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# Cost-outcome benefits of fibrate therapy in type 2 diabetes

MICHAEL D FEHER,<sup>1</sup> CLARE E LANGLEY-HAWTHORNE,<sup>2</sup> CHRISTOPHER D BYRNE<sup>3</sup>

## Abstract

**To date there have been few studies focusing on economic assessments of fibrate therapy in the management of coronary heart disease (CHD), particularly in patients with type 2 diabetes. A cost-effectiveness model for an economic analysis was established by an assessment of 'cost per CHD event avoided' for fibrate therapy. This model was derived from: i) data on CHD events in patients with and without diabetes from randomised controlled trials of lipid-lowering agents, ii) comparisons of fibrate and HMG CoA reductase inhibitor (statin) treatment compared to no treatment and iii) current UK-based drug and clinical event costs. Treatment benefits over a five-year period were calculated, and the sensitivity of the model to the individual variables tested.**

**Fibrate therapy was substantially more cost-effective than statin therapy in patients with diabetes. Economic costings for fenofibrate, as the index fibrate commonly used in the UK, confirmed an annual cost of £2,642–£3,700 per CHD event avoided over a five-year assessment period. Cost-effectiveness ratios derived in the economic model demonstrated that fibrate therapy was equally effective as statin therapy, but at a 54% reduction in annual cost. Current and future CHD treatment guidelines should incorporate pharmaco-economic data for fibrate as well as statin therapy.**

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**Key words:** diabetes, fibrate, cost-effectiveness, guidelines.

## Introduction

Diabetes is an increasingly common metabolic condition with epidemic proportions across the globe and has a major impact

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## Abbreviations

ADA	=	American Diabetes Association
CHD	=	coronary heart disease
CVD	=	cardiovascular disease
HDL-c	=	high density lipoprotein cholesterol
HRG	=	Healthcare Resource Group
LDL-c	=	low density lipoprotein cholesterol
MI	=	myocardial infarction
NCEP	=	National Cholesterol Education Program
NHS	=	National Health Service
NICE	=	National Institute for Clinical Excellence

## Trial acronyms

4S	=	Scandinavian Simvastatin Survival Study
CARE	=	Cholesterol And Recurrent Events trial
DAIS	=	Diabetes Atherosclerosis Intervention Study
FIELD	=	Fenofibrate Interventions and Event Lowering in Diabetes
HPS	=	Heart Protection Study
LIPID	=	Long-Term Intervention with Pravastatin in Ischaemic Disease trial
MRFIT	=	Multiple Risk Factor Intervention Trial
VA-HIT	=	Veterans Affairs High-density lipoprotein cholesterol Intervention Trial

on health resources, as well as important health implications for individuals with the condition. However, due to the potential size of the treatment population, economic factors specific to drug therapies used to prevent diabetic vascular complications are an increasingly important consideration.

People with type 2 diabetes are at a markedly greater risk of cardiovascular events, in particular coronary heart disease (CHD), than individuals who do not have diabetes.<sup>1</sup> Results of the MRFIT found that even in the small group of patients without additional risk factors, the excess risk of cardiovascular mortality in patients with diabetes is up to four-fold greater than those without diabetes.<sup>2</sup> Recent data has indicated that patients with diabetes without a history of myocardial infarction (MI) have a similar risk of developing CHD as individuals without diabetes who have experienced a MI.<sup>3</sup> Additionally, the presence of CHD in patients with diabetes is associated with a further increase in coronary risk, compared to a similar group without diabetes.<sup>4</sup> Cardiovascular disease accounts for up to 80% of the mortality observed in patients with type 2 diabetes. The major randomised controlled clinical trials of lipid lowering in secondary CHD pre-

**Table 1.** Parameters and values of cost-outcomes models

Parameter	Value
Risk in patient population	30% absolute risk of a CHD event (non-fatal MI or CHD death) over a 10-year period (Generating a 15% risk over a five-year period)
Time scale	Five years
Effectiveness data*	Extrapolating VA-HIT data on absolute risk reduction associated with fibrate (gemfibrozil) therapy in diabetes to fenofibrate. Effectiveness assumption tested in sensitivity analysis and confirmed by preliminary DAIS data for fenofibrate
Clinical effectiveness end point*	Cost per CHD event avoided
'Low' risk reduction scenario*	2.7% absolute risk reduction for statins vs. 7.6% absolute risk reduction for fibrate
'Medium' risk reduction scenario*	5.5% absolute risk reduction for statins vs. 7.6% absolute risk reduction for fibrate
'High' risk reduction scenario*	7.6% absolute risk reduction for statins vs. 7.6% absolute risk reduction for fibrate
No treatment scenario	No treatment vs. 7.6% absolute risk reduction for fibrate
<b>Note:</b> Given the analysis by Robins <sup>10</sup> differences in absolute risk reduction rather than relative risk reductions have been used.	
*Indicates parameters tested in sensitivity analysis	

vention, have reported CHD outcomes in diabetic subgroups with the use of both statin (CARE, LIPID) and (VA-HIT) fibrate drugs. The DAIS study was the only trial of secondary prevention in an exclusive diabetic group.

To date, few guidelines have incorporated extensive pharmacoeconomic data specific to lipid-lowering treatments in patients with diabetes. The recent UK-based NICE guidelines for the management of lipids in type 2 diabetes<sup>5</sup> did not endorse fibrate derivatives at the same level as statins in first-line treatment in diabetes. By comparison, the American Diabetes Association (ADA) places fibrate therapy as a treatment choice, in particular to raise high density lipoprotein cholesterol (HDL-c) and lower serum triglycerides.<sup>6</sup> The aims of the present study were to evaluate the cost-effectiveness of fibrate therapy in type 2 diabetes and to place this analysis within the context of the recent UK guidelines.

### Research design and methods

A cost-effectiveness model was developed based upon the absolute CHD risk reductions associated with treatment of dyslipidemia in type 2 diabetes. The model incorporated randomised clinical trial data and UK costs (tables 1 and 2) using the *a priori criteria* listed below. Fibrate treatment (using fenofi-

**Table 2.** Costings (with sources) of the parameters used in the models

Parameter	Value
<b>Weighted average cost per CHD event</b>	
Reference cost (derived from 2000 CHD British Heart Foundation statistics)	£2,416
Lower cost limit in sensitivity analysis (derived from all Finished Consultant Episodes codes)	£1,823
Normalised reference cost (excluding code E12, MI without complications or comorbidities)	£3,093
Upper cost limit in sensitivity analysis (derived from 2000 CHD British Heart Foundation statistics)	£3,941
<b>Discount rate per annum</b>	
Applied to costs	6.0%
Applied to benefits (CHD events avoided)	1.5%
<b>Drug costings</b>	
Fibrate reference case (supramicronized fenofibrate, Supralip®, 160 mg tablets, pack of 28)	£14.75
Alternative fibrate treatment (micronized fenofibrate, Lipantil® Micro 200 capsules, pack of 28)	£21.75
Statin reference case (either pravastatin or simvastatin, 40 mg/day, pack of 28)	£29.69

brate as the index fibrate drug for analysis) was compared to statin treatment (using pravastatin and simvastatin as reference drugs) in a hypothetical patient population with diabetic dyslipidaemia, using the evidentiary standards set out in the revised *Technical Guidance for Manufacturers and Sponsors on Making a Submission to a Technology Appraisal* issued by NICE in March 2001.<sup>7</sup>

### A priori criteria

#### Treatment population

The cost-effectiveness model concentrated on secondary rather than primary CHD prevention. Accordingly data from the recent HPS study, which was a primary prevention study for the diabetic subgroup, was not included.

The hypothetical treatment population used in the present model has the characteristics of those patients with type 2 diabetes enrolled in the VA-HIT.<sup>8</sup> Given the limited trial data on clinical outcomes for fenofibrate, the current model extrapolates the results from another fibrate based trial (VA-HIT) in order to evaluate the potential cost-outcomes associated with fenofibrate therapy. Justification for this was confirmed by the results of the most recent large-scale trial for fenofibrate (the DAIS study), although this study was designed to examine angiographic coronary artery disease progression rather than CHD events, it showed similar percent reduction in clinical events as shown in the clinical end point trials of lipid lowering.

In comparing fibrate therapy to statin treatment we have used data available from the large-scale statin trials, including the CARE trial.<sup>9</sup> In contrast to other large lipid intervention studies that excluded many patients with diabetes, a high proportion of patients in VA-HIT (25%; 627 patients) and CARE (14%; 603 patients) had diabetes.

In both the VA-HIT and CARE studies, patients with diabetes had similar mean body weight, waist circumference, ratio of total cholesterol:HDL-c and fasting glucose concentration. However, mean concentrations of HDL-c and low density lipoprotein cholesterol (LDL-c), differed among these populations as did the absolute risk reductions in CHD events observed. Combined risk

**Table 3.** Absolute risk reduction estimates for non-fatal MI or CHD death in statin and fibrate trials: subjects with and without diabetes

Trial (drug)	Subgroup	n	Absolute risk of non-fatal MI or CHD death		% Absolute risk reduction	
			Placebo	Drug	Drug	NNT*
CARE (statin)	Non-diabetes	3,553	12.0	9.1	3.1	32
	Diabetes	586	20.4	17.7	<b>2.7</b>	37
LIPID (statin)	Non-diabetes	8,232	15.2	11.7	3.5	29
	Diabetes	782	22.8	19.2	3.2	31
4S/CARE/LIPID (statin)	Diabetes (combined data)	1,570	n/a	n/a	<b>5.5</b>	18
VA-HIT (fibrate)	Non-diabetes	1,904	19.0	15.7	3.3	30
	Diabetes	627	29.9	22.3	<b>7.6</b>	13

\*NNT is the number of patients needed to treat to avoid one CHD event and is equivalent to 100/absolute risk reduction. **Bold values used in model**

reduction estimates from the CARE as well as 4S and LIPID trials are also included in the analyses. The results of the 4S, are not analysed separately in the model due to the low number of patients with type 2 diabetes included in the trial and trial inclusion criteria which focused on patients with high LDL-c levels, which is not a feature of type 2 diabetes.

### Time-frame

A prevalence-based approach was used in which the costs and outcomes associated with treating patients was estimated in a given time interval, irrespective of the date patients were first diagnosed, or the stage reached in disease progression. A five-year time frame was used as this accorded with risk reductions observed in key clinical outcome trials. It is also a useful time horizon for a budget impact analysis.

### Clinical effectiveness

Cost-effectiveness needs to be linked to clinical CHD end points and not lipid parameters. On the basis of the available evidence, we used the analysis undertaken by Robins<sup>10</sup> on the absolute risk reductions observed in the VA-HIT fibrate trial,<sup>9</sup> and the statin trials – CARE,<sup>9</sup> 4S,<sup>11</sup> and LIPID<sup>12</sup> (table 3).

### UK costings

Resources and costs were based on UK experience and focused on direct costs borne by the NHS. Indirect costs (productivity impacts) were not included in the analysis. Direct costs of managing CHD events (death and non-fatal MI) were analysed using the National Schedule of Reference Costs (produced annually by the NHS) and cost estimates produced by the British Heart Foundation.

Given the sensitivity of the weighted average cost to the Healthcare Resource Group (HRG) codes and cost variations experienced within the NHS, the 2000 CHD statistics produced by the British Heart Foundation were used in the reference cost-effectiveness model.<sup>13</sup> The £2,416 cost-estimate was used as the reference case with higher and lower cost-estimates (£1,823–£3,941) tested in the sensitivity analysis.

Pharmaceutical costs were based on costs to the NHS.<sup>14</sup> For statin treatment (pravastatin or simvastatin), a 40 mg (daily) dose was used in the analysis as this corresponded to the dose used in the statin based lipid-lowering trials. This assumption was tested as part of our sensitivity analysis to measure the impact of a lower statin dose on the results of our model. For fenofibrate (the index fibrate drug used), costs for Supralip® 160 mg tablets were used, as this is the commonly used initial dose in current clinical practice.

Discounts were applied over the five-year period with the assumption that costs and benefits (in terms of CHD events avoided) were spread equally over the five years. Choice of discount rate (6%) and parameters for sensitivity analysis were based on the recommendations made by the National Institute for Clinical Excellence (NICE) in its *Technical Guidance for*

*Manufacturers and Sponsors on Making a Submission to a Technology Appraisal* (March 2001).<sup>7</sup>

The cost-effectiveness model focused on the incremental cost-effectiveness between two classes of drugs (fibrates versus statins). Although the assumption that benefits are spread equally over a five-year period may over-estimate the short-term benefits of treatment, this assumption does not affect the relative cost-effectiveness of the treatments under study.

### Model estimation

A cost-effectiveness model was developed to estimate, for a hypothetical patient population with diabetes (n=1,000), the number of CHD events that could be expected to occur (and the costs associated with treating these events) based on an assumed 15% absolute risk rate of CHD over a five-year period.

Using the analysis undertaken by Robins<sup>10</sup> on the absolute risk reductions observed with fibrate therapy in the VA-HIT study, a 7.6% absolute risk reduction for fibrate treatment was compared with three alternate scenarios for statin treatment (table 4):

- 1) A 'low' risk reduction scenario of a 2.7% absolute risk reduction. This is based on the results observed for pravastatin in the CARE trial.
- 2) A 'medium' risk reduction scenario of a 5.5% absolute risk reduction, based on the combined results from 4S, CARE and LIPID trial.
- 3) A 'high' risk reduction scenario of a 7.6% absolute risk reduction. This scenario assumed fibrate and statin treatment were equivalent.

A further analysis was also undertaken with respect to combined CHD event rates as reported in the CARE and VA-HIT trials. These trial data showed a slightly higher absolute risk reduction associated with statin treatment (8.1%) versus fibrate (8.0%) when all CHD events were included.

In the cost-effectiveness model, annual costs of treating CHD events were estimated and a 6% discount rate<sup>7</sup> applied to produce a baseline estimate of CHD costs against which the benefits of fibrate treatment (using fenofibrate as the index drug) or statin treatment (either pravastatin or simvastatin as the reference case) could be assessed. The reduction in absolute risk associated with either fibrate or statin treatment was applied to the model to recalculate the number of CHD events that could be expected to occur and the number of CHD events that were avoided as a result of treatment. Total costs of treatment (fibrate or statin drug costs plus CHD event costs) were then discounted and compared with baseline (untreated) costs. The cost per CHD event avoided was estimated as well as the incremental costs associated with providing either fibrate or statin treatment. Incremental cost-effectiveness ratios were calculated by comparing the incremental cost of fibrate versus statin treatment with the incremental benefits in terms of additional CHD events avoided.

### Sensitivity analysis

The following parameters were varied to test the sensitivity of the model outcomes to changes in the costs of treatments and outcomes. The fibrate refer-

**Table 4.** Scenario outcomes: costs and effectiveness

Outcome	Absolute risk reduction		Absolute risk reduction with statin		
	No treatment	Fenofibrate (7.6%)	'Low' (2.7%)	'Medium' (5.5%)	'High' (7.6%)
(n=1,000 patients, 15% absolute risk rate)					
Number of patients with CHD event	150	74	123	95	74
Discounted costs over five years	305,314.75	960,568.68	1,880,684.77	1,823,692.69	1,780,978.62
CHD events avoided over five years (discounted benefits)		72.7	25.8	52.6	72.7
Annual cost per CHD event avoided (as discounted)		2,642.69	14,564.12	6,932.99	4,899.70
Incremental cost (fenofibrate versus pravastatin)			-920,116.09	-863,124.01	-820,409.94
Incremental benefit (fenofibrate versus pravastatin)			46.9	20.09	0
Incremental cost-effectiveness ratio (incremental cost-incremental benefit)			(19,618.68)	(42,962.87)	

ence case used in the model was supramicronised fenofibrate (Supralip® 160 mg tablets). A sensitivity analysis was also undertaken to assess the impact of using a different fibrate formulation – micronised fenofibrate (Lipantil®) Micro 200 capsules. Similarly, costs for 20 mg and 10 mg pravastatin and simvastatin were analysed as part of the sensitivity analysis. The reference formulation in our cost-effectiveness model was 40 mg. The sensitivity of the weighted average cost per CHD event was also tested by using cost estimates lower (£1,823) and higher (£3,941) than the reference (£2,416) (table 2).

In accordance with the NICE guidance, the effect on the cost-effectiveness model of:

- 1) a 6% discount rate for both drug costs and clinical benefits
- 2) a 6% discount on drug costs
- 3) 0% discount for clinical benefits, was undertaken.

In addition, the effectiveness of fibrate therapy was tested in our sensitivity analysis using a 10% and 20% reduction from the 7.6% absolute risk reduction assumed (based on the results of VA-HIT).

## Results

Fenofibrate was found to be more cost-effective than pravastatin or simvastatin in all scenarios (table 4). In the 'high' risk reduction scenario, the calculations for fenofibrate (the index fibrate drug) confirmed an annual cost of £2,642.69 per CHD event avoided. By comparison, when modelled in a 'high' risk reduction scenario, the cost for pravastatin was £4,899.70. In comparison, when pravastatin treatment was modelled in the 'low' risk reduction scenario, the cost was £14,564.12. When statin treatment (i.e. pravastatin or simvastatin) – as the reference case was modelled in the 'medium' risk reduction scenario, the cost for treatment was £6,932.99.

When compared with pravastatin modelled in the 'low' risk reduction scenario, fibrate treatment (using fenofibrate as the index drug) was associated with 47 fewer CHD events than pravastatin. In the 'medium' risk reduction scenario, fenofibrate was still associated with an additional 20 CHD events avoided. Even when, as in the 'high' risk reduction scenario, pravastatin was assumed to be as effective as fenofibrate in terms of absolute risk reduction, pravastatin was still associated with an additional £164,081.98 annually. The analysis demonstrated that a 13.2% absolute risk reduction was needed for pravastatin to be as cost-effective as fenofibrate.

Table 5 extends the analysis to combined CHD event rates reported in the CARE and VA-HIT trials. This table demonstrates the cost-effectiveness of fibrates even on the basis of a slightly higher absolute risk reduction associated with pravastatin (8.1%) versus fenofibrate (8.0%) when all CHD events are included. On this basis, pravastatin is associated with an additional £2,081.70 per CHD event avoided.

The outcomes of this sensitivity analysis are outlined in table 6. When fenofibrate was modelled at a 10% reduction in effectiveness from the 7.6% absolute risk reduction assumed in the model, the annual (discounted) cost per CHD event avoided was £2,983.61. A 20% reduction in effectiveness for fenofibrate resulted in an annual (discounted) cost of £3,409.76 per CHD event avoided. The results of the sensitivity analysis suggest that pravastatin and simvastatin would need to be associated with an absolute risk reduction rate of 9.8% to be as equally cost-effective as fenofibrate.

Following the NICE guidelines we also undertook an evaluation of the impact of different discounting rates for outcomes incorporated in the model. The impact of these changes is also outlined in table 6. The CHD cost estimates used were also altered, and while these changed the cost impact of fenofibrate versus no treatment these did not alter the relative cost-effectiveness of fenofibrate versus pravastatin or simvastatin.

## Discussion

### Cost-effectiveness of fibrates

The present economic analysis suggests that fibrates are a cost-effective alternative to statin therapy in subjects with type 2 diabetes. Fenofibrate (used as the index fibrate drug in the analyses) was found to be cost-effective across all the scenarios modelled. These results were confirmed by the sensitivity analysis conducted. Even when statins were assumed to be equally effective as fibrates, fenofibrate yielded the same benefit in terms of the number of CHD events avoided at half (54%) of the annual cost. Alternatively, both pravastatin and simvastatin needed to be associated with an absolute risk reduction rate of 9.8% to be as equally cost-effective as fenofibrate.

**Table 5.** Combined CHD end points: costs and benefits

Outcome	Absolute risk reduction		
	No treatment	Fenofibrate (8.0%)	Pravastatin (8.1%)
(n=1,000 patients, 15% absolute risk rate)			
Number of patients with CHD event	150	70	69
Discounted costs over five years	305,314.75	952,426.95	1,770,771.46
CHD events avoided over five years (discounted benefits)		76.5	77.5
Annual cost per CHD event avoided (as discounted)		2,489.28	4,570.98
Incremental cost (fenofibrate versus pravastatin)		-2,081.70	
Incremental benefit (fenofibrate versus pravastatin)		-1	
Incremental cost-effectiveness ratio (incremental cost-incremental benefit)		2,081.70	

**Table 6.** Sensitivity analysis

	Absolute risk reduction: assumed equivalency at 7.6%					
	Fenofibrate reference: Supralip®	Discounted: costs 6% benefits 0%	Costs and benefits discounted 6%	Alternative fenofibrate: Lipantil®	Pravastatin 10 mg	Simvastatin 10 mg
Discounted costs over five years	960,568.68	960,568.68	960,568.68	1,344,950.18	1,039,092.33	1,140,678.87
CHD events avoided over five years (discounted benefits)	72.7	76	64	72.7	72.7	72.7
Annual cost per CHD event avoided (as discounted)	2,642.69	2,527.81	3,000.44	3,700.19	2,858.73	3,138.21
% difference to reference case		-4.35%	+13.54%	+40.02%	+8.18%	+18.75%
% difference compared to lipantil®					-22.74%	-15.19%

The present findings on the cost-effectiveness of fenofibrate confirms results in previous studies in patients without diabetes. One recent study concluded on the basis of reductions in absolute risk of CHD, that fenofibrate, simvastatin and atorvastatin produced the greatest cost savings when analysed as the number of cardiovascular events avoided over a five-year period.<sup>15</sup> Another lifetime analysis of statins and fibrates found that the cost-effectiveness of the different medications varied according to patient population over a 3.7-fold range for statins and a 3.5-fold range for fibrates.<sup>16</sup>

The current cost-effectiveness model specifically focused on type 2 diabetes and appears to be one of the first to assess cost-effectiveness of lipid-lowering treatments in this group. There are only limited data assessing the cost-effectiveness of statins in people with diabetes and there are no comparable studies with fenofibrate that assess cost-effectiveness in diabetic patients over a timescale suitable for budget analysis. It is of interest that short-term (12 weeks) cost-effectiveness data from two randomised controlled clinical trials demonstrated that fenofibrate was more cost-effective than simvastatin in the short time frame.<sup>17,18</sup>

#### Implications of results: CHD event rates

As there are no fenofibrate (the index fibrate drug) clinical end point trials assessing CHD events as a primary end point, the

results of another fibrate (gemfibrozil) trial was used as the basis of a fibrate outcome data. Justification for this was derived from the most recent large scale trial for fenofibrate (the DAIS Study) which was specifically designed to examine whether correcting lipid abnormalities with fenofibrate in type 2 diabetes affected the (primary end point) angiographic progression or regression of coronary atherosclerosis. The trial was not powered for clinical CHD end points, but results showed a non-significant 23% reduction in clinical coronary events with fenofibrate.<sup>19</sup> This reduction was similar to the event reductions in the analyses of the diabetic subgroups of the statin based trials: 4S (-55%), CARE (-25%), LIPID (-19%) and HPS (-20%). Given the greater impact on absolute risk reduction observed with gemfibrozil in the VA-HIT the benefits of fenofibrate were considered to be similar to gemfibrozil and thus are likely to be greater than that observed for statins with regard to the clinical benefits due to fibrate effects on modifying a diabetic dyslipidaemia. Comparing fenofibrate with gemfibrozil is therefore appropriate in CHD event management.

#### Implications of results: treatment of diabetic dyslipidaemia

The VA-HIT results suggest that treating a diabetic patient with

low HDL and/or high triglycerides with a fibrate is more cost-effective than treating a diabetic patient with high or slightly high total cholesterol with a statin. In the analysis of the current statin and fibrate trials some important observations can be made with regard to treatment-induced cholesterol reduction and CHD events. This is highlighted in the recent analysis by Durrington and Illingworth<sup>20</sup> who assessed the relationships between cholesterol reduction and decreases in new CHD events for a 1% fall in serum cholesterol. The authors concluded that the impact of drugs which aim principally to lower triglycerides (i.e. fibrates) appear to have a greater impact on CHD events even though they do not reduce serum cholesterol to the same extent as the statins. Its effect on lowering triglycerides may account for some of the additional benefit of fibrate treatment observed in the VA-HIT trial. Alternatively, it is possible that the benefit may be linked to the initial risk of CHD. What these observations bring to light is that intermediate end points such as the concentration of LDL cholesterol may not be the only lipid factor linked to CHD end points in diabetes. In the present economic study, therefore, cost-effectiveness was linked to clinical end points rather than lipid end points.

### Possible model limitations

There are other considerations that need to be taken into account when assessing the trial results used in our analyses. The absolute risk of CHD in the placebo groups of VA-HIT and CARE were markedly different. People with type 2 diabetes in CARE appeared to be at a lower absolute risk to those recruited to VA-HIT. This may be a consequence of other treatments (e.g. aspirin) received during the trials. On the other hand, the absolute risk of the placebo group in 4S was higher than in CARE and VA-HIT. To overcome some of these issues we used the combined results of three statin studies (4S, LIPID, and CARE) in the comparison with VA-HIT.

Although the current cost-effectiveness model focused on secondary prevention, we note that the absolute risk of the hypothetical population was 3% per year, similar to the risk of a primary event among people with diabetes. Data from a major primary prevention trial in people with diabetes, the HPS study (40 mg simvastatin)<sup>21</sup> are likely to play an important role in future health economic analyses of lipid interventions in type 2 diabetes. This is not merely because of the large size of the trial (5,000 diabetic patients – more than those recruited for all other fibrate and statin studies put together) but also because of the inclusion of high-risk patients such as those with type 2 diabetes. The HPS study results show risk reductions not dissimilar to VA-HIT.<sup>10,21,22</sup> The HPS study carries with it, however, the caveat that the trial was primary prevention for the diabetic subgroup. Once the further HPS data are published (in particular with respect to patients with diabetic dyslipidaemia) and we have results from large scale fibrate studies such as the FIELD study,<sup>23</sup> we will have a more comprehensive evidence base upon which a more detailed economic evaluation of the comparative benefits of fibrate versus statin therapy can be undertaken.

### UK and USA comparisons

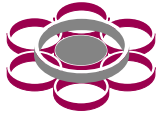
The management of lipid disorders requires advice on modification of life-style, non-lipid risk factors as well as an assessment of cholesterol (total cholesterol, LDL and HDL) and/or triglycerides. Several guidelines (e.g. the American Diabetic Association, the US NCEP<sup>24</sup> and the European Atherosclerosis Society)<sup>25</sup> provide detailed information on the appropriate treatment thresholds and targets. In the USA, the ADA's position statement<sup>6</sup> explicitly takes into account HDL-c levels in treatment recommendations. Indeed the ADA position statement states that if HDL is < 40 mg/dL (< 1.05 mmol/L) a fibrate such as fenofibrate should be used in patients whose LDL is between 100 and 129 mg/dL (2.6 and 3.5 mmol/L). The ADA recommends fibrate therapy as the treatment of choice for raising HDL-c and lowering triglycerides, and recommends fenofibrate as second choice therapy for lowering LDL-c.

In the UK, joint guidelines from the British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society and British Diabetic Association (now Diabetes UK) also specify targets for the modification of non-lifestyle factors.<sup>26</sup> It is recommended that treatment of hypertension and hyperlipidaemia in non-diabetic patients be strongly determined by the absolute level of risk, but patients with diabetes are considered an exception, and a staged approach to management is advised. Currently, in high-risk persons such as those with diabetes and those with an absolute CHD risk  $\geq$  30% over 10 years should be targeted for treatment. These guidelines identify six categories of patients with type 2 diabetes defined in terms of lipoprotein profile, history of cardiovascular disease and absolute risk of coronary event in the succeeding 10 years. Pharmacological treatment is not recommended in patients with no history of cardiovascular disease and a risk of coronary events  $\leq$  15% in the succeeding 10 years. Many patients with type 2 diabetes and dyslipidaemia will not receive treatment according to these criteria. However, this patient profile (CHD risk > 30% over 10 years, secondary prevention) matches that of the hypothetical patient population used in the present analysis.

In terms of circumstances in which a fibrate would be therapy of choice the NICE guidelines for the UK appear to be more restrictive than those from the ADA. Although the NICE guidelines do not explicitly consider the cost-effectiveness of lipid interventions, this appears to have been at least indirectly considered as part of the outcomes assessment process that led to the formulation of the recommendations made on treatment practice. The preliminary recommendations and comments from the UK panel also indicate that the panel believes that further evidence is needed to obtain consensus on the role of HDL-c and the position of fibrates as therapy for primary and secondary prevention.

### Conclusions

Cost-effectiveness is an increasingly important consideration in healthcare management. The overall cost for diabetes management to the NHS in the UK was estimated to be £5.2 billion in 2000,<sup>27</sup> with CHD the leading cause of death in patients with diabetes running at £553 million per year.<sup>28</sup> At least one third of all



## Key messages

- Few studies have reported pharmaco-economic assessments of fibrate therapy in diabetes
- Cost-effectiveness models for 'cost per CHD event avoided' were derived from data on CHD events in diabetes (fibrate and statin) trials, and drug and clinical event costs
- Economic costings were used for a commonly prescribed fibrate (fenofibrate)
- Fibrate, compared to statin, therapy was substantially more cost-effective in patients with diabetes
- Future CHD guidelines should incorporate fibrate and statin pharmaco-economic data

patients with diabetes would require lipid-lowering therapy using current national guidelines. However there is a shortfall of prescribing with recent data indicating that over 90% of those patients requiring treatment are not receiving appropriate lipid-lowering medications.<sup>29</sup> The current cost-effectiveness model presented is one of the first to evaluate the role of several years of fibrate therapy, and to consider the potential implications for cost-effective management based on UK costings. The analysis highlights the important cost-effectiveness of fenofibrate therapy. The available data suggest a role for fibrate therapy in cost-effective prevention of CHD in people with diabetes and highlights the importance of pharmacoeconomic data for inclusion in management guidelines of lipid-lowering therapy.

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