diabetic subgroup analysis in the trials on PCSK9 inhibitors (FOURIER and ODYSSEY) and hold promise for its use in the management of DM dyslipidemia.[52] However, unlike the

Table 3
Pharmacology of Non-statin Therapies in Lipid Management[28–35]

	Ezetimibe[30]	Alirocumab[31]	Evolucumab[28]	Inclisiran[32]	Bempedoic acid[33]	IPE[34]	Canakinumab[35]
Mechanism of action	Inhibits intestinal cholesterol absorption	PCSK9 inhibitor (antibody)	PCSK9 inhibitor (antibody)	PCSK9 inhibitor (siRNA)	ACL inhibitor	PPAR inhibitor	IL-1β inhibitor (antibody)
Route of administration	Oral	SubQ	SubQ	SubQ	Oral	Oral	SubQ
Dosing	10 mg/day	75-150 mg q2W	140 mg q2W or 420 mg q1M	300 mg on day 1 and day 90	180 mg daily	4 g/day	150 mg q2-4W
Peak action	2 weeks	3-7 days	3-4 days	30 days		5 hours	7-8 days
Bioavailability	Variable	85%	72%				66%
Metabolism	Active metabolite in intestine and liver	Proteolysis	Proteolysis		Converted to active metabolite liver	De-esterified to active metabolite EPA	
Common adverse effects	Myalgia, diarrhea,nausea, vomiting	Injection site reactions	Nasopharyngitis	cough, musculoskeletal pain, and nasopharyngitis	Gout, headache		Infection, diarrhea, nausea

trials on PCSK9 inhibitors, there is no data currently available to demonstrate the role of inclisiran in people with DM or to assess its effects on CVD outcomes. Multiple phase III trials are now underway in the ORION program to address this gap. The largest in the series, the ORION-4 trial, is recruiting about 15,000 patients with a 5-year follow up period to assess CVD outcomes. Also, the ORION-10 and ORION-11 trials are randomized control trials, each for 18 months, designed to evaluate the time-adjusted change in LDL-C in high-risk individuals.[53] Although the initial trial data looks promising, more data are needed before this drug can make it to clinical practice.

Bempedoic acid

Introduced as ETC 1002, bempedoic acid acts by inhibiting the adenosine triphosphate citrate lyase (ACL) enzyme responsible for catalyzing the production of acetyl coenzyme A, an integral substrate in the cholesterol synthesis pathway in the liver. This step is upstream to the target step of statins, potentially allowing bempedoic acid to enhance the lipid-lowering action of statins.[54]

Following the publication of data indicating a significant reduction in LDL-C (28.5%) at 12 weeks in hyperlipidemic patients intolerant to statins and managed with ezetimibe,[55] Ray et al. designed the Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen (CLEAR) Harmony trial. The primary goal was to study the safety of the drug after a 52 week follow up in 2230 patients with LDL-C ≥ 70 mg/dL on maximally tolerated statins therapy. The secondary endpoint was the percentage drop in LDL-C levels at 12 weeks. The results concluded that bempedoic acid had similar rates of overall adverse effects and serious adverse effects, but was associated with a significantly higher incidence of gout resulting in decreased patient retention.[56] It also showed that LDL-C decreased by 16.5% over the same time period. A subsequent trial, the results of which were presented at the recent 2019 ACC Annual Scientific Session, similarly followed 779 patients with atherosclerosis for 52 weeks to study the efficacy and safety. The results were consistent with the previous trial indicating a decrease in LDL-C at 12 weeks of 15.1%, which was sustained at 52 weeks. Interestingly, patients who were not taking statins at baseline had similar results. There was no worsening of DM in patients who received bempedoic acid.[57]

Although bempedoic acid has various attractive properties for use in DM dyslipidemia (such as a reduction in apoB lipoprotein and highly sensitive C-reactive/hsCRP protein), more data on CVD outcomes is required. Future data from head-on comparison with statins, ezetimibe, and PCSK9 inhibitors for similar endpoints and cost-benefit ratio will determine its status in dyslipidemia management.

Fibrates

Fibrates have long been known for their use in lowering TGs and blood cholesterol. Many trials have been published showing benefits of fibrates, and a few of them are listed here. The post hoc analysis of the early Helsinki Heart Study on use of gemfibrozil in men with hypercholesterolemia, without any previous CVD, revealed fibrates lowered CVD events in people with DM as compared to non-DM.[58] Another trial VA-HIT revealed that gemfibrozil reduced the frequency of CVD death and non-fatal MI in CHD patients, with higher relative benefits seen in DM compared to non-DM.[59] In the SENDCAP study, there were 150 DM patients (without previous CVD) who showed significant lowering of risk of CVD events using fibrates,[60] backed by similar results from the Diabetes Atherosclerosis Intervention Study (DAIS) conducted in a DM population with established CHD.[61]

In 2010, Jun et al. conducted a meta-analysis of 18 trials to more conclusively study the effect of fibrates in the reduction of CVD risk. Results of this analysis indicated that the benefits of fibrates in the reduction of coronary events, especially in populations with combined dyslipidemia, was not unlike the one seen in DM.[62]

Canakinumab

The cytokine IL-1β is responsible for the inflammation-mediated CVD complications of DM. Canakinumab, which is not a hypolipidemic but an anti-inflammatory drug, is a human monoclonal antibody that binds explicitly to soluble IL-1β and renders it useless. IL-1β is an important pro-inflammatory cytokine that mediates adhesion of inflammatory cells (monocytes and leukocytes) to the endothelium and promotes vascular smooth muscle proliferation. Although still in the early stages of development, multiple trials have indicated the safety of the drug and more are underway to examine the full extent of its efficacy.[35]

The Canakinumab Anti-Inflammatory Thrombosis Outcome Study or CANTOS trial was a randomized double-blinded trial that was conducted on 10,071 patients. The inclusion criteria included a recent MI and raised levels of hsCRP, despite aggressive secondary prevention. Current data from the trial indicates a significantly lower rate of CVD events with canakinumab at a dose of 150 mg given every 3 months (3.85%/year vs 4.5%/year).[64]

Although the overall CANTOS trial data was encouraging, a subgroup analysis highlighting canakinumab's role in reducing the risk of development of new-onset type 2 DM from pre-diabetes was disappointing.[63] The molecule also demonstrated no significant difference in the reduction of major CVD events among DM, prediabetics, and the normal population despite large reductions in hsCRP and IL-6.[65] This, along with an absolute increase in fatal infections by 0.13%, makes canakinumab a less attractive option in the management of DM dyslipidemia.

Conclusion and future directions

The risk of development of ASCVD in people with DM is relatively high. The culprits, which are the targets of lipid-lowering therapy in this population group, are TG rich lipids. Routine monitoring of lipids does not typically involve measurement of the surrogate markers (apoB and non-HDL-C) of hypertriglyceridemia associated with DM and should be specifically ordered by physicians in DM patients. There is robust evidence supporting the role of statins in reducing the risk of CVD morbidity and mortality in high-risk individuals (including DM), and there remains a high degree of residual risk in DM patients. The presence of this residual risk is the primary reason for further improvement in CVD outcomes with newer lipid-lowering therapy in patients already receiving maximal benefit from statins. Ezetimibe and then PCSK9 inhibitors should be considered the first and second line 'non-statin pharmacotherapy' in DM dyslipidemia. With the promising CVD outcomes of the REDUCE-IT trial, IPE has the potential to become another first line 'non-statin pharmacotherapy'. The other emerging hypolipidemic drugs, including bempedoic acid, inclisiran, and RVX-208 will need more CVD outcome data from the prospective large randomized control trials before any further recommendation can be made (Table 4).

Table 4
Key points of the article.

1. Diabetic dyslipidemia is characterized by hypertriglyceridemia, high levels of apoB, non-HDL-C, and small dense LDL particles
2. Moderate to high-intensity statins remain the cornerstone for treatment of diabetic dyslipidemia based on ASCVD risk and other risk enhancers
3. Ezetimibe showed significant reduction of ischemic stroke and myocardial infarction in DM patients in the IMPROVE-IT trial and is now recommended as the first add on therapy to statins because of the cost considerations
4. PCSK9 are the next class of drugs added to lipid management as they have proven safety and efficacy, with expected future decreases in cost
5. Icosapent ethyl holds promise in diabetic dyslipidemia as it reduces TG and improves cardiovascular outcomes

Credits and grant information supporting the research

We did not receive any grant or funding.

Declaration of competing interest

None.

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