Cost-effectiveness of adding prolonged-release nicotinic acid in statin-treated patients who achieve LDL cholesterol goals but remain at risk due to low HDL cholesterol: a UK-based economic evaluation

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Abstract

Clinical guidelines focus on statins for dyslipidaemia management for prevention of cardiovascular disease. It is clear, however, that there remains an unacceptably high residual risk of further events among patients who achieve target low-density lipoprotein (LDL) cholesterol levels. Low high-density lipoprotein (HDL) cholesterol levels, an independent predictive factor, is likely to be an important contributor to this excess risk, and is also common among dyslipidaemic patients. The ARBITER 2 study (ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol) showed that raising HDL cholesterol with prolonged-release (PR) nicotinic acid in addition to lowering LDL cholesterol with a statin slows progression of atherosclerosis, and would therefore be expected to improve cardiovascular risk reduction in this setting. This economic analysis evaluated the cost-effectiveness of this strategy using computer simulation economic modelling incorporating two decision analytic sub-models.

In the first sub-model, a cohort of 2,000 patients was generated using baseline characteristics and statin effect from the Heart Protection Study. Treatment effects observed with PR nicotinic acid (1,000 mg/day) in the ARBITER 2 study were then applied. The second model evaluated long-term clinical and economic outcomes using Framingham risk estimates. Direct medical costs were accounted from a National Health Service (NHS) perspective and discounted by 3.5%. In the UK setting, the addition of PR nicotinic acid to statin therapy resulted in long-term reduction in CHD events and increased life expectancy in patients who had achieved target LDL cholesterol levels but had persistently low HDL cholesterol, and this was achieved at a cost well within the threshold (< £30,000 per life years gained) considered good value for money in the UK. This strategy was highly cost-effective in patients with diabetes. Thus, adding PR nicotinic acid to statin therapy in these patients is both clinically and cost-effective and could be recommended for routine use in this setting in the UK.

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Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the UK. In 2004, CVD accounted for just over 216,000 deaths, more than one in three of all cases. Coronary heart disease (CHD) was the primary cause in nearly half of these deaths – about one in five in men and one in six in women.[1] CVD also imposes a major economic burden. Overall, CHD is estimated to cost the UK economy over £7.9 billion per year, over 50% of total healthcare system costs.[1]

National and international guidelines[2-5] emphasise the importance of risk factor modification for prevention of CVD. In particular, dyslipidaemia is identified as a prominent factor that warrants aggressive intervention. Treatment guidelines focus on lowering low-density lipoprotein (LDL) cholesterol levels with a statin (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor) as the

Table 1. Baseline characteristics of the Heart Protection Study population (no patients with diabetes included)[17]

- 78% male
- Mean age 64.7 years
- 78% had a history of smoking
- Mean systolic blood pressure 143 mmHg
- Mean (± SD) LDL cholesterol 3.4 (± 0.82) mmol/L
- Mean (± SD) HDL cholesterol 1.06 (± 0.31) mmol/L
- Mean (± SD) triglycerides 2.0 (± 1.27) mmol/L
- 51% had a history of MI
- 28% had a history of other CHD
- 20% had a history of other vascular disease

Key: SD = standard deviation; LDL = low-density lipoprotein; HDL = high-density lipoprotein; MI = myocardial infarction; CHD = coronary heart disease

Table 2. Treatment effect of prolonged-release nicotinic acid (1,000 mg/day) observed in the ARBITER 2 study[15]

Variable	Change with prolonged-release nicotinic acid
High-density lipoprotein (HDL) cholesterol	+ 21.0%
Low-density lipoprotein (LDL) cholesterol	-2.3%
Triglycerides	-13.0%

primary lipid-modifying therapy. A recent meta-analysis including 90,056 subjects in 14 randomised prospective trials has demonstrated that statin therapy improves clinical outcome in all patient subgroups, resulting in a 21% proportional reduction in the incidence of major vascular events per mmol/L reduction in LDL cholesterol during a mean of five years of treatment.[6] Statins are also considered highly cost-effective in the treatment of CVD.[7,8] They even have incremental benefits.[7] Yet among those patients on statin therapy who achieve target LDL cholesterol levels, more than one in six experience further events in the following five years.[6]

Dyslipidaemia is not a single defect. Evidence from population-based studies such as AMORIS (Apolipoprotein-related Mortality Risk Study)[9] and INTERHEART[10] indicate that the balance between atherogenic lipoproteins (mainly apolipoprotein B-containing particles, indicative of LDL cholesterol levels) and anti-atherogenic lipoproteins (mainly apolipoprotein A-I-containing particles, indicative of high-density lipoprotein [HDL] cholesterol levels) is the most important risk factor for myocardial infarction (MI). In INTERHEART, a case-control study involving 52 countries, this ratio accounted for up to 60% of the population attributable risk for MI.[10]

A low HDL cholesterol level is established as an independent predictive factor for CVD, supported by a wealth of evidence from epidemiological studies.[11,12] The recently updated Joint British Societies guidelines[2] has highlighted the importance of low HDL cholesterol (< 1.0 mmol/L in men and < 1.2 mmol/L in women) and recommended its inclusion in lipid assessment, especially in patients at target LDL cholesterol levels. Low HDL cholesterol makes a significant independent contribution to CHD risk among patients with type 2 diabetes, as demonstrated in the UK Prospective Diabetes Study,[13] as well as in statin-treated patients who achieve LDL cholesterol goals but have low HDL cholesterol levels.[6]

Nicotinic acid is the most effective therapeutic agent currently available to clinicians for raising HDL cholesterol. A prolonged-release (PR) formulation has been developed that effectively raises HDL cholesterol levels by up to 26% at clinically recommended doses of 1,000–2,000 mg/day, and offers improved tolerability compared with previous formulations.[14] The addition of PR nicotinic acid to statin therapy in patients with pre-existing CHD, as in the ARBITER 2 study,[15] raised HDL cholesterol levels and reduced progression of atherosclerosis, as assessed by carotid intima-media thickness (CIMT), over 12 months. In contrast, patients treated with statin alone had no change in HDL cholesterol and a significant increase in CIMT, indicative of progression of atherosclerosis.[15] Moreover, continuation of PR nicotinic acid combination treatment for a further 12 months induced regression of atherosclerosis.[16] These data therefore indicate that a strategy aimed at raising HDL cholesterol with PR nicotinic acid in statin-treated patients who have achieved target LDL cholesterol levels but have persistently low HDL cholesterol levels (< 1.0 mmol/L), is likely to be important for improving cardiovascular risk reduction. The aim of this economic analysis was to evaluate the cost-effectiveness of this strategy from a UK NHS perspective.

Materials and methods

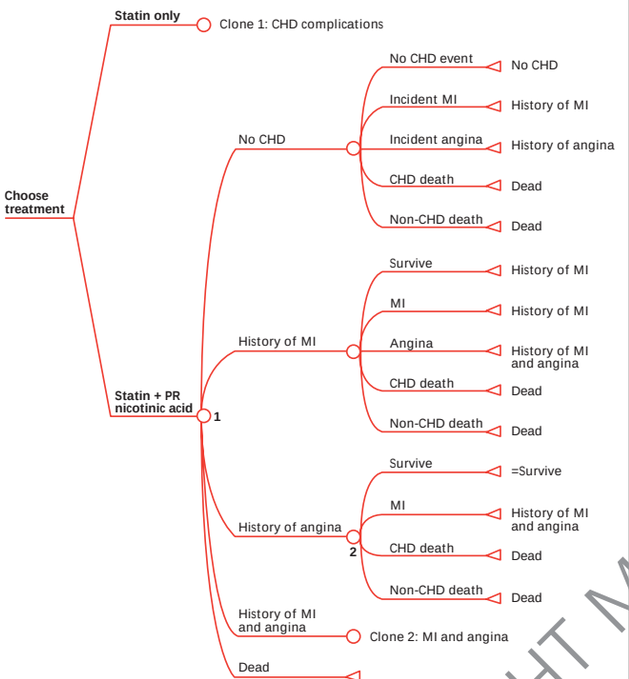
Economic modelling

As there were no data available from ongoing long-term outcome studies evaluating the effect of adding PR nicotinic acid to statin-treated patients on which to base economic modelling, two analytic decision sub-models were developed to project the long-term clinical and economic outcomes of treating patients with dyslipidaemia.

The first model, based on a second order Monte Carlo simulation, was used to determine lipid levels after treatment in a dyslipidaemic population. A cohort of 2,000 patients was created using baseline characteristics of patients without diabetes[17] and statin treatment effect[18] in the Heart Protection Study (HPS) (table 1). This cohort was predominantly male (78%), older (mean age 64.7 years) and the majority had a history of CHD (79%). In these patients mean LDL cholesterol was 3.4 mmol/L and mean HDL cholesterol was 1.06 mmol/L.[17] Individual lipid profiles were randomly assigned to each patient, and those patients with HDL cholesterol < 1.0 mmol/L and LDL cholesterol < 3 mmol/L were selected for add-on therapy with PR nicotinic acid. Treatment effects (mean and standard deviation values) associated with combination therapy with a statin and PR nicotinic acid 1,000 mg/day observed in the ARBITER 2 study[15] (table 2) were then applied to the lipid profile of statin-treated patients.

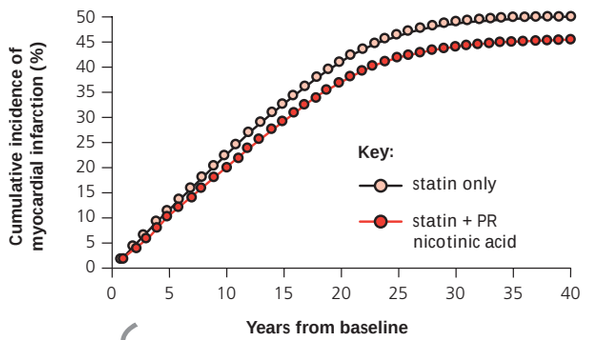
The second model (a standard Markov model) used risk estimates from the Framingham study to evaluate the cumulative incidence of CHD events (MI, angina and CHD death) after 40

Figure 1. Structure of the Markov model used to evaluate the cumulative incidence of CHD events (MI, angina and CHD death) after 40 years of simulation



Key: CHD = coronary heart disease; MI = myocardial infarction; PR = prolonged release

Figure 2. Addition of PR nicotinic acid (1,000 mg/day) to statin therapy was projected to reduce the cumulative incidence of MI from 50.2% to 45.4%



Key: MI = myocardial infarction; PR = prolonged release

years of simulation (figure 1), as well as the economic impact of these events. Full details of economic modeling used in the analysis are given in a separate reference.[19]

Costs

Direct medical costs, including drug costs and the cost of treating CHD complications, were accounted from the perspective of the UK NHS based on 2005 prices. As all patients in the model received the same statin treatment, only the cost of PR nicotinic acid, based on current UK prices (£17.25 for 56 tablets of PR nicotinic acid 500 mg),[20] was considered in the analysis. It was assumed that 2 x 500 mg tablets would be used to provide a daily maintenance dose of 1,000 mg, resulting in annual costs of £225.

Mean annual costs were used to account for the health states history of MI, history of angina and history of MI and angina. Annual cost data for angina (£1,421 based on costs reported for ischaemic heart disease), non-fatal MI (£3,966) and post-MI (£1,587) were obtained from two recent cost estimate reports submitted to the National Institute for Health and Clinical Excellence (NICE)[21,22] based on resource use data from the 1998 cohort of the Nottingham Heart Attack Register. These data included information on the frequency and duration of hospital in-patient stays, day case admissions and out-patient visits. For the combined health state history of MI and angina, the annual cost of post-MI care was applied. The cost of a fatal MI was used as a proxy for CHD-related death (£1,152).[23]

Costs and clinical benefits were discounted at a rate of 3.5% per annum. The time horizon of the analysis was set to 40 years to capture patient lifetimes; after this period it was assumed that all simulated patients had died.

Outcomes

The clinical outcomes estimated in this analysis were life expectancy (years) and life years gained (LYG) (base case analysis). In addition, quality-adjusted life expectancy (years) and quality-adjusted life years gained (QALYG) were estimated in a subsequent analysis. In order to translate the remaining lifetime into quality-adjusted life years (QALYs), utility weights of 0.80 were attached to the relevant health states of the model (history of angina, history of MI, and history of MI and angina), based on data from the previously mentioned sources.[21,22] The economic outcome was expressed as the incremental cost-effectiveness ratio (ICER), defined as the ratio of the incremental cost per life years gained (£/LYG) or incremental cost per quality-adjusted life years gained (£/QALYG).

Sensitivity analyses were performed to evaluate the effect of changing variables that had an impact on the ICER. These included varying the efficacy of PR nicotinic acid (± 20%), the cost of cardiovascular complications (± 30%), discount rates (6% or 0%), the average age (± 10 years) and sex distribution of the population (50% to 100% male) and the HDL cholesterol target value (1.2 mmol/L instead of 1.0 mmol/L). A simulation was also performed based on the characteristics of the diabetes subgroup of the HPS (29% of the study population).[17]

Results

Of the 2,000 simulated patients included in the cohort, 46%

Table 3. Cost-effectiveness results for prolonged-release nicotinic acid (1,000 mg/day) added to statin therapy versus statin monotherapy

	Statin monotherapy	Statin + prolonged-release nicotinic acid
Life expectancy, years	12.41	12.59
Quality-adjusted life expectancy, years	9.86	10.00
Life Years Gained (LYG), years	-	0.1798
Quality-adjusted Life Years Gained (QALYG), years	-	0.1384
Total costs	£20,482	£23,377
Incremental cost	-	£2,895
ICER*, per LYG	-	£16,101
ICER*, per QALYG	-	£20,915

Key: * ICER (Incremental cost-effectiveness ratio) defined as the ratio of incremental cost/life years gained or quality-adjusted life years gained

Table 4. Impact of factors on the base-case incremental cost-effectiveness ratio (ICER)

Factor	ICER (£ per life years gained)	Change in base-case ICER
Efficacy of prolonged-release nicotinic acid (mean and SD) - Increase by 20%; decrease by 20%	14,338; 18,539	-1,763; +2,438
Costs of cardiovascular complications - Increase by 30%; decrease by 30%	16,232; 15,971	+131; -130
Discount rates applied - Increase to 6%; decrease to 0%	18,296; 13,348	+2,195; -2,753
Change in proportion of males in cohort - Increase to 100%, decrease to 50%	14,992; 17,897	-1,109; +1,796
Change in the age for starting treatment - Increase by 10 years, decrease by 10 years	19,044; 14,669	+2,943; -1,432

with LDL cholesterol levels < 3 mmol/L still had HDL cholesterol levels < 1 mmol/L on statin treatment and were therefore selected for add-on treatment with PR nicotinic acid (1,000 mg/day). The mean discounted life expectancy in these patients was 12.59 years compared with 12.41 years in patients treated with statin alone, corresponding to an increase in life expectancy of 0.18 life years with the combination treatment. The addition of PR nicotinic acid to statin therapy was projected to reduce the cumulative incidence of MI from 50.2% to 45.4% (figure 2), new angina from 8.9% to 8.2% and CHD death from 25.8% to 23.4%, leading to an absolute risk reduction for all CHD events of 8%.

Addition of PR nicotinic acid to statin therapy was associated with an incremental total cost of £2,895 (£23,377 with the combination treatment versus £20,482 with statin monotherapy). The ICER for the combination treatment was £16,101 per LYG (table 3). When expressed as quality-adjusted life expectancy, the QALYG by addition of PR nicotinic acid was 0.14, resulting in a slight increase in the ICER to £20,915 per QALYG (table 3).

Sensitivity analyses showed that the base case ICER was robust to variations in the efficacy of PR nicotinic acid, the cost of cardiovascular complications, discount rate applied, as well as changes in the sex distribution or age of the cohort (table 4). The small increase in the ICER (£17,897 per LYG) associated with a cohort with 50% male patients (versus 78% in the base case) was due to the notably lower risk of cardiovascular complications in women than men. When the HDL cholesterol target was set to 1.2 mmol/L instead of 1.0 mmol/L (thus resulting in 69% of the initial cohort becoming eligible for combination treatment), the ICER was increased to £17,381 per LYG.

In the HPS baseline population, 29% of the patients had diabetes.[17] Sub-group analysis using the baseline characteristics of these patients showed that in a higher risk cohort with a history of diabetes, the ICER was reduced from £16,101 per LYG to £9,568 per LYG.

Discussion

The present economic evaluation from a UK NHS perspective demonstrates that the clinical benefits of adding PR nicotinic acid (1,000 mg/day) to statin therapy in terms of long-term reduction in CHD events and substantial increase in life expectancy was achieved at a cost well within the range (< £30,000) that is generally considered good value for money in the UK. In particular, addition of PR nicotinic acid to statin therapy in patients with diabetes was highly cost-effective, as indicated by reduction in the ICER by over 40% to < £10,000 per LYG. Sensitivity analyses showed that the results of this economic evaluation remained robust to a range of plausible assumptions including changes in the cost of cardiovascular complications and the characteristics of the cohort. Subsequent evaluations have shown that adding PR nicotinic acid to a statin in dyslipidaemic patients is also cost-effective in other country settings, including France, Germany, Austria, Sweden and Norway.[24-26]

When considered in the context of other lipid-modifying interventions, the clinical benefits associated with combination therapy with PR nicotinic acid and a statin were achieved at a cost comparable to that observed with rosuvastatin (ICER versus simvastatin £9,735 per QALY in men and £15,184 per QALY in women), and atorvastatin.[27] However, adding PR nicotinic acid to a statin offers advantages over ezetimibe/statin therapy, which aims to further reduce LDL cholesterol levels but has marginal impact (< 5%) in raising HDL cholesterol levels.[28] Compared with a recent analysis, adding PR nicotinic acid to statin therapy was more cost-effective than ezetimibe statin combination therapy, particularly in diabetic patients (ICER £17,800 [26,000 Euros] per LYG *vs.* < £10,000 per LYG with PR nicotinic acid combination therapy).[29]

Currently there is no agreed consensus or defined limits for cost-effectiveness thresholds implemented by regulatory authorities. Retrospective analysis of previous resource allocation decisions made by NICE indicate a threshold cost of £20,000 to

Key messages

- Statin-treated patients who achieve low-density lipoprotein (LDL) cholesterol targets but have persistently low high-density lipoprotein (HDL) cholesterol levels remain at excess cardiovascular risk
- Raising HDL cholesterol levels by adding prolonged-release (PR) nicotinic acid to statin therapy results in long-term reduction in coronary heart disease events and a substantial increase in life expectancy. These clinical benefits are achieved at a cost well within the threshold (< £30,000) considered good value for money in the UK. This strategy was highly cost-effective in diabetic patients
- Adding PR nicotinic acid to statin therapy in these patients is both clinically and cost-effective and could be recommended for routine use in this setting in the UK

£30,000, below which an intervention was considered cost-effective compared with standard treatment.[30] However, a recent report which analysed the consistency of decisions made by NICE suggests that in practice this threshold is likely to be even higher (£35,000 to £40,000).[31] This is also consistent with a review of cost-effectiveness analysis in healthcare resource decision-making[32] which identified a cost-effectiveness threshold of $65,000 (£35,400) per LYG.[33] Taken together, these inferred thresholds emphasise that the increase in life expectancy associated with adding PR nicotinic acid to statin-treated patients who remain at excess cardiovascular risk due to low HDL cholesterol levels despite achieving LDL cholesterol targets, is indeed cost-effective – and highly cost-effective in the diabetic setting.

The implications of this economic evaluation are particularly important given that low HDL cholesterol is common among dyslipidaemic statin-treated patients, as highlighted by recent findings from the Pan-European Survey on HDL-C.[34] This survey, which included data from 8,545 dyslipidaemic patients (85% on statin therapy) from 11 European countries, demonstrated a prevalence of low HDL cholesterol (defined as < 1.03 mmol/L in men and < 1.29 mmol/L in women) of over 30%.[34] Moreover, among 1,548 of these patients recruited in the UK, the prevalence of low HDL cholesterol was even higher – 40% (38% of men and 44% of women) – and 19% had very low HDL cholesterol levels (< 0.9 mmol/L).[34] Low HDL cholesterol is also a characteristic feature of the atherogenic dyslipidaemia typically observed in patients with type 2 diabetes.[35] Raising HDL cholesterol by adding PR nicotinic acid to statin therapy in these patients would be anticipated to offer substantial clinical and economic benefits.

In conclusion, this economic evaluation has shown that in the UK setting, increased life expectancy associated with raising HDL cholesterol levels in statin-treated patients who have achieved target LDL cholesterol levels but have persistently low HDL cholesterol is achieved at a cost well within reported thresholds for cost-effectiveness. This strategy also compares favourably with other lipid-modifying interventions. Adding PR nicotinic acid (1,000 mg/day) to statin therapy in these patients, in particular those with diabetes, is both clinically and cost-effective and could be recommended for routine use in this setting in the UK.

Conflict of interest

SR is employed by CORE, a unit of IMS Health. The economic model referred to in this article was developed independently by CORE without external funding. ASW has received honoraria for lectures and advisory boards as well as travel and research grants from Astra-Zeneca, Bristol Myers Squibb, GlaxoSmithKline, Merck KGaA, Merck, Sharp & Dohme, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, Solvay-Fournier and Takeda. DL and CR are employees of Merck Santé, France.

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