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# Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management

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Even at low-density lipoprotein cholesterol (LDL-C) goal, patients with cardiometabolic abnormalities remain at high risk of cardiovascular events. This paper aims (i) to critically appraise evidence for elevated levels of triglyceride-rich lipoproteins (TRLs) and low levels of high-density lipoprotein cholesterol (HDL-C) as cardiovascular risk factors, and (ii) to advise on therapeutic strategies for management. Current evidence supports a causal association between elevated TRL and their remnants, low HDL-C, and cardiovascular risk. This interpretation is based on mechanistic and genetic studies for TRL and remnants, together with the epidemiological data suggestive of the association for circulating triglycerides and cardiovascular disease. For HDL, epidemiological, mechanistic, and clinical intervention data are consistent with the view that low HDL-C contributes to elevated cardiovascular risk; genetic evidence is unclear however, potentially reflecting the complexity of HDL metabolism. The Panel believes that therapeutic targeting of elevated triglycerides ( $\geq 1.7$  mmol/L or 150 mg/dL), a marker of TRL and their remnants, and/or low HDL-C ( $< 1.0$  mmol/L or 40 mg/dL) may provide further benefit. The first step should be lifestyle interventions together with consideration of compliance with pharmacotherapy and secondary causes of dyslipidaemia. If inadequately corrected, adding niacin or a fibrate, or intensifying LDL-C lowering therapy may be considered. Treatment decisions regarding statin combination therapy should take into account relevant safety concerns, i.e. the risk of elevation of blood glucose, uric acid or liver enzymes with niacin, and myopathy, increased serum creatinine and cholelithiasis with fibrates. These recommendations will facilitate reduction in the substantial cardiovascular risk that persists in patients with cardiometabolic abnormalities at LDL-C goal.

## Keywords

High-density lipoprotein cholesterol • Triglycerides • Triglyceride-rich lipoproteins • Remnants • Cholesterol • Atherogenic dyslipidaemia • Cardiovascular disease • Atherosclerosis • Guidelines

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## Introduction and rationale

Despite considerable improvements in medical care over the past 25 years, cardiovascular disease (CVD) remains a major public health challenge. In Europe, CVD is responsible for nearly 50% of all deaths and is the main cause of all disease burden,<sup>1</sup> with management costs estimated at €192 billion annually.<sup>2</sup> However, with the increasing incidence of obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM),<sup>3</sup> this burden is projected to escalate dramatically. At a time when Europe, like other developed regions, is faced with the need to contain expenditure, urgent action is needed to address this critical problem.

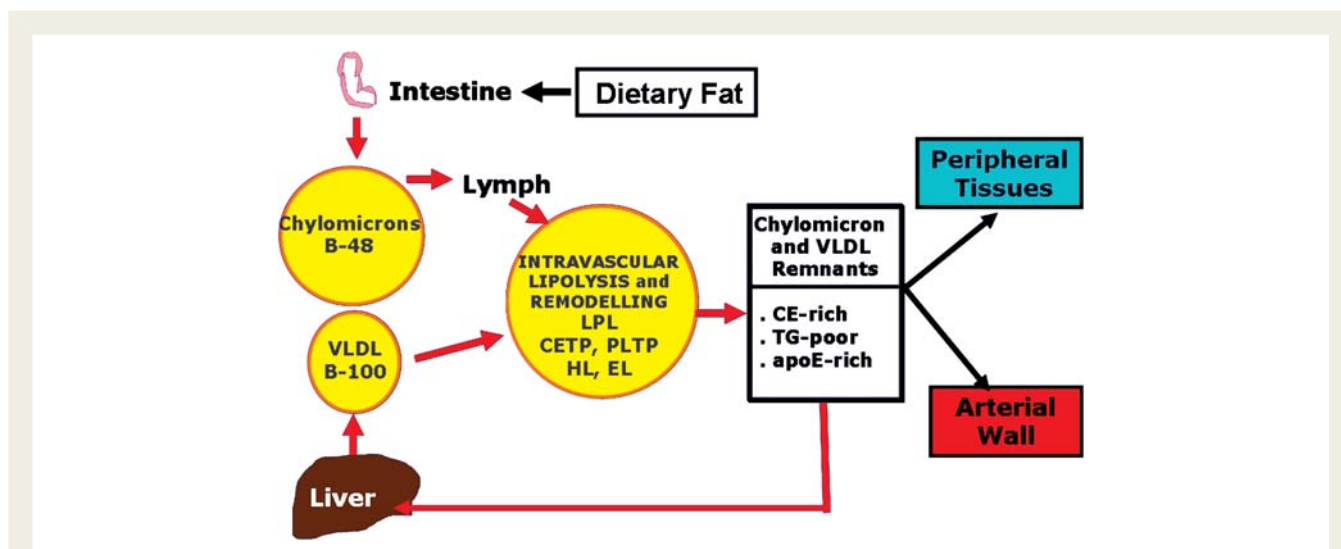
Current best treatment including lifestyle intervention and pharmacotherapy aimed at lowering plasma concentrations of low-density-lipoprotein cholesterol (LDL-C), reducing blood pressure, and preventing thrombotic events fails to 'normalize' risk in people at high risk of CVD (i.e. SCORE > 5% for CVD death<sup>4</sup> or 10-year Framingham risk score >20% for CVD events<sup>5</sup>). Individuals with acute coronary syndromes (ACS) are at very high risk of recurrent events: ~10% occur within the first 6–12 months,<sup>6,7</sup> and ~20–30% within 2 years.<sup>8,9</sup> As the risk of recurrent events in statin-treated coronary heart disease (CHD) patients increases incrementally with each additional feature of the metabolic syndrome,<sup>10</sup> this implies that other CV risk factors beyond LDL-C may deserve attention. These risk factors may be modifiable, e.g. non-LDL-C dyslipidaemia, hypertension, and abdominal obesity, or non-modifiable, e.g. age and gender. Therapeutic interventions targeted to the former group clearly hold

potential for reducing this high CV risk that persists even with optimal treatment of LDL-C.

*Post hoc* analyses of prospective trials in ACS and stable CHD patients reveal that elevated plasma levels of triglycerides and low plasma concentrations of high-density lipoprotein cholesterol (HDL-C) are intimately associated with this high risk, even at or below recommended LDL-C goals.<sup>11–14</sup> Furthermore, in T2DM patients, the UKPDS identified HDL-C as the second most important coronary risk factor, after LDL-C.<sup>15</sup> Despite these data, guidelines are inconsistent in their recommendations for proposed levels of HDL-C or triglycerides either for initiation of additional therapies or for targets for such treatments in patients at LDL-C goal.<sup>4,5,16–19</sup>

The aim of this paper is to critically appraise the current evidence relating to triglycerides and HDL-C as CV risk factors or markers and to consider therapeutic strategies for their management. The focus is on individuals with cardiometabolic risk, characterized by the clustering of central obesity, insulin resistance, dyslipidaemia, and hypertension, which together increase the risk of CVD and T2DM.<sup>18</sup>

The EAS Consensus Panel is well aware of uncertainties and controversies regarding triglycerides and HDL-C levels, both as risk markers or targets of therapy. Triglycerides are predominantly carried in fasting conditions in very low-density lipoproteins (VLDLs) and their remnants, and postprandially in chylomicrons and their remnants. The generic term 'triglyceride-rich lipoprotein remnants', therefore, relates to chylomicron and VLDL particles which have undergone dynamic remodelling in the plasma after secretion from the intestine (chylomicrons) or liver (VLDL) (Figure 1). This remodelling results in a spectrum of particles



**Figure 1** Upon entry into the circulation, chylomicrons (containing apo B-48) produced by the small intestine, and VLDL (containing apo B-100) produced by the liver undergo LPL-mediated lipolysis mainly in peripheral tissues, notably adipose tissue and muscle. Intravascular remodelling of TRL equally involves the actions of lipid transfer proteins (CETP, PLTP) and additional lipases (HL and EL) with the formation of remnant particles. TRL remnants are typically enriched in cholesterol and apo E, but depleted in triglyceride; they are principally catabolized in the liver upon uptake through the LRP and LDL receptor pathways. TRL remnants can contribute either directly to plaque formation following penetration of the arterial wall at sites of enhanced endothelial permeability,<sup>21</sup> or potentially indirectly following liberation of lipolytic products (such as FFA and lysolecithin) which may activate pro-inflammatory signalling pathways in endothelial cells.<sup>20,21</sup> Abbreviations: apo, apolipoprotein; CETP, cholesteryl ester transfer protein; EL, endothelial lipase; FFA, free fatty acids; HL, hepatic lipase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; LRP, lipoprotein receptor-related protein; PLTP, phospholipid transfer protein; TRL, triglyceride-rich lipoprotein; VLDL, very-low density lipoprotein.

which are heterogeneous in size, hydrated density, and lipid and protein composition<sup>20</sup> and include intermediate-density lipoprotein (IDL) particles. No single biochemical trait allows the differentiation of remnants from newly secreted chylomicrons, VLDL and IDL.<sup>21</sup> Thus, plasma triglyceride levels correspond essentially to the sum of the triglyceride content in nascent VLDL and their remnants in the fasting state, together with that in chylomicrons and their remnants in the postprandial state. Consequently, the Panel has used the generic term 'triglyceride-rich lipoprotein (TRL) remnants' as a surrogate for plasma levels of both newly secreted TRLs and their remnants, the latter predominating in the typical person with cardiometabolic risk.<sup>21</sup> As discussed below, increasing evidence suggests that remodelled chylomicrons and VLDL are atherogenic, primarily as a result of their progressive enrichment with cholesterol and depletion of triglycerides in the plasma compartment. This process also results in progressive reduction in their size. The term 'TRL remnants' has been used to emphasize our focus on atherogenic lipoproteins themselves rather than their major lipids.

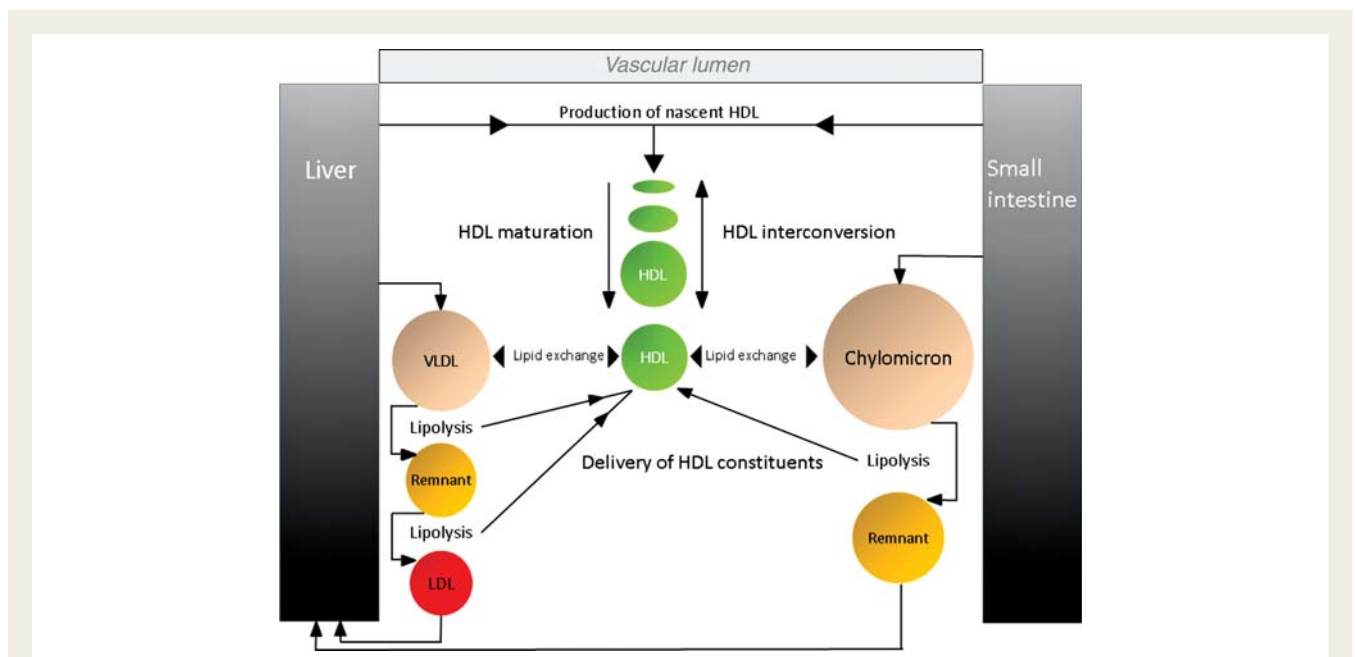
Similarly, the Panel understands that, despite epidemiologic data and evidence from some animal models<sup>22</sup> implying a role for HDL as anti-atherogenic and vasculoprotective lipoproteins, the metabolic and functional pathways linking HDL-C levels and protection

from CVD are poorly defined. The Panel also recognizes that HDL represent a highly dynamic pool of heterogeneous particles.<sup>23</sup> As HDL particles vary greatly in terms of lipid and protein composition, it was decided to focus on HDL-C as the marker of CVD risk.

## Lipid and lipoprotein metabolism

Cholesterol, in both free and esterified forms, and triglycerides are the two main lipids in plasma. They are transported in lipoproteins, pseudomicellar lipid–protein complexes, in which the main apolipoproteins, apo B-100/48, apo A-I, apo A-II, apo E, and the apo Cs, are integral components. Apo B is a component of all atherogenic lipoproteins (chylomicron remnants, VLDL and their remnants, IDL, lipoprotein(a) [Lp(a)] and LDL), whereas apo A-I and apo A-II are components of HDL. The apo B-containing lipoproteins and the apo A-I/A-II lipoprotein classes are closely inter-related via several metabolic pathways (Figure 2).<sup>23–25</sup>

In dyslipidaemic patients with cardiometabolic risk, increased free fatty acid flux may represent a significant abnormality driving increased hepatic assembly and secretion of VLDL, IDL, and/or LDL particles, although other mechanisms are also implicated.<sup>26,27</sup> Low plasma levels of HDL-apo A-I are associated with its increased



**Figure 2** Metabolic pathways for HDL and triglyceride-rich lipoprotein remnants highlight their close interrelationship. *De novo* production of nascent HDL (discs) occurs in the liver and small intestine through the production of apo A-I (the major HDL protein) and lipidation (with cholesterol and phospholipids) of this protein by the ATP-binding cassette transporter (ABCA1) in these organs. Upon secretion, lecithin: cholesterol acyltransferase (LCAT) esterifies cholesterol on these discs which *mature* into spherical particles (due to the formation of a hydrophobic core resulting from generation of cholesteryl esters by LCAT). HDL undergoes extensive *interconversion* through triglyceride lipolysis (hepatic lipase, HL), phospholipid hydrolysis (endothelial lipase, EL), fusion (phospholipid transfer protein, PLTP), and lipid exchange among the HDL subpopulations (cholesteryl ester transfer protein, CETP). CETP also mediates major *lipid transfer and exchange* between HDL and triglyceride-rich lipoproteins (VLDL, chylomicrons) and their remnants [VLDL remnants = intermediate-density lipoproteins (IDLs), chylomicron remnants]. During this process, cholesteryl esters are transferred from HDL to VLDL and triglycerides move from VLDL to HDL.<sup>24</sup> Chylomicrons also act as cholesteryl ester acceptors from LDL and HDL during the post-prandial phase.<sup>25</sup> A second route that contributes to the plasma HDL pool involves *hydrolysis* of triglycerides in VLDL, IDL, and chylomicrons. In this process which is catalysed by lipoprotein lipase (LPL), phospholipids, as well as several apolipoproteins (such as apo C I, C II, C III, AV) are transferred to HDL. PLTP contributes significantly to this remodelling process.

fractional removal.<sup>26</sup> This is driven by both cholesteryl ester transfer protein (CETP)-mediated heteroexchange of triglycerides from apo B lipoproteins with cholesteryl ester from apo A-I lipoproteins, and dissociation of apo A-I from triglyceride-enriched HDL with clearance via the kidney.<sup>26,28,29</sup> Such metabolic perturbations are frequently associated with insulin resistance, which may in turn influence the activities of lipoprotein lipase (LPL), CETP and potentially, hepatic lipase (HL), phospholipid transfer protein, and endothelial lipase. Within this large dyslipidaemic group, however, many patients do not exhibit insulin resistance but nonetheless display a mixed dyslipidaemia characterized by elevated levels of TRL and LDL. This lipid phenotype typically involves subnormal concentrations of HDL-C and increased cardiovascular risk.<sup>30</sup> Finally, although there are close links, both pathophysiologic and genetic, between the dyslipidaemia of insulin resistance and the phenotype of familial combined hyperlipidaemia (FCHL),<sup>31</sup> some individuals with elevated levels of TRL remnants do not have insulin resistance or T2DM.<sup>30,32,33</sup> Such individuals are at increased risk for premature CVD, although it is not clear if this risk is higher or lower than in those with the dyslipidaemia of insulin resistance and/or T2DM.

Pharmacological correction of hypertriglyceridaemia in T2DM does not usually normalize low apo A-I levels, which probably reflects the complex mechanisms involved.<sup>26,29</sup> The complexity of HDL metabolism is clearly relevant when strategies to raise HDL-C are reviewed; indeed, HDL-C concentration is at most an indirect marker of the anti-atherogenic activities that are associated with this lipoprotein.<sup>28</sup>

## What is the experimental evidence that triglyceride-rich lipoprotein remnants and high-density lipoprotein play a role in the pathophysiology of atherothrombosis?

The retention of cholesterol-rich lipoproteins within the subendothelial matrix of the arterial wall is a key initiator of atherosclerosis.<sup>34</sup> Sites of endothelial dysfunction constitute preferential arterial locations for lipoprotein penetration, accumulation, and plaque formation.<sup>34</sup> Although LDL is considered the main atherogenic cholesterol-rich particle, other apo B-containing lipoproteins (TRL, their remnants, and Lp(a)) also contribute to intimal cholesterol deposition, particularly as they contain a similar number of cholesterol molecules per particle (~ 2000) as LDL.<sup>21,35</sup> In contrast, HDLs were originally thought to readily enter the subendothelial space and then return to the circulation,<sup>36</sup> although recent studies highlight the need to reconsider this notion.<sup>37</sup>

Experimental studies show that particle size is a key determinant. While large chylomicrons and VLDL fail to penetrate the arterial wall, their smaller remnants not only penetrate the arterial intima but may be bound and retained by connective tissue matrix.<sup>38,39</sup> Accumulation of both chylomicron and VLDL remnants enriched in apo E has been demonstrated in human and rabbit atherosclerotic plaques.<sup>20,39–41</sup> Such particles, also referred to as 'β-VLDL', can be

taken up directly by arterial macrophages with massive cholesterol loading and foam cell formation.<sup>42,43</sup> Elevated levels of TRL remnants have also been linked to the progression of coronary artery disease<sup>44</sup> and the presence of echolucent carotid artery plaques.<sup>45</sup> Clearly, TRL remnant cholesterol can contribute directly to plaque formation and progression.<sup>20</sup>

Triglyceride-rich lipoprotein remnants may also drive atherogenesis via indirect mechanisms, particularly those involving binding and lipolysis at the artery wall.<sup>20</sup> Such mechanisms provide a key link to accelerated atherogenesis in the postprandial phase. Acutely elevated TRL remnants occurring in this phase are associated with impaired vasodilation,<sup>46</sup> upregulated pro-inflammatory cytokine production,<sup>47</sup> and enhanced inflammatory response and monocyte activation.<sup>48–51</sup> All of these mechanisms may underlie endothelial dysfunction. Moreover, TRL remnants are of relevance to plaque disruption and subsequent thrombus formation, key events in the onset of most ACS.<sup>52,53</sup> Triglyceride-rich lipoprotein remnants stimulate the secretion of tissue factor from endothelial cells and monocytes,<sup>54</sup> and promote thrombin generation at levels similar to those caused by activated platelets.<sup>55</sup> Elevated triglycerides are linked with raised concentrations of fibrinogen and coagulation factors VII and XII, and with impaired fibrinolysis as determined by enhanced gene expression and concentrations of plasminogen activator inhibitor-1.<sup>56,57</sup>

In contrast to TRL remnants, HDLs display a wide spectrum of biological activities (*Box 1*), of which cellular cholesterol efflux activity, and anti-inflammatory and anti-oxidative actions are key.<sup>23,28</sup> HDLs also contribute to pancreatic beta-cell function.<sup>58–60</sup> The functionality of HDL is potentially highly vasculo-protective. HDLs maintain endothelial vasoreactivity, attenuate oxidative stress, inhibit endothelial cell apoptosis, contribute to the repair of damaged endothelium,<sup>61,62</sup> inhibit monocyte activation,<sup>63</sup> and reduce the expression of adhesion molecules and cytokines.<sup>28</sup> Apo A-I may also immunoregulate lymphocytes and mononuclear cells.<sup>63,64</sup> All of these actions may potentially attenuate component steps of atherosclerotic plaque formation.<sup>23,28,65</sup>

### Box 1 HDL functionality: relevance to athero/vasculo-protection

- Cellular cholesterol efflux and cholesterol homeostasis
- Regulation of glucose metabolism
- Anti-inflammatory activity
- Anti-oxidative activity
- Anti-apoptotic activity
- Endothelial repair
- Vasodilatory activity
- Anti-thrombotic activity
- Anti-protease activity
- Anti-infectious activity

To what degree can HDL counteract the prothrombotic activity of TRL remnants, particularly since insulin-resistant states associate with thrombotic risk clustering?<sup>57</sup> HDL and apo A-I protect erythrocytes against the generation of procoagulant activity<sup>66</sup> and augment the anticoagulant activity of protein S. The latter enhances the function of activated protein C, a critical factor in regulating



blood coagulation by proteolytic inactivation of factors Va and VIIIa.<sup>67</sup> HDL also affect platelet aggregation, inhibiting thrombin-induced binding of fibrinogen to platelets.<sup>68</sup> Finally, in T2DM, in which HDL anti-atherogenic function is defective,<sup>28</sup> infusion of reconstituted (r)HDL increases the anti-inflammatory and *in vitro* cholesterol efflux potential of HDL<sup>69</sup> and reduces platelet hyperreactivity by lowering the cholesterol content of platelet membranes.<sup>70</sup> Considered together, these data suggest a unifying hypothesis for the anti-atherothrombogenic actions of HDL and point to a crucial role in cellular cholesterol homeostasis. Significantly, HDL-mediated cholesterol efflux activity from macrophages was recently shown to be relevant both to carotid-intima thickness and coronary artery disease.<sup>71</sup>

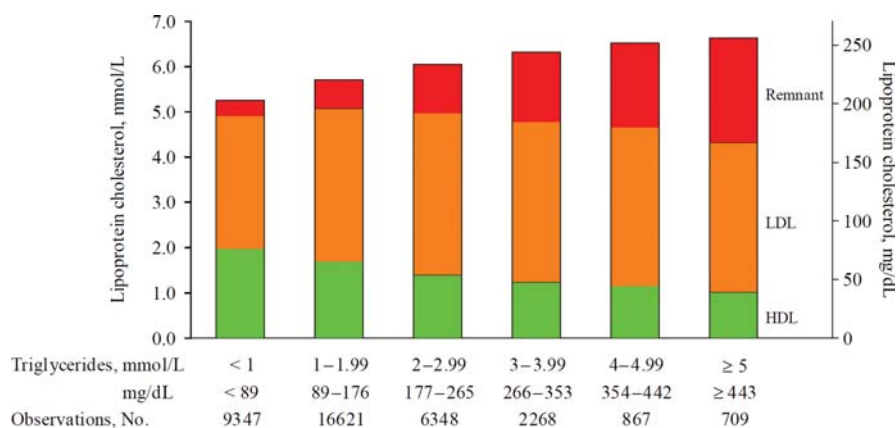
A critical question is whether HDL impact long-term CV risk via these effects on the atherosclerotic process. The data from animal models have shown that overexpression of the human apo A-I gene increases HDL-C levels, protecting against diet-induced atherosclerosis.<sup>72</sup> In addition, infusion of HDL or apo A-I<sub>Milano</sub>/phospholipid complexes reduced aortic lipid deposition and induced regression of atherosclerosis in rabbits.<sup>73,74</sup> In humans, infusion of synthetic rHDL restored endothelial function in hypercholesterolaemic patients.<sup>75</sup> Infusion of recombinant apo A-I<sub>Milano</sub>/phospholipid complexes reduced coronary atherosclerosis in ACS patients, although there was no dose-dependent effect.<sup>76</sup> More recently, rHDL infusion reduced atheroma volume in subjects with premature coronary<sup>77</sup> or peripheral atherosclerosis.<sup>78</sup> Observational data from four intravascular ultrasound trials (two with statins) showed that lowering plasma apo B lipoprotein concentrations together with simultaneous minor elevation of HDL-C levels achieved plaque regression and stabilization.<sup>79</sup> All of these findings urgently require confirmation in larger randomized studies.

Thus, in summary, the data indicate that TRL remnants and HDL are relevant throughout all stages of atherothrombosis, especially within the context of the insulin resistance syndrome.<sup>57</sup>

## Prevalence of elevated triglyceride-rich lipoprotein remnants and low high-density lipoprotein cholesterol

First, it is important to ascertain the prevalence of atherogenic dyslipidaemia, i.e. the combination of elevated TRL remnants and/or low HDL-C.<sup>80</sup> Among the general population plasma concentrations of total cholesterol, LDL-C and HDL-C are normally distributed. In contrast, the distributions of triglycerides, remnant cholesterol, apo B, and non-HDL-C (i.e. total cholesterol – HDL-C) tend to be skewed with a tail toward the highest levels. In the Copenhagen General Population Study, low HDL-C levels were frequently associated with elevated levels of cholesterol and TRL remnants (Figure 3). Approximately 45% of men and 30% of women in the study had triglycerides  $\geq 1.7$  mmol/L (150 mg/dL) with or without HDL-C  $< 1.0$  mmol/L (40 mg/dL) (BG Nordestgaard, unpublished results). HDL-C levels are lower in Turkish populations, largely due to genetic predisposition.<sup>81,82</sup> The Turkish Heart Study reported that  $\sim 50\%$  of men and  $\sim 25\%$  of women had HDL-C levels  $\leq 0.9$  mmol/L (35 mg/dL).<sup>82</sup> As in other countries, atherogenic dyslipidaemia is on the rise, due to the increasing prevalence of the metabolic syndrome. In the Turkish Adults Risk Factor Study,  $\sim 40\%$  of men and 35% of women had triglycerides  $> 1.7$  mmol/L with or without low HDL-C ( $\leq 0.9$  mmol/L or 35 mg/dL).<sup>83</sup>

Atherogenic dyslipidaemia is more prevalent in individuals at high risk of CVD. In the Swedish National diabetes register including  $> 75\,000$  T2DM subjects, 37–38% had untreated hypertriglyceridaemia ( $> 1.7$  and  $\leq 4.0$  mmol/L, i.e.  $> 150$  and  $\leq 354$  mg/dL) with or without low HDL-C.<sup>84</sup> More than one-third of the CHD patients in EUROASPIRE III had elevated triglycerides ( $\geq 1.7$  mmol/L or 150 mg/dL) and/or low HDL-C;  $\sim 50\%$  of patients from Turkey had low HDL-C.<sup>85</sup> In the PROCAM study,



**Figure 3** Lipoprotein cholesterol as a function of increasing levels of non-fasting triglycerides in the general population. Based on non-fasting samples from 36 160 men and women from the Copenhagen General Population Study collected over the period 2003–2007; 9% of men and 6% of women were on statins, mainly 40 mg/day simvastatin. Remnant cholesterol is calculated from a non-fasting lipid profile as total cholesterol minus HDL cholesterol minus LDL cholesterol; under these conditions, remnant cholesterol represents the total cholesterol transported in IDL, VLDL, and chylomicron remnants. Variable levels of chylomicrons are present in non-fasting samples and usually will only contribute minimally to the calculated remnant cholesterol. Nordestgaard BG 2010, unpublished results.

about twice as many myocardial infarction (MI) survivors had elevated triglycerides ( $\geq 2.28$  mmol/L or 200 mg/dL) and/or low HDL-C ( $< 1.05$  mmol/L or 40 mg/dL) vs. matched controls; CV risk associated with this dyslipidaemic profile was higher also at low LDL-C levels.<sup>86</sup> Together, these observational data highlight an unmet clinical need for treatment beyond LDL-C lowering in patients at high risk of CVD with atherogenic dyslipidaemia.

## What is the evidence that triglyceride-rich lipoprotein remnants and high-density lipoprotein cholesterol contribute to cardiovascular risk?

The data from epidemiological and genetic studies are relevant to this question.

### Epidemiology

#### General populations

Large observational studies clearly show that both elevated triglycerides (either fasting or non-fasting)<sup>87–90</sup> and reduced plasma levels of HDL-C<sup>91–93</sup> are associated with increased CV risk. Scepticism of the role of elevated levels of TRL remnants in atherosclerosis and CVD has persisted despite the observation that patients with dysbetalipoproteinaemia (remnant hyperlipidaemia) with accumulation of apo E and cholesterol-rich remnants typically display premature atherosclerosis and high CVD risk.<sup>94</sup> Some suggested that individuals with lifelong, extremely high triglycerides (25–300 mmol/L or 2200–26550 mg/dL) and familial chylomicronaemia (e.g. due to LPL deficiency) did not present with accelerated atherosclerosis.<sup>94</sup> Others observed the opposite,<sup>95</sup> consistent with experimental data in animal models.<sup>96,97</sup> However, the rarity of this disease prevents firm conclusions to be made.

The Emerging Risk Factors Collaboration (ERFC)<sup>93</sup> provides the most robust evidence for the association of HDL-C with CV risk (Figure 4). This analysis of 68 studies in 302 430 participants without prior history of CVD used individual participant data, allowing for harmonization and consistent adjustment of confounding factors, hitherto unfeasible. HDL-C was strongly associated with coronary risk even after adjustment for non-HDL-C and  $\log_e$  triglycerides and non-lipid risk factors. Each unit of standard deviation (SD) increase in HDL-C concentration (0.38 mmol/L or 15 mg/dL) was associated with 22% reduction in CHD risk. Importantly, this protective effect was equal across the range of triglyceride levels. However, it is acknowledged that the data are not clear for HDL-C levels  $< 0.5$  or  $> 2.2$ – $2.5$  mmol/L ( $< 19$  mg/dL or  $> 85$ – $100$  mg/dL). Non-HDL-C and apo B each had very similar associations with CHD. Both HDL-C and non-HDL-C were also modestly associated with ischaemic stroke (Figure 4), but not haemorrhagic stroke.

While coronary risk was increased by 37% (95% CI 31–42%) per SD increase in  $\log_e$  triglycerides, this association was weakened after adjustment for HDL-C and abrogated after correction for non-HDL-C. Additionally, triglycerides were not associated with stroke risk after adjustment for other lipid factors.<sup>93</sup> These data are compatible with the view that it is the number of TRL and

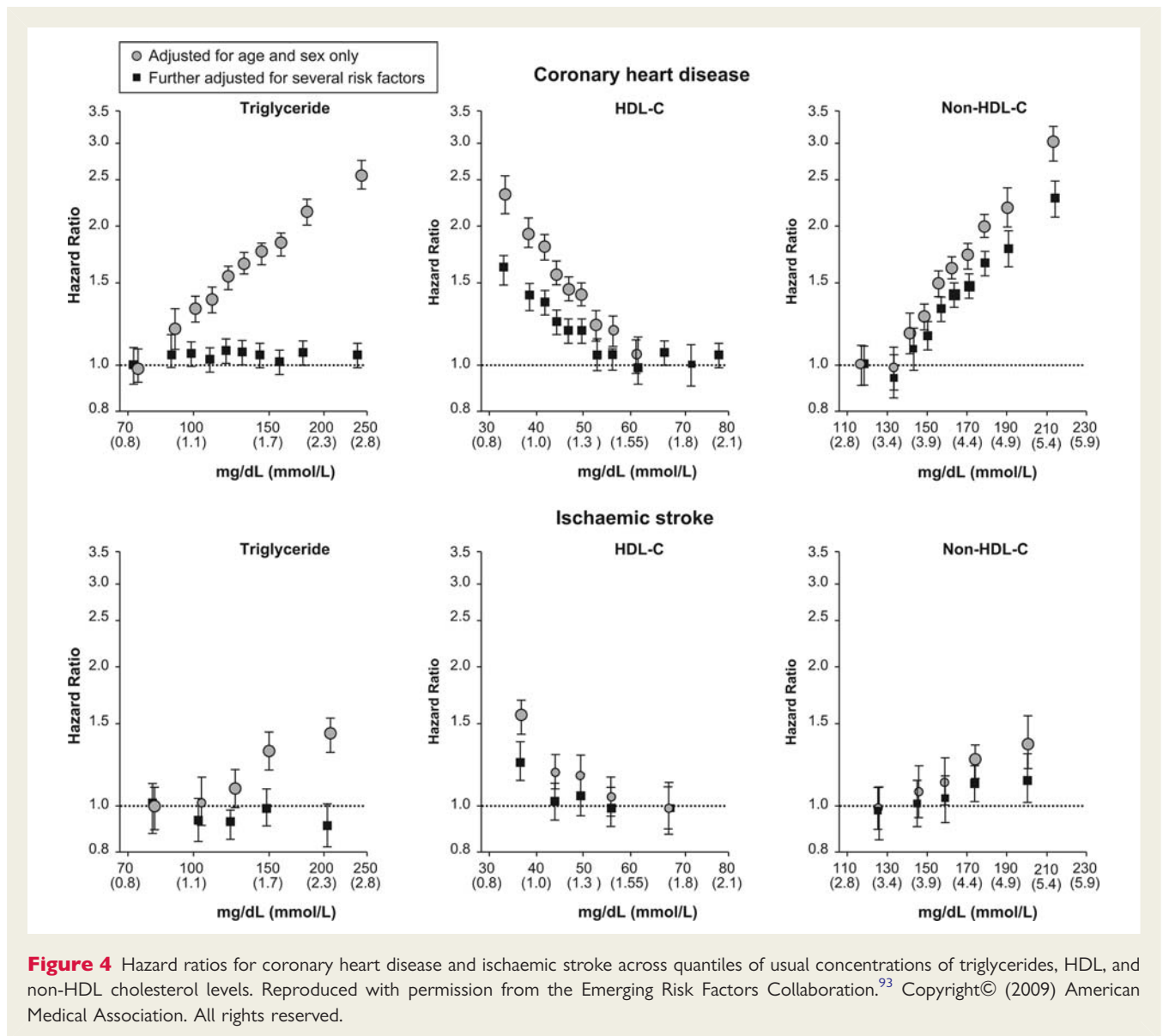
remnant particles that cause CVD. Thus, the risk associated with elevated triglycerides can be explained by this lipid acting as a marker for increased numbers of TRL, which in turn are closely associated with the combination of higher levels of non-HDL-C and low levels of HDL-C. In the Copenhagen City Heart Study, increased risk for MI, ischaemic stroke, and mortality was evident at markedly elevated triglycerides ( $> 5.0$  mmol/L or  $> 450$  mg/dL), although these data were not adjusted for non-HDL-C (Figure 5).<sup>89,90</sup> Thus, low HDL-C and elevated non-HDL-C and triglycerides appear to be relevant to CV risk beyond LDL-C.

#### Clinical trial populations

Epidemiological evidence for low HDL-C as a major, independent CV risk factor is strengthened when considering clinical trial data in high-risk statin-treated patients (Table 1).<sup>12,98–100</sup> In the TNT study, low on-treatment HDL-C concentration was a significant predictor for coronary events at low LDL-C ( $< 1.8$  mmol/L or 70 mg/dL), even after adjustment for CV risk factors, including on-treatment LDL-C and triglycerides and baseline HDL-C.<sup>12</sup> A meta-regression analysis questioned the relevance of HDL-C to CV risk, although methodological issues may limit its validity<sup>101</sup> [the analysis included 299 310 participants at risk of CV events in 108 studies of any lipid-modifying agent (either as monotherapy or in combination) or diet/surgery with a minimum of 6 months follow-up. There were no significant associations between the treatment-induced change in HDL-C and risk ratios for CHD events, CHD death, or total mortality after adjustment for changes in LDL-C. However, there are a number of important methodological issues with this analysis including: (i) the use of aggregated data rather than individual subject data; (ii) the method of analysis which describes an observational association and therefore risks bias by confounding; (iii) the combination of treatments and diets with important differences in pharmacology or mechanism of action; and (iv) failure to take account of the effect of baseline lipid profile which is known to influence the extent of HDL-C-raising]. Recently, a meta-analysis of 170 000 subjects in 26 statin trials (24 332 CVD events) showed that irrespective of the achieved LDL-C level or the intensity of statin therapy, CV risk was always lower at higher levels of achieved HDL-C, with no attenuation of this relationship at low LDL-C levels. The lowest risk was observed in those with both a low LDL-C and a high HDL-C.<sup>100</sup> This largely refutes suggestions that HDL-C concentration may be less predictive at very low LDL-C levels as in the JUPITER trial (393 CV events).<sup>102</sup>

While the 4S trial showed no association between on-treatment levels and changes from baseline levels for triglycerides and reduction in CV risk,<sup>103</sup> data from more recent trials are indicative of association.<sup>11,104,105</sup> In the PROVE IT-TIMI 22 trial, on-treatment triglycerides  $< 1.7$  mmol/L ( $< 150$  mg/dL) were independently associated with a lower risk of recurrent coronary events in ACS patients at LDL-C goal ( $< 1.8$  mmol/L or 70 mg/dL).<sup>11</sup> Further, pooled analysis of the TNT and IDEAL trials showed a trend for decreased CV event risk with lowering of triglycerides ( $P < 0.001$ ), although this was attenuated by adjustment for HDL-C and the ratio of apo B/apo A-I.<sup>104</sup>

In T2DM patients, the FIELD and ACCORD Lipid studies showed that marked atherogenic dyslipidaemia (triglycerides  $\geq 2.3$  mmol/L or 204 mg/dL and low HDL-C levels ( $\leq 0.88$  mmol/L or 34 mg/dL



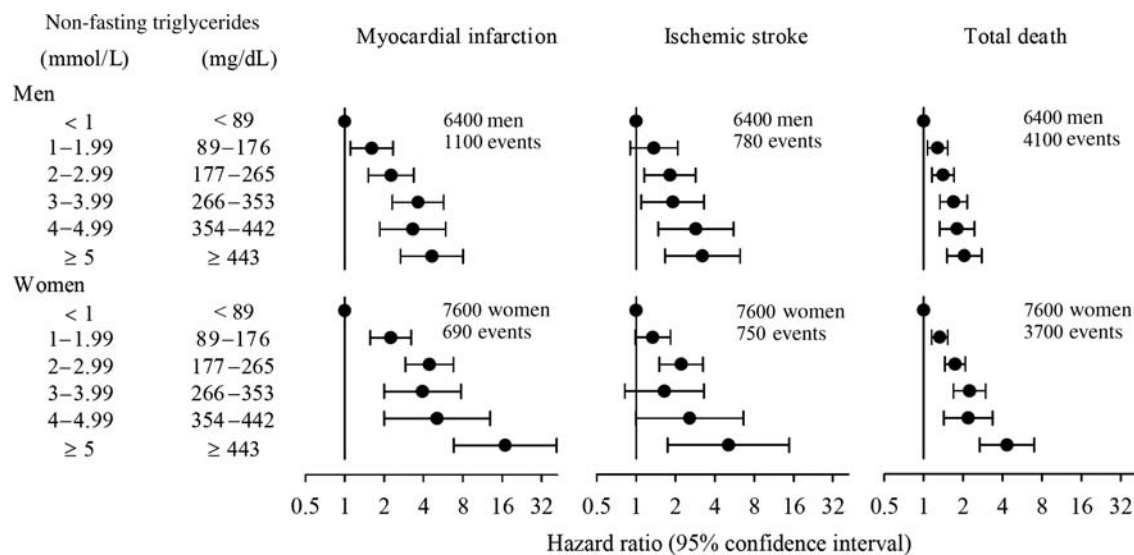
in ACCORD Lipid) was associated with increased CV event rates (by ~30–70% vs. those without this profile).<sup>106,107</sup> Analyses from FIELD show that the hazard ratios for HDL-C, apo A-I, apo B, and non-HDL-C were comparable for the prediction of CV risk whereas that for serum triglycerides was attenuated by adjustment for HDL-C ( $P = 0.07$ ),<sup>108</sup> concordant with the ERFC analysis.

Taken together, these observational and clinical trial data support the view that (i) a low HDL-C concentration is associated with CVD independent of LDL-C (or non-HDL-C) levels, and (ii) that elevated triglycerides are moderately associated with CVD, potentially largely through the number of TRL remnants. Thus, while LDL-C lowering remains the first priority, therapeutic targeting of low HDL-C and elevated TRL remnants may offer the possibility of incremental reduction in CV risk in high-risk populations.

### Genetic studies of triglyceride and high-density lipoprotein metabolism

In contrast, genetic studies do not provide clear insights into CV risk associated with changes in plasma triglycerides and HDL-C levels. This is not unexpected as predictions based on epidemiological studies may be inappropriate tools to assess complex biological pathways, especially for HDL metabolism. Monogenic disorders of triglyceride metabolism (involving functional mutations in the *LPL*, *APOCIII*, *APOAV*, *LMF1*, and *GPIIIBP1* genes) and HDL metabolism (involving the *APOAI*, *LCAT*, *ABCA1*, *LIPC*, *LIPG*, *CETP*, and *SCARB1* genes) have so far failed to provide answers,<sup>109</sup> probably due to the rarity of these disorders. On the other hand, there is unequivocal evidence for markedly accelerated atherosclerosis and CVD in dysbetalipoproteinaemia, a familial dyslipidaemia in which the critical defect is homozygosity for the receptor binding-defective form of apo E, i.e. apo E2/E2,<sup>94</sup> resulting in





**Figure 5** Relationship of non-fasting triglycerides (up to and >5 mmol/L or 440 mg/dL) and risk of myocardial infarction, ischaemic stroke, and total mortality. Results are shown as age-adjusted hazard ratios from the Copenhagen City Heart Study with 26–31 years of follow-up. Reproduced with modification from Nordestgaard et al.<sup>89</sup> and Freiberg et al.<sup>90</sup> Copyright© (2007, 2008) American Medical Association. All rights reserved.

**Table 1** Overview of epidemiological evidence in community and clinical intervention populations supporting the association of low high-density lipoprotein cholesterol and/or elevated triglycerides with cardiovascular disease

Data source	Population	Key findings
<b>HDL-C</b>		
ERFC <sup>93</sup>	General population, no prior CVD	HDL-C was independently predictive of coronary events and ischaemic stroke, even after adjustment for lipid and non-lipid risk factors
SPARCL <sup>98</sup>	Patients with previous cerebrovascular disease	Greater decrease in recurrent stroke risk with on-treatment HDL-C levels above vs. below the median (1.2 mmol/L), independent of change in LDL-C
CTT <sup>99,100</sup>	Primary and secondary prevention, on statin	Irrespective of achieved LDL-C levels or statin intensity, CV risk was lower at higher levels of achieved HDL-C. This was not attenuated at low LDL-C levels
TNT <sup>12</sup>	CHD, on potent statin therapy	Predictive power of low on-treatment HDL-C concentrations remained even at low LDL-C (<1.8 mmol/L)
MIRACL <sup>13</sup>	ACS, on statin	HDL-C but not LDL-C was an independent predictor of short-term prognosis after ACS
<b>Triglycerides</b>		
ERFC <sup>93</sup>	General population, no prior CVD	The association of triglycerides and CV outcomes disappeared after adjustment for HDL-C and non-HDL-C
PROVE-IT TIMI 22 <sup>11</sup>	ACS, on potent statin therapy	On treatment triglycerides <1.7 mmol/L were independently associated with a lower risk of recurrent coronary events in ACS patients at LDL-C goal (<1.8 mmol/L)
Pooled analysis of IDEAL and TNT <sup>104,105</sup>	Secondary prevention (CHD, ACS) on potent statin therapy	Decrease in CV events with lowering of triglycerides ( $P < 0.001$ for trend); association attenuated by adjustment for HDL-C and apo B/apo A-I

ACS, acute coronary syndromes; apo, apolipoprotein; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CTT, Cholesterol Treatment: Trialists' Collaboration; ERFC, Emerging Risk Factors Collaboration; IDEAL, Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; PROVE-IT TIMI 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22; TNT, Treating to New Targets (study).

markedly elevated plasma levels of TRL remnants enriched in cholesterol and apo E.

Studies of frequent genetic coding variants and single-nucleotide polymorphisms (SNPs) in non-coding DNA (with no known direct

functional significance), such as in the LPL gene, show an association between the combination of elevated triglycerides and low HDL-C and an increase in CV risk.<sup>110–114</sup> In the initial genome-wide association studies (GWAS), variation at HDL loci was not associated with

CVD risk; however, a recent meta-analysis identified four novel loci associated with CHD that were related to HDL-C or triglycerides (but not LDL-C), suggesting that pathways specifically relating to HDL or triglyceride metabolism may also modulate coronary risk.<sup>115</sup> Collaborative analysis of a specific *APOA5* variant ( $-1131T>C$ ) that regulates triglycerides showed an association with coronary risk. The odds ratio for CHD (1.18, 95% CI 1.11–1.26) per C allele was also concordant with the hazard ratio (1.10, 95% CI 1.08–1.12) per 16% higher triglyceride concentrations in prospective studies, suggesting a causal association between triglyceride-mediated pathways (specifically high levels of remnant lipoproteins and low HDL-C) and CHD.<sup>116</sup>

Data for gene variants associated with isolated changes in plasma HDL-C levels are more conflicting. For example, increased plasma levels of HDL-C were correlated with increased CV risk in individuals with SNPs in the *LIPC* gene associated with reduced HL activity.<sup>117–119</sup> In contrast, genetic variants in *ABCA1* associated with substantial reductions in HDL-C levels (with no changes in other lipids) were not associated with increased CV risk.<sup>120</sup> On the other hand, three common CETP genotypes (*TaqIB*, *I405V*, and  $-629C>A$ ) associated with lower CETP activity and higher HDL-C levels were inversely associated with coronary risk.<sup>114</sup> In GWAS of genes known to impact HDL metabolism, the effects that such variants exert on HDL-C levels account for <5% and frequently <2% of variability.<sup>121,122</sup> These data imply that in the general population, HDL-C concentration represents the integral sum of many gene effects on HDL metabolism. The current literature on the human genetics of HDL and TRL and their remnants highlights the need for clarification of the interaction between genes and different metabolic pathways, particularly for HDL.

## What is the clinical evidence that modulation of triglyceride-rich lipoprotein, their remnants, and high-density lipoprotein cholesterol impacts atherosclerosis and cardiovascular disease?

### Lifestyle approaches

Lifestyle interventions influence the metabolism of HDL and TRL remnants (Table 2).<sup>123–140</sup> Smoking increases TRL remnants and decreases HDL-C levels,<sup>141</sup> secondary to insulin resistance and hyperinsulinaemia;<sup>142</sup> these effects are rapidly reversed on quitting.<sup>123</sup> Aerobic exercise causes long-lasting reduction in triglycerides by up to 20% and increases in HDL-C by up to 10%, although the same effects should not be assumed with progressive resistance training (Table 2). In T2DM subjects, intensive lifestyle intervention (weight loss, diet, and increased physical activity) had beneficial effects on glycaemic control and cardiometabolic risk factors, including HDL-C and triglycerides,<sup>143–145</sup> and, in the longer term was associated with reduction in CVD risk.<sup>146</sup> Other trials showed reduction in risk of progression to diabetes in people with impaired glucose tolerance,<sup>147,148</sup> and improvement in other atherogenic processes including inflammation with physical activity.<sup>127</sup>

In CHD patients, lifestyle intervention trials have shown reduced progression of atherosclerosis,<sup>149–151</sup> as well as reduction in the risk of CV events.<sup>152–154</sup> Both the Diet and Reinfarction Trial<sup>153</sup> and the Lyon Diet Heart Study<sup>154</sup> showed substantial reduction in coronary events (by at least 50%) with lifestyle intervention in MI survivors, but require replication to confirm these benefits. However, while a healthy lifestyle clearly is important in reducing CV risk, poor long-term adherence is a problem, and therefore many of these patients require additional pharmacological intervention.

### Clinical intervention studies

Statin therapy alone, in addition to best standards of care, is unable to completely normalize CV risk associated with atherogenic dyslipidaemia. Higher doses may partially correct residual dyslipidaemia, but can also increase the risk of side effects, especially myopathy. Addition of ezetimibe or bile acid resins to statin therapy has little effect on triglycerides and HDL-C levels; resins may even raise triglycerides. Evidence is supportive of therapeutic approaches aimed at concomitantly lowering TRL and raising HDL-C to reduce CV risk.<sup>155</sup> Of these options, both niacin and fibrates influence levels of multiple lipids and lipoproteins (Box 2<sup>35,156,157</sup>) and therefore clinically beneficial effects observed cannot be ascribed solely to changes in any single lipoprotein fraction. Pathways implicated in the lipid effects of niacin, fibrates, and omega-3 fatty acids are summarized in Table 3.<sup>158–170</sup>

#### Box 2 Lipid effects of niacin, fibrates and omega-3 fatty acids

	Δ LDL-C	Δ HDL-C	Δ TG	Δ Lp(a)
Niacin (ER, 2 g/day)	↓ 20%	↑ up to 30% <sup>a</sup>	↓ up to 35%	↓ up to 30–40%
• Effects are dose-dependent	↑ large LDL	↑ large HDL		
Fibrates	Variable <sup>b</sup>	↑ by 5–20% <sup>c</sup>	↓ by 25–50%	No effect
• Response dependent on baseline levels <sup>b</sup>	↑ large LDL			
Omega-3 fatty acids	↑/no change	↑/no change	↓ by 20–50%	No effect

<sup>a</sup> Consistent HDL-C raising by up to 25% has been observed in patients with T2DM.

<sup>b</sup> Effects depend on the individual fibrate, baseline lipid profile, and metabolic nature of dyslipidaemia.

<sup>c</sup> Although increases in HDL-C with fibrates may be up to 20% in short-term studies, in long-term outcome studies in patients with T2DM the response to fenofibrate was much less (<5% at study close out), suggesting that fibrate treatment may be ineffective for raising HDL-C in this patient group.

### Niacin

Niacin at therapeutic doses has a broad spectrum of effects on lipid and lipoprotein metabolism, including raising of HDL-C (Box 2).<sup>156</sup> While various pathways are implicated,<sup>158–161</sup> its mechanism of action is incompletely elucidated (Table 3). Niacin may also promote beneficial vasoprotective and anti-inflammatory effects independent of its lipid-modifying activity.<sup>171–173</sup>

**Table 2** Effects of lifestyle interventions on plasma concentrations of HDL cholesterol and triglycerides

Intervention	Δ HDL-C	Mechanism	Δ triglycerides	Mechanism
Smoking cessation <sup>123</sup>	↑ 5–10%	↑ LCAT and cholesterol efflux; ↓ CETP	No significant change reported	–
Weight loss <sup>124</sup>	↓ during active weight loss  ↑ after weight stabilization by 0.009 mmol/L per kg weight lost	↑ LCAT, LPL, cholesterol efflux  ↓ catabolism of HDL, apo A-I	↓ by 0.015 mmol/L per kg weight loss	↑ VLDL clearance  ↓ hepatic VLDL secretion
Exercise <sup>125–131</sup>				
Aerobic	↑ 5–10% (moderate to high intensity)	↑ pre-β HDL, cholesterol efflux, LPL ↑ in HDL size	↓ 10–20% (moderate to high intensity) ↓ ~30% in VLDL-TG	↓ hepatic VLDL-TG secretion; Beneficial adaptations in muscle fibre area, capillary density, glycogen synthase, and GLUT4 protein expression in T2DM or impaired glucose tolerance
Resistance	No significant change reported	Improved HDL functionality	↓ ~5%	
Alcohol <sup>132–134</sup>	↑ 5–10% (1–3 drinks/day)	↑ ABCA1, apo A-I  ↓ CETP	Variable response, ↑↑ in obese subjects ↑↑ with excess intake	↑ synthesis of VLDL-TG with excess intake
Dietary factors <sup>135–140</sup>				
n-3-PUFAs, n-6-PUFAs, MUFAs	0 to ↑ 5%	Improves ratio of LDL-C/ HDL-C  Improves HDL anti-inflammatory activity	↓ 10–15%	↑ TG-rich lipoprotein clearance via pathways mediated by apo CIII and apo E ↓ VLDL apo B secretion
Omni-Heart	↑ by <5%		↓ 56% (increased protein) ↓ 33% (increased USFA)	

ABCA1, ATP-binding cassette transporter; apo, apolipoprotein; CETP, cholesteryl ester transfer protein; GLUT4, glucose transporter type 4; HDL, high-density lipoprotein; LCAT, lecithin:cholesterol acyltransferase; LDL, low-density lipoprotein; LPL, lipoprotein lipase; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; TG, triglycerides; T2DM, type 2 diabetes mellitus; USFA, unsaturated fatty acids; VLDL, very low-density lipoprotein.

Imaging trials clearly document attenuated progression of atherosclerosis and intima-media thickening by niacin (Supplementary material online, Table S1).<sup>174–182</sup> The only major outcome study to date, the Coronary Drug Project, showed that niacin (immediate-release 3 g/day) was associated with a 26% reduction in non-fatal MI ( $P < 0.005$ ) at 6–7 years, and 11% reduction in all-cause mortality ( $P = 0.0004$ ) at 15 years (~9 years after the end of treatment).<sup>183,184</sup> These clinical benefits were similar in patients with or without hyperglycaemia, diabetes, or metabolic syndrome.<sup>185,186</sup> A recent meta-analysis of niacin studies has confirmed these findings.<sup>187</sup>

Niacin may increase insulin resistance to a minor degree, although this may be potentially counterbalanced by recently documented protective effects of HDL on pancreatic beta cells.<sup>58,59</sup> In the ADMIT and ADVENT studies in diabetic patients, potentially deleterious effects on glycaemia were effectively counteracted by adjusting anti-diabetic medication.<sup>188,189</sup> However, the risk of new incident diabetes induced by niacin in insulin-resistant or pre-diabetic individuals remains indeterminate.

In patients with atherogenic dyslipidaemia, the combination of niacin plus statin improved the lipid-modifying efficacy of statin alone and was generally well-tolerated.<sup>190–192</sup> Combination of niacin with laropiprant, an inhibitor of the prostaglandin D<sub>2</sub> receptor,<sup>193</sup> significantly reduced but did not abolish flushing, the main tolerability issue. Among patients with T2DM, transient impairment of glucose control was reported (median increase in HbA<sub>1c</sub> 0.3% over 12 weeks),<sup>194,195</sup> consistent with known effects with niacin.<sup>188,189</sup> Emerging evidence suggests that statin plus niacin can reduce progression of atherosclerosis in high-risk patients, including those with low LDL-C, as in the Oxford Niaspan trial<sup>182</sup> (Supplementary material online, Table S1). There are limited data concerning the risk of myopathy with niacin-statin combination therapy. Definitive evidence regarding the longer-term risks of incident diabetes, myotoxicity, and hepatotoxicity are awaited from the HPS2–THRIVE and AIM-HIGH trials (projected enrolment 25 000 and 3300, respectively). Data from AIM-HIGH are expected in early 2013.

In summary (Box 3), evidence for the anti-atherosclerotic action of niacin is robust.<sup>156</sup> A meta-analysis also suggests that adding niacin to

**Table 3** Mechanisms implicated in the lipid-modifying activity of niacin, fibrates and omega-3 fatty acids

Drug	Proposed mechanisms
Niacin <sup>156,158–161,166</sup>	Not clear. the following have been implicated: ↓ TG synthesis and hepatic secretion of VLDL Possibly, direct inhibition of DGAT-2 Partial inhibition of hormone sensitive TG lipase in adipose tissue Up-regulation of apo A-I production Possibly, delayed catabolism of larger HDL particles Potential attenuation of CETP activity
Fibrate <sup>156,162–166</sup>	Transcriptional regulation mediated via interaction with PPAR $\alpha$ . Pathways involved include: ↑ catabolism of VLDL, IDL, and LDL apo B100 due to ↑ LPL expression and activity ↓ production rate of apo CIII, thereby potentiating LPL activity (fenofibrate) ↑ VLDL apo B or VLDL-TG turnover (bezafibrate, gemfibrozil) ↑ production of apo A-II and lipoprotein AI:All although no change in lipoprotein A-I with fenofibrate ↑ HDL <sub>2a</sub> /HDL <sub>3a</sub> , linked to reduced CETP activity
Omega-3 fatty acids <sup>138,157,167–170</sup>	Transcriptional regulation of SREBP-1c and PPAR $\alpha$ Inhibition of hormone-sensitive TG lipase and stimulation of LPL possibly through regulation of PPAR $\delta$ ↓ TG secretion and and lipogenesis ↑ mitochondrial and peroxisomal fatty acid oxidation Inhibition of DGAT-2 ↓ VLDL B secretion, specifically VLDL <sub>1</sub> ↑ conversion of VLDL to LDL ↓ catabolism of HDL apo A-I

apo, apolipoprotein; CETP, cholesteryl ester transfer protein; DGAT-2, diacylglycerol O-acyltransferase 2; IDL, intermediate-density lipoproteins; LPL, lipoprotein lipase; PPAR, peroxisome proliferator-activated receptor; SREBP, sterol regulatory element binding proteins; TG, triglycerides; VLDL, very low-density lipoproteins.

a statin may provide superior reduction in CV risk beyond that achieved with statin alone.<sup>187</sup> The results of HPS2-THRIVE and AIM-HIGH will help discern whether niacin-statin therapy is effective across a wide spectrum of dyslipidaemic patients, or only in those with high triglycerides/low HDL-C dyslipidaemia.

### Box 3 Impact of niacin on atherosclerosis and clinical outcomes

- Anti-atherosclerotic effects of niacin in combination with a statin have been extensively documented in plaque imaging studies in coronary and carotid arteries (see Supplementary material online, *Table S1*)
- Meta-analysis of niacin trials, several of which involved small patient numbers, is indicative of clinical benefit in patients with cardiometabolic disease<sup>187</sup>
- Ongoing trials (AIM-HIGH, HPS2-THRIVE) will evaluate whether ER niacin on top of statin therapy can reduce the CV risk that typically persists despite statin monotherapy in patients with atherogenic dyslipidemia and cardio-metabolic disease
- HPS2-THRIVE, given the broad range of patients, will reveal whether niacin-statin therapy is effective across a wide spectrum of dyslipidaemic patients or only in those with high triglycerides/low HDL-C dyslipidaemia

### Fibrates

Fibrates impact multiple pathways of lipid metabolism and may equally exert pleiotropic effects via regulation of genes influencing vascular inflammation and thrombogenesis. Their lipid-modifying

effects (*Box 2*) are mediated primarily via interaction with peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) (*Table 3*).<sup>156,162–166</sup>

Angiographic trials showed that fibrate therapy may attenuate atherosclerosis progression,<sup>196–198</sup> although the impact on the progression of intima-media thickening has not been consistent<sup>199–201</sup> (Supplementary material online, *Table S2*). Results from individual monotherapy outcomes trials have been variable and primarily indicate a reduction in nonfatal MI and revascularization, with no effect on stroke or CV death,<sup>202–207</sup> subsequently confirmed by a meta-analysis.<sup>208</sup> *Post hoc* analyses of several of these trials provided consistent evidence suggestive of clinical benefit in the subgroup of patients with elevated triglycerides and low HDL-C (*Table 4*).<sup>106,206,209,210</sup> Indeed, a recent meta-analysis confirmed enhanced benefit with fibrates in patients with atherogenic dyslipidaemia vs. those without.<sup>211</sup> On the basis of such evidence, fibrate treatment appears appropriate in this subgroup (*Box 4*).

### Box 4 Statin-fibrate combination therapy: current status

- Recent evidence from a meta-analysis suggests that fibrate therapy on a background of statin treatment provides clinical benefit in subgroups of patients with atherogenic dyslipidemia (*Table 4*)
- A large prospective trial to determine the long-term cardiovascular effects of a statin-fibrate combination in patients with the high triglyceride and low HDL-C phenotype is urgently needed

**Table 4** Subgroup analyses of cardiovascular outcome studies with fibrates

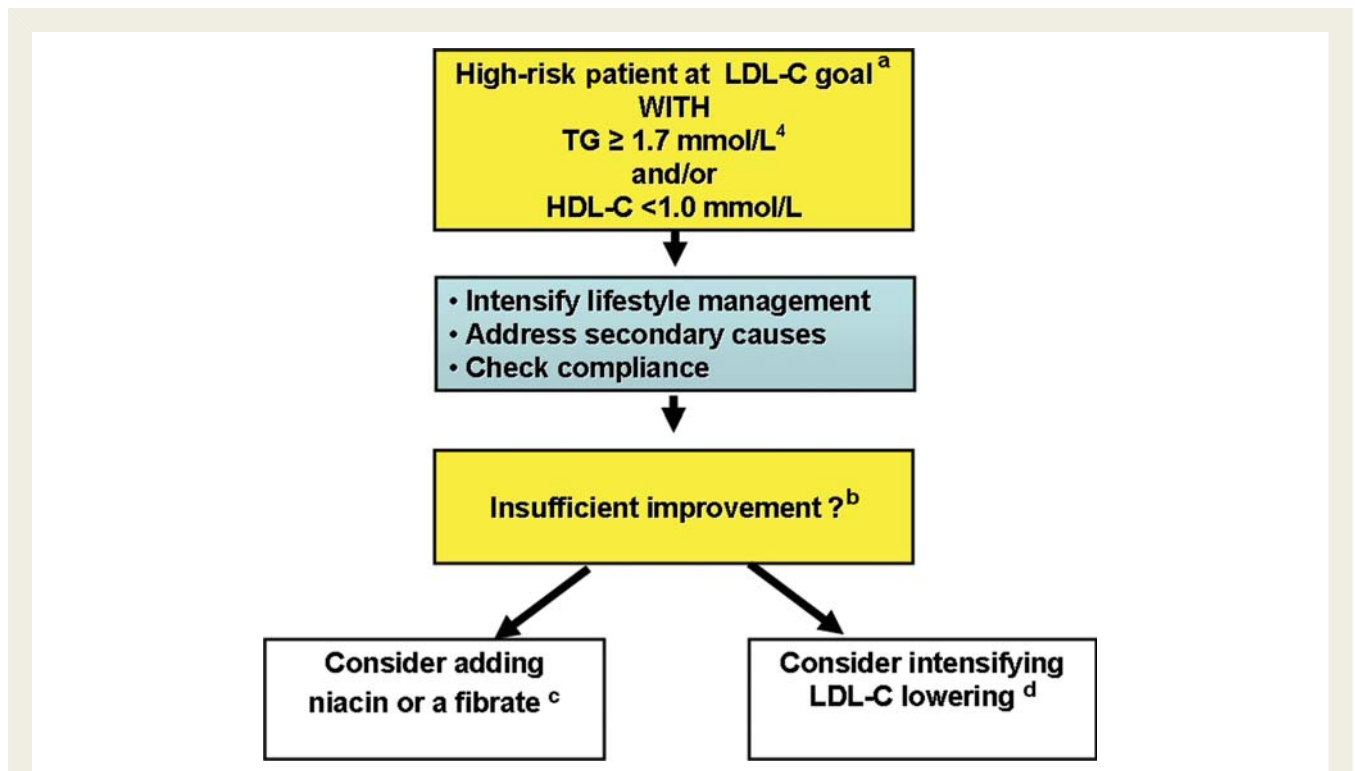
Trial	Treatment (mg/day)	Patient characteristics	All patients		Elevated triglycerides and low HDL-C subgroup		
			Primary endpoint	Relative risk reduction	Primary endpoint	Lipid criteria mmol/L	Relative risk reduction
Fibrate monotherapy vs. placebo							
WHO trial <sup>202</sup> (n = 5331)	Clofibrate 1600	Upper-third of cholesterol values, without CHD	Non-fatal MI + CHD death	20% (P < 0.05)	–	–	–
CDP <sup>203</sup> (n = 3892)	Clofibrate 1800 (n = 1103)	CHD	Nonfatal MI + CHD death	9% (P = 0.12)	–	–	–
HHS <sup>204,209</sup> (n = 4081)	Gemfibrozil 1200	Non-HDL-C ≥200 mg/dL without CHD	Fatal + non-fatal MI + cardiac death	34% (P < 0.02)	As for all patients	TG >2.3 + HDL-C <1.08	65% (P = 0.01)
VA-HIT <sup>205,210</sup> (n = 2531)	Gemfibrozil 1200	CHD + low HDL-C (<40 mg/dL)	Non-fatal MI + CHD death	22% (P = 0.006)	As for all patients	TG >2.03 + HDL-C ≤1.03	28% (P < 0.05)
BIP <sup>206</sup> (n = 3090)	Bezafibrate 400	Previous MI or angina	Fatal + non-fatal MI + sudden death	9.4% (P = 0.26)	As for all patients	TG ≥2.26 + HDL-C <0.91	42% (P = 0.02)
FIELD <sup>106,207</sup> (n = 9795)	Fenofibrate 200	Type 2 diabetes (22% with CVD)	Non-fatal MI + CHD death	11% (P = 0.16)	Total CV events	TG ≥2.30 + low HDL-C <sup>a</sup>	27% (P = 0.005)
Statin-fibrate vs. statin monotherapy							
ACCORD Lipid <sup>107</sup> (n = 5518)	Fenofibrate 160 + simvastatin	Type 2 diabetes (37% with CVD)	CVD death, nonfatal MI + non-fatal stroke	8% (P = 0.32)	As for all patients	TG ≥2.30 + HDL-C ≤0.88	31%; P-value not reported

<sup>a</sup>In FIELD, low HDL-C was defined as <1.03 mmol/L in men and <1.29 mmol/L in women.

CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction; WHO, World Health Organization.

ACCORD, Action to Control Cardiovascular Risk in Diabetes; BIP, Bezafibrate Infarction Prevention study; CDP, Coronary Drug Project; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes study; HHS, Helsinki Heart Study; VA-HIT, Veterans Affairs HDL Intervention Trial.





**Figure 6** Proposed algorithm for the management of high-risk individuals with elevated triglycerides and/or low HDL cholesterol at LDL cholesterol goal. <sup>a</sup>LDL-C at goal as recommended by the most recent European guidelines (2007);<sup>4</sup> <2.5 mmol/L in high-risk patients, decreasing to <2.0 mmol/L in very high risk patients. High-dose omega-3 fatty acids, fibrate, or niacin may be considered if the patient has very high TG (>5.0 mmol/L) to prevent pancreatitis. <sup>b</sup>If the patient still has elevated TG (≥1.7 mmol/L, as recommended by the most recent European guidelines<sup>4</sup>) and/or low HDL-C (<1.0 mmol/L) despite intensive lifestyle intervention, and addressing compliance with pharmacotherapy and secondary causes of dyslipidaemia, additional lipid-modifying therapy may be considered. <sup>c</sup>Based on clinical outcome data and safety considerations for combination statin–fibrate therapy, fenofibrate is the preferred fibrate. This fibrate may have particular value in patients with T2DM and mild-to-moderate retinopathy. <sup>d</sup>Greater LDL-C lowering may be achieved by the addition of ezetimibe to a statin. Ezetimibe has a dose-sparing advantage in patients intolerant of higher dose statins, although outcome evidence to support its use is awaited. Note: To convert LDL-C or HDL-C from mmol/L to mg/dL multiply by 38.7; to convert TG from mmol/L to mg/dL multiply by 88.5. Abbreviations: TG, triglycerides; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol.

Combination of a statin with a fibrate (primarily fenofibrate) incrementally decreased plasma triglycerides by 15–20% and raised HDL-C by 5–20% vs. statin monotherapy.<sup>212–215</sup> Similar effects were seen in FIELD and ACCORD Lipid, although the placebo-corrected increments in HDL-C in the total study cohorts were less than 3%.<sup>107,207</sup> In ACCORD Lipid, the only completed outcome study of combination therapy, fenofibrate–simvastatin had no effect on the primary outcome vs. simvastatin alone for all patients. Importantly, however, in the fenofibrate–simvastatin group, there was a 31% reduction in CV risk in the subgroup with baseline triglycerides in the upper tertile (≥2.3 mmol/L or 204 mg/dL) and HDL-C levels in the lower tertile (≤0.88 mmol/L or 34 mg/dL) vs. simvastatin monotherapy (Table 4).<sup>107</sup> The available data also suggest that fenofibrate exerts microvascular benefits, notably in preventing progression of retinopathy in T2DM patients.<sup>216,217</sup>

Concerns about the safety of statin–fibrate combination therapy relate chiefly to the risk of myopathy, although this is substantially lower with fenofibrate than gemfibrozil.<sup>218</sup> Current evidence based on ACCORD Lipid suggests that the incidence of myopathy with

fenofibrate–statin combination therapy is similar to that with niacin–statin combination therapy.<sup>107,219</sup> There were no reports of rhabdomyolysis with fenofibrate–statin combination therapy in either FIELD or ACCORD Lipid,<sup>107,207</sup> and in ACCORD Lipid no increase in the incidence of venous thromboembolic disease, pancreatitis, or non-CV mortality.<sup>107</sup> Fenofibrate increased serum creatinine and homocysteine (a rapidly reversible effect),<sup>107,220</sup> and in the FIELD Helsinki cohort, decreased creatinine clearance and estimated glomerular filtration rate, with no effect on the urinary albumin creatinine ratio.<sup>221</sup> Elevated serum homocysteine levels have been suggested as the basis for the neutral effect of fenofibrate on apo A-I.<sup>222</sup> The clinical significance of these effects remains unclear. Finally, all fibrates are known to increase the long-term risk of cholelithiasis.<sup>218</sup>

In summary, statins firmly remain the first line treatment of choice for attainment of LDL-C goal in patients at high risk of CVD.<sup>4,5</sup> After LDL-C goal attainment however, and if triglyceride levels remain elevated (≥1.7 mmol/L or 150 mg/dL, as defined by recent European guidelines<sup>4</sup>) and HDL-C low (<1.0 mmol/L

**Table 5** Evidence supporting the contention that elevated LDL-C, elevated fasting or non-fasting TRL and their remnants, and subnormal HDL-C alone and/or together play causal roles in CVD

Type of evidence	Elevated LDL-C	Elevated TRL, their remnants or low HDL-C
Human epidemiology	Direct association between LDL-C and CVD in numerous studies	Direct association between TG and CVD in numerous studies; association lost on correction for non-HDL-C and HDL-C in ERFC <sup>93</sup> Strong inverse association between low HDL-C and CVD in numerous studies; association maintained after correction for TG and non-HDL-C in ERFC <sup>93</sup>
Mechanistic studies	Definitive mechanistic evidence; LDL accumulate in arterial intima and promote atherosclerosis	Arterial accumulation of TRL and their remnants to promote atherosclerosis like LDL, with potential pro-inflammatory and pro-thrombotic/anti-fibrinolytic effects <i>In vitro</i> and <i>ex vivo</i> evidence for potential anti-inflammatory vasculoprotective, anti-thrombotic and cytoprotective effects of HDL particles; central implication of cholesterol acceptor activity
Animal models	Pro-atherogenic effect in numerous studies	Pro-atherogenic and pro-inflammatory effects for TRL and their remnants Atheroprotection exerted by elevated HDL or apo A-I levels
Human genetic studies	Direct causal association in numerous studies, and notably in familial hypercholesterolaemia	Dysbetalipoproteinaemia (remnant hyperlipidaemia, apo E2/E2) provides causal evidence for the atherogenicity of elevated TRL and their remnants Lack of definitive insight for HDL-C, potentially due to the complexity of HDL metabolism
Human intervention studies	Statin trials provided conclusive proof of causality	Imaging trials reveal that fibrate therapy may impact atherosclerosis progression but fails to slow intima-media thickening; see Supplementary material online, Table S2 Meta-analysis of fibrate trials (+statin) show clinical benefit limited to non-fatal CV events. <sup>208</sup> Subgroup analyses reveal major reduction in CV events in patients with high TG and low HDL-C <sup>211</sup> Niacin imaging trials showed consistent stabilization and/or regression of atherosclerosis or intima-media thickening in monotherapy or in combination; see Supplementary material online, Table S1 Reduction in CV events and total mortality with niacin monotherapy <sup>183,184</sup>
Interpretation 2010 <sup>a</sup>	Definite causality	Evidence suggestive of a strong causal association of atherogenic dyslipidaemia, i.e. elevated TRL and their remnants combined with low HDL-C Insufficient evidence for TRL and their remnants alone Insufficient evidence for low HDL-C alone

<sup>a</sup>For an interpretation of causality given the data available in 2010, all five types of evidence should favour causality and all three types of human studies (epidemiology, genetics, and intervention trials) must be consistent; this is clearly the case for elevated LDL-C.

or 40 mg/dL) despite intensive lifestyle intervention, then addition of a fibrate or niacin may be considered (Figure 6).

### Omega-3 fatty acids

Long chain omega-3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) 2–4 g/day] are approved as an adjunct to diet for lowering plasma triglycerides when >5.5 mmol/L (490 mg/dL) to prevent pancreatitis. The profile of lipid-modifying activity is given in Box 2 and mechanisms involved are summarized in Table 3.<sup>138,157,167–170</sup>

Outcome benefits for omega-3 fatty acids have been reported but relate to lower doses than required clinically to lower triglycerides (Supplementary material online, Table S3).<sup>223–225</sup> These benefits may be explained by anti-arrhythmic effects, independent of triglycerides.<sup>226</sup> The AFORRD trial in T2DM patients showed no benefit after 4 months of omega-3 fatty acids (2 g/day) in combination with atorvastatin on estimated CV risk.<sup>227</sup> Adverse effects are limited to minor dyspepsia, with no evidence of increased risk of significant bleeding, even with concomitant aspirin or warfarin.

### Future options

HDL-C-raising *per se* may represent a key determinant of the clinical benefits associated with lipid-modifying therapy,<sup>228</sup> although this concept still needs proof from randomized intervention trials.

CETP inhibitors increase HDL-C levels substantially, and some also affect LDL-C and triglyceride levels.<sup>166</sup> Dalcetrapib (JTT-705) exerts moderate effects on plasma lipids (raising HDL-C by up to 37%),<sup>229</sup> whereas torcetrapib was far more potent (increases in HDL-C >70%), and modestly reduced LDL-C (~20%) and triglycerides (9%).<sup>166</sup> Despite this, the first outcome study with torcetrapib, ILLUMINATE, was prematurely terminated due to excess mortality.<sup>230</sup> However, recent evidence<sup>231,232</sup> suggests that off-target pharmacological effects of torcetrapib were responsible for this adverse outcome rather than a class effect of CETP inhibitors. In all trials, torcetrapib treatment was associated with an increase in systolic blood pressure and electrolyte changes, mediated via hyperaldosteronism. Concerns that large HDL generated through CETP inhibition would be dysfunctional have not been supported by *in vitro* studies.<sup>233,234</sup> Other CETP inhibitors (e.g. dalcetrapib and anacetrapib) do not show

the off-target effects associated with torcetrapib, as indicated by recent studies.<sup>235,236</sup> Clinical outcome data from ongoing or planned studies (dal-OUTCOMES with dalcetrapib and REVEAL with anacetrapib) are awaited.

## What is the evidence for a causal role of elevated triglyceride-rich lipoprotein and their remnants and/or low high-density lipoprotein cholesterol in premature atherosclerosis and cardiovascular disease?

The EAS Consensus Panel considers that for an interpretation of causality, five types of evidence should each favour causality (Table 5) with consistent evidence required from all three types of clinical evidence (epidemiology, genetics, and intervention trials).<sup>237</sup> For elevated LDL-C, the consensus is definite causality. The Panel contends, on the basis of available evidence, that elevated TRL and their remnants combined with low HDL-C may also play a causal role in premature atherosclerosis, whereas insufficient data are currently available for assessing the causality of TRL and remnants alone. The clinical relevance of isolated low HDL-C to CVD also remains unclear.<sup>238</sup>

## Guidance for clinical management

The EAS Consensus Panel believes that targeting a high triglyceride/low HDL-C phenotype is likely to be beneficial in patients with CVD or at high risk of CVD, especially those with cardiometabolic abnormalities. The therapeutic needs of these patients are likely to exceed LDL-C lowering by statin monotherapy.<sup>239</sup> The recommended steps for managing these patients after achieving LDL-C goal, as defined by the most recent European guidelines,<sup>4</sup> are summarized in Figure 6. The Panel proposes triglycerides as a marker for TRL and their remnants. Elevated triglycerides ( $\geq 1.7$  mmol/L or 150 mg/dL, consistent with European guidelines<sup>4</sup>) and/or low HDL-C ( $< 1.0$  mmol/L or 40 mg/dL) are triggers for considering further treatment in both men and women. HDL-C levels  $< 1.0$  mmol/L (40 mg/dL) in men and  $< 1.2$  mmol/L (45 mg/dL) in women are also considered a CV risk factor in current European guidelines.<sup>4</sup> It is noteworthy that in ACCORD Lipid, a cutoff for triglycerides of  $\geq 2.3$  mmol/L identified statin-treated patients at high CV risk, who may respond to fibrates.<sup>107</sup> For simplicity and convenience, measurement of non-fasting plasma lipids is recommended, supported by data from the ERFC,<sup>93</sup> but care should be taken when interpreting triglyceride levels in individuals who have recently consumed a high-fat meal.

The Panel stresses that lifestyle modifications (Box 5) should underpin the management of all patients at increased CV risk, especially those with elevated triglycerides ( $\geq 1.7$  mmol/L or 150 mg/dL) and/or low plasma levels of HDL-C ( $< 1.0$  mmol/L or 40 mg/dL). As non-compliance can be a significant issue, addressing its causes and identifying solutions, including improvement in

physician–patient alliance is essential. Secondary causes of dyslipidaemia, including poor glycaemic control, obesity, diets high in refined carbohydrates, alcohol excess, lack of exercise, and smoking must be addressed. Despite adherence to lifestyle interventions, it is likely that many of these patients with atherogenic dyslipidaemia will require pharmacotherapy. At least 50% of all high-risk patients on a statin may require optimization of treatment to further lower LDL-C,<sup>240</sup> and about 10–15%<sup>107</sup> may need additional treatment for elevated triglycerides and/or low HDL-C. In these patients, clinicians may consider adding niacin or a fibrate, while taking into account potential safety issues, as discussed in this paper.

### Box 5 Recommended basic lifestyle interventions to lower triglycerides and increase HDL-C

- Stop smoking: all smokers at high cardiovascular risk unable to quit smoking should be referred to specialized smoking cessation clinics
- Increase physical activity: aim for at least 30 min of moderate aerobic activity (activity producing a heart rate of 60–75% of age-related maximum heart rate) for at least 5 days per week
- Adopt a Mediterranean-type diet characterized by high monounsaturated and low saturated fatty acids, and low-carbohydrate content. Avoid refined sugar and fructose rich diets which aggravate dyslipidaemia. Increase intake of complex carbohydrates, viscous fibre, and whole-grains
- Lose weight: obese and overweight subjects should adopt a calorie restriction diet, aiming to achieve optimal weight or at least to lose 10% of body weight
- Restrict alcohol intake to less than 30 g per day ( $< 20$  g/day in women). Avoid alcohol consumption in case of high triglyceride levels

In view of its broad spectrum lipid-modulating actions in atherogenic dyslipidaemia (Box 2), niacin may be of special value for reducing TRL and their remnants concomitant with raising HDL-C levels among patients with cardiometabolic abnormalities, particularly those with insulin resistance. However, definitive data from AIM-HIGH and HPS2-THRIVE are needed. Niacin is also unique in lowering Lp(a) levels.<sup>35</sup> Treatment with niacin is supported by clinical evidence of stabilization or regression of atherosclerosis in clinical trials (see *Niacin subsection*). In practice, plasma glucose and urate levels should be monitored regularly for the possibility of hyperglycaemia and hyperuricaemia, respectively, and liver function tests should be monitored to exclude hepatotoxicity. In patients with impaired fasting glucose or impaired glucose tolerance, lifestyle modification is the first option to control glucose, and if niacin is introduced glucose levels should be monitored.

The current level of evidence for clinical outcomes benefits and safety suggests that fenofibrate may be the preferred fibrate for combination with a statin, and may also have particular value in T2DM patients with mild-to-moderate retinopathy.<sup>216,217</sup> From a safety perspective, pre-treatment serum transaminases, creatine

(phospho)kinase, and creatinine should be measured. Creatine (phospho)kinase should be repeated if myalgia is reported, or there are known risk factors for myopathy, and treatment discontinued if levels exceed five times the upper limit of normal and/or symptoms are severe. Alanine and aspartate transaminases should be monitored 3 months after starting therapy and annually thereafter, but more frequently if the dose of statin is uptitrated. Serum creatinine should be monitored with statin–fenofibrate combinations.

If patients are intolerant of both niacin and fenofibrate, a high dose of omega-3 fatty acids ethyl esters may be considered. In patients with very high triglycerides ( $>5.5$  mmol/L or 490 mg/dL), fenofibrate, niacin, or high-dose omega-3 fatty acids (3–4 g/day), together with a very low fat diet ( $<10\%$  of calorie intake) and reduced alcohol intake, are recommended to prevent acute pancreatitis consistent with current guidelines.<sup>4</sup>

The Panel believes there is insufficient evidence to permit definition of targets for triglycerides or HDL-C for these high-risk patients. Instead, the Panel proposes that treatment should be tailored to the individual to achieve desirable levels below (for triglycerides or non-HDL-C) or above (for HDL-C) the recommended cut-offs (Box 6). The Panel acknowledges that other expert bodies recommend apo B as a secondary therapeutic target in hypertriglyceridaemic patients,<sup>18,19</sup> but considers that the precise clinical yield of this approach has yet to be demonstrated. The Panel also recognizes the limitations of the current evidence base for fibrates, niacin, and omega-3 fatty acids, including the lack of hard outcome data for statin–niacin and statin–omega-3 fatty acid combination therapies. Clearly, there is a need for well-defined trials to evaluate the efficacy and safety of these therapeutic combinations in high-risk patients at LDL-C goal with elevated triglycerides and/or low HDL-C.

### Box 6 Desirable lipid levels in patients at high risk of CVD, according to recent European guidelines<sup>4</sup>

LDL-C	$<2.5$ mmol/L (100 mg/dL) in high risk; $<2.0$ mmol/L (80 mg/dL) in very high risk
Triglycerides	$<1.7$ mmol/L (150 mg/dL)
HDL-C	$>1.0$ mmol/L (40 mg/dL) in men; $>1.2$ mmol/L (45 mg/dL) in women
Non-HDL-C	$<2.5$ mmol/L (100 mg/dL)

## Conclusions

The EAS Consensus Panel believes that adoption of these recommendations for clinical management of elevated triglycerides, a marker of TRL and their remnants, and/or low concentrations of HDL-C, supported by appraisal of the current evidence, will facilitate reduction in the substantial CV risk that persists in high-risk patients at LDL-C goal, especially those with cardiometabolic abnormalities (Box 7).

## Box 7 Key messages

- High-risk individuals, especially with cardiometabolic disease, who achieve LDL-C goals remain at high risk of CV events
- Appraisal of the current evidence base implicates elevated triglycerides, a marker of TRL and their remnants, and low levels of HDL-C in this excess CV risk
- In clinical intervention studies using surrogate outcome measures, the addition of niacin to statin reduced atherosclerosis progression in high-risk patients with low LDL-C and elevated triglycerides and/or low HDL-C. Subgroup analyses also showed additional reduction in CV events with fibrate therapy, either alone or in combination with a statin, in patients with atherogenic dyslipidaemia
- Consistent with European guidelines,<sup>4</sup> elevated triglycerides ( $\geq 1.7$  mmol/L or 150 mg/dL) and/or low HDL-C levels ( $<1.0$  mmol/L or 40 mg/dL) should be triggers for considering further treatment in high-risk individuals
- Lifestyle intervention and addressing compliance and secondary causes of dyslipidaemia constitutes the first step in management
- Adding niacin or a fibrate, or intensifying LDL-C lowering, are suggested options for correction of atherogenic dyslipidaemia

## Authors' contribution

*European Atherosclerosis Society Consensus Panel:*

*Co-chairs:* John Chapman and Henry Ginsberg.

The EAS Consensus Panel met four times during the preparation of this manuscript. At the first meeting, members of the Panel critically reviewed the available evidence based on the published literature and at subsequent meetings scrutinized the draft manuscript. All members of the EAS Consensus Panel were involved in the writing of the manuscript and approved the final manuscript before submission.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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