



# Reducing risk by raising HDL-cholesterol: the evidence

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## KEYWORDS

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Low HDL-cholesterol is common among patients with cardiovascular disease. Well-designed epidemiological studies carried out over the previous three decades have defined the prognostic significance of low HDL-cholesterol. Indeed, a recent evaluation of patients undergoing coronary angiography showed that factors related to HDL-cholesterol, but not to LDL-cholesterol, were primarily responsible for driving the elevated risk of atherosclerosis and cardiovascular events associated with dysglycaemia within this population. Randomized intervention studies have demonstrated significant inhibition of atherosclerosis and/or improvement in cardiovascular event rates with treatments that increase HDL-cholesterol (nicotinic acid or a fibrate). Nicotinic acid is the most powerful HDL-cholesterol raising agent currently available, and a combination of this agent with a statin facilitates simultaneous control of both HDL-cholesterol and LDL-cholesterol. Indeed, the HDL Atherosclerosis Treatment Study demonstrated a reduction in major cardiovascular events of 90% vs. placebo in patients randomized to nicotinic acid + simvastatin. In addition, patients randomized to nicotinic acid in the Coronary Drug Project benefited from a significant reduction in mortality after 15 years, 9 years after the trial ended. A new prolonged-release formulation of nicotinic acid, Niaspan<sup>®</sup>, has superior tolerability compared with immediate-release nicotinic acid and facilitates the delivery of this therapy. The evidence base supporting intervention to correct low HDL-cholesterol in addition to reducing LDL-cholesterol is now sufficiently strong to support the introduction of this strategy into routine clinical practice.

## Introduction

Current guidelines for the management of cardiovascular risk regard establishing control of LDL-cholesterol as the primary goal of lipid modification. Guidelines relevant to the European practice have been proposed jointly by leading European expert societies.<sup>1</sup> These recommend that total cholesterol and LDL-cholesterol should be reduced to below 5 (193 mg/dL) and 3 mmol/L (116 mg/dL), respectively, with more stringent goals of total cholesterol <4.5 mmol/L (174 mg/dL) and LDL-cholesterol <2.5 mmol/L (97 mg/dL)

for patients with pre-existing cardiovascular disease or diabetes. Similarly, the US guidelines specify goals for LDL-cholesterol of <160 mg/dL (4.1 mmol/L) for patients with not more than a single cardiovascular risk factor, <130 mg/dL (3.4 mmol/L) for patients with two or more cardiovascular risk factors and a 10-year (Framingham) risk of major cardiovascular events of ≤20%, and <100 mg/dL (2.6 mmol/L) for patients with coronary heart disease (CHD) or diabetes and 10-year Framingham risk >20%, respectively.<sup>2</sup>

Thus, guidance for the management of LDL-cholesterol is both detailed and explicit and takes into account the important comorbidities. Moreover, the demonstration of additional protection for cardiovascular events from reduction of LDL-cholesterol to levels below those

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recommended by these guidelines in trials, such as A to Z,<sup>3</sup> Treating to New Targets (TNT),<sup>4</sup> Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT),<sup>5</sup> and more recently, Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL),<sup>6</sup> has raised expectations of even lower goal values being set for LDL-cholesterol in the future.<sup>7</sup> In contrast, HDL-cholesterol is only regarded a marker of risk in these guidelines, despite the inclusion of a cut-off value for HDL-cholesterol [ $<1.03$  mmol/L (40 mg/dL) in men and  $<1.29$  mmol/L (50 mg/dL) in women] in the most widely used diagnostic criteria for the metabolic syndrome.<sup>2,8</sup> Although a level of HDL-cholesterol above this cut-off value is regarded as 'normal', there is little emphasis on management of levels of HDL-cholesterol independently or in addition to other cardiovascular risk factors.

There is no doubt that low HDL-cholesterol is an important and independent risk factor for adverse cardiovascular outcomes.<sup>9,10</sup> Indeed, epidemiological data from the Framingham and other studies suggest that every decrease of 1 mg/dL in HDL-cholesterol (0.03 mmol/L) may be associated with an increase of 2–3% in the risk of CHD.<sup>11</sup> Accordingly, there is a growing view among experts in the field of cardiovascular risk management that greater emphasis should be placed on the management of HDL-cholesterol in addition to the proven benefits arising from tight control of LDL-cholesterol.<sup>12</sup> The purpose of this review is to evaluate the strength of the evidence base that underpins intervention for correcting low HDL-cholesterol as a component of overall strategies for the management of cardiovascular risk. In doing so, this review will consider the prevalence of low HDL-cholesterol among patients with cardiovascular morbidity, the prognostic importance of low HDL-cholesterol in comparison with other lipid parameters in these patients, and the clinical implications of such interventions for the management of cardiovascular disease.

### The prevalence of low HDL-cholesterol in patients with cardiovascular morbidity

The Pan-European survey of HDL-cholesterol recently measured lipid profiles in a population of 8545 patients receiving treatment for dyslipidaemia from a specialist physician across 11 countries within Europe.<sup>13</sup> Low HDL-cholesterol was a common finding in this population and little affected by lipid-modifying treatment (almost always a statin): HDL-cholesterol  $<1.03$  mmol/L (40 mg/dL) was found in 33 and 34% of men receiving and not receiving such treatment, respectively, with corresponding figures of 40 and 39% in women, respectively. Severely low HDL-cholesterol [ $<0.91$  mmol/L (35 mg/dL)] was found in 14% of the survey population.

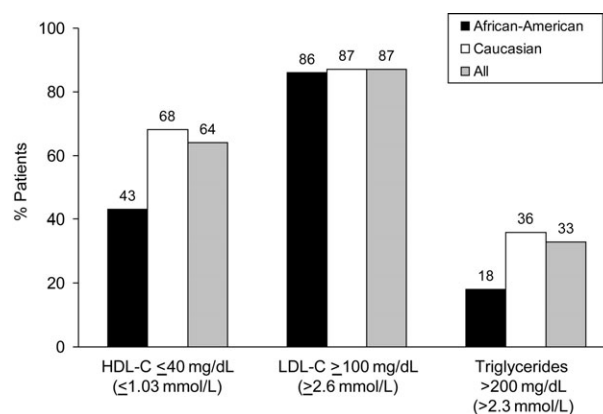
A population of  $>8000$  men screened for potential enrolment in the Veterans Affairs HDL Intervention Trial (VA-HIT) provided an opportunity to estimate the prevalence of low HDL-C in patients with objective evidence

of coronary artery disease ( $\geq 3$  months after a myocardial infarction).<sup>14</sup> Lipid abnormalities were common in this population (Figure 1). Low HDL-cholesterol was present in about two-thirds of Caucasian subjects and in about two-fifths of African-American subjects. The overall prevalence of low HDL-cholesterol was in excess of 60% in this mostly Caucasian population. Hypercholesterolaemia and hypertriglyceridaemia were also common findings in this study.

### HDL-cholesterol as a determinant of clinical outcomes in patients at high cardiovascular risk

The strong associations between low HDL-cholesterol and adverse outcomes in epidemiological studies, and the high prevalence of this condition in patients at elevated coronary risk identify low HDL-cholesterol as an important clinical problem. However, classical epidemiological techniques, although useful for generating hypotheses relating to pathophysiological mechanisms, provide little evidence to substantiate a causative role for low HDL-cholesterol in the pathogenesis of atherosclerotic cardiovascular disease. Such analyses may also be hampered by confounding due to clustering of related risk factors or inadequate adjustment in multivariate analysis.

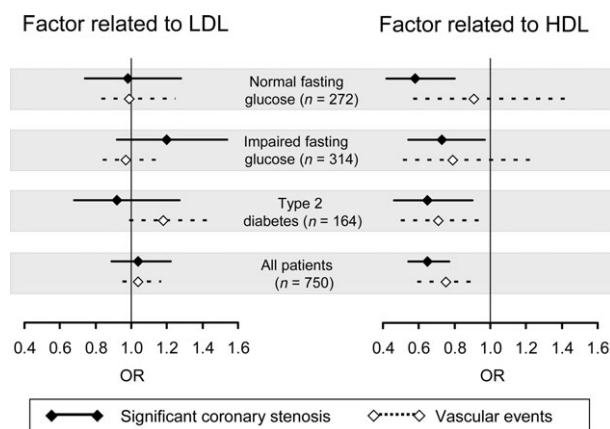
The application of factor analysis to such data helps to overcome some of these problems. Factor analysis is a mathematical technique by which a large number of interrelated variables are reduced to a smaller number of 'factors' that represent their overall effect on the process under study. This technique was applied to data from a consecutive series of 750 patients with coronary artery disease undergoing angiography at the Vorarlberg Institute for Vascular Investigation and Treatment, Feldkirch, Austria.<sup>15</sup> Two principal factors emerged



**Figure 1** Prevalence of lipid abnormalities among men screened for enrolment in the VA-HIT. Lipid profiles were derived from 2728–2911 Caucasian patients and 567–583 African-American patients, for whom data on ethnicity were recorded. Data for the overall patient population, including other patients for whom ethnicity was not recorded, were from 8117–8641 patients. Drawn from data presented by Rubins *et al.*<sup>14</sup>

from the analysis. One was related to HDL and incorporated HDL cholesterol, triglycerides, ApoA1, and LDL particle diameter. The other factor was related to LDL and incorporated LDL cholesterol, total cholesterol, and ApoB. The importance of each factor in predicting the presence of clinically significant coronary atherosclerotic lesions (stenosis of at least 50% of the coronary lumen) was determined after the population was stratified for glycaemic status at baseline. In addition, patients were followed prospectively for an average of 2.3 years for cardiovascular outcomes, using a composite cardiovascular endpoint including coronary death, non-fatal myocardial infarction, non-fatal stroke, and the need for coronary or peripheral revascularization.

The factor related to HDL was strongly and significantly related to a reduced risk of clinically significant coronary stenosis irrespective of glycaemic status at baseline (Figure 2).<sup>16</sup> In contrast, the factor related to LDL did not significantly influence the risk of coronary stenosis. The presence of pre-diabetic or diabetic dysglycaemia increased the cardiovascular event rate ( $P = 0.007$ ), with the incidence more than twice in diabetic patients than in the normoglycaemic patients (19.2 and 9.5%, respectively). The HDL-related factor from the factor analysis was associated with a reduced risk of coronary events in the overall patient population and in the diabetic sub-population, who are at markedly increased risk of coronary disease. In the diabetic group, the odds ratio (OR) for vascular events associated with the HDL-related factor was 0.71 (95% CI 0.51–0.99;  $P = 0.044$ ). Once again, the LDL-related factor did not exert a significant effect on the risk of coronary events in the overall population or in the diabetic subgroup (OR 1.36, 95% CI 0.99–1.88;  $P = 0.061$ ).



**Figure 2** Relationships between factors related to HDL and LDL on the prevalence of coronary stenosis at baseline and on the risk of adverse cardiovascular outcomes during an average of 2.3 years of follow-up. Standardized OR were adjusted for age, gender, and lipid-lowering medication and were derived from logistic regression analysis (coronary stenosis) or Cox regression analysis (vascular events). Non-diabetic glycaemic status was determined on the basis of fasting plasma glucose (FPG) as follows. Normal fasting glucose: FPG < 5.6 mmol/L; impaired fasting glucose: FPG 5.6–6.9 mmol/L. Type 2 diabetes was defined according to World Health Organization criteria.<sup>16</sup> Adapted with permission from: Drexel H *et al.*<sup>14</sup>

A preliminary report has described the results of a longer duration of follow-up (4 years) in this cohort.<sup>17</sup> At this time point, a significant protective effect of the HDL-related factor was still present in the subgroup with diabetes, with an OR for vascular events of 0.70 (95% CI 0.51–0.97), whereas the LDL-factor was still without significant effect on the cardiovascular event rate in this group (OR of 1.16, 95% CI 0.90–1.50;  $P = 0.26$ ). Overall, these analyses showed that cardiovascular risk factors related to HDL on factor analysis appeared to exert a stronger influence of atherosclerosis-related outcomes than factors related to LDL. The particularly strong relationship between the HDL-related factor and angiographic or clinical outcomes in diabetic patients is consistent with the proposed role of atherogenic dyslipidaemia (low HDL-cholesterol, elevated triglycerides, and small, dense LDL) as a principal driver of atherosclerosis in insulin-resistant states.<sup>18</sup>

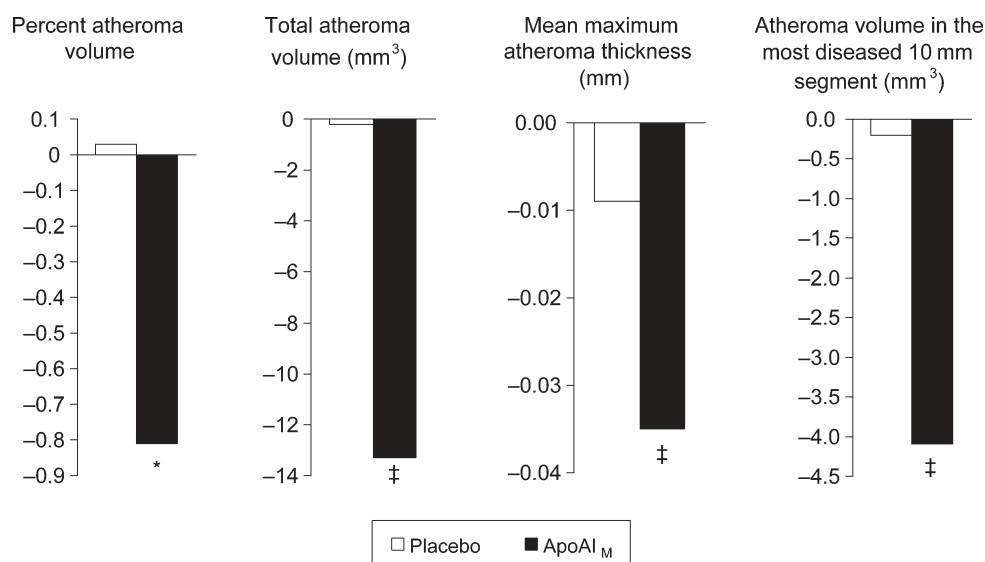
## Anti-atherogenic actions of HDL-cholesterol raising: evidence from intervention studies

### HDL mimetic therapy

Studies using quantitative coronary angiography or ultrasonography have demonstrated the potential of interventions that increase HDL-cholesterol to inhibit the progression of atherosclerosis. The discovery of a spontaneously arising mutation in ApoA1, termed ApoA1-Milano (ApoA1<sub>M</sub>) in a remote region of northern Italy provided an opportunity to evaluate the effects on atherosclerosis of intervening with an HDL mimetic agent.<sup>19–21</sup> People carrying this mutation were apparently at low risk of cardiovascular disease.<sup>22</sup> Accordingly, a study in 47 patients with acute coronary syndromes was conducted which involved randomization to weekly infusions of one or two doses of recombinant ApoA1<sub>M</sub> (15 or 45 mg/kg) in a phospholipid complex or placebo.<sup>23</sup> There was a clear evidence of inhibition of atherosclerosis in patients randomized to receive ApoA1<sub>M</sub>, whether this was measured as the total atheroma volume, as the average maximum thickness of atheroma in the target coronary segment, as the maximum thickness of atheroma, or as the volume of atheroma in the most severely diseased section of the coronary segment under study (Figure 3). ApoA1<sub>M</sub> and a number of other synthetic HDLs are under development for the treatment of atherosclerosis.<sup>24</sup>

### Oral pharmacotherapy

Several trials have evaluated the effect of interventions with oral pharmacotherapy on atherosclerosis progression. Most of these have involved regimens including nicotinic acid (niacin), the most effective agent currently available for this purpose.<sup>2</sup> These studies include the Cholesterol-Lowering Atherosclerosis Study (CLAS),<sup>25–27</sup> the HDL-Atherosclerosis Treatment Study (HATS),<sup>28</sup> the Familial Atherosclerosis Treatment Study (FATS),<sup>29</sup> and the Arterial Biology for the Investigation of the



**Figure 3** Mean changes from baseline in indices of coronary atherosclerosis in 47 patients with acute coronary syndromes randomized to placebo or recombinant ApoAI-Milano (ApoAI<sub>M</sub>) at doses of 15 or 45 mg/kg in a 1:2:2 ratio who completed 1 year of treatment (data shown reflect the results from a pooled analysis of either dose). Target segments of coronary arteries for evaluation were selected for  $\leq 50\%$  luminal narrowing over a length of  $\geq 30$  mm in a major epicardial vessel. \* $P = 0.02$ ; † $P < 0.001$ . Drawn from data presented by Nissen *et al.*<sup>23</sup>

**Table 1** Key features of and findings from trials using quantitative arteriography to evaluate the effects on atherosclerosis progression of pharmacological interventions aimed at increasing levels of HDL-cholesterol

Trial	n	Patients	Treatments	Years	Main findings
CLAS <sup>25-27</sup>	162	Prior coronary bypass graft; documented CAD; elevated cholesterol	NA + colestipol Placebo	2-4	↑37% HDL-C, ↓43% LDL-C Significant reductions in progression of lesions and new lesion formation in the active treatment group vs. placebo
HATS <sup>28</sup>	160	Documented CAD, low HDL-C <sup>a</sup> , near-normal LDL-C	NA + simvastatin <sup>b</sup> Antioxidants Placebo <sup>b</sup>	3	↑42% HDL-C, ↓26% LDL-C in NA group Atherosclerosis regression observed with NA + simvastatin
FATS <sup>29</sup>	146	Elevated ApoB, documented CAD, family CVD history	Lovastatin <sup>c</sup> NA <sup>c</sup> Placebo <sup>c</sup>	2.5	↑43% HDL-C, ↓32% LDL-C in NA group More regression and less progression of lesions in active treatment groups
ARBITER 2 <sup>30</sup>	167	Documented CAD, statin treatment, low HDL-C <sup>d</sup>	Niaspan + statin Placebo + statin	1	↑18% HDL-C Significantly less progression of atherosclerosis on Niaspan-based therapy

All were randomized, double-blind trials, except CLAS, which was single-blind. See text for full names of trials. NA, immediate-release nicotinic acid; CAD, coronary artery disease; CVD, cardiovascular disease.

<sup>a</sup>Below 0.91 mmol/L (35 mg/dL) in men and below 1.03 mmol/L (40 mg/dL) in women.

<sup>b</sup>With or without antioxidants.

<sup>c</sup>Plus colestipol as required.

<sup>d</sup>Less than 1.2 mmol/L (45 mg/dL).

Treatment Effects of Reducing Cholesterol (ARBITER 2) study.<sup>30</sup>

CLAS evaluated a combination of nicotinic acid and the bile acid sequestrant, colestipol, in patients with previous coronary bypass surgery. At 2 years, a marked reduction in LDL-cholesterol and a marked increase in HDL-cholesterol had occurred (Table 1). These beneficial changes in lipids were accompanied by a reduction in the active treatment group relative to placebo in the average number of progressing atherosclerotic lesions ( $P < 0.03$ ) and the formation of new atherosclerotic lesions

( $P < 0.03$ ); a global test showed that these changes were highly significant ( $P < 0.0001$ ). At 4 years, non-progression of atherosclerosis was more common in the active treatment group (52 vs. 15% on placebo), as was atherosclerosis regression (18 vs. 6%).

The FATS study recruited patients with elevated ApoB and documented CAD and randomized them to receive a statin, nicotinic acid, or placebo, with additional colestipol as required. Once again, marked improvements in HDL-C and LDL-C were accompanied by improvements in angiographic status of coronary arteries. In this trial,

46% of the placebo group demonstrated atherosclerosis progression, compared with 21% of the lovastatin group and 25% of the nicotinic acid group. Similarly, atherosclerosis regression was less common with placebo (11%) than with lovastatin-based or nicotinic acid-based treatment (32 and 39%, respectively,  $P < 0.005$  for differences between groups).

HATS also evaluated nicotinic acid + a statin, this time in comparison with placebo. Similar improvements in the lipid profile compared with FATS in the nicotinic acid-based treatment group were observed. Atherosclerosis progressed by 3.9% in the placebo group, compared with regression of atherosclerosis by 0.4% in the nicotinic acid-simvastatin group ( $P < 0.001$  vs. placebo), and progression by 0.7% when antioxidants were added to the nicotinic acid-based regimen ( $P < 0.004$  vs. placebo).

The ARBITER 2 study set out to test the hypothesis that correcting low HDL-cholesterol with nicotinic acid-based therapy in patients with this abnormality, despite adequate control of LDL-cholesterol with a statin, would inhibit carotid atherosclerosis (a validated surrogate for coronary atherosclerosis) compared with placebo. This trial evaluated the effects of Niaspan<sup>®</sup>, a prolonged-release formulation of nicotinic acid with superior tolerability relative to the immediate-release formulation used in other studies.<sup>31</sup> After 1 year of treatment, carotid intima-media thickness had progressed significantly on placebo [by 0.044 mm (SD 0.011 mm);  $P < 0.011$ ], whereas there was no significant progression with Niaspan [mean change 0.014 mm (SD 0.011 mm);  $P = 0.23$ ].

An open-label follow-up to this study, ARBITER 3, involved switching patients previously on placebo to Niaspan (both still combined with a statin) for a further year of treatment.<sup>32</sup> Altogether, 104 patients completed the study. An additional effect on atherosclerosis was observed, compared with the preceding ARBITER 2 study, with significant regression of atherosclerosis observed in the Niaspan group after 2 years.

## Improved clinical outcomes associated with increasing levels of HDL-cholesterol

A strong evidence base underpins the principle of HDL-cholesterol raising as a therapeutic strategy for improving cardiovascular outcomes in high-risk populations. Several randomized, double-blind outcome studies in patients with documented coronary artery disease have evaluated the effects of HDL-cholesterol raising treatments (nicotinic acid or a fibrate), including the VA-HIT,<sup>33</sup> the Coronary Drug Project (CDP),<sup>34-37</sup> the HATS trial (for which the angiographic findings are discussed above) and the Stockholm Ischaemic Heart Disease (IHD) trial.<sup>38</sup>

Table 2 summarizes the treatments administered in these trials together with their key findings. Significant reductions in major cardiovascular events were observed in patients randomized to an HDL-cholesterol raising treatment in all four studies. The high-risk population of the HATS trial derived the largest benefit, with a reduction in the risk of the primary endpoint (death, myocardial infarction, stroke, or revascularization) of 90% vs. placebo when nicotinic acid + simvastatin was given without antioxidants ( $P = 0.03$ ) (Figure 4). The inclusion of patients who also received antioxidant vitamins attenuated the effect, although the risk reduction of 60% vs. patients who did not receive nicotinic acid-simvastatin therapy was still significant ( $P = 0.02$ ) (Figure 4).

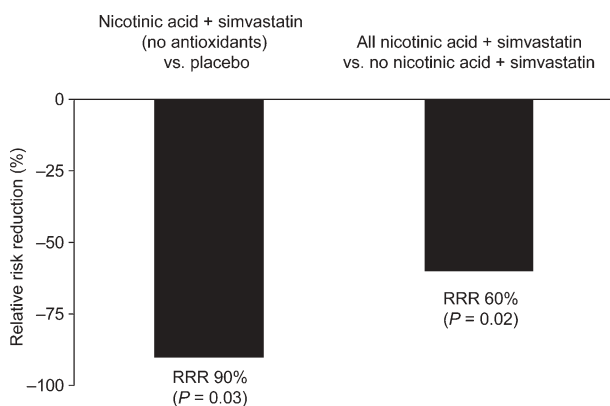
In addition to these effects observed during the double-blind phase of the trials, a retrospective analysis of outcomes in the CDP population was conducted 9 years after the termination of the double-blind phase of the study, i.e. a 15-year follow-up overall.<sup>35</sup> A significant ( $P = 0.0012$ ) 11% reduction in total mortality was observed in patients who had previously been randomized to treatment with nicotinic acid, compared with placebo (Table 2 and Figure 5). Importantly, these long-term benefits are preserved in the settings of increased blood glucose<sup>37</sup> or the metabolic syndrome.<sup>36</sup>

**Table 2** Study treatments and selected clinical outcomes in outcome studies evaluating nicotinic acid or a fibrate

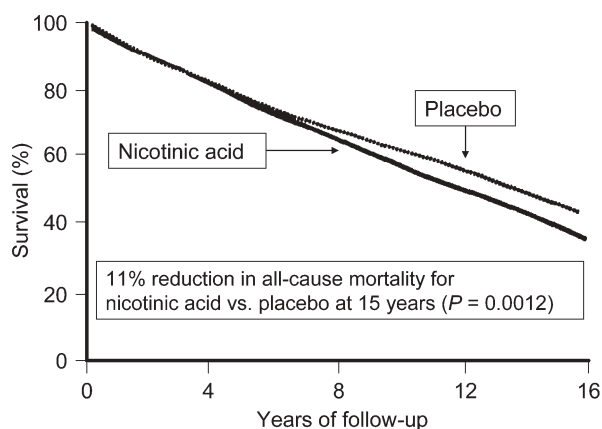
Study	Treatments (n)	Duration (years)	Main results
VA-HIT <sup>33</sup>	Gemfibrozil (1264) Placebo (1267)	5	Non-fatal MI or CHD death ↓22% ( $P = 0.006$ ) Non-fatal MI ↓23% ( $P = 0.02$ )
CDP <sup>34-37</sup>	NA (1119) Clofibrate (1103) D-thyroxine (1110) Oestrogens (2220) <sup>a</sup> Placebo (2789)	6 (double-blind) 15 (double-blind + retrospective follow-up)	5-year outcomes Non-fatal MI or CHD death ↓14% ( $P < 0.05$ ) Non-fatal MI ↓27% ( $P < 0.05$ ) Stroke/TIA ↓26% ( $P < 0.05$ ) 15-year outcomes Total mortality ↓11% ( $P = 0.0004$ )
HATS <sup>28</sup>	NA + simvastatin (33) NA + simvastatin + antioxidants (33) Antioxidants (39) Placebo (34)	3	Composite endpoint (CHD mortality, non-fatal MI, revascularization) ↓90% (simvastatin-NA) ( $P = 0.03$ ) ↓60% (simvastatin-NA-antioxidants) ( $P = 0.02$ )
IHD <sup>38</sup>	Nicotinic acid + clofibrate (279) Controls (usual care) (276)	5	Total mortality ↓26% ( $P < 0.05$ ) CHD mortality ↓36% ( $P < 0.01$ )

Clinical CHD in HATS was defined as previous MI, coronary interventions, or confirmed angina. TIA, transient ischaemic attack; NA, nicotinic acid.

<sup>a</sup>The low HDL-C definition in HATS.



**Figure 4** Risk reductions for the primary endpoint of death, myocardial infarction, stroke, or revascularization in patients randomized to receive nicotinic acid + simvastatin. The left-hand column represents a comparison of nicotinic acid + simvastatin vs. placebo, whereas the right-hand column represents a comparison of events in all patients who received nicotinic acid + simvastatin (irrespective of concomitant antioxidant treatment) compared with patients who received any treatment not including nicotinic acid + simvastatin (placebo or antioxidants). Drawn from data presented by Brown *et al.*<sup>28</sup>



**Figure 5** Survival curves for patients randomized to nicotinic acid or placebo in the CDP. Reprinted from Canner *et al.*<sup>23</sup> © 1986, with permission from the American College of Cardiology Foundation.

These are remarkable findings given that no attempt had been made to maintain trial conditions or treatments after the end of the double-blind phase of the study, and attests to the durability of cardiovascular benefit arising from intervention to increase HDL-cholesterol.

## Discussion

Current cardiovascular management guidelines continue to focus on ever-lower levels of LDL-cholesterol in the pursuit of greater reductions in cardiovascular event rates than the 20–40% risk reductions routinely obtained with statins in intervention trials.<sup>39</sup> We know that cardiovascular risk is multifactorial in nature, and an abundance of clinical evidence from epidemiological studies points to low HDL-cholesterol as an additional clinically

important cardiovascular risk factor in its own right. Moreover, low HDL-cholesterol is a common source of excess cardiovascular risk, especially in patients with CHD and diabetes mellitus.

Statins exert relatively little effect on HDL-cholesterol in most patients,<sup>40</sup> and we must look to the use of other agents in combination with statins if we are to make significant inroads into the residual cardiovascular risk in statin-treated patients. HDL-cholesterol raising interventions have not received the intensive evaluations in clinical trials that have established the statins as the core pharmacotherapy for the management of atherosclerotic risk. Nevertheless, the beneficial effects on cardiovascular outcomes of agents that act mainly by raising HDL-cholesterol, namely fibrates and nicotinic acid, have been demonstrated in a number of well-designed outcome trials that have produced highly significant results. We have enough clinical evidence today to incorporate strategies to increase HDL-cholesterol into our routine care of the patient at risk of an adverse cardiovascular outcome.

## Conclusions

Low HDL-cholesterol is common among the population at risk of adverse cardiovascular outcomes and is highly prognostically significant. Intervention to correct low HDL-cholesterol is well supported by randomized intervention trials, and this strategy should be introduced into routine clinical practice alongside control of LDL-cholesterol.

**Conflict of interest:** none declared.

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