The prevalence of low levels of high-density lipoprotein cholesterol among patients treated with lipid-lowering drugs

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Abstract

Some patients with initial normal levels of high-density lipoprotein cholesterol (HDL-C) have lower HDL-C levels during lipid-lowering treatment. The aim of this study was to estimate the prevalence of low HDL-C (< 1.0 mmol/L; < 40 mg/dL) before and during lipid-lowering treatment. Additionally, the prevalence of low HDL-C during fibrate and statin treatment was compared. All patients attending two Health Insurance Associations during February and March 2002 for continuing reimbursement of their lipid-lowering drug were included in this study. Date of birth, sex and the actual lipid-lowering drug were recorded. The most recent lipoprotein levels and those after a three-month diet before the start of the treatment were recorded. In total, 2,259 patients (56% women) were included; 69% were treated with statins and 31% with fibrates. Low HDL-C levels were found before the initiation of the treatment in 7% of the statin patients and in 11% of the fibrate patients. During treatment, 10% of the statin patients and 13% of the fibrate patients had low HDL-C levels. The proportion of patients whose HDL-C decreased below 1.0 mmol/L (40 mg/dL) during treatment was 6% for statins and 4% for fibrates. Although lipid-lowering drugs are known to increase HDL-C levels slightly, not all patients benefit from this effect.

Key words: lipids, lipoproteins, cholesterol, statin, fibrate.

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Introduction

Reduction of low-density lipoprotein cholesterol (LDL-C) is the primary approach to decrease the risk of coronary heart disease (CHD) in both primary and secondary prevention.[1] A number of epidemiological studies, however, have found that low levels of high-density lipoprotein cholesterol (HDL-C) are also strongly associated with an increased risk of CHD. Already in 1951, the relationship between low levels of HDL-C and CHD was noticed.[2] In 1986, the Framingham study confirmed the association between low HDL-C and CHD.[3] The Adult Treatment Panel III (ATP-III) sets HDL-C levels of < 1.0 mmol/L (40 mg/dL) as a categorical risk factor and designates it as a factor that modifies the low-density lipoprotein cholesterol (LDL-C) goal.[1] According to the ATP-III guidelines, non-HDL cholesterol is the secondary target in the treatment of hypercholesterolaemia. Once adequate LDL-C levels have been obtained, other lipid risk factors such as low HDL-C deserve attention.

Several clinical trials suggest that raising HDL-C levels contributes to a decreased risk for CHD. For example, AFCAPS/TexCAPS,[4] LCAS[5] and LOCAT[6] provided information on the benefit of lipoprotein modification in patients with low baseline HDL-C. The VA-HIT study specially targeted patients with isolated low HDL-C for gemfibrozil therapy.[7] The reduction in major cardiovascular events was attributed in part to raising HDL-C. Likewise, the decrease in major coronary events during gemfibrozil therapy in the Helsinki Heart Study[8] was estimated to be partly due to an increase in HDL-C.

Nonetheless, in these trials, changes in other lipoproteins have also occurred. For this reason, the benefit of raising HDL-C is not recognised with certainty. On the other hand, the conclusions of the landmark statins trials cannot be attributed to the decrease of LDL-C only because HDL-C also increased in these trials.[9,10]

Statins as well as fibrates lower total cholesterol (TC) and LDL-C and increase HDL-C. With statins, HDL-C generally rises by 5–10% but greater increases usually occur in patients with low HDL-C and elevated triglycerides (TG).[9-11] Fibrates usually raise HDL-C by 10–15% but greater increases can occur in patients with very low HDL-C levels.[12]

However, some patients show a similar decrease for HDL-C as for LDL-C resulting in lower HDL-C levels during treatment than before the initiation of the treatment. This sometimes results in higher ratios of TC to HDL-C and LDL-C to HDL-C during the treatment with a statin than before it. This phenomenon was firstly described for statins and was called 'bad HDL-C response to statins'.[13] The existence of these bad HDL-C responders to statins was confirmed by an observational study.[14]

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Table 1. Average lipoprotein levels (SD) before and during treatment with fibrates and statins for all patients

	Fibrates (n=711)				Statins (n=1,548)			
	Before treatment		During treatment		Before treatment		During treatment	
	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L
TC	276 (40)	7.1 (1.0)	208 (35)	5.4 (0.9)	289 (48)	7.5 (1.2)	208 (44)	5.4 (1.1)
LDL-C	174 (45)	4.5 (1.2)	126 (30)	3.3 (0.8)	196 (37)	5.1 (1.0)	121 (34)	3.1 (0.9)
HDL-C	59 (19)	1.5 (0.5)	58 (17)	1.5 (0.4)	63 (22)	1.6 (0.6)	58 (17)	1.5 (0.4)
TG	234 (151)	2.6 (1.7)	121 (99)	1.4 (1.1)	173 (72)	2.0 (0.8)	151 (104)	1.7 (1.2)
TC/HDL-C ratio	5.0 (1.6)		3.9 (1.4)		5.1 (1.5)		3.9 (1.2)	
LDL-C/HDL-C ratio	3.3 (1.3)		2.4 (1.0)		3.5 (1.3)		2.3 (0.9)	

Key: TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides

Figures about the occurrence of low HDL-C levels before and during lipid-lowering treatment are only available from the treat-to-goal trials but only few epidemiological figures in real-life conditions are available.

The aim of this study was to estimate the prevalence of low HDL-C < 1.0 mmol/L (< 40 mg/dL) before and during lipid-lowering treatment. Additionally the prevalence of low HDL-C and the bad HDL-C response to lipid-lowering treatment was compared for fibrates and statins.

Methods

The Belgian reimbursement system

In Belgium, lipid-lowering drugs are reimbursed by the National Health Insurance (RIZIV = Rijksinstituut voor Ziekte-en Invaliditeitsverzekering) when, after a non-specified diet of at least three months, fasting TC remains higher than 6.5 mmol/L (250 mg/dL), TG remains higher than 2.3 mmol/L (200 mg/dL), or LDL-C remains higher than 4.1 mmol/L (160 mg/dL).

Authorisation needs to be renewed at 12 monthly intervals. All requests are centralised in the regional offices of the health insurance associations where medical advisers decide on reimbursement according to Belgian criteria. Whether authorisation is renewed does not depend on lipoprotein levels reached during treatment.

Data collection and study population

Data collection was based on reviewing requests for continued reimbursement of lipid-lowering drugs. During February and March 2002 all requests for continued reimbursement were recorded at the regional offices of two Health Insurance Associations (Liberale Mutualiteit Brabant and Vlaams Neutraal Ziekenfonds Aalst). The requests were completed by family physicians as well as by specialists.

The following data were available: date of birth, sex, the actual lipid-lowering drug and dose. The most recent fasting lipoprotein levels (TC, TG, HDL-C and LDL-C) and those after a three-month diet before the start of the treatment were recorded. All patients studied had received a lipid-lowering drug for at least three months but most patients had been treated for several years.

Plasma lipid measurements were taken from venous blood samples collected after the subjects had fasted for 12 hours. Samples were transported in glass serum tubes and serum TC, TG and HDL-C were measured enzymatically. LDL-C levels were calculated with the Friedewald formula, unless TG levels were above 3.4 mmol/L (300 mg/dL),[15] when LDL-C levels were then measured enzymatically. All tests were performed by local laboratories. According to Belgian guidelines for clinical biology, laboratory performance is regularly subjected to internal and external quality control.

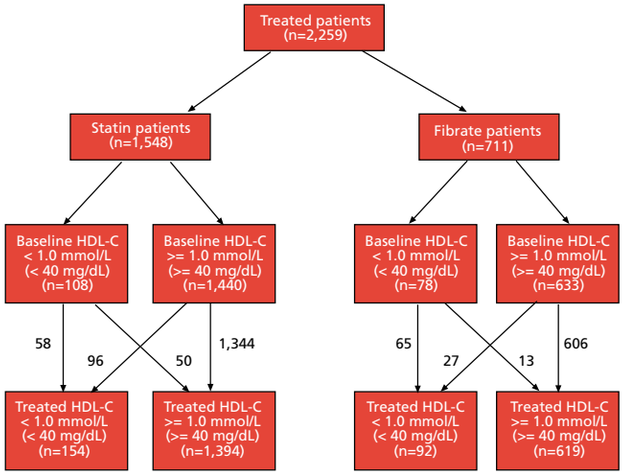
Low HDL-C was defined as HDL-C levels below 1.0 mmol/L (40 mg/dL). A difference was made between i) patients with initially normal levels of HDL-C (> or = 1.0 mmol/L > or = 40 mg/dL) presenting with low levels of HDL-C (< 1.0 mmol/L; < 40 mg/dL) during treatment and ii) patients with initially low levels of HDL-C which remained low despite treatment. We suggest the first group is defined as 'bad HDL-C responders' and the second as 'non HDL-C responders'.

Unfortunately no uniform information about cardiovascular risk factors is available from the medical files at the Health Insurance Associations. Only for a few patients with familial hypercholesterolaemia were some of the risk factors recorded. For this reason, our study population contains patients in both primary and secondary prevention.

Statistical analysis

SPSS-PC 11® (SPSS Inc., Chicago, IL, USA) was used for analysis and statistical processing. Significant differences between continuous variables were detected with the independent-samples *t*-test, as far as data were normally distributed. The cross-tables were used to detect differences between groups by means of chi-square tests. Multivariate analyses were performed with forward stepwise logistic regression.

Figure 1. Distribution of statin and fibrate patients according to their high-density lipoprotein cholesterol (HDL-C) levels at baseline and during treatment



Results

Baseline values

In total, 2,259 patients were included with an average age of 66 years (56% were women). The baseline fasting lipoprotein levels after a diet of at least three months were: TC = 7.4 mmol/L (286 mg/dL), HDL-C = 1.6 mmol/L (61 mg/dL), LDL-C = 4.8 mmol/L (184 mg/dL) and TG = 2.4 mmol/L (209 mg/dL). Baseline fasting lipoprotein levels before treatment with statins or fibrates, are shown in table 1. Patients who received fibrates had initially higher TG and lower HDL-C levels, whereas those who were prescribed statins had initially higher levels of TC and LDL-C. Before the initiation of lipid-lowering drugs, low HDL-C levels (1.0 mmol/L; < 40 mg/dL) were found among 9% of patients (7% of patients who later received statins and 11% for those who later received fibrates). In total, 21% of men and 4% of women had low HDL-C levels before the start of lipid-lowering treatment.

Pharmaceutical treatment

Sixty-nine per cent of patients in the study received statins and 31% received fibrates. The average age of patients treated with fibrates was 68 years (53% women) compared with 65 years (63% women) with statins. The follow-up for both fibrate and statin patients was carried out in 96% of cases by family physicians and in 4% of cases by specialists. The following drugs were prescribed: atorvastatin (34%), fenofibrate (23%), simvastatin (19%), pravastatin (13%), ciprofibrate (9%) and other drugs such as bezafibrate and fluvastatin (1%). In total, 55% of patients treated with statins received low doses (atorvastatin 10 mg, pravastatin 20 mg or simvastatin 20 mg) and 45% received high doses (atorvastatin 20 mg, pravastatin 40 mg or simvastatin 40 mg).

Table 2. Average lipoprotein levels (SD) before and during treatment with fibrates and statins for the bad HDL-C responders only (n=123)

	Before treatment		During treatment	
	mg/dL	mmol/L	mg/dL	mmol/L
TC	276 (44)	7.1 (1.1)	226 (36)	5.9 (0.9)
LDL-C	192 (45)	5.0 (1.2)	157 (38)	4.1 (1.0)
HDL-C	44 (11)	1.1 (0.3)	33 (6)	0.9 (0.2)
TG	199 (100)	2.2 (1.1)	181 (90)	2.0 (1.0)
TC/HDL-C ratio	6.5 (1.5)		7.0 (1.5)	
LDL-C/HDL-C ratio	4.5 (1.0)		4.9 (1.3)	

Key: TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides

Treatment results

Mean lipoprotein levels during treatment were: TC = 5.4 mmol/L (208 mg/dL), HDL-C = 1.5 mmol/L (58 mg/dL), LDL-C = 3.2 mmol/L (122 mg/dL) and TG = 1.6 mmol/L (141 mg/dL). Lipoprotein levels during treatment are shown for both fibrates and statins in table 1. During treatment 11% of patients had low HDL-C levels (10% of statin patients and 13% of fibrate patients). Some 18% of men and 5% of women had low HDL-C levels (< 1.0 mmol/L; < 40 mg/dL) during treatment.

Of patients treated with statins, 6% had low HDL-C levels during treatment although their HDL-C was initially normal. We termed these patients 'bad HDL-C responders to statins' (figure 1). Of the patients treated with fibrates, 4% had such a bad HDL-C response (i.e. initially normal HDL-C levels and low levels during treatment). Thus, the proportion of bad HDL-C responders to treatment (i.e. HDL-C levels which decreased below 1.0 mmol/L [40 mg/dL]) was higher among the patients treated with statins (6%) than among those treated with fibrates (4%) (p=0.019). In total, 76% of bad HDL-C responders to statins and 62% of bad HDL-C responders to fibrates were men.

Some 3% of patients treated with statins and 2% of those treated with fibrates had initially low levels of HDL-C which increased to above 1.0 mmol/L (40 mg/dL) with treatment. This difference was not significant (p=0.06).

There were no significant differences between the different statins in terms of bad HDL-C response; nor were such differences observed for fibrates.

The ratios of TC to HDL-C and LDL-C to HDL-C increased for the bad HDL-C responders from 6.5 and 4.5 respectively before treatment to 7.0 (p<0.05) and 4.9 (p<0.05) respectively during treatment (table 2).

Discussion

Lipoprotein levels during treatment

Although most patients were treated with statins there was a relatively high proportion of patients treated with fibrates. This may be related to the considerable proportion of patients in primary

prevention. Unfortunately we could not measure the proportion of patients in primary or secondary prevention. We may assume that large proportions of patients are treated with statins in primary prevention since they have several risk factors for cardiovascular disease and are at increased risk. This is confirmed by the Canadian FAMUS registration (1992–96) in which 68% of the patients treated in primary prevention had two or more risk factors for CHD.[16]

The average lipoprotein levels found in our study were lower than those found in other comparable registrations. In the FAMUS study, mean lipoprotein levels among treated patients in primary prevention were TC = 6.3 mmol/L (245 mg/dL), LDL-C = 4.2 mmol/L (161 mg/dL), HDL-C = 1.1 mmol/L (44 mg/dL) and TG = 2.4 mmol/L (211 mg/dL).[16] In the same registration, mean lipoprotein levels among treated patients in secondary prevention were: TC = 5.9 mmol/L (227 mg/dL), LDL-C = 3.7 mmol/L (144 mg/dL), HDL-C = 1.1 mmol/L (42 mg/dL) and TG = 2.4 mmol/L (211 mg/dL).[17] A Swedish secondary prevention registration in 1995/96 showed mean TC at 5.5 mmol/L (212 mg/dL), LDL-C at 3.6 mmol/L (138 mg/dL), HDL-C at 1.1 mmol/L (42 mg/dL) and TG at 1.9 mmol/L (171 mg/dL).[18]

It is difficult to compare our results with those above because we studied a mixed population in primary and secondary prevention. On the other hand, a decreasing trend in lipoprotein levels is observed in the course of time as guidelines become stricter and consequently more physicians are implementing them.[17,19,20]

Low HDL-C levels

The proportion of patients with low HDL-C levels at baseline in our study is comparable with that of the Belgian LIPI-GOAL trial.[21] It concerned a mixed primary (45%) and secondary (55%) treat-to-target study with atorvastatin and 9% of patients had baseline HDL-C below 1.0 mmol/L (40 mg/dL). A Norwegian study demonstrated in 1997/98 that fewer men than women attained HDL-C targets (64% and 86%, respectively).[18] The prevalence of low HDL-C was lower in our registration but we also found more women than men attaining the HDL-C target.

In EUROASPIRE, low HDL-C levels were found among 20% of treated patients (24% men, 8% women).[22] In this European registry, 72% of patients received statins, 25% fibrates and 3% other lipid-lowering drugs.

Reasons for 'bad HDL-C response to lipid-lowering drugs'

In general, statins raise HDL-C less than fibrates but the absolute HDL-C increase is relatively small with both drug classes.[7-10] Some occasional paradoxical HDL-C responses in individual patients were observed earlier for fibrates but less for statins. Bad HDL-C response to lipid-lowering drugs, in terms of HDL-C levels which decrease below 1.0 mmol/L (40 mg/dL) during treatment, has already been described for statins.[13,14] The present study confirms the existence of bad HDL-C responders among patients treated with fibrates. However, the proportion of bad HDL-C responders is higher for statins than for fibrates.

The decrease in HDL-C levels during treatment may be partly related to differences in dietary compliance between those patients taking fibrates and those taking statins. Lack of dietary compliance can result in lower levels of HDL-C. Statins have more important influences on lipoprotein levels than fibrates,[9-12] and statin patients may, therefore, be less compliant to their diet than those receiving fibrates.

A less probable hypothesis is that myalgia amongst patients receiving lipid-lowering drugs could result in physical inactivity and, consequently, decrease HDL-C levels. Moreover, myalgia seems to occur more often among patients treated with statins than among those treated with fibrates.[23]

More probable is the hypothesis that the higher proportion of bad HDL-C responders found during treatment with statins compared to fibrates could be related to differences in the metabolic pathway and action between fibrates and statins. If bad HDL-C responders are switched from statins to fibrates, this can result in increased levels of HDL-C with more favourable TC to HDL-C and LDL-C to HDL-C ratios.[13]

The genetic profile of the patient can also play an important role. The known polymorphisms in the beta-fibrinogen gene, the lipoprotein lipase gene and the hepatic lipase gene also have an influence on the effects of statins in the general population.[24] The expectation is that, in future, a subject's genotype may determine whether he will be treated with statins or fibrates.

Inter-individual variability in LDL-C response during treatment with statins is well documented. Poor LDL-C responders to statins have a low basal rate of cholesterol synthesis that may be secondary to a genetically determined increase in cholesterol absorption, possibly mediated by apolipoprotein E4.[25]

Bad HDL-C response to statins does not seem to be related to the type of statin or fibrate used. No differences between the different statins or fibrates were demonstrated.

Treatment of patients with low HDL-C

In secondary prevention, favourable results from the VA-HIT study have led some authorities to favour fibrates over statins in the treatment of patients with CHD and low-HDL-C. Clinical trials with statins, however, have been more robust in their outcome. In addition, the combined use of statins with either a fibrate or nicotinic acid is attractive for high-risk patients with isolated low HDL-C levels to improve the whole lipoprotein profile. Using drugs in combination, however, could increase the likelihood of side effects. Recent studies with ezetimibe, combined with statins, appear promising in raising HDL-C levels without side effects.[26]

On the other hand, low HDL-C levels can be secondary to other modifiable risk factors such as cigarette smoking, obesity, or physical inactivity. Therapeutic lifestyle changes that focus on these factors should be encouraged among bad HDL-C responders. Weight reduction and physical activity should be particularly emphasised.

In patients without CHD or CHD risk equivalents, low HDL-C levels count as a risk factor that modifies the goal for LDL-C.[1] The first line of therapy for isolated low HDL-C is to maximise life habit changes. Whether fibrates or nicotinic acid may achieve a similar benefit in primary prevention as in secondary prevention

is uncertain because primary prevention trials with these drugs have not targeted people with isolated low HDL-C levels.

Limitations of the study

The study was limited because important risk factors, such as cigarette smoking, hypertension, diabetes, obesity, insulin resistance, physical inactivity, family history, socio-economic factors, ethnicity and behavioural factors, were not taken into account since this information was not available from health insurance associations' medical records. Changes in weight, smoking habits, exercise patterns and use of other drugs can significantly change HDL-C levels.

The estimation of the prevalence of low HDL-C levels is limited to patients who received lipid-lowering drugs. No data are available for patients who received a dietary intervention only and no lipid-lowering drugs.

The most important study limitation is the fact that no central laboratory was used to co-ordinate all blood tests. This would have minimised laboratory variation since HDL-C measurement is rarely standardised and can be performed using many different kits with wide variations in their results. In addition, variation in results is greater when HDL-C levels are low and small absolute HDL-C changes are easily confounded by measurement variation. This kind of laboratory variation could bias the results of this study.

Besides the paradoxical HDL-C response to statins and fibrates, some (other) patients show a poor LDL-C response to these drugs. Although the concept of bad HDL-C responders might be important for some patients, the problem of bad LDL-C response is of major importance. Lowering LDL-C remains the main objective of the management of dyslipidaemia. The current evidence suggests that getting LDL-C levels down to target levels correlates best with event reduction, even when HDL-C levels are low.[27] However, some risk calculation tables use the ratio of TC to HDL-C or LDL-C to HDL-C and, from this point of view, the level of HDL-C has an important impact on cardiovascular risk calculation. More evidence is needed about the influence on morbidity and mortality.

Strengths of the study

One of the major strengths of our study is that data were obtained retrospectively from family physicians as well as specialists who were unaware that the lipoprotein levels of their patients and the management of dyslipidaemia during their daily work was being evaluated.

In our study, the proportions of patients with low HDL-C levels are almost incomparable with those from the randomised controlled trials. In such trials, the results are considerably better because the compliance is carefully monitored and a high standard of care is usually maintained over several years by specialists with follow-up visits at frequent intervals to ensure continuity of management.

According to the nationwide figures of the RIZIV, of Belgian patients treated with lipid-lowering drugs, 40% are treated with atorvastatin, 19% with simvastatin, 17% with fenofibrate, 13% with pravastatin, 9% with ciprofibrate and 2% with other lipid-lowering drugs. In our study, the proportions of patients treated with these drugs are quite similar. We therefore believe that we have examined a representative sample of the concerned population.

The high proportion of patients using fibrates (31%) could be related to the Belgian reimbursement criteria for lipid-lowering drugs. Patients with isolated hypertriglyceridaemia are only eligible for reimbursement of fibrates.

Another important strength of this study is that, in contrast to most randomised clinical trials, our sample population is not limited by inclusion criteria. The included patients only had to fulfil the Belgian reimbursement criteria mentioned in the methodology. The high proportion of women treated with lipid-lowering drugs was an unexpected finding.

Key messages

- Although lipid-lowering drugs are known to increase HDL-C levels slightly, not all patients benefit from this effect
- 'Bad HDL-C responders' to lipid-lowering drugs are characterised by HDL-C levels which decrease below 1.0 mmol/L (40 mg/dL) during treatment, despite higher HDL-C levels before the treatment
- The proportion of 'bad HDL-C responders' is higher for statins than for fibrates
- The benefits of fibrates for these 'bad HDL-C responders' to statins should be evaluated in randomised controlled trials with hard end points

Conclusion

Unfortunately, most studies consider low HDL-C levels at baseline only and rarely during treatment. Since HDL-C is accepted as an independent risk factor for CHD, decreasing levels of HDL-C during lipid-lowering treatment should be considered an undesired effect. HDL-C levels should be increased by therapeutic lifestyle changes and therapy with fibrates or the combination of statins and fibrates, ezetimibe or nicotinic acid. The beneficial effects of such therapeutic changes on morbidity and mortality should be evaluated in randomised controlled trials.

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Conflict of interest

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References

1. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;**285**:2486-97.
2. Barr DP, Russ EM, Eder HA. Protein-lipid relationships in human plasma. *Am J Med* 1951;**11**:480-5.
3. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *JAMA* 1986;**256**:2835-8.
4. Downs GR, Clearfield M, Weiss S *et al*. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TEXCAPS (Air Force/Texas Coronary Atherosclerosis Study). *JAMA* 1998;**279**:1615-22.
5. Herd JA, Ballantyne CM, Farmer JA *et al*. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study, LCAS). *Am J Cardiol* 1997;**80**:278-86.
6. Frick MH, Syvanne M, Nieminen MS *et al*. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL-cholesterol. Lipid Coronary Angiography Trial (LOCAT) Study Group. *Circulation* 1997;**96**:2137-43.
7. Rubins HB, Robins SJ, Collins D *et al*. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;**341**:410-18.
8. Frick MH, Elu O, Haapa K *et al*. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;**317**:1237-45.
9. Shepherd J, Cobbe SM, Ford I *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; **333**:1301-07.
10. The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383-9.
11. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;**282**:2340-6.
12. Leaf DA, Connor WE, Illingworth DR, Bacon SP, Sexton G. The hypolipidemic effects of gemfibrozil in type V hyperlipidemia. A double-blind, crossover study. *JAMA* 1989;**262**:3154-60.
13. Devroey D, Betz W, Coigniez P, Lauwers R, Velkeniers B. A 'bad responder' to statins. *Cardiology* 2002;**97**:230-2.
14. Devroey D, Velkeniers B, Duquet W, Betz W. Serum lipid comparison in patients treated by statins or fibrates: existence of bad HDL-C responders to statins. *Acta Cardiol* 2003;**58**:179-84.
15. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;**18**:499-502.
16. Xhignesse M, Laplante P, Grant AM *et al*. Antiplatelet and lipid-lowering therapies for the secondary prevention of cardiovascular disease: are we doing enough? *Can J Cardiol* 1999;**15**:185-9.
17. Stagmo M, Westin L, Carlsson R, Israelsson B. Long-term effects on cholesterol levels and the utilisation of lipid-lowering drugs of a hospital-based programme for secondary prevention of coronary artery disease. *J Cardiovasc Risk* 2001;**8**:243-8.
18. Svilaas A, Thoresen M, Kristoffersen JE, Hjartaaker J, Westheim A. How well are patients with atherosclerotic disease treated? Secondary prevention in primary care. *Scand J Prim Health Care* 2000;**18**:232-6.
19. De Henauw S, De Bacquer D, de Smet P, Kornitzer M, De Backer G. Trends and regional differences in coronary risk factors in two areas in Belgium: final results from the MONICA Ghent-Charleroi Study. *J Cardiovasc Risk* 2000;**7**:347-57.
20. Muls E, De Backer G, De Bacquer D, Brohet C, Heller F. LIPI-WATCH, a Belgian/Luxemburg survey on achievements of European Atherosclerosis Society Lipid goals. *Clin Drug Invest* 2000;**19**:219-29.
21. Muls E, De Backer G, Brohet C, Heller F. The efficacy of atorvastatin in treating patients with hypercholesterolaemia to target LDL-cholesterol goals: the LIPI-GOAL trial. *Acta Cardiol* 2001;**56**:109-14.
22. Vanuzzo D, Pilotto L, Ambrosio GB *et al*. Potential for cholesterol lowering in secondary prevention of coronary heart disease in Europe: findings from EUROASPIRE study. European Action on Secondary Prevention through Intervention to Reduce Events. *Atherosclerosis* 2000;**153**:505-17.
23. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Full report available at www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm
24. Maitland-van der Zee AH, Klungel OH, Stricker BH *et al*. Genetic polymorphisms: importance for response to HMG-CoA reductase inhibitors. *Atherosclerosis* 2002;**163**:213-22.
25. O'Neill FH, Patel DD, Knight BL *et al*. Determinants of variable response to statin treatment in patients with refractory familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 2001;**21**:832-7.
26. Gagne C, Bays HE, Weiss SR *et al.* Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002;**90**:1084-91.
27. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7-22.