HHS Public Access

Author manuscript

Curr Opin Endocrinol Diabetes Obes. Author manuscript; available in PMC 2020 October 26.

Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2020 August ; 27(4): 207–214. doi:10.1097/MED.0000000000000551.

Lipid management for cardiovascular risk reduction in type 1 diabetes

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Abstract

Purpose of review—To review the recent evidence for lipid management in type 1 diabetes (T1D) for cardiovascular risk reduction.

Recent findings—Individuals with T1D are at increased risk for cardiovascular morbidity and mortality, with atherosclerosis beginning as early as adolescence. Elevated low-density lipoprotein cholesterol (LDL-C), triglycerides, and lipoprotein (a) are associated with increased cardiovascular risk in T1D. Although high-density lipoprotein cholesterol (HDL-C) in T1D is often normal or higher than in nondiabetic controls, HDL in T1D has structural alterations, which make it proatherogenic rather than cardioprotective. Similarly, although LDL-C is not particularly elevated in T1D, LDL still contributes to cardiovascular risk. Studies in individuals with diabetes have primarily included T2D participants, with a much smaller number of T1D participants; such studies have shown that lipid-lowering therapies, such as statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce LDL-C levels and cardiovascular events in both those with and without diabetes. Individuals with T1D have increased cholesterol absorption, suggesting that ezetimibe may be particularly effective in T1D. Results of the REDUCE-IT trial show cardiovascular risk reduction from high-dose omega-3 fatty acid (Icosapent Ethyl) therapy in patients with diabetes (primarily type 2 diabetes), independent of triglyceride lowering, but similar data in T1D are currently lacking.

Summary—Individuals with T1D are at high risk of cardiovascular disease, necessitating close lipid monitoring and management from adolescence through adulthood.

Keywords

cardiovascular disease; lipid; low-density lipoprotein cholesterol; type 1 diabetes

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Conflicts of interest

R.H.E. is on the Scientific Advisory board for PROMI-NENT CVOT - KOWA, with related travel supported.

INTRODUCTION

Type 1 diabetes (T1D) is the most common type of diabetes in youth, with 1 in 300 people developing T1D by age 18 years [1]. Adolescents with T1D show early subclinical atherosclerotic changes that are similar to those seen in children with heterozygous familial hypercholesterolemia [2,3]. Individuals with T1D are at increased risk for cardiovascular events and mortality, even in young adulthood [4■]. Therefore, the close management of cardiovascular risk factors is crucial, including dyslipidemia, nephropathy, hypertension, smoking, obesity, glycemic control, insulin resistance, nutrition and physical activity.

Adults and adolescents with T1D are insulin-resistant compared with nondiabetic individuals, although their lipid profiles do not display the metabolic syndrome features classically associated with insulin resistance [5]. For example, youth with T1D have higher high-density lipoprotein cholesterol (HDL-C) and similar or lower triglyceride values compared with nondiabetic controls. Low-density lipoprotein cholesterol (LDL-C) concentrations in youth with T1D are generally similar to or slightly higher than controls, with higher LDL-C values seen in those with HbA1c greater than 7.5% [6]. Adults with T1D generally have lower LDL-C, lower triglycerides, and higher HDL-C values compared with nondiabetic peers [7]. However, recent evidence shows that changes in HDL-C composition and function are present in T1D, which may make HDL proatherogenic rather than cardio-protective in T1D [8■]. In addition, many individuals with T1D, particularly youth and women, have a shift to smaller and/or denser LDL, also thought to be proatherogenic [9,10]. The purpose of this review is to summarize and assess the recent scientific evidence and clinical guidelines for lipid management in T1D, with a focus on cardiovascular disease (CVD) risk reduction.

CARDIOVASCULAR DISEASE AND INSULIN RESISTANCE IN TYPE 1 DIABETES

Individuals with T1D have a high burden of cardiovascular morbidity and mortality. Subclinical atherosclerotic vascular changes begin as early as childhood, with several studies showing arterial stiffness and endothelial dysfunction in adolescents with T1D [2,11,12]. Children with T1D also have increased carotid and aortic intima–media thickness versus nondiabetic controls, both markers of early atherosclerotic changes [13,14].

Obesity is increasing in T1D, with 56% of adults in the T1D exchange either overweight or obese [15]. This increase in obesity is exacerbating the insulin resistance already present in T1D [16,17], and insulin resistance correlates strongly with both coronary artery calcification and cardiovascular events [18–20]. Treatment with metformin in T1D has been shown to improve insulin sensitivity, carotid intima–media thickness, and aortic stiffness, demonstrating the important rule of insulin resistance in promoting cardiovascular disease in T1D [21,22■]. Recent evidence from youth with T1D suggests that the elevated arterial stiffness associated with increased LDL-C was attenuated when controlling for insulin sensitivity, suggesting that the adverse vascular effects from elevated LDL-C in T1D may be partially explained by insulin resistance [23■■].

Young adults with T1D ages 21–30 years have 11-fold increased risk and those ages 31–40 years have 13-fold increased risk of cardiovascular mortality compared with their age-matched and sex-matched nondiabetic peers [4■]. Developing T1D before age 10 years results in a loss of 17.7 life-years for women and 14.2 life-years for men. Those who develop T1D in adulthood also have significantly increased mortality, with an estimated loss of 10 life-years for those diagnosed after age 20 years [24].

LIPIDS AND LIPOPROTEINS IN TYPE 1 DIABETES

Although levels of lipids and lipoproteins are often within the normal range in T1D, alterations in lipoprotein composition may be important to CVD risk in T1D. This article will, therefore, review the contribution of cholesterol and lipoprotein types to CVD risk in T1D, as well as assess the evidence regarding therapeutic management for each lipoprotein phenotype.

Low-density lipoprotein-cholesterol

LDL-C is a significant predictor of cardiovascular events and mortality in T1D, with each 1 mmol/l (38.7 mg/dl) increase in LDL-C associated with 35–50% greater risk, according to a study using Swedish National Diabetes Registry data [25■].

In the landmark Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) trial in adults with T1D, LDL-C was a significant risk factor for the primary outcome of CVD and the secondary outcome of major atherosclerotic cardiovascular events (MACE) [26]. In the prospective Pittsburgh Epidemiology of Diabetes Complications (EDC) study, which followed individuals with childhood-onset T1D, LDL-C was similarly found to be a risk factor for CVD and MACE [27]. Data from the Pittsburgh EDC study suggest that maintaining an LDL-C less than 100 mg/dl is optimal for primary CVD prevention in T1D [28]. Current available interventions for elevated LDL-C include lifestyle modification and therapeutic management with statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

Adopting a Mediterranean-style or DASH (Dietary Approaches to Stop Hypertension) diet is recommended for LDL-lowering [29]. Statin therapy, the mainstay of treatment for LDL-lowering, has been shown to reduce mortality and cardiovascular events by approximately 25% in individuals with diabetes (including both T1D and T2D); however, the large majority of participants in these studies had T2D [30]. This benefit was also seen in individuals with diabetes with a pretreatment LDL-C less than 116 mg/dl, who experienced a 27% reduction in cardiovascular events on statin therapy [30]. In a prospective cohort study in Sweden, lipid-lowering therapy (97% statins) was associated with decreased all-cause mortality in adults with T1D without underlying CVD, when matched to a cohort with similar baseline risk [31]. In the AdDIT trial in adolescents with T1D, treatment with statin therapy for 2–4 years reduced LDL-C concentrations, but did not improve carotid intima–media thickness [32].

Recent studies have also demonstrated the LDL-C-lowering benefits offered by newer medications, such as ezetimibe and PCSK9 inhibitors. Ezetimibe inhibits cholesterol

absorption in the small intestine. The IMPROVE-IT trial showed the superiority of ezetimibe/statin combination therapy versus statin monotherapy, particularly in participants with recent acute coronary syndrome and diabetes [33]. For participants with diabetes on ezetimibe/statin therapy, there was an absolute risk reduction of 5.5% in the composite endpoint of major coronary events, cardiovascular death, and stroke, compared with an absolute risk reduction of only 0.7% in those without diabetes. Ezetimibe/statin combination led to a 40 mg/dl LDL-C reduction following 1 year of therapy, compared with only a 22 mg/dl reduction with statin therapy alone [33]. In an exploratory nonrandomized cross-over study comparing ezetimibe with statin therapy in T1D and T2D individuals, ezetimibe was more effective in LDL-lowering for those with T1D versus T2D, and within the T1D group ezetimibe lowered LCL-C more than statins [34]. Of interest is recent evidence showing increased cholesterol absorption in T1D versus T2D. Moreover, these data demonstrated decreased cholesterol synthesis in adolescents with T1D compared with nondiabetic controls [35■■]. The results of these studies suggest that ezetimibe may be a particularly potent lipid-lowering agent in individuals with T1D, given its direct effects on decreasing cholesterol absorption.

PCSK9 inhibitors, a newer class of lipid-lowering drugs, act by inhibiting the PCSK9-mediated degradation of LDL receptors in hepatocytes, therefore, increasing LDL-receptor expression and decreasing LDL-C levels [36]. Youth with T1D have increased PCSK9 concentrations versus matched nondiabetic controls, and PCSK9 concentrations in T1D youth are correlated with HbA1c, triglycerides, total cholesterol, and LDL-C [37]. In youth with T1D and suboptimal or poor glycemic control, PCSK9 concentrations correlate with the presence of increased small, dense LDL (sdLDL), a relationship inversely correlated with good glycemic control in T1D individuals (HbA1c <7.5%). This finding may be because of the effects of insulin administration, which include both increasing PCSK9 as well as lowering sdLDL [38]. PCSK9 inhibitors have potent lipid-lowering activity and reduce LDL-C by 47.8% on average versus placebo in individuals with T1D [39]. They also reduce cardiovascular events in patients who have underlying cardiovascular disease and are on statin therapy, with no significant difference in cardiovascular risk reduction in those with or without diabetes; 97% of participants in this study had T2D, highlighting the limited evidence for CVD prevention specifically in T1D [40]. PCSK9 inhibitors are, therefore, highly beneficial for LDL-lowering and are cardio-protective; however, for those with diabetes, they are most often used for secondary prevention for individuals with a history of CVD unable to achieve optimal LDL-C levels on maximally tolerated statin therapy [29]. For specific clinical guideline recommendations regarding LDL-C lowering, see Tables 1 and 2.

Triglycerides

In individuals with T1D from both the PittsburghEDC and DCCT/EDIC studies, increased triglycerides were associated with increased risk of cardiovascular events [26,27]. However, the relationship between hypertriglyceridemia and CVD is likely only an association as atherosclerotic plaque primarily contains cholesteryl ester derived from cholesterol-rich lipoprotein remnants of triglyceride-rich lipoproteins (such as very-low-density lipoproteins and chylomicrons), rather than triglycerides [41].

In addition to diet/exercise changes, medication classes that lower triglycerides include moderate-intensity or high-intensity statins, fibrates, niacin, and omega-3 fatty acids. Fibrate therapy has not shown consistent CVD benefit in people with T2D, and those taking fibrates combined with statins are at increased risk of muscle and liver side effects. For this reason, fibrate therapy is only currently recommended for prevention of acute pancreatitis in people with fasting triglycerides greater than 500. Niacin similarly has not been shown to provide cardiovascular benefit in patients with T2D, and is therefore, not currently recommended for CVD prevention [29].

Numerous studies have been performed with omega-3 fatty acids, containing various combinations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), with inconsistent findings. In the ASCEND trial in individuals with diabetes without underlying CVD (only 6% with T1D), treatment with 840 g/day of omega-3 fatty acid (460 mg EPA, 380 mg DHA) did not reduce the primary end point of serious vascular events or all-cause mortality; however, omega-3 fatty acid treatment did reduce vascular deaths [42]. In the ORIGIN trial studying individuals with dysglycemia or diabetes with preexisting CVD, nephropathy, or peripheral neuropathy, taking 840 g/day of omega-3 fatty acids (465 mg EPA and 375 mg DHA) similarly did not impact the rate of cardiovascular events [43].

In the recent REDUCE-IT trial, the effect of 4 g/day of purified EPA in the form of the medication icosapent ethyl was evaluated for both primary and secondary CVD prevention. Specifically, REDUCE-IT included participants on statin therapy, with fasting triglycerides of 135–499 mg/dl, LDL-C of 41–100 mg/dl, and either established CVD or diabetes in conjunction with other CVD risk factors. About 58% of participants had diabetes, but only approximately 0.7% of those with diabetes had T1D. For those with diabetes, the primary outcome (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina) was reduced by 23% versus placebo, with a number needed to treat of 21. In addition, the secondary endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke was reduced by 30% for those with diabetes. Of note, cardiovascular benefits did not differ based upon baseline triglyceride values or attained triglyceride levels at 1 year of treatment, suggesting that the mechanism of cardioprotection was likely independent of its triglyceride-lowering effect, and instead because of possible metabolic, anti-inflammatory, or antiplatelet effects [44■]. Cardiovascular benefits were even more pronounced in the REDUCE-IT USA subgroup with diabetes, with this subgroup's primary outcome reduced by 31% and secondary endpoint reduced by 34%. In the USA subgroup with diabetes, only 1% of participants had T1D [45]. Given these data, both the American Diabetes Association (ADA) and National Lipid Association (NLA) recommend the use of icosapent ethyl for adults with diabetes and underlying CVD or multiple cardiovascular risk factors who are on maximally tolerated statin therapy with fasting triglycerides 135–499 mg/dl [29,46]. However, additional data are still needed in T1D.

High-density lipoprotein-cholesterol

Insulin resistance, metabolic syndrome, and T2D are classically associated with decreased HDL-C. Although individuals with T1D have insulin resistance, paradoxically, HDL-C is often higher in people with T1D than in nondiabetic controls [6,7]. However, growing

evidence suggests that HDL in T1D may become dysfunctional and proatherogenic, rather than cardioprotective. In a study of adolescents with T1D, HDL dysfunction was noted in those with inflammation and/or albuminuria [8■]. HDL particles isolated from individuals with T1D also show impaired anti-inflammatory capacity [47], and those with T1D have greater triglyceride enrichment in HDL versus nondiabetic controls [48]. Youth with T1D also have proteomic alterations in their HDL compared with healthy controls, including increased levels of the protein FHR2, a complement factor, which may be linked to inflammation [49]. In a study of T1D youth and young adults, reduced HDL function was noted soon after diabetes onset and persisted over time [50]. This is consistent with the finding of decreased cholesterol efflux capacity in T1D versus nondiabetic controls, as cholesterol efflux is an important component of reverse cholesterol transport attributed to HDL [51].

Pharmacological attempts to increase HDL-C have failed to result in clinical benefit, and therefore are not currently recommended [52].

Lipoprotein(a)

Lipoprotein(a), or Lp(a), is a low-density lipoprotein particle with an additional apolipoprotein(a) covalently linked to the apolipoprotein(B) component of the LDL particle. Lp(a) concentrations are genetically determined, pro-atherogenic, and pro-inflammatory. In a study of Lp(a) in T1D individuals, participants with high Lp(a) values (>120 nmol/l) had higher rates of macrovascular complications, calcified aortic valve disease, and albuminuria compared with those with very low Lp(a) [52]. In this study, those with good glycemic control (HbA1C <6.9%) had lower Lp(a) concentrations than those with suboptimal control, although previous studies have shown conflicting results regarding the relationship between HbA1c and Lp(a) [53■■].

In the FOURIER trial, examining the effect of the PCSK9 inhibitor evolocumab in adults with established CVD on statin therapy, evolocumab reduced Lp(a) concentrations, and participants with higher baseline Lp(a) concentrations had greater cardiovascular benefit. In the FOURIER trial, 40% of participants had diabetes, but only 3% of those with diabetes had T1D, and subgroup analysis by diabetes status was not performed [54].

In the ODYSSEY OUTCOMES study evaluating the effect of the PCSK9 inhibitor alirocumab in individuals with recent acute coronary syndrome on statin therapy (29% of whom had diabetes), alirocumab reduced LDL-C, Lp(a), and MACE. Lp(a) reduction independently contributed to MACE reduction, suggesting that it may have value as an independent treatment target for CVD prevention [55■].

PCSK9 inhibitors and niacin lower Lp(a), whereas statins do not [53■■]. Current clinical guidelines do not recommend universal Lp(a) testing or specific therapeutic management to lower elevated Lp(a). However, the most recent american college of cardiology (ACC)/ american heart association (AHA) guidelines and NLA guidelines suggest that an Lp(a) > 50 mg/dl (100 nmol/ls) is a risk-enhancing factor for atherosclerotic cardiovascular disease (ASCVD), which may guide more aggressive LDL-C lowering [56,57].

CLINICAL GUIDELINES

Current guidelines which address targets and interventions for LDL-C lowering in T1D include the 2020 ADA Standards of Medical Care in Diabetes (SOMC) (with separate pediatric and adult sections) [29,58], the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for Management of Dyslipidaemias [52], and the 2018 ACC/AHA Guidelines on Management of Blood Cholesterol [56]. Pediatric-specific guidelines in T1D include the 2018 International Society of Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Guidelines [59], and the 2019 AHA Scientific Statement on Cardiovascular Risk Reduction in High-Risk Pediatric Patients [60].

For youth with T1D, both the 2018 ISPAD Guidelines and 2019 AHA Statement recommend statin therapy for persistent LDL at least 130 mg/dl [59,60], with the 2020 ADA SOMC less aggressively recommending a threshold of LDL at least 160 mg/dl unless other CVD risk factors are present [58]. The AHA Statement also discusses the potential use of cholesterol absorption inhibitors (such as ezetimibe) if LDL-C goals are not met with statins, whereas ezetimibe is not specifically addressed in the pediatric population in either the ISPAD or ADA Guidelines [60]. For a summary of pediatric guidelines, see Table 1.

Unfortunately, most guidelines for the adult T1D population fail to distinguish T1D from T2D. This position reflects the absence of randomized controlled trials in patients with T1D. The 2020 ADA SOMC and the 2018 ACC/AHA Guidelines are very similar, although subtle differences are present. For example, for those age 20–39 years old without ASCVD, the ACC/AHA Guidelines consider a diabetes duration of at least 20 years an indication for starting statin therapy, whereas this is not a specific indication in the ADA SOMC. Another difference is the therapeutic approach to individuals with underlying ASCVD at very-high-risk per ACC/AHA criteriaz. For people in this group unable to achieve goal LDL-C less than 70, the ADA SOMC recommends adding either ezetimibe or PCSK9 inhibitor therapy, whereas the ACC/AHA Guidelines explicitly recommend adding ezetimibe first and only adding PCSK9 inhibitor therapy if unable to reach an optimal level of LDL-C on combined statin and ezetimibe therapy [29,56].

The 2019 ESC/EAS Guidelines differ from the other adult guidelines, with more aggressive LDL-C lowering recommended as well as a strong emphasis on T1D diabetes duration as a CVD risk factor. For example, those with a T1D duration of 10 years or more are categorized as high-risk with an LDL-C goal of less than 70 mg/dl, and those with a T1D duration of 20 years or more are considered very-high-risk with goal LDL-C less than 55 mg/dl [52]. For a summary of adult guidelines, see Table 2.

CONCLUSION

Adults with T1D are at increased risk of CVD. Elevated HDL-C levels in T1D are falsely reassuring, with HDL often dysfunctional rather than protective. Individuals with T1D benefit from LDL-C lowering with statins, ezetimibe, and PCSK9 inhibitors; however, randomized controlled trials assessing CVD reduction to date have grouped all participants with diabetes and enrolled many more patients with T2D, making it difficult to specifically

assess the outcomes in T1D. For this reason, current clinical SOMC and guidelines are extrapolated from studies in T2D or cohort studies in T1D. Future research is warranted to better understand the best approaches to CVD risk reduction in T1D, including the effect of ezetimibe versus PCSK9 inhibitors, particularly given the increased cholesterol absorption observed in T1D. Addressing insulin resistance and the increasing rates of obesity, poor nutrition, and inactivity in T1D are also necessary for CVD risk reduction in T1D.

Financial support and sponsorship

K.J.N. is supported by an NIDDK K24 award. S.T. is supported by an NIH T32 grant.

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KEY POINTS

- Individuals with T1D have increased risk of CVDmorbidity and mortality, yet T1D-specific data on CVD risk reduction remain sparse in the literature.
- LDL-cholesterol (LDL-C) is an important predictor of cardiovascular events and mortality in T1D; statin, ezetimibe, and PCSK9 inhibitor therapy are effective in reducing LDL-C in T1D, with statin therapy currently the recommended first-line therapy for LDL-C lowering.
- Although HDL-C is classically increased in T1D versusthose without diabetes, HDL in T1D is often dysfunctional, with increased triglyceride enrichment as well as proteomic alterations.
- Obesity, insulin resistance, dietary composition, and physical activity are additional areas in need of focus in T1D to reduce dyslipidemia and CVD risk.

Table 1.

Pediatric type 1 diabetes low-density lipoprotein cholesterol management guidelines

	2020 ADA SOMC	2018 ISPAD Guidelines	2019 AHA Statement
LDL-C goal	LDL-C <100 mg/dL (2.6 mmol/L).	LDL-C <100 mg/dL (2.6 mmol/L).	LDL-C <100 mg/dL (2.6 mmol/L).
Pharmacological therapy	From age 10 years, consider statin if despite lifestyle changes, LDL-C >160 mg/dL (4.1 mmol/L) or LDL-C >130 mg/dL (3.4 mmol/L) with one or more ASCVD risk factors.	From age 11 years, statins should be started if LDL-C ≥130 mg/dL despite interventions to improve metabolic control and lifestyle.	From age 10 years, initiate statin therapy and lifestyle change if LDL-C ≥130 mg/dL. Consider adding cholesterol absorption inhibitor if LDL-C goal not met with statin.

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Curr Opin Endocrinol Diabetes Obes. Author manuscript; available in PMC 2020 October 26.

Table 2.

Adult type 1 diabetes low-density lipoprotein-cholesterol management guidelines

2020 ADA SOMC		2018 ACC/AHA guidelines		2019 ESC/EAS guidelines	
Age 20–39 without ASCVD	If additional ASCVD risk factors, consider moderate-intensity statin therapy.	**Age 20–39 without ASCVD**	If T1D duration ≥20 years, or patient with nephropathy, retinopathy, or neuropathy, reasonable to start statin therapy.	**Moderate-risk: Age <35 years old with T1D duration <10 years, without other ASCVD risk factors**	Statin therapy may be considered if LDL-C >2.5 mmol/L (97 mg/dL).
	Goal LDL-C <100 mg/dL (2.6 mmol/L).		Goal LDL-C <100 mg/dL (2.6 mmol/L).		Goal LDL-C <100 mg/dL (2.6 mmol/L).
Age ≥40 without ASCVD	Moderate-intensity statin therapy.	**Age ≥40 without ASCVD**	Moderate-intensity statin therapy.	**High-risk: Diabetes duration ≥10 years or additional ASCVD risk factor, without target organ damage (nephropathy, retinopathy, neuropathy)**	If LDL-C above goal, recommend statin therapy.
	If multiple ASCVD risk factors or age 50–70 years, reasonable to use high-intensity statin.		If multiple ASCVD risk factors or 50–75 years old, reasonable to use high-intensity statin.		If goal not achieved with maximum tolerated statin therapy, combination with ezetimibe recommended.
	If 10-year ASCVD risk ≥20%, reasonable to add ezetimibe to maximally tolerated statin therapy.		If 10-year ASCVD risk ≥20%, reasonable to add ezetimibe to maximally tolerated statin therapy.		
	Goal LDL-C <100 mg/dL (2.6 mmol/L). If 20-year ASCVD risk ≥20%, goal 50% LDL-C reduction.		Goal LDL-C <100 mg/dL (2.6 mmol/L).		Goal LDL-C <70 mg/dL (1.8 mmol/L), with goal reduction of ≥50% from baseline.
			If 20-year ASCVD risk ≥20% or multiple ASCVD risk factors, goal 50% LDL-C reduction.		
With ASCVD	High-intensity statin therapy.	**With ASCVD**	High-intensity statin therapy.	**Very-high-risk: Presence of either diabetes duration >20 years, target organ damage (nephropathy, retinopathy, neuropathy), three major ASCVD risk factors, or underlying ASCVD**	If LDL-C above goal, recommend statin therapy.
	If very high risk[†] and LDL-C ≥70 mg/dL on maximally tolerated statin therapy, consider adding ezetimibe or PCSK9 inhibitor for additional LDL-lowering.		If LDL-C ≥70 mg/dL on maximally tolerated statin therapy, reasonable to add ezetimibe.		If goal not achieved with maximum tolerated statin therapy, combination with ezetimibe recommended.
			If very-high risk[a] and LDL-C ≥70 on maximally tolerated statin therapy and ezetimibe, reasonable to add PCSK9 inhibitor.		If no underlying ASCVD and LDL-C still above goal, consider adding PCSK9 inhibitor.
					If underlying ASCVD and LDL-C still not at goal, recommend adding PCSK9 inhibitor.
	Goal LDL-C <70 mg/dL (1.8 mmol/L).		Goal LDL-C <70 mg/dL (1.8 mmol/L).		Goal LDL-C <1.4 mmol/L (55 mg/dL), with goal reduction of ≥50% from baseline.
					If two ASCVD events within 2 years, consider goal LDL-C <1.0 mmol/L (40 mg/dL).
Special considerations for Age >75	If on statin therapy, reasonable to continue.	**Special considerations for Age >75**	If on statin therapy, reasonable to continue.	**Special Considerations for Age >75**	Initiation of statin therapy for primary prevention may be considered if at high-risk or very-high-risk. Start statin at low

2020 ADA SOMC	2018 ACC/AHA guidelines	2019 ESC/EAS guidelines	
	May be reasonable to initiate statin therapy after discussion of benefits and risks.	May be reasonable to initiate statin therapy after discussion of benefits and risks.	dose if significant renal impairment and/or the potential for drug interactions, and then titrate upwards to achieve LDL-C goals.

ACC/AHA, American College of Cardiology/American Heart Association; ADA, American Diabetes Association; ESC/EAS, European Society of Cardiology/European Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; SOMC, Standards of Medical Care in Diabetes.

[a]Very high-risk as defined by 2018 ACC/AHA Guidelines: history of multiple major ASCVD events, or one major atherosclerotic cardiovascular disease (ASCVD) event and multiple high-risk conditions. Major ASCVD events include history of recent acute coronary syndrome (ACS) within past 12 months, myocardial infarction (other than recent ACS), ischemic stroke, and symptomatic peripheral arterial disease. High-risk conditions include diabetes, persistent LDL _100 mg/dL (2.6 mmol/L), age _65 years, heterozygous familial hypercholesteremia, hypertension, chronic kidney disease, current smoking, congestive heart failure, and coronary bypass surgery/percutaneous coronary intervention outside of major ASCVD event(s).