Resource utilization and costs in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme


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 study examined the addition of candesartan to conventional treatment for patients with heart failure (HF). Candesartan was compared with conventional treatment, which could consist of a combination of a diuretic, digoxin, angiotensin-converting enzyme (ACE)-inhibitor, beta-blocker and spironolactone, as indicated and tolerated. The target dose of candesartan was 32 mg once daily, but lower doses were generally given (mean daily dose of 17.7 mg in the pivotal clinical trial).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with New York Heart Association (NYHA) Class II - IV HF.

Setting
The setting was secondary care. The economic study was carried out in France, Germany and the UK.

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 1999 and 2004. The price year was 2003.

Source of effectiveness data
The clinical data used in the analysis were a composite end point of cardiovascular death and hospital admissions for worsening HF, and all-cause mortality.

Sources searched to identify primary studies
The clinical data came from the CHARM trials, which involved a total of 7,599 patients in 26 countries:

- 1,015 patients received placebo and 1,013 candesartan in the CHARM-Alternative trial;
- 1,272 received placebo and 1,276 candesartan in the CHARM-Added trial; and
- 1,509 patients received placebo and 1,514 candesartan in the CHARM-Preserved trial.
The authors reported the results of each trial and of the whole programme in detail. In addition to the composite values, they provided the percentage of hospital admission by specific causes, the number and type of cardiovascular procedures, and the average length of admission for each group of patients.

Methods used to judge relevance and validity, and for extracting data
The clinical trials were identified selectively in the sense that the current economic evaluation was carried out alongside the CHARM programme. The authors justified the selection of these trials on the grounds that they included a broad spectrum of patients and provided data for a long period of follow-up (median follow-up was 38 months for the overall CHARM programme).

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of life-years (LYs) associated with treatment over no treatment. The LYs were derived directly from the clinical trials. LYs were not calculated for the CHARM-Preserved trial because of the non statistically significant reduction in cardiovascular or all-cause mortality. The benefits were discounted but the discount rate was not explicitly reported. Also, in a cost-consequences analysis, a composite end point of cardiovascular death and hospital admissions for worsening HF was considered but not combined with the costs.

Direct costs
The analysis of the costs was restricted to the perspective of the third-party payer in France and Germany, and the National Health Service in the UK. The categories of costs included were those associated with drug treatment, patients admitted to hospital (proportion admitted, number of admissions per patient, number of hospital days per patient), admissions for cardiovascular reasons (number, duration, ward type), and procedures or operations. The unit costs and the quantities of resources used were presented separately. Resource use was derived prospectively from the samples of patients enrolled in the clinical trials. Hospital costs were estimated using two different approaches. The first analysis used diagnosis-related group (DRG) costs that were obtained from government sources in each country. The second analysis measured per diem (hospital bed-day) costs that were also derived from official sources in each country. The drug costs came from standard tariffs using average wholesale prices, including dispensing fees and costs of physician visits and blood chemistry. The costs for cardiovascular procedures were based on DRG tariffs. Discounting was relevant, as the long-term costs were measured, and an annual rate of 3% was used. The price year was 2003.

Statistical analysis of costs
The costs were treated deterministically, but statistical analyses of the quantities of resources used were performed. These analyses tested the statistical significance of differences between the groups.

Indirect Costs
Productivity costs were not considered.

Currency
Euros (EUR). The exchange rate from US dollars ($) and UK pounds sterling () into euros was EUR 1 = $1.20 = 0.67.

Sensitivity analysis
A deterministic sensitivity analysis was carried out to assess the robustness of the cost-effectiveness ratios under the following scenarios:

the length of non-cardiovascular hospital stay was increased by 30% to model for the potential additional cost of certain adverse effects in the candesartan group;

the costs related to adverse effects not leading to hospital admission were added, namely one extra general practice visit
for each patient requiring dose reduction or treatment discontinuation for an adverse effect or laboratory abnormality; the length of hospital stay in the per diem analysis was varied by +20%; and for the UK only, the costs were discounted by 3.5%.

**Estimated benefits used in the economic analysis**

There was a 12% reduction in cardiovascular death and 21% reduction in HF admissions with candesartan over conventional care in the overall CHARM programme. The corresponding reductions in the individual trials were, respectively, 15% and 32% in the CHARM-Alternative trial, 16% and 17% in the CHARM-Added trial, and 1% and 15% in the CHARM-Preserved trial. With the exception of cardiovascular death in the CHARM-Preserved trial, all differences were statistically significant.

The LYs gained with candesartan over conventional care were 0.078 (95% confidence interval, CI: 0.003 to 0.15) in the CHARM-Alternative trial and 0.061 (95% CI: -0.002 to 0.12) in the CHARM-Added trial.

The pooled estimate of LYs gained for all patients with reduced LVEF was 0.068 (95% CI: 0.02 to 0.12).

**Cost results**

In France, the additional costs of candesartan over placebo ranged from cost-saving in the CHARM-Alternative and CHARM-Added trials to a net increase of EUR 299 (+/- 630) per year in the CHARM-Preserved trial and EUR 73 (+/- 548) per year in the overall CHARM programme.

In Germany, the additional costs of candesartan over placebo were EUR 117 (+/- 1,164) per year in the CHARM-Alternative trial, EUR 29 (+/- 631) per year in the CHARM-Added trial, EUR 327 (+/- 460) per year in the CHARM-Preserved trial, and EUR 176 (+/- 421) per year in the overall CHARM programme.

In the UK, the additional costs of candesartan over placebo ranged from cost-saving in the CHARM-Added trial to a net increase of EUR 76 (+/- 1,150) per year in the CHARM-Preserved trial, EUR 246 (+/- 337) per year in the CHARM-Preserved trial, and EUR 116 (+/- 352) per year in the overall CHARM programme.

These results refer to costs estimated using DRGs. When per diem costs were calculated, candesartan was also cost-saving in France for the overall CHARM programme, in Germany for the CHARM-Added and CHARM-Alternative trials, and in the UK for the CHARM-Alternative trial and overall CHARM programme.

**Synthesis of costs and benefits**

Incremental cost-effectiveness ratios were calculated in order to combine the costs and benefits of the alternative strategies.

The incremental analysis showed that candesartan was dominant (more effective and less expensive) in France in all patient sub-groups.

In Germany, the incremental cost per LY gained with candesartan over conventional treatment was EUR 3,881 (95% CI: -17,728 to 1,105,920) in the CHARM-Alternative trial, EUR 1,427 (95% CI: -14,479 to 984,755) in the CHARM-Added trial, and EUR 2,997 (95% CI: -19,183 to 121,500) in the pooled sample.

In the UK, candesartan was dominant in the CHARM-Added trial, while the incremental cost per LY gained was EUR 2,547 (95% CI: -18,171 to 1,059,150) in the CHARM-Alternative trial and EUR 1,348 (95% CI: -16,225 to 106,600) in the pooled trial.

All these results were calculated using DRG costs.

The results of the sensitivity analysis showed that increasing the length of stay for non-cardiovascular admissions by
30% increased the cost per day in the candesartan group by 15 to 20%, and candesartan was no longer cost-saving in any comparison. The other changes considered in the sensitivity analysis did not alter the conclusions of the base-case analysis.

**Authors’ conclusions**
The addition of candesartan to conventional care for patients with heart failure (HF) was cost-saving in most scenarios considered in France, Germany and the UK. The maximum cost per LY gained in comparison with conventional care reached EUR 3,881. This favourable result was based on the substantial reduction in the proportion of patients admitted with worsening HF.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear in that it reflected the standard of care for all sub-groups of patients with HF. The target dose and real dosage was reported for all sub-groups of patients. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The clinical data came from published clinical trials, which were identified selectively. All clinical trials formed part of a large study that involved 7,599 patients in 26 countries. The patients were also followed up for a relative long period. Thus, the choice of the primary studies appears to have been justified and appropriate. The nature of the trials should ensure the validity of the clinical estimates. Statistical tests were conducted in order to estimate the significance of differences in the clinical results.

**Validity of estimate of measure of benefit**
LYs were an appropriate benefit measure as they are the final end point of treatment for HF. Other disease-specific outcome measures were also used in the cost-consequences analysis. LYs have the further advantage of being comparable with the benefits of other health care interventions. The impact of candesartan on quality of life was not investigated, although an assessment of quality-adjusted life-years would have been helpful in terms of evaluating the impact of side effects on patients.

**Validity of estimate of costs**
The analysis of the costs was consistent with the perspective adopted in the study. Extensive information on the unit costs and quantities of resources used was given, which will enable the analysis to be replicated in other settings. Statistical analyses were performed for some estimates of resources used, and key costs were varied in the sensitivity analysis. Resource use was obtained prospectively. The sources of the costs were reported and reflected national tariffs for all countries. The price year was reported, which enhances the possibility of replicating the cost analysis in other time periods.

**Other issues**
The authors stated that their findings were similar to those from other economic analyses of treatments for HF, although direct comparisons were difficult to make. The issue of the generalisability of the study results to other settings was not explicitly addressed, although three countries were considered in the analysis and these provided relatively similar results. However, an extensive sensitivity analysis was not performed and it could be difficult to transfer the results to countries with a different health care system. The authors noted some limitations of their analysis, such as the short time horizon of the study and the fact that deaths outside of the hospital were not accounted for.

**Implications of the study**
The study results support the use of candesartan added to conventional care for a broad spectrum of patients with HF.
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None stated.

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Other publications of related interest
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McMurray J, Ostergren J, Pfeffer, M et al. Clinical features and contemporary management of patients with low and preserved ejection fracture heart failure: baseline characteristics of patients in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme. Eur J Heart Fail 2003;5:261-70.


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