

Dyslipidaemia of Obesity, Metabolic Syndrome and Type 2 Diabetes Mellitus: the Case for Residual Risk Reduction After Statin Treatment

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Abstract: Dyslipidaemia is frequently present in obesity, metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM). The predominant features of dyslipidaemia in these disorders include increased flux of free fatty acids (FFA), raised triglyceride (TG) and low high density lipoprotein cholesterol (HDL-C) levels, a predominance of small, dense (atherogenic) low density lipoprotein cholesterol (LDL) particles and raised apolipoprotein (apo) B values. Postprandial hyperlipidaemia may also be present. Insulin resistance (IR) appears to play an important role in the pathogenesis of dyslipidaemia in obesity, MetS and T2DM. The cornerstone of treatment of this IR-related dyslipidaemia is lifestyle changes and in diabetic patients, tight glycaemic control. In addition to these measures, recent clinical trials showed benefit with statin treatment. Nevertheless, a substantial percentage of patients treated with statins still experience vascular events. This residual vascular risk needs to be addressed. This review summarizes the effects of hypolipidaemic drug combinations (including statins with cholesterol ester protein inhibitors, niacin, fibrates or fish oil, as well as fibrate-ezetimibe combination) on the residual vascular risk in patients with obesity, MetS or T2DM.

Keywords: Dyslipidaemia, obesity, metabolic syndrome, type 2 diabetes mellitus, residual vascular risk.

INTRODUCTION

Dyslipidaemia is an important modifiable vascular risk factor [1, 2]. Elevated low density lipoprotein cholesterol (LDL-C) levels are the major target in the management of dyslipidaemia and statins are the most widely used hypolipidaemic agents for cardiovascular disease (CVD) prevention. However, the gains from CVD prevention over the last 4 decades are being challenged by a global epidemic of obesity, metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) [3]. Recent epidemiological data from the USA [4] and UK [5] show an unfavourable trend in CVD mortality in younger men and women (35 to 44 years), related to the obesity, MetS and T2DM epidemic. In these age groups, CVD mortality increased significantly for the first time in over 2 decades [4, 5]. Visceral adiposity, a marker of “dysfunctional adipose tissue”, plays a key role in the development of the MetS and T2DM. It is characterised by accumulation of fat in the central part of the body and correlates with insulin resistance (IR) [6]. Visceral adipocytes are large, insulin-resistant and highly active metabolically. Through the production of a variety of adipokines, adipocytes play a role in the pathogenesis of inflammation, dyslipidaemia and hypertension [7]. The co-existence of these risk factors increases the CVD morbidity and mortality

associated with obesity, MetS and T2DM [8]. In these disorders, the phenotype of dyslipidaemia is highly atherogenic. It usually manifests as the so-called “atherogenic lipid triad” consisting of elevated serum triglyceride (TG) levels, increased levels of small-dense LDL (sdLDL) particles and decreased levels of high density lipoprotein cholesterol (HDL-C) [9, 10].

We review the pathophysiology and treatment of dyslipidaemia associated with obesity, MetS and T2DM, focusing on strategies aiming at reducing the residual CVD risk [11] after statin treatment to LDL-C goal.

PATHOPHYSIOLOGY OF DYSLIPIDAEMIA ASSOCIATED WITH OBESITY, METS AND T2DM

Patients with obesity, MetS or T2DM show specific lipid abnormalities that promote atherosclerosis and contribute to the residual CVD risk observed in these patients after LDL-C reduction to treatment goals with statins and optimum treatment of comorbidities [11-14].

A. The Atherogenic Lipid Triad

In most cases, dyslipidaemia in patients with obesity, MetS and T2DM is characterized by (a) increased flux of free fatty acids (FFA), (b) raised TG values, (c) low HDL-C values, (d) increased small, dense LDL particles, and (e) raised apolipoprotein (apo) B levels [15, 16].

IR appears to play an important role in the pathogenesis of this type of dyslipidaemia [17]. IR is associated with enhanced lipolysis as well as reduced FFA uptake and esterifi-

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cation leading to an increased flux of FFA into non-adipose tissues, including the liver and muscle [17, 18]. Since FFA compete with glucose for cellular uptake and metabolism, they can further reduce insulin sensitivity, instituting a vicious cycle [19, 20].

Adipose tissue, through the secretion of adipokines [7], plays a central role in whole body homeostasis including food intake, regulation of energy balance, insulin action, lipid and glucose metabolism, angiogenesis and vascular remodelling, regulation of blood pressure (BP) and coagulation [21]. Excessive visceral adiposity increases the availability of FFA through the hydrolysis of adipocyte TG by a variety of lipases, including triglyceride lipase, lipoprotein lipase (LpL), hormone-sensitive lipase and endothelial lipase [22, 23]. Such increases in circulating FFA lead to TG accumulation in muscle and liver (fatty liver) and raise circulating TG levels due to enhanced hepatic production of very low density lipoprotein (VLDL) cholesterol [22, 24]. Excess VLDL secretion increases the flux of FFA and TG to muscle and other tissues, further inducing IR. When influx of FFA to the liver exceeds efflux, there is increased hepatic FFA uptake, synthesis and secretion that can lead to hepatic steatosis, which in turn exacerbates IR [25, 26], giving rise to a new vicious cycle. In addition, overloading of the white adipose tissue (WAT) beyond its storage capacity can also adversely affect skeletal and cardiac muscle, liver as well as pancreatic function [27].

Cholesteryl ester transfer protein (CETP) is secreted by the adipose tissue and is an important determinant of lipoprotein composition because it mediates the transfer of cholesteryl esters (CE) from CE-rich lipoproteins to TG-rich lipoproteins in exchange for TG [28]. In obese patients, CETP activity and mass are increased [29]. This contributes to the increased flux of FFA but also to the rise in circulating TG levels. However, increased flux of FFA from the periphery to the liver in IR states stimulates hepatic TG synthesis, which in turn promotes the production of VLDL and apoB [16, 29]. Several studies showed that hepatic apoB secretion is metabolically regulated [15]. The apoB gene is constitutively expressed and in most cases the modulation of apoB production does not involve changes in apoB mRNA levels [15]. These observations suggest that post-translational mechanisms play a role in the regulation of apoB levels, including endoplasmic reticulum translocation and protein degradation. Thus, reduced apoB degradation might be the main contributor to the increase in plasma apoB levels [17, 30]. On the other hand, hepatic IR can lead to increased availability of apoB and might predispose to higher rates of hepatic VLDL assembly and secretion, the key steps in the development of metabolic dyslipidaemia [25]. In lean subjects, all these factors would stimulate adiponectin production from the WAT [7, 21]. Adiponectin reduces hepatic TG production and increases insulin sensitivity [7, 31]. However, this compensatory mechanism is blunted in obesity, because adiponectin levels are low and do not increase under physiological stimuli [7, 21].

In IR, circulating HDL-C levels are also decreased and this appears to be linked to the overproduction of TG-rich lipoproteins. Low HDL-C levels represent an independent risk factor for CVD [32-34]. Even though the mechanisms are not entirely clear, the enrichment of HDL particles with

TG appears to be implicated, leading to HDL particle instability and degradation. CETP plays an important role in lipid exchange between TG-rich lipoproteins and HDL [35, 36]. In the presence of raised plasma TG levels, CETP mediates the exchange of TG (from VLDL) for CEs (from HDL), resulting in HDL particles enriched in TG and depleted of CE, which are prone to degradation [37]. These TG-rich but cholesterol-depleted HDL particles undergo hydrolysis of their TG component by hepatic lipase (HL), which plays an important role in the enhanced catabolism of HDL in IR states [38]. ApoA, the main protein of HDL, is then dissociated from HDL particles [39]. Coupled with increased catabolic rate, these changes result in reduced and TG-rich HDL particles, which cannot carry out reverse cholesterol transport effectively [40]. Another possibility is that the altered (due to IR) lipid flux in the liver may reduce the hepatic production of apoA [41]. Thus, both depletion of HDL particles from CE by CETP and alterations in apoA might contribute to the reduction in HDL-C mass and HDL particle size (HDL-3) [37-41]. It was shown that as the number of MetS components increases, the HDL phenotype shifts to a greater percentage of small HDL-3 and less large HDL-2 particles, resulting in a decreased HDL-2/HDL-3 ratio [42]. In addition, HDL-2 levels and the HDL-2/HDL-3 ratio independently correlated with HDL-C (positively) and TG levels (negatively). HDL-3 concentration positively correlated with HDL-C and TG levels. This phenomenon may contribute to an impaired reverse cholesterol transport and to attenuated antiatherogenic activity of HDL in MetS [42].

Patients with IR have normal or slightly elevated LDL-C levels but significantly higher concentrations of the atherogenic sdLDL subfractions [43-45]. Hypertriglyceridaemia is implicated in the increased presence of sdLDL particles in IR. In hypertriglyceridaemic states, large TG-rich VLDL (VLDL1) molecules accumulate [43]. When VLDL1 is lipolysed by LpL, a population of LDL particles with changed apoB conformation is produced. These particles fail to bind efficiently to LDL receptors and have a prolonged residence time in the circulation. Through the action of CETP, CEs are replaced by TG in LDL and HDL particles [43]. HL also acts on TG-rich LDL to generate sdLDL, which is associated with higher vascular risk [46, 47]. This is because sdLDL particles have reduced LDL receptor-mediated clearance, increased retention in the arterial wall, increased susceptibility to oxidation and are enriched in apoB [44, 48]. It was shown that higher apoB levels predict CVD better than the absolute LDL-C levels [49] and are the most prevalent lipid disorder in patients with premature coronary artery disease (CAD) [50]. Interestingly, both sdLDL and the sdLDL-C/LDL-C ratio are inversely related with adiponectin levels [51]. Thus, hypo adiponectinaemia may provide a useful index for qualitative changes in LDL particles in IR states, especially when combined with the measurement of apoB levels [15].

B. Postprandial Lipaemia

Postprandial lipaemia refers to the state of lipid metabolism between food intake and the post-absorptive state. Fasting hypertriglyceridaemia is an independent risk factor for CVD [52, 53]. Moreover, TG levels are predictive of subsequent CVD events in statin-untreated high-risk patients and the statin-induced reduction in TG levels is associated with

lower vascular risk [54]. This beneficial effect of statins was more pronounced in patients with MetS or T2DM [54]. On the other hand, postprandial hyperlipidaemia (mainly postprandial hypertriglyceridaemia) is frequently present in patients with premature CVD [55]. It was suggested that fasting plasma TG concentrations are the best predictor of postprandial lipaemia [56, 57]. However, postprandial lipaemia occurs even in subjects who are normolipidaemic in the fasting state [58, 59].

Since postprandial hyperlipidaemia is relatively common in IR states [60, 61], it is probable that the clearance of both chylomicrons and VLDL from the circulation is impaired in these patients. In IR, the antilipolytic effect of insulin in adipose tissue is attenuated [62]. This might contribute to the postprandial increase in FFA levels [15]. The mechanisms underlying postprandial hyperlipidaemia also include a modest reduction in LpL and HL activity, increased production and higher plasma levels of apoC-III (an inhibitor of LpL) and the defective suppression of hepatic VLDL secretion postprandially [63-65]. Because VLDL and chylomicrons compete for the same LpL- and receptor-mediated TG-removing pathways, nonsuppressed VLDL secretion reduces the clearance of chylomicrons and their remnants. Postprandial hyperlipidaemia also promotes the formation of atherogenic LDL and HDL particles in a way similar to fasting hypertriglyceridaemia, as described above [60].

TREATMENT

A. Weight Loss

Obesity is an important vascular risk factor [1, 66]. Weight loss with lifestyle measures (diet and exercise) remains the first priority in IR patients in order to control dyslipidaemia and prevent T2DM, but is difficult to achieve and maintain [67, 68]. Therefore, drugs that facilitate weight loss might prove useful. Modest weight loss (>5%) with either sibutramine or orlistat appears to be associated with a reduction in TG levels and with favourable changes in adipokines, including an increase in serum adiponectin and a decrease in serum resistin levels [69, 70]. In obese T2DM patients with MetS, orlistat plus diet improved several vascular risk factors including fasting glucose, HbA1c, total cholesterol and LDL-C levels, systolic BP, waist circumference and homeostasis model assessment index (HOMA) compared with diet and exercise alone [71]. Similar were the findings in the XENical in the prevention of Diabetes in Obese Subjects (XENDOS) Trial [72] in obese subjects without T2DM, in patients with T2DM on oral hypoglycaemic drugs [73] and in patients with T2DM on insulin [74]. Thus, the combination of weight loss with the beneficial effects on adipokine levels during orlistat treatment might provide additional clinical benefits in obese patients with T2DM.

Young morbidly obese patients (body mass index (BMI) > 40 kg/m² or BMI > 35 kg/m² in the presence of significant comorbidities) have an estimated 22% reduction in expected remaining lifespan, representing an approximate loss of 12 years of life [75]. In these patients, bariatric surgery is an effective treatment [76]. Bariatric surgery results in significant weight loss (approximately 50-70% of excessive body weight), has a 70% long-term success rate and improves associated comorbidities (hypertension, dyslipidaemia, T2DM

and obstructive sleep apnea) [77-79]. The beneficial effects of bariatric surgery on adipokine levels might play a role in the observed weight loss [80-82].

B. Drug Treatment

1. Statin Treatment

As mentioned above, IR-associated dyslipidaemia is characterized by elevated TG and low HDL-C levels and a preponderance of sdLDL particles, while LDL-C levels are similar to subjects without IR. The cornerstone of treatment for IR-related dyslipidaemia is lifestyle changes and in diabetic patients, tight glycaemic control. In addition to these measures, recent clinical trials demonstrated the benefits of statin treatment [83]. In the Collaborative Atorvastatin Diabetes Study (CARDS), atorvastatin (10 mg/day) reduced vascular events, including stroke, in patients with T2DM without high LDL-C [3.1 mmol/l (120 mg/dl)] and without CVD at baseline [84]. In post hoc analyses of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) study, we showed that patients with CAD and MetS [85] or T2DM [86] benefit from statin treatment more than those without MetS or T2DM. Statin treatment (mainly atorvastatin) substantially reduced total mortality and CVD events by nearly one-half compared with untreated patients within a 3-year follow-up period. The Heart Protection Study (HPS) [87] showed a reduction in CVD events in patients with T2DM with or without CVD with simvastatin (40 mg/day). The Treating to New Targets (TNT) study also showed that patients with CAD and MetS [88] or T2DM [89] are at higher risk compared with patients without MetS or T2DM. Moreover, these 2 prespecified analyses of the TNT study showed that patients with CAD and MetS or T2DM benefit from aggressive LDL-C lowering with atorvastatin more than CAD patients without MetS or T2DM [88, 89]. Furthermore, a recent meta-analysis of 14 randomized statin trials including 18, 686 patients with T2DM showed a 21% reduction in major vascular events and 13% reduction in vascular mortality for every 1 mmol/l (37 mg/dl) reduction in LDL-C levels [90]. In the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, 7, 375 participants (41.4% of the study population) had MetS without T2DM [91]. Patients enrolled in the JUPITER trial had LDL-C levels < 130 mg/dl (3.4 mmol/l) and no T2DM or established vascular disease but had elevated high sensitivity C-reactive protein (hsCRP) levels (≥ 2 mg/l) [91]. Those treated with 20 mg of rosuvastatin had significant reductions in vascular morbidity and mortality and in total mortality after a median follow-up of 1.9 years [91]. In JUPITER, rosuvastatin significantly reduced the risk for the primary end-point (myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, vascular death) in both patients with and without MetS, with no evidence of heterogeneity between these subgroups (p for interaction = 0.14) [91]. JUPITER is the first study that showed a reduction in vascular events with statin treatment in patients with MetS but without established vascular disease or T2DM [91].

Nevertheless, even after the statin-induced reductions in CVD morbidity and mortality in the above studies it is obvious that a substantial percentage of patients still have a vascular event. Thus, it seems that there is a residual CVD risk

that needs to be targeted [92]. Therefore, it might be useful to combine statins with other lipid-lowering agents to manage residual CVD risk. These agents might include a fibrate, niacin, fish oil or (possibly in the future) CETP inhibitors [93]. This is supported by the findings of an analysis of the Get With The Guidelines database (136, 905 patients hospitalized with CAD from 2000 to 2006). Almost half of the patients had admission LDL-C levels < 2.6 mmol/l (100 mg/dl) but more than half had admission HDL-C levels < 1.0 mmol/l (40 mg/dl). Less than 10% had HDL-C levels ≥ 1.5 mmol/l (60 mg/dl) [94]. These findings suggest that target LDL-C goals should be lower and that effective treatments to raise HDL-C should be used or developed [95]. In A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden [ASTEROID]), rosuvastatin 40 mg/day achieved an average LDL-C concentration of 1.6 mmol/l (60.8 mg/dl) and increased HDL-C by 14.7%, resulting in significant regression of coronary atherosclerosis assessed with intravascular ultrasound (IVUS) [96]. A meta-analysis of IVUS trials showed that statin treatment is associated with regression of coronary atherosclerosis when LDL-C levels are substantially reduced and HDL-C levels are increased by more than 7.5% [97]. These findings suggest that statin benefits result from both the reduction in LDL-C levels and the increase in HDL-C. In the GREACE study, the statin-induced HDL-C increase was independently associated with lower CVD event rates [32, 98]. This suggests that the vascular risk reduction associated with HDL-C rise is significant even during aggressive LDL-C-lowering treatment (46% mean reduction in LDL-C levels) [32, 98]. Interestingly, rosuvastatin increased HDL-C levels by increasing the cholesterol mass only in the larger HDL particles in a dose-dependent manner, suggesting a more effective reverse cholesterol transport [99]. Atorvastatin also reduced all LDL subclasses, resulting in a significant reduction in LDL particle number and in an increase in LDL particle size [100]. In addition, HDL particle size increased [100]. Statins also have beneficial effects on postprandial lipaemia [101].

Statin-induced HDL-C increase is also related to a significant improvement in renal function [102]. High-risk patients with dyslipidaemia show a decline in renal function over time, which further increases the risk for vascular events [85, 103-106]. Statin treatment improved renal function and the statin-induced HDL-C increase appears to contribute to this effect [106]. Improved reverse cholesterol transport or other "pleiotropic" actions of HDL particles might play a role in the beneficial effects of HDL-C on renal function [102]. In addition, this improvement in renal function is independently associated with a reduction in vascular events [85, 103-106]. These findings support the concept that improving lipid variables other than LDL-C also benefit renal function.

2. Statin Combined with Novel Agents for Raising HDL-C

After attaining the LDL-C goals, the most promising lipid risk factor to target seems to be HDL-C. The effects of statins on HDL-C levels depend on the compound, dose and lipid phenotype [107]. Statins do not appear to be the most appropriate hypolipidaemic agents to increase HDL-C levels [96]. In this respect, novel agents (which might be available in the near future) including apo-I (Milano), anti CETP vac-

cine (CETi-1) and CETP inhibitors (anacetrapib or JTT-705), might prove to be useful. The most promising regimen appears to be CETP inhibition combined with a statin [95, 108]. A recent publication suggests that anacetrapib (which is well tolerated and had no effect on BP), as monotherapy or co-administered with atorvastatin, significantly lowered LDL-C and increased HDL-C levels [108]. The net result of treatment with anacetrapib + atorvastatin was $\approx 70\%$ lowering of LDL-C and more than doubling of HDL-C levels [108]. In contrast, torcetrapib (a CETP inhibitor whose development was halted because of increased mortality) raised BP independently of CETP inhibition [109, 110]. An increase in circulating aldosterone levels appears to contribute to this BP rise with torcetrapib [110]. It appears that this adverse action is not a drug class effect but compound-specific. Anacetrapib was associated with a dose-dependent lipoprotein a [Lp(a)] lowering, with up to 50% reduction at the highest doses [108]. It remains to be established whether these effects of anacetrapib on lipid parameters will translate into clinical benefit.

3. Statin-Niacin Combination Treatment

In the HDL-Atherosclerosis Treatment Study (HATS) [111] and the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 3 (ARBITER 3) study [112], niacin-statin combination vs statin alone resulted in greater reduction in carotid intima-media thickness (cIMT) in patients with CAD, T2DM and/or MetS. Combining niacin with statins to optimize the lipid profile [lower TG levels below 1.7 mmol/l (150 mg/dl) and non-HDL-C levels below 3.4 mmol/l (130 mg/dl)] might be useful in T2DM. However, higher doses of niacin can impair glycaemic control [67]. Therefore, niacin therapy should be instituted only in patients with well-controlled diabetes and glucose levels should be monitored. In patients with T2DM but without CAD, it is recommended to achieve LDL-C levels below 2.6 mmol/l (100 mg/dl) whereas in patients with T2DM and CAD the goal is to achieve LDL-C levels below 1.8 mmol/l (70 mg/dl) [113]. In both groups, non-HDL-C levels should be < 3.4 mmol/l (130 mg/dl) and < 2.6 mmol/l (100 mg/dl), respectively [113]. In diabetic patients, it is also desirable to achieve TG levels < 1.7 mmol/l (150 mg/dl) and HDL-C levels > 1.0 mmol/l (40 mg/dl) and > 1.3 mmol/l (50 mg/dl) in men and women, respectively [114]. Niacin-statin combination therapy could possibly help achieve these additional goals; however, there is no clear evidence that this combination will reduce vascular events more than statins alone in diabetic patients [67].

4. Statin-Fibrate Combination Treatment

Mounting evidence suggests that TG play a role in the pathogenesis of atherothrombosis [115]. Recent post hoc analyses of statin trials suggest that lowering TG levels is associated with a reduction in vascular events [54, 116]. Statin-induced TG lowering may translate in clinical benefit both in patients with acute coronary syndromes and stable CAD, beyond LDL-C lowering to < 1.8 mmol/l (70 mg/dl) or < 2.6 mmol/l (100 mg/dl), respectively [54, 116].

The main effect of fibrates is a decrease in TG levels (by about 20-30% in major outcomes studies [117-121], although larger reductions may be seen in patients with above average pre-treatment TG levels) [122, 123]. There is also a

reduction in postprandial TG levels and remnant lipoprotein particles, especially in patients with T2DM or MetS [122, 123-126]. Fibrates also raise HDL-C (by 5-10%) by stimulating apoA-I and apoA-II expression [123, 127]. Fenofibrate also lowers LDL-C, more so in patients with average than in those with high baseline TG levels [117, 128]. A study using nuclear magnetic resonance (NMR) analysis showed that fenofibrate lowered TG levels by 58% and increased HDL-C levels by 18% [129]. NMR analysis revealed that VLDL, particularly large VLDL, intermediate density lipoprotein (IDL) and sdLDL were also significantly decreased and LDL distribution was shifted towards larger particles. HDL distribution was also altered; there was an increase in small HDL and a decrease in large HDL particles, resulting in a significant decrease in HDL particle size, from 9.1 to 8.9 nm, as well as a 27% increase in HDL particle number. Among inflammation markers, hsCRP was significantly decreased by 42% [129]. Moreover, fenofibrate also lowers apoCIII levels [130-132] and exerts anti-inflammatory actions [123, 129, 133].

The Fenofibrate Intervention and Even Lowering in Diabetes (FIELD) study evaluated the effect of treatment with fenofibrate 200 mg/day in reducing macrovascular and microvascular complications in 9,795 patients with T2DM [134]. At the end of the 5-year follow-up period, treatment with fenofibrate was associated with a nonsignificant 11% reduction in relative risk for the primary end point. There was, however, a significant 11% relative reduction in risk for the secondary end point of total cardiovascular events, excluding unstable angina, and this was largely driven by significant reduction in risk for nonfatal MI and coronary and all revascularization procedures. Regarding the microvascular complications of T2DM, fenofibrate significantly decreased the need for retinal laser therapy by 30% and reduced the progression of albuminuria [134]. Therefore, combining statins with fenofibrate might further reduce vascular risk in IR states [135]. However, it should be emphasized there is limited evidence to support this recommendation.

Long-term statin-fibrate combination in patients with familial combined hyperlipidaemia (FCHL) resulted in more effective control of multiple lipid parameters including LDL-C, TG and HDL-C as well as plasma fibrinogen levels, than either monotherapy alone, with a similar safety profile [136-138]. Moreover, statin-fibrate combination increased LDL particle size in patients with FCHL [139]. However, statin-fibrate combinations are not widely used. This might be due to safety concerns, particularly for myopathy and rhabdomyolysis, which was reported with lovastatin-gemfibrozil combination [140]. However, this increased risk for rhabdomyolysis was not confirmed in studies with other statin-fibrate combinations [136-139, 141, 142]. Uncontrolled studies suggested that statin-fibrate combination reduces total and CAD mortality in patients with FCHL [143]. The combined targeting of LDL-C, TG, apoB and fibrinogen, as well as the increase in LDL particle size, HDL-C and apoA-I might play a role in these beneficial effects of statin-fibrate combination.

The features of dyslipidaemia of IR states are similar to those of FCHL [144]. Moreover, metabolic abnormalities, such as the predominance of sdLDL particles and increased glycation of LDL [145], raise the vascular risk in these pa-

tients. Glycaemic control appears to improve but does not normalize these abnormalities [146]. Statin or fibrate monotherapy can improve the lipid profile in patients with T2DM; however, they affect different aspects of lipoprotein metabolism [147-149]. Hence, it is difficult to normalize all lipid abnormalities in patients with T2DM using monotherapy with either a statin or a fibrate [114]. In contrast, atorvastatin-fenofibrate combination improved multiple lipid and coagulation abnormalities and reduced the estimated CAD risk by 80% in patients with T2DM [148]. Therefore, combining statins with fibrates appears to expand the spectrum of therapeutic choices and allow the individualization of hypolipidaemic treatment in patients with IR.

Non-alcoholic fatty liver disease (NAFLD) is a common condition (with a prevalence of 10-39% in the general population) characterized by significant lipid deposition in the hepatocytes in patients without a history of excessive alcohol ingestion [150]. It was shown that IR is associated with NAFLD [151]. It was suggested that NAFLD might represent another feature of MetS [152] with decreased insulin sensitivity being the common underlying factor [153]. The strong association of NAFLD with other features of the MetS including obesity, central fat distribution, T2DM, dyslipidaemia, hypertension and CVD, further supports this hypothesis [154, 155]. Both MetS and NAFLD appear to be independent vascular risk factors [156]. A multifactorial approach reversed both MetS and NAFLD and reduced estimated CAD risk [157, 158]. Atorvastatin-fenofibrate combination was more effective than either monotherapy [157, 158].

5. Statin-Omega 3 Combination Treatment

Omega-3 fatty acids [n-3 polyunsaturated fatty acids (PUFA)], including the 20-carbon eicosapentaenoic acid (EPA) and the 22-carbon docosahexaenoic acid (DHA), lower TG levels and atherogenic remnant lipoproteins both in patients with or without T2DM [159-161]. In the former, n-3 PUFA might raise LDL-C levels but do not affect glycaemic control [160].

Until recently, there were only a few data regarding the efficacy of n-3 PUFA supplementation in the primary prevention of CVD. Thus, the results of the Japan EPA Lipid Intervention Study (JELIS) offer a new insight in the role of n-3 PUFA in this setting. In this study, 18,645 hypercholesterolaemic patients were randomly assigned to receive either 1,800 mg of EPA daily with statin (EPA group; n = 9,326) or statin only (controls; n = 9,319) [162]. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting or coronary artery bypass grafting (CABG) [162]. After a mean follow-up of 4.6 years, a 19% relative reduction in the primary endpoint was detected in the EPA group (2.8% in the EPA group vs 3.5% in the control group; p = 0.011) [162]. Even though the JELIS trial was underpowered for analysis of subgroups, EPA treatment resulted in a significant 19% reduction in major coronary events among patients with a history of CAD (secondary prevention subgroup; n=3,664); the primary end-point occurred in 8.7% in the EPA group vs 10.7% in the control group (p=0.048) [162]. In patients without CAD (primary prevention subgroup; n=14,981),

EPA treatment reduced major coronary events by 18%, but this was not significant (1.4% in the EPA group vs 1.7% in the control group; $p = 0.132$) [162]. The relationship between incident CAD, the number of CAD risk factors and EPA treatment was also investigated [163]. Compared with patients with normal serum TG and HDL-C levels, those with abnormal levels had significantly higher CAD hazard ratio (HR) (1.71; 95% confidence interval (CI): 1.11-2.64; $p = 0.014$). In this higher risk group, EPA treatment reduced CAD risk by 53% (HR: 0.47; 95% CI: 0.23-0.98; $p = 0.043$) [163]. Therefore, the beneficial effects of EPA on top of statin treatment were similar in magnitude in both the primary prevention and the secondary prevention subgroups, but were significant only in the latter subgroup probably because of a greater number of events [162].

It is of interest that, in the JELIS study, the reduced risk associated with EPA treatment was confined to non-fatal coronary events [162]. No effect of EPA was observed in terms of coronary death or sudden cardiac death [162]. These findings differ from those in most previous observational studies, where fish intake primarily reduced the risk of fatal coronary events or sudden cardiac deaths, but not of non-fatal coronary events [164-166]. It has been speculated that the absence of significant effect on cardiac death in JELIS might be due to the increased consumption of fish among Japanese, which is approximately 900 mg EPA+DHA per day [167]. A recent study also showed that EPA supplementation (1.8 g/day) reduced the progression of cIMT in patients with T2DM [168]. Thus, it has been suggested that the main benefit at lower levels of consumption (e.g. 1 g/day of EPA+DHA) might be prevention of ventricular arrhythmia and sudden cardiac death [169], whereas at high levels of consumption (e.g. 2-4 g/day of EPA+DHA), modest benefits for non-fatal coronary events could also begin to occur because of the other cardioprotective effects of n-3 PUFA [170]. The above suggest that when considering adding a second agent to statins in patients with combined dyslipidaemia, omega-3 fatty acids provide additional lipid improvements without increasing the risk for adverse muscle or liver effects [171].

6. Statin-Ezetimibe Combination Treatment

In patients who cannot reach LDL-C target with statin monotherapy, adding ezetimibe is a therapeutic option [172]. When added to a statin, ezetimibe lowered LDL-C levels by approximately 23% [173, 174]. Besides its LDL-C lowering action, ezetimibe may reduce the percentage of sdLDL particles in patients with high TG levels [175, 176]. In a meta-analysis of 5, 039 patients, ezetimibe significantly increased HDL-C levels and lowered TG levels [174]. Ezetimibe also exerts anti-inflammatory effects and a recent meta-analysis reported an additional 10% reduction in hsCRP levels when this agent was added to statins [173, 177]. Ezetimibe also appears to improve renal function [178-180]. In patients with T2DM or MetS, statin-ezetimibe combination lowered LDL-C, TG, non-HDL-C and hsCRP levels and increased HDL-C levels more than statin monotherapy [181, 182]. In other studies in patients with MetS, simvastatin 80 mg/day induced similar or greater improvements in postprandial lipaemia compared with ezetimibe plus simvastatin 10 mg/day [183, 184]. However, only the combination prevented fat-

load-induced endothelial dysfunction [184]. Endothelial dysfunction appears to be present in patients with MetS [185].

7. Ezetimibe-Fibrate Combination Treatment

In dyslipidaemic patients with IR who are intolerant to statins, ezetimibe-fibrate combination is a reasonable treatment option [186]. This strategy induces changes reflecting the combined effects of fenofibrate in reducing TG-rich lipoproteins and promoting a shift in the LDL particle distribution profile toward larger, more buoyant particles and of ezetimibe in promoting reductions in cholesterol mass across the apoB particle spectrum [187]. Thus, it seems that this co-administration provides a complementary therapy that improves the atherogenic lipid profile of patients with mixed hyperlipidaemia or postprandial hyperlipidaemia [186-188].

CONCLUSIONS

In order to address the residual CVD risk and optimize the lipid profile in patients with IR (obesity, MetS and T2DM), it appears that, in addition to targeting the LDL-C (to below 2.6 mmol/l <100 mg/dl), there is a potential benefit from raising the HDL-C level and lowering TG-rich particles [(non-HDL-C levels to below 3.4 mmol/l (130 mg/dl)] in patients without CAD. In those with IR and CAD we have to aim at lower targets [LDL-C level < 1.8 mmol/l (70 mg/dl) and non-HDL-C level < 2.6 mmol/l (100 mg/dl)] [113]. ApoB might be more predictive of CVD events than LDL-C, at least in patients with higher cardiometabolic risk [189]. Elevated apoB levels might also play a role in the increased vascular risk in patients with MetS who belong to other ethnic groups (e.g. South Asians) [190]. The effects of lifestyle modification and drug treatment on LDL particle size [191, 192], HDL particle size [99] and reverse cholesterol transport [193, 194] appear to play an important role in reducing residual CVD risk [195].

To address the challenge posed by the global epidemic of obesity, MetS and T2DM, we need to emphasize education and communication to increase awareness of the important contribution of IR-associated atherogenic dyslipidaemia to the residual vascular risk. Lifestyle modification is an important, effective and underutilised first step in reducing this risk. Pharmacological interventions aiming at achievement of all lipid targets is also likely to be required, with a combination of statin with other hypolipidaemic agents being the treatment of choice in most cases.

DECLARATION OF INTEREST

This review was written independently; no company or institution supported it financially. Some of the authors attended conferences, given lectures and participated in advisory boards or other trials sponsored by various pharmaceutical companies.

ABBREVIATIONS

BMI	=	Body mass index
BP	=	Blood pressure
CAD	=	Coronary artery disease
CETP	=	Cholesteryl ester transfer protein

CVD	=	Cardiovascular disease
HDL-C	=	High density lipoprotein cholesterol
HL	=	Hepatic lipase
HOMA	=	Homeostasis model assessment index
hsCRP	=	High sensitivity C-reactive protein
IR	=	Insulin resistance
LpL	=	Lipoprotein lipase
Lp-PLA(2)	=	Lipoprotein-associated phospholipase A2
LDL-C	=	Low density lipoprotein cholesterol
MetS	=	Metabolic syndrome
PUFA	=	Polyunsaturated fatty acids
T2DM	=	Type 2 diabetes mellitus
VLDL-C	=	Very low density lipoprotein cholesterol
WAT	=	White adipose tissue

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