Cost-effectiveness of gemfibrozil for coronary heart disease patients with low levels of high-density lipoprotein cholesterol

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of gemfibrozil (GEM) (1,200 or 600 mg/day) for the prevention of coronary heart disease (CHD) in men with low levels of both high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised men younger than 74 years, with a history of CHD, and HDL-C level of 40 mg/dL (1.03 mmol/L) or less, and a LDL-C level of 140 mg/dL (3.6 mmol/L) or less. Patients with long-term stable conditions, such as diabetes and hypertension, were included. However, those with clinically evident chronic heart failure, or with other major medical problems likely to result in mortality within 5 years, were excluded.

Setting
The setting was the community. The economic study was carried out at 20 VA medical centres throughout the USA.

Dates to which data relate
The effectiveness data were gathered from September 1991 through July 1998. No dates for the resource use data were reported. The price year was 1998.

Source of effectiveness data
The effectiveness evidence came from a single published study (see Other Publications of Related Interest). Several assumptions on effectiveness were also made and used in the decision model.

Link between effectiveness and cost data
The costing was performed retrospectively on a different sample of patients from that used in the effectiveness study.

Study sample
Power calculations suggested that, at a type I error rate of 0.05, the study would require 2,500 patients to detect a 20% reduction in the primary outcome with 90% power. However, the study was underpowered (20% power to detect a 10% reduction in total mortality with a type I error rate of 0.05). The method used to select the sample was unclear. Over the study period, 2,531 patients were enrolled. In the GEM group, 1,264 patients with a mean age of 64 (+/- 7) years (77%
older than 60 years) were included. Of these, 25% had diabetes and 57% hypertension. In the placebo group, 1,267 patients with a mean age of 64 (+/- 7) years (76% older than 60 years) were included. Of these, 24% had diabetes and 57% hypertension.

study design
This was a randomised controlled trial, which was carried out in 20 VA medical centres. Patients were allocated randomly to the study groups using a permuted-block design, with stratification according to centre. The average follow-up period was 5.1 years (range: 0 - 6.9 years). The follow-up visits took place one month after randomisation, and then every 3 months until the end of the study. Sixty patients were lost to follow-up and assessment was uncertain in three patients. The study was double-blinded since both the patients and local study personnel were blinded to treatment assignment.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. Several clinical outcomes were evaluated in the analysis, but the primary outcome (which was used in the present economic evaluation) was the combined incidence of nonfatal myocardial infarction (MI) or death from CHD. A secondary outcome was represented by the combined outcome of death from CHD, nonfatal MI or confirmed stroke. The study groups were comparable at baseline with respect to their demographic and clinical factors.

Effectiveness results
Overall, 275 patients (21.7%) in the placebo group and 219 patients (17.3%) in the GEM group had a primary event (nonfatal MI or death from CHD). Thus, GEM was associated with a 22% (95% confidence interval, CI: 7 - 35; p=0.006) relative reduction in the rate of death from CHD or nonfatal MI.

The authors reported that the beneficial effect of GEM appeared about 2 years after randomisation.

When considering the combined outcome of death from CHD, nonfatal MI or confirmed stroke, the relative reduction with GEM over placebo was 24% (95% CI: 11 - 36; p<0.001).

The authors reported that GEM was well tolerated and that no major adverse event was observed during the study period.

Clinical conclusions
The effectiveness analysis showed that GEM was significantly effective in reducing the risk of death from CHD, nonfatal MI or confirmed stroke among patients with CHD and low HDL-C levels, but without high-risk LDL-C levels.

Modelling
A Markov model was used to estimate the costs and benefits of GEM, compared with placebo, in a cohort of patients until the age of 110 years. The patients had the same characteristics as those in the effectiveness study. The treatment was administered for 5 years.

Methods used to derive estimates of effectiveness
The authors made a number of assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
The authors assumed that patients experiencing a nonfatal event would remain in a temporary state during the subsequent year, during which the risk of death increased, and would then enter a period of chronic disease. They also assumed that after 5 years of treatment, GEM was stopped and the risk of cardiovascular disease in treatment patients...
would revert to the level found in the control group. In addition, the reduction in risk applied only to the first event (conservative assumption). Further assumptions were made in relation to the annual risks of a CHD patient dying from a non-CHD-related cause, a CHD patient experiencing a cardiovascular event, a patient dying in the first year after a nonfatal event, and a patient dying in the chronic state. These values were not reported. On the basis of a published study, the authors assumed that the quality value required for the calculation of quality-adjusted survival of CHD patients was 1 or 0.88.

**Measure of benefits used in the economic analysis**

The benefit measures used in the economic analysis were the life-years saved and the quality-adjusted life years (QALYs). Survival was calculated using hazard functions that were derived from trial data and used as inputs in the decision model. The utility weights required to calculate the QALYs were based on the authors' assumptions. No discounting was applied in the base-case.

**Direct costs**

No discounting was applied in the base-case, but several discount rates were tested in the sensitivity analyses. The unit costs were not reported separately from the quantities of resources used. The costs of health services included in the economic evaluation were annual drug provision, one yearly additional fasting lipid profile, and hospital expenses related to the treatment of fatal and nonfatal cardiovascular events. The cost/resource boundary adopted in the study was that of a health care organisation, such as the VA. The costs were estimated on the basis of VA tariffs and Medicare reimbursement rates. Wholesale prices were also used to estimate drug costs as an alternative (more expensive) source of data. The source of the resource use data was not reported. The price year was 1998.

**Statistical analysis of costs**

The costs were treated deterministically in the base-case.

**Indirect Costs**

The indirect costs were not included in the economic evaluation.

**Currency**

US dollars ($).

**Sensitivity analysis**

Sensitivity analyses were conducted to evaluate the robustness of the estimated cost-effectiveness ratios to variations in some model inputs, such as discount rate (0, 4 and 5%), utility weights used in the cost-utility analysis (1.0 and 0.88), and drug costs (those contracted by VA and wholesale prices). The type of analysis appears to have been univariate. The analysis was also replicated using lognormal and Weibull hazard functions in place of those used in the base-case.

**Estimated benefits used in the economic analysis**

The undiscounted life expectancy was 23.15 years in the treatment (t) group and 22.55 years in the control group (c) for a 55-year-old patient. These values were 18.07(t) and 17.45(c) years, respectively, for a 65-year-old patient, and 13.98(t) and 13.36(c) years for a 75-year-old patient.

The undiscounted QALYs were 20.37(t) and 19.84(c) years for a 55-year-old patient, 15.90(t) and 15.35(c) years for a 65-year-old patient, and 12.30(t) and 11.76(c) years for a 75-year-old patient when a utility weight of 0.88 was used. The corresponding values when using a utility weight of 1.0 were 23.15(t) and 22.55(c) years for a 55-year-old patient, 18.07(t) and 17.45(c) years for a 65-year-old patient, and 13.98(t) and 13.36(c) years for a 75-year-old patient.

In any scenario tested in the sensitivity analyses, the values of survival and QALYs were higher in the treatment group.
than in the control group.

Cost results
The lifetime undiscounted costs were $13,259(t) and $13,464(c) for a 55-year-old patient, $10,300(t) and $10,462(c) for a 65-year-old patient, and $8,232(t) and $8,284(c) for a 75-year-old patient when VA prices were used. The corresponding costs when wholesale prices were used were $17,428(t) and $13,464(c) for a 55-year-old patient, $14,431(t) and $10,462(c) for a 65-year-old patient, and $12,193(t) and $8,284(c) for a 75-year-old patient.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios were calculated to combine the costs and benefits (both life-years and QALYs).

When VA prices were used, GEM always dominated placebo as it was associated with lower costs and higher effectiveness in terms of both survival and QALYs.

When wholesale prices were used, the cost per life-year saved was $6,607 for a 55-year-old patient, $6,403 for a 65-year-old patient, and $6,305 for a 75-year-old patient with no discounting. The values were, respectively, $11,246 (55-year-old), $9,707 (65-year-old) and $8,849 (75-year-old) with a 3% discount rate, and $15,574 (55-year-old), $12,656 (65-year-old) and $10,539 (75-year-old) with a 5% discount rate.

When wholesale prices were used, the cost per QALY (0.88) was $7,480 for a 55-year-old patient, $7,217 for a 65-year-old patient, and $7,239 for a 75-year-old patient with no discounting. The values were, respectively, $12,797 (55-year-old), $10,849 (65-year-old) and $9,806 (75-year-old) with a 3% discount rate, and $17,058 (55-year-old), $13,629 (65-year-old) and $11,993 (75-year-old) with a 5% discount rate.

A break-even analysis showed that, if the costs of GEM were below $100, then the treatment was cost-saving. The use of lognormal and Weibull hazard functions affected the estimated incremental cost-effectiveness ratios.

Authors’ conclusions
Treatment with gemfibrozil (GEM) dominated placebo when low drug prices negotiated by large health plans, such as VA, were used. The cost-effectiveness ratio of GEM over placebo ranged from $6,305 to $17,075 when wholesale prices were used. Thus, GEM should be used for the secondary prevention of coronary heart disease (CHD) in men with low levels of both high- and low-density lipoprotein cholesterol (HDL-C and LDL-C, respectively).

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. Placebo was selected because the aim of the study was to evaluate the active value of GEM in the study patients. The authors stated that there is no useful alternative strategy for patients with low levels of both HDL-C and LDL-C. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used a double-blind, multicentre, randomised trial, which was appropriate for the study question. The method of randomisation was stratified by centre. Power calculations were conducted in the preliminary phase of the study. The loss to follow-up was low and all the analyses were conducted on an intention to treat basis. The study groups were comparable at baseline. These issues increase the internal validity of the analysis. The authors made some conservative assumptions used in the decision model. The authors acknowledged that the follow-up carried out in the trial was quite intense, and thus may not have reflected real practice.

Validity of estimate of measure of benefit
Survival and QALYs were used in the economic analysis to estimate the benefits of the GEM treatment. These were
calculated using both trial data and assumptions. The use of (quality-adjusted) survival permits the benefits of the study intervention to be compared with those of other treatments funded in the health care system.

Validity of estimate of costs
The perspective adopted in the study was explicitly reported, and it appears that all the direct costs relevant to that perspective have been included in the analysis. The authors noted that the adoption of a societal perspective, and the inclusion of indirect costs, would have further improved the cost-effectiveness of GEM in comparison with placebo. Discounting was relevant and three different discount rates were applied. The costs were treated deterministically in the base-case, but two different price sources were used. Details on resource use were not reported. The price year was given, thus making reflation exercises in other settings feasible. A break-even analysis was also conducted.

Other issues
The authors stated that their study represented the first economic evaluation based on trial data, which assessed the costs and benefits of a strategy consisting of raising HDL-C levels and lowering triglyceride levels in a setting where LDL-C levels were not lowered. Thus, they compared their findings with those from studies evaluating other cholesterol treatments. The authors noted that the study conclusions should not be extrapolated to different patient populations and caution is required when interpreting the study results.

Implications of the study
The main study implication was that GEM should be adopted for the secondary prevention of CHD in patients with low levels of HDL-C. The administration of GEM to all patients enrolled in VA would lead to undiscounted cost-savings of about $19 million. Such savings could be realised by other health care organisation with sufficient market power to contract low drug prices.

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Other publications of related interest

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