Lipid management in Type 2 diabetes: the case for combination therapy?

Cardiovascular disease determines the prognosis of patients with Type 2 diabetes, and because lipids play a central role in atherogenesis, lipid management in diabetic patients is of paramount importance. Given the large body of evidence demonstrating the cardiovascular risk reduction with the primarily low-density lipoprotein-lowering statins, these drugs represent the basis of lipid management in patients with Type 2 diabetes. However, the majority of cardiovascular events even with potent statin therapy cannot be prevented. Combination therapy with other lipid-lowering interventions therefore appears interesting as it may provide additional benefit. Data on the safety and efficacy of combination lipid therapy from large outcome trials are still limited. However, the evidence already available provides a rationale for combination lipid therapy in patients with Type 2 diabetes.

KEYWORDS: anion exchange resins ■ ezetimibe ■ fibrates ■ lipid therapy ■ niacin ■ omega-3 fatty acids ■ pioglitazone ■ statins ■ Type 2 diabetes

Christoph H Saely[1,2,3]*, Veronika Drexel[1]*, Alexander Vonbank[1,2,3] & Heinz Drexel[†1,2,3,4]

[1]Vorarlberg Institute for Vascular Investigation & Treatment (VIVIT), Feldkirch, Austria
[2]Department of Medicine & Cardiology, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
[3]Private University of the Principality of Liechtenstein, Triesen, Liechtenstein
[4] Drexel University College of Medicine, Philadelphia, PA, USA
[†]Author for correspondence: Department of Medicine & Cardiology & VIVIT Institute, Academic Teaching Hospital, Feldkirch, Austria
Tel.: +43 5522 303 2670
Fax: +43 5522 303 7533
vivit@lkhf.at
**Authors contributed equally*

Cardiovascular disease determines prognosis in patients with Type 2 diabetes

Atherosclerosis determines the prognosis of patients with diabetes. Cardiovascular risk in Type 2 diabetic patients is increased by a factor of two to three, and diabetes approximately doubles the risk of death after cardiovascular events. Mainly owing to their increased cardiovascular risk, the life expectancy of patients with Type 2 diabetes is reduced by more than 7 years [1]. Lipids and lipoproteins play a key role in the pathogenesis of atherosclerosis; therefore, lipid therapy in diabetic patients is of paramount importance.

Lipid metabolism in Type 2 diabetes

The typical lipid problem in patients with Type 2 diabetes is not high low-density lipoprotein (LDL)-cholesterol but rather a combination of low high-density lipoprotein (HDL)-cholesterol, high triglycerides and highly atherogenic small, dense LDL particles [2]. This cluster of lipid abnormalities is referred to as diabetic dyslipidemia.

Diabetic dyslipidemia is closely related to insulin resistance, the key pathophysiological feature of Type 2 diabetes [3]. Insulin resistance is associated with an increased release of free fatty acids from adipose tissue and consequently with an increased production of triglycerides, which are secreted from the liver packed in very-low-density lipoprotein (VLDL) particles. Blood triglycerides thus increase. Mediated by the cholesteryl ester transfer protein (CETP), triglycerides from the triglyceride-rich VLDL particles are exchanged for cholesterol from the cholesterol-rich LDL and HDL particles. From these triglyceride-enriched LDL and HDL particles triglycerides are then removed by lipases, rendering both LDL and HDL particles smaller than before the modification.

Smaller LDL particles enter into the vessel wall more readily, are oxidized more rapidly and are therefore more atherogenic than larger LDL particles. In addition, given the smaller size of LDL particles in patients with Type 2 diabetes, more LDL particles are present at a given LDL-cholesterol level in these patients than in nondiabetic individuals. More LDL particles, in turn, mean more danger for the vessel walls. With respect to HDL, the smaller particles are more rapidly cleared from circulation, which explains the low HDL-cholesterol observed in diabetic patients. Moreover, the smaller HDL particles are dysfunctional and have impaired atheroprotective properties [3].

We and others have demonstrated that diabetic dyslipidemia is not only characteristic for patients with diabetes but that it is also an important cardiovascular risk factor in diabetic individuals. In a large population of coronary patients who have undergone angiography we found that the triad of low HDL-cholesterol, high triglycerides and small LDL particles is a better predictor of cardiovascular events than serum levels of LDL-cholesterol [4]. This observation concords with an important sub-group

part of future medicine fsg

analysis of the Treating to New Targets (TNT) trial, which demonstrated that even with LDL-cholesterol levels lowered to less than 70 mg/dl, low HDL-cholesterol is significantly associated with a high incidence of cardiovascular events [5]. In particular, we found that high levels of triglycerides, low HDL-cholesterol and small LDL particles are of paramount importance for the prognosis of coronary patients with diabetes who receive statin therapy [6]. In another study, we demonstrated that from all metabolic syndrome traits the dyslipidemic stigmata (i.e., low HDL-cholesterol and high triglyceride levels) are the strongest predictors of cardiovascular events [7].

Thus, diabetic dyslipidemia is clinically important and its specific treatment appears to be promising. Apart from lifestyle interventions, such as reduction of bodyweight, increased physical activity and nicotine abstinence [8–10], fibrates, omega-3 fatty acids and niacin are available pharmaceutical options to improve this pattern of dyslipidemia. Fibrates and omega-3 fatty acids primarily lower triglyceride levels; niacin also lowers triglyceride levels and in addition is the best option currently available to increase HDL-cholesterol [3]. Furthermore, the glucose-lowering drug pioglitazone significantly lowers triglycerides and significantly increases HDL-cholesterol [11]. The major effects of important lipid-modifying drugs are summarized in Table 1.

Statins: the basis of lipid management in patients with diabetes

Even though statins primarily lower LDL-cholesterol and do not strongly improve the high triglycerides, low HDL-cholesterol, small LDL particle size pattern of diabetic dyslipidemia, they represent the basis of lipid management in patients with diabetes, given the ample evidence for cardiovascular risk reduction with statin therapy.

Statins inhibit the *de novo* synthesis of cholesterol in the liver and in other tissues [2]. Consequently, the liver produces less VLDL and the serum concentration of LDL-cholesterol is lowered. Furthermore, triglyceride levels are also lowered by statins and HDL-cholesterol is marginally increased, but the main effect of statins remains lowering of LDL-cholesterol. Statins are among the most successful therapeutic interventions of the past 15 years.

Numerous randomized controlled clinical trials prove the safety and efficacy of statin therapy to reduce cardiovascular events in various patient populations. A large meta-analysis including more than 90,000 patients from 14 randomized trials and recording over 14,000 severe vascular events showed a significant reduction of serious cardiovascular events by 21% per mM (i.e., per 39 mg/dl) LDL-cholesterol lowering by statins as well as a significant 12% reduction in total mortality [12].

Statins in particular are effective in patients with diabetes. The Collaborative Atorvastatin Diabetes Study (CARDS) [13] demonstrated a significant reduction of cardiovascular events with atorvastatin 10 mg/day in patients with diabetes who did not have known atherosclerotic disease over a follow-up period of 3.9 years. In addition, in secondary prevention, statin therapy is highly effective in reducing cardiovascular events in diabetic patients. This is illustrated by an analysis from the TNT trial. Overall, more than 10,000 patients with stable artery disease were included in that trial [14] and were randomized to atorvastatin 10 mg/day or to atorvastatin 80 mg/day. From the total cohort, 1501 patients had diabetes; these patients were followed-up for a mean of 4.1 years. As with the total study population, atorvastatin 80 mg/day significantly reduced cardiovascular event risk in patients with diabetes [15]. Due to the very high absolute risk

Table 1. Average effects of lipid-lowering drugs.

Drug	Change in total cholesterol (%)	Change in triglycerides (%)	Change in LDL-cholesterol (%)	Change in HDL-cholesterol (%)	Ref.
Statins	-20	-14	-29	+3	[104]
Resins	-9	0	-13	0	[3]
Ezetimibe	-12	-2	-18	+1	[105]
CETP inhibitors	14	14	-11	+62	[106]
Niacin	-20	-25	-15	+25	[3]
Fibrates	-10	-30	-10	+10	[107]
Pioglitazone	0	-12	0	+15	[108]
Omega-3 fatty acids	0	-25	0	+3	[109]

CETP: Cholesteryl ester transfer protein; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

of the included diabetic patients with coronary artery disease, the number needed to treat was low (only 24 patients). Subgroup analyses from other trials have also demonstrated the efficacy of statin therapy in diabetic patients. A meta-analysis of the Cholesterol Treatment Trialists Collaborators (CTTC), including more than 16,000 patients, confirmed that the relative risk of cardiovascular events is reduced to almost an identical amount in diabetic patients as in patients without diabetes [12].

Statins differ considerably with respect to their LDL-cholesterol-lowering power [16]. For example, pravastatin 40 mg/day lowers LDL-cholesterol by approximately 30%, the more potent simvastatin at the same dosage lowers LDL-cholesterol by almost 40%; atorvastatin 40 mg/day achieves approximately 50% LDL-cholesterol reduction and 40 mg/day rosuvastatin, on average, reduces LDL-cholesterol by 55%. However, with all statins, doubling the dose helps to reduce LDL-cholesterol by only approximately an additional 7%. Therefore, when a standard dose of statin with moderate LDL-cholesterol-lowering power is insufficient to reach LDL-cholesterol goals, it is recommended to switch to more potent statins (in particular to the highly potent statins rosuvastatin or atorvastatin) rather than to increase the statin dose. Alternatively, combination lipid therapy could be considered. Potential partners for combination therapy with statins are described in the following sections.

To summarize, statins significantly lower the cardiovascular event risk in diabetic patients and thus help to improve their prognosis. Therefore, statins are a cornerstone in the lipid management of patients with Type 2 diabetes and the majority of diabetic patients qualify for statin therapy. As a consequence, lipid-lowering drugs other than statins will usually be given in combination therapy with statins.

Combination therapy appears to be important. Despite the great success with statins, the majority of cardiovascular events cannot be prevented by statin monotherapy, and vascular risk in high-risk patients remains high despite statin treatment. As many as one in seven statin-treated patients in the CTTC meta-analysis suffered cardiovascular events over a period of 5 years [12]. Considering that the high triglycerides, low HDL, small LDL particle size pattern of diabetic dyslipidemia is a major driving force behind cardiovascular risk in patients with diabetes [6], drugs that specifically improve diabetic dyslipidemia are of significant interest as add-on therapies in statin-treated patients with diabetes and shall be discussed in more detail in the following sections.

Fibrates

Fibrates activate transcription factors, referred to as peroxisome proliferator-activated receptor-α (PPAR-α), which alter the transcription rate of target genes that play an important role in the development of atherosclerosis [17].

Fibrates primarily lower triglyceride levels. A pooled meta-analysis of placebo-controlled fibrate trials reported a reduction in triglyceride levels by approximately 30%, a reduction in total cholesterol by approximately 8% and an increase in HDL-cholesterol by approximately 9% with fibrates [18]. Fibrates have also been shown to change the LDL particle profile from small dense to less atherogenic large particles [19,20]. Clinical studies with fibrate plus statin combination treatment have shown superior lipid-modifying efficacy compared with statin monotherapy [21]. It is recommended that fibrates are used with caution in combination with statins owing to an increased risk of myopathy. However, severe muscle problems, such as rhabdomyolysis, are rare, in particular with fenofibrate. Fenofibrate does not adversely influence the metabolism or pharmacokinetics of any of the commonly prescribed statins [22]. Further safety issues of statin plus fibrate combination therapy, such as a possible rise in liver enzymes or gastrointestinal problems, are of minor importance [21,23].

The evidence supporting cardiovascular risk reduction by fibrates is clearly inferior to the broad evidence for the efficacy of statin treatment to prevent cardiovascular events. However, there are clinical end point data that demonstrate a cardiovascular risk reduction with fibrate therapy.

In the Helsinki Heart Study, gemfibrozil reduced cardiovascular events in middle-aged dyslipidemic men without established coronary heart disease by 34%; however, the benefit at 5 years was limited to those with increased triglyceride levels and low HDL-cholesterol [24]. Interestingly, diabetic patients treated with gemfibrozil experienced a greater event reduction of 41% [25].

In the Veterans Affairs HDL Intervention Trial (VA-HIT) [26], gemfibrozil treatment in men with low HDL-cholesterol resulted in a 22% reduction in nonfatal myocardial infarction and coronary heart disease death at a median follow-up of 5.1 years. Interestingly, the cardiovascular benefit in VA-HIT was strongly correlated with on-treatment HDL-cholesterol,

but not with on-treatment triglyceride levels or LDL-cholesterol [25]. As in the Helsinki Heart Study, cardiovascular risk reduction in the VA-HIT trial was greater (24 and 32%, respectively, depending on which criteria for the diagnosis of diabetes were applied) among patients with diabetes [12,25].

Thus, gemfibrozil has proven beneficial to reduce cardiovascular events in monotherapy, particularly in patients with diabetes. However, no data are available to determine whether gemfibrozil is effective in further reducing cardiovascular risk in patients already receiving statins. Statins are usually very well tolerated, but in clinical practice up to 15% of patients receiving statins report muscular symptoms [27]. In a managed care setting, the relative risk of clinical myositis (symptoms of muscle pain plus elevated creatinine kinase) compared with controls was increased by a factor of three with statin therapy and by a factor of nine with statin plus fibrate therapy [28]. Since the combination of gemfibrozil with a statin puts patients at an increased risk of myopathy, this combination is not recommended in the absence of direct proof of its efficacy to reduce cardiovascular events.

In the Bezafibrate Infarction Prevention (BIP) study, bezafibrate did not reduce all-cause or cardiac mortality in the entire study population, but was associated with a 31% relative reduction in the risk of myocardial infarction among patients with metabolic syndrome [29]. Of note, bezafibrate is not only a PPAR-α, but also a PPAR-δ and γ-ligand [30]. Furthermore, bezafibrate, like fenofibrate (the major trials for which are discussed below), can increase adiponectin and improve insulin sensitivity [31].

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial [32] 9725 patients with Type 2 diabetes were randomized to fenofibrate or placebo. In the fenofibrate arm, a 22% reduction in triglyceride levels, a 6% decrease in LDL-cholesterol and a 1% increase in HDL-cholesterol was observed. The primary outcome of coronary heart disease, death and nonfatal myocardial infarction was not significantly reduced. However, during the trial 70% of the placebo versus 8% of the fenofibrate group started another lipid therapy (mainly statins), which may have concealed the effect of fenofibrate. Nonfatal myocardial infarction was significantly reduced by 24% and also total cardiovascular events (comprising cardiovascular death, myocardial infarction, stroke and revascularization) were reduced significantly by 11%. Importantly, a *post hoc* analysis demonstrated a 27% reduction in cardiovascular events among participants with hypertriglyceridemia and low HDL-cholesterol [201]. Given its methodological limitations, the FIELD trial therefore should not be interpreted to prove a lack of benefit with fenofibrate. Indeed, the secondary study outcomes, in particular the cardiovascular risk reduction achieved with fenofibrate in dyslipidemic subjects, do provide evidence in favor of fenofibrate.

The lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial addressed the important question of whether the combination of simvastatin and fenofibrate can prevent cardiovascular events in patients with diabetes over and above simvastatin monotherapy [33]. Simvastatin was given open labeled at baseline, and fenofibrate or placebo were started 4 weeks later. During 4.7 years of follow-up, the combination therapy of fenofibrate plus simvastatin did not reduce the rate of cardiovascular events compared with simvastatin monotherapy. Similar to the *post hoc* evaluations from the FIELD trial, there was a significant reduction in major cardiovascular events among patients with high triglyceride levels and low HDL-cholesterol in the ACCORD trial. In patients without dyslipidemia this favorable effect was absent [34]. Other subgroup analyses suggested a benefit for men and possible harm for women. Importantly, despite its failure to show a significant reduction of the primary study end point with fenofibrate, the ACCORD trial by no means disproves the potential of fenofibrate to reduce cardiovascular events in dyslipidemic patients. On the contrary, the trial provides evidence in favor of fenofibrate plus statin combination in dyslipidemic patients with diabetes.

In the Diabetes Atherosclerosis Intervention Study (DAIS), 418 patients with Type 2 diabetes were randomized to fenofibrate or placebo and followed for 3 years [35]. In the group randomized to fenofibrate there was significantly less coronary angiographic progression in minimum lumen diameter and percentage diameter stenosis, whereas there was no significant effect on the average mean segment diameter.

A meta-analysis of the effects of fibrates on cardiovascular outcomes indicated that fibrate therapy is associated with a clinically important decrease in nonfatal myocardial infarction, but has little, if any, effect on all-cause mortality [36]. Another meta-analysis including five randomized trials with fibrates (ACCORD,

FIELD, BIP, Helsinki Heart Study and VA-HIT) demonstrated that fibrates induced a significant 35% reduction in major cardiovascular events in patients with diabetic dyslipidemia [37]. The lipid arm of the ACCORD trial was the only investigation addressing the question of whether a fibrate added to statin treatment can reduce cardiovascular events. It was neutral with respect to the primary end point. Therefore, the evidence in favor of cardiovascular event reduction by a combination therapy with statins plus fibrates is not very strong at present. Nevertheless, the secondary results from the ACCORD trial showing a benefit with the combination of simvastatin plus fenofibrate in dyslipidemic patients, which are in line with previous results from the FIELD trial, provide a rationale for this combination.

Omega-3 fatty acids

Omega-3 fatty acids at relatively high doses of about 3–4 g/day significantly reduce triglyceride levels by approximately 8% for every gram of the drug (the dose responses are highly variable between patients) [38]. In an investigation involving patients with coronary heart disease and serum triglyceride levels greater than 205 mg/dl, the addition of omega-3 fatty acids 4 g/day to simvastatin 10–40 mg/day significantly decreased triglyceride levels by 28%, non-HDL-cholesterol by 18% and VLDL-cholesterol by 40% at 12 weeks compared with simvastatin monotherapy [39].

Omega-3 fatty acids operate by various mechanisms of action. Incorporation into cell membranes is followed by modification of the physical characteristics and activity of membrane-bound proteins. After being released by intracellular phospholipases omega-3 fatty acids interact with ion channels, are converted into bioactive eicosanoids and act as ligands for nuclear transcription factors, thereby altering gene expression [40]. Putative mechanisms for how omega-3 fatty acids might reduce the risk for cardiovascular events, besides a decrease in triglyceride levels, include antiarrhythmic, antiplatelet and anti-inflammatory effects [41,42]. Potential adverse effects of omega-3 fatty acids include an increase in LDL-cholesterol and increased bleeding time as a result of interference with platelet function, as well as fishy aftertaste and gastrointestinal disturbances, which are common and may compromise compliance [43]. Overall, however, a statin plus omega-3 fatty acid combination therapy is definitely considered safe and is not associated with an increased risk of myopathy [44]. Fish consumption and dietary marine oil are associated with a reduced incidence of cardiovascular events and coronary disease mortality [45]. Three large trials – the Gruppo Italiano per le Studio della Sopravivenza nell' Infarto miocardio (GISSI)-Preventione trial [46], the Japan Eicosapentaenoic acid Lipid Intervention Study (JELIS) [46] and the GISSI heart failure trail [47] – demonstrated clinical outcome benefits of dietary supplementation with omega-3 fatty acids. However, a systematic review could not demonstrate a clear effect of omega-3 fatty acid supplementation on total mortality or combined cardiovascular events [48]. The Outcome Reduction with Intitial Glargine InterventioN (ORIGIN) trial is currently investigating the effects of omega-3 fatty acids versus placebo on cardiovascular death in more than 12,000 patients with impaired glucose metabolism [49]. No data are currently available to determine whether omega-3 fatty acids reduce cardiovascular events when given in combination with statins over and above statin monotherapy.

Pioglitazone

Pioglitazone is an agonist of the PPAR-γ receptor with beneficial effects on insulin sensitivity, lipid levels and inflammatory markers. In addition to its glucose-lowering effect, pioglitazone raises HDL-cholesterol by 15–20% and lowers triglyceride levels by 40–50% [50].

The Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial demonstrated that pioglitazone slowed the progression of carotid intima-media thickness [51], and the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial demonstrated that pioglitazone slowed the progression of coronary atherosclerosis [52]. Interestingly, *post hoc* analyses showed that the rise in HDL-cholesterol with pioglitazone was the strongest predictor of its ability to slow carotid intima-media thickness progression [53].

In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study, a large trial that tested the impact of pioglitazone on the incidence of cardiovascular events in diabetic patients with established cardiovascular disease, pioglitazone did not reduce the primary end point of cardiovascular events [54]. However, severe clinical end points (myocardial infarction and stroke) were significantly reduced in this trial. In addition,

a meta-analysis demonstrated a significant cardiovascular benefit with pioglitazone [55]. Interestingly, the thiazolidindione rosiglitazone does not share the favorable effects of pioglitazone on lipid parameters, does not reduce cardiovascular events and, recently, because there is a concern that cardiovascular events may be increased with rosiglitazone [56,57], it has been withdrawn from the European market. Unfortunately, pioglitazone also has some adverse effects, most importantly an increased risk of heart failure (but importantly not of heart failure mortality) and a reduction in bone mineral density, which confers an increased fracture risk, particularly among elderly women [58].

Niacin

Niacin acts by inhibiting the hepatic catabolism of apolipoprotein A1, the major apolipoprotein of HDL, resulting in longer HDL half-life and higher HDL plasma concentrations. In addition, by inhibiting the hepatic enzymes required for triglyceride synthesis, niacin lowers the secretion of VLDL from the liver and consequently serum triglyceride levels [59].

A combination therapy of niacin with simvastatin is more effective in raising HDL-cholesterol, in lowering triglyceride levels and in lowering LDL-cholesterol compared with simvastatin monotherapy (by 27, 30 and 23%, respectively) [60]. Interestingly, there is no increased risk of myopathy or rhabdomyolysis when niacin is used in combination with a statin [61].

A meta-analysis of 23 lipid trials found that the sum of the percentage LDL-cholesterol lowering and the percentage HDL-cholesterol raising is the best predictor of clinical events [62]. Niacin addresses both parameters. In line with this, evidence exists to demonstrate cardiovascular risk reduction with niacin.

In monotherapy, niacin has a proven potential to reduce cardiovascular events. The Coronary Drug Project in the prestatin era demonstrated a reduction of reinfarction by 29% with niacin, which is a magnitude of efficacy comparable to statin therapy [63]. Total mortality 10 years after study completion was significantly decreased in the niacin group compared with the placebo group [64]. The relative reduction in long-term mortality risk attributable to niacin was comparable in patients with and in those without the metabolic syndrome [65].

In the HDL Atherosclerosis Treatment Study (HATS) [66] a lipid therapy of simvastatin plus niacin resulted in 23% higher HDL-cholesterol and 40% lower LDL-cholesterol versus placebo. This combination therapy was associated with a small but detectable regression of proximal coronary plaques at angiography compared with the mean progression observed in the placebo group. Cardiovascular events were also significantly reduced. However, this trial was rather small and the results concerning cardiovascular event reduction cannot be considered definite. Only 16% of the 160 patients enrolled in this trial had diabetes, which does not allow meaningful subgroup analyses with respect to diabetes status.

In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER)-2 trial, 167 patients with well-controlled LDL-cholesterol levels but with marginally low HDL-cholesterol and elevated triglyceride levels were randomized to treatment with extended-release niacin plus simvastatin, or to monotherapy with simvastatin [67]. In this study, 27% of the enrolled patients had Type 2 diabetes and 50% had features of the metabolic syndrome. Combination therapy increased HDL-cholesterol by 21% and decreased triglyceride levels by 14%. The primary end point, the change in carotid intima-media thickness, did not significantly differ between study groups over a 12-month period. However, patients treated with statin alone had a significant increase in carotid intima-media thickness, whereas carotid intima-media thickness did not significantly change in the treatment group. Although ARBITER-2 was not powered to investigate the effect of niacin plus statin treatment on clinical outcomes, the frequency of clinical cardiovascular events tended to be higher among patients treated with statin monotherapy than in those treated with the combination therapy. In ARBITER-3, patients from the ARBITER-2 trial were followed-up for 24 months; carotid intima-media thickness regression became evident with the simvastatin–niacin combination therapy [68].

In two studies exploring the combination of niacin and the anion exchange resin colestipol, a higher percentage of subjects receiving combination therapy showed regression of coronary lesions compared with those receiving double placebo [69,70]. The Armed Forces REGression Study (AFREGS) likewise demonstrated a mean regression of coronary stenoses with combined niacin–gemfibrocil–cholestyramine treatment [71]. The lesion regression in these studies is noteworthy because only a few of the many statin monotherapy trials could achieve this goal [72,73]. In addition, it is noteworthy

that in the AFREGS trial, as in HATS, a statistically significant clinical event reduction was observed.

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6–HDL and LDL Treatment Strategies (ARBITER 6–HALTS) trial compared the effects of a combination therapy of niacin plus statin with the effects of a combination of ezetemibe plus statin on changes in the carotid intima-media thickness over a 14-month period in 208 patients [74]. Enrolled patients had established coronary artery disease or were otherwise at high risk and had a baseline LDL-cholesterol of less than 100 mg/dl and a baseline HDL-cholesterol of less than 50 mg/dl in men and less than 55 mg/dl in women. From these patients, 40% of those taking ezetimibe and 42% of those taking niacin had diabetes. With the niacin–statin combination a greater reduction in carotid intima-media thickness was observed when compared with the ezetemibe–statin combination. The effect of niacin therapy on mean carotid intima-media thickness was consistent across prespecified subgroups, including presence or absence of diabetes. As with the HATS trial, a significant reduction in cardiovascular events was observed with the niacin–statin combination. However, the number of clinical events in this trial was small and, therefore, cardiovascular event reduction over and above simvastatin monotherapy should not yet be considered as definitely proven.

Two large ongoing clinical outcome trials will answer the question of whether addition of niacin to statin-treated patients leads to further reduction of cardiovascular events, the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) trial [202] and the Heart Protection Study-2 – Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2-THRIVE) trial [203].

Overall, niacin is safe, both in monotherapy and also in combination with statins. While elevation of liver enzymes is possible, it is rare. Niacin has the potential to worsen glycemic control, but most studies have demonstrated that niacin therapy has only a minor effect on glucose levels in diabetic patients [75]. This must be weighed against the beneficial effects of niacin on diabetic dyslipidemia, which, as we have shown previously, is a major driving force behind cardiovascular event risk in statin-treated high-risk patients with Type 2 diabetes [6]. Importantly, the use of niacin has for a long time been limited as it causes vasodilation, known as a 'flush', which significantly impairs compliance with the drug. An extended-release formulation considerably improved flush symptoms and more recently the addition of the prostaglandin inhibitor laropiprant resulted in a formulation that is even more tolerable [76].

Cholesteryl transfer protein inhibitors

The first CETP inhibitor to be tested was torcetrapib. Although the drug increased HDL-cholesterol by 46% and in addition lowered LDL-cholesterol by 25%, it also significantly increased mortality in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial and all clinical trials with torcetrapib were consequently halted [77]. The reason for the failure of torcetrapib is unclear at present. One potential reason for the link between torcetrapib and unfavorable outcome may be an increase in aldosterone and blood pressure conferred by torcetrapib, but not by other CETP inhibitors. Therefore, other inhibitors of CETP are still tested, for example dalcetrapib and anacetrapib [78]. Recently, preliminary data from an ongoing anacetrapib trial have been presented which demonstrated that anacetrapib reduces LDL-cholesterol levels by nearly 40% and more than doubles HDL-cholesterol levels in patients with or at high risk of coronary heart disease [79]. Importantly, these preliminary trial data, at least for a time period of approximately 3 years, demonstrate a favorable safety profile of anacetrapib [80]. Therefore, a carefully optimistic attitude towards the concept of CETP inhibition may be justified.

Combination lipid therapy to further reduce LDL-cholesterol

Fibrates and omega-3 fatty acids primarily lower triglyceride levels, pioglitazone and niacin lower triglyceride levels and in addition efficaciously raise HDL-cholesterol. Niacin lowers triglyceride levels, raises HDL-cholesterol and lowers LDL-cholesterol. It thus has a hybrid position between drugs improving diabetic dyslipidemia and drugs lowering LDL-cholesterol. Statins are the most important LDL-lowering drugs. However, ezetimibe and anion exchange resins help to further reduce LDL-cholesterol in statin-treated patients [3]. Considering that LDL-cholesterol has a causal role in atherogenesis and because lower LDL-cholesterol is associated with a lower risk of cardiovascular events, combination lipid therapy to further reduce

LDL-cholesterol appears to be an interesting option to reduce cardiovascular risk in high-risk patients, particularly in patients with diabetes.

Ezetimibe

Ezetemibe reduces cholesterol absorption from the intestine and is highly effective in lowering LDL-cholesterol, achieving an average decrease of 18% [81]. The combination of ezetimibe 10 mg/day with a standard statin (e.g., simvastatin 40 mg/day) reduces LDL-cholesterol to approximately the same amount as a highly potent statin such as rosuvastatin 40 mg/day [82]. Ezetimibe is extremely well tolerated and is considered safe, particularly in combination with statin therapy. Possible adverse effects, such as gastrointestinal discomfort, are of minor importance. Previous concerns regarding an increased cancer risk with ezetimibe have not been supported by meta-analyses [83].

Unfortunately, to date there is no evidence that the addition of ezetemibe to a standard statin further reduces cardiovascular events over and above statin monotherapy. The Effect of Ezetimibe plus Simvastatin versus Simvastatin alone on Atherosclerosis in Carotid Artery (ENHANCE) trial investigated the effect of a combination of ezetimibe plus simvastatin versus simvastatin monotherapy on the progression of carotid intima-media thickness over 2 years in patients with familial hypercholesterolemia. With regard to the primary comparison the trial was indeterminate [84]. However, the baseline carotid intima-media thickness in the ENHANCE trial was considerably lower than in previous intervention trials using carotid intima-media thickness as a primary end point; this may have concealed a beneficial effect of ezetimibe.

The Stop Atherosclerosis in Native Diabetics Study (SANDS) compared carotid intima-media thickness progression between a patient group randomized to an aggressive target for LDL-cholesterol (≤70 mg/dl) and blood pressure (systolic blood pressure ≤115 mmHg) and a patient group randomized to standard treatment. Overall, the carotid intima-media thickness regressed over 3 years with aggressive treatment and progressed with standard treatment [85]. In the aggressive treatment group approximately 30% of subjects received ezetimibe because of insufficient LDL-cholesterol lowering with statins alone. *Post hoc* analyses demonstrated that this subgroup achieved the same degree of LDL-cholesterol lowering and almost identical regression of carotid intima-media thickness as the subgroup of subjects treated aggressively without ezetimibe. This result is considered by some as an indirect support for the efficacy of ezetimibe to prevent the progression of carotid atherosclerosis [86].

The fact that there has been no evidence to date from clinical trials that demonstrate a benefit with ezetimbe plus statin combination therapy over and above the benefit achieved with statin monotherapy does not indicate that no such benefit exists; lack of evidence does not mean evidence of lack. Indeed, there are arguments in favor of ezetimibe plus statin combination therapy. There is very strong evidence for a causal role of LDL particles in the pathogenesis of atherosclerosis. Furthermore, meta-analyses of clinical trials employing both statin and non-statin therapy have confirmed the role of LDL lowering in determining clinical benefit and provided evidence against a substantial impact of pleiotropic statin effects on their efficacy to reduce cardiovascular events [87].

In line with this reasoning, recent data from the Simvastatin Ezetimibe Aortic Stenosis (SEAS) study demonstrate an efficacy of the combination simvastatin plus ezetimibe to reduce ischemic coronary end points in patients with aortic stenosis, although no effect of this combination on the progression of aortic stenosis was observed [88]. The effect of the combination on the incidence of coronary events was particularly strong in patients with mild aortic stenosis [89].

The Study of Heart And Renal Protection (SHARP) examined whether simvastatin 20 mg/day plus ezetimibe 10 mg/day compared with double placebo can reduce cardiovascular clinical events in 9438 patients with chronic kidney disease, of whom one-third were on dialysis and two-thirds in the predialysis state [90]. The trial clearly demonstrated a reduction of cardiovascular events with the simvastatin–ezetimibe combination therapy versus placebo [204]. However, as a consequence of the study design, the question of whether the same effect could also have been achieved with simvastatin monotherpy remains unanswered.

The ongoing IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) [205] is testing the effect of simvastatin 40 mg/day alone or in combination with ezetimibe 10 mg/day in reducing major cardiovascular events following acute coronary syndromes in approximately 25,000 patients.

Anion exchange resins

Anion exchange resins interact with cholesterol absorption from the intestine; unlike ezetimibe they are not taken up systemically. Their effect

on LDL-cholesterol is relatively modest; on average LDL-cholesterol reductions of 10–15% can be achieved [91,92]. Resins slightly increase triglyceride levels and do not significantly affect HDL-cholesterol. In the Primary Prevention Trial, cholestyramin monotherapy reduced the combined end point of coronary death or nonfatal myocardial infarction by 19% [92]. Anion exchange resins therefore have a role as an adjunct to statin treatment if LDL-cholesterol targets are not achieved. The safety of resins is well established. Their major disadvantage was low tolerability due to gastrointestinal side effects. Tolerability, however, could be significantly improved with the novel colesevelam hydrochloride formulation, which as an additional benefit lowers HbA_{1c} in patients with diabetes [93].

Compared with the first generation of bile acid sequestrants, the second generation colesevelam hydrochloride has a greater binding capacity for bile acids [94]. Clinical studies have shown that colesevelam monotherapy can lower LDL-cholesterol levels by 15–19% [95,96]. Furthermore, colesevelam hydrochloride can be safely combined with existing statin therapy in patients who would benefit from additional LDL-cholesterol lowering. Colesevelam hydrochloride, in combination with statin therapy, can result in LDL-cholesterol reductions of 42% (with simvastatin 10 mg) to 48% (with atorvastatin 10 mg) [97,98]. Importantly, there is evidence that colesevelam hydrocholride, in addition to lowering LDL-cholesterol, improves glycemic control in patients with diabetes [93,99–101]. Therefore, colesevelam hydrochloride is the only drug currently approved as an adjunct in the treatment of both hyperglycemia and hypercholesterolemia. It is thus a very interesting option for add-on therapy in diabetes patients treated with statins.

Cholesterol guidelines in patients with diabetes

Given the overwhelming evidence for cardiovascular risk reduction with primarily LDL-cholesterol-lowering statins, current guidelines on lipid therapy in patients with diabetes are strongly focused on LDL-cholesterol [102]. Type 2 diabetes is considered a coronary heart disease risk equivalent and, therefore, for all patients with Type 2 diabetes an LDL-cholesterol goal of at least less than 100 mg/dl is set. For the very high-risk subgroup of diabetic patients with established cardiovascular disease a lower LDL-cholesterol goal of less than 70 mg/dl is referred to as an option. Importantly, statin therapy is recommended irrespective of lipid values in patients with the combination of diabetes plus cardiovascular disease as well as in diabetic patients without cardiovascular disease who are over the age of 40 years and have one or more other cardiovascular disease risk factors.

Triglyceride levels of less than 150 mg/dl and HDL-cholesterol of less than 40 mg/dl in men and less than 50 mg/dl in women are considered desirable, but the current clinical practice recommendations of the American Diabetes Association do not explicitly recommend combination therapy to reach these goals. LDL-cholesterol-targeted statin therapy remains the preferred strategy; however, if targets are not reached on maximally tolerated doses of statins, it is recommended to consider combination therapy using statins and other lipid-lowering agents in order to achieve lipid targets.

Unfortunately, there is a considerable gap between guideline recommended targets or trial evidence and clinical reality. For example, an interesting recent evaluation of the real world treatment of mixed dyslipidemia in patients with diabetes revealed that over 40% of diabetes patients with mixed dyslipidemia received no lipid-modifying therapy at all and those who were treated were primarily prescribed statin monotherapy [103].

Conclusion

Given the large body of evidence from numerous large clinical trials, statin therapy is currently the basis for lipid management in patients with Type 2 diabetes. However, the majority of cardiovascular events even with potent statin therapy are not prevented. Combination therapy with other lipid-lowering interventions may provide additional benefits. Data from large outcome trials are still limited; however, currently available evidence to date already provides a rationale for combination lipid therapy in Type 2 diabetic patients.

Acknowledgements

The authors would like to thank Susanne Greber, Vlado Jankovic and Veronika Kiene for their help in the preparation of the manuscript.

Financial & competing interests disclosure

Christoph H Saely has received lecture fees from Pfizer, Merck Sharp & Dohme and Takeda, consulting fees from AstraZeneca, Merck Sharp & Dohme, Pfizer and Genzyme, and educational support from Merck, Pfizer and Takeda; Heinz Drexel has received lecture and consulting fees from

AstraZeneca, Merck, Pfizer, Merck Sharp & Dohme and Takeda. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Cardiovascular disease determines the prognosis of patients with Type 2 diabetes, and lipids play a key role in the development of cardiovascular disease.
- Statins primarily lower low-density lipoprotein (LDL)-cholesterol and in numerous controlled randomized trials have been shown to reduce cardiovascular events in various patient populations, in particular in patients with Type 2 diabetes.
- Statins are therefore the basis of lipid therapy in patients with Type 2 diabetes and lipid-lowering drugs other than statins are usually given in combination with statins.
- The majority of cardiovascular events, however, is not prevented by statin therapy.
- Patients with Type 2 diabetes typically exhibit a pattern of dyslipidemia with high triglyceride levels, low high-density lipoprotein (HDL)-cholesterol and small, dense LDL particles, which is hardly improved by LDL-cholesterol-lowering statin therapy.
- Fibrates and omega-3 fatty acids, alone and in combination with statin therapy, primarily reduce triglyceride levels.
- Niacin alone and in combination with statins reduces triglyceride levels and also efficaciously raises HDL-cholesterol and lowers LDL-cholesterol.
- Both ezetimibe and anion exchange resins alone and, in particular, in combination with statins lower LDL-cholesterol.
- Data from large clinical end point trials providing definitive proof for the efficacy of combination lipid therapy to prevent cardiovascular events over and above statin monotherapy in patients with diabetes are not yet available.

Bibliography

Papers of special note have been highlighted as:
- of interest

1 Franco OH, Steyerberg EW, Hu FB, Mackenbach J, Nusselder W: Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. *Arch. Intern. Med.* 167, 1145–1151 (2007).

2 Stancu C, Sima A: Statins: mechanism of action and effects. *J. Cell. Mol. Med.* 5, 378–387 (2001).

3 Drexel H: Statins, fibrates, nicotinic acid, cholesterol absorption inhibitors, anion-exchange resins, omega-3 fatty acids: which drugs for which patients? *Fundam. Clin. Pharmacol.* 23, 687–692 (2009).

- **Overview covering the current options of lipid management.**

4 Drexel H, Aczel S, Marte T *et al.*: Is atherosclerosis in diabetes and impaired fasting glucose driven by elevated LDL cholesterol or by decreased HDL cholesterol? *Diabetes Care* 28, 101–107 (2005).

5 Barter P, Gotto AM, LaRosa JC *et al.*: HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N. Engl. J. Med.* 357, 1301–1310 (2007).

6 Drexel H, Aczel S, Marte T, Vonbank A, Saely CH: Factors predicting cardiovascular events in statin-treated diabetic and non-diabetic patients with coronary atherosclerosis. *Atherosclerosis* 208, 484–489 (2010).

7 Saely CH, Aczel S, Marte T, Langer P, Hoefle G, Drexel H: The metabolic syndrome, insulin resistance, and cardiovascular risk in diabetic and nondiabetic patients. *J. Clin. Endocrinol. Metab.* 90, 5698–5703 (2005).

8 Knowler WC, Barrett-Connor E, Fowler SE *et al.*: Reduction in the incidence of Type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 346, 393–403 (2002).

9 Gardner CD, Kiazand A, Alhassan S *et al.*: Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA* 297, 969–977 (2007).

10 Johnson JL, Slentz CA, Houmard JA *et al.*: Exercise training amount and intensity effects on metabolic syndrome (from Studies of a Targeted Risk Reduction Intervention through Defined Exercise). *Am. J. Cardiol.* 100, 1759–1766 (2007).

11 Deeg MA, Buse JB, Goldberg RB *et al.*: Pioglitazone and rosiglitazone have different effects on serum lipoprotein particle concentrations and sizes in patients with Type 2 diabetes and dyslipidemia. *Diabetes Care* 30, 2458–2464 (2007).

12 Baigent C, Keech A, Kearney PM *et al.*: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366, 1267–1278 (2005).

- **This meta-analysis firmly establishes the efficacy and safety of statin therapy.**

13 Colhoun HM, Betteridge DJ, Durrington PN *et al.*: Primary prevention of cardiovascular disease with atorvastatin in Type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 364, 685–696 (2004).

14 LaRosa JC, Grundy SM, Waters DD *et al.*: Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N. Engl. J. Med.* 352, 1425–1435 (2005).

- **Proves the efficacy of high-dose atorvastatin to reduce cardiovascular events in patients with stable coronary artery disease over and above standard statin therapy.**

15 Shepherd J, Barter P, Carmena R *et al.*: Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 29, 1220–1226 (2006).

16 Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E: Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin and pravastatin across doses (STALLAR trial). *Am. J. Cardiol.* 92, 152–160 (2003).

17 Auwerx J, Schoonjans K, Fruchart JC, Staels B: Transcriptional control of triglyceride metabolism: fibrates and fatty acids change the expression of the LPL and apo C-III genes by activating the nuclear receptor PPAR. *Atherosclerosis* 124(Suppl.), S29–S37 (1996).

18 Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR: The role of fibrates in the prevention of cardiovascular disease – a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. *Am. Heart J.* 154, 943–953 (2007).

19 Feher MD, Caslake M, Foxton J, Cox A, Packard CJ: Atherogenic lipoprotein phenotype in Type 2 diabetes: reversal with micronised fenofibrate. *Diabetes Metab. Res. Rev.* 15, 395–399 (1999).

20 Vakkilainen J, Steiner G, Ansquer JC *et al.*: Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: the Diabetes Atherosclerosis Intervention Study (DAIS). *Circulation* 107, 1733–1737 (2003).

21 Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J: Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). *Am. J. Cardiol.* 95, 462–468 (2005).

22 Franssen R, Vergeer M, Stroes ES, Kastelein JJ: Combination statin–fibrate therapy: safety aspects. *Diabetes Obes. Metab.* 11, 89–94 (2009).

23 Jones PH, Davidson MH: Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am. J. Cardiol.* 95, 120–122 (2005).

24 Frick MH, Elo O, Haapa K *et al.*: Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N. Engl. J. Med.* 317, 1237–1245 (1987).

25 Rubins HB, Robins SJ, Collins D *et al.*: Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch. Intern. Med.* 162, 2597–2604 (2002).

26 Rubins HB, Robins SJ, Collins D *et al.*: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N. Engl. J. Med.* 341, 410–418 (1999).

27 Harper CR, Jacobson TA: The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. *Curr. Opin. Lipidol.* 18, 401–408 (2007).

28 McClure DL, Valuck RJ, Glanz M, Murphy JR, Hokanson JE: Statin and statin-fibrate use was significantly associated with increased myositis risk in a managed care population. *J. Clin. Epidemiol.* 60, 812–818 (2007).

29 Tenenbaum A, Motro M, Fisman EZ, Tanne D, Boyko V, Behar S: Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch. Intern. Med.* 165, 1154–1160 (2005).

30 Peters JM, Aoyama T, Burns AM, Gonzalez FJ: Bezafibrate is a dual ligand for PPARα and PPARβ: studies using null mice. *Biochim. Biophys. Acta* 1632, 80–89 (2003).

31 Hiuge A, Tenenbaum A, Maeda N *et al.*: Effects of peroxisome proliferator-activated receptor ligands, bezafibrate and fenofibrate, on adiponectin level. *Arterioscler. Thromb. Vasc. Biol.* 27, 635–641 (2007).

32 Keech A, Simes RJ, Barter P *et al.*: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with Type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 366, 1849–1861 (2005).

33 Ginsberg HN, Elam MB, Lovato LC *et al.*: Effects of combination lipid therapy in Type 2 diabetes mellitus. *N. Engl. J. Med.* 362, 1563–1574 (2010).

▪ **Addresses the efficacy of fenofibrate to reduce cardiovascular events over and above simvastatin monotherapy.**

34 Tenenbaum A, Fisman EZ: "If it ain't broke, don't fix it": a commentary on the positive-negative results of the ACCORD Lipid study. *Cardiovasc. Diabetol.* 9, 24 (2010).

35 Diabetes Atherosclerosis Intervention Study Investigators: Effect of fenofibrate on progression of coronary-artery disease in Type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet* 357, 905–910 (2001).

36 Jun M, Foote C, Lv J *et al.*: Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 375, 1875–1884 (2010).

37 Perkins WJ Jr: Combination lipid therapy in Type 2 diabetes. *N. Engl. J. Med.* 363, 694–695 (2010).

38 Rubenfire M, Brook RD, Rosenson RS: Treating mixed hyperlipidemia and the atherogenic lipid phenotype for prevention of cardiovascular events. *Am. J. Med.* 123, 892–898 (2010).

39 Durrington PN, Bhatnagar D, Mackness MI *et al.*: An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. *Heart* 85, 544–548 (2001).

40 Harris WS: Omega-3 fatty acids and cardiovascular disease: a case for omega-3 index as a new risk factor. *Pharmacol. Res.* 55, 217–223 (2007).

41 Balk E, Chung M, Lichtenstein A *et al.*: Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. *Evid. Rep. Technol. Asses* 93, 1–6 (2004).

42 Davidson MH: Mechanisms for the hypotriglyceridemic effect of marine omega-3 fatty acids. *Am. J. Cardiol.* 98, 27I–33I (2006).

43 Donnelly SM, Ali MA, Churchill DN: Effect of n-3 fatty acids from fish oil on hemostasis, blood pressure, and lipid profile of dialysis patients. *J. Am. Soc. Nephrol.* 2, 1634–1639 (1992).

44 Bays HE, Maki KC, McKenney J *et al.*: Long-term up to 24-month efficacy and safety of concomitant prescription omega-3-acid ethyl esters and simvastatin in hypertriglyceridemic patients. *Curr. Med. Res. Opin.* 26, 907–915 (2010).

45 Burr ML, Fehily AM, Gilbert JF *et al.*: Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet And Reinfarction Trial (DART). *Lancet* 2, 757–761 (1989).

46 Yokoyama M, Origasa H, Matsuzaki M *et al.*: Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 369, 1090–1098 (2007).

47 Tavazzi L, Maggioni AP, Marchioli R *et al.*: Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 372, 1223–1230 (2008).

48 Hooper L, Thompson RL, Harrison RA *et al.*: Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ* 332, 752–760 (2006).

49 Gerstein H, Yusuf S, Riddle MC, Ryden L, Bosch J*:* Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine InterventioN). *Am. Heart J.* 155, 26–32 (2008).

50 Nicholls SJ, Lundman P, Tardif JC: Diabetic dyslipidemia: extending the target beyond LDL cholesterol. *Eur. J. Cardiovasc. Prev. Rehabil.* 17 (Suppl. 1), S20–S24 (2010).

51 Mazzone T, Meyer PM, Feinstein SB *et al.*: Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in Type 2 diabetes: a randomized trial. *JAMA* 296, 2572–2581 (2006).

52 Nissen SE, Nicholls SJ, Wolski K *et al.*: Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with Type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA* 299, 1561–1573 (2008).

53 Davidson M, Meyer PM, Haffner S *et al.*: Increased high-density lipoprotein cholesterol predicts the pioglitazone-mediated reduction of carotid intima-media thickness progression in patients with Type 2 diabetes mellitus. *Circulation* 117, 2123–2130 (2008).

54 Dormandy JA, Charbonnel B, Eckland DJ *et al.*: Secondary prevention of macrovascular events in patients with Type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 366, 1279–1289 (2005).

55 Lincoff AM, Wolski K, Nicholls SJ, Nissen SE: Pioglitazone and risk of cardiovascular events in patients with Type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 298, 1180–1188 (2007).

56 Nissen SE, Wolski K: Rosiglitazone Revisited: An updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch. Intern. Med.* 170, 1191–1201 (2010).

57 Graham DJ, Ouellet-Hellstrom R, MaCurdy TE *et al.*: Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 304, 411–418 (2010).

58 Shah P, Mudaliar S: Pioglitazone: side effect and safety profile. *Expert Opin. Drug Saf.* 9, 347–354 (2010).

59 Kamanna VS, Kashyap ML: Mechanism of action of niacin. *Am. J. Cardiol.* 101, 20B–26B (2008).

60 Ballantyne CM, Davidson MH, McKenney J, Keller LH, Bajorunas DR, Karas RH: Comparison of the safety and efficacy of a combination tablet of niacin extended release and simvastatin vs simvastatin monotherapy in patients with increased non-HDL cholesterol (from the SEACOAST I study). *Am. J. Cardiol.* 101, 1428–1436 (2008).

61 Guyton JR, Bays HE: Safety considerations with niacin therapy. *Am. J. Cardiol.* 99, 22C–31C (2007).

62 Brown BG, Stukovsky KH, Zhao XQ: Simultaneous low-density lipoprotein-C lowering and high-density lipoprotein-C elevation for optimum cardiovascular disease prevention with various drug classes, and their combinations: a meta-analysis of 23 randomized lipid trials. *Curr. Opin. Lipidol.* 17, 631–636 (2006).

63 The Coronary Drug Project Research Group: Clofibrate and niacin in coronary heart disease. *JAMA* 231, 360–381 (1975).

64 Canner PL, Berge KG, Wenger NK *et al.*: Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J. Am. Coll. Cardiol.* 8, 1245–1255 (1986).

65 Canner PL, Furberg CD, McGovern ME: Benefits of niacin in patients with versus without the metabolic syndrome and healed myocardial infarction (from the Coronary Drug Project). *Am. J. Cardiol.* 97, 477–479 (2006).

66 Brown BG, Zhao XQ, Chait A *et al.*: Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N. Engl. J. Med.* 345, 1583–1592 (2001).

67 Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA: Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol (ARBITER) 2, a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 110, 3512–3517 (2004).

68 Taylor AJ, Lee HJ, Sullenberger LE: The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. *Curr. Med. Res. Opin.* 22, 2243–2250 (2006).

69 Brown G, Albers JJ, Fisher LD *et al.*: Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N. Engl. J. Med.* 323, 1289–1298 (1990).

70 Cashin-Hemphill L, Mack WJ, Pogoda JM, Sanmarco ME, Azen SP, Blankenhorn DH: Beneficial effects of colestipol-niacin on coronary atherosclerosis. A 4-year follow-up. *JAMA* 264, 3013–3017 (1990).

71 Zhao XQ, Krasuski RA, Baer J *et al.*: Effects of combination lipid therapy on coronary stenosis progression and clinical cardiovascular events in coronary disease patients with metabolic syndrome: a combined analysis of the Familial Atherosclerosis Treatment Study (FATS), the HDL-Atherosclerosis Treatment Study (HATS), and the Armed Forces REGression Study (AFREGS). *Am. J. Cardiol.* 104, 1457–1464 (2009).

72 Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF: Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 357, 577–581 (2001).

73 Crouse JR III, Raichlen JS, Riley WA *et al.*: Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA* 297, 1344–1353 (2007).

74 Taylor AJ, Villines TC, Stanek EJ *et al.*: Extended-release niacin or ezetimibe and carotid intima-media thickness. *N. Engl. J. Med.* 361, 2113–2122 (2009).

▪ **Compares the impact of niacin versus ezetimibe on the change in carotid intima-media thickness in patients receiving statin treatment.**

75 Bitzur R, Cohen H, Kamari Y, Shaish A, Harats D: Triglycerides and HDL cholesterol: stars or second leads in diabetes? *Diabetes Care* 32(Suppl. 2), S373–S377 (2009).

76 Paolini JF, Mitchel YB, Reyes R *et al.*: Effects of laropiprant on nicotinic acid-induced flushing in patients with dyslipidemia. *Am. J. Cardiol.* 101, 625–630 (2008).

77 Barter PJ, Caulfield M, Eriksson M *et al.*: Effects of torcetrapib in patients at high risk for coronary events. *N. Engl. J. Med.* 357, 2109–2122 (2007).

78 Miyares MA: Anacetrapib and dalcetrapib: two novel cholesteryl ester transfer protein inhibitors. *Ann. Pharmacother.* 45(1), 84–94 (2011).

79 Cannon CP, Shah S, Dansky HM *et al.*: Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N. Engl. J. Med.* 363, 2406–2415 (2010).

80 King A: Coronary heart disease: new hope for CETP inhibitors. *Nat. Rev. Cardiol.* 8, 5 (2011).

81 Bays HE, Neff D, Tomassini JE, Tershakovec AM: Ezetimibe: cholesterol lowering and beyond. *Expert Rev. Cardiovasc. Ther.* 6, 447–470 (2008).

82 Rossebo AB, Pedersen TR, Allen C *et al.*: Design and baseline characteristics of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. *Am. J. Cardiol.* 99, 970–973 (2007).

83 Peto R, Emberson J, Landray M *et al.*: Analyses of cancer data from three ezetimibe trials. *N. Engl. J. Med.* 359, 1357–1366 (2008).

84 Kastelein JJ, Akdim F, Stroes ES *et al.*: Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N. Engl. J. Med.* 358, 1431–1443 (2008).

85 Howard BV, Roman MJ, Devereux RB *et al.*: Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. *JAMA* 299, 1678–1689 (2008).

86 Fleg JL, Mete M, Howard BV *et al.*: 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.* 52, 2198–2205 (2008).

87 Robinson JG, Smith B, Maheshwari N, Schrott H: Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J. Am. Coll. Cardiol.* 46, 1855–1862 (2005).

88 Rossebo AB, Pedersen TR, Boman K *et al.*: Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N. Engl. J. Med.* 359, 1343–1356 (2008).

89 Holme I, Boman K, Brudi P *et al.*: Observed and predicted reduction of ischemic cardiovascular events in the Simvastatin and Ezetimibe in Aortic Stenosis trial. *Am. J. Cardiol.* 105, 1802–1808 (2010).

90 Baigent C, Landry M: Study of Heart And Renal Protection (SHARP). *Kidney Int.* 84(Suppl.), S207–S210 (2003).

91 Black DM: Gut-acting drugs for lowering cholesterol. *Curr. Atheroscler. Rep.* 4, 71–75 (2002).

92 Lipid Research Clinics Program: The Lipid Research Clinics Coronary Primary Prevention Trial results. I: Reduction in incidence of coronary heart disease. *JAMA* 251, 351–364 (1984).

93 Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR: Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled Type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care* 31, 1479–1484 (2008).

94 Braunlin W, Zhorov E, Guo A *et al.*: Bile acid binding to sevelamer HCl. *Kidney Int.* 62, 611–619 (2002).

95 Insull W Jr, Toth P, Mullican W *et al.*: Effectiveness of colesevelam hydrochloride in decreasing LDL cholesterol in patients with primary hypercholesterolemia: a 24-week randomized controlled trial. *Mayo Clin. Proc.* 76, 971–982 (2001).

96 Davidson MH, Dillon MA, Gordon B *et al.*: Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch. Intern. Med.* 159, 1893–1900 (1999).

97 Hunninghake D, Insull W Jr, Toth P, Davidson D, Donovan JM, Burke SK: Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis* 158, 407–416 (2001).

98 Knapp HH, Schrott H, Ma P *et al.*: Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. *Am. J. Med.* 110, 352–360 (2001).

99 Garg A, Grundy SM: Cholestyramine therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. A short-term, double-blind, crossover trial. *Ann. Intern. Med.* 121, 416–422 (1994).

100 Zieve FJ, Kalin MF, Schwartz SL, Jones MR, Bailey WL: Results of the glucose-lowering effect of WelChol study (GLOWS): a randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with Type 2 diabetes. *Clin. Ther.* 29, 74–83 (2007).

101 Bays HE, Goldberg RB, Truitt KE, Jones MR: Colesevelam hydrochloride therapy in patients with Type 2 diabetes mellitus treated with metformin: glucose and lipid effects. *Arch. Intern. Med.* 168, 1975–1983 (2008).

102 American Diabetes Association: Standards of medical care in diabetes – 2011. *Diabetes Care* 34(Suppl. 1), S11–S61 (2011).

▪ **Summarizes the American Diabetes Association's current recommendations on the clinical management of patients with diabetes.**

103 Toth PP, Zarotsky V, Sullivan JM, Laitinen D: Dyslipidemia treatment of patients with diabetes mellitus in a US managed care plan: a retrospective database analysis. *Cardiovasc. Diabetol.* 8, 26 (2009).

104 Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 360, 23–33 (2002).

105 Knopp RH, Gitter H, Truitt T *et al.*: Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur. Heart J.* 24, 729–741 (2003).

106 Clark RW, Sutfin TA, Ruggeri RB *et al.*: Raising high-density lipoprotein in humans through inhibition of cholesteryl ester transfer protein: an initial multidose study of torcetrapib. *Arterioscler. Thromb. Vasc. Biol.* 24, 490–497 (2004).

107 Robinson JG, Wang S, Smith BJ, Jacobson TA: Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. *J. Am. Coll. Cardiol.* 53, 316–322 (2009).

108 Derosa G, Salvadeo SA: Pioglitazone and rosiglitazone: effects of treatment with a thiazolidinedione on lipids and non conventional cardiovascular risk factors. *Curr. Clin. Pharmacol.* 3, 77–84 (2008).

109 Harris WS: n-3 fatty acids and serum lipoproteins: human studies. *Am. J. Clin. Nutr.* 65, 1645S–1654S (1997).

Websites

201 NHMRC Clinical Trials Centre. Fenofibrate reduces the risk of amputations in patients with Type 2 diabetes www.fieldstudy.info/investigators/CTC_PR_2008.asp (Accessed 19 January 2011)

202 AIM – HIGH trial Niacin Plus Statin to Prevent Vascular Events http://clinicaltrials.gov/ct2/show/NCT00120289 (Accessed 19 January 2011)

203 Treatment of HDL to Reduce the Incidence of Vascular Events HPS2-THRIVE http://clinicaltrials.gov/ct2/show/NCT00461630?term=HPS-2-THRIVE&rank=1 (Accessed 19 January 2011)

204 SHARP: Study of Heart and Renal Protection www.ctsu.ox.ac.uk/~sharp/ (Accessed 19 January 2011)

205 IMPROVE-IT: Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin (Study P04103AM3) http://clinicaltrials.gov/ct2/show/NCT00202878?term=improve+it&rank=1 (Accessed 19 January 2011)