ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2025) **00**, 1–14
https://doi.org/10.1093/ehjcvp/pvaf076

REVIEW

Management of dyslipidaemia in patients with comorbidities: facing the challenge: type 2 diabetes mellitus

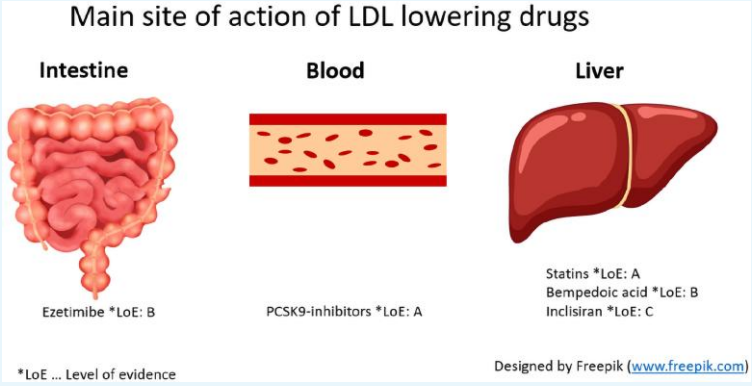
Heinz Drexel [1,2,3,4,*], Andreas Festa[1], Thomas A. Schmidt[5,6], Bianca Rocca [7], Dobromir Dobrev [8,9,10], Stefan Agewall[11], Juan Tamargo[12], and Susanne Kaser[13]

[1]Academic Teaching Hospital Feldkirch, Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Carinagasse 47, Feldkirch 6800, Austria; [2]Medical Faculty, Private University in the Principality of Liechtenstein, Dorfstrasse 24, Triesen 9495, Liechtenstein; [3]Vorarlberger Landeskrankenhausbetriebsgesellschaft, Carinagasse 47, Feldkirch 6800, Austria; [4]Drexel University College of Medicine, 2900 Queen Lane, Philadelphia PA 19129, USA; [5]Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark; [6]Department of Emergency Medicine, Holbaek Hospital, University of Copenhagen, 2200 Copenhagen, Denmark; [7]Department of Medicine, LUM University, Casamassima (BA) 70010 Italy; [8]Institute of Pharmacology, West-German Heart and Vascular Centre, University Duisburg-Essen, DE 45122 Essen, Germany; [9]Department of Medicine, Montreal Heart Institute and Université de Montréal Montréal, Canada H1Y 3N1; [10]Department of Integrative Physiology, Baylor College of Medicine, Houston, TX 77030, USA; [11]Institute of Clinical Sciences, Karolinska Institute, Danderyd Hospital, Stockholm 171 77, Sweden; [12]Department of Pharmacology and Toxicology, School of Medicine, Universidad Complutense, Instituto De Investigación Sanitaria Gregorio Marañón, Madrid 28040, Spain; and [13]Department of Internal Medicine I, Medical University of Innsbruck, Anichstrasse 35, Innsbruck 6020, Austria

Received 1 August 2025; revised 25 September 2025; accepted 29 September 2025; online publish-ahead-of-print 27 October 2025

Type 2 diabetes mellitus typically has the lipid features of elevated trigycerides, reduced HDL-cholesterol (both parts of the metabolic syndrome) and average or slightly elevated LDL-cholesterol. In consequence of hypertriglyceridemia, LDL particles are small and dense and therefore highly atherogenic. Outcome studies reveal that LDL-C lowering drugs have an above-average efficacy in type 2 diabetes as compared with non-diabetic patients. A minor increase of glycaemia in statin trials does not impair the beneficial cardiovascular results. Non-statin lipid lowering drugs do not impair glycaemia. Type 2 diabetes mellitus is now considered a major indication for lipid lowering drugs, thus there is a high value of and no major limitation for those compounds.

Graphical abstract



Central illustration: the central illustration depicts the major site of action as well as the level of evidence for cardiovascular risk reduction.

Keywords Type 2 diabetes mellitus • Dyslipidaemia • Lipid-lowering drugs • Comorbidities

*Corresponding author. Tel: +43 5522 303 6900, Fax: +43 5522 303 7533, Email: heinz.drexel@vivit.at

Preface and background

The aspect of comorbidities and the value and limitations of lipid lowering drugs have been previously reported from three review articles in this journal[1-3] and we now focus on type 2 diabetes mellitus (T2DM).

Pathophysiologically, T2DM has two characteristic features: insulin resistance mainly due to obesity, and deficient insulin secretion due to impaired pancreatic beta cell function. The former reduces the activity of lipoprotein lipase leading among other effects to impaired clearance of triglycerides (TGs) from the blood. The latter primarily reduces the first spike of the post-prandial insulin response by the beta cells and prolongs the duration of post-prandial hyperinsulinemia.

Epidemiology of cardiovascular disease in type 2 diabetes

Due to the obesity epidemic and other factors the prevalence of T2DM is steadily increasing. It is estimated that currently 589 million people are affected globally, that is 1 in 9 of the adult population.[4]

T2DM increases the likelihood of atherosclerotic cardiovascular disease (ASCVD) two- to three-fold. In fully adjusted models, individuals with diabetes using insulin exhibited a five-fold higher risk among women (RR: 5.44; 95% CI: 4.90–6.05) and a three-fold higher risk among men (RR: 3.13; 95% CI: 2.84–3.45) for incident ASCVD events compared with those without diabetes[5] Life expectancy of individuals with T2DM is reduced by 6 years when compared with non-diabetic controls and by 12 years, if T2DM and ASCVD coexist.[6] T2DM increases the risk for progression of ASCVD by a comparable amount irrespective of the pre-existing degree of atherosclerosis.[7] The duration of diabetes and/or glycaemic control have not been tested as modifiers of lipid lowering efficacy, e.g. in the 'Improved Reduction of Outcomes: Vytorin Efficacy International Trial' IMPROVE-IT.[8]

Pathophysiology of cardiovascular disease in T2DM

The pathophysiology of ASCVD in T2DM is multi-factorial, including obesity, hyperglycaemia, insulin resistance, elevated blood pressure, low-grade/chronic inflammation, and diabetic dyslipidaemia.[9] Overnutrition and obesity are the most common causes of insulin resistance and are often associated with low-grade inflammation.[10]

Lipoprotein metabolism in type 2 diabetes

Excess release of free fatty acids from the adipose tissue promotes ectopic lipid accumulation especially in the liver, but also in the heart and the skeletal muscle, in states of overnutrition and obesity, which then induce tissue-specific insulin resistance. As a consequence of hepatic insulin resistance, *de novo* lipogenesis and gluconeogenesis are activated, fatty acid metabolism is impaired and VLDL secretion increased.[11,12]

In terms of lipoproteins, the TG-rich lipoproteins are elevated and therefore the plasma level of TG is elevated to various degrees, typically between 150 and 300 mg/dL (1.69 and 3.39 mmol/L). As typical for hypertriglyceridemic states, HDL-cholesterol is reduced both in men and in women with T2DM. The total level of LDL-cholesterol is average or slightly elevated. However, evidence from genetic, observational, and interventional studies has firmly established a dose-dependent relationship between low-density lipoprotein cholesterol (LDL-C) and the development of ASCVD. In essence, higher levels of LDL-C are directly associated with an increased risk of ASCVD.[13,14]

Fundamental changes are observed in the composition of lipoproteins due to the action of the cholesterol ester transfer protein (CETP). Increased activation of CETP[15] causes TG enrichment of LDL and HDL particles and cholesteryl ester enrichment of TG-rich lipoproteins, resulting in small dense (sd) LDL particles and a shift from larger HDL2 towards smaller HDL3 particles. sdLDL particles are more prone to oxidation and enter the sub-endothelial space more easily and rapidly, and thus are considered highly atherogenic.[16] LDL enriched in TG ultimately become a target for lipoprotein and hepatic lipase. Small dense LDL have been shown to be more atherogenic than typical LDL.[17]

Besides elevated TG and preponderance of sdLDL particles, diabetic dyslipidaemia is also characterized by low HDL-C and apolipoprotein AI levels, reduced size and dysfunctional HDL particles.[18-20] The latter is related to the formation of advanced glycation end products (AGEs), which activate a molecular cascade inducing the expression of caveolin-1, the key protein in LDL internalization.[21] As a consequence, cholesterol efflux capacity and antioxidant capacity of HDL particles are impaired, thereby further increasing vascular vulnerability.[22-26] Together this dysfunctional lipid pattern commonly is termed 'diabetic dyslipidaemia'.

Other pathophysiological aspects

T2DM is recognized not only as a metabolic disorder but also as a chronic low-grade inflammatory condition, which plays a key role in the pathogenesis of insulin resistance and β-cell dysfunction, while diabetes can, in turn, exacerbate inflammation. Pro-inflammatory cytokines, which are usually elevated as a consequence of macrophage infiltration in the adipose tissue in metabolically unhealthy obese patients, deteriorate tissue-specific insulin signalling, especially in the heart. This further diminishes whole body insulin sensitivity.[27,28] Additionally, elevated neutrophil extracellular trap activation might also contribute to atherogenesis in patients with T2DM, thus linking inflammation with cardiovascular disease.[29]

Insulin resistance is also associated with reduced endothelial nitric oxide (NO) synthase and NO production and increased expression of adhesion molecules on endothelial cells inducing endothelial dysfunction and enhanced vascular permeability for inflammatory cells.[30] Elevated inflammatory markers in T2DM include C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1), increased white blood cell counts and other innate immune cell activity and adipose tissue macrophage infiltration and secretion of pro-inflammatory cytokines. Obesity, especially visceral fat, leads to immune cell recruitment (e.g. M1 macrophages).[31]

Despite advancements in controlling traditional risk factors like dyslipidaemia and hypertension, a considerable residual cardiovascular risk persists, highlighting the need for innovative therapeutic approaches. Advances in multi-omics and systems biology are deepening our understanding of the molecular drivers of atherosclerosis.[32] In epidemiological terms however, clinical trials targeting inflammation in T2D never showed any benefit. Moreover, whether the side effect profile of lipid lowering drugs changes in light of the underlying low-grade inflammation in T2D is not known.

The role of hyperglycaemia in atherogenesis is less clear. AGE as a consequence of chronic hyperglycaemia enhances adhesion molecule expression and activation of endothelial cells thus promoting the initial steps of atherogenesis. Additionally, AGE not only modify HDL particles leading to reduced cholesterol efflux capacity but also further

augment atherogenicity of LDL particles.[33-35] Increased intra-cellular glucose levels or metabolites induce reactive oxygen species (ROS) and pro-inflammatory responses which further promotes atherosclerosis in T2DM.[36,37]

Current guidelines for lipid-lowering treatment in type 2 diabetes

Epidemiological studies have shown that high levels of LDL-C and non-HDL-C and low levels of HDL-C are associated with an increased risk of CV events and mortality in patients with and without T2DM.[13] Conversely, RCTs with lipid-lowering agents in patients at risk of CV events (including patients with T2DM) have demonstrated a log-linear proportional reduction of CV events and mortality for each 1 mmol reduction of LDL-C (38.7 mg).[38] LDL-C is the primary target of lipid-lowering therapies, non-HDL-C the secondary target particularly in T2DM. Non-HDL-C should therefore be considered in patients with T2DM and combined dyslipidaemias, although there are limited data from interventional trials. Treatment goals among patients with T2DM are based on their cardiovascular risk.

Due to the lack of evidence, no clear recommendations can be given for patients with T2DM at low CV risk.[6]

Lipid-lowering agents

For the drug classes discussed below, the main site of action and the level of evidence for cardiovascular risk reduction are summarized in the central illustration.

Statins

Table 1 summarizes the key aspects of statin trials that included patients with T2DM.

Among the earlier randomized clinical trials, T2DM patients represented a variable proportion in the whole trial cohorts, since no trial focused specifically on T2DM patients. The breakthrough trial—the Scandinavian Simvastatin Survival Study (4S)—did not specifically look at T2DM, e.g. only 201 diabetes patients were among the 4444 of the 4S cohort).[39]

Sub-group analyses have the major methodological limitation that there is no randomization according to presence of T2DM and that the diabetes sub-groups are not large enough to fulfil the requirements of a sample size calculation and adequate statistical power.[55] Specifically, 4S was event-driven. It appeared that the T2DM sub-group responded similarly to the non-diabetic one to statin intervention. Further, placebo-controlled trials as the West of Scotland Coronary Prevention Study (WOSCOPS)[40] and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[41] in primary prevention settings as well as, e.g. CARE, LIPID[43,44] in the secondary prevention setting, did not specify on event rates in T2DM vs. non-T2DM.

It was therefore very important to conduct a separate trial specifically on patients with T2DM. Here, the Collaborative Atorvastatin Diabetes Study (CARDS) represents a milestone.[42] In 2838 patients, atorvastatin 10 mg was tested against placebo. The intervention was so effective, that the trial had to be stopped pre-maturely for efficacy,[56] i.e. 37% reduction in first major CV events (HR not stated), 48% fewer strokes, with a 27% lower overall mortality ($P = 0.059$).[42]

As early as in 2008 the highly respected Cholesterol Treatment Trialist's (CTT) Collaborators from Oxford[38] published data on the efficacy on cholesterol-lowering therapy in 18 686 people with diabetes.

Table 1 Placebo-controlled outcome studies with statins[39-54]

Study	Active drug	Comparator	Number of participants (*n*)	People with Diabetes (%)	Duration (Median, years)	Endpoint	Outcome	References
4S (1994)	Simvastatin 20 mg	Placebo	4444	5	5.4	The primary endpoint: total mortality. Secondary endpoint: analysed by time of first event, 'major coronary events', (coronary deaths, definite or probable hospital-verified non-fatal acute MI, resuscitated cardiac arrest, and definite silent MI verified by electrocardiogram).	Not specific for diabetes; long-term treatment with simvastatin improved survival in CHD patients.	[39]
WOSCOPS (1995)	Pravastatin 40 mg	Placebo	6595	1	4.9	Primary endpoint: occurrence of non-fatal myocardial infarction or death from coronary heart disease as a first event. Other principal endpoints were the occurrence of death from coronary heart disease and non-fatal myocardial infarction.	Not specific for diabetes; pravastatin significantly reduced incidence of MI and death from cv causes.	[40]

Continued

Table 1 *Continued*

Study	Active drug	Comparator	Number of participants (*n*)	People with Diabetes (%)	Duration (Median, years)	Endpoint	Outcome	References
AFCAPS/ TexCAPS (2000)	Lovastatin 20–40 mg	Placebo	6605	3	5.0 (at least)	First acute major coronary event defined as fatal or non-fatal myocardial infarction, unstable angina, or sudden cardiac death.	History of diabetes not a significant predictor of outcome; lovastatin reduces risk for first acute major coronary event in men and women with average TC and LDL-C levels and below-average HDL-C.	[41]
CARDS (2004)	Atorvastatin 10 mg	Placebo	2838	100	3.9	Primary endpoint: time to first occurrence of acute coronary heart disease events, coronary revascularization, or stroke.	Atorvastatin is efficacious in reducing the risk of first cv disease events, including stroke, in patients with type 2 diabetes without high LDL-cholesterol.	[42]
CARE (1996)	Pravastatin 40 mg	Placebo	4159	15	5.0	Primary endpoint: a fatal coronary event or a non-fatal myocardial infarction.	The benefit of cholesterol-lowering therapy extends to the majority of patients with coronary disease who have average cholesterol levels.	[43]
LIPID (1998)	Pravastatin 40 mg	Placebo	9014	6	6.0	Primary endpoint: death from CHD or non-fatal myocardial infarction (combined).	Patients with diabetes or IFG; Cholesterol-lowering treatment with pravastatin therapy prevents cardiovascular events, including stroke, in patients with diabetes or IFG and established CHD.	[44]
JUPITER (2008)	Rosuvastatin 20 mg	Placebo	17 802	0	1.9	Primary outcome: the occurrence of a first major cardiovascular event, defined as non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes. Secondary endpoints: the components of the primary endpoint considered individually—arterial revascularization or hospitalization for unstable angina, myocardial infarction, stroke, or death from cardiovascular causes—and death from any cause.	Rosuvastatin significantly reduced the incidence of major cardiovascular events of apparently healthy persons without hyperlipidaemia but with elevated high-sensitivity C-reactive protein levels.	[45]
ASPEN (2006)	Atorvastatin 10 mg	Placebo	2410	100	4.0	Composite primary endpoint: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, recanalization, coronary artery bypass surgery, resuscitated cardiac	Composite endpoint reductions were not statistically significant.	[46]

Continued

Table 1 *Continued*

Study	Active drug	Comparator	Number of participants (*n*)	People with Diabetes (%)	Duration (Median, years)	Endpoint	Outcome	References
						arrest, and worsening or unstable angina requiring hospitalization.		
HPS (2002, 2003) (Prim. + Sec.Prev.)	Simvastatin 40 mg	Placebo (Prim.Prev.) or Usual care (Sec.Prev.)	20 536 (5963 with diabetes) 2912 of those in Prim.Prev., 3051 in Sec.Prev.	15.0	5.0	Prim.prev. Primary outcomes: mortality (for overall analyses) and fatal or non-fatal vascular events (for sub-category analyses), with subsidiary assessments of cancer and of other major morbidity. Sec.prev. First major coronary event (i.e. non-fatal myocardial infarction or coronary death) and of first major vascular event (i.e. major coronary event, stroke or revascularization).	Significant reduction (33%) in defined endpoint for sub-categories. 24–27% reduction in major vascular events; in diabetics, coronary events fell from 11.8% to 8.7% (HR 0.73, $P < 0.0001$).	[47,48]
ALLHAT-LLT (2002)	Pravastatin 40 mg	Usual care	10 355	35	4.8	Primary outcome: all-cause mortality.	No significant reduction in primary endpoint.	[49]
ASCOT-LLA (2003, 2005)	Atorvastatin 10 mg	Placebo	10 305 2532 with diabetes	25	3.3	Primary endpoint: non-fatal myocardial infarction and fatal CHD.	Significant reduction (36%) in primary endpoint. Diabetes patients (23% reduction in cardiovascular and coronary endpoints). 36% reduction in MI/CAD death overall; diabetic sub-group saw a 23% decrease in CV events ($P = 0.036$).	[50,51]
MEGA (2006)	Pravastatin 10–20 mg	Usual care	7832	21	5.3	Primary endpoint: the first occurrence of coronary heart disease.	Significant reduction (33%) in coronary heart disease events.	[52]
4D (2005)	Atorvastatin 20 mg	Placebo	1255	100	4.0	Primary endpoint: composite of death from cardiac causes, non-fatal myocardial infarction, and stroke. Secondary endpoints: death from all causes and all cardiac and cerebrovascular events combined.	No statistically significant effect on the composite primary endpoint.	[53]
SPARCL (2018)	Atorvastatin 80 mg	Placebo	4731	17	4.9	Primary endpoint: first non-fatal or fatal stroke.	No significant reduction in strokes, significant reduction in incidence of strokes and of cardiovascular events.	[54]

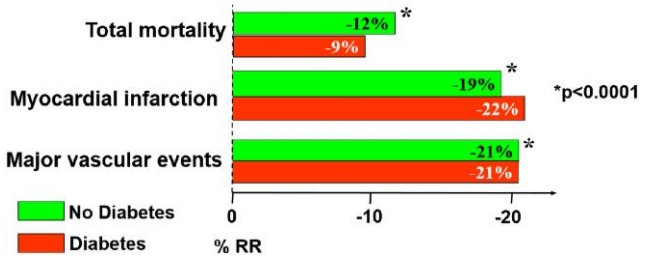


Figure 1 Statins in patients with diabetes. Relative risk reduction per 1 mmol/L LDL-C (38.7 mg/dL) reduction with and without diabetes.[37,56]

They undertook a prospective meta-analysis in the diabetic individuals (1466 with type 1 and 17 220 with T2DM) and compared their outcomes with those of 71 370 without diabetes, by collecting data from 14 randomized trials of statins. During a mean follow-up of 4.3 years, 3247 major vascular events were observed in the diabetes group. The proportional reductions in diabetic vs. non-diabetic patients are depicted in *Figure 1*.[38,57] In synopsis, diabetic and non-diabetic patients had similar proportional reduction of endpoints per 1 mmol/L (38.7 mg/dL) reduction in LDL-cholesterol. Furthermore, in diabetic participants there were reductions of these endpoints irrespective of whether there was a prior history of vascular disease or other baseline characteristics. After 5 years, 42 fewer persons with diabetes had major vascular events per 1000 allocated to statin therapy. Importantly, the similar reduction of major vascular events and myocardial infarction were significantly higher in absolute terms in diabetic patients. As mentioned above, it is important to remember that the absolute risk of the diabetic patients is at least two- to three-fold higher than in non-diabetic ones.[5,58] Consequently, the number needed to prevent one event is much lower in diabetes.

Statins can increase glycaemia to a minor degree, a fact that does not reduce their positive effect on ASCVD. Thus, the minor increase of glycaemia in statin trials does not impair the beneficial cardiovascular results. Any theoretical adverse effects of statins on cardiovascular risk that might arise from these small increases in glycaemia (or, indeed, from any other mechanism) are already accounted for in the overall reduction in cardiovascular risk that is seen with statin therapy in these trials.[59] Details are given in the previous article on T1DM.[3]

Ezetimibe

Lowering of LDL-C can be further intensified by adding ezetimibe to a statin. Ezetimibe affects cholesterol absorption by inhibiting intestinal uptake of dietary and biliary cholesterol. The site of ezetimibe`s action is the brush border of the intestinal enterocytes (mainly jejunum), where it blocks the Nieman–Pick C1-like protein responsible for cholesterol uptake into enterocytes, without affecting the absorption of fat-soluble nutrients. By doing so, less cholesterol is packaged into chylomicrons and ezetimibe reduces the amount of cholesterol delivered to the liver. This, in turn, leads to an up-regulation of the LDL-receptor, which leads to an increased clearance of LDL particles from the bloodstream.[13,60] Because lowering LDL-C by statins may also lead to a compensatory increase in intestinal cholesterol absorption[61] and ezetimibe, in turn, may induce HMG-CoA reductase expression,[62] a combination of statins and ezetimibe is considered particularly useful.[63,64]

Clinical studies have shown that ezetimibe monotherapy at the standard daily dose of 10 mg reduces LDL-cholesterol levels by 15–22% in various populations with hypercholesterolemia. A meta-analysis of RCTs including over 2700 people showed an 18.5% reduction in LDL-cholesterol vs. placebo.[65] Several trials have evaluated the use of ezetimibe in patients with diabetes. In the VYTAL trial (Vytorin vs. Atorvastatin in patients with T2DM and hypercholesterolaemia), 1229 patients with T2DM were randomized to receive ezetimibe in combination with varying doses of a moderate-intensity (simvastatin) or a high-intensity (atorvastatin) statin. After 6 weeks of treatment, ezetimibe plus simvastatin had greater LDL-C reductions as compared with atorvastatin, irrespective of its dose.[66] In general, given the mode of action of ezetimibe, combination studies adding ezetimibe to statins, bile acid sequestrates, bempedoic acid or pro-protein convertase subtilisin/kexin type-9 (PCSK9) inhibitors showed consistent and clinically meaningful lipid-lowering effects. Accordingly, in a recent study in patients with T2DM comparing the combination of a low-dose of high-intensity statin with ezetimibe to a high-dose of a high-intensity statin monotherapy, favourable biomarker outcomes (such as LDL-C and HOMA-B) for the former over the latter were seen,[67] which is supported by another report.[68]

Several studies have used carotid intima-media thickness (C-IMT) as surrogate endpoint for vascular disease. The ENHANCE trial, a study in patients with familial hypercholesterolemia (FH), included only 1.8% patients with diabetes.[69] The SANDS trial enrolled 427 patients with diabetes investigating a combination of statin and ezetimibe, showing that aggressive lipid-lowering (with or without the inclusion of ezetimibe), can positively affect C-IMT.[70] However, an ezetimibe-specific effect, beyond aggressive lipid-lowering, could not be demonstrated, hence primarily confirming a '*the lower the better*' approach, irrespective of the drug being used for lipid-lowering.

The SEAS study[71] had T2DM as an exclusion criterion. Therefore, the first RCT to yield information about clinical endpoints when using ezetimibe in patients with diabetes was the SHARP trial.[72] This was a placebo-controlled study in patients with chronic kidney disease, 23% of whom had diabetes. The study showed that reduction of LDL-cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease. No difference in outcome in any of the studied sub-groups was shown, including in patients with diabetes.

Finally, the IMPROVE-IT trial showed significantly reduced MACE (composite of CV death, non-fatal MI, unstable angina requiring rehospitalization, coronary revascularization ≥30 days after randomization, or non-fatal stroke; HR 0.94; 95% CI, 0.89–0.99) in patients post-ACS receiving simvastatin plus ezetimibe vs. simvastatin alone.[8] In the sub-group of patients with diabetes, the effect was more pronounced, indicating an even greater benefit in T2DM (HR 0.85; 95% CI, 0.78–0.94; $P < 0.001$).[73] The largest relative reductions in patients with T2DM were in myocardial infarction (24%) and ischaemic stroke (39%). No differences in safety outcomes by treatment were observed regardless of diabetes. When stratified further by age, patients ≥75 years of age had a 20% relative reduction in the primary endpoint

regardless of diabetes (Pint = 0.91), whereas patients <75 years of age with diabetes had greater benefit than those without (Pint = 0.011).[73]

Studies comparing high intensity statin vs. low-to-moderate intensity statin plus ezetimibe in patients at high-risk of ASCVD, including diabetes, have been performed more recently. In a pre-specified sub-group analysis of the diabetes cohort in the RACING trial,[74] similar efficacy results were seen with respect to the primary endpoint, a 3-year composite of CV death, major CV events, or non-fatal stroke, with more favourable results in terms of LDL reduction and overall tolerability of the moderate-intensity statin with ezetimibe combination therapy (vs. high-intensity statin alone). Based on these and similar findings,[75] alternative LDL-lowering strategies (vs. a high-intensity statin strategy), involving ezetimibe in combination with low-dose statin have gained interest, indicating similar clinical efficacy and favourable reductions in LDL levels, along with better drug tolerability and lower risk of new-onset diabetes.[76]

Ezetimibe is a valuable adjunct to statin therapy in minimizing CV risk in various populations, including patients with diabetes, which are in the higher risk categories for ASCVD.[6] Ezetimibe can be used as monotherapy (in case of statin intolerance), and in combination with statins, with bempedoic acid (in case of statin intolerance), in triple combination (with a statin and bempedoic acid) and in combination with drugs targeting the PCSK9 pathway. The combination of ezetimibe with a statin is recommended in patients with diabetes and a recent ACS, especially when an LDL-C target <55 mg/dL (1.42 mmol/L) is required and not achieved with a statin alone.[6] Accordingly, a statin-ezetimibe combination as first choice treatment in very high-risk patients with high LDL levels is recommended.[64,77]

PCSK9 inhibitors

PCSK9 is a molecule that binds to LDL particles in the circulation. The PCSK9/LDL complex then binds to the LDL-receptor and enters the cell. Due to the degradation of the LDL and its receptor it prevents the recycling of the LDL-receptor to the cell membrane. The reduced number of LDL-receptors ensues in reduced cellular uptake of LDL particles and therefore increases the level of circulating LDL. Around 2012, gain-of-function and lack-of-function mutations were discovered, which showed that the PCSK9 molecule is very strongly associated with LDL-C levels.

The first approach to inhibit PCSK9 was to trap it in the circulation by humanized monoclonal antibodies. Two antibodies were tested in outcome trials: Evolocumab in 'Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk' (FOURIER),[78] and Alirocumab in the trial 'Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab' (ODYSSEY OUTCOMES).[79] A third trial, Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE), was stopped because of inhibiting secondary antibodies and ensuing loss of efficacy.[80]

The proportion of diabetic patients was 37% in FOURIER which included 27 564 patients with ASCVD and 29% of patients out of 18 924 participants in ODYSSEY OUTCOMES with recent ACS.

The efficacy of PCSK9 inhibitors in patients with diabetes has been summarized by Imbalzano *et al.*[81] In FOURIER, evolocumab reduced LDL-cholesterol levels by 59%[78] and the relative risk reduction for major adverse cardiovascular events (primary composite endpoint) was slightly greater in diabetic patients than in non-diabetic counterparts (17% vs. 13%, $P < 0.0001$).[82] Incidence of serious adverse events, muscle-related events, new-onset diabetes, haemorrhagic stroke, and neurocognitive events with long-term evolocumab were similar to the placebo arm during the study and afterwards.[83]

In ODYSSEY OUTCOMES, LDL-cholesterol was reduced by ~60%[79] and in patients with diabetes alirocumab showed a greater absolute risk reduction that was attributable to their higher baseline risk (2.3%).[84]

Notably, in both trials there was no signal of worsening glycaemia. Moreover, a ODYSSEY OUTCOMES sub-study definitely showed that LDL-cholesterol lowering does not increase the likelihood of haemorrhagic stroke.[85] Finally, the safety of alirocumab was reportedly favourable in an analysis of 47 296 patient-years.[86]

In summary, the two studies revealed high efficacy and safety. As a limitation, neither all-cause nor cardiovascular mortality incidence in FOURIER was significantly reduced, only MACE were reduced. Therefore, the FOURIER trialists decided to make an open label extension that showed that cardiovascular mortality was significantly reduced (23%).[83] By comparison, in ODYSSEY OUTCOMES all-cause mortality was reduced significantly by 15% but based on hierarchical testing this finding was not over-emphasized.[79]

The broad use of PCSK9 antibodies in clinical practice is limited by their high cost. Thus, in most European countries restrictive reimbursement regulations exist due to problems in affordability. Thus, these antibodies are not yet used as first-line therapy. The Guideline recommend use of PCSK9 inhibitors in patients with established ASCVD who do not reach LDL-cholesterol goals despite maximally tolerated statins and ezetimibe as well as familial hypercholesterolemia patients, or statin intolerant individuals.[13] Generally, clinical observations show that these antibodies are very well tolerated.[82] Statins remain the first-line therapy also in diabetic patients.

Inclisiran

Inclisiran offers a different approach to reduce PCSK9, since it is a small interfering RNA (siRNA) that decreases the intra-cellular production of PCSK9 through a different mechanism: a reduced production rather than neutralization by antibodies. The efficacy of this drug is well documented.[87] LDL-cholesterol lowering is slightly less than with the antibodies, around 50%.[88] The efficacy is higher in diabetic patients than in those with normoglycaemia or pre-diabetes and in those with a higher vs. lower BMI.[89] The drug is well tolerated and has the enormous advantage that it is administered sub-cutaneously only twice a year (with antibodies the interval of injections is 2–4 weeks). The safety record of inclisiran is extremely good.[87,90-92] No results of outcome studies are available at the moment, data from the 'Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease' (ORION-4) (cardiovascular outcome trial) is expected in 2026.[88]

Bempedoic acid

The cholesterol lowering via bempedoic acid [ECT1002], an ACL-inhibiting regimen trial (CLEAR OUTCOME) was conducted in 13 970 statin-intolerant patients and compared with placebo.[93] This is an important difference to the PCSK9 inhibitor trials that used the antibodies on top of statins. The reason is that one inclusion criterion in CLEAR OUTCOME was statin intolerance.

The main observation was that LDL-cholesterol was reduced by around 16%[93] and in combination with ezetimibe by about 36%,[94] comparable to a moderate intensity statin, e.g. simvastatin 40 mg/d. The outcome was very positive with a 13% reduction of the primary efficacy endpoint (four component MACE—death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or coronary revascularization).[93] A systematic review of cardiovascular events has been published earlier in this journal by Mutschlechner *et al.*[95]

Additional interesting published results from CLEAR OUTCOME were that patients in primary prevention benefited equally or even slightly better than patients in secondary prevention. Here it should be noted, that the percentage of diabetes patients was 46% in the whole trial and 65% in the primary prevention sub-group.[96] In other words, this was not

a usual primary prevention population for two reasons: a high proportion of diabetic patients and the inclusion criterion of statin intolerance.

A further remarkable positive finding in the CLEAR OUTCOME trial was that glycaemic levels were not deteriorated, nor was the incidence of newly diagnosed diabetes increased.[93,97]

A summary of the lipid-lowering and antihyperglycaemic drugs that have just arrived at the market or that are expected to arrive soon has been recently published.[98,99] Among the future topics Lp(a) will become very important, however, at the time of this writing no outcome data are available.[100]

Effects of glucose-lowering medication on lipoprotein profile

Improvement of glycaemic control and/or weight loss in T2DM is usually associated with a significant amelioration of the lipoprotein profile characterized by reductions in total cholesterol, TGs and increases in HDL-cholesterol. Despite these general effects, some antidiabetic drugs additionally exert direct effects on lipoprotein metabolism. The following paragraph focuses on specific effects of antidiabetic medications on lipid metabolism.

Metformin

Little is known about specific effects of metformin therapy on lipoprotein metabolism. In a meta-analysis investigating studies in non-diabetic patients, metformin therapy was associated with a slight but significant decrease in LDL-C and total cholesterol levels (LDL-C: −4.69 mg/dL (0.12 mmol/L) [95% CI, −7,39−2)], total cholesterol: −6.57 mg/dL (0.17 mmol/L) [95% CI, −9,66−3,47]) while HDL-C and TG levels remained unchanged. Also, TG levels were significantly reduced in metformin-treated patients with polycystic ovarian syndrome suggesting indirect effects by improving insulin sensitivity.[101]

Sodium–glucose transport protein 2 inhibitors

While Sodium–glucose transport protein 2 (SGLT-2) inhibitor treatment is consistently associated with increases in HDL-C levels by about 2 mg/dL (0.05 mmol/L),[102] their effect on LDL-C levels is inconsistent showing decreasing, neutral, or increasing effects.[102-107] Mechanistically, increased LDL-C levels might result from reduced clearance resulting from greater lipolysis of TG-rich lipoproteins.[108] In HepG2 cells, dapagliflozin exposure resulted in a down-regulation of PCSK9 and up-regulation of the LDL-receptor was reported.[109] In contrast to human studies, dapagliflozin treatment was associated with reduced LDL-C levels in high-fat diet fed mice while no effect was observed in the chow-fed control mice. Additionally, dapagliflozin therapy was associated with a decrease of harmful sdLDL particles and an increase in less atherogenic large buoyant LDL particles.[107]

Taken together these studies suggest that anti-atherogenic effects of SGLT-2 inhibitors might partly be driven by improving lipoprotein profile in patients with diabetic dyslipidaemia. However, further studies are required to validate the effects of SGLT-2 inhibitors on blood lipid profiles and to demonstrate the underlying mechanisms of action. From a Scandinavian cohort study positive cardiovascular and renal effectiveness was reported for empagliflozin and dapagliflozin.[110]

Thiazolidindione

Improved insulin sensitivity upon pioglitazon treatment is associated with a marked decrease in fasting and post-prandial TG levels and an increase in HDL-C levels.[111-114] In a study comparing pioglitazon and metformin treatment in patients with T2DM, TG levels decreased by 19% in the pioglitazon group and by 10% in the metformin group. Accordingly, HDL-C levels increased by 14% in the piogltiazon and 7% in the metformin group.[113]

While pioglitazon treatment is associated with a slight increase in LDL-C concentration, LDL-particle number and size are reduced. In contrast, rosiglitazon is associated with moderate increases in LDL-C concentrations, TG concentrations and LDL particle concentrations.[115] Mechanistically, increases in total VLDL particle concentration is more pronounced by rosiglitazone than by pioglitazon. On the other hand, pioglitazon has stronger decreasing effects on VLDL particle size than rosigltiazon. Both, pioglitazon and rosiglitazon lead to an increase in LDL particle size with stronger effects with pioglitazon than with rosiglitazon. Finally, pioglitazon but not rosiglitazon therapy is associated with increased HDL-C levels.[116]

Incretin mimetics

Incretin mimetics have been widely investigated in patients with obesity, T2DM, but metabolic dysfunction-associated fatty liver disease and heart failure, respectively.[117-129]

Dependent on the inclusion criteria and the study design, effects on body weight, insulin sensitivity and glycaemic control vary widely and observed alterations in lipid profile might often reflect metabolic improvements rather than direct effects.

In a network meta-analysis by Yao *et al.*[130] semaglutide was reported to be the only glucagon-like peptide-1 (GLP-1) receptor agonist, which reduced LDL-C by 6.19 mg/dL (0.16 mmol/L) 95% CI (−0.3–0.02) while exenatide and tirzepatide displayed TG lowering effects when compared with placebo (exenatide: −140.72 mg/dL (−1.59 mmol/L) [95%CI, −2.86 −0.32]; tirzepatide: −78.77 mg/dL (−0.89 mmol/L) [95%CI, −1.64 −0.13]). Polyethylene glycol-loxenatide was associated with a slight increase in HDL-C. Decreased chylomicron secretion via reductions in apoB48 secretion and intestinal microsomal TG transfer protein (MTP) activity might explain beneficial effects on TG metabolism.[131-133] Additionally, *in vitro* and animal models suggest that GLP-1 receptor agonists lower VLDL secretion by modulating hepatic lipid metabolism.[134,135]

Dipeptidyl peptidase-IV (DPP-IV) inhibitors

Several clinical studies and meta-analysis reported reduced total cholesterol and TG levels in DPP IV inhibitor treated patients as reviewed elsewhere in detail.[136,137] However, in a recent meta-analysis, DPP-IV inhibitor treatment was associated only with a slight but significant increase of HDL-C while no effect was found on TG or LDL-C levels.[138] *In vitro* and *in vivo* studies revealed various beneficial effects of DPP-IV inhibitors on hepatic lipid metabolism and intestinal cholesterol reabsorption.[139-142]

Sulfonylureas

Data on effects of sulfonylurea on lipid profile are limited, reaching from lacking or inconclusive effects[143-146] to small reductions in TG, total cholesterol[147,148] or LDL-C levels.[149] It should be noted however, that clinical trials with sulfonylureas were performed 'in the old times' when RCTs had not the standards we would expect today, this partly also applies to metformin studies.

Insulin

Insulin initiation in hyperglycaemic patients with T2DM is usually associated with dose-dependent reductions in free fatty acids, total cholesterol and triglyzeride levels. In parallel HDL-C levels increase and reverse cholesterol transport improves explaining an increase in LDL particle size.[150,151] In a mechanistic study, reductions in HbA1c levels were directly correlated with increases in HDL-C. TG reductions were not associated with falling HbA1c levels suggesting that neither insulin treatment nor improvement or normalization of glycaemia were capable to normalize reverse cholesterol transport and fatty acid metabolism in patients with T2DM.[152]

Insulin effects independent of glycaemia were reported from euglycaemic clamp studies in non-diabetic subjects. In this study, insulin infusion was associated with a marked decrease in TG levels, reductions in total cholesterol and LDL-C and a slight increase in HDL-C levels.[153] Acute insulin infusion reduces VLDL-1, apolipoprotein B100 and also intestinal apolipoprotein B48 secretion suggesting suppressive effects on TG secretion by insulin in the liver and the intestine.[154,155] The effects of insulin on lipoprotein lipase are tissue-specific with stimulating effects in the adipose tissue and suppressing effects in skeletal muscle.[156-162]

Additionally, acute insulin therapy reduces cholesterol synthesis and cholesterol absorption by reducing 12 α hydroxylated bile acids thus in an animal model further suggesting direct effects on cholesterol metabolism.[163]

Overall conclusion

Many experts now consider type 1 diabetes as a sugar disease and type 2 diabetes as a fat disease.

Acknowledgements

We thank Dr. Cornelia Malin for excellent assistance in preparing the manuscript.

Conflict of interest. S.A. and J.T. are Editors of the European Heart Journal—Cardiovascular Pharmacotherapy and were not involved in the peer review process or publication decision. H.D., A.F., T.A.S., B.R., D.D., and S.K. declared no conflict of interest.

Data availability

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

References

1. Mayer G, Dobrev D, Kaski JC, Semb AG, Huber K, Zirlik A, Agewall S, Drexel H. Management of dyslipidaemia in patients with comorbidities: facing the challenge. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:608–613. https://doi.org/10.1093/ehjcvp/pvae058
2. Frühwald L, Fasching P, Dobrev D, Kaski JC, Borghi C, Wassmann S, Huber K, Semb AG, Agewall S, Drexel H. Management of dyslipidaemia in patients with comorbidities-facing the challenge. *Eur Heart J Cardiovasc Pharmacother* 2025;**11**:164–173. https://doi.org/10.1093/ehjcvp/pvae095
3. Kaser S, Dobrev D, Rocca B, Kaski JC, Agewall S, Drexel H. Management of dyslipidaemia in patients with comorbidities-facing the challenge: type 1 diabetes mellitus. *Eur Heart J Cardiovasc Pharmacother* 2025;**11**:380–386. https://doi.org/10.1093/ehjcvp/pvaf023
4. IDF Diabetes Atlas 11th Edition—2025, Online version of the IDF Diabetes Atlas. https://diabetesatlas.org/media/uploads/sites/3/2025/04/IDF_Atlas_11th_Edition_2025.pdf
5. Rana JS, Farrukh F, Moffet HH, Liu JY, Bhatt AS, Sabouret P, Karter AJ. Diabetes and risk of premature atherosclerotic cardiovascular disease. *Nutr Metab Cardiovasc Dis* 2025;**35**:103869. https://doi.org/10.1016/j.numecd.2025.103869
6. Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, Christodorescu RM, Crawford C, Di Angelantonio E, Eliasson B, Espinola-Klein C, Fauchier L, Halle M, Herrington WG, Kautzky-Willer A, Lambrinou E, Lesiak M, Lettino M, McGuire DK, Mullens W, Rocca B, Sattar N, Prescott E, Cosentino F, Abdelhamid M, Aboyans V, Antoniou S, Asteggiano R, Baumgartner I, Buccheri S, Bueno H, Čelutkienė J, Chieffo A, Christersson C, Coats A, Cosyns B, Czerny M, Deaton C, Falk V, Ference BA, Filippatos G, Fisher M, Huikuri H, Ibanez B, Jaarsma T, James S, Khunti K, Køber L, Koskinas KC, Lewis BS, Løchen M-L, McEvoy JW, Mihaylova B, Mindham R, Neubeck L, Nielsen JC, Parati G, Pasquet AA, Patrono C, Petersen SE, Piepoli MF, Rakisheva A, Rossello X, Rossing P, Rydén L, Standl E, Tokgozoglu L, Touyz RM, Visseren F, Volpe M, Vrints C, Witkowski A, Hazarapetyan L, Zirlik A, Rustamova Y, van de Borne P, Sokolović Š, Gotcheva N, Milicic D, Agathangelou P, Vrablík M, Schou M, Hasan-Ali H, Viigimaa M, Lautamäki R, Aboyans V, Klimiashvili Z, Kelm M, Siasos G, Kiss RG, Libungan B, Durkan M, Zafrir B, Colivicchi F, Tundybayeva M, Bytyçi I, Mirrakhimov E, Trusinskis K, Saadé G, Badarienė J, Banu C-A, Magri CJ, Boskovic A, Hattaoui ME, Martens F, Bosevski M, Knudsen EC, Burchardt P, Fontes-Carvalho R, Vinereanu D, Mancini T, Beleslin B, Martinka E, Fras Z, Conde AC, Mellbin L, Carballo D, Bsata W, Mghaieth F, Gungor B, Mitchenko O, Wheatcroft S, Trigulova R, Prescott E, James S, Arbelo E, Baigent C, Borger MA, Buccheri S, Ibanez B, Køber L, Koskinas KC, McEvoy JW, Mihaylova B, Mindham R, Neubeck L, Nielsen JC, Pasquet AA, Rakisheva A, Rocca B, Rosselló X, Vaartjes I, Vrints C, Witkowski A, Zeppenfeld K. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J* 2023;**44**:4043–4140. https://doi.org/10.1093/eurheartj/ehad192 Erratum in: Eur Heart J. 2023 Dec 21;44(48):5060. doi: 10.1093/eurheartj/ehad774. Erratum in: Eur Heart J. 2024 Feb 16;45(7):518. doi: 10.1093/eurheartj/ehad857. PMID: 37622663.
7. Mader A, Haeberli D, Larcher B, Dopheide JF, Saely CH, Heinzle CF, Amann P, Schindewolf M, Festa A, Drexel H. Contribution of type 2 diabetes to major adverse cardiovascular events (MACE) in a long-term observational study with different stages of atherosclerosis. *Sci Rep* 2025;**15**:2792. https://doi.org/10.1038/s41598-024-84985-x
8. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397. https://doi.org/10.1056/NEJMoa1410489
9. Almourani R, Chinnakotla B, Patel R, Kurukulasuriya LR, Sowers J. Diabetes and cardiovascular disease: an update. *Curr Diab Rep* 2019;**19**:161. https://doi.org/10.1007/s11892-019-1239-x
10. Sowers JR. Obesity as a cardiovascular risk factor. *Am J Med* 2003;**115**:37S–41S. https://doi.org/10.1016/j.amjmed.2003.08.012
11. Ameer F, Scandiuzzi L, Hasnain S, Kalbacher H, Zaidi N. De novo lipogenesis in health and disease. *Metabolism* 2014 Jul;**63**:895–902. https://doi.org/10.1016/j.metabol.2014.04.003
12. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1963;**1**:785–789. https://doi.org/10.1016/S0140-6736(63)91500-9
13. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O, Mueller C, Drexel H, Aboyans V, Corsini A, Doehner W, Farnier M, Gigante B, Kayikcioglu M, Krstacic G, Lambrinou E, Lewis BS, Masip J, Moulin P, Petersen S, Petronio AS, Piepoli MF, Pintó X, Räber L, Ray KK, Reiner Ž, Riesen WF, Roffi M, Schmid J-P, Shlyakhto E, Simpson IA, Stroes E, Sudano I, Tselepis AD, Viigimaa M, Vindis C, Vonbank A, Vrablik M, Vrsalovic M, Zamorano JL, Collet J-P, Koskinas KC, Casula M, Badimon L, John Chapman M, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O, Windecker S, Aboyans V, Baigent C, Collet J-P, Dean V, Delgado V, Fitzsimons D, Gale CP, Grobbee D, Halvorsen S, Hindricks G, Iung B, Jüni P, Katus HA, Landmesser U, Leclercq C, Lettino M, Lewis BS, Merkely B, Mueller C, Petersen S, Petronio AS, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Sousa-Uva M, Touyz RM, Nibouche D, Zelveian PH, Siostrzonek P, Najafov R, van de Borne P, Pojskic B, Postadzhiyan A, Kypris L, Špinar J, Larsen ML, Eldin HS, Viigimaa M, Strandberg TE, Ferrières J, Agladze R, Laufs U, Rallidis L, Bajnok L, Gudjónsson T, Maher V, Henkin Y, Gulizia MM, Mussagaliyeva A, Bajraktari G, Kerimkulova A, Latkovskis G, Hamoui O, Slapikas R, Visser L, Dingli P, Ivanov V, Boskovic A, Nazzi M, Visseren F, Mitevska I, Retterstøl K, Jankowski P, Fontes-Carvalho R, Gaita D, Ezhov M, Foscoli M, Giga V, Pella D, Fras Z, de Isla LP, Hagström E, Lehmann R, Abid L, Ozdogan O, Mitchenko O, Patel RS. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188. https://doi.org/10.1093/eurheartj/ehz455
14. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Sperling L, Virani SS, Yeboah J. 2018. 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* 2019;**73**:e285–e350. https://doi.org/10.1016/j.jacc.2018.11.003
15. Ebenbichler CF, Laimer M, Kaser S, Ritsch A, Sandhofer A, Weiss H, Aigner F, Patsch JR. Relationship between cholesteryl ester transfer protein and atherogenic lipoprotein profile in morbidly obese women. *Arterioscler Thromb Vasc Biol* 2002;**22**:1465–1469. https://doi.org/10.1161/01.ATV.0000032007.14355.21
16. Vekic J, Zeljkovic A, Cicero AFG, Janez A, Stoian AP, Sonmez A, Rizzo M. Atherosclerosis development and progression: the role of atherogenic small, dense LDL. *Medicina* 2022;**58**:299. https://doi.org/10.3390/medicina58020299
17. Drexel H, Larcher B, Mader A, Vonbank A, Heinzle CF, Moser B, Zanolin-Purin D, Saely CH. The LDL-C/ApoB ratio predicts major cardiovascular events in patients with established atherosclerotic cardiovascular disease. *Atherosclerosis* 2021;**329**:44–49. https://doi.org/10.1016/j.atherosclerosis.2021.05.010
18. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia* 2003;**46**:733–749. https://doi.org/10.1007/s00125-003-1111-y
19. Hwang YC, Ahn HY, Park SW, Park CY. Association of HDL-C and apolipoprotein A-I with the risk of type 2 diabetes in subjects with impaired fasting glucose. *Eur J Endocrinol* 2014;**171**:137–142. https://doi.org/10.1530/EJE-14-0195
20. Asleh R, Levy AP. Divergent effects of alpha-tocopherol and vitamin C on the generation of dysfunctional HDL associated with diabetes and the Hp 2–2 genotype. *Antioxid Redox Signal* 2010;**12**:209–217. https://doi.org/10.1089/ars.2009.2829
21. Shu M, Cheng W, Jia X, Bai X, Zhao Y, Lu Y, Zhu L, Zhu Y, Wang L, Shu Y, Song Y, Jin S. AGEs promote atherosclerosis by increasing LDL transcytosis across endothelial cells via RAGE/NF-κB/Caveolin-1 pathway. *Mol Med* 2023;**29**:113. https://doi.org/10.1186/s10020-023-00715-5
22. Curtiss LK, Witztum JL. Plasma apolipoproteins AI, AII, B, CI, and E are glucosylated in hyperglycemic diabetic subjects. *Diabetes* 1985;**34**:452–461. https://doi.org/10.2337/diab.34.5.452
23. Low H, Hoang A, Forbes J, Thomas M, Lyons JG, Nestel P, Bach LA, Sviridov D. Advanced glycation end-products (AGEs) and functionality of reverse cholesterol transport in patients with type 2 diabetes and in mouse models. *Diabetologia* 2012;**55**:2513–2521. https://doi.org/10.1007/s00125-012-2570-9
24. Hoang A, Murphy AJ, Coughlan MT, Thomas MC, Forbes JM, O'Brien R, Cooper ME, Chin-Dusting JPF, Sviridov D. Advanced glycation of apolipoprotein A-I impairs its anti-atherogenic properties. *Diabetologia* 2007 Aug;**50**:1770–1779. https://doi.org/10.1007/s00125-007-0718-9
25. Duell PB, Oram JF, Bierman EL. Nonenzymatic glycosylation of HDL and impaired HDL-receptor-mediated cholesterol efflux. *Diabetes* 1991;**40**:377–384. https://doi.org/10.2337/diab.40.3.377
26. Ouimet M, Barrett TJ, Fisher EA. HDL and reverse cholesterol transport. *Circ Res* 2019;**124**:1505–1518. https://doi.org/10.1161/CIRCRESAHA.119.312617
27. Gallagher EJ, Leroith D, Karnieli E. Insulin resistance in obesity as the underlying cause for the metabolic syndrome. *Mt Sinai J Med* 2010;**77**:511–523. https://doi.org/10.1002/msj.20212
28. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest* 2005;**115**:1111–1119. https://doi.org/10.1172/JCI25102
29. Menegazzo L, Ciciliot S, Poncina N, Mazzucato M, Persano M, Bonora B, Albiero M, Vigili de Kreutzenberg S, Avogaro A, Fadini GP. NETosis is induced by high glucose and associated with type 2 diabetes. *Acta Diabetol* 2015;**52**:497–503. https://doi.org/10.1007/s00592-014-0676-x
30. Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. *Cell Metab* 2011;**14**:575–585. https://doi.org/10.1016/j.cmet.2011.07.015
31. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract* 2014;**105**:141–150. https://doi.org/10.1016/j.diabres.2014.04.006
32. Karakasis P, Theofilis P, Patoulias D, Vlachakis PK, Antoniadis AP, Fragakis N. Diabetes-driven atherosclerosis: updated mechanistic insights and novel therapeutic strategies. *Int J Mol Sci* 2025;**26**:2196. https://doi.org/10.3390/ijms26052196
33. Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The diabetes Mellitus-atherosclerosis connection: the role of lipid and glucose metabolism and chronic inflammation. *Int J Mol Sci* 2020;**21**:1835. https://doi.org/10.3390/ijms21051835
34. Khan MI, Pichna BA, Shi Y, Bowes AJ, Werstuck GH. Evidence supporting a role for endoplasmic reticulum stress in the development of atherosclerosis in a hyperglycaemic mouse model. *Antioxid Redox Signal* 2009;**11**:2289–2298. https://doi.org/10.1089/ars.2009.2569
35. Katakami N. Mechanism of development of atherosclerosis and cardiovascular disease in diabetes Mellitus. *J Atheroscler Thromb* 2018;**25**:27–39. https://doi.org/10.5551/jat.RV17014
36. Tabit CE, Shenouda SM, Holbrook M, Fetterman JL, Kiani S, Frame AA, Kluge MA, Held A, Dohadwala MM, Gokce N, Farb MG, Rosenzweig J, Ruderman N, Vita JA, Hamburg NM. Protein kinase C-β contributes to impaired endothelial insulin signaling in humans with diabetes mellitus. *Circulation* 2013;**127**:86–95. https://doi.org/10.1161/CIRCULATIONAHA.112.127514
37. Katakami N. Mechanism of development of atherosclerosis and cardiovascular disease in diabetes Mellitus. *J Atheroscler Thromb* 2018;**25**:27–39. https://doi.org/10.5551/jat.RV17014
38. Cholesterol Treatment Trialists' (CTT) Collaborators; Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;**371**:117–125. https://doi.org/10.1016/S0140-6736(08)60104-X
39. Pedersen TR, Kjekshus J, Berg K, Haghfelt T, Faergeman O, Thorgeirsson G, Pyörälä K, Miettinen T, Wilhelmsen L, Olsson AG, Wedel H. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–1389.
40. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;**333**:1301–1307. https://doi.org/10.1056/NEJM199511163332001
41. Clearfield M, Whitney EJ, Weis S, Downs JR, Shapiro DR, Stein EA, Watson DJ, Langendörfer A, Beere PA, Stamler J, Gotto AM. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): baseline characteristics and comparison with USA population. *J Cardiovasc Risk* 2000;**7**:125–133. https://doi.org/10.1177/204748730000700207
42. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;**364**:685–696. https://doi.org/10.1016/S0140-6736(04)16895-5
43. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JMO, Wun C-C, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;**335**:1001–1009. https://doi.org/10.1056/NEJM199610033351401
44. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–1357. https://doi.org/10.1056/NEJM199811053391902
45. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;**359**:2195–2207. https://doi.org/10.1056/NEJMoa0807646
46. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the atorvastatin study for prevention of coronary heart disease endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* 2006;**29**:1478–1485. https://doi.org/10.2337/dc05-2415
47. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22. https://doi.org/10.1016/S0140-6736(02)09327-3
48. Collins R, Armitage J, Parish S, Sleigh P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;**361**:2005–2016. https://doi.org/10.1016/S0140-6736(03)13636-7
49. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The antihypertensive and lipid-lowering treatment to prevent heart attack trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT). *JAMA* 2002;**288**:2998–3007. https://doi.org/10.1001/jama.288.23.2998
50. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Östergren J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;**361**:1149–1158. https://doi.org/10.1016/S0140-6736(03)12948-0
51. Sever PS, Poulter NR, Dahlöf B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). *Diabetes Care* 2005;**28**:1151–1157. https://doi.org/10.2337/diacare.28.5.1151
52. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M, Yamamoto A, Mizuno K, Ohashi Y. MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA

Study): a prospective randomised controlled trial. *Lancet* 2006;**368**:1155–1163. https://doi.org/10.1016/S0140-6736(06)69472-5
53. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**:238–248. https://doi.org/10.1056/NEJMoa043545. Erratum in: N Engl J Med. 2005;353(15):1640
54. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Alfred C 3rd, Hennerici M, Simunovic L, Zivin JA, Welch KMA; SPARCL Investigators. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;**355**:549–559. https://doi.org/10.1056/NEJMoa061894
55. Drexel H, Pocock SJ, Lewis BS, Saely CH, Kaski JC, Rosano GMC, Tautermann G, Huber K, Dopheide JF, Mader A, Niessner A, Savarese G, Schmidt TA, Semb AG, Tamargo J, Wassmann S, Clodi M, Kjeldsen KP, Agewall S. Subgroup analyses in randomized clinical trials: value and limitations. Review #3 on important aspects of randomized clinical trials in cardiovascular pharmacotherapy. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:302–310. https://doi.org/10.1093/ehjcvp/pvab048
56. Drexel H, Lewis BS, Rosano GMC, Saely CH, Tautermann G, Huber K, Dopheide JF, Kaski JC, Mader A, Niessner A, Savarese G, Schmidt TA, Semb A, Tamargo J, Wassmann S, Per Kjeldsen K, Agewall S, Pocock SJ. The age of randomized clinical trials: three important aspects of randomized clinical trials in cardiovascular pharmacotherapy with examples from lipid, diabetes, and antithrombotic trials. *Eur Heart J Cardiovasc Pharmacother* 2021;**7**:453–459. https://doi.org/10.1093/ehjcvp/pvaa126
57. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**:1267–1278. https://doi.org/10.1016/S0140-6736(05)67394-1
58. Emerging Risk Factors Collaboration; Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;**375**:2215–2222. https://doi.org/10.1016/S0140-6736(10)60484-9
59. Cholesterol Treatment Trialists' (CTT) Collaboration. Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis. *Lancet Diabetes Endocrinol* 2024;**12**:306–319. https://doi.org/10.1016/S2213-8587(24)00040-8
60. Phan BA, Dayspring TD, Toth PP. Ezetimibe therapy: mechanism of action and clinical update. *Vasc Health Risk Manag* 2012;**8**:415–427. https://doi.org/10.2147/VHRM.S33664
61. Huff MW, Burnett JR. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and hepatic apolipoprotein B secretion. *Curr Opin Lipidol* 1997;**8**:138–145. https://doi.org/10.1097/00041433-199706000-00003
62. Bays H. Ezetimibe. *Expert Opin Investig Drugs* 2002;**11**:1587–1604. https://doi.org/10.1517/13543784.11.11.1587
63. Guyton JR. Combination regimens with statin, niacin, and intestinally active LDL-lowering drugs: alternatives to high-dose statin therapy? *Curr Opin Lipidol* 2010;**21**:372–377. https://doi.org/10.1097/MOL.0b013e32833c1f16
64. Averna M, Banach M, Bruckert E, Drexel H, Farnier M, Gaita D, Magni P, März W, Masana L, Mello e Silva A, Reiner Z, Ros E, Vrablik M, Zambon A, Zamorano JL, Stock JK, Tokgözoğlu LS, Catapano 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* 2021;**325**:99–109. https://doi.org/10.1016/j.atherosclerosis.2021.03.039
65. Pandor A, Ara RM, Tumur I, Wilkinson AJ, Paisley S, Duenas A, Durrington PN, Chilcott J. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. *J Intern Med* 2009;**265**:568–580. https://doi.org/10.1111/j.1365-2796.2008.02062.x
66. Goldberg RB, Guyton JR, Mazzone T, Weinstock RS, Polis A, Edwards P, Tomassini JE, Tershakovec AM. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. *Mayo Clin Proc* 2006;**81**:1579–1588. https://doi.org/10.4065/81.12.1579
67. Moon JS, Park IR, Kim SS, Kim HS, Kim NH, Kim SG, Ko SH, Lee JH, Lee I, Lee BK, Won KC. The efficacy and safety of moderate-intensity rosuvastatin with ezetimibe versus high-intensity rosuvastatin in high atherosclerotic cardiovascular disease risk patients with type 2 diabetes Mellitus: a randomized, multicenter, open, parallel, phase 4 study. *Diabetes Metab J* 2023;**47**:818–825. https://doi.org/10.4093/dmj.2023.0171
68. Lee J, Hwang YC, Lee WJ, Won JC, Song KH, Park CY, Ahn KJ, Park J-Y. Comparison of the efficacy and safety of rosuvastatin/ezetimibe combination therapy and rosuvastatin monotherapy on lipoprotein in patients with type 2 diabetes: multicenter randomized controlled study. *Diabetes Ther* 2020;**11**:859–871. https://doi.org/10.1007/s13300-020-00778-1
69. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FLJ, Sijbrands EJG, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;**358**:1431–1443. https://doi.org/10.1056/NEJMoa0800742
70. Fleg JL, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, Silverman A, Galloway JM, Henderson JA, Weir MR, Wilson C, Stylianou M, Howard WJ. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. *J Am Coll Cardiol* 2008;**52**:2198–2205. https://doi.org/10.1016/j.jacc.2008.10.031
71. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerdts E, Gohlke-Bärwolf C, Holme I, Kesäniemi YA, Malbecq W, Nienaber CA, Ray S, Skjærpe T, Wachtell K, Willenheimer R. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;**359**:1343–1356. https://doi.org/10.1056/NEJMoa0804602
72. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181–2192. https://doi.org/10.1016/S0140-6736(11)60739-3
73. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špinar J, Park J-G, White JA, Bohula EA, Braunwald E. 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* 2018;**137**:1571–1582. https://doi.org/10.1161/CIRCULATIONAHA.117.030950
74. Lee YJ, Cho JY, You SC, Lee YH, Yun KH, Cho YH, Shin W-Y, Im SW, Kang WC, Park Y, Lee SY, Lee S-J, Hong S-J, Ahn C-M, Kim B-K, Ko Y-G, Choi D, Hong M-K, Jang Y, Kim J-S. Moderate-intensity statin with ezetimibe vs. high-intensity statin in patients with diabetes and atherosclerotic cardiovascular disease in the RACING trial. *Eur Heart J* 2023;**44**:972–983. https://doi.org/10.1093/eurheartj/ehac709
75. Park SY, Jun JE, Jeong IK, Ahn KJ, Chung HY, Hwang YC. Comparison of the efficacy of ezetimibe combination therapy and high-intensity statin monotherapy in type 2 diabetes. *J Clin Endocrinol Metab* 2024;**109**:1883–1890. https://doi.org/10.1210/clinem/dgad714
76. Lee YJ, Hong BK, Yun KH, Kang WC, Hong SJ, Lee SH, Hong S-J, Ahn C-M, Kim J-S, Kim B-K, Ko Y-G, Choi D, Jang Y, Hong M-K. Alternative LDL cholesterol-lowering strategy vs high-intensity statins in atherosclerotic cardiovascular disease: a systematic review and individual patient data meta-analysis. *JAMA Cardiol* 2025;**10**:137–144. https://doi.org/10.1001/jamacardio.2024.3911
77. Krychtiuk KA, Ahrens I, Drexel H, Halvorsen S, Hassager C, Huber K, Kurpas D, Niessner A, Schiele F, Semb AG, Sionis A, Claeys MJ, Barrabes J, Montero S, Sinnaeve P, Pedretti R, Catapano A. Acute LDL-C reduction post ACS: strike early and strike strong: from evidence to clinical practice. A clinical consensus statement of the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Association of Preventive Cardiology (EAPC) and the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy. *Eur Heart J Acute Cardiovasc Care* 2022;**11**:939–949. https://doi.org/10.1093/ehjacc/zuac123
78. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–1722. https://doi.org/10.1056/NEJMoa1615664
79. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby J-F, Tricoci P, White HD, Zeiher AM. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;**379**:2097–2107. https://doi.org/10.1056/NEJMoa1801174
80. Ridker PM, Rose LM, Kastelein JJP, Santos RD, Wei C, Revkin J, Yunis C, Tardif J-C, Shear CL. Cardiovascular event reduction with PCSK9 inhibition among 1578 patients with familial hypercholesterolemia: results from the SPIRE randomized trials of bococizumab. *J Clin Lipidol* 2018;**12**:958–965. https://doi.org/10.1016/j.jacl.2018.03.088
81. Imbalzano E, Ilardi F, Orlando L, Pintaudi B, Savarese G, Rosano G. The efficacy of PCSK9 inhibitors on major cardiovascular events and lipid profile in patients with diabetes: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother* 2023;**9**:318–327. https://doi.org/10.1093/ehjcvp/pvad019
82. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, Murphy SA, Kuder JF, Gouni-Berthold I, Lewis BS, Handelsman Y, Pineda AL, Honarpour N, Keech AC, Sever PS, Pedersen TR. 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* 2017;**5**:941–950. https://doi.org/10.1016/S2213-8587(17)30313-3
83. O'Donoghue ML, Giugliano RP, Wiviott SD, Atar D, Keech A, Kuder JF, Im K, Murphy SA, Flores-Arredondo JH, López JAG, Elliott-Davey M, Wang B, Monsalvo ML, Abbasi S, Sabatine MS. Long-term evolocumab in patients with established atherosclerotic cardiovascular disease. *Circulation* 2022;**146**:1109–1119. https://doi.org/10.1161/CIRCULATIONAHA.122.061620
84. Ray KK, Colhoun HM, Szarek M, Baccara-Dinet M, Bhatt DL, Bittner VA, Budaj AJ, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Loizeau V, Lopes RD, Moryusef A, Murin J, Pordy R, Ristic AD, Roe MT, Tuñón J, White HD, Zeiher AM, Schwartz GG, Steg PG; ODYSSEY OUTCOMES Committees and Investigators. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;**7**:618–628. https://doi.org/10.1016/S2213-8587(19)30158-5
85. Jukema JW, Zijlstra LE, Bhatt DL, Bittner VA, Diaz R, Drexel H, Goodman SG, Kim Y-U, Pordy R, Reiner Ž, Roe MT, Tse H-F, Montenegro Valdovinos PC, White HD, Zeiher AM, Szarek M, Schwartz GG, Steg PG. Effect of alirocumab on stroke in ODYSSEY OUTCOMES. *Circulation* 2019;**140**:2054–2062. https://doi.org/10.1161/CIRCULATIONAHA.119.043826
86. Goodman SG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Harrington RA, Jukema JW, White HD, Zeiher AM, Manvelian G, Pordy R, Poulouin Y, Stipek W, Garon G, Schwartz GG. Safety of the PCSK9 inhibitor alirocumab: insights from 47 296 patient-years of observation. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:342–352. https://doi.org/10.1093/ehjcvp/pvae025
87. Ray KK, Troquay RPT, Visseren FLJ, Leiter LA, Scott Wright R, Vikarunnessa S, Talloczy Z, Zang X, Maheux P, Lesogor A, Landmesser U. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. *Lancet Diabetes Endocrinol* 2023;**11**:109–119. https://doi.org/10.1016/S2213-8587(22)00353-9
88. Marrs JC, Anderson SL. Inclisiran for the treatment of hypercholesterolaemia. *Drugs Context* 2024;**13**:2023–12–3. https://doi.org/10.7573/dic.2023-12-3
89. Leiter LA, Raal FJ, Schwartz GG, Koenig W, Ray KK, Landmesser U, Han J, Conde LG, Wright RS. Inclisiran in individuals with diabetes or obesity: post hoc pooled analyses of the ORION-9, ORION-10 and ORION-11 phase 3 randomized trials. *Diabetes Obes Metab* 2024;**26**:3223–3237. https://doi.org/10.1111/dom.15650
90. Leiter LA, Teoh H, Kallend D, Wright RS, Landmesser U, Wijngaard PLJ, Kastelein JJP, Ray KK. Inclisiran lowers LDL-C and PCSK9 irrespective of diabetes Status: the ORION-1 randomized clinical trial. *Diabetes Care* 2019;**42**:173–176. https://doi.org/10.2337/dc18-1491
91. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, Bisch JA, Richardson T, Jaros M, Wijngaard PLJ, Kastelein JJP. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020;**382**:1507–1519. https://doi.org/10.1056/NEJMoa1912387
92. Wright RS, Koenig W, Landmesser U, Leiter LA, Raal FJ, Schwartz GG, Lesogor A, Maheux P, Stratz C, Zang X, Ray KK. Safety and tolerability of inclisiran for treatment of hypercholesterolemia in 7 clinical trials. *J Am Coll Cardiol* 2023;**82**:2251–2261. https://doi.org/10.1016/j.jacc.2023.10.007
93. Nissen SE, Lincoff AM, Brennan D, Ray KK, Mason D, Kastelein JJP, Thompson PD, Libby P, Cho L, Plutzky J, Bays HE, Moriarty PM, Menon V, Grobbee DE, Louie MJ, Chen CF, Li N, Bloedon L, Robinson P, Horner M, Sasiela WJ, McCluskey J, Davey D, Fajardo-Campos P, Petrovic P, Fedacko J, Zmuda W, Lukyanov Y, Nicholls SJ. CLEAR Outcomes Investigators. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. *N Engl J Med* 2023;**388**:1353–1364. https://doi.org/10.1056/NEJMoa2215024
94. Ballantyne CM, Laufs U, Ray KK, Leiter LA, Bays HE, Goldberg AC, Stroes ES, MacDougall D, Zhao X, Catapano AL. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol* 2020;**27**:593–603. https://doi.org/10.1177/2047487319864671
95. Mutschlechner D, Tscharre M, Huber K, Gremmel T. Cardiovascular events in patients treated with bempedoic acid vs. Placebo: systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2023;**9**:583–591. https://doi.org/10.1093/ehjcvp/pvad052
96. Nissen SE, Menon V, Nicholls SJ, Brennan D, Laffin L, Ridker P, Ray KK, Mason D, Kastelein JJP, Cho L, Libby P, Li N, Foody J, Louie MJ, Lincoff AM. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. *JAMA* 2023;**330**:131–140. https://doi.org/10.1001/jama.2023.9696
97. Leiter LA, Banach M, Catapano AL, Duell PB, Gotto AM Jr, Laufs U, Mancini GBJ, Ray KK, Hanselman JC, Ye Z, Bays HE. Bempedoic acid in patients with type 2 diabetes mellitus, prediabetes, and normoglycaemia: a post hoc analysis of efficacy and glycaemic control using pooled data from phase 3 clinical trials. *Diabetes Obes Metab* 2022;**24**:868–880. https://doi.org/10.1111/dom.14645
98. Tamargo J, Agewall S, Ambrosio G, Borghi C, Cerbai E, Dan GA, Drexel H, Ferdinandy P, Grove EL, Klingenberg R, Morais J, Parker W, Rocca B, Sulzgruber P, Semb AG, Sossalla S, Kaski JC, Dobrev D. New pharmacological agents and novel cardiovascular pharmacotherapy strategies in 2024. *Eur Heart J Cardiovasc Pharmacother* 2025;**11**:pvaf012. https://doi.org/10.1093/ehjcvp/pvaf012
99. Zheng WC, Chan W, Dart A, Shaw JA. Novel therapeutic targets and emerging treatments for atherosclerotic cardiovascular disease. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:53–67. https://doi.org/10.1093/ehjcvp/pvad074
100. Sun Y, Hasegawa K, Drexel H. Should pharmacotherapy targeting lipoprotein(a) be further expanded for patients with diabetes? *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:278. https://doi.org/10.1093/ehjcvp/pvae033
101. Weng S, Luo Y, Zhang Z, Su X, Peng D. Effects of metformin on blood lipid profiles in nondiabetic adults: a meta-analysis of randomized controlled trials. *Endocrine* 2020;**67**:305–317. https://doi.org/10.1007/s12020-020-02190-y
102. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128. https://doi.org/10.1056/NEJMoa1504720
103. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–657. https://doi.org/10.1056/NEJMoa1611925
104. Johnson JF, Parsa R, Bailey R. Real world clinical outcomes and patient characteristics for canagliflozin treated patients in a specialty diabetes clinic. *Curr Med Res Opin* 2017;**33**:77–84. https://doi.org/10.1080/03007995.2016.1238354
105. Calapkulu M, Cander S, Gul OO, Ersoy C. Lipid profile in type 2 diabetic patients with new dapagliflozin treatment; actual clinical experience data of six months retrospective lipid profile from single center. *Diabetes Metab Syndr* 2019;**13**:1031–1034. https://doi.org/10.1016/j.dsx.2019.01.016
106. Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W, Meininger G. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care* 2013;**36**:2508–2515. https://doi.org/10.2337/dc12-2491
107. Hayashi T, Fukui T, Nakanishi N, Yamamoto S, Tomoyasu M, Osamura A, Ohara M, Yamamoto T, Ito Y, Hirano T. Correction to: dapagliflozin decreases small dense low-density lipoprotein-cholesterol and increases high-density lipoprotein 2-cholesterol in patients with type 2 diabetes: comparison with sitagliptin. *Cardiovasc Diabetol* 2017;**16**:149. https://doi.org/10.1186/s12933-017-0608-5
108. Basu D, Huggins LA, Scerbo D, Obunike J, Mullick AE, Rothenberg PL, Di Prospero NA, Eckel RH, Goldberg IJ. Mechanism of increased LDL (low-density lipoprotein) and decreased triglycerides with SGLT2 (Sodium-Glucose Cotransporter 2) inhibition. *Arterioscler Thromb Vasc Biol* 2018;**38**:2207–2216. https://doi.org/10.1161/ATVBAHA.118.311339
109. Lu F, Li E, Gao Y, Zhang Y, Kong L, Yang X. Dapagliflozin modulates hepatic lipid metabolism through the proprotein convertase subtilisin/kexin type 9/low density lipoprotein receptor pathway. *Diabetes Obes Metab* 2025;**27**:2096–2109. https://doi.org/10.1111/dom.16202
110. Engström A, Söderling J, Hviid A, Eliasson B, Gudbjörnsdottir S, Wintzell V, Hveem K, Jonasson C, Melbye M, Pasternak B, Ueda P. Comparative cardiovascular and renal effectiveness of empagliflozin and dapagliflozin: scandinavian cohort study. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:432–443. https://doi.org/10.1093/ehjcvp/pvae045
111. Betteridge DJ. Effects of pioglitazone on lipid and lipoprotein metabolism. *Diabetes Obes Metab* 2007;**9**:640–647. https://doi.org/10.1111/j.1463-1326.2007.00715.x
112. Tan MH, Johns D, Strand J, Halse J, Madsbad S, Eriksson JW, Clausen J, Konkoy CS, Herz M. Sustained effects of pioglitazone vs. Glibenclamide on insulin sensitivity, glycaemic control, and lipid profiles in patients with type 2 diabetes. *Diabet Med* 2004;**21**:859–866. https://doi.org/10.1111/j.1464-5491.2004.01258.x
113. Schernthaner G, Matthews DR, Charbonnel B, Hanefeld M, Brunetti P; Quartet [corrected] Study Group. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. *J Clin Endocrinol Metab* 2004;**89**:6068–6076. https://doi.org/10.1210/jc.2003-030861. Erratum in: J Clin Endocrinol Metab. 2005 Feb;90(2):746.
114. Majali A, Cooper K, Staels MB, Luc B, Taskinen MR, Betteridge DJ. The effect of sensitisation to insulin with pioglitazone on fasting and postprandial lipid metabolism, lipoprotein modification by lipases, and lipid transfer activities in type 2 diabetic patients. *Diabetologia* 2006;**49**:527–537. https://doi.org/10.1007/s00125-005-0092-4
115. Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, Tan MH, Khan MA, Perez AT, Jacober SJ. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005;**28**:1547–1554. https://doi.org/10.2337/diacare.28.7.1547
116. Deeg MA, Buse JB, Goldberg RB, Kendall DM, Zagar AJ, Jacober SJ, Khan MA, Perez AT, Tan MH. Pioglitazone and rosiglitazone have different effects on serum lipoprotein particle concentrations and sizes in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2007;**30**:2458–2464. https://doi.org/10.2337/dc06-1903

117. Sanyal AJ, Newsome PN, Kliers I, Østergaard LH, Long MT, Kjær MS, Cali AMG, Bugianesi E, Rinella ME, Roden M, Ratziu V. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med* 2025;**392**:2089–2099. https://doi.org/10.1056/NEJMoa2413258
118. McGuire DK, Marx N, Mulvagh SL, Deanfield JE, Inzucchi SE, Pop-Busui R, Mann JFE, Emerson SS, Poulter NR, Engelmann MDM, Ripa MS, Hovingh GK, Brown-Frandsen K, Bain SC, Cavender MA, Gislum M, David J-P, Buse JB. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. *N Engl J Med* 2025;**392**:2001–2012. https://doi.org/10.1056/NEJMoa2501006
119. Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, Kitzman DW, Møller DV, Treppendahl MB, Verma S, Jensen TJ, Liisberg K, Lindegaard ML, Abhayaratna W, Ahmed FZ, Ben-Gal T, Chopra V, Ezekowitz JA, Fu M, Ito H, Lelonek M, Melenovský V, Merkely B, Núñez J, Perna E, Schou M, Senni M, Sharma K, van der Meer P, Von Lewinski D, Wolf D, Shah SJ. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. *N Engl J Med* 2024;**390**:1394–1407. https://doi.org/10.1056/NEJMoa2313917
120. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, Lingvay I, Oral TK, Michelsen MM, Plutzky J, Tornøe CW, Ryan DH. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;**389**:2221–2232. https://doi.org/10.1056/NEJMoa2307563
121. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, Hovingh GK, Kitzman DW, Lindegaard ML, Møller DV, Shah SJ, Treppendahl MB, Verma S, Abhayaratna W, Ahmed FZ, Chopra V, Ezekowitz J, Fu M, Ito H, Lelonek M, Melenovsky V, Merkely B, Núñez J, Perna E, Schou M, Senni M, Sharma K, Van der Meer P, von Lewinski D, Wolf D, Petrie MC. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med* 2023;**389**:1069–1084. https://doi.org/10.1056/NEJMoa2306963
122. Arslanian SA, Hannon T, Zeitler P, Chao LC, Boucher-Berry C, Barrientos-Pérez M, Bismuth E, Dib S, Cho JI, Cox D. Once-weekly dulaglutide for the treatment of youths with type 2 diabetes. *N Engl J Med* 2022;**387**:433–443. https://doi.org/10.1056/NEJMoa2204601
123. Aronne LJ, Horn DB, le Roux CW, Ho W, Falcon BL, Gomez Valderas E, Das S, Lee CJ, Glass LC, Senyucel C, Dunn JP. Tirzepatide as compared with semaglutide for the treatment of obesity. *N Engl J Med* 2025;**393**:26–36. https://doi.org/10.1056/NEJMoa2416394
124. Packer M, Zile MR, Kramer CM, Baum SJ, Litwin SE, Menon V, Ge J, Weerakkody GJ, Ou Y, Bunck MC, Hurt KC, Murakami M, Borlaug BA. Tirzepatide for heart failure with preserved ejection fraction and obesity. *N Engl J Med* 2025;**392**:427–437. https://doi.org/10.1056/NEJMoa2410027
125. Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, Yoneda M, Behling C, Cummings OW, Tang Y, Brouwers B, Robins DA, Nikooie A, Bunck MC, Haupt A, Sanyal AJ. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med* 2024;**391**:299–310. https://doi.org/10.1056/NEJMoa2401943
126. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med* 2022;**387**:205–216. https://doi.org/10.1056/NEJMoa2206038
127. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;**385**:503–515. https://doi.org/10.1056/NEJMoa2107519
128. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**:311–322. https://doi.org/10.1056/NEJMoa1603827
129. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DCW, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JPH. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med* 2015;**373**:11–22. https://doi.org/10.1056/NEJMoa1411892
130. Yao H, Zhang A, Li D, Wu Y, Wang CZ, Wan JY, Yuan C-S. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. *BMJ* 2024;**384**:e076410. https://doi.org/10.1136/bmj-2023-076410
131. Hsieh J, Longuet C, Baker CL, Qin B, Federico LM, Drucker DJ, Adeli K. The glucagon-like peptide 1 receptor is essential for postprandial lipoprotein synthesis and secretion in hamsters and mice. *Diabetologia* 2010;**53**:552–561. https://doi.org/10.1007/s00125-009-1611-5
132. Vergès B, Duvillard L, Pais de Barros JP, Bouillet B, Baillot-Rudoni S, Rouland A, Sberna A-L, Petit J-M, Degrace P, Demizieux L. Liraglutide reduces postprandial hyperlipidemia by increasing ApoB48 (apolipoprotein B48) catabolism and by reducing ApoB48 production in patients with type 2 diabetes Mellitus. *Arterioscler Thromb Vasc Biol* 2018;**38**:2198–2206. https://doi.org/10.1161/ATVBAHA.118.310990
133. Vergès B. Intestinal lipid absorption and transport in type 2 diabetes. *Diabetologia* 2022;**65**:1587–1600. https://doi.org/10.1007/s00125-022-05765-8
134. Parlevliet ET, Wang Y, Geerling JJ, Schröder-Van der Elst JP, Picha K, O'Neil K, Stojanovic-Susulic V, Ort T, Havekes LM, Romijn JA, Pijl H, Rensen PCN. GLP-1 receptor activation inhibits VLDL production and reverses hepatic steatosis by decreasing hepatic lipogenesis in high-fat-fed APOE*3-Leiden mice. *PLoS One* 2012;**7**:e49152. https://doi.org/10.1371/journal.pone.0049152
135. Patel VJ, Joharapurkar AA, Shah GB, Jain MR. Effect of GLP-1 based therapies on diabetic dyslipidemia. *Curr Diabetes Rev* 2014;**10**:238–250. https://doi.org/10.2174/1573399810666140707092506
136. Piccirillo F, Mastroberardino S, Nusca A, Frau L, Guarino L, Napoli N, Ussia GP, Grigioni F. Antidiabetic agents and their effects on lipid profile: a single shot for several cardiovascular targets. *Int J Mol Sci* 2023;**24**:10164. https://doi.org/10.3390/ijms241210164
137. Fan M, Li Y, Zhang S. Effects of sitagliptin on lipid profiles in patients with type 2 diabetes Mellitus: a meta-analysis of randomized clinical trials. *Medicine (Baltimore)* 2016;**95**:e2386. https://doi.org/10.1097/MD.0000000000002386
138. Dar S, Siddiqi AK, Alabduladhem TO, Rashid AM, Sarfraz S, Maniya T, Menezes Ritesh G, Almas T. Effects of novel glucose-lowering drugs on the lipid parameters: a systematic review and meta-analysis. *Ann Med Surg* 2022;**77**:103633. https://doi.org/10.1016/j.amsu.2022.103633
139. Rufinatscha K, Radlinger B, Dobner J, Folie S, Bon C, Profanter E, Ress C, Salzmann K, Staudacher G, Tilg H, Kaser S. Dipeptidyl peptidase-4 impairs insulin signaling and promotes lipid accumulation in hepatocytes. *Biochem Biophys Res Commun* 2017;**485**:366–371. https://doi.org/10.1016/j.bbrc.2017.02.071
140. Aroor AR, Habibi J, Ford DA, Nistala R, Lastra G, Manrique C, Dunham MM, Ford KD, Thyfault JP, Parks EJ, Sowers JR, Rector RS. Dipeptidyl peptidase-4 inhibition ameliorates Western diet-induced hepatic steatosis and insulin resistance through hepatic lipid remodeling and modulation of hepatic mitochondrial function. *Diabetes* 2015;**64**:1988–2001. https://doi.org/10.2337/db14-0804
141. Xu B, Shen T, Chen L, Xia J, Zhang C, Wang H, Yu M, Lei T. The effect of sitagliptin on lipid metabolism of fatty liver mice and related mechanisms. *Med Sci Monit* 2017;**23**:1363–1370. https://doi.org/10.12659/MSM.900033
142. Piccirillo F, Mastroberardino S, Nusca A, Frau L, Guarino L, Napoli N, Ussia GP, Grigioni F. Novel antidiabetic agents and their effects on lipid profile: a single shot for several cardiovascular targets. *Int J Mol Sci* 2023;**24**:10164. https://doi.org/10.3390/ijms241210164
143. Bergman M, Gidez LI, Eder HA. The effect of glipizide on HDL and HDL subclasses. *Diabetes Res* 1986;**3**:245–248.
144. Campbell IW, Menzies DG, Chalmers J, McBain AM, Brown IR. One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. *Diabete Metab* 1994;**20**:394–400.
145. Buse JB, Tan MH, Prince MJ, Erickson PP. The effects of oral anti-hyperglycaemic medications on serum lipid profiles in patients with type 2 diabetes. *Diabetes Obes Metab* 2004;**6**:133–156. https://doi.org/10.1111/j.1462-8902.2004.00325.x
146. Chen KW, Juang JH, Huang HS, Lin JD, Huang BY, Huang MJ. Effect of gliclazide on plasma lipids and pancreatic beta cell function in non-insulin-dependent diabetes mellitus. *Changgeng Yi Xue Za Zhi* 1993;**16**:246–250.
147. Zurro Hernandez J, Lavielle R. Is sulphonylurea therapy effective long term? A 3-year study with gliclazide. *Curr Med Res Opin* 1986;**10**:351–358. https://doi.org/10.1185/03007998609111102
148. Mailhot J. Efficacy and safety of gliclazide in the treatment of non-insulin-dependent diabetes mellitus: a Canadian multicenter study. *Clin Ther* 1993;**15**:1060–1068.
149. Salman S, Salman F, Satman I, Yilmaz Y, Ozer E, Sengül A, Demirel HÖ, Karşıdağ K, Dinççağ N, Yılmaz MT. Comparison of acarbose and gliclazide as first-line agents in patients with type 2 diabetes. *Curr Med Res Opin* 2001;**16**:296–306. https://doi.org/10.1185/030079901750120231
150. Li Y, Xu W, Liao Z, Yao B, Chen X, Huang Z, Hu G, Weng J. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. *Diabetes Care* 2004;**27**:2597–2602. https://doi.org/10.2337/diacare.27.11.2597
151. Aslan I, Kucuksayan E, Aslan M. Effect of insulin analog initiation therapy on LDL/HDL subfraction profile and HDL associated enzymes in type 2 diabetic patients. *Lipids Health Dis* 2013;**12**:54. https://doi.org/10.1186/1476-511X-12-54
152. Fadini GP, Iori E, Marescotti MC, Vigili de Kreutzenberg S, Avogaro A. Insulin-induced glucose control improves HDL cholesterol levels but not reverse cholesterol transport in type 2 diabetic patients. *Atherosclerosis* 2014;**235**:415–417. https://doi.org/10.1016/j.atherosclerosis.2014.05.942
153. Sadur CN, Eckel RH. Insulin-mediated increases in the HDL cholesterol/cholesterol ratio in humans. *Arteriosclerosis* 1983;**3**:339–343. https://doi.org/10.1161/01.ATV.3.4.339
154. Lewis GF, Uffelman KD, Szeto LW, Weller B, Steiner G. Interaction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans. *J Clin Invest* 1995;**95**:158–166. https://doi.org/10.1172/JCI117633
155. Pavlic M, Xiao C, Szeto L, Patterson BW, Lewis GF. Insulin acutely inhibits intestinal lipoprotein secretion in humans in part by suppressing plasma free fatty acids. *Diabetes* 2010;**59**:580–587. https://doi.org/10.2337/db09-1297

156. Ruge T, Sukonina V, Kroupa O, Makoveichuk E, Lundgren M, Svensson MK, Olivecrona G, Eriksson JW. Effects of hyperinsulinemia on lipoprotein lipase, angiopoietin-like protein 4, and glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 in subjects with and without type 2 diabetes mellitus. *Metabolism* 2012;**61**:652–660. https://doi.org/10.1016/j.metabol.2011.09.014
157. Semenkovich CF, Wims M, Noe L, Etienne J, Chan L. Insulin regulation of lipoprotein lipase activity in 3T3-L1 adipocytes is mediated at posttranscriptional and posttranslational levels. *J Biol Chem* 1989;**264**:9030–9038. https://doi.org/10.1016/S0021-9258(18)81898-1
158. Yost TJ, Froyd KK, Jensen DR, Eckel RH. Change in skeletal muscle lipoprotein lipase activity in response to insulin/glucose in non-insulin-dependent diabetes mellitus. *Metabolism* 1995;**44**:786–790. https://doi.org/10.1016/0026-0495(95)90193-0
159. Farese RJ, Yost TJ, Eckel RH. Tissue-specific regulation of lipoprotein lipase activity by insulin/glucose in normal-weight humans. *Metabolism* 1991;**40**:214–216. https://doi.org/10.1016/0026-0495(91)90178-Y
160. Sadur CN, Eckel RH. Insulin stimulation of adipose tissue lipoprotein lipase. Use of the euglycemic clamp technique. *J Clin Invest* 1982;**69**:1119–1125. https://doi.org/10.1172/JCI110547
161. Yki-Järvinen H, Taskinen MR, Koivisto VA, Nikkilä EA. Response of adipose tissue lipoprotein lipase activity and serum lipoproteins to acute hyperinsulinaemia in man. *Diabetologia* 1984;**27**:364–369. https://doi.org/10.1007/BF00304851
162. Vidal H, Auboeuf D, De Vos P, Staels B, Riou JP, Auwerx J, Laville M. The expression of ob gene is not acutely regulated by insulin and fasting in human abdominal subcutaneous adipose tissue. *J Clin Invest* 1996;**98**:251–255. https://doi.org/10.1172/JCI118786
163. Semova I, Levenson AE, Krawczyk J, Bullock K, Gearing ME, Ling AV, Williams KA, Miao J, Adamson SS, Shin D-J, Chahar S, Graham MJ, Crooke RM, Hagey LR, Vicent D, de Ferranti SD, Kidambi S, Clish CB, Biddinger SB. Insulin prevents hypercholesterolemia by suppressing 12α-hydroxylated bile acids. *Circulation* 2022;**145**:969–982. https://doi.org/10.1161/CIRCULATIONAHA.120.045373