Thieme

Position Paper on Lipid Therapy in Patients with Diabetes Mellitus

A Joint Statement by the Commission on Lipometabolism and The Heart and Diabetes Working Group of the German Diabetes Society (DDG), The Diabetes, Obesity, and Metabolism Section of The German Society of Endocrinology (DGE), The Heart and Diabetes Working Group of the German Cardiology Society (DGK) and The Joint Heart – Hormones – Diabetes Working Group of the DGK, DGE and DDG

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Introduction

Patients with diabetes mellitus generally have a significantly increased cardiovascular risk. For this reason, lipid therapy and a reduction in LDL cholesterol based on risk stratification are an integral part of diabetes therapy. This following position paper should therefore also be viewed as a topic-related supplement to the annually updated recommendation for the treatment of type 2 diabetes and should also be updated annually in future together with the DDG's practical recommendations.

The published guidelines and recommendations of the European Society of Cardiology (ESC), the European Atherosclerosis Society (EAS), the American Association of Clinical Endocrinologists (AACE), the American Diabetes Association (ADA) and the American National Lipid Society (NLA) [1–5] form the basis for the information contained below.

This position paper is therefore to be understood as a short, current, clinically-oriented recommendation for action in patients with diabetes; for in-depth explanations on lipid metabolism and the use of lipid disorders, please refer to the literature provided.

Stratification of cardiovascular risk

Patients with diabetes mellitus usually have a significantly increased cardiovascular risk [6]. It is nonetheless recommended to break this risk down further. The same risk factors apply as for patients with-

out diabetes (▶ **Tab. 1**). It should be noted that the presence of several risk factors has a cumulative effect on the overall risk [7]. The estimated overall risk is an essential determinant of whether and, if so, how intensively a lipid-lowering therapy should be carried out.

Lipid diagnostics

The basis is made up of the determination of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides as well as the calculation of the of the non-HDL cholesterol level. The lipoprotein(a) value should be determined once only. If there is no hypertriglyceridemia and the LDL cholesterol is determined directly, the determination can be carried out in a non-fasting state [8]. If the LDL cholesterol is calculated using the Friedewald formula, the patient should be fasting as the triglyceride level is included in the calculation. Genetic diagnosis is clinically justified in cases of high suspicion of familial hypercholesterolemia, if this has consequences for the indication and therapy strategy.

Lipid phenotype

A distinction is made between hypercholesterolemia, hypertriglyceridemia and combined hyperlipidemia. Clinically, secondary causes must be excluded or treated and important primary disorders, e. g. familial hypercholesterolemia, must be considered (▶ **Tab. 2**).

Treatment of lipid metabolism disorders in patients with diabetes mellitus

The primary goal of the treatment is to reduce the increased cardiovascular risk of patients with diabetes mellitus. The most important measure is the reduction of LDL cholesterol. Furthermore, the risk of acute pancreatitis can be reduced by lowering excessively elevated triglyceride levels. Normalization of elevated triglyceride levels can also improve blood glucose control (▶ **Tab. 3**).

Therapy strategies aimed at lowering LDL cholesterol levels

In accordance with the recommendations of the European specialist societies, the reduction of LDL cholesterol levels is "target value-oriented", taking into account the cardiovascular risk [1]. A distinction is made between 3 categories that apply equally to patients with type 1 and type 2 diabetes mellitus (▶ **Tab. 4**):

- Proven atherosclerotic disease and/or additional serious risk factors and/or end organ damage or early manifesting type 1 diabetes with long duration of diabetes (> 20 years).
- Without proven atherosclerotic disease, end-organ damage with diabetes duration > 10 years, or additional risk factors
- Young patients with type 1 diabetes (< 35 years) and type 2 diabetes (< 50 years) with diabetes duration < 10 years and no other risk factors.

Secondary target values are the concentrations of non-HDL cholesterol and apolipoprotein B. This reflects the fact that probably all lipoproteins containing apolipoprotein B are atherogenic [9].

The non-HDL cholesterol value (= total cholesterol minus HDL cholesterol) also approximately reflects this and includes VLDL cholesterol and remnant cholesterol in addition to LDL cholesterol. The non-HDL cholesterol target value is therefore relevant in patients with hypertriglyceridemia or mixed hyperlipidemia (typically in patients with diabetes mellitus). In normotriglyceridemia, the VLDL/remnant cholesterol concentration is < 30 mg/dl (0.8 mmol/l) (which corresponds to a triglyceride value of approximately 150 mg/dl; 1.7 mmol/l), which is why non-HDL cholesterol target values are each 30 mg/dl (0.8 mmol/l) above the LDL cholesterol target value (▶ **Tab. 4**). For patients who meet the LDL cholesterol target but not the non-HDL cholesterol target, the non-HDL cholesterol level can be achieved by either lowering the triglyceride level (reduction of VLDL/remnant cholesterol) or further reducing the LDL cholesterol.

In addition, it should be mentioned that the American Diabetes Association (ADA) solely considers the age criteria (under/over 40 years) and presence of atherosclerosis (yes/no) [5]. All patients with atherosclerosis receive a high dose of statin (atorvastatin 40–80 mg/d or rosuvastatin 20–40 mg/d) and can also be treated with ezetimibe and PCSK9 inhibitors if the LDL cholesterol level remains above 70 mg/dl. For patients without atherosclerosis, those under 40 years of age do not generally receive a statin and those over 40 years of age receive a moderate statin dose (e. g. atorvastatin 20 mg/d or rosuvastatin 10 mg/d).

Even if, at first glance, there are clear differences between the ADA and ESC recommendations, in both cases the fact is that the vast majority of patients with diabetes mellitus should be treated with statins.

▶ **Tab. 1** Further risk factors to be considered.

Risk factor	Comment
Positive family history for premature atherosclerosis events	Only in atherosclerosis before the age of 55 or 65 in men and women respectively; this age limit is currently not evidence-based and should possibly be shifted upwards in the future in view of increasing life expectancy.
Nicotine abuse	Number of "pack years" is relevant.
Impaired renal function	The impairment of kidney function leads to an increase in the risk of atherosclerosis depending on the stage.
Hypertriglyceridemia	Independent risk factor; probably also as an indicator for elevated non-HDL cholesterol with atherogenic remnant particles
HDL cholesterol reduction	Inverse risk factor in population studies; low HDL-cholesterol especially increases CV risk; frequent with high triglycerides
Elevated blood pressure values	> 130/85 mmHg or with antihypertensives

CV = cardiovascular

▶ **Tab. 2** Classification of lipid metabolic disorders

Lipid metabolism	Cholesterol	Triglyceride	LDL chol	HDL chol	non-HDL chol
LDL hypercholesterolemia	↑	n	↑	n	↑
Hypertriglyceridemia	↑	↑	n	↓	↑
Combined hyperlipoproteinemia	↑	↑	↑	↓	↑
Isolated HDL cholesterol reduction	n	n	n	↓	n or ↑
Lipoprotein(a) increase	Can occur in isolation or in combination with any lipid metabolism disorder.				

n = not changed; Chol = cholesterol.

▶ **Tab. 3** Treatment targets for lipid metabolism disorders.

Treatment	Clinical effect	Evidence
LDL cholesterol reduction	Reduction of atherosclerosis events	Proven
Non-HDL cholesterol reduction	Reduction of atherosclerosis events	Proven
Lipoprotein(a) reduction	Reduction of atherosclerosis events	Presumed
Triglycerides reduction	Reduction of atherosclerosis events	Presumed
Reduction of highly elevated triglycerides	Reduction of the incidence of acute pancreatitis	Proven

In order to achieve the ESC target values mentioned above, a stepwise use of statins, ezetimibe and PCSK9 antibodies should be applied (▶ **Abb. 1**) [10]. After excluding or treating secondary causes of hyperlipidemia, statins are used as the therapy of choice. If, despite a sufficient dose, this is not sufficient to achieve the individual target value, the next step is to combine it with ezetimibe and, as a third step, to combine it with PCSK9 inhibitors, especially in cases of clinical progression of cardiovascular disease. Bempedoic acid has been available since November 2020 and Inclisiran since February 2021 as further lipid-lowering drugs. Bempedoic acid is used in particular in patients with statin intolerance (in combination with ezetimibe and/or statins). Inclisiran is an alternative to PCSK9 antibodies, although endpoint studies are still lacking for both drugs.

According to the decision of the Federal Joint Committee/Gemeinsamen Bundesausschuss (G-BA), PCSK9 inhibitors must be prescribed by a specialist in cardiology, nephrology, endocrinology, angiology or by a specialized lipid outpatient clinic and can then be further prescribed by the family doctor. As a last option, regular lipoprotein apheresis therapy is also possible, however, this should only be used when all other drug approaches have been exhausted. If the clinical indication is LDL apheresis, the G-BA decision is that the administration of a PCSK9 inhibitor is considered an alternative and economical option. In patients who are already on lipoprotein apheresis therapy primarily to lower LDL cholesterol, the administration of a PCSK9 antibody should reduce the apheresis frequency and even aim to terminate this therapeutic concept [11].

Therapy strategies for elevated triglycerides

Lifestyle measures and blood glucose control are in the foreground for hypertriglyceridemia and for the reduction of triglycerides in combined hyperlipidemia [1]. The use of fibrates to further lower markedly elevated triglyceride levels must be decided on an individual basis, as endpoint studies in combination with statins have not shown a clear cardiovascular benefit (▶ **Tab. 5**) [12], although it is unclear whether the lack of effect is due to the study methodology or whether fibrates do not induce risk reduction in this situation.

With regard to the administration of omega-3 fatty acids, the picture has changed with the publication of the REDUCE-IT study. In this study, it was shown that in high-risk patients who had hypertriglyceridemia on high-dose statin therapy (approximately 60 % diabetes), the administration of 4 g/d of the omega-3 fatty acid icosapentethyl (equivalent to eicosapentaenoic acid, EPA) resulted in a highly significant risk reduction [13]. Icosapent-ethyl (Vazkepa) has received European approval and is available in Germany since the end of 2021. Further study results should be awaited before a final assessment of this approach.

Therapy strategies for special situations

Increased lipoprotein(a) levels

Elevated Lp(a) values (or also low HDL cholesterol levels) cannot currently be specifically influenced by medication, therefore in these cases the remaining risk profile must be optimized and thus, e. g., an optimal adjustment of the LDL cholesterol should be sought. It is important to note that approx. 20 % of the Lp(a) concentration is included in the LDL cholesterol determination, i. e. the LDL cholesterol value must be "corrected" for this. If lipoprotein(a) values are significantly higher (> 60 mg/dl) and there is evidence of progressive atherosclerosis over one year despite optimal control of all other risk factors, regular lipoprotein apheresis therapy can be started to lower elevated lipoprotein(a) values.

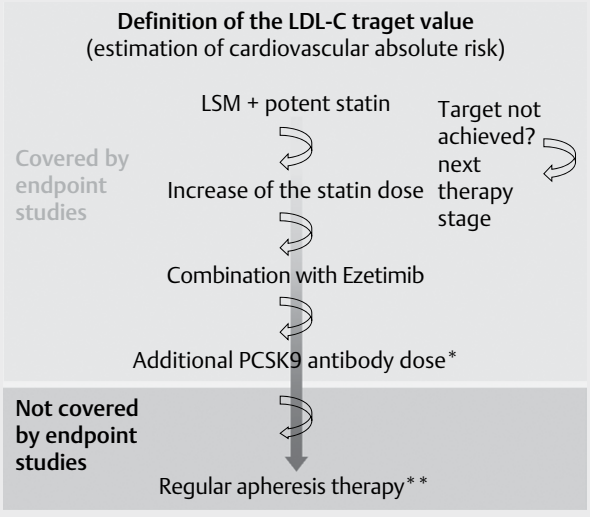
Statin intolerance

Patients with diabetes mellitus and statin intolerance should be treated similarly to patients without diabetes and with statin intolerance. At least 3 different statins should be used before a statin intolerance is diagnosed (exception: rhabdomyolysis – then a second statin should only be used very cautiously). In many patients, it is possible to use a low statin dose in combination with ezetimibe to significantly reduce LDL cholesterol levels. PCSK9 inhibitors are well-tolerated by a high number of patients with statin intolerance and can be used in patients with very high risk and significant distance to the target value. Data from Germany show that PCSK9 inhibitors are used in 70-80 % of patients with statin intolerance. As an alternative, bempedoic acid has been available since November

▶ **Tab. 4** Lipid target values in patients with diabetes mellitus.

		Primary goal	Secondary targets	
Risk group	**Definition**	**LDL chol**	**Non-HDL chol**	**ApoB**
Very high risk	Proven atherosclerosis and/or additional serious risk factors[1] and/or end organ damage[2] or early manifested type 1 diabetes with long diabetes duration (> 20 years)	≥ 50 % reduction and target < 55 mg/dl (1.4 mmol/l) *	< 85 mg/dl (2.2 mmol/l)	< 65 mg/dl
		"ideal" target value and clinically "good" value at < 70 mg/dl (1.8 mmol/l) [3]		
High risk	Without proven atherosclerosis, without terminal organ damage[2] with diabetes duration > 10 years or other risk factors[1]	< 70 mg/dl (1.8 mmol/l) and ≥ 50 % reduction of initial value	< 100 mg/dl	< 80 mg/dl
Moderately increased risk	Young patients with type 1 diabetes (< 35 years) and type 2 diabetes (< 50 years) with diabetes duration < 10 years and no other risk factors	< 100 mg/dl (2.6 mmol/l)	< 130 mg/dl (3.4 mmol/l)	undefined

For patients at the age of ≤ 30 years and without indications for vascular damage or microalbuminuria, it seems reasonable to wait until the age of 30 years before beginning a statin therapy.; [1] Hypertension, nicotine abuse, severe dyslipoproteinemia ; [2] E.g., microalbuminuria, retinopathy or neuropathy ; [3] For patients with confirmed atherosclerotic disease who experience a recurrence within 2 years despite maximal statin therapy, an LDL cholesterol target of < 40 mg/dl (< 1.0 mmol/l) may be considered.; * This addition to a clinical evaluation by the author group of this practical recommendation is based on the fact that the evidence for a further effective absolute risk reduction when comparing LDL-C values in treatment between < 70 mg/dl and < 55 mg/dl is still low and depends very much on the individual patient risk; ApoB = apolipoprotein B; Chol = cholesterol.



▶ **Abb. 1** Therapy algorithm to achieve LDL cholesterol target levels. Bempedoic acid and inclisiran have been available since 11/2020, and 2/2021, respectively (not yet covered by endpoint studies). Bempedoic acid can be used alone or in combination with other lipid-lowering agents; inclisiran is an alternative to proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies. LSM: Lifestyle measures; * according to the Federal Joint Committee (G-BA); ** as per individual benefit-risk assessment; LDL-C = LDL cholesterol.

2020, which inhibits cholesterol biosynthesis similarly to statins, but only acts in the liver, which is why myopathies are less common. Cardiovascular endpoint studies are currently not available.

Severe hypertriglyceridemia

Triglyceride values above 1000 mg/dl significantly increase the risk of acute pancreatitis [12]. By consistently implementing lifestyle measures (alcohol abstinence, largely abstaining from refined carbohydrates) and a strict blood glucose control it is usually possible to lower the values significantly. In order to minimize the risk of pancreatitis in severe hypertriglyceridemia, fibrates and/or high doses of omega-3 fatty acids can be used to significantly reduce triglyceride levels. Statins in high doses can lower triglyceride concentrations somewhat, but this is usually not sufficient to treat severe hypertriglyceridemia. If acute pancreatitis occurs at triglyceride concentrations above 1000 mg/dl (approx. 10 mmol/l), plasmapheresis is a treatment option to rapidly reduce the triglyceride concentration. Further treatment options include the administration of heparin and/or insulin (activation of lipoprotein lipase) and fasting. It is particularly worth trying a replacement of dietary fats with Medium-chain triglyceride (MCT) fatty acids in cases of very high triglyceride values. In very severe hypertriglyceridemia in the setting of familial chylomicronemia syndrome, the antisense oligonucleotide Volanesorsen, which inhibits the synthesis of apolipoprotein C-III, can be used.

Conclusion

Cardiovascular events are a major cause of premature mortality and multimorbidity in people with diabetes. Risk stratified patient-related LDL cholesterol reduction is an evidence-based integral part of diabetes therapy and can improve the clinical prognosis of our patients. High-dose statin therapy, if necessary, in combination with ezetimibe, is the most important drug therapy. In cases of moderate hypertriglyceridemia, an individual decision must be made as to whether the additional administration of high-dose omega-3 fatty acids or fibrates is justified. As a secondary goal, attention should be paid to non-HDL cholesterol concentration. In the case of severe hypertriglyceridemia with values above 1000 mg/dl (approx. 10 mmol/l), the following measures reduce triglyceride concentrations and therefore significantly reduce the risk of pancreatitis: lifestyle measures (alcohol abstinence, largely abstaining from refined carbohydrates), good blood glucose control, possible administration of fibrates and/or omega-3 fatty acids.

▶ **Tab. 5** Therapy strategies for elevated triglycerides.

Measure	Comment
Reaching LDL cholesterol target value	Always; normally necessary to administer statins
Reaching non-HDL cholesterol target value	If possible, either further LDL cholesterol reduction or reduction of VLDL/remnant cholesterol (and thus triglyceride reduction).
Lifestyle measures	Always, as this can usually significantly improve hypertriglyceridemia.
Blood glucose control	Always, as this can usually significantly improve hypertriglyceridemia.
Fibrates	Individual assessment, possibly after achieving LDL cholesterol target values in cases of very high risk and persistent hypertriglyceridemia; 1 cautious use, as no convincing endpoint studies in combination with statins have been conducted so far; note: increased risk of myopathy in combination with statins. This particularly affects combinations with gemfibrozil, whereas no increased myopathy incidence is observed in combinations with fenofibrate.
Omega-3 fatty acids	Individual assessment, possibly after achieving LDL cholesterol target values in cases of very high risk and persistent hypertriglyceridemia; cautious use, as no convincing endpoint studies in combination with statins have been conducted so far. However, a recent study (REDUCE-IT) using 4 g icosapentethyl showed a very significant risk reduction even in patients on statin treatment.
MCT fatty acids	As a dietary fat substitute for very high triglyceride levels.

[1] Repeated fasting triglyceride levels > 500 mg/dl (5.7 mmol/l) should be treated with fibrates and/or high-dose omega-3 fatty acids to reduce the risk of acute pancreatitis; MCT = Medium-chain triglyceride.

Company representatives

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Conflict of Interest

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