Evidence to support aggressive management of HDL-cholesterol: implications of recent trials

Allen J. Taylor

Cardiology Service, Walter Reed Army Medical Center, 6900 Georgia Ave, NW, Bldg 2, Room 4A34, Washington, DC 20307-5001, USA

Low HDL-cholesterol is an independent risk factor for coronary disease and its prevalence is high and increasing. Lifestyle interventions are recommended for all patients at risk of cardiovascular disease, but exercise has limited effects on HDL-cholesterol. Nicotinic acid is currently the most effective pharmacological agent available for increasing levels of HDL-cholesterol. The HDL Atherosclerosis Treatment study (HATS) showed that combining nicotinic acid with a statin improved HDL-cholesterol and LDL-cholesterol, inhibited the progression of atherosclerosis, and reduced cardiovascular event rates in a high-risk population with established coronary heart disease. A prolonged-release formulation of nicotinic acid (Niaspan®) has been developed that is as effective as the immediate-release version, but is better tolerated. The double-blind, randomized Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) study, and its open-label follow-up study, ARBITER 3, showed that Niaspan shares the anti-atherogenic benefits of immediate-release nicotinic acid. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL-C/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) study will define the potential of correcting low HDL-cholesterol to improve clinical outcomes in patients with well-controlled LDL-cholesterol.

In summary, the current evidence base clearly shows that aggressive intervention to correct low HDL-cholesterol as well as high LDL-cholesterol is a proven strategy for preventing atherosclerotic cardiovascular disease.

Introduction

The Scandinavian Simvastatin Survival Study (4S), published in 1994, was the first major evaluation of an HMG-CoA reductase inhibitor (statin).¹ This trial, conducted in a population at high risk of adverse cardiovascular outcomes through hyperlipidaemia and a history of myocardial infarction, demonstrated a 30% reduction (P = 0.0003) in its primary endpoint of all-cause mortality and a 42% reduction in the risk of coronary death during an average follow-up of 5 years. This landmark study set the scene for numerous other evaluations of statins in various patient populations at high cardiovascular risk.² The results of these studies were consistent, with reductions in primary cardiovascular outcomes ranging roughly between 20 and 40%, relative to placebo. Moreover, the implication of these trials for clinical practice was clear: all patients with a history of coronary disease (or equivalent, such as clinical evidence of carotid or other peripheral atherosclerosis, or diabetes) require intensive intervention to limit their LDL-cholesterol to <100 mg/dL (2.6 mmol/L), and most will require treatment with a statin.³

We are nevertheless faced with the problem of addressing the substantial residual burden of cardiovascular risk in statin-treated patients. Two main approaches have been the subject of intense clinical investigation in recent years. Firstly, we can go beyond the "standard" doses of statins used in the earlier
intervention trials, and pursue ever-lower levels of LDL-cholesterol for as long as we derive additional benefit from doing so. Alternatively, we can address sources of cardiovascular risk other than those driven by levels of ApoB-containing lipoproteins. The first approach is covered in detail in the accompanying paper by Professor Terje Pedersen, who has been closely involved in key trials in this area, and will be dealt with briefly here. The main purpose of this review is to explore the anti-atherogenic benefits of strategies designed to correct low levels of the cardio-protective lipoprotein, HDL-cholesterol.

Strategies for improving cardiovascular outcomes in statin-treated patients

Intensive management of LDL-cholesterol

Recent trials evaluating the effectiveness of intensive lowering of LDL-cholesterol include the Treat to New Targets (TNT),6 the Incremental Decrease in Endpoints through Aggressive Lipid lowering (IDEAL),4 A to Z,7 and the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT-TIMI 22) studies.7 These trials achieved final mean LDL-cholesterol levels of 1.6–2.1 mmol/L (62–81 mg/dL), which are well below the current 100 mg/dL (2.6 mmol/L) guideline target for patients at elevated cardiovascular risk.3 Patients in control groups in these trials received less-intensive intervention with a statin; their average LDL-cholesterol remained very close to this goal value: 101 mg/dL (2.6 mmol/L) in the TNT study and 104 mg/dL (2.7 mmol/L) in the IDEAL study, or below this value for the control group of the PROVE IT-TIMI 22 and A to Z studies, who achieved a final LDL-cholesterol level of 95 mg/dL (2.5 mmol/L) and 77 mg/dL (2 mmol/L), respectively. Cardiovascular event rates (all trials employed composite cardiovascular primary endpoints) were lower in the intensive management arms of all trials, with modest risk reductions relative to the less-intensive management groups of 11–16%. Observed risk reductions achieved statistical significance (P < 0.05) for TNT (P < 0.001) and PROVE-IT (P = 0.005), but not for IDEAL and A to Z.

Thus, it appears that intensive management of LDL-cholesterol does indeed provide additional clinical cardiovascular benefit to ‘standard’ intervention with these agents. However, these benefits are modest, and the potential for further benefits may be limited. A recent meta-analysis of 14 randomized interventions with statins, involving >45,000 patients randomized to these agents and >45,000 patients randomized to placebo, has shown that the relative risk of CHD or of any adverse vascular event during statin treatment declined by about 20% for each 1 mmol/L (39 mg/dL) reduction in LDL-cholesterol.8 In addition, for some patients, increased cost or emergence of side-effects may limit the practicability of intensive statin treatment.

Rationale for simultaneous correction of high LDL-cholesterol and low HDL-cholesterol

Relationships between HDL-cholesterol, LDL-cholesterol, and coronary risk

Simultaneous control of ApoB-containing lipoproteins and other sources of cardiovascular risk represents a practicable and proven alternative strategy for improving cardiovascular outcomes to the pursuit of very low levels of HDL-cholesterol. A strong base of clinical evidence supports a strategy based on combined treatment to address elevated levels of LDL-cholesterol and low HDL-cholesterol for improving cardiovascular outcomes in these patients.

The Framingham Study provided the first compelling evidence of a role for low HDL-cholesterol as an independent risk factor for cardiovascular disease.9–11 Figure 1 shows the relationship between HDL-cholesterol and LDL-cholesterol in the Framingham cohort. The levels of HDL-cholesterol analysed in Figure 1 cover a range of values highly relevant to current clinical practice: 100 mg/dL (2.6 mmol/L) is the guideline goal value for intensive management of this parameter in high-risk patients, as described above, 160 mg/dL (4.1 mmol/L) is the guideline goal value for patients at low cardiovascular risk (no prior cardiovascular disease and one cardiovascular risk factor or less), and 220 mg/dL (5.7 mmol/L) represents marked hyperlipidaemia requiring immediate pharmacologic intervention.12 Similarly, the values of HDL-cholesterol shown straddle the 40 mg/dL (1.02 mmol/L) and 50 mg/dL (1.29 mmol/L) cut-off values used to define low HDL-cholesterol in men and women, respectively, according to guidelines from the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII),3 and diagnostic criteria for the metabolic syndrome proposed by NCEP/ATPIII and the International Diabetes Federation.12

Low HDL-cholesterol levels are associated with a higher risk of coronary heart disease irrespective of the level of LDL-cholesterol (Figure 1). Conversely, higher
levels of HDL-cholesterol are associated with lower cardiovascular risk at any prevailing level of LDL-cholesterol (Figure 1). The magnitude of the potential risk reductions achieved follows the ‘rule of ones’: every change of 1% in HDL-cholesterol (increase) or LDL-cholesterol (decrease) decreases coronary risk by roughly 1%. The results of intervention trials with agents that increase HDL-cholesterol as a principal mechanism of their action support this concept. Significant reductions in coronary event rates have been observed in evaluations of a fibrate, such as the Veterans Affairs HDL Intervention Trial or of nicotinic acid, such as the Coronary Drug Project or the HDL Atherosclerosis Treatment Study (HATS). In addition, the Armed Forces Regression Study (AFREGS) showed that randomization to a combination of immediate-release nicotinic acid, a bile acid sequestrant and a fibrate was associated with a significant reduction in the incidence of a composite cardiovascular endpoint.

Increasing burden of cardiovascular risk due to low HDL-cholesterol

Increasing evidence suggests a high prevalence of low HDL-cholesterol. For example, a recent survey carried out in >8500 patients under treatment for dyslipidaemia across Europe suggested that more than one in three of the survey population had low HDL-cholesterol, despite a high rate of use of statins in these patients. Moreover, the ongoing epidemic of obesity may be driving an increasing prevalence of low HDL-cholesterol, along with other components of the metabolic syndrome. For example, recent data from the US National Health and Nutrition Examination Survey, which recruits a survey population representative of the US general population, showed that the age-adjusted prevalence of low HDL-cholesterol increased from 38–40% within a single decade.

In a further observational study, levels of HDL-cholesterol were measured every 2 years over a 12-year period in a cohort of more than 12,000 residents in a town in the eastern USA. The average level of HDL-cholesterol declined during this period in both men and women (Figure 2). The design of this analysis included stratification of patients for well-known confounding factors for HDL-cholesterol measurement, namely use of alcohol (Figure 2A), smoking (Figure 2B), or overweight/obesity (Figure 2C). Although each of these factors affected the absolute level of HDL-cholesterol at any time during the survey period, the same trends towards a fall in average HDL-cholesterol levels over time were evident in each subgroup.

Figure 2 Declining HDL-cholesterol over time in a community in the eastern USA. Adjusted mean HDL-cholesterol levels are shown with respect to use of alcohol or tobacco, and with respect to body mass index (BMI), as indicated. Values were adjusted for age, education, smoking, BMI, alcohol use within 24 h, exercise, lipid-lowering medication, β-blockers, anti-diabetic medication, location, survey, batch, menopause status, oral contraceptives, and hormone replacement therapy. Survey years were 1: 1981–82; 2: 1983–84; 3: 1985–86; 4: 1987–89; 5: 1989–90; 6: 1992–93. Significance of linear trends across surveys: *P < 0.01, **P < 0.001. from Derby et al. with permission from Elsevier © 1998. (A) Alcohol use within the previous 24 h. (B) Smoking (current smoker or non-smoker) (C) Upper and lower tertiles of BMI in the study population corresponding to BMI values as follows: lower tertile <22.9 kg/m2 for women and <24.5 kg/m2 for men; upper tertile ≥27.6 kg/m2 for women and ≥27.9 kg/m2 for men.
Management of low HDL-cholesterol

Lifestyle factors

Alcohol consumption and smoking have opposite effects on levels of HDL-cholesterol, as shown in Figure 2A and B, respectively.20 The increase in HDL-cholesterol associated with moderate alcohol consumption apparently results from increased rates of reverse cholesterol transport, and is most evident in subjects with low HDL-cholesterol.21,22 Obesity is a major determinant of low HDL-cholesterol (Figure 2C). Abdominal obesity, frequently present in insulin resistant states such as type 2 diabetes or the metabolic syndrome, is strongly associated with low HDL-cholesterol.23–25 Further lipid abnormalities, notably hypertriglyceridaemia and small dense LDL particles, are also often observed in these patients.25 Thus, whereas it is impractical to encourage patients to drink, smoking cessation, and weight loss are practical options for increasing levels of HDL-cholesterol.

Exercise exerts relatively little effect on HDL-cholesterol. The Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study showed that endurance exercise training did not increase HDL-cholesterol levels in men with isolated low HDL-cholesterol, while men with hypertriglyceridaemia and low HDL-cholesterol benefited from a modest (5%) but significant (P = 0.005) increase in HDL-cholesterol.26 This change was apparently driven entirely by the reduction in visceral adipose tissue induced by the exercise. A further study quantified the relationship between effects on HDL-cholesterol and the intensity of exercise.27 Exercise up to and including an intensity equivalent to that undertaken by a 90 kg individual jogging for 12 miles (19 km) per week at 65–80% of peak oxygen consumption had no significant effect on HDL-cholesterol. Very intense exercise, equivalent to our 90 kg subject jogging for 20 miles (32 km) per week at 65–80% of peak oxygen consumption, was required to increase mean HDL-cholesterol by ~4 mg/dL (0.1 mmol/L) from a baseline value of 44 mg/dL (1.1 mmol/L).

Pharmacological interventions

Lifestyle interventions remain the cornerstone of cardiovascular care, but the modest effects of such interventions on levels of HDL-cholesterol often renders pharmacological treatment with nicotinic acid or a fibrate necessary for correction of low HDL-cholesterol. Nicotinic acid is the most effective agent currently available for increasing levels of HDL-cholesterol.3,28 A prolonged-release formulation of nicotinic acid, Niaspan86, has been shown to be as effective as the immediate-release formulation, but is better tolerated with a lower incidence of flushing, the main side-effect associated with nicotinic acid therapy.26 Figure 3 shows the effects of Niaspan on the lipid profile when given as monotherapy or when given alongside a statin. When given alone, Niaspan induced marked elevations of HDL-cholesterol, with a 24% increase in this parameter observed at the highest recommended dose (Figure 3A).29,30 Useful additional reductions in triglycerides, Lp(a) and, to some extent, LDL-cholesterol were also observed. The efficacy of Niaspan on HDL-cholesterol was unaffected by co-administration with a statin, and these effects were well maintained over 1 year of treatment (Figure 3B).30,31 Much larger effects on LDL-cholesterol were observed with Niaspan–statin combination treatment than with Niaspan alone, as would be expected.

These data confirm that simultaneous treatment with Niaspan and a statin has the potential to correct both hypercholesterolaemia and low HDL-cholesterol. The potential of this combination to inhibit atherosclerosis is discussed in the following section.
Anti-atherogenic benefits of nicotinic acid

Inhibition or reversal of the progression of coronary atherosclerosis is a key goal of lipid-modifying therapy. The HATS trial undertook a careful and systematic study of atherosclerosis progression at nine predefined proximal sites in the coronary circulation of 160 patients with coronary disease and low HDL-cholesterol (<35 mg/dL [0.9 mmol/L] in men and <40 mg/dL [1.0 mmol/L] in women).16 Three years of treatment with a combination of simvastatin and immediate-release nicotinic acid increased HDL-cholesterol by 26% and decreased LDL-cholesterol by 42%, relative to baseline. These improvements were accompanied by regression of atherosclerosis, measured as percent luminal diameter of coronary arteries, compared with progression of atherosclerosis on placebo. The 3-year primary event rate was reduced by 90% in patients receiving simvastatin–nicotinic acid therapy, compared with placebo \((P = 0.03).\)

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER 2) study confirmed that Niaspan shares these anti-atherogenic benefits.32 This was a randomized, double-blind comparison of Niaspan (1000 mg, once-daily) and placebo, when added to existing statin therapy in 167 men or women with HDL-cholesterol <45 mg/dL (1.2 mmol/L) and LDL-cholesterol <130 mg/dL (3.4 mmol/L). The treatment duration was 1 year. The primary endpoint was the change in carotid intima-media thickness (CIMT), assessed using ultrasound. This endpoint is highly predictive of coronary events, as shown by a long-term (9 years) follow-up of 146 men who underwent periodic carotid ultrasound and coronary angiography.33 CIMT on ultrasound was significantly related to the risk of coronary events \((P < 0.02),\) and an annual increase in this parameter of 0.03 mm was associated with a two-fold increase in the risk of myocardial infarction or coronary heart disease death, and a three-fold increase in the risk of any coronary event \((P < 0.001).\) The authors concluded that measurement of CIMT using ultrasound provided prognostic information beyond that available from coronary angiography, and that CIMT provides a meaningful surrogate marker for coronary atherosclerosis.

The ARBITER 2 population was at high risk of coronary events. All patients had known coronary heart disease at baseline (this was a recruitment criterion), 28% had diabetes, 75% were hypertensive, and 51% had NCEP/ATP III metabolic syndrome. Mean HDL-cholesterol at baseline was 39 mg/dL (1.02 mmol/L) and mean LDL-cholesterol at baseline was 89 mg/dL (2.3 mmol/L). Mean HDL-cholesterol did not change in the placebo group, but was 20% higher after treatment with Niaspan (Figure 4). Niaspan also reduced triglycerides, compared with placebo (Figure 4). The lack of effect of study treatment on LDL-cholesterol was unsurprising, as this parameter was already well controlled by pre-existing statin treatment, on an average, before Niaspan was administered. Overall, the effects on the lipid profile of adding Niaspan to the regimen were consistent with the known therapeutic profile of this agent.3,28

Looking ahead: potential benefit of aggressive management of HDL-cholesterol and LDL-cholesterol

Combining nicotinic acid with a statin addresses two key sources of cardiovascular risk: low HDL-cholesterol and elevated LDL-cholesterol. The availability of Niaspan, a prolonged-release formulation of nicotinic acid with improved tolerability compared with the immediate-release version facilitates the delivery of this therapy. The randomized, double-blind ARBITER 2 study demonstrated the benefits of Niaspan plus a statin in terms of inhibition of atherosclerosis. Although ARBITER 2 was not powered to detect significant differences in event rates, there was a trend towards a reduction in...
cardiovascular events in the Niaspan group, compared with placebo (Figure 5).

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL-C/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) study will explore quantitatively the potential of aggressive intervention with Niaspan and a statin to improve cardiovascular event rates. This trial, jointly sponsored by the US National Heart, Lung, and Blood Institute and Kos Pharmaceuticals Inc., is currently recruiting a population of 3300 patients with established coronary heart disease, atherogenic dyslipidaemia (low HDL-cholesterol and high triglycerides), and LDL-cholesterol controlled to current US guideline goals at 60 sites in the US and Canada. Patients will be randomized to receive double-blind treatment with Niaspan plus a statin or to statin monotherapy for 6 years. The primary outcome measure will be a composite of cardiovascular death, non-fatal myocardial infarction, non-hemorrhagic stroke, or hospitalization for acute coronary syndrome with objective evidence of ischaemia. AIM-HIGH will define the potential of aggressive management of both low HDL-cholesterol and hyperlipidaemia to reduce cardiovascular event rates.

Conflict of interest: A.J.T. has received research grant support and educational honoraria from Kos Pharmaceuticals, Inc.

References


Figure 5. Atherosclerosis progression (A) and clinical outcomes (B) in patients receiving a statin plus Niaspan 1000 mg or placebo for 1 year in the ARBITER 2 study. Left-hand panel adapted from Taylor et al.32 with permission from Lippincott Williams & Wilkins (www.lww.com).


30. Data on file Merck, KGaA.


