

European survey highlights need for targeted increase of HDL-C in patients with dyslipidaemia

Sinéad Jeffrey

Results from the first pan-European survey of high-density lipoprotein cholesterol (HDL-C) in patients with dyslipidaemia¹ have emphasised the importance of treating HDL-C levels to optimise the lipid profile and reduce cardiovascular risk.

The survey found that 40% of women and 33% of men receiving lipid-modifying therapy, such as statins, to treat dyslipidaemia have low HDL-C, significantly increasing their risk of myocardial infarction, stroke and other cardiovascular events.²

Professor Eric Bruckert, Professor of Endocrinology at Hôpital Pitié-Salpêtrière, Paris, and lead author of the survey, said that the study was conducted to correct the paucity of data on the frequency of low HDL-C in patients with dyslipidaemia. It aimed to determine the prevalence of low HDL-C (defined in accordance with current treatment guidelines³⁻⁵ as $<1.03\text{mmol/l}$ in men and $<1.29\text{mmol/l}$ in women) in a large ($n=8,545$) population of patients receiving treatment for dyslipidaemia under the care of specialist physicians in 11 European countries. The UK arm of the study recruited 182 physicians and 1,819 patients.

Patients enrolled in the study had received diet and exercise counselling plus pharmacological treatment for at least three months, or had a serum cholesterol $\geq 5.3\text{mmol/l}$ and/or serum triglycerides (TG) $\geq 2.03\text{mmol/l}$, despite at least three months of diet and exercise modification.

The survey found that cardiovascular risk factors were common in the study population. The majority of patients were male (61%), overweight (79% had an average body mass index [BMI] $\geq 25\text{kg/m}^2$) and had hypertension (72%). Forty-five per cent had type 2 diabetes and about one patient in six smoked. Sixty-eight per cent of patients were sedentary (exercised less than once a week). Between 21% and 57% of the patients had clinical evidence of cardiovascular disease.

The treated population totalled 6,756. Of these, 85% were following lifestyle intervention and 93% were receiving pharmacological therapy, most commonly a statin (85% of patients).

Despite this statin therapy and lifestyle modification, low HDL-C was common in European patients. Thirty-three per cent of men and 40% of women had low HDL-C (with similar figures in both the treated and untreated populations).

Crucially, about 14% of both genders had very low HDL-C levels of $<0.90\text{mmol/l}$. Almost 50% of all patients had hypertriglyceridaemia (elevated TG levels). The survey also found that 22% of men and 24% of women had both low HDL-C and hypertriglyceridaemia, a characteristic of atherogenic dyslipidaemia typically associated with type 2 diabetes and metabolic syndrome.

Of patients in the UK who are treated for dyslipidaemia, 40% (44% of women and 38% of men) have low HDL-C ($<1.04\text{mmol/l}$ for men and $<1.3\text{mmol/l}$ for women) and more than 50% (49% of women and 59% of men) have high TG ($\geq 3.88\text{mmol/l}$).

The treated population in the UK was more likely to be overweight than its European counterparts, with 84% having a BMI $>25\text{kg/m}^2$ compared to 78% in the European treated population. Seventeen per cent of the UK population had a BMI $>35\text{kg/m}^2$ compared to 11% in Europe. Furthermore, treated patients in the UK were more likely to have type 2 diabetes, with 61% of the UK treated population having the condition compared to 46% of the overall study population.

Lifestyle factors were more pronounced in the UK treated population — 75% were sedentary, 19% were smokers and 11% were heavy drinkers (at least three glasses of wine per day for women and four for men). In the European treated population, these figures were lower — 68%, 16% and 7%, respectively. Ninety-three per cent of treated patients in the UK are undergoing lifestyle changes to modify their lipid profile compared to 85% of the European treated patients.

Professor Bruckert stressed the need to improve current therapeutic approaches, stating that the survey results clearly illustrate that low HDL-C is highly prevalent and undertreated.

Professor John Feely, Consultant Clinical Pharmacologist at St James's Hospital in Dublin, said: "Surveys such as this are essential to document current practice and identify where we need to focus future efforts."

Low HDL-C is a major cardiac risk factor

Chairing the launch of the survey results, Professor James Shepherd, Honorary Consultant in Vascular Biochemistry at Glasgow Royal Infirmary, Scotland, and former Chair of the

European Atherosclerosis Society, said that dyslipidaemia is a major cardiovascular risk factor.

Statin therapy, said Professor Shepherd, is the current gold standard treatment for cholesterol lowering. However, patients with normal levels of low-density lipoprotein cholesterol (LDL-C) after statin therapy are still at significantly increased risk of coronary events.³⁻⁵

Epidemiological evidence shows that dyslipidaemia is not a single defect,⁶ Professor Shepherd stated, as HDL-C is a critical independent risk factor for cardiovascular disease (CVD) and coronary events.^{2,7} Analysis of large, prospective studies has shown that, regardless of LDL-C levels and other risk factors, each 0.026mmol/l decrease in HDL-C is associated with a 2-3% increase in the risk of coronary heart disease (CHD).⁷

"If we ignore HDL-C, we are missing out on a vital element of management in our patients," Professor Shepherd concluded.

Statin treatment not enough on its own

Professor M John Chapman, Director of the Dyslipidaemia and Atherosclerosis Research Unit of the National Institute of Health and Medical Research (INSERM) at Hôpital Pitié-Salpêtrière, Paris, said that statins do increase HDL-C levels but by <10%.

The Framingham Study, which examined the relationship between HDL-C and LDL-C, showed that low HDL-C levels elevate the risk of CHD even after four years of treatment to lower LDL-C levels.⁸

HDL-C exerts a vascular-protective action at the level of the cellular wall, said Professor Chapman.^{9,10} HDL-C enhances cholesterol efflux from plaque tissue and may be a critical component of atherosclerotic plaque regression, he added.¹¹

The HDL-Atherosclerosis Treatment Study (HATS) showed that combination therapy of low dose simvastatin and nicotinic acid resulted in a greater increase in HDL-C levels than statin monotherapy.¹² It also revealed that this combination treatment results in greater decreases in LDL-C, TG and lipoprotein(a) (Lp[a]) than treatment with statins alone. Treatment with a combination of simvastatin and nicotinic acid compared to placebo resulted in significant angiographic regression of stenosis and reduced major cardiovascular events.¹²

New strategies for treating dyslipidaemia

Professor Eberhard Windler, Professor of Internal Medicine at University Hospital, Hamburg, Germany, said that Niaspan (a new formulation of nicotinic acid with improved tolerability) can be used to raise HDL-C levels and contribute (alongside statin therapy) to LDL-C and TG lowering.

Little clinical attention has been paid to the fact that a low level of HDL-C is the predominant lipid abnormality in patients with cardiovascular disease, said Professor Windler.

With increasing age, the predictive power of HDL-C for cardiovascular risk rises beyond that of LDL-C. "Low HDL-C appears to be decisive in determining the risk of cardiovascular events at age 60 years," said Professor Windler.

Nicotinic acid is the most potent agent currently available for raising HDL-C. The Coronary Drug Project demonstrated, for the first time, that treatment with nicotinic acid reduces mortality in coronary patients. However, clinical application has been limited by the main side effect of flushing.

Niaspan is a new prolonged-release formulation of nicotinic acid that is not associated with liver toxicity and reduces the risk of flushing to less than one-quarter compared with immediate-release nicotinic acid. The use of a single daily dose, taken at night, means that flushing occurs during sleep.

The ARBITER 2 Study demonstrated that treatment with Niaspan and a statin halted the progression of atherosclerosis.¹³ ARBITER 3, an open-label extension of ARBITER 2, indicated that this combination therapy led to a regression of atherosclerosis.¹⁴

Studies are ongoing to compare comprehensive lipid therapy that combines lowering of LDL-C with HDL-C raising (simvastatin plus Niaspan) with simvastatin monotherapy.

Conclusion

Professor Bruckert concluded by stating: "This HDL-survey points to the future of lipid-modifying therapy. We clearly show that we must reduce LDL-C to goal as established in guidelines. But this may not be sufficient to reduce the unacceptably high residual risk of heart disease in these patients. Raising HDL-C is the next logical step for many of them."

Professor Feely stated: "In many patients, despite statins, cholesterol remained above 5.0mmol/l. The identification of some 40% with low HDL-cholesterol suggests in Europe the importance of raising HDL is not fully appreciated.

"While Ireland was not surveyed, there is little reason to think we are different. Here, in a preliminary analysis of some 10,000 patients in Heartwatch (secondary prevention) over half had raised triglycerides and 36% low HDL. Now that convenient therapy to raise HDL and lower triglycerides has become available, it will be interesting to follow improvements in this area."

References available on request.