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REVIEW
Prevention and epidemiology

Management of dyslipidaemia in patients with comorbidities—facing the challenge: type 1 diabetes mellitus

Susanne Kaser[1], Dobromir Dobrev[2,3,4,†], Bianca Rocca[5,†], Juan Carlos Kaski[6,†], Stefan Agewall[7,†], and Heinz Drexel[8,9,10,11,*,†]

[1]Department of Internal Medicine I, Medical University of Innsbruck, 6020 Innsbruck, Austria; [2]Institute of Pharmacology, West German Heart and Vascular Center, University Duisburg-Essen, 45122 Essen, Germany; [3]Department of Medicine and Research Center, Montreal Heart Institute and Université de Montréal, H1T 1C8 Montréal, Canada; [4]Department of Integrative Physiology, Baylor College of Medicine, 77030 Houston, TX, USA; [5]Department of Medicine, LUM University, 70010 Casamassima (BA), Italy; [6]Division of Cardiovascular Medicine, Molecular and Clinical Sciences Research Institute, St George's University of London, SW17 0RE London, UK; [7]Institute of Clinical Sciences, Karolinska Institute of Danderyd, 171 77 Stockholm, Sweden; [8]Vorarlberg Institute for Vascular Investigation & Treatment (VIVIT) at the Academic Teaching Hospital Feldkirch, Carinagasse 47, 6800 Feldkirch, Austria; [9]Private University in the Principality of Liechtenstein, Medical Sciences, Dorfstrasse 24, 9495 Triesen, Liechtenstein; [10]Vorarlberger Landeskrankenhausbetriebsgesellschaft, 6800 Feldkirch, Austria; and [11]Drexel University College of Medicine, 2900 Queen Ln, Philadelphia PA 19129, USA

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Type 1 diabetes is associated with excess cardiovascular risk. In contrast to type 2 diabetes, however, age at the onset of type 1 diabetes and sex are major predictors of cardiovascular risk, while the role of low-density lipoprotein cholesterol (LDL-C) and lipid-lowering therapy is less clear.

Since most data on the effects of lipid-lowering treatments are obtained from randomized clinical trials that included very predominantly patients with type 2 diabetes, it is almost impossible to specifically discern endpoints in type 1 diabetes. Inversely, most data specific for type 1 diabetes are obtained from real world findings. Consequently, the evidence on efficacy and safety of lipid-lowering therapies available from randomized clinical trials arises very predominantly from type 2 diabetes. Thus, this specific review summarizes the evidence of lipid-lowering drug classes in reducing cardiovascular risk in patients with type 1 diabetes.

Keywords Type 1 diabetes mellitus • Lipid lowering drugs • Dyslipidaemia • Cardiovascular risk • Comorbidities • Randomized clinical trials

Preface

Type 1 and type 2 diabetes mellitus (T1DM and T2DM) have distinct underlying pathobiology and may exert quite different effects on lipid metabolism. In T1DM, characterized by the absence of endogenous insulin, subcutaneous insulin substitution therapy provides insulin to the body via the peripheral circulation. In contrast, physiologically and in T2DM, endogenous insulin from the pancreatic beta cell via the portal route first arrives at the liver and only then reaches the peripheral circulation.

Insulin is an activator of lipoprotein lipase, the key enzyme for triglyceride hydrolysis. Thus, management of triglycerides and other aspects of lipid metabolism are fundamentally different between T1DM and T2DM. Therefore, this article specifically addresses lipid-lowering therapy in T1DM, and a subsequent review article will focus on T2DM.

Effects of lipid-lowering agents on cardiovascular risk in type 1 diabetes

Background

Epidemiology of cardiovascular disease in type 1 diabetes

Type 1 diabetes is associated with highly increased cardiovascular risk and mortality.[1–3]

In a previous study, cardiovascular disease was the most common underlying cause of death in patients with type 1 diabetes.[4] Excess total and cardiovascular mortality strongly depend on sex and the onset of disease being highest in patients diagnosed with type 1 diabetes before the age of 10 years resulting in a 17.7 life years loss in women and a 14.2 life years loss in men.[1] In a Swedish cohort,

* Corresponding author. Tel: +43 5522 303 6900, Fax: +43 5522 303 7533, Email: heinz.drexel@vivit.at, www.vivit.at
† Present or past nucleus members of the ESC Working Group on Cardiovascular Pharmacotherapy.

adjusted hazard ratio (HR) for cardiovascular mortality was 7.38 [95% Confidence Interval (CI) 3.65–14.94] in patients diagnosed before the age of 10 years and 3.64 (95% CI 2.34–5.66) for patients diagnosed at an age between 26 and 30 years.[1] In general, excess cardiovascular risk is significantly higher in female than in male patients with type 1 diabetes when compared with nondiabetic women and men,[5] showing the highest excess cardiovascular mortality with a HR of 9.35 (95% CI 2.68–32.62) in women and a HR of 6.9 (95% CI 3.11–15.33) in men with type 1 diabetes diagnosed before age of 10 years when compared to healthy controls.[1]

Pathophysiology of cardiovascular disease in type 1 diabetes

LDL cholesterol

Underlying mechanisms of cardiovascular disease in type 1 diabetes are multifactorial, including both classical and nonclassical risk factors. Remarkably, the contribution of classical risk factors, especially LDL-cholesterol on atherogenesis is less clear in patients with type 1 diabetes when compared to type 2 diabetes. Pathophysiological aspects have recently been reviewed in detail elsewhere.[6]

LDL-cholesterol was identified as an independent risk factor for cardiovascular disease in several studies.[7–9]

In an observational study, 1 mmol/L increase in LDL-C was associated with a 9% increase in cardiovascular disease in type 1 diabetics without lipid-lowering therapy and a 2% increase in those with lipid-lowering medication, suggesting a prominence of nonclassical risk factors in atherogenesis in type 1 diabetes.[10] In a retrospective longitudinal study analysing 6192 adult patients with type 1 diabetes, the risk of nonfatal cardiovascular events was lower in patients with higher adherence. Paradoxically, there was a negative, nonsignificant trend towards an indirect association between discontinuation of lipid-lowering therapies and fatal cardiovascular events in this study probably explained by a relatively low number of fatal cardiovascular events.[11] While the predictive value of LDL-C concentration on cardiovascular risk in type 1 diabetes is partly controversial, high atherogenicity of LDL particles in type 1 diabetes is beyond dispute; LDL particles are typically smaller in type 1 diabetes[12] resulting in increased oxidation, enhanced uptake into macrophages and formation of foam cells.[13] Paradoxically, HDL-cholesterol is usually normal or increased in well-controlled patients with type 1 diabetes. However, the structure of HDL particles is altered in type 1 diabetes, leading to dysfunctional particles with reduced atheroprotective properties.[13]

Hypertension

Increased blood pressure, especially increased systolic blood pressure, was found to be independently associated with cardiovascular disease and major cardiovascular in the The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interactions and Complications (EDIC) trial.[14]

Hyperglycaemia and glycaemic fluctuation

HbA1c is strongly related to cardiovascular disease in type 1 diabetes (DCCT/EDIC, Diabetes, 2016).[14] Accordingly, intensive treatment was associated with a marked decrease of major cardiovascular events in the DCCT/EDIC study.[15] Mechanistically, hyperglycaemia and glycaemic variability trigger expression of pro-inflammatory cytokines, procoagulant factors, growth factors, matrix proteins and vasoconstrictors, activation of the polyol pathway and formation of advanced glycation end products.[6]

Nonclassical risk factors and comorbidities

Underlining the relevance of nontraditional risk factors in cardiovascular disease (CVD) in type 1 diabetes, acute myocardial infarction was increased by 80% in type 1 diabetic individuals with five modifiable risk factors including HbA1c, blood pressure, LDL-C at target (LDL-C <3 mmol/L), albuminuria and smoking, when compared to nondiabetic matched controls.[16] When none of these risk factors were at target, risk for acute myocardial infarction was increased more than 12 folds.[16] Supporting this finding, a recent Korean study revealed more than six- and four-fold increased risks for myocardial infarction and stroke [myocardial infarction: HR 6.7 (95% CI 2.44–18.72), stroke: HR 4.65 (95% CI 1.70–12.71)] even after adjusting for sex, age, family income, hypertension, and dyslipidaemia.[17]

Subclinical inflammation has also been widely discussed to contribute to atherogenesis in type 1 diabetes. In a prospective randomized trial in patients with acute myocardial infarction, low-dose colchicine for 30 days was associated with a lower risk of ischaemic cardiovascular events. In this trial, 20.2% of patients suffered from diabetes, however no details on the diabetes type of included patients were shown.[18] Beneficial effects on cardiovascular morbidity and mortality of low dose colchicine therapy were also found in patients with chronic coronary disease, including 18.2% of patients with diabetes.[19]

These data suggest a more prominent role of anti-inflammatory therapies in cardiovascular disease in the future. Besides colchicine, these treatment options also include bempedoic acid, which has also shown to reduce inflammatory markers in treated patients.[20–23] Further data including randomized trials are warranted to test the effect of anti-inflammatory therapies on cardiovascular risk in type 1 diabetes.

Based on a recent population-based study reporting increased cardiovascular risk of patients with autoimmune disease,[24] impaired immune function might also contribute to enhanced atherogenesis in type 1 diabetes.[6]

Importantly, frequent comorbidities such as diabetic nephropathy which importantly is strongly genetically determined[25] and autonomic cardiac neuropathy are also independently associated with cardiovascular risk.[26,27]

Further supporting a major role of nontraditional risk factors in cardiovascular disease in type 1 diabetes, neither Framingham nor UKPDS CHD models turned out to adequately predict cardiovascular disease in patients with type 1 diabetes.[28] In contrast, arterial stiffness, which is highly prevalent in patients with longstanding type 1 diabetes, was found to be associated with the STENO risk score for cardiovascular events.[29] Inhibitors of the renin-angiotensin system, calcium channel antagonists and lipid-lowering agents including statins, ezetimibe, and PCSK9 inhibitors might exert beneficial effects on arterial stiffness.[30,31]

Besides inflammation and arterial stiffness, procoagulation is also discussed to contribute to increased cardiovascular risk in patients with type 1 diabetes. Increased platelet activation was found in young adult subjects with type 1 diabetes without overt cardiovascular disease and stable glycaemic control.[32] Even stressing the close interaction between nonclassical and classical risk factors in patients with type 1 diabetes increased platelet activation and was found to be related to glycaemic control.[33]

Current guidelines for lipid-lowering treatment in type 1 diabetes

Information on lipid-lowering effects on cardiovascular events in type 1 diabetes is very limited as only a very small number of patients with type 1 diabetes were included in cardiovascular outcome trials. Actually, recommendations for lipid-lowering therapy are often based on real-world data from different sources, including large national registries. In a prospective observational study, data were analysed from the Swedish National Diabetes Register showing that lipid-lowering therapy is associated with a strong decrease in cardiovascular risk in patients with type 1 diabetes.[34]

Table 1 Current ESC guidelines on lipid lowering therapies in type 1 diabetes

	Class[a]	Evidence level
Statins should be considered for LDL-C lowering in adults older than 40 years with T1DM without a history of CVD to reduce CV risk.	IIa	B
Statins should be considered for use in adults younger than 40 years with T1DM and other risk factors of CVD or microvascular end-organ damage or 10-year CVD risk ≥10% to reduce CVD risk.	IIa	B
The use of the Scottish/Swedish risk prediction model may be considered to estimate 10-year CVD risk in patients with T1DM.	IIb	B

Adapted from Table 3, 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes, European Heart Journal (2023) 44, 4043–4140.[35]

[a] Class of recommendation.

In contrast to type 2 diabetes and reflecting limited data availability from randomized trials, international recommendations for lipid-lowering therapies in type 1 diabetes are rather vague.

Table 1 shows the current ESC guidelines on lipid-lowering therapies in type 1 diabetes.[35] While statins should be considered in all patients with type 1 diabetes older than 40 years, statin treatment is only recommended in younger patients with high cardiovascular risk or microvascular end-organ damage.

Lipid-lowering agents

Statins

A meta-analysis of 14 trials including 18 686 patients with diabetes in total and 1466 patients with type 1 diabetes found a 21% decrease per mmol/L LDL-C reduction irrespective of underlying diabetes diagnosis. Although a subgroup analysis revealed similar risk reduction for patients with type 1 and type 2 diabetes (relative risk: 0.79, 95% CI 0.72–0.86), no significant risk reduction was found when patients with type 1 diabetes were analysed separately (relative risk: 0.79, 95% CI 0.62–1.01).[36] In this meta-analysis, 56% of patients with type 1 diabetes, 36% of patients with type 2 diabetes, and 60% of nondiabetic controls suffered from cardiovascular disease. Mean LDL-C was 3.4 mmol/l in type 1 and type 2 diabetics and 3.9 mmol/l in nondiabetic controls at baseline.

In a Korean study analysing national health insurance data, statin treatment was associated with lower cardiovascular events in patients with type 1 diabetes (HR 0.76, 95% CI 0.66–0.88).[37]

Initiation of and adherence to statin treatment is often challenging due to concerns of muscular side effects and worsening of hyperglycaemia or new-onset diabetes. However, and in contrast to real-world data, statin treatment was associated only with a small excess of mild myalgia in randomized trials.[38] A meta-analysis shows that statin treatment is associated with a very slight mean increase of HbA1c levels of 0.06–0.08%.[39] In a previous prospective, observational study, the risk for deterioration of insulin sensitivity attributable to statin treatment was 36.7% in patients with type 1 diabetes.[40]

To conclude from these studies, cardiovascular risk reduction clearly overweighs the risk of worsening glycaemic control in patients with type 1 diabetes at increased cardiovascular risk. Nevertheless, low adherence to statin therapy in patients with type 1 diabetes was shown in a Swedish registry study which reported that 42% of patients had discontinued their treatment after 36 months.[11] In contrast, 79% of participants of the Adolescent Type 1 Diabetes Cardio-renal Intervention Trial AdDIT Study Group were still on statin therapy at the end of the study.[41]

Ezetimibe

Cardiovascular benefits were shown for the cholesterol absorption inhibitor ezetimibe in the IMPROVE-IT trial.[42] In this study, patients after a recent acute coronary syndrome were allocated to simvastatin + ezetimibe or simvastatin alone. After 7 years, a difference in LDL-C of 0.4 mmol/L (1.4 vs. 1.8 mmol/L) resulted in an absolute risk reduction of 2% of the composite endpoint of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke. A pre-specified subgroup analysis revealed that among patients younger than 75 years, reduction of the primary end point differed significantly between those with and without diabetes, showing a significant risk reduction only in diabetic patients. Cardiovascular risk reduction was comparable in patients with or without diabetes older than 75 years. While no information on diabetes type was given in this study, antidiabetic medication suggests predominant inclusion of patients with type 2 diabetes.[43] The benefit of adding ezetimibe to statin was also enhanced in high-risk patients without diabetes.[43] In another study combination therapy of ezetimibe and low-dose atorvastatin was found to be associated with decreased cardiovascular mortality, nonfatal myocardial infarction, coronary artery revascularization, hospitalization for heart failure or nonfatal stroke in patients after drug eluting stent implantation. A total of 49.2% of included patients suffered from diabetes in this study, however, no data on the diabetes type of participants are available from this study.[44] In an open label noninferiority trial, patients with cardiovascular disease received either moderate-intensity statin with ezetimibe or high-intensity statin monotherapy. In this study, including only a few patients with diabetes, the combination therapy was noninferior to the high-intensity statin treatment.[45]

PCSK9 inhibitors

In the Odyssey Outcome trial, the efficacy and safety of alirocumab treatment was tested in patients with established coronary artery disease, including 28.8% of patients with diabetes.[46,47]

The composite endpoint encompassing death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischaemic stroke, or unstable angina requiring hospitalization was 12.5% in the alirocumab group and 14.5% in the control group. LDL-C levels were 1.7 mmol/L in the alirocumab group and 2.7 mmol/L in the control group.

While no further information on the diabetes type of participants was given in the Odyssey Outcome trial, baseline characteristics of another pooled analysis of all phase 3 Odyssey trials showed a total number of only 15 patients with type 1 diabetes.[48]

In the Fourier trial[49] investigating the effect of evolocumab therapy in patients with established cardiovascular disease on statin treatment pre-specified subgroup analysis showed comparable reductions in the composite primary endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization in patients with and without diabetes [HR 0.83 (95% CI 0.75–0.93) vs. 0.87 (95% CI 0.79–0.96), $P = 0.60$).[50] Baseline LDL-C levels (2.3 mmol/L vs. 2.4 mmol/L) and LDL-reductions were comparable in patients with and without diabetes and LDL-C reductions were 57% in patients with diabetes (95% CI 56–58) and 60% in patients without diabetes (95% CI 60–61). Two hundred eighty-six of 10 081 diabetic patients (3%) were classified as type 1 diabetics.[50]

In a meta-analysis, treatment with alirocumab or evolocumab was associated with a mean decrease in LDL-C levels by 58%, a mean

reduction of Lp(a) levels of 30%, and a decrease in MACE by 18% after 51 years in patients with diabetes, including 76 patients with type 1 diabetes from of the ODYSSEY DM-Insulin trial also.[51,52]

No studies on the effects of inclisiran treatment on cardiovascular events are available yet.

Access to PCSK9 inhibitor treatment might be limited in some countries and the cost-effectiveness of PCSK9 inhibitor therapy remains controversial.[53]

ATP citrate lyase inhibitor

Efficacy of bempedoic acid treatment in cardiovascular risk reduction in patients with high cardiovascular risk and statin intolerance or poor statin tolerance was shown in the CLEAR outcome trial.[54] While 6373 of 13 970 patients suffered from diabetes in this trial, the definition of diabetes as indicated in the baseline characteristics table suggests predominant or exclusive enrolment of patients with type 2 diabetes.

Other lipid-lowering agents. To the best of our knowledge, there are no specific trials available investigating the effects of fibrates on cardiovascular outcome in patients with type 1 diabetes. In contrast, in patients with type 2 diabetes, recent real-world data suggested a cardiovascular benefit of fenofibrate therapy.[55,56]

Noteworthy, fibrate therapy is currently under investigation for the treatment or prevention of diabetic retinopathy in the LENS trial.[57] Only very recently, fibrate treatment did not preserve residual beta cell function in patients with newly diagnosed type 1 diabetes.[58]

Data on omega 3 fatty acids on cardiovascular effects in type 1 diabetes are very limited. In a small-sized and short-term prospective study, no benefit of n3-PUFA on vascular health in type 1 diabetes was found.[59]

Summary and conclusion

In summary, while real-world data suggest protective effects of lipid-lowering therapy in type 1 diabetes, only little evidence from randomized trials is available. In randomized clinical trials, most data on the efficacy and safety of lipid-lowering drugs in patients with type 1 diabetes are available from subgroup analyses only with the most robust data for statins. Importantly, data from subgroup analyses are most often hypothesis-generating but less credible than data obtained from the whole study population, while selection bias might limit the interpretation of real-world data.[60]

Thus, prospective cardiovascular outcome trials in patients with type 1 diabetes are warranted to determine optimal LDL-C goals, the best choice of lipid-lowering agent and identify patients with the highest benefit of treatment. These include huge prospective, randomized studies of lipid-lowering therapy on cardiovascular disease in both, a primary prevention and secondary prevention setting as well.

Importantly, early onset of diabetes and female sex are associated with very high excess cardiovascular risk and should be included in cardiovascular risk prediction in patients with type 1 diabetes.

Novel prediction models for cardiovascular risk including age at onset of type 1 diabetes and sex are urgently needed to optimize cardiovascular risk reduction in patients with type 1 diabetes.

Noteworthy, no safety concerns were found for very low LDL-C levels in a meta-analysis including patients with diabetes also.[61]

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Data availability

No new data were generated or analysed in support of this research.

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