Atherosclerosis xxx (xxxx) xxx

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Lipid-lowering in diabetes: An update

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A B S T R A C T

Atherosclerotic cardiovascular disease (ASCVD) is accelerated in people with diabetes. Dyslipidemia, hyperglycemia, oxidative stress, and inflammation play a role via a variety of mechanisms operative in the artery wall. In addition, some unique features predispose people with type 1 diabetes to accelerated atherosclerosis. Various organizations have created guidelines that provide advice regarding screening, risk assessment, and roadmaps for treatment to prevent ASCVD in diabetes. Management of dyslipidemia, especially with statins, has proven to be of immense benefit in the prevention of clinical CVD. However, since many patients fail to attain the low levels of low-density lipoproteins (LDL) recommended in these guidelines, supplemental therapy, such as the addition of ezetimibe, bempedoic acid or PCSK9 inhibitors, is often required to reach LDL goals. As a result, the upfront use of combination therapies, particularly a statin plus ezetimibe, is a rational initial approach. The addition to statins of drugs that specifically lower triglyceride levels has not proven beneficial, although the addition of icosapent-ethyl has been shown to be of value, likely by mechanisms independent of triglyceride lowering. Newer treatments in development, including apoC-III and ANGPTL3 inhibitors, seem promising in further reducing apoB-containing lipoproteins.

1. Epidemiology of cardiovascular disease in diabetes

Atherosclerotic cardiovascular disease (ASCVD) is the major cause of morbidity and mortality in patients living with diabetes [1,2]. Studies indicate the risk is increased several folds compared to individuals without diabetes [3]. Moreover, the risk is increased in metabolic syndrome (MetS) and prediabetes [4–6]. Much of the increased risk in type 2 diabetes (T2DM), prediabetes and MetS can be attributable to the clustering of several CVD risk factors, such a dyslipidemia, hypertension, hyperglycemia, obesity, systemic inflammation, and a pro-thrombotic tendency.

Although 90–95% of individuals with diabetes have type 2 diabetes, ASCVD risk is also increased in type 1 diabetes (T1DM) [2]. Although atherosclerosis begins early in life even in the absence of diabetes, early onset atherosclerosis occurs more commonly in the presence of T1DM [7,8]. Autopsy studies have shown accelerated atherosclerosis in young individuals with T1DM compared to age-matched non-diabetic controls [9]. In addition, a high prevalence of asymptomatic coronary atheromatous lesions was detected in T1DM by coronary artery calcification [10] and intra-coronary ultrasound [11].

ASCVD mortality has declined in people living with and without diabetes in the past decades [1,2,12], likely attributable in large part to better glycemic control, advances in the treatment of its associated CVD risk factors, and the use of emerging drugs with favorable cardiovascular benefits. However, these benefits are offset by an alarming increase in diabetes prevalence [13]. Nonetheless, a relatively recent systematic review of 57 articles involving 4 million people with diabetes indicated an overall prevalence of ASCVD of 32.2%, with coronary artery disease (CAD) being the most frequent type of CVD reported [14].

This article will focus on pathogenesis, prevention and treatment of lipid and lipoprotein disorders related to ASCVD and stroke in people living with diabetes, including the value of guidelines published by various organizations, as well as newer approaches to therapy that are under development.

2. Mechanisms of atherosclerosis in diabetes

The presence of increased macrophage and T lymphocyte content, larger necrotic cores, and more healed plaque ruptures [15] suggests a more active atherogenic process in diabetes. One possible explanation is an increased prevalence of classical CVD risk factors in both types of diabetes. Alternatively, mechanisms specific to diabetes may be operative. Attempts to understand potential mechanisms derive mainly from pathological studies and studies in experimental animals, usually mice, which are then extrapolated to humans with diabetes. Clinical trials that show benefit from modifying particular risk factors suggest involvement

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https://doi.org/10.1016/j.atherosclerosis.2023.117313
Received 23 June 2023; Received in revised form 11 September 2023; Accepted 22 September 2023
Available online 6 October 2023

of those factors in the pathogenesis of atherosclerosis in diabetes, although they do not provide insights into the related mechanisms. This section will begin by describing factors and mechanisms involved in T2DM and its antecedent, MetS, after which we will briefly discuss how atherosclerosis might be accelerated in T1DM. Since this article is focused on lipids and lipoproteins in diabetes, it will deal mainly with the section on dyslipidemia, while briefly discussing some of the other mechanisms involved.

2.1. Dyslipidemia

The strongest evidence to explain increased atherosclerotic CVD in both MetS and T2DM is dyslipidemia, characterized by hypertriglyceridemia, low levels of HDL-cholesterol (HDL-C), normal to slightly elevated levels of LDL-cholesterol (LDL-C), with high apo B levels and accumulation of small, dense LDL particles. Postprandial dyslipidemia [16], due to enterocytic production of chylomicrons and their remnants, as well as impaired clearance [17], also occurs in MetS and T2DM.

Dyslipidemia can facilitate retention of atherogenic lipoproteins by proteoglycans in the arterial intima, after which they can undergo oxidative and enzymatic modification, generating toxic products that can promote atherogenesis. Small, dense LDL are more easily retained by vascular proteoglycans [18], contain less cholesterol per particle than larger, more buoyant LDL, and are more susceptible to oxidative modification [19], which plays an important role in atherogenesis (see further below). In addition, in chronic inflammatory states such as those in MetS and diabetes, HDL particles can acquire the inflammatory molecule, serum amyloid A (SAA), the presence of which on HDL can lead to its binding to vascular proteoglycans [20]. Once bound, it loses its anti-inflammatory and antiatherogenic properties [21], including facilitation of reverse cholesterol transport. HDL that is bound in the arterial intima can undergo the same modifications and generate the same toxic products as retained LDL, VLDL, and their atherogenic remnants. Triglyceride-rich lipoproteins (TRLs) may be directly atherogenic by virtue of their cholesterol content. In addition, apo C-III might play a role in atherogenesis by inducing adhesion molecules [22] and stimulating inflammation, migration and proliferation of vascular smooth muscle cells [23].

Perhaps the most convincing evidence for dyslipidemia playing a causal role in the pathogenesis of atherosclerotic CVD in diabetes is provided by clinical trials in which lipid-lowering drugs, particularly statins [24], but also ezetimibe [25] and proprotein convertase subtilisin-kexin 9 (PCSK-9) inhibitors [26,27], have resulted in beneficial clinical outcomes in people living with diabetes. Interestingly, these drugs primarily lower LDL, with minimal to modest effects on TRLs, increases of which are the hallmark of diabetic dyslipidemia. No therapeutic approach has had more profound effects on the prevention of CVD in MetS and T2DM than statins.

2.2. Hyperglycemia

Hyperglycemia is a hallmark of diabetes. While initial results from clinical trials that targeted hyperglycemia were either negative or borderline positive [28], more long-term follow up glucose-lowering therapies support a role for hyperglycemia in the pathogenesis of vascular disease in both T2DM [29] and T1DM [30], despite follow-ups being after the end of the randomization period, at which time glucose control was similar in the two groups.

High glucose levels can lead to endothelial dysfunction [31], characterized by impaired endothelium-dependent vasodilation due to reduced nitric oxide (NO) bioavailability [32], as well as increased permeability [33] and inflammatory adhesion molecule expression [34], all of which play a role in atherogenesis. Endothelial dysfunction can also be caused by advanced glycation end-products (AGEs), which interact with the Receptor for AGEs (RAGE). AGE-RAGE interactions activate signaling pathways in vascular endothelial cells, macrophages and VSMCs, which can facilitate leukocyte recruitment into the arterial intima, and enhance the release of pro-inflammatory molecules, all of which can play a role in atherogenesis [35,36]. GLP1 receptor agonists can affect atherosclerosis by reducing glucose and lipid levels, increasing nitric oxide production, reducing inflammation, and smooth muscle cell migration and proliferation [37], whereas SGLT2 inhibitors have several effects on the artery wall that might inhibit atherogenesis, including reduction of dyslipidemia and plaque size, inhibition of leukocyte adhesion and transmigration, and reduction of endothelial dysfunction, oxidative stress and inflammation [38]. These effects are the same in people with and without diabetes.

2.3. Oxidative stress

Oxidative stress, characterized by increased oxidant production in cells, is common in diabetes [39]. Metabolic abnormalities present in diabetes, including AGE-RAGE interactions, cause mitochondrial superoxide overproduction in endothelial cells, which can activate several pathways involved in the pathogenesis of diabetes-related complications. Established ASCVD risk factors, including diabetes, enhance ROS generation and decrease endothelial NO production [40]. ROS can cause endothelial dysfunction and directly activate NFkB, which has multiple downstream targets that can recruit macrophages and T-cells to the artery wall, thereby increasing inflammation (see below) and atherosclerosis [41].

Oxidative stress may play a role in atherogenesis by oxidizing lipoproteins in the artery wall. Oxidized LDL can activate endothelial cells to secrete MCPs, thereby recruiting monocytes and T cells into the intima [42]. Lipid peroxidation products in oxidized LDL are broken down to reactive aldehyde products that form adducts with lysine residue of apo B on LDL, leading to reduced affinity for vascular proteoglycans, but increased binding to non-proteoglycan components of extracellular matrices [43]. However, the most likely mechanism by which oxidized LDL contributes to atherogenesis is via uptake by scavenger receptor A, CD36 and LOX-1 on macrophages, leading to formation of lipid-laden foam cells [44–46], which are a major feature of fatty streaks, as well as more mature arterial lesions. Uptake by LOX-1 can lead to foam cell formation in VSMCs [46]. As lesions mature, macrophages secrete factors that cause migration and proliferation of VSMCs, and further secretion of extracellular matrix molecules. Oxidized LDL-mediated death of foam cells leads to necrotic core formation, which is prevalent in advanced lesions and more prevalent in diabetes [47]. Finally, oxidized LDL can be involved in thrombogenesis [48], a precursor of clinical events.

Small, dense LDL, which are associated with hypertriglyceridemia and characteristically present in MetS and T2DM, are more susceptible to oxidation *in vitro* than more buoyant, large LDL species [19]. Moreover, LDL from patients with diabetes showed increased susceptibility to oxidation [49], and oxidized LDL levels in plasma were increased in diabetes and improved with insulin treatment [50]. Thus, diabetes may accelerate many adverse effects of oxidized LDL on the artery wall.

Although there is abundant evidence to support an important role for oxidative stress and oxidized LDL in all stages of the atherogenic process, and although some antioxidants have been shown to reduce atherosclerotic lesions in experimental animals [51,52] they have not been shown to benefit cardiovascular events in clinical trials [53,54].

2.4. Inflammation

Inflammation has long been known to be an integral part of the atherosclerotic process [55]. A recent proof-of-concept clinical trial, the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), for the first time showed that inhibition of inflammation using an antibody against Il-1β decreased cardiovascular events [56], providing further evidence for the importance of inflammation in

atherosclerosis. Inflammation is a hallmark of visceral obesity, MetS and T2DM, in which inflammatory markers such as CRP and SAA are elevated [57,58] and associate with increased CVD risk [59], suggesting a link between inflammation, diabetes and CVD. In CANTOS, in which about 40% of the subjects had T2DM and 49% had prediabetes, the benefits of treatment were comparable to those who were normoglycemic [60]. Another anti-inflammatory agent, colchicine, also reduced recurrent CVD events in patients with a recent myocardial infarction [61].

Several mechanisms by which chronic inflammatory states, such as those present in visceral obesity, MetS and T2DM, can accelerate atherosclerosis, as reviewed in [62], are beyond the scope of this article.

These diabetes-associated factors (dyslipidemia, hyperglycemia, oxidative stress, and inflammation) can adversely affect thrombosis [63], which often triggers clinical events such as myocardial infarctions. Finally, complications associated with diabetes are associated with an even greater acceleration of CVD complications. For example, the presence of renal complications and diabetic retinopathy [64,65] is associated with a marked increase in CVD risk by mechanisms that are not clear but may relate to increased endothelial dysfunction and dyslipidemia associated with nephropathy [66,67], cardiac autonomic neuropathy [68] and retinopathy [69]. Thus, several factors associated with the diabetic state can influence the atherothrombotic process at multiple stages, all the way from initiation of the fatty streak to precipitation of clinical events.

2.5. Type 1 diabetes

Several mechanisms by which atherosclerosis and ASCVD are accelerated in T2DM and MetS are operative in T1DM, but some mechanisms may be unique to T1DM. Arterial stiffness, a surrogate measure of early onset vascular disease, was highly prevalent and associated with poor glycemic control, reduced insulin sensitivity, body mass index, blood pressure, and elevated lipid levels in the SEARCH study, which evaluated CVD risk factors in children and adolescents with T1DM [70], suggesting that its rate of progression in T1DM is determined by the same risk factors as in adult CHD.

However, CVD risk remains increased even in well-controlled T1DM patients without additional cardiovascular risk factors, suggesting that other factors may be involved. Chronic hyperglycemia and its consequences may be one such factor [71], which although present in T2DM, may be more pronounced and prolonged in T1DM. Increasing evidence from the Swedish National Diabetes Registry of T1DM indicates the important association of levels of glycemia in addition to other CVD risk factors and major CAD events [72]. Data from the DCCT:EDIC also implicates an important role for levels of glycosylated hemoglobin [73] and lipid and lipoprotein disorders [74] in CVD complications. Moreover, hypoglycemia and glucose variability, which are likely to be more common in T1DM, could potentially enhance CVD risk by exacerbating oxidative stress, vascular inflammation, and endothelial dysfunction [75]. Repeated episodes of hypoglycemia may cause endothelial dysfunction [76] and glucose variability can stimulate the release of proinflammatory cytokines such as IL-6 and TNF-α and trigger oxidative stress [77].

Interestingly, lipid abnormalities in well controlled patients with T1DM do not appear to be a major factor, although statin therapy clearly reduces ASCVD events in T1DM [78] (see below). However, even though HDL-C levels are often normal or even elevated in T1DM [79], cholesterol efflux capacity of HDL [80] and anti-oxidative properties of HDL [81,82] can be reduced. In addition, individuals with T1DM can simultaneously have features of MetS and T2DM, such as weight gain, dyslipidemia, and hypertension, especially when well controlled [83,84]. Therefore, they can concomitantly have dyslipidemia, chronic inflammation and other ASCVD risk factors associated with MetS and T2DM. T1DM is an autoimmune disease, in which a dysfunctional immune system has been suggested to promote CVD through inflammatory pathways [81]. Finally, complications such as diabetic nephropathy [85], cardiac autonomic neuropathy [68] and retinopathy [69], all of which are common in long-standing T1DM, are associated with increased CVD risk, although direct causality between microvascular disease and ASCVD has not been shown.

Thus, in summary, T1DM shares several risk factors with T2DM, but has some unique factors that may a play a role in atherogenesis in this disorder.

3. Current ESC/EASD, ESC/EAS, and AHA/ACC guidelines

Screening, assessment and management of lipid and lipoprotein disorders in patients living with diabetes are among the most important steps to reduce ASCVD events. Recommendations of how to approach this topic have been offered by many organizations worldwide but the most complete evidenced-based guidelines currently available are those of the European Society of Cardiology/European Association for the Study of Diabetes (ESC/EASD) in 2020 [86], the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) also in 2020 [87], the American Heart Association (AHA)/American College of Cardiology (ACC) Multisociety Guideline on the Management of Blood Cholesterol in 2018 [88], with a subsequent paper that includes the recommendations listed specifically for patients living with diabetes by the AHA/ACC in Diabetes Care in 2020 [89]. These guidelines have used the well accepted and standard methods of grading strength of class of recommendations (COR) ranging from Class 1 which is strong, where benefit far outweighs risk, to Class 3 where no benefit from clinical trials and/or even possible harm has been experienced. Reported levels of evidence (LOE) range from level A, where there is strong evidence provided by multiple populations in which results have been evaluated from data obtained in randomized controlled trials or from meta-analyses, to Class C-LD where data are from randomized or non-randomized observational or registry studies with limitations in design or implementation, meta-analyses of such studies and/or clinical research in humans subjects that is mostly physiological or mechanistic.

To compare the three guidelines, a table has been created which presents a summary of recommendations for each set of guidelines adjoined by class of recommendations (COR) and levels of evidence (LOE) (columns) that are pertinent to each specific area of recommendations (rows) (Table 1). Recommendations related to management are presented in bold text. The following text will be used to point out important differences between the three organizations.

3.1. Screening

In the AHA/ACC and ESC/EAS guidelines, screening for the measurement of lipids can be performed in individuals who fast for 10–12 h or do not fast. However, ESC/EAS states that for non-fasting values '*the determination of some key analytes, such as fasting glucose, may be compromised*', yet non-fasting glucose may still be meaningful for patients with diabetes. For patients with diabetes, the ESC/EASD guidelines fail to stipulate ages for screening, however, a more detailed set of assessments in their guidelines are listed in subsequent sections. In screening, AHA/ACC guidelines qualify a TG level ≥200 mg/dL (2.3 mmol/L) to recommend measuring apo B whereas ESC/EASD guidelines give no such guidance and ESC/EAS state that apo B may be a secondary objective for people with diabetes. The ESC/EASD guidelines do provide a more detailed description of screening for the presence of CVD in patients with diabetes, but the LOE is C rather than A.

3.2. Lifestyle

The ESC/EASD, ESC/EAS, and AHA/ACC recommend the importance of a heart healthy lifestyle for primary and secondary prevention of ASCVD in all patients. Although many of these recommendations are not specific to patients with diabetes, the overall intent is that ASCVD

Table 1
Summary of recommendations for each set of guidelines adjoined by class of recommendations (COR) and levels of evidence (LOE) (columns) that are pertinent to each specific area of recommendations (rows).

	ESC/EAS	ESC/EASD	ACC/AHA	COR	LEVEL OF EVIDENCE
Screening in Patients with DM	**Age ≥10 years - Lipid profile, fasting or non-fasting.** Non-HDL-C and apoB recommended for DM patients and may be a secondary objective.	**Not addressed**	**Age ≥10 years - Lipid profile, fasting or non-fasting.** Elevated apoB ≥130 mg/dL and a relative indication for its measurement would be TG ≥ 200 mg/dL.	ACC/AHA -1 ESC/EAS 1	ESC/EAS A ACC/AHA –C
Heart Healthy Lifestyle	**DASH and Mediterranean-style dietary patterns; physical activity; weight loss for patients living with overweight/obesity.**	**Lifestyle changes are key to prevent DM and its CV complications. • Reduced calorie intake.**	**DASH and Mediterranean-style dietary patterns; physical activity; weight loss for patients living with overweight/obesity.**	ACC/AHA -1 ESC/EAS 1 ESC/EASD – 2A	ACC/AHA -A ESC/EAS A ESC/EASD -B
ASCVD History	History of acute coronary syndrome (ACS), history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin and unequivocally documented ASCVD on imaging known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50 % stenosis), or on carotid ultrasound. **If present, LDL-C lifestyle intervention and concomitant drug intervention is ≥ 1.4 mmol/L (55 mg/dL).**	See very high or high risk. History of coronary heart disease, non-fatal MI, ischemic stroke.	History of acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all atherosclerotic origin. **High intensity statin ↓ LDL-C ≥50%.**	ACC/AHA -1 ESC/EAS 1	ACC/AHA -A ESC/EAS A
Defining Very-High Risk	In primary prevention, for individuals at very-high risk but without FH or at very-high risk (that is, with another risk factor but without ASCVD). **LDL-C reduction of >50% from baseline and an LDL-C goal of <1.4 mmol/L (55 mg/dL). Non-HDL-C <2.2 mmol/L (<85 mg/dL) and apoB <65 mg/dL. Statins are recommended in patients with T1D who are at high or very-high risk.**	Patients with diabetes and established CVD or other target organ damage (proteinuria, renal impairment defined as eGFR <30 mg/min/1.73 m [2], LVH or retinopathy) or ≥ 3 major risk factors (age, hypertension, dyslipidemia, smoking, obesity) or early onset T1DM of long duration (>20 years) **In patients with T2DM at very high CV risk, an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50 % is recommended. In patients at very high risk, with persistent high LDL-C despite treatment with maximum tolerated statin dose in combination with ezetimibe, or in patients with intolerance to statins, a PCSK9 inhibitor is recommended. In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (85 mg/dL).**	Major risk factors (e.g., cigarette smoking, elevated BP, LDL-C, hemoglobin A1C, and calculated 10-year risk of ASCVD); the presence of risk-enhancing factors. **Multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high intensity statin to reduce the LDL-C level by ≥ 50%.**	ACC/AHA -1 ESC/EAS 1 ESC/EASD -1	ACC/AHA -A ESC/EAS A ESC/EASD -B
Defining High Risk	No target organ damage, DM duration ≥10 years or another risk factor. SCORE ≥5% and <10% **LDL-C reduction of >50% from baseline and an LDL-C goal of <1.8 mmol/L (55 mg/dL). Non-HDL-C <2.6 mmol/L (<100 mg/dL) and apoB<80 mg/dL mg/dL. Statins are recommended in patients with T1D who are at high or very-high risk.**	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor. **In patients with T2DM at high CV risk, an LDL-C target of,1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended. In patients with T2DM, a secondary goal of a non-HDL-C target of,2.6 mmol/L (<100 mg/dL) in high-risk patients is recommended.**		ESC/EAS 1	ESC/EAS A

(*continued on next page*)

Table 1 (*continued*)

	ESC/EAS	ESC/EASD	ACC/AHA	COR	LEVEL OF EVIDENCE
Defining Moderate Risk	T1D age <35 years, T2D age <50 years with duration <10 years without another risk factor and calculated SCORE ≤1% and <5% for 10-year risk off fatal CVD. **LDL-C goal of <2.6 mmol/L (100 mg/dL).** **Non-HDL-C <3.4 mmol/L (<130 mg/dL) and apoB<100 mg/dL.**	Young patients (T1DM aged <35 years or T2DM < 50 years) with duration of DM < 10 years, without other risk factors. **In patients with T2DM at moderate CV risk, an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended.**		ESC/EAS 1 ESC/EASD -1	ESC/EAS A ESC/EAS - A
Statins	1)-Recommended in T1D with high or very-high risk; 2) -In T1D and T2D intensity statin before adding ezetimibe. 3)-Statins not recommended in women who are pregnant or considering pregnancy.	Administration of statins is defined based on the CV risk profile of the patient and the recommended LDL-C (or non-HDL-C) target levels. **Statins may be considered in asymptomatic patients with T1DM aged >30 years.** **Statins should be considered in patients with T1DM at high CV risk, irrespective of the baseline LDL-C level.** **Statins are recommended as the first-choice lipid-lowering treatment in patients with DM and high LDL-C levels.** **Statins are not recommended in women of childbearing potential.**	**In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of non -statins to statin therapy. In patients with DM at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high intensity statin to reduce the LDL-C level by ≥ 50%.**	ESC/EAS 1) –2A ESC/EAS 2) – 2A ESC/EAS 3) 3	1) - C 2) - B 3) - C
Age 40–75 years LDL-C 70–189 mg/dL (1.7–4.8 mmol/L)			Reasonable to assess 10-year risk of a 1st ASCVD event by using the race and sex-specific PCE to help stratify ASCVD risk.	ACC/AHA - 2A	ACC/AHA B-
Age 40–75 years LDL-C ≥70 mg/dL (≥1.8 mmol/L)			**Moderate-intensity statin therapy without calculating 10- year ASCVD risk.**	ACC/AHA 1	ACC/AHA A
Age 50–75 years + multiple risk factors			**Reasonable to recommend high intensity statin to ↓ LDL-C ≥50%.**	ACC/AHA 2A	ACC/AHA BR
Older Adults or Age >75 years on statin			**Reasonable to continue statin.**	ACC/AHA 2A	ACC/AHA BR
10-Year Risk ≥20%			**Reasonable to add ezetimibe to maximally tolerated statin to ↓ LDL-C ≥50%.**	ACC/AHA 2B	ACC/AHA C-LD
Older Adults or Age >75 years	**Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.** **Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75 years.**		**With LDL-C of 70–189 mg/dL (1.7 mmol/L to 4.8 mmol/L) - reasonable to add statin after discussion of risks vs. benefits.** **It may also be reasonable to obtain a CAC and if score is zero to withhold statin.**	ACC/AHA 2B ESC/EAS - 1	ACC/AHA C-LD ESC/EAS -A
Age 20–39 years DM duration ≥10 years (T2D) or ≥20 years (T1D) + ≥30 µg albumin/mg creatinine, eGFR <60 mL/min/1.73 m^2, retinopathy, neuropathy, or ABI<0.9	**Statin therapy may be considered in both T1DM and T2DM patients aged ≤30 years with evidence of end organ damage and/or LDL-C >2.5 mmol/L, if pregnancy is not being planned.**		**Reasonable to start statin.**	ACC/AHA 2B ESC/EAD 2B	ACC/AHA-CLD ESC/EAD –C
Atherogenic dyslipidemia (↑TG, ↓HDL-C)	**Lifestyle modification with weight loss.** **Drug treatments of patients with hypertriglyceridemia in high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent-ethyl (2 4 g/day) should be considered in combination with statins.**	**Lifestyle intervention (with a focus on weight reduction, and decreased consumption of rapidly absorbed carbohydrates and alcohol), and fibrates should be considered in patients with low HDL-C and high triglyceride levels.**	Not Addressed.	ESC/EAD –EPA, 1 ESC/EAD -fibtrate,2 ESC/EASD – fibrate,2A	ESC/EAD -EPA, B ESC/EAD-fibrate, C ESC/EASD – fibrate, B

risk reduction would be similar if not identical to patients with disorders of lipid/lipoprotein metabolism with or without diabetes. The reduction in LDL-C that relates to avoidance of trans fat (Level A), reduction of dietary saturated fats and body weight if overweight/obesity are present (Level A), and dietary cholesterol (Level B) is consistent with dietary patterns such as the Dietary Approaches to Stop Hypertension (DASH) diet [90] as well as the Mediterranean style diet [91], with the Mediterranean dietary pattern recommended in all three guidelines. For weight reduction, caloric restriction to achieve a weight reduction of 5–10% will reduce LDL-C modestly, but also reduce TG, increase HDL-C, and decrease blood pressure, biomarkers of inflammation, the prothrombotic state, and levels of glycemia in patients with diabetes and prediabetes/MetS. Unfortunately, despite all these cardiometabolic benefits of weight loss, evidence that weight reduction in patients living with T2DM reduces ASCVD events, ASCVD mortality or all-cause mortality is lacking [92]. Increases in physical activity are also part of a heart healthy lifestyle, however, the AHA/ACC and ESC/EAS guidelines do not specify recommendations for patients living with diabetes whereas the ESC/EASD guidelines provide more direction for patients with diabetes. The AHA Essential 8s provide a series of lifestyle recommendations that are important for all individuals if not even more so in patients living with diabetes [93].

3.3. Risk assessment

3.3.1. ASCVD

AHA/ACC and ESC/EAS criteria to define ASCVD are similar except ESC/EAS distinguish their recommendations to include imaging predictive of clinical events, such as significant plaque on coronary or CT angiography (multivessel coronary disease with two major epicardial arteries having >50% stenosis). For patients with diabetes and ASCVD, ESC/EAS and ESC/EASD state that after lifestyle intervention, the LDL-C goal should be ≤1.4 mmol/L (55 mg/dL) whereas AHA/ACC recommends high intensity statin to decrease LDL-C ≥50%. ESC/EASD guidelines include patients with known ASCVD and those classified as being at very high risk.

3.3.2. Very high risk

ESC/EASD criteria for very-high risk include patients with diabetes and established CVD or other target organ damage (proteinuria, renal impairment defined as eGFR <30 mg/min/1.73 m^2, LVH or retinopathy) or ≥3 major risk factors (age, hypertension, dyslipidemia, smoking, obesity) or early onset T1DM of long duration (>20 years) which for T1DM is like ESC/EAS. Here, the ESC/EASD guidelines use Systematic Coronary Risk Estimation (SCORE - see Risk Calculation section below) to estimate CVD mortality risk, i.e., ≥10% and add goals for other biomarkers which may be particularly applicable in patients with diabetes i.e., non-HDL-C and apo B. The ESC/EAS guidelines define very-high risk for primary prevention or secondary prevention for patients with diabetes, who have another major risk factor that is assumed but not clearly defined whereas AHA/ACC lists major risk factors as cigarette smoking, elevated BP, LDL-C, hemoglobin A1C, and calculated 10-year risk of ASCVD. The AHA/ACC also list the presence of risk-enhancing factors which may contribute to very-high risk: family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L); MetS; chronic kidney disease; history of preeclampsia or premature menopause (age <40 years), chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (e.g., South Asian); persistent elevations of TG ≥175 mg/dL (≥1.97 mmol/L); and, if measured in selected individuals, apo B ≥130 mg/dL, high-sensitivity CRP ≥2.0 mg/L, ankle brachial index (ABI) <0.9 and lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a). In these patients with multiple risk factors or those 50–75 years of age, it is reasonable to use a high intensity statin to reduce the LDL-C level by ≥50%.

3.3.3. High risk

The ESC/EASD guidelines define high risk as patients with diabetes duration ≥10 years without target organ damage plus any other additional risk factor. In addition, detection of atherosclerotic plaque in carotid or femoral arteries by CT, or magnetic resonance imaging, may be considered as a risk modifier in patients with diabetes at moderate or high-risk CVD. AHA/ACC guidelines fail to distinguish high risk from very high risk. However, ESC/EAS defines high risk as patients with no target organ damage and duration ≥10 years or another risk factor and a SCORE of ≥5% and <10% CVD risk is expected. Guidance for non-HDL-C and apo B levels is again provided.

3.3.4. Moderate risk

ESC/EASD and ESC/EAS guidelines define moderate risk as patients with T1DM age <35 years, T2DM age <50 years with duration <10 years without another risk factor and calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD. In asymptomatic patients living with diabetes, ESC/EASD indicates that carotid and/or femoral plaque burden with arterial ultrasonography should be considered as a risk modifier. Ankle-brachial index and/or coronary calcium score (CAC) with CT may also be considered as a risk modifier in CV risk assessment of asymptomatic patients with diabetes at moderate risk. CT Coronary Angiography (CTCA) or functional imaging (radionuclide myocardial perfusion imaging, stress cardiac magnetic resonance imaging, or exercise or pharmacological stress echocardiography) may be considered in asymptomatic patients with diabetes for screening of CAD. AHA/ACC guidelines do not define moderate risk but have similar treatment goals for individuals aged 40–75 years and feel that it is reasonable to assess 10-year risk of a first ASCVD event by using the race and sex-specific pooled cohort equation (PCE) (see Risk Calculation section) to help stratify risk. Treatment goals again include non-HDL-C and apo B in addition to LDL-C. Rather than addressing levels of risk as high or moderate, AHA/ACC categorizes risk based on age and level of LDL-C.

3.3.5. Risk calculation

AHA/ACC use PCE to assess the 10-year risk for an ASCVD event [94] whereas ESC/EAS use SCORE, which is based on large, representative European cohort data sets and includes gender, age, systolic BP, total cholesterol, and smoking status [95]. PCE is best used to estimate 10-year risk in US adults 40–75 years of age and its major attribute is that it includes major, independent factors such as age, gender, race, total cholesterol, HDL-C, systolic BP, presence, or absence of BP lowering medications, diabetes, and smoking. Yet importantly, SCORE can be recalibrated for use in different populations by adjusting for secular changes in CVD mortality and risk factor prevalence. SCORE risk is also influenced by a large series of factors that can modify risk calculations, i.e., central obesity, physical inactivity, psychosocial stress, family history of premature CVD, inflammatory disorders, major psychiatric disorders, HIV treatment, atrial fibrillation, left ventricular hypertrophy. chronic kidney disease, obstructive sleep apnea syndrome., and non-alcoholic fatty liver disease. The ESC/EASD guidelines list only the STNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score but only to determine the type of revascularization in patients with diabetes with stable coronary artery disease, suitable coronary anatomy, and low predicted surgical mortality for CABG *vs.* PCI [96].

3.3.6. Older adults

The ESC/EASD provides guidance for management of BP and levels of glycemia in older patients living with diabetes, but no recommendation is made for lipid management. The ESC/EAS state that because older people frequently have comorbidities and have altered drug pharmacokinetics, lipid-lowering medications should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger people. AHA/ACC states that in adults 75 years of age or older with LDL-C of 70–189 mg/dL (1.7 mmol/L to 4.8

mmol/L) it is reasonable to add a statin after discussion of risks vs. benefits with the patient. It may also be reasonable to obtain a CAC, and if the score is zero to withhold statin.

3.4. Atherogenic dyslipidemia

This lipid/lipoprotein disorder is defined by TG ≥150 mg/dL (1.7 mmol/L), HDL-C <40 mg/dL (1.0 mmol/L) for men and <50 mg/dL (1.3 mmol/dL) for women, and an increased concentration of small, dense LDL and HDL is common in patients with T2DM [97]. AHA/ACC guidelines do not address patients with atherogenic dyslipidemia whereas ESC/EAS and ESC/ESAD recommend lifestyle modification with weight loss and limitation of rapidly absorbed dietary carbohydrate and alcohol. Drug treatments can be considered in High-Risk patients with hypertriglyceridemia (see the following section).

4. Approach to implementing current guidelines

As per the previous section on guidelines, first-line treatments of lipid and lipoprotein disorders in patients with T2DM, are drugs that target LDL-C, specifically statins. Ezetimibe, bempedoic acid, and PCSK9 monoclonal antibodies (evolocumab and alirocumab), and small-interfering RNA (siRNA) molecules (inclisiran) may be used singly or in combination to reduce levels of atherogenic apo B-containing lipoproteins in certain circumstances. In the next section, we discuss the specific lipid lowering options for both monotherapy and combination therapy for the prevention and treatment of CVD in diabetes.

5. Drugs targeting LDL cholesterol

5.1. Statins

Competitive inhibitors of hydroxy-methylglutaryl-CoA reductase (HMGCoA reductase) - statins - remain the cornerstone of treatment of dyslipidemia in patients living with diabetes. As in those without T2DM, statins reduce the risk of ASCVD in patients with diabetes by an average of 20% for every 1 mmol/L (39 mg/dL) decrease in LDL-C, independent of other characteristics [78]. These data from the Cholesterol Treatment Trialists meta-analysis, as well as landmark studies in diabetes such as CARDS (Collaborative Atorvastatin Diabetes Study) [98] and HPS (Heart Protection Study) [99], support the use of statins as first line therapy to lower LDL-C and reduce ASCVD risk [78]. Intensive statin treatment, leading to lower LDL-C levels, results in a greater benefit than low-to-moderate intensity statin treatment. Metanalyses comparing these two approaches demonstrated an additional 9% relative risk reduction for CVD events with high-intensity statin [100]. Current guidelines recommend titrating to the maximally tolerated dose of a high-intensity statin (e.g., atorvastatin 40–80 mg daily, rosuvastatin 20–40 mg daily). In patients with intolerance to either of these drugs, other statins at their maximum tolerated dose can be tried [87]. Moderate and high intensity statins can increase the risk of diabetes, especially in people with the MetS, which is offset by a ~10 greater relative benefit on major vascular outcomes [101].

5.2. Ezetimibe

Ezetimibe is a highly selective inhibitor of intestinal absorption of cholesterol through interaction with the specific cholesterol-transporting protein Nieman-Pick C1-Like 1 protein, which results in reduced concentrations of cholesterol in portal blood and liver, and hence up-regulation of LDL-receptors on the surface of hepatocytes, leading to reduced LDL-C plasma levels. The mainstay of its use is in combination with statins, where ezetimibe decreases LDL-C concentrations by an additional 20% on average. In a subgroup of 4933 patients with T2DM in the IMPROVE-IT study, addition of ezetimibe to a statin was associated with an absolute decrease in the primary outcome by an additional 5.5%, while in patients without diabetes it was only 0.7% [25], providing an important rationale for the use of this combination in people living with diabetes. The more pronounced effect of ezetimibe in people with diabetes may be explained by ezetimibe's influence on postprandial hyperlipemia, which characterizes the lipid phenotype in diabetes [102]. Of interest is the observation that patients with T1DM have an increase in cholesterol absorption markers and a decrease in markers of cholesterol synthesis [103], which might account for the preferential LDL-C lowering effect of ezetimibe in these patients.

5.3. Upfront combination therapy

Most patients with T2DM fall within high and very high CVD risk categories and, according to guidelines, require attainment of very low levels of LDL-C, which may be difficult with monotherapy alone. Evidence from the DA VINCI [104] and SANTORINI [105] studies demonstrate that among high/very high-risk primary and secondary prevention patients receiving Lipid Lowering Therapy (LLT), only one-fifth of patients achieved ESC/EAS 2019 goals. In a large Italian cohort of patients with diabetes, only 10% of those at high CV risk and 9% of those at very high risk were at goal for LDL-C [106]. A practical approach to overcome this failure to achieve LDL-C goals in real life settings is to consider alternate lipid lowering approaches that are effective, easy to implement, safe and associated with acceptable adherence. Because very high-risk patients often require a reduction of LDL-C by more than 50% to reach their LDL-C goals when starting therapy, the concept of upfront combination therapy (for the first time introduced by the International Lipid Expert Panel and further supported by the consensus of the EAS), is gaining traction [107,108]. To achieve these goals, initial LLT in patients with diabetes could include two steps, as suggested in Fig. 1. STEP 1 would focus on LDL-C and would use a combination of a statin and ezetimibe as initial therapy, with the goal of achieving >50% LDL-C reduction. Fixed drug combinations could be used to minimize the number of pills required [109]. A pooled analysis of 27 clinical trials with 21,000 subjects' therapy with ezetimibe plus statin produced greater reductions in LDL-C, total--cholesterol, non-HDL-C, apo B, TGs, and greater achievement of LDL-C levels <70 mg/dl by 18.2%, and <100 mg/dl by 23.4% ($p < 0.0001$ for all). These results were similar in patients with or without diabetes [110]. In the diabetes subgroup of the RACING study [111], a combination of moderate dose statin and ezetimibe, as compared to high intensity statin monotherapy, was associated with lower intolerance-related discontinuation and greater proportion of patients with an LDL-C level <70 mg/dL at 1, 2, and 3 years (81.0%, 83.1%, and 79.9% *vs*. 64.1%, 70.2%, and 66.8% respectively, all $p < 0.001$); the primary outcome of cardiovascular death, myocardial infarction, coronary revascularization, hospitalization for heart failure or non-fatal stroke was not different between the two groups, as originally shown in the whole population of the RACING trial [112].

Moreover, a recent post-PCI study showed that a combination of moderate dose statin and ezetimibe was associated with a lower occurrence of cardiovascular death, myocardial infarction, coronary artery revascularization, hospitalization for heart failure, or nonfatal stroke than high dose statin alone in patients with ASCVD [113]. These studies support the use of moderate-intensity statin with ezetimibe combination therapy as a reasonable alternative to high-intensity statin monotherapy, as recommended by the current guidelines for secondary prevention among patients with DM and ASCVD. In the event this goal is not reached with initial combination therapy, the addition of bempedoic acid or, in extremely high CV risk patients, PCSK9-targeted therapy could be considered. STEP 2 would focus on residual elevation of apo B-containing lipoproteins and non-HDL-C. including TG-rich apo B containing particles.

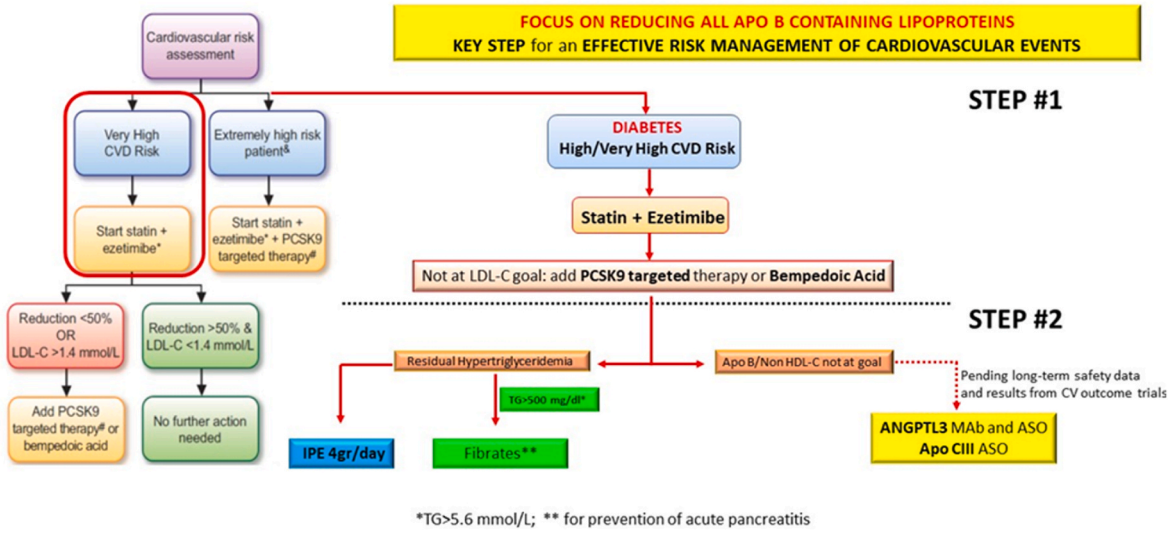

Fig. 1. Simplified lipid-lowering treatment algorithm to reduce cardiovascular risk in very high and extremely high CV risk patients leaving with and without diabetes. (Modified from Ray KK et al., European Heart Journal (2022) 43, 830–833).
In statin-intolerant patients, consider ezetimibe + bempedoic acid or PCSK9 targeted therapy.
[&] Extremely high risk = post ACS + history of other vascular event/peripheral artery disease/polyvascular disease/multivessel coronary artery disease/familial hypercholesterolemia.
[#] Monoclonal antibodies directed against PCSK9 or PCSK9 siRNA therapy (Inclisiran).
Apo B: Apolipoprotein B; APO C-III: Apolipoprotein C-III; IPE: Icosapent-ethyl; ANGPTL3: Angiopoietin-like protein 3; MAb: Monoclonal antibody; ASO: Antisense oligonucleotide, PCSK9: Proprotein Convertase Subtilisin/Kexin type 9.

5.4. Bile acid sequestrants

The bile acid sequestrants (BAS), cholestyramine, colestipol, and colesevelam, bind to bile acids in the intestine to form an insoluble complex that is excreted in the feces, ultimately decreasing LDL-C levels by15–18 % [114]. BAS have also been demonstrated to improve glycaemic control in patients with T2DM with further reduction of HbA1c and fasting plasma glucose of 0.22 mmol/L [115]. However, GI side effects in addition to modest LDL-C lowering limit their application.

5.5. Proprotein convertase subtilisin-kexin 9 (PCSK9) inhibitors

Pharmacological approaches that inhibit PCSK9 can reduce LDL-C by >50 % when used alone or in combination with statins and/or ezetimibe [116,117]. The currently available fully human monoclonal antibodies, evolocumab and alirocumab, reduce CVD events in high-risk subjects with established ASCVD in the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) [118] and ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trials [119]. Prespecified analyses compared the CV outcomes and safety in patients with and without diabetes at baseline in both trials [26,120]. Relative reduction in the primary endpoint was similar in patients with diabetes, prediabetes or normoglycemia; however, since the absolute incidence of the primary endpoint was higher in patients with diabetes, the absolute reduction also was greater in patients with diabetes than in those with prediabetes or normoglycemia. No excess risk of new-onset diabetes for patients with prediabetes, as previously demonstrated for statins [121] has been noted with PSCK9 antibodies to date [120].

Inclisiran is a small-interfering RNA (siRNA), which inhibits PCSK9 synthesis [122]. Inclisiran acts selectively in the liver as it is conjugated to triantennary *N*-acetylgalactosamine (GalNAc), which provides high-affinity binding to hepatocyte asialoglycoprotein receptors [122]. Several trials have shown that inclisiran is well tolerated, and that subcutaneous injections of 300 mg every 6 months reduced LDL-C by approximately 50% in several populations of subjects including those with diabetes [123]. No impact was observed on glucometabolic parameters or the prevalence of new onset diabetes. A major appeal of this medication is that it only has to be administered twice per year, which likely will be associated with better adherence than other available lipid-lowering approaches (i.e., statins and ezetimibe), although its cost might limit its use. Inclisiran is currently being evaluated in ORION-4 (NCT03705234), a 5-year CV outcome trial in about 15,000 very high-risk subjects, including patients with diabetes.

5.6. Bempedoic acid

Bempedoic acid is an inhibitor of ATP citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase in the pathway for cholesterol synthesis [124]. It is selectively activated in the liver and therefore is unlikely to cause problems with skeletal muscle symptoms that can occur with statins [125]. In CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen) Outcomes, a randomized controlled clinical trial in 13.970 subjects, 45% of whom had diabetes, and only 29% were receiving statins (mostly moderate intensity). bempedoic acid, 180 mg/day significantly decreased LDL-C by 21.1% and the primary composite end-point (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) by 13% without an impact on glucose metabolism and, unlike statins, it was not associated with increased incidence of new onset diabetes [126]. Moreover, previous observations performed during 24-h continuous glucose monitoring showed a trend towards improved glycemic control with bempedoic acid, particularly associated with reduced postprandial meal peaks in plasma glucose [127]. Bempedoic acid may be used in patients with diabetic dyslipidemia as an addition or alternative to statins to help achieve LDL-C and non-HDL-C goals, particularly in those with statin-intolerance.

6. Drugs targeting TG-rich and other lipoproteins

Growing evidence has established that TG-rich lipoproteins (TRLs) and their remnants are associated with ASCVD, and their relationship to the atherothrombotic processes appears independent of, and additional

to, that of LDL [128]. Moreover, TRLs appear to contribute to the residual risk of ASCVD events in patients who had well-treated LDL-C levels [129]. ASCVD risk mediated by TRLs appears to be determined in part by downstream effects of residual lipoprotein cholesterol content after TG removal by the hydrolytic enzyme lipoprotein lipase (LPL), and thus, the circulating concentration of apo B-containing particles rather than their TG content [130]. Patients with diabetes and CAD have been shown to have mildly to moderately elevation of plasma TG-rich apo B-containing lipoproteins even at extremely low LDL-C levels [131]. It would therefore seem reasonable to consider combination therapies that address both LDL and TG-rich apo B-containing lipoproteins to lower residual ASCVD risk associated with the TRLs.

6.1. Fibrates

Fibrates, which are peroxisome proliferator-activated receptor alpha (PPAR-α) agonists, have been in use for more than five decades. PPAR-α is a transcription factor regulated by free fatty acids and is a major regulator of hepatic lipid and lipoprotein metabolism, including increased fatty acid oxidation, and reduced synthesis of fatty acids, apo C-III, TGs and VLDL, while LPL activity is enhanced [132]. In the pre-statin era, gemfibrozil therapy resulted in a reduction in the risk of major CVD events in men with CAD whose primary lipid abnormality was a low HDL-C level in the VA-HIT trial [133]. A post-hoc analysis of several fibrate trials suggested that fibrate treatment reduces CVD events among patients with dyslipidemia characterized by TG $>$ 200 mg/dL (2.3 mmol/L) and HDL-C $<$34 mg/dL (0.9 mmol/L) [134]. However, primary clinical outcome endpoints in the later outcome trials with fibrates, including fenofibrate monotherapy and statin-fenofibrate combination and more recently a novel, highly selective PPAR-α receptor modulator – pemafibrate, all failed to show a reduction in ASCVD events [135–137]. The Prominent trial with pemafibrate was initiated to finally evaluate the potential cardiovascular benefit of adding a fibrate to a statin in patients with T2DM and diabetic dyslipidaemia, who had high TGs and low HDL-C levels. The trial showed no clinical benefit of adding pemafibrate to a statin despite a significant decrease of TG and remnant cholesterol levels. LDL-C and Apo B levels increased slightly [138], which could in part explain the observed lack of efficacy of the drug [137]. This trial reinforces the concept that TG lowering per se is not associated with CV benefits [139], but that it is the decrease in the number of atherogenic apo B particles, which would be reflected by a decrease in apo B levels, that drives cardiovascular benefits associated to any lipid-lowering approach. Fibrates generally are not associated with a significant decrease in plasma apo B levels in patients with diabetes. However, fenofibrate, both as monotherapy and in combination with simvastatin, had a favorable impact on the progression of diabetic retinopathy independently of the presence of elevated TG levels (FIELD and ACCORD EYE) [140]. Therefore, fibrates could be used for the prevention of retinopathy, as well as for prevention of severe hypertriglyceridemia and pancreatitis in patients with moderate to severe hypertriglyceridemia (500–999 mg/dL) [141].

6.2. Omega-3 fatty acids

The major omega-3 fatty acids in fish oils are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). They lower TGs and VLDL at doses of 3–4 g/day; the effect on other lipoproteins is trivial. The type of omega-3 fatty acid and its dose may affect ASCVD events differentially. Treatment with 4 g/day of highly purified Icosapent Ethyl (IPE) in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) resulted in a 25% risk reduction of a clinically relevant combined endpoint (cardiovascular death, stroke, MI, coronary revascularization, and unstable angina) in a statin-treated population with well-controlled baseline LDL-C (73 mg/dl), mostly composed by patients with diabetes (58%) with established CVD (71 %) [142]. In REDUCE-IT, the use of mineral oil as placebo was associated with a moderate increase in LDL-C and hsCRP, raising some criticism of the real clinical benefits observed with IPE. Review of trials using mineral oil suggest that only 3–4% of the benefits on ASCVD seen in the group on IPE and statin could be accounted for by the negative effect of mineral oil in the placebo group [143]. Importantly, the ASCVD event reduction in REDUCE-IT was independent of baseline and the achieved TG concentrations, suggesting that any CV benefits of IPE supplementation are more likely due to concomitant effects on inflammation, platelet aggregation and plaque stabilization than to an effect on TGs [139], possibly due to a reduction in levels of proinflammatory eicosanoids and increased production of anti-inflammatory mediators [144]. Moreover, a 19% reduction of major coronary events was previously observed in the JELIS trial in a population of Japanese patients with a history of CAD treated with 1.8 g/day EPA [145]. Outcomes trials with mixed EPA/DHA preparations, including The Long-Term Outcomes Study to Assess STatin Residual Risk with EpaNova in HiGh Cardiovascular Risk PatienTs with Hypertriglyceridemia (STRENGTH), Omega-3 Fatty Acids in Elderly With Myocardial Infarction (OMEMI) and VITamin D and OmegA-3 TriaL (VITAL) have subsequently been shown to have no benefit on ASCVD events, although a low dose of omega-3 fatty acids (1 gr/day) was used in OMEMI. The lack of benefit in STRENGTH [146] with a DHA/EPA combination raises the question of whether DHA and EPA differ in their effects on ASCVD. The results of REDUCE-IT have been incorporated into recent guidelines and scientific statements [87] and, on the basis of current scientific evidence, IPE at 4 g/day should be added to a statin in high-risk patients with TG levels between 135 and 499 mg/dL.

Overall, from the multiple clinical outcome studies that have used fibrates or omega-3 fatty acids including IPE, the ASCVD benefit of specific TG lowering in patients with or without diabetes is non-existent.

6.3. Apo C-III and ANGPLT3 inhibitors

Another approach to lowering plasma TRL levels is to increase their catabolism. The activity of LPL and of other extracellular lipases is controlled by several proteins including apo C-III [147] and angiopoietin protein like 3 (ANGPTL3) [148]. Genetic studies in subjects with loss of function mutations in these two proteins showed a profile with low plasma TG levels setting the stage for investigating strategies targeting either apo C-III or ANGPTL3. Moreover, recent evidence highlights that there are catabolic processes promoting TRL clearance that are independent of LPL but are still controlled by apo C-III and ANGPTL3. These observations set the stage for testing apo C-III gene silencing (volanesorsen and olezarsen) or ANGPTL3 inhibition by monoclonal antibodies (evinacumab) as therapeutic approaches to lower TG levels [149,150].

6.3.1. Apo C-III gene inhibition

In humans, loss-of-function (LOF) mutations in apo C-III have been associated with low TG levels and reduced risk of ASCVD [147]. Subcutaneous administration of volanesorsen, a second-generation antisense oligonucleotide (ASO), inhibits apo C-III production. TGs were reduced by ~60% after 3 months of weekly administration of volanesorsen in phase III studies in patients with familial chylomicronemia syndrome (FCS) [151]. However, the drug increased the risk of thrombocytopenia. A GalNAc-conjugated ASO targeting apo C-III (AKCEA-APO–CIII–LRx) that reduces apo C-III by 85%, TGs by 65% and apo B levels without reducing platelet counts, appears to be safer than volanesorsen [152]. However, no data on clinical outcomes are currently available in patients with diabetes.

6.3.2. ANGPTL3 inhibition

Evinacumab, an antibody against ANGPTL3, reduced TGs in healthy volunteers, in homozygous familial hypercholesterolemic patients, in individuals with TGs $>$150 but $\leq$450 mg/dL, as well as in subjects with severe hypertriglyceridemia with up $>$70 % reduction of plasma TG

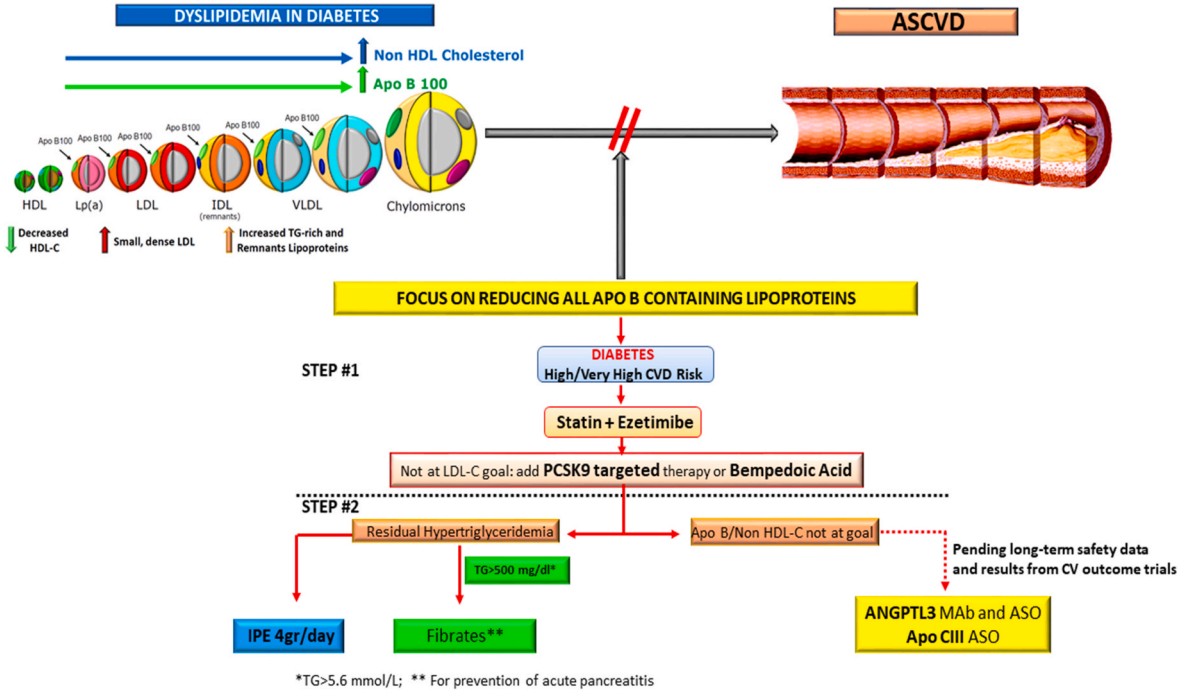

Fig. 2. Key points of the manuscript: Graphical summary.
Dyslipidemia in diabetes is characterized by increased levels of triglyceride-rich and remnant lipoproteins, the presence of small, dense LDL particles, and decreased levels of HDL-cholesterol. This dyslipidemia is a major cause of the increased ASCVD seen in diabetes.
Treatment of diabetic dyslipidemia should focus on reducing all apo B-containing lipoproteins. Patients living with diabetes are likely to be at very high CVD risk and often fail to achieve lipid and lipoprotein goals with statins monotherapy, a reasonable approach is to initiate therapy with a combination of a statin and ezetimibe. If LDL-C values are still above goal, a PCSK9 inhibitor or bempedoic acid can be added.
With residual hypertriglyceridemia, icosapent-ethyl can be added. Fibrates can be used to prevent acute pancreatitis in patients with severe hypertriglyceridemia. Inhibition of ANGPTL3 and apoCIII with monoclonal antibodies (MaAB) or antisense oligonucleotides (ASO) may have a role in treating diabetes dyslipidemia and reducing ASCVD in the future.

levels [153], but predictably not in subjects with absent LPL activity [154]. A GalNAc-modified ASO that targets ANGPTL3, given weekly for 6 weeks, reduced atherogenic lipoproteins in human volunteers with elevated TGs and is undergoing further clinical trials [155]. These novel ANGPTL3-targeting approaches may represent an effective future approach to reduce the burden of atherogenic apo B-containing lipoproteins in both LDL as well as TG-rich (VLDL and remnant) particles.

6.4. CETP inhibitors

Cholesteryl ester transfer protein (CETP) inhibitors interfere with the transfer of cholesteryl esters from HDL into TRLs. Large clinical trials testing their use have in general failed to reduce CVD events [156]. Studies with anacetrapib in combination with a statin showed a reduction in plasma apo B levels, apo B content of VLDL and LDL, a modest decrease in plasma TGs and decreased ASCVD events seen in the Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial [157], which may be explained by lowering of non-HDL cholesterol. More recently, similar results were obtained with obicetrapib, so far the most potent CETP inhibitor available [158]. Clinical trials to further assess the safety and clinical effect on ASCVD events of obicetrapib, specifically in patients with diabetes, are needed.

7. Conclusions

Dyslipidemia, characterized by hypertriglyceridemia, low levels of HDL-C, normal to slightly elevated levels of LDL-C and apo B levels, and the accumulation of small, dense LDL particles (associated with increased oxidative stress), is a major risk factor contributing to ASCVD in patients with T2DM. Most patients with diabetes are at high or very high CVD risk. International guidelines (ESC/EASD, ESC/EAS, AHA/ACC) support LDL-C as primary target for screening and lipid management with non-HDL-C and, more recently, apo B as co-primary targets in individuals with diabetes. Effective LDL-C management with at least a >50% reduction and a comprehensive reduction of all apo B-containing lipoproteins should represent the top priority to prevent ASCVD. While statins remain the mainstay treatment addressing apo B-containing lipoproteins, the concept of a new therapeutic strategy with upfront combination therapy of statin and ezetimibe, together with PCSK9 inhibitors when needed, is gaining traction in patients living with diabetes. Additional lipid management, when TG-rich apo B-containing lipoproteins levels remain moderately elevated after LDL-C is reduced to target levels, includes the use of highly purified EPA ethyl ester. Finally, newer treatments in development, particularly ASO and RNA-based therapies targeting apo C-III and ANGPTL3, may prove to have additional CVD benefits by further decreasing apo B-containing atherogenic lipoproteins (Fig. 2).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] E.W. Gregg, Y.J. Cheng, M. Srinivasan, et al., Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data, Lancet 391 (2018) 2430–2440.
[2] A. Rawshani, A. Rawshani, S. Franzen, et al., Mortality and cardiovascular disease in type 1 and type 2 diabetes, N. Engl. J. Med. 376 (2017) 1407–1418.

[3] C. Emerging Risk Factors, N. Sarwar, P. Gao, et al., Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies, Lancet 375 (2010) 2215–2222.
[4] P.Z. Zimmet, K.G. Alberti, The changing face of macrovascular disease in non-insulin-dependent diabetes mellitus: an epidemic in progress, Lancet 350 (Suppl 1) (1997) SI1–4.
[5] G.M. Singh, G. Danaei, F. Farzadfar, et al., The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis, PLoS One 8 (2013), e65174.
[6] R.H. Eckel, S.M. Grundy, P.Z. Zimmet, The metabolic syndrome, Lancet 365 (2005) 1415–1428.
[7] S.P. Laing, A.J. Swerdlow, S.D. Slater, et al., Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes, Diabetologia 46 (2003) 760–765.
[8] G.S. Berenson, Childhood risk factors predict adult risk associated with subclinical cardiovascular disease. The Bogalusa Heart Study, Am. J. Cardiol. 90 (2002) 3L–7L.
[9] K. Dahl-Jorgensen, J.R. Larsen, K.F. Hanssen, Atherosclerosis in childhood and adolescent type 1 diabetes: early disease, early treatment? Diabetologia 48 (2005) 1445–1453.
[10] D. Dabelea, G. Kinney, J.K. Snell-Bergeon, et al., Effect of type 1 diabetes on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study, Diabetes 52 (2003) 2833–2839.
[11] J. Larsen, M. Brekke, L. Sandvik, H. Arnesen, K.F. Hanssen, K. Dahl-Jorgensen, Silent coronary atheromatosis in type 1 diabetic patients and its relation to long-term glycemic control, Diabetes 51 (2002) 2637–2641.
[12] J.L. Harding, J.E. Shaw, A. Peeters, S. Davidson, D.J. Magliano, Age-specific trends from 2000-2011 in all-cause and cause-specific mortality in type 1 and type 2 diabetes: a cohort study of more than one million people, Diabetes Care 39 (2016) 1018–1026.
[13] S.N. Bhupathiraju, F.B. Hu, Epidemiology of obesity and diabetes and their cardiovascular complications, Circ. Res. 118 (2016) 1723–1735.
[14] T.R. Einarson, A. Acs, C. Ludwig, U.H. Panton, Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017, Cardiovasc. Diabetol. 17 (2018) 83.
[15] K. Yahagi, F.D. Kolodgie, C. Lutter, et al., Pathology of human coronary and carotid artery atherosclerosis and vascular calcification in diabetes mellitus, Arterioscler. Thromb. Vasc. Biol. 37 (2017) 191–204.
[16] J. Pang, D.C. Chan, P.H. Barrett, G.F. Watts, Postprandial dyslipidaemia and diabetes: mechanistic and therapeutic aspects, a 23 (2012) 303–309.
[17] P. Stahel, C. Xiao, A. Nahmias, G.F. Lewis, Role of the gut in diabetic dyslipidemia, Front. Endocrinol. 11 (2020) 116.
[18] K. Olin-Lewis, R.M. Krauss, M. La Belle, et al., ApoC-III content of apoB-containing lipoproteins is associated with binding to the vascular proteoglycan biglycan, J. Lipid Res. 43 (2002) 1969–1977.
[19] A. Chait, R.L. Brazg, D.L. Tribble, R.M. Krauss, Susceptibility of small, dense low density lipoproteins to oxidative modification in subjects with the atherogenic lipoprotein phenotype, pattern B, Am. J. Med. 94 (1993) 350–356.
[20] T. Chiba, M.Y. Chang, S. Wang, et al., Serum amyloid A facilitates the binding of high-density lipoprotein from mice injected with lipopolysaccharide to vascular proteoglycans, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 1326–1332.
[21] C.Y. Han, C. Tang, M.E. Guevara, et al., Serum amyloid A impairs the antiinflammatory properties of HDL, J. Clin. Invest. 126 (2016) 266–281.
[22] A. Kawakami, M. Aikawa, P. Libby, P. Alcaide, F.W. Luscinskas, F.M. Sacks, Apolipoprotein CIII in apolipoprotein B lipoproteins enhances the adhesion of human monocytic cells to endothelial cells, Circulation 113 (2006) 691–700.
[23] C. Li, M. Zhang, Y. Dai, Z. Xu, MicroRNA-424-5p regulates aortic smooth muscle cell function in atherosclerosis by blocking APOC3-mediated nuclear factor-kappaB signalling pathway, Exp. Physiol. 105 (2020) 1035–1049.
[24] C. Cholesterol Treatment Trialists, P.M. Kearney, L. Blackwell, et al., Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis, Lancet 371 (2008) 117–125.
[25] R.P. Giugliano, C.P. Cannon, M.A. Blazing, et al., Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (improved reduction of outcomes: vytorin efficacy international trial), Circulation 137 (2018) 1571–1582.
[26] M.S. Sabatine, L.A. Leiter, S.D. Wiviott, et al., Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial, Lancet Diabetes Endocrinol. 5 (2017) 941–950.
[27] B.H. Marouf, Z. Iqbal, J.B. Mohamad, et al., Efficacy and safety of PCSK9 monoclonal antibodies in patients with diabetes, Clin. Therapeut. 44 (2022) 331–348.
[28] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group, Lancet 352 (1998) 837–853.
[29] R.R. Holman, S.K. Paul, M.A. Bethel, D.R. Matthews, H.A. Neil, 10-Year follow-up of intensive glucose control in type 2 diabetes, N. Engl. J. Med. 359 (15) (2008) 1577–1589.
[30] D.M. Nathan, P.A. Cleary, J.Y. Backlund, et al., Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes, N. Engl. J. Med. 353 (2005) 2643–2653.
[31] M. Lorenzi, E. Cagliero, S. Toledo, Glucose toxicity for human endothelial cells in culture. Delayed replication, disturbed cell cycle, and accelerated death, Diabetes 34 (1985) 621–627.
[32] U. Chakravarthy, R.G. Hayes, A.W. Stitt, E. McAuley, D.B. Archer, Constitutive nitric oxide synthase expression in retinal vascular endothelial cells is suppressed by high glucose and advanced glycation end products, Diabetes 47 (1998) 945–952.
[33] A. Hempel, C. Maasch, U. Heintze, et al., High glucose concentrations increase endothelial cell permeability via activation of protein kinase C alpha, Circ. Res. 81 (1997) 363–371.
[34] M. Richardson, S.J. Hadcock, M. DeReske, M.I. Cybulsky, Increased expression in vivo of VCAM-1 and E-selectin by the aortic endothelium of normolipemic and hyperlipemic diabetic rabbits, Arterioscler. Thromb. 14 (1994) 760–769.
[35] A.M. Schmidt, D. Stern, Atherosclerosis and diabetes: the RAGE connection, Curr. Atherosclerosis Rep. 2 (2000) 430–436.
[36] S. Park, S.J. Yoon, H.J. Tae, C.Y. Shim, RAGE and cardiovascular disease, Front. Biosci. 16 (2011) 486–497.
[37] E. Gallego-Colon, W. Wojakowski, T. Francuz, Incretin drugs as modulators of atherosclerosis, Atherosclerosis 278 (2018) 29–38.
[38] A. Pahud de Mortanges, D. Salvador Jr., M. Laimer, T. Muka, M. Wilhelm, A. Bano, The role of SGLT2 inhibitors in atherosclerosis: a narrative mini-review, Front. Pharmacol. 12 (2021), 751214.
[39] J.W. Baynes, Role of oxidative stress in development of complications in diabetes, Diabetes 40 (1991) 405–412.
[40] U. Forstermann, N. Xia, H. Li, Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis, Circ. Res. 120 (2017) 713–735.
[41] M.J. Morgan, Z.G. Liu, Crosstalk of reactive oxygen species and NF-kappaB signaling, Cell Res. 21 (2011) 103–115.
[42] C. Khatana, N.K. Saini, S. Chakrabarti, et al., Mechanistic insights into the oxidized low-density lipoprotein-induced atherosclerosis, Oxid. Med. Cell. Longev. 2020 (2020), 5245308.
[43] M.Y. Chang, S. Potter-Perigo, T.N. Wight, A. Chait, Oxidized LDL bind to nonproteoglycan components of smooth muscle cell extracellular matrices, J. Lipid Res. 42 (2001) 824–833.
[44] J.L. Witztum, D. Steinberg, Role of oxidized low density lipoprotein in atherogenesis, J. Clin. Invest. 88 (1991) 1785–1792.
[45] A. Chait, J.W. Heinecke, Lipoprotein modification: cellular mechanisms, Curr. Opin. Lipidol. 5 (1994) 365–370.
[46] G. Renie, F. Maingrette, L. Li, Diabetic vasculopathy and the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), Curr. Diabetes Rev. 3 (2007) 103–110.
[47] M.O.J. Grootaert, M. Moulis, L. Roth, et al., Vascular smooth muscle cell death, autophagy and senescence in atherosclerosis, Cardiovasc. Res. 114 (2018) 622–634.
[48] G. Obermayer, T. Afonyushkin, C.J. Binder, Oxidized low-density lipoprotein in inflammation-driven thrombosis, J. Thromb. Haemostasis 16 (2018) 418–428.
[49] L. Cominacini, U. Garbin, A.M. Pastorino, et al., Increased susceptibility of LDL to in vitro oxidation in patients with insulin-dependent and non-insulin-dependent diabetes mellitus, Diabetes Res. 26 (1994) 173–184.
[50] F. Galland, L. Duvillard, J.M. Petit, et al., Effect of insulin treatment on plasma oxidized LDL/LDL-cholesterol ratio in type 2 diabetic patients, Diabetes Metab. 32 (2006) 625–631.
[51] C.P. Sparrow, T.W. Doebber, J. Olszewski, et al., Low density lipoprotein is protected from oxidation and the progression of atherosclerosis is slowed in cholesterol-fed rabbits by the antioxidant N,N'-diphenyl-phenylenediamine, J. Clin. Invest. 89 (1992) 1885–1891.
[52] R.S. Crawford, E. Kirk, M.E. Rosenfeld, R.C. LeBoeuf, A. Chait, Dietary antioxidants inhibit the development of fatty streak lesions in the LDL-receptor deficient mouse, Arterioscler. Thromb. Vasc. Biol. 18 (1998) 1506–1513.
[53] B.G. Brown, X.Q. Zhao, A. Chait, et al., Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease, N. Engl. J. Med. 345 (2001) 1583–1592.
[54] B.G. Brown, M.C. Cheung, A.C. Lee, X.Q. Zhao, A. Chait, Antioxidant vitamins and lipid therapy: end of a long romance? Arterioscler. Thromb. Vasc. Biol. 22 (2002) 1535–1546.
[55] R. Ross, Atherosclerosis–an inflammatory disease, N. Engl. J. Med. 340 (1999) 115–126.
[56] P.M. Ridker, B.M. Everett, T. Thuren, et al., Antiinflammatory therapy with Canakinumab for atherosclerotic disease, N. Engl. J. Med. 377 (2017) 1119–1131.
[57] P. Reddy, D. Lent-Schochet, N. Ramakrishnan, M. McLaughlin, I. Jialal, Metabolic syndrome is an inflammatory disorder: a conspiracy between adipose tissue and phagocytes, Clin. Chim. Acta 496 (2019) 35–44.
[58] J.C. Pickup, M.A. Crook, Is type II diabetes mellitus a disease of the innate immune system? Diabetologia 41 (1998) 1241–1248.
[59] T.M. Powell-Wiley, P. Poirier, L.E. Burke, et al., Obesity and cardiovascular disease: a scientific statement from the American heart association, Circulation 143 (2021) e984–e1010.
[60] B.M. Everett, M.Y. Donath, A.D. Pradhan, et al., Anti-inflammatory therapy with Canakinumab for the prevention and management of diabetes, J. Am. Coll. Cardiol. 71 (2018) 2392–2401.
[61] J.C. Tardif, S. Kouz, D.D. Waters, et al., Efficacy and safety of low-dose colchicine after myocardial infarction, N. Engl. J. Med. 381 (2019) 2497–2505.
[62] P. Libby, Inflammation in atherosclerosis, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 2045–2051.

[63] R. Kaur, M. Kaur, J. Singh, Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: molecular insights and therapeutic strategies, Cardiovasc. Diabetol. 17 (2018) 121.
[64] Y. Aso, Cardiovascular disease in patients with diabetic nephropathy, Curr. Mol. Med. 8 (2008) 533–543.
[65] J. Barrot, J. Real, B. Vlacho, et al., Diabetic retinopathy as a predictor of cardiovascular morbidity and mortality in subjects with type 2 diabetes, Front. Med. 9 (2022), 945245.
[66] W.K. Leung, L. Gao, P.M. Siu, C.W. Lai, Diabetic nephropathy and endothelial dysfunction: current and future therapies, and emerging of vascular imaging for preclinical renal-kinetic study, Life Sci. 166 (2016) 121–130.
[67] H.C. Gerstein, J.F. Mann, Q. Yi, et al., Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals, JAMA 286 (2001) 421–426.
[68] R.E. Maser, B.D. Mitchell, A.I. Vinik, R. Freeman, The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis, Diabetes Care 26 (2003) 1895–1901.
[69] A.S. Pena, G. Liew, J. Anderson, et al., Early atherosclerosis is associated with retinal microvascular changes in adolescents with type 1 diabetes, Pediatr. Diabetes 19 (2018) 1467–1470.
[70] E.M. Urbina, S. Isom, R.A. Bell, et al., Burden of cardiovascular risk factors over time and arterial stiffness in youth with type 1 diabetes mellitus: the SEARCH for diabetes in youth study, J. Am. Heart Assoc. 8 (2019), e010150.
[71] R. Retnakaran, B. Zinman, Type 1 diabetes, hyperglycaemia, and the heart, Lancet 371 (2008) 1790–1799.
[72] V. Matuleviciene-Anangen, A. Rosengren, A.M. Svensson, et al., Glycaemic control and excess risk of major coronary events in persons with type 1 diabetes, Heart 103 (2017) 1687–1695.
[73] D.E.R.G. Writing Group for the, T.J. Orchard, D.M. Nathan, et al., Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality, JAMA 313 (2015) 45–53.
[74] C. Diabetes, Complications trial/epidemiology of diabetes I, complications research G. Risk factors for cardiovascular disease in type 1 diabetes, Diabetes 65 (2016) 1370–1379.
[75] J.S. Yun, S.H. Ko, Current trends in epidemiology of cardiovascular disease and cardiovascular risk management in type 2 diabetes, Metabolism 123 (2021), 154838.
[76] M. Gimenez, R. Gilabert, J. Monteagudo, et al., Repeated episodes of hypoglycemia as a potential aggravating factor for preclinical atherosclerosis in subjects with type 1 diabetes, Diabetes Care 34 (2011) 198–203.
[77] K. Esposito, F. Nappo, R. Marfella, et al., Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress, Circulation 106 (2002) 2067–2072.
[78] P.M. Kearney, L. Blackwell, R. Collins, et al., Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis, Lancet 371 (2008) 117–125.
[79] R.H. Eckel, J.J. Albers, M.C. Cheung, P.W. Wahl, F.T. Lindgren, E.L. Bierman, High density lipoprotein composition in insulin-dependent diabetes mellitus, Diabetes 30 (1981) 132–138.
[80] E. Gourgari, M.P. Playford, U. Campia, et al., Low cholesterol efflux capacity and abnormal lipoprotein particles in youth with type 1 diabetes: a case control study, Cardiovasc. Diabetol. 17 (2018) 158.
[81] B. Verges, Dyslipidemia in type 1 diabetes: AMaskedDanger, Trends Endocrinol. Metabol. 31 (2020) 422–434.
[82] S. Manjunatha, K. Distelmaier, S. Dasari, R.E. Carter, Y.C. Kudva, K.S. Nair, Functional and proteomic alterations of plasma high density lipoproteins in type 1 diabetes mellitus, Metabolism 65 (2016) 1421–1431.
[83] J.Q. Purnell, J.E. Hokanson, S.M. Marcovina, M.W. Steffes, P.A. Cleary, J. D. Brunzell, Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. Diabetes Control and Complications Trial, JAMA 280 (1998) 140–146.
[84] J.Q. Purnell, B. Zinman, J.D. Brunzell, D.E.R. Group, The effect of excess weight gain with intensive diabetes mellitus treatment on cardiovascular disease risk factors and atherosclerosis in type 1 diabetes mellitus: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) study, Circulation 127 (2013) 180–187.
[85] T.J. Orchard, T. Costacou, Cardiovascular complications of type 1 diabetes: update on the renal link, Acta Diabetol. 54 (2017) 325–334.
[86] F. Cosentino, P.J. Grant, V. Aboyans, et al., ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD, Eur. Heart J. 41 (2019) 255–323, 2020.
[87] F. Mach, C. Baigent, A.L. Catapano, et al., ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk, Eur. Heart J. 41 (2019) 111–188, 2020.
[88] S.M. Grundy, N.J. Stone, A.L. Bailey, et al., AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines, J. Am. Coll. Cardiol. 73 (2018) e285–e350, 2019.
[89] R.B. Goldberg, N.J. Stone, S.M. Grundy, The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guidelines on the management of blood cholesterol in diabetes, Diabetes Care 43 (2020) 1673–1678.
[90] E. Obarzanek, F.M. Sacks, W.M. Vollmer, et al., Effects on blood lipids of a blood pressure-lowering diet: the dietary approaches to Stop hypertension (DASH) trial, Am. J. Clin. Nutr. 74 (2001) 80–89.
[91] A. Hernaez, O. Castaner, A. Goday, et al., The Mediterranean Diet decreases LDL atherogenicity in high cardiovascular risk individuals: a randomized controlled trial, Mol. Nutr. Food Res. 61 (2017).
[92] A.R.G. Look, Effects of intensive lifestyle intervention on all-cause mortality in older adults with type 2 diabetes and overweight/obesity: results from the look AHEAD study, Diabetes Care 45 (2022) 1252–1259.
[93] D.M. Lloyd-Jones, N.B. Allen, C.A.M. Anderson, et al., Life's essential 8: updating and enhancing the American heart association's construct of cardiovascular health: a presidential advisory from the American heart association, Circulation 146 (2022) e18–e43.
[94] D.C. Goff Jr., D.M. Lloyd-Jones, G. Bennett, et al., ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American heart association task force on practice guidelines, J. Am. Coll. Cardiol. 63 (2013) 2935–2959, 2014.
[95] M.T. Cooney, A. Dudina, P. Whincup, et al., Re-evaluating the Rose approach: comparative benefits of the population and high-risk preventive strategies, Eur. J. Cardiovasc. Prev. Rehabil. 16 (2009) 541–549.
[96] A.P. Kappetein, S.J. Head, M.C. Morice, et al., Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial, Eur. J. Cardio. Thorac. Surg. 43 (2013) 1006–1013.
[97] A. Pirillo, M. Casula, E. Olmastroni, G.D. Norata, A.L. Catapano, Global epidemiology of dyslipidaemias, Nat. Rev. Cardiol. 18 (2021) 689–700.
[98] H.M. Colhoun, D.J. Betteridge, P.N. Durrington, et al., Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial, Lancet 364 (2004) 685–696.
[99] G. Heart Protection Study Collaborative, MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial, Lancet 360 (2002) 7–22.
[100] F.M. de Vries, J. Kolthof, M.J. Postma, P. Denig, E. Hak, Efficacy of standard and intensive statin treatment for the secondary prevention of cardiovascular and cerebrovascular events in diabetes patients: a meta-analysis, PLoS One 9 (2014), e111247.
[101] N. Sattar, Statins and diabetes: what are the connections? Best Pract. Res. Clin. Endocrinol. Metabol. 37 (2023), 101749.
[102] K. Yunoki, K. Nakamura, T. Miyoshi, et al., Ezetimibe improves postprandial hyperlipemia and its induced endothelial dysfunction, Atherosclerosis 217 (2011) 486–491.
[103] I. Semova, A.E. Levenson, J. Krawczyk, et al., Type 1 diabetes is associated with an increase in cholesterol absorption markers but a decrease in cholesterol synthesis markers in a young adult population, J Clin Lipidol 13 (2019) 940–946.
[104] K.K. Ray, B. Molemans, W.M. Schoonen, et al., EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study, Eur J Prev Cardiol 28 (2021) 1279–1289.
[105] K.K. Ray, I. Haq, A. Bilitou, et al., Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in Europe between 2020 and 2021: the multinational observational SANTORINI study, Lancet Reg Health Eur 29 (2023), 100624.
[106] M.L. Morieri, E. Longato, B. Di Camillo, G. Sparacino, A. Avogaro, G.P. Fadini, Management of type 2 diabetes with a treat-to-benefit approach improved long-term cardiovascular outcomes under routine care, Cardiovasc. Diabetol. 21 (2022) 274.
[107] M. Banach, P.E. Penson, M. Vrablik, et al., Optimal use of lipid-lowering therapy after acute coronary syndromes: a Position Paper endorsed by the International Lipid Expert Panel (ILEP), Pharmacol. Res. 166 (2021), 105499.
[108] M. Averna, M. Banach, E. Bruckert, et al., Practical guidance for combination lipid-modifying therapy in high- and very-high-risk patients: a statement from a European Atherosclerosis Society Task Force, Atherosclerosis 325 (2021) 99–109.
[109] R.H. Chapman, J.S. Benner, A.A. Petrilla, et al., Predictors of adherence with antihypertensive and lipid-lowering therapy, Arch. Intern. Med. 165 (2005) 1147–1152.
[110] D. Morrone, W.S. Weintraub, P.P. Toth, et al., Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials, Atherosclerosis 223 (2012) 251–261.
[111] Y.J. Lee, J.Y. Cho, S.C. You, et al., Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial, Eur. Heart J. 44 (2023) 972–983.
[112] B.K. Kim, S.J. Hong, Y.J. Lee, et al., Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial, Lancet 400 (2022) 380–390.
[113] S.J. Lee, J.H. Joo, S. Park, et al., Combination lipid-lowering therapy in patients undergoing percutaneous coronary intervention, J. Am. Coll. Cardiol. 82 (2023) 401–410.
[114] The lipid research clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease, JAMA 251 (1984) 351–364.
[115] V.A. Fonseca, Y. Handelsman, B. Staels, Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence, Diabetes Obes. Metabol. 12 (2010) 384–392.
[116] E.A. Stein, R.P. Giugliano, M.J. Koren, et al., Efficacy and safety of evolocumab (AMG 145), a fully human monoclonal antibody to PCSK9, in hyperlipidaemic patients on various background lipid therapies: pooled analysis of 1359 patients in four phase 2 trials, Eur. Heart J. 35 (2014) 2249–2259.

[117] P.P. Toth, S.R. Jones, M.L. Monsalvo, M. Elliott-Davey, J.A.G. Lopez, M. Banach, Effect of evolocumab on non-high-density lipoprotein cholesterol, apolipoprotein B, and lipoprotein(a): a pooled analysis of phase 2 and phase 3 studies, J. Am. Heart Assoc. 9 (2020), e014129.
[118] M.S. Sabatine, R.P. Giugliano, A.C. Keech, et al., Evolocumab and clinical outcomes in patients with cardiovascular disease, N. Engl. J. Med. 376 (2017) 1713–1722.
[119] G.G. Schwartz, P.G. Steg, M. Szarek, et al., Alirocumab and cardiovascular outcomes after acute coronary syndrome, N. Engl. J. Med. 379 (2018) 2097–2107.
[120] P. Deedwania, S.A. Murphy, A. Scheen, et al., Efficacy and safety of PCSK9 inhibition with evolocumab in reducing cardiovascular events in patients with metabolic syndrome receiving statin therapy: secondary analysis from the FOURIER randomized clinical trial, JAMA Cardiol 6 (2021) 139–147.
[121] K.C. Maki, M.R. Dicklin, S.J. Baum, Statins and diabetes, Endocrinol Metab. Clin. N. Am. 45 (2016) 87–100.
[122] T. Nishikido, K.K. Ray, Inclisiran for the treatment of dyslipidemia, Expet Opin. Invest. Drugs 27 (2018) 287–294.
[123] K.K. Ray, R.S. Wright, D. Kallend, et al., Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol, N. Engl. J. Med. 382 (2020) 1507–1519.
[124] S.L. Pinkosky, S. Filippov, R.A. Srivastava, et al., AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism, J. Lipid Res. 54 (2013) 134–151.
[125] M. Ruscica, C.R. Sirtori, S. Carugo, M. Banach, A. Corsini, Bempedoic acid: for whom and when, Curr. Atherosclerosis Rep. 24 (2022) 791–801.
[126] S.E. Nissen, A.M. Lincoff, D. Brennan, et al., Bempedoic acid and cardiovascular outcomes in statin-intolerant patients, N. Engl. J. Med. 388 (2023) 1353–1364.
[127] M.J. Gutierrez, N.L. Rosenberg, D.E. Macdougall, et al., Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus, Arterioscler. Thromb. Vasc. Biol. 34 (2014) 676–683.
[128] H.N. Ginsberg, C.J. Packard, M.J. Chapman, et al., Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society, Eur. Heart J. 359 (15) (2021) 1577–1589.
[129] C.J. Packard, Remnants, LDL, and the quantification of lipoprotein-associated risk in atherosclerotic cardiovascular disease, Curr. Atherosclerosis Rep. 24 (2022) 133–142.
[130] U. Laufs, K.G. Parhofer, H.N. Ginsberg, R.A. Hegele, Clinical review on triglycerides, Eur. Heart J. 41 (2020) 99–109c.
[131] S. Tani, T. Yagi, W. Atsumi, K. Kawauchi, R. Matsuo, A. Hirayama, Relation between low-density lipoprotein cholesterol/apolipoprotein B ratio and triglyceride-rich lipoproteins in patients with coronary artery disease and type 2 diabetes mellitus: a cross-sectional study, Cardiovasc. Diabetol. 16 (2017) 123.
[132] B. Staels, J. Dallongeville, J. Auwerx, K. Schoonjans, E. Leitersdorf, J.C. Fruchart, Mechanism of action of fibrates on lipid and lipoprotein metabolism, Circulation 98 (1998) 2088–2093.
[133] H.B. Rubins, S.J. Robins, D. Collins, et al., Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group, N. Engl. J. Med. 341 (1999) 410–418.
[134] F.M. Sacks, V.J. Carey, J.C. Fruchart, Combination lipid therapy in type 2 diabetes, N. Engl. J. Med. 363 (2010) 692–694, author reply 4-5.
[135] A. Keech, R.J. Simes, P. Barter, et al., Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial, Lancet 366 (2005) 1849–1861.
[136] A.S. Group, H.N. Ginsberg, M.B. Elam, et al., Effects of combination lipid therapy in type 2 diabetes mellitus, N. Engl. J. Med. 362 (2010) 1563–1574.
[137] A. Das Pradhan, R.J. Glynn, J.C. Fruchart, et al., Triglyceride lowering with pemafibrate to reduce cardiovascular risk, N. Engl. J. Med. 387 (2022) 1923–1934.
[138] B.A. Ference, J.J.P. Kastelein, K.K. Ray, et al., Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease, JAMA 321 (2019) 364–373.
[139] R.P. Mason, R.H. Eckel, Mechanistic insights from REDUCE-IT STRENGTHen the case against triglyceride lowering as a strategy for cardiovascular disease risk reduction, Am. J. Med. 134 (2021) 1085–1090.
[140] E.Y. Chew, W.T. Ambrosius, M.D. Davis, et al., Effects of medical therapies on retinopathy progression in type 2 diabetes, N. Engl. J. Med. 363 (2010) 233–244.
[141] A. Chait, R.H. Eckel, The chylomicronemia syndrome is most often multifactorial: a narrative review of causes and treatment, Ann. Intern. Med. 170 (2019) 626–634.
[142] D.L. Bhatt, P.G. Steg, M. Miller, et al., Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia, N. Engl. J. Med. 359 (15) (2018) 1577–1589.
[143] B. Olshansky, M.K. Chung, M.J. Budoff, et al., Mineral oil: safety and use as placebo in REDUCE-IT and other clinical studies, Eur. Heart J. Suppl. 22 (2020) J34–J48.
[144] J.J.P. Kastelein, E.S.G. Stroes, FISHing for the miracle of eicosapentaenoic acid, N. Engl. J. Med. 380 (2019) 89–90.
[145] M. Yokoyama, H. Origasa, M. Matsuzaki, et al., Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis, Lancet 369 (2007) 1090–1098.
[146] S.J. Nicholls, A.M. Lincoff, M. Garcia, et al., Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial, JAMA 324 (2020) 2268–2280.
[147] Tg, Hdl Working Group of the Exome Sequencing Project NHL, I. Blood, et al., Loss-of-function mutations in APOC3, triglycerides, and coronary disease, N. Engl. J. Med. 371 (2014) 22–31.
[148] M. Arca, L. D'Erasmo, I. Minicocci, Familial combined hypolipidemia: angiopoietin-like protein-3 deficiency, Curr. Opin. Lipidol. 31 (2020) 41–48.
[149] A. Zambon, M. Averna, L. D'Erasmo, M. Arca, A. Catapano, New and emerging therapies for dyslipidemia, Endocrinol Metab. Clin. N. Am. 51 (2022) 635–653.
[150] H.N. Ginsberg, I.J. Goldberg, Broadening the scope of dyslipidemia therapy by targeting APOC3 (apolipoprotein C3) and ANGPTL3 (Angiopoietin-Like protein 3), Arterioscler. Thromb. Vasc. Biol. 43 (2023) 388–398.
[151] J.L. Witztum, D. Gaudet, S.D. Freedman, et al., Volanesorsen and triglyceride levels in familial chylomicronemia syndrome, N. Engl. J. Med. 381 (2019) 531–542.
[152] V.J. Alexander, S. Xia, E. Hurh, et al., N-acetyl galactosamine-conjugated antisense drug to APOC3 mRNA, triglycerides and atherogenic lipoprotein levels, Eur. Heart J. 40 (2019) 2785–2796.
[153] Z. Ahmad, P. Banerjee, S. Hamon, et al., Inhibition of angiopoietin-like protein 3 with a monoclonal antibody reduces triglycerides in hypertriglyceridemia, Circulation 140 (2019) 470–486.
[154] Z. Ahmad, R. Pordy, D.J. Rader, et al., Inhibition of angiopoietin-like protein 3 with evinacumab in subjects with high and severe hypertriglyceridemia, J. Am. Coll. Cardiol. 78 (2021) 193–195.
[155] M.J. Graham, R.G. Lee, T.A. Brandt, et al., Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides, N. Engl. J. Med. 377 (2017) 222–232.
[156] S.J. Nicholls, A.J. Nelson, CETP inhibitors: should we continue to pursue this pathway? Curr. Atherosclerosis Rep. 24 (2022) 915–923.
[157] H.T.R.C. Group, L. Bowman, J.C. Hopewell, et al., Effects of anacetrapib in patients with atherosclerotic vascular disease, N. Engl. J. Med. 377 (2017) 1217–1227.
[158] S.J. Nicholls, M. Ditmarsch, J.J. Kastelein, et al., Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial, Nat. Med. 28 (2022) 1672–1678.