A cost-effectiveness analysis of bisoprolol for heart failure
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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 bisoprolol, a beta-blocker, for the treatment of chronic heart failure (CHF). The initial drug dose was 1.25 mg. This was increased to 2.50, 3.75, 5.00, 7.50 and 10.00 mg according to patient tolerance.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised ambulatory patients, aged 18 to 80 years with a left-ventricular ejection fraction of 35% or less. The patients were categorised as class III or IV according to the New York Heart Association (NYHA). Patients were excluded if they had uncontrolled hypertension, myocardial infarction or unstable angina pectoris in the preceding 3 months, percutaneous transluminal coronary angioplasty or coronary-artery bypass graft in the preceding 6 months, or prior or scheduled heart transplant. They were also excluded if they had atrioventricular block greater than first degree without a chronically implanted pacemaker, a resting heart rate of less than 60 beats/minute and a systolic blood pressure at rest of less than 100 mmHg. Other criteria for exclusion were renal failure (serum creatinine greater than 300 mmol/L), reversible obstructive lung disease, or pre-existing or planned therapy with beta-adrenoreceptor blockers.

Setting
The setting appears to have been secondary care (hospital outpatient clinic). The economic study was carried out in the UK.

Dates to which data relate
No dates for the effectiveness and resource use data were reported. The price year was 2000.

Source of effectiveness data
The effectiveness evidence came from a single study (the CIBIS-II trial), whose results had been published in a separate paper (see Other Publications of Related Interest).

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

Study sample
Preliminary power calculations were conducted. From these, it was estimated that the required sample size had to include 2,500 patients to have a 5% significance level and a power of 95% to detect a minimum of 25% lower mortality in the bisoprolol group. The method of sample selection was not reported. An overall sample of 2,647 patients was enrolled in the study. There were 1,327 patients in the bisoprolol group and 1,320 patients in the placebo group. The mean age in the bisoprolol group was 61 years (range: 22 - 80), 80% of the patients were men, and 83% were NYHA class III. The mean age in the placebo group was 61 years (range: 26 - 80), 81% of the patients were men, and 83% were NYHA class III.

Study design
This was a randomised, double-blind placebo-controlled trial, which was carried out in 274 hospitals in 18 European countries. Randomisation was carried out by a computerised sequence of random numbers generated by an independent statistical centre. The mean follow-up was 1.3 years. Five patients in the bisoprolol group and one patient in the placebo group were lost to follow-up. Details on the method of blinding were not reported.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The primary end point used in the analysis was all-cause mortality, which was also the primary end point used in the present study. Hazard ratios and 95% confidence intervals (CIs) were calculated using Cox’s proportional hazards regression model. Secondary end points (e.g. hospital admissions, all cardiovascular deaths and treatment withdrawals) were also evaluated, but were not relevant in the present economic evaluation. At baseline, the study groups were comparable in terms of their demographics, clinical conditions and use of concomitant medications.

Effectiveness results
The rate of all-cause mortality was 12% (156 patients) in the bisoprolol group and 17% (228 patients) in the placebo group.

The hazard ratio was 0.66 (95% CI: 0.54 - 0.81, p<0.0001).

Clinical conclusions
The effectiveness analysis showed that bisoprolol, as an adjunct to standard treatment, was effective in improving survival among patients with CHF in comparison with placebo.

Measure of benefits used in the economic analysis
Survival, and hence life-years gained (LYG), was the summary benefit measure in the economic analysis. It was discounted as future years of life were calculated. The LYG was estimated under both the limited and the extended benefits scenarios.

Direct costs
Discounting was performed since the time horizon of the study was 5 years. A 6% rate was used on the basis of recommendations by the UK treasury. The unit costs were not reported separately from the quantities of resources used. The health services included in the economic analysis were drugs, hospitalisation and therapy initiation (including blood tests). The cost/resource boundary adopted in the study was that of the UK NHS. The costs of therapy initiation were also included in the analysis due to the intensive titration period observed in the trial. Resource use was evaluated mostly alongside the clinical trial (CIBIS II). The drug costs were derived from the acquisition prices reported in the British National Formulary at September 2000. The hospitalisation costs were calculated using data from the Department of Health. The personnel costs were based on Personal Social Services Research Unit data from the University of Kent. The blood test costs were estimated from the Southern Regional Trusts. All of the costs were inflated to 2000 values (price year) using inflationary factors available from official sources, such as the NHS Department of Health.
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
UK pounds sterling ( ).

Sensitivity analysis
Standard sensitivity analyses were conducted to evaluate the robustness of the estimated cost-effectiveness ratio of bisoprolol to variations in several variables. These variables included the discount rate, inpatient costs (+/- 20%), change in hospitalisation rate (data from the CIBIS II trial or the author's assumptions) and the drug costs (50% increase).

The author considered different scenarios after identifying the critical variables. The first critical variable considered the assumption required to extend the time horizon of the analysis, due to the fact that the trial data referred to an average follow-up period of 1.3 years. Two scenarios were considered. One was a limited benefits scenario, in which it was assumed that there was no additional benefit from bisoprolol after the end of the trial. Thus, the data were extrapolated on the basis of the average survival advantage observed in the trial. The other was an extended benefits scenario, where the data were extrapolated on the basis of the last survival advantage observed in the trial, assuming that the benefits would extend on after the trial period. The second critical factor was the cost of initiating bisoprolol. The two scenarios were that initiation was either undertaken by a nurse working in the community or by shared care between a general practitioner and hospital outpatient clinic.

Estimated benefits used in the economic analysis
Over the 5-year period, the estimated discounted LYG was 0.228 years under the limited benefits scenario and 0.368 years under the extended benefits scenario.

Cost results
The total costs were not reported.

Synthesis of costs and benefits
A typical cost-effectiveness approach, in which the incremental cost-effectiveness ratio (ICER) was calculated, was used to model the costs and benefits (LYG) of the bisoprolol treatment in comparison with placebo.

Under the extended benefit scenario, the ICER of bisoprolol over placebo was:

- 1,917 with shared care and CIBIS II hospitalisation data,
- 2,043 with community care and CIBIS II hospitalisation data,
- 286 with shared care and assumptions on hospitalisation,
- 412 with community care and assumptions on hospitalisation,
- 199 with shared care and no discount rate,
- 301 with community care and no discount rate,
619 with shared care and 20% decrease in inpatient costs,
745 with community care and 20% decrease in inpatient costs,
47 with shared care and 20% increase in inpatient costs,
78 with community care and 20% increase in inpatient costs,
761 with shared care and 50% increase in drug costs, and
887 with community care and 50% increase in drug costs.

Under the limited benefit scenario, the ICER of bisoprolol over placebo was:
2,557 with shared care and CIBIS II hospitalisation data,
2,761 with community care and CIBIS II hospitalisation data,
cost-saving with shared care and assumptions on hospitalisation,
69 with community care and assumptions on hospitalisation,
cost-saving with shared care and no discount rate,
cost-saving with community care and no discount rate,
502 with shared care and 20% decrease in inpatient costs,
705 with community care and 20% decrease in inpatient costs,
cost-saving with shared care and 20% increase in inpatient costs,
cost-saving with community care and 20% increase in inpatient costs,
583 with shared care and 50% increase in drug costs, and
786 with community care and 50% increase in drug costs.

Assuming that 850,000 patients could receive bisoprolol in the UK, the economic impact for the NHS over 5 years
would be about 8.9 million.

**Authors' conclusions**
The treatment with bisoprolol improved the patients' survival and reduced the rate of hospitalisation in comparison with
placebo. Thus, it represented a cost-effective treatment under different scenarios.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. Placebo was selected, as the aim of the study was to evaluate
the active value of bisoprolol as adjunctive therapy to standard treatments for patients with CHF. The author
acknowledged that other treatments for patients with CHF were available. You should decide whether it represents a
valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis of the effectiveness used a double-blind multi-centre randomised controlled trial, which was appropriate
for the study question. Power calculations were performed in the preliminary phase of the study and the basis of the
effectiveness analysis was intention to treat. The study sample was representative of the study population. The inclusion and exclusion criteria were reported in detail. The length of and loss to follow-up were reported, as was the method of randomisation. These issues enhance the internal validity of the analysis.

Validity of estimate of measure of benefit
The main benefit measure was the LYG. It was appropriately discounted and two assumptions were made when extrapolating the trial data over a longer period of time. The use of survival allows comparisons to be made with the benefits of other interventions funded by the NHS. The author stated that quality of life issues were not raised, as utility data were not collected alongside the clinical trial.

Validity of estimate of costs
The perspective adopted in the study was reported. It appears that all the relevant categories of costs have been included in the economic evaluation. The price year was reported, thus facilitating reflation exercises in other settings. Although the costs were treated deterministically, sensitivity analyses were conducted on the most critical cost and resource use variables. However, the unit costs and the quantities of resources used were not reported separately. The cost estimates were specific to the NHS setting. Discounting was relevant and was performed. The costs were inflated to the price year using reliable tools. The author stated that the data on hospitalisation gathered in the clinical trial were highly aggregated, thus some assumptions were required when it was not possible to disaggregate by cause of admission. To overcome this problem, the author also considered some conservative scenarios. The author provided budget impact data for the NHS for the likely number of patients who could receive bisoprolol. This is very useful information for the decision-maker.

Other issues
The author compared the findings with those from studies evaluating other cardiovascular therapies over 5 years. The issue of the generalisability of the study results to other settings was not addressed. The sensitivity analyses conducted in the study aimed to verify the robustness of the conclusions to uncertainty in the data. Further, the cost estimates were specific to the NHS. Thus, the external validity of the analysis was low. The study referred to patients with CHF and this was reflected in the conclusions of the analysis. The author noted a number of limitations of the analysis, such as the need for data extrapolation and for assumptions in the cost analysis.

Implications of the study
The study suggests that beta-blockers may be a cost-effective option for patients with CHF. However, the labour intensive and time-consuming up-titration process may represent a problem in the adoption of bisoprolol as routine treatment for CHF in UK. The likely budget impact of the intervention is of the order of 8.9 million over 5 years.

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None stated.

Bibliographic details

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Other publications of related interest
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