

Review

Treating patients with low HDL-cholesterol: choices, issues and opportunities

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Abstract

Three clinical trials have recently focused on the benefits of lipid-regulating therapy in populations with normocholesterolaemia and low high-density lipoprotein (HDL)-cholesterol. Two secondary prevention studies (Veterans Affairs HDL-Cholesterol Intervention Trial [VA-HIT] and Bezafibrate Infarction Prevention [BIP] trial) testified to the efficacy of fibrates in decreasing cardiovascular events, particularly in patients with coexisting risk factors, including hypertriglyceridaemia. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) demonstrated that a statin could decrease acute coronary events in patients with isolated low HDL-cholesterol in a primary prevention setting. The absolute risk reduction in coronary events in the VA-HIT study compares favourably with those reported from the statin-based Cholesterol and Recurrent Events (CARE) and Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trials. The absolute risk reduction in AFCAPS-TexCAPS is similar to that in West of Scotland Coronary Pravastatin Study (WOSCOPS). Recommendations are given concerning lifestyle and pharmacological management of low HDL-cholesterol. Optimal management also requires review of current treatment targets for HDL-cholesterol and triglycerides levels.

Keywords fibrates, HDL-cholesterol, statins, trials, triglycerides

Low plasma high-density lipoprotein (HDL)-cholesterol concentration is encountered in clinical practice as part of mixed hyperlipidaemia, hypertriglyceridaemia, or as an isolated abnormality. Low HDL-cholesterol is common among patients with premature coronary artery disease (CAD) [1]. The cardioprotective effect of HDL-cholesterol is well supported by both observational and experimental studies [2]. Although the favourable effect of lowering elevated plasma low-density lipoprotein (LDL)-cholesterol has been well emphasized [3–5], the therapeutic benefits of raising low HDL-cholesterol has only recently been demonstrated in clinical trials. The present review describes the evidence and implications of these recent trials, and places them into the wider context of the management of patients with low HDL-cholesterol.

Recent trials of raising low high-density lipoprotein cholesterol

Table 1 compares the characteristics and outcomes of three clinical trials that employed a fibrate or a statin in patients with low plasma HDL-cholesterol [6–8]. Veterans Affairs HDL-Cholesterol Intervention Trial (VA-HIT) [6] was a secondary prevention study that examined the effect of gemfibrozil (1200 mg/day) on the combined incidence of nonfatal myocardial infarction and death from CAD in middle-aged men. Many patients exhibited the metabolic syndrome (obesity, dyslipidaemia, hypertension, insulin resistance), and 25% had diabetes. The trial was carried out over a mean period of 5 years. The Bezafibrate Infarction Prevention (BIP) study [7] was a secondary prevention study of the effect of bezafibrate

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; BIP = Bezafibrate Infarction Prevention; CAD = coronary artery disease; CARE = Cholesterol and Recurrent Events; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; NNT = number needed to treat; VA-HIT = Veterans Affairs HDL-Cholesterol Intervention Trial; WOSCOPS = West of Scotland Coronary Pravastatin Study.

Table 1**Comparison of recent clinical end-point trials that employed a fibrate (VA-HIT, BIP) or a statin (AFCAPS/TexCAPS) in patients with low plasma HDL-cholesterol**

	Trial		
	VA-HIT	BIP	AFCAPS/TexCAPS
Drug	Gemfibrozil	Bezafibrate	Lovastatin
Indication	Secondary prevention	Secondary prevention	Primary prevention
Duration (years)	5.2	6.2	5.2
Primary end-point	Nonfatal myocardial infarction/ CAD mortality	Myocardial infarction/ sudden death	Acute major coronary event
Patient characteristics			
Age (years)	64	60	58
<i>n</i> (male/female)	2531/0	2825/265	5608/997
Diabetes (%)	25	10	3
Hypertension (%)	57	32	22
Current smokers (%)	20	12	12
Total cholesterol (mmol/l)	4.5	5.6	5.7
Triglycerides (mmol/l)	1.8	1.6	1.8
LDL-cholesterol (mmol/l)	2.9	3.9	3.9
HDL-cholesterol (mmol/l)	0.8	0.9	0.9
Outcome variables			
Total cholesterol (%)	-6	-4	-18
Triglycerides (%)	-31	-21	-15
LDL-cholesterol (%)	-4	-6	-25
HDL-cholesterol (%)	+6	+18	+6
Effect of treatment on primary end-point			
Relative risk reduction (%)	-22	-9	-37
Absolute risk reduction (%)	-4.4	-1.4	-2.0
NNT to prevent an event	23	71*	50 [†]

*NNT = 12 for patients with baseline triglycerides greater than 2.25 mmol/l. [†]NNT = 125 for patients with baseline HDL-cholesterol greater than 0.9 mmol/l.

retard (400 mg/day) on myocardial infarction and sudden death in middle-aged persons, most of whom were men and 10% of whom had diabetes. It lasted for approximately 6 years. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [8] was a primary prevention trial of the effect of lovastatin (20–40 mg/day) on first major acute coronary events in middle-aged persons, most of whom were male and only 3% of whom had diabetes. Its duration was approximately 5 years.

The entry plasma HDL-cholesterol level was lower in VA-HIT than in the BIP study and AFCAPS/TexCAPS, and the LDL-cholesterol at entry in the latter two trials was approximately 1 mmol/l higher than in the VA-HIT population. VA-HIT also included older patients, and more of these had diabetes, hypertension and obesity, and were current smokers. As shown in Table 1, the percentage increase in HDL-cholesterol was similar in VA-HIT and AFCAPS/TexCAPS,

but significantly less than in the BIP study. The dominant plasma lipid changes were a reduction in triglycerides in VA-HIT and a reduction on LDL-cholesterol in AFCAPS/TexCAPS – changes that are consistent with the effects of a fibrate and statin, respectively. In the BIP study the reduction in triglycerides was less than in VA-HIT, but a greater increase in HDL-cholesterol was seen with bezafibrate than with gemfibrozil.

Risk reduction, subsets and other trials

Although the relative risk reduction in the primary end-point was greater in AFCAPS/TexCAPS than in VA-HIT, the absolute risk reduction was greater in the latter than the former trial. This is consistent with the differences in background risk of CAD between the study populations. The overall relative risk reduction in the primary end-point in the BIP study was not statistically significant. In patients with entry plasma triglycerides in excess of 2.25 mmol/l, however, there was a significant 40% reduction in relative

risk, with a corresponding 8% decrease in the absolute risk. After 5 years the incidence curve of the primary end-point appeared to level off in the placebo group in the BIP study, and this might have been related to the use of open-label statin therapy by primary care physicians [9].

In VA-HIT the number of patients needed to treat (NNT) to prevent one event over the duration of the trial was approximately 24. This compares favourably with the 5-year NNT to prevent one fatal myocardial infarction/death from CAD of 33 and 28 in Cholesterol and Recurrent Events (CARE) [10] and Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) [11], respectively, two trials that employed pravastatin. The NNT for persons with triglycerides greater than 2.25 mmol/l was 12 in the BIP study [9], which was significantly less than the NNT of 42 in patients with triglycerides greater than 2.42 mmol/l in the Helsinki Heart Study (HHS) [12]; this is consistent with the secondary and primary prevention settings of these trials, respectively. In AFCAPS/TextCAPS the overall NNT to prevent one event was 50, and this was chiefly attributable to patients with a baseline HDL-cholesterol below 0.9 mmol/l [13], in whom the relative risk reduction of cardiovascular events was 45%; this was significantly greater than for those with a baseline HDL cholesterol greater than 1.08 mmol/l. The overall efficacy of lovastatin in AFCAPS/TextCAPS is similar to that of pravastatin in the West of Scotland Coronary Pravastatin Study (WOSCOPS) [14], an earlier primary prevention trial in hypercholesterolaemic patients.

Mechanisms of benefit

The mechanisms of the benefits of fibrates and statins in the above trials is not clear, although angiographic data [15–17] support the notion of regression of atherosclerosis. Because statins and fibrates not only increase plasma HDL, but also lower the concentration of other proatherogenic lipoproteins, such as LDL and remnants, it is not possible to ascertain how much of the benefit seen in the trials is attributable to the increase in HDL [9].

The greatest relative risk reduction in AFCAPS/TextCAPS, however, was seen in patients with a baseline HDL-cholesterol below 0.9 mmol/l, with the on-treatment apolipoprotein B to apolipoprotein A1 ratio being the most significant predictor of subsequent coronary risk [13]. An independent treatment effect on outcomes was not specifically identified in this analysis of the trial, but is likely to have been operational [18]. In VA-HIT multivariate analysis [19] showed that only on-trial HDL-cholesterol and treatment group assignment predicted coronary events at 5 years; the lowest coronary event rate was seen in patients with on-treatment HDL-cholesterol in excess of 0.9 mmol/l. However, only 23% of the benefit achieved with gemfibrozil could be explained by the on-treatment plasma levels of HDL-cholesterol, triglycerides and

LDL-cholesterol. Hence, it is possible that the pleiotropic effects shared by fibrates and statins that directly inhibit atherogenesis and thrombogenesis may be responsible for the reduction in coronary events in the trials reviewed here [18,20]. It is likely, but unproven, that the cardiovascular benefits seen with gemfibrozil and lovastatin in normocholesterolaemic low-HDL populations reflect a class effect of fibrates and statins, respectively.

Clinical implications

The VA-HIT results therefore suggest that when LDL-cholesterol levels are optimal, or near optimal, increasing HDL-cholesterol with reduction in triglyceride-rich lipoproteins may be a cost-effective approach to decreasing the incidence of coronary events in secondary prevention. The BIP subgroup analysis shows that, in hypertriglyceridaemic persons with coronary disease, bezafibrate is a cost-effective treatment for dyslipidaemia if triglycerides levels are greater than 2.2 mmol/l, despite the background risk being less than in patients included in VA-HIT. The AFCAPS/TextCAPS results have implications for primary prevention in the general population, and in particular for individuals with low HDL-cholesterol in whom the increased risk of coronary disease appears to be diminished. Significantly, in AFCAPS/TextCAPS only 17% of the patients in the trial met National Cholesterol Education Program LDL-cholesterol cut-points for the initiation of statin therapy [3]. In all the trials reviewed, the safety of fibrate and statin therapies was reaffirmed.

Managing low high-density lipoprotein cholesterol

Lifestyle and pharmacotherapy

The initial approach to treating low HDL-cholesterol should involve lifestyle modification, including cessation of cigarette smoking, weight reduction, regular physical exercise and possibly a moderate regular intake of alcohol [21]. In secondary prevention, if this metabolic abnormality is not corrected nonpharmacologically, then a statin should be employed initially to lower LDL-cholesterol to below 2.6 mmol/l; if HDL still remains below 0.9 mmol/l with or without elevation of triglycerides, then the trial evidence supports employing a fibrate as adjunctive therapy. However, the benefit of fibrates in patients whose LDL has been reduced by statins has not been formally demonstrated. If LDL-cholesterol is initially below 3.4 mmol/l, then a fibrate may be used as first-line therapy, especially if triglycerides are also greater than 1.6 mmol/l [22], with the option of adding a statin later if the LDL-cholesterol remains above 2.6 mmol/l. Again, this remains to be specifically corroborated in a clinical trial, but the advice given is consistent with existing evidence.

Broadly similar recommendations could apply to primary prevention in patients with multiple cardiovascular risk factors, and this may be particularly pertinent to asymptotic

matic patients with type 2 diabetes or visceral obesity [23,24]. The value of treating diabetic patients with fenofibrate is presently being addressed in the Fenofibrate in Event Lowering in Diabetes (FIELD) trial, and the role of statins in the Heart Protection Study (HPS) and the Collaborative Atorvastatin in Diabetes Study (CARDS) [9]. Hypertensive patients in routine practice are likely to have the metabolic syndrome or diabetes, and constitute a special group that merits fibrate or statin treatment in order to raise coexistent low HDL levels.

However, whether there is incremental benefit in both primary and secondary prevention settings of employing a fibrate together with a statin in treating patients with low HDL-cholesterol remains to be rigorously demonstrated. This issue is being addressed in diabetic patients in the Oxford-based Lipids in Diabetes Study (LDS) [9]. Although niacin is the most potent agent for raising HDL levels and trial evidence suggests that it may decrease coronary events in hyperlipidaemic patients with previous myocardial infarction [25], it has never been tested in populations similar to those in VA-HIT and AFCAPS/TexCAPS. Tolerability and adherence is a major problem with niacin. The efficacy of the new niacin formulations as monotherapy and combined therapy for patients with low HDL levels needs to be confirmed in clinical trials with cardiovascular end-points. Caution should be exercised when employing combination therapy of fibrates or niacin with statins, because of potential hepatotoxicity and myopathy; close monitoring of liver and muscle enzymes is therefore recommended. Finally, many patients with low HDL levels will have diabetes and insulin resistance [9], so that another important question for future trials is whether metformin or thiazolidinediones confer cardiovascular benefit over and above that due to lipid-regulating therapy.

Concerning women

Although a similar strategy for managing low HDL-cholesterol is at present recommended for both men and women, the specific use of oestrogen in postmenopausal women merits consideration. Oestrogen supplementation is well recognized to increase plasma HDL-cholesterol effectively [26], but it also increases triglycerides, and this may explain its lack of benefit on CAD risk in clinical trials [27]. The potential synergistic benefit of oestrogen replacement, including selective oestrogen receptor modulators, and that of other pharmacotherapies for increasing HDL requires further research.

Other considerations

Finally, in hypertensive patients with low HDL that is refractory to the aforementioned therapies, consideration should be given to employing α -blockers, such as prazosin and doxazosin. However, the efficacy of α -blockers alone and in combination with other agents that elevate HDL-cholesterol still needs to be demonstrated in clinical end-

point trials. Recent findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [28] have also cast some doubt on the use of doxazosin. Drug and gene therapies that selectively elevate HDL are under development [29], and may eventually find a place in clinical practice.

Conclusion

Translation of the trial data presented above into effective clinical management requires more accurate methods for assessing cardiovascular risk and reconsideration of the optimal therapeutic targets for plasma lipid and lipoprotein levels [9,22,30]. Although the guidelines for total cholesterol and LDL-cholesterol in risk assessment are well established [3–5], treatment recommendations concerning HDL-cholesterol are not as rigorous or aggressive. Failure to recognize HDL in assessing patients significantly underestimates their risk of CAD [31]. Also, measuring triglycerides has not generally been recommended in risk assessment, but its inclusion may be critical in patients with visceral obesity, hypertension and diabetes [9,30]. Serial, fasting blood tests will provide a more precise evaluation of triglyceride-mediated cardiovascular risk, particularly in the presence of an elevated HDL-cholesterol.

Given the results of VA-HIT and related studies, the National Cholesterol Education Program guidelines of a triglycerides level below 2.2 mmol/l and an HDL-cholesterol greater than 1 mmol/l as 'normal' certainly need to be reviewed [3]. Of relevance, data from the Prospective Cardiovascular Munster (PROCAM) Heart Study suggest that plasma triglycerides should be lowered to below 1.1 mmol/l and HDL increased to above 1.2 mmol/l in high-risk individuals to prevent coronary events [32,33], which is consistent with the aggregate findings of the trials reviewed here. Accordingly, expert bodies need to review their guidelines for assessing and treating plasma triglycerides and HDL-cholesterol levels [3–5]. Some consideration should also be given to employing apolipoproteins B and A1 in risk assessment and treatment, based on the AFCAPS/TEXCAPS findings [13].

Finally, for many patients with low HDL-cholesterol, treatment with statins and fibrates will need to be complemented with lifestyle changes and other drugs, including antihypertensive and antidiabetic agents. Ensuring patient adherence to all of these potentially effective measures probably remains the major challenge for the prevention and reversal of CAD.

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