Lipid-lowering therapies and cardiovascular risk-stratification strategies in adults with type 1 diabetes

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Purpose of review
Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of mortality in adults with type 1 diabetes (T1D). Although dyslipidaemia is a modifiable and prevalent risk factor in individuals with T1D, determining when to initiate lipid-lowering therapy for primary prevention of ASCVD can be challenging. In this article, recommendations for lipid-lowering therapy from updated clinical guidelines over the last 5 years, additional risk-stratification methods, hypertriglyceridaemia management and potential barriers to optimal care in adults with T1D are discussed.

Recent findings
Low-density lipoprotein cholesterol (LDL-C) is the primary target for lipid-lowering. However, international guidelines recommend differing approaches to ASCVD risk-stratification, lipid-lowering, and LDL-C goals in individuals with diabetes, predominantly reflecting evidence from studies in type 2 diabetes. Despite guideline recommendations, several studies have demonstrated that statins are underused, and LDL-C goals are not attained by many individuals with T1D. Additional risk-stratification methods including T1D-specific ASCVD risk calculators, coronary artery calcium scoring, and lipoprotein(a) may provide additional information to define when to initiate lipid-lowering therapy.

Summary
Clinical trial evidence for lipid-lowering therapies in T1D is lacking, and further studies are needed to inform best practice. Optimization and harmonization of ASCVD risk-stratification and lipid management in individuals with T1D is required.

Keywords
cardiovascular diseases, diabetes mellitus type 1, dyslipidaemias, risk factors, statins

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of premature morbidity and mortality in individuals with type 1 diabetes (T1D) [1]. Owing to long duration of diabetes and early atherosclerosis, individuals diagnosed with T1D at younger ages are at increased ASCVD risk [2]. T1D may also be an ASCVD risk equivalent with respect to myocardial infarction [3▪]. Although intensive glycaemic control reduces ASCVD risk in T1D, significant residual risk remains, highlighting the importance of early ASCVD risk assessment and multifactorial risk factor control [3▪,4,5▪▪,6▪]. Dyslipidaemia is a modifiable risk factor that is prevalent and contributes to accelerated atherosclerosis in T1D. Even if glycaemia is well controlled, qualitative changes in lipoproteins that are potentially atherogenic can occur, such as smaller and denser low-density lipoprotein (LDL) and dysfunctional high-density lipoprotein (HDL) particles [7▪]. Poor glycaemic control can result in increased LDL-cholesterol

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KEY POINTS

- International guidelines provide varying recommendations for low-density lipoprotein cholesterol goals and thresholds for lipid-lowering therapy in individuals with type 1 diabetes.
- Further clarity on when to initiate lipid-lowering therapy in younger adults with type 1 diabetes without vascular complications is required.
- Clinical trial evidence for lipid-lowering therapies in type 1 diabetes is lacking, thus best practice guidelines are often based off evidence from studies in type 2 diabetes.
- Additional risk-stratification approaches including coronary artery calcium score and lipoprotein(a) may be considered to personalize vascular risk assessment.
- Optimising and promoting the use of cardiovascular risk calculators formulated for individuals with type 1 diabetes is required.

(LDL-C), triglycerides and non-HDL-cholesterol (non-HDL-C) [8]. Dyslipidaemia can also be exacerbated by concurrent obesity, insulin resistance, and nephropathy, which can increase triglyceride-rich lipoproteins [9,10].

Despite the plasma lipid and lipoprotein alterations and increased ASCVD risk associated with T1D, lipid-lowering therapies remain underused and LDL-C goals are often not attained [11–13]. This may be because determining when to initiate 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) for primary prevention is challenging, especially in the young with T1D without vascular complications. Here, we summarize recommendations for statin use from updated guidelines over the last 5 years, discuss select risk-stratification methods to consider given that risk-stratification is the prelude to lipid management, briefly review hypertriglyceridaemia management, and consider barriers to optimal care in adults with T1D.

GUIDELINE RECOMMENDATIONS FOR LIPID-LOWERING

Statins are the cornerstone lipid-lowering agent for reducing ASCVD risk. Recommendations from select guidelines for initiating statin therapy in T1D are summarized in Table 1 [14▪▪,15▪▪,16–18]. These guidelines recommend statins in at-risk groups or for reducing LDL-C, non-HDL-C and/or apolipoprotein B levels to certain goals depending on risk categories, which often requires lipid-lowering therapies. Lifestyle modifications, a heart-healthy diet, glycaemic control and exclusion of secondary causes of dyslipidaemia are fundamental but may be insufficient to mitigate ASCVD risk. Individualized diabetes-specific medical nutrition therapy provided by dietitians is recommended, with carbohydrate counting and insulin dose adjustment being a common approach in T1D [19]. Very-low carbohydrate diets have gained popularity because of lay media as it can reduce hyperglycaemia; however, such diets have not been extensively studied in T1D and may increase the risk of ketoacidosis, hypoglycaemia and atherogenic dyslipidaemia [20]. Marked elevations in LDL-C can occur with low-carbohydrate ketogenic diets in individuals with T1D, thus education should be provided in regards to replacing saturated fats with unsaturated fat, especially polyunsaturated fat, and the lipid profile should be closely monitored in such individuals [20,21].

Despite differences in pathophysiology between T1D and type 2 diabetes (T2D), guidelines often suggest a similar approach to reducing LDL-C (the primary lipid target) in both, and the two are often not separated, highlighting a lack of evidence to guide management [14▪▪]. Observational data suggests that LDL-C is a predictor of ASCVD in T1D, and that reducing LDL-C is associated with reduced ASCVD risk [1,22,23]. Whilst there are no T1D-specific statin trials, a meta-analysis of randomised trials by the Cholesterol Treatment Trialists' Collaboration demonstrated that statins safely reduce ASCVD risk in 18 686 individuals with diabetes for primary and secondary prevention [24]. Although only 1466 individuals had T1D and ASCVD event rates were too small to be definitive, the reduction in events was found to be similar to that with T2D [24].

Ezetimibe and proprotein convertase subtilisin-kexin type 9 monoclonal antibodies (e.g. evolocumab and alirocumab) are recommended by guidelines in the high-risk or very high-risk as add-on therapies to statins if further lipid-lowering is required to attain LDL-C goals, or if LDL-C is above the threshold for adding these therapies (Table 1) [14▪▪,15▪▪,16–18]. Although landmark trials for ezetimibe (IMPROVE-IT), evolocumab (FOURIER) and alirocumab (ODYSSEY OUTCOMES) enrolled individuals with diabetes, this was predominantly T2D [25–27]. In the FOURIER trial, 27 564 participants were studied, of who 11 031 (40.0%) had diabetes and 286 had T1D [28]. In the ODYSSEY OUTCOMES trial, 18 924 participants were studied, of who 5444 (28.8%) had diabetes and 37 had T1D [29]. Thus, trial evidence for these therapies in T1D is lacking.

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Table 1. Summary of recommendations for statin use in adults with type 1 diabetes based on recent international guidelines

Guideline	Risk category	Treatment recommendations
American Diabetes Association 2022	Diabetes and ASCVD	High-intensity statin Add ezetimibe (preferred because of lower cost) or monoclonal antibody to PCSK9 if LDL-C ≥1.8 mmol/l (70 mg/dl) and very high risk[e]
	Diabetes and 10-year ASCVD risk ≥20%	High-intensity statin Add ezetimibe to reduce LDL-C by ≥50%
	Diabetes and higher risk (e.g. multiple ASCVD risk factors or age 50–70 years)	High-intensity statin
	Diabetes and age 40–75 years[a]	Moderate-intensity statin
	Diabetes and age 20–39 years[b] with ASCVD risk factors	Reasonable to initiate statin
Canadian Cardiovascular Society 2021	Diabetes and ASCVD	Statin is indicated with the following goals: LDL-C <1.8 mmol/l (70 mg/dl) and ≥50% reduction ApoB <0.70 g/l Non-HDL-C <2.4 mmol/l (93 mg/dl)
	Diabetes and age ≥40 years	Statin is indicated with the following goals: LDL-C <2.0 mmol/l (77 mg/dl) ApoB <0.80 g/l Non-HDL-C <2.6 mmol/l (100 mg/dl)
	Diabetes and age ≥30 years with diabetes duration ≥15 years	Statin is indicated with the following goals: LDL-C <2.0 mmol/l (77 mg/dl) ApoB <0.80 g/l Non-HDL-C <2.6 mmol/l (100 mg/dl)
	Diabetes and microvascular disease	Statin is indicated with the following goals: LDL-C <2.0 mmol/l (77 mg/dl) ApoB <0.80 g/l Non-HDL-C <2.6 mmol/l (100 mg/dl)
American Association of Clinical Endocrinologists and American College of Endocrinology 2020	Extreme-risk Diabetes and ASCVD	Statin is indicated with the following goals: LDL-C <1.4 mmol/l (55 mg/dl) Non-HDL-C <2.1 mmol/l (80 mg/dl) ApoB <70 mg/dl
	Very high-risk Diabetes and additional ASCVD risk factor	Statin may be indicated with the following goals: LDL-C <1.8 mmol/l (70 mg/dl) Non-HDL-C <2.6 mmol/l (100 mg/dl) ApoB <80 mg/dl
	High-risk Diabetes and no other ASCVD risk factors	Statin may be indicated with the following goals: LDL-C <2.6 mmol/l (100 mg/dl) Non-HDL-C <3.4 mmol/l (130 mg/dl) ApoB <90 mg/dl
	Moderate-risk and low-risk	Not applicable

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Table 1 (*Continued*)

Guideline	Risk category	Treatment recommendations
European Society of Cardiology and European Atherosclerosis Society 2019	Very high-risk Diabetes and ASCVD Diabetes with target organ damage[c] Diabetes with ≥3 ASCVD risk factors T1D and diabetes duration >20 years	Statin is indicated with the following goals[f]: LDL-C <1.4 mmol/l (55 mg/dl) and ≥50% reduction Non-HDL-C <2.2 mmol/l (85 mg/dl) ApoB <65 mg/dl
	High-risk Diabetes with diabetes duration >10 years duration Diabetes and additional ASCVD risk factors	Statin may be indicated with the following goals: LDL-C <1.8 mmol/l (70 mg/dl) and ≥50% reduction Non-HDL-C <2.6 mmol/l (100 mg/dl) ApoB <80 mg/dl
	Moderate-risk T1D and age <35 years with diabetes duration <10 years and no other ASCVD risk factors	Statin may be indicated with the following goals: LDL-C <2.6 mmol/l (100 mg/dl) Non-HDL-C <3.4 mmol/l (130 mg/dl) ApoB <100 mg/dl
	Low-risk	Not applicable
American Heart Association and American College of Cardiology 2018	Diabetes and ASCVD	High-intensity statin aiming to reduce LDL-C by ≥50% Add ezetimibe if very high risk[e] and LDL-C ≥1.8 mmol/l (70 mg/dl) Add monoclonal antibody to PCSK9 to statin and ezetimibe if very high risk[e] and LDL-C ≥1.8 mmol/l (70 mg/dl) or non-HDL-C ≥2.6 mmol/l (100 mg/dl)
	Diabetes and multiple ASCVD risk factors or 10-year ASCVD risk ≥20%	High-intensity statin aiming to reduce LDL-C by ≥50% Add ezetimibe to reduce LDL-C by ≥50%
	Diabetes and age 40–75 years	Moderate-intensity statin
	Diabetes and age 20–39 years with a risk-enhancing factor[d]	Consider moderate-intensity statin

ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; T1D, type 1 diabetes.

[a]In individuals aged older than 75 years, it may be reasonable to initiate or continue statin therapy after discussion of benefits and risks.

[b]Statins are contraindicated in pregnancy and lactation.

[c]Target organ damage is defined as nephropathy (microalbuminuria), retinopathy or neuropathy.

[d]Risk-enhancing factors include long diabetes duration (≥20 years for T1D), albuminuria (≥30 μg of albumin/mg creatinine), estimated glomerular filtration rate less than 60 ml/min/1.73 m^2, retinopathy, neuropathy or ankle–brachial index less than 0.9.

[e]Very high risk is defined as a history of multiple ASCVD events or one major ASCVD event with multiple high-risk conditions.

[f]LDL-C less than 1.0 mmol/l (<40 mg/dl), non-HDL-C less than 1.8 mmol/l (<70 mg/dl) and ApoB <65 mg/dl goals may be considered in patients who experience a second ASCVD event within 2 years while taking maximally tolerated statin therapy.

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ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK-STRATIFICATION BY GUIDELINES AND RISK CALCULATORS

In individuals with T1D and established ASCVD, the decision to start lipid-lowering therapy is relatively straightforward. However, in individuals with T1D and without clinical ASCVD, the decision to start statin therapy for primary prevention relies on risk-stratification, with the optimal age of initiation being uncertain. ASCVD risk categories (often based on age, other risk factors, duration of diabetes and complications) and LDL-C goals differ according to guideline, as seen in Table 1. Guideline recommendations for risk-stratification in T1D are also similar to that for T2D [14▪▪,15▪▪,16–18]. The presence of microvascular disease (i.e. nephropathy, retinopathy and neuropathy) identifies individuals at higher ASCVD risk and the American College of Cardiology (ACC) and American Heart Association (AHA) 2018 guidelines include these as 'risk-enhancing factors' (Table 1 footnote), which can help determine whether lipid-lowering therapy should be initiated or intensified [18]. Importantly, the presence of albuminuria, a marker of nephropathy, has been shown to be a significant predictor of adverse outcomes in individuals with T1D, with an associated two to four times greater risk of ASCVD complications and mortality [23,30]. Studies also suggest that individuals with T1D without nephropathy may have similar long-term survival to the general population [31]. Furthermore, although guidelines now recognize T1D duration as a risk-enhancer, age at diagnosis is still not considered [2,15▪▪,16,18].

Whilst T1D is often considered a high-risk condition for ASCVD, it is a heterogenous condition where some individuals, especially the young, could be at moderate or even low ASCVD risk [16,17,32]. Nonetheless, some guidelines do not ever consider individuals with diabetes to be low risk or moderate risk [16,33]. Primary prevention calculators for the general population require further validation in individuals with T1D, as diabetes-specific factors such as duration of diabetes, diabetes type, glycaemic control, urinary albumin and microvascular disease are not all considered. Importantly, renal complications have a marked impact on cardiovascular mortality in people with T1D as previously mentioned [3▪]. Mode of insulin delivery in T1D is also not considered, although insulin pump therapy has been associated with lower ASCVD risk compared with multiple daily insulin injections [34]. Furthermore, patterns and trajectory of glycaemic control may impact ASCVD risk, which is not captured by risk-stratification methods using single glycaemic measures [35▪]. Sex is also a risk-modifier, as women with T1D have lower burden of risk factors but do not have lower ASCVD event burden than men with T1D [36▪▪].

T1D-specific risk calculators have, therefore, been developed but require further validation studies. Examples include the Steno Type 1 Risk Engine (www.sdcc.dk/T1riskengine) and QRISK3 (https://qrisk.org/three) for estimating 10-year ASCVD risk [37,38]. Although some individuals may be considered very high-risk by some guidelines, they may be at low 10-year ASCVD risk (<10%) according to the Steno Type 1 Risk Engine and QRISK3 calculators [16,17,37,38]. However, while 10-year ASCVD risk may be low in young individuals with T1D, their lifetime risk may be high. Contemporary ASCVD rates in T1D across two countries generated a risk predication model that demonstrated current guidance likely overestimates 10-year ASCVD risk in younger age groups, nonetheless statin therapy may still be indicated because of high lifetime risk [39,40▪▪]. As there is discordance, additional risk-stratification methods may be required to help determine need for statin therapy [32,41▪].

ADDITIONAL ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK-STRATIFICATION METHODS

The coronary artery calcium (CAC) score can be used to personalize ASCVD risk-stratification in asymptomatic individuals, by providing a measure of atherosclerosis using noncontrast computed tomography (CT) [42,43▪▪]. Increasing CAC is associated with increasing ASCVD risk in individuals with T1D, whilst zero scores are associated with low 10-year risk [42]. However, the scan does not detect noncalcified plaque, requires radiation and adds costs. The CAC score can help decide whether to initiate or intensify preventive therapies, such as statins [43▪▪]. In general, CAC scores at least 100 Agatston units (AU) or at least 75th percentile for age, sex and race would classify individuals as high-risk, thus favouring statin [15▪▪,16,18,43▪▪]. On the contrary, a score of 0 AU would stratify individuals as low-risk, thus avoiding statin in the short-term [15▪▪,16,18,43▪▪].

In individuals with T2D aged 40–75 years, statin therapy may be indicated regardless of CAC score, because of statin trials showing benefit in this age group [43▪▪]. Whether this applies to individuals with T1D remains unclear, thus the recent National Lipid Association (NLA) 2021 guidelines state that CAC scoring may be reasonable in T1D and age 40–75 years to refine risk assessment [43▪▪]. The guideline also recommends that CAC scoring can be considered in individuals with T1D and age 30–39 years with diabetes duration at least 20 years and ASCVD risk factors

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to aid in risk-stratification and statin use [43▪▪]. In individuals with diabetes and a CAC score of 0 AU, it is recommended that the scan be repeated in 3 years, rather than 5 years, because of the high-risk nature of diabetes [43▪▪].

Lipoprotein(a) [Lp(a)] is a predominantly genetically determined LDL-like particle with an apolipoprotein B covalently linked to apolipoprotein(a) [apo(a)] and is considered a causal risk factor for ASCVD and calcific aortic valve stenosis [44,45, 46▪▪]. An Lp(a) level at least 50 mg/dl (or ≥125 nmol/l) is considered a risk-enhancing factor, which can reclassify individuals into higher ASCVD risk categories [15▪▪,18,44,45]. The ASCVD risk associated with Lp(a) is modulated by high-sensitivity C-reactive protein (hsCRP) (also considered a risk-enhancing factor), whereby Lp(a) is significantly associated with ASCVD events only in individuals with elevated hsCRP (≥2 mg/l) according to some recent studies [47,48▪▪]. However, in T1D, there is also an association between good glycaemic control and lower Lp(a) levels, suggesting that insulin may affect apo(a) synthesis [49]. Despite this, Lp(a) remains a significant predictor of ASCVD in T1D [49]. Whilst ASCVD outcome trials for Lp(a)-lowering therapies are ongoing [such as molecular therapies targeting apo(a) production], management of elevated Lp(a) remains intensive risk factor control and statin therapy [44,45].

It is recommended that Lp(a) be measured using an apo(a) isoform independent assay [44,45,46▪▪]. Repeated measurements over time may not be necessary as Lp(a) molar concentrations are generally stable over a lifetime in the absence of Lp(a)-lowering therapies, and modest changes in Lp(a) level do not significantly change ASCVD risk [50▪]. Formal cascade screening for elevated Lp(a) is not yet well established and genetic testing for Lp(a) single nucleotide polymorphisms is not currently recommended for clinical practice [44,45]. Testing of Lp(a) in youth is controversial because of the absence of targeted therapies and potential for emotional harm, but on the other hand may lead to the opportunity to emphasize early and lifelong adoption of heart-healthy lifestyles, which may be of particular benefit in individuals with T1D [45,51▪▪]. Echocardiography to screen for aortic valve stenosis is not discussed in Lp(a) or valvular heat disease guidelines [44,45,52,53]. However, noncontrast cardiac CT imaging may be a promising method to screen for early aortic valve calcification [54]. Although oestrogen can reduce Lp(a), oestrogen also increases the risk of ASCVD and venous thrombosis [51▪▪,55,56]. If statins are used and contraceptives are required in female individuals, barrier methods or progesterone-only methods (e.g. intrauterine device, subdermal implant or progesterone pill) should be considered, but this decision must be individualized, noting that Lp(a) is no longer considered a risk factor for venous thromboembolism [46▪▪,57].

Utilizing both CAC score and Lp(a) concurrently may be useful for risk-stratification in the primary prevention setting; however, the evidence for individuals with T1D is not well established [58▪▪]. Individuals with both a high CAC score (≥100 AU) and elevated Lp(a) (≥50 mg/dl) are at higher ASCVD risk than those with a high CAC score but without elevated Lp(a) [58▪▪]. Importantly, the 10-year ASCVD risk for concurrently high CAC score and elevated Lp(a) may be similar to that for the secondary prevention population [58▪▪]. When the CAC score is less than 100 AU, ASCVD risk may be similar between those with and without elevated Lp(a) [58▪▪]. However, 10-year ASCVD risk is likely to be low with CAC scores of zero, regardless of whether or not Lp(a) is elevated [58▪▪].

HYPERTRIGLYCERIDAEMIA MANAGEMENT IN TYPE 1 DIABETES

In well controlled T1D, the lipid profile may appear normal or 'supernormal', characterized by low triglycerides and elevated HDL-C, because of subcutaneous administration of insulin, which upregulates lipoprotein lipase activity [7▪,59]. However, smaller and denser LDL particles, which are atherogenic, or dysfunctional HDL particles may be present, but are not reflected in the standard lipid profile test [7▪,59]. Larger HDL particle size and lower particle numbers have been observed in T1D, but whether impaired HDL function and changes in the HDL proteome is causally linked to premature ASCVD remains indeterminant [7▪]. On the other hand, elevated triglycerides and low HDL-C can occur in poorly controlled T1D, and dyslipidaemia can be exacerbated by concurrent nephropathy, obesity and insulin resistance (that is, 'double diabetes') [7▪,59]. In this setting, ASCVD risk associated with remnant lipoproteins (that is, triglyceride-rich particles) can be assessed with apolipoprotein B (apoB) or non-HDL-C, which also have guideline-recommended treatment goals (see Table 1) [15▪▪,16–17].

ApoB has been shown to be a predictor of ASCVD and all-cause mortality in individuals with T1D [60]. Furthermore, one study showed that in individuals with T1D, the presence of both elevated non-HDL-C and apoB is associated with greater progression of coronary atherosclerosis than elevated apoB alone [61]. In a study of lipid variables in individuals with T1D, the apoB/apolipoprotein AI ratio was the strongest predictor of incident coronary artery disease events in those who were

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normoalbuminuric, whilst apoB was the strongest predictor in those with macroalbuminuria [62]. However, the use of apoB and non-HDL-C for ASCVD risk-stratification in T1D is not well established, as data are limited [61–63,64▪]. Whilst hypertriglyceridaemia has also been associated with increased ASCVD risk in T1D, there is a lack of studies to inform management [65].

If an individual with T1D has persistent hypertriglyceridaemia, it is important to optimize glycaemic control, manage secondary causes or exacerbating factors, and implement lifestyle modifications such as healthy diets, increased physical activity, weight loss and moderation of alcohol intake. Statins remain the first-line lipid-lowering agents for reducing ASCVD risk in hypertriglyceridaemia [66▪▪]. Triglyceride-lowering agents that are available include fibrates, omega-3 fatty acids and niacin; however, there is little cardiovascular outcome trial data for these agents in individuals with T1D. The recently published PROMINENT trial demonstrated that pemafibrate did not reduce ASCVD events compared with placebo in individuals with T2D, mild–moderate hypertriglyceridemia, low HDL-C level, and well controlled LDL-C level, thereby providing further evidence for the lack of ASCVD benefits of fibrates in residual hypertriglyceridemia [67▪▪]. However, addition of icosapent ethyl, a highly purified ethyl ester of eicosapentaenoic acid, to statin therapy is now recommended for ASCVD risk reduction in T2D and hypertriglyceridaemia, owing to the results of the REDUCE-IT trial [14▪▪,15▪▪,16–18,66▪▪]. Of note, of 8179 participants in the REDUCE-IT trial, only 57 had T1D. This again highlights the lack of clinical trial evidence in T1D [68].

In the absence of evidence, and despite differences in underlying pathophysiology, hypertriglyceridaemia management in individuals with T1D generally continues to follow that for T2D. Recommendations from the ACC 2021 pathway for persistent hypertriglyceridaemia are shown in Table 2, where an LDL-C based approach to lipid-lowering is recommended for reducing ASCVD risk [66▪▪]. It must be noted that these guidelines could be applied to individual with T1D, but the evidence is not established. Fibrates are not recommended by the guideline for ASCVD risk reduction because of the lack of strong evidence but continue to play a role in preventing pancreatitis in severe hypertriglyceridemia [66▪▪]. In addition, according to a recent meta-analysis of large cardiovascular outcome trials, fibrates (specifically fenofibrate) may have a role in reducing the progression of diabetic retinopathy and need for laser treatment, a benefit not seen with statins [69▪]. There are ongoing trials of fibrates in reducing retinopathy in individuals with diabetes, including T1D (NCT01320345, NCT03439345, NCT04661358).

Table 2. Summary of recommendations for hypertriglyceridaemia management and cardiovascular risk reduction in adults with diabetes based on the American College of Cardiology guidelines

Risk category	Triglyceride levels[a]	Initial management	Persistent hypertriglyceridaemia[b]
Diabetes and ASCVD	Fasting TG ≥1.7 mmol/l (150 mg/dl) or nonfasting TG ≥2.0 mmol/l (175 mg/dl) and TG <5.6 mmol/l (500 mg/dl)	Evaluate and manage secondary causes Optimize glycaemic control Optimize diet and lifestyle Guideline-directed statin therapy to reduce ASCVD risk Monitor response and adherence to therapy Conduct clinician–patient discussion	LDL-C <1.8 mmol/l (70 mg/dl) Consider icosapent ethyl LDL-C 1.8–2.5 mmol/L (70–99 mg/dL) TG risk-based (icosapent ethyl may be considered) or LDL-C risk-based or combined approach LDL-C ≥2.6 mmol/l (100 mg/dL) Optimize statin therapy and consider nonstatin therapy to reduce LDL-C
Diabetes and age ≥40 years with no ASCVD	Fasting TG ≥1.7 mmol/l (150 mg/dl) or nonfasting TG ≥2.0 mmol/l (175 mg/dl) and TG <5.6 mmol/l (500 mg/dl)	As per above	Age <50 years or ≥50 years with no additional ASCVD risk-enhancing factors Continue LDL-C risk-based approach Age ≥50 years with additional ASCVD risk factors Consider icosapent ethyl
Diabetes and age 20–39 years	Fasting TG ≥1.7 mmol/l (150 mg/dl) or nonfasting TG ≥2.0 mmol/l (175 mg/dl) and TG <5.6 mmol/l (500 mg/dl)	No management algorithm provided by guideline	

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.
[a]Pathway for management of severe hypertriglyceridaemia (triglycerides ≥5.6 mmol/l or ≥500 mg/dl) not included in table.
[b]Persistent hypertriglyceridaemia defined as fasting triglycerides 1.7–5.6 mmol/l (150–500 mg/dl) following 4–12 weeks of lifestyle modifications.

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BARRIERS TO OPTIMAL CARE

Despite the importance of lipid-lowering for reducing ASCVD risk, dyslipidaemia remains under-recognized and under-treated, particularly in individuals with T1D who have not developed vascular complications [12,41▪,70–72]. Reasons for suboptimal lipid management in individuals with T1D are likely multifactorial, relating to clinicians, patients and healthcare funding models that do not prioritize prevention or chronic care. Statin underutilization may occur because of concerns of side-effects, polypharmacy and medication costs. However, statins are well tolerated and adverse effects were rare in randomized trials [73]. T1D is considered a risk factor for statin-associated muscle symptoms [74▪]. However, in the AdDIT study, a randomized trial of angiotensin-converting enzymes and statins in adolescents with T1D, muscle symptoms were only reported by one of the 443 participants [75]. Clinician uncertainty around indications for lipid-lowering therapy because of numerous treatment guidelines with varying recommendations, lack of T1D-specific trial evidence for lipid-lowering therapies, as well as a limited understanding of 10-year versus lifetime ASCVD risk may affect utilization of lipid-lowering therapy [41▪]. Clinicians may also be reluctant to prescribe statins in T1D during child-bearing ages, as statins are contraindicated in pregnancy and in women planning pregnancy because of risk of foetal malformation. Studies also show that women with T1D tend to receive fewer preventive therapies than men with T1D [36▪▪].

Furthermore, the consultation for T1D already must consider many aspects including intensive insulin therapy, diabetes-related technology, other ASCVD risk factors, screening for microvascular complications, and behavioural self-care, which can be challenging because of the time-constraints of a busy clinic [19]. Adherence to medications other than insulin may present a barrier, particularly during adolescence [76]. Dyslipidaemia has no symptoms and the risk of ASCVD seems distant [77]. As glycaemic control and lifestyle modifications also improve lipid profiles in T1D, ongoing efforts to address these initially might be prioritized over statin use. Additionally, increased ASCVD risk may not be evident in well controlled T1D when the lipid profile is 'supernormal'. This may be incorrectly considered cardioprotective, thus leading to underutilization of preventive measures.

CONCLUSION

Lowering LDL-C is important for reducing ASCVD risk but deciding when to initiate statin therapy remains challenging in T1D. Recent international guidelines provide differing recommendations for risk-stratification, thresholds for statin use and LDL-C goals in individuals with T1D, based predominantly on evidence from trials in T2D. ASCVD risk calculators formulated for individuals with T1D are available, but more evidence is needed. The presence of factors such as microvascular disease (especially nephropathy and albuminuria) and duration of diabetes are strong predictors of ASCVD; however, additional risk-stratification approaches including the CAC score and lipoprotein(a) can be considered to personalize ASCVD risk assessment. Barriers to optimal care should be identified and addressed, especially in young individuals with T1D who may be undertreated. Lipid care in T1D needs to be harmonized. In the meantime, guideline recommendations should inform clinical judgement and be tailored to the individual.

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Conflicts of interest

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- ▪ of special interest
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