An economic evaluation of atenolol vs. captopril in patients with type 2 diabetes (UKPDS 54)


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 health interventions under study were two antihypertensive therapies, atenolol (a beta-blocker, daily dose of 50 mg, increasing to 100 mg if required) and captopril (an angiotensin converting enzyme inhibitor (ACE), 25 mg twice daily increasing to 50 mg twice daily), in patients with type-2 diabetes.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study sample comprised patients aged 25-65 years with type-2 diabetes. The main study entry criterion was fasting plasma glucose concentration greater than 6 mmol/l on two mornings. The following exclusion criteria were used: ketonuria greater than 3 mmol/l; a history of myocardial infarction in the previous year; current angina or heart failure; more than one major vascular episode; serum creatinine concentration greater than 175 micromol/l; retinopathy requiring laser treatment; malignant hypertension; an uncorrected endocrine abnormality; an occupation which would preclude insulin treatment (such as heavy goods vehicle driver); a severe concurrent illness likely to limit life or require extensive systemic treatment; or inadequate understanding or unwillingness to enter the study.

Setting
The setting was hospital-based clinic. The economic study was conducted in the UK (England, Scotland, and Northern Ireland).

Dates to which data relate
Patient enrolment took place between 1987 and 1991. However, the period for the collection of effectiveness and resource use data was not reported. The price year was 1997.

Source of effectiveness data
The effectiveness data were derived from a single study, which was published elsewhere (see "Other Publications of Related Interest").

Link between effectiveness and cost data
The costing was conducted prospectively on the sample of patients that were included in the effectiveness study.

Study sample
Power calculations were not reported, but the sample size was large. Of an initial group of 4,297 patients enrolled at the 20 participating centres, 758 cases were selected to reach a tight control of blood pressure (aim lower than 150/85 mm Hg): 400 patients (mean age: 56.3 +/- 8.1 years; 51% men) were given captopril and 358 patients (mean age: 56 +/- 8.2 years; 57% men) received atenolol.

**Study design**
This was a randomised clinical trial, which was conducted in 20 centres within the UK. Randomisation was conducted using sealed opaque envelopes and was stratified by the coordinating centre for those with or without previous treatment for hypertension. Patients were followed for nine years and final data were available for almost all patients. No blind assessment of the outcomes was reported.

**Analysis of effectiveness**
Primary analysis was based on intention to treat. The analysis used twenty-one endpoints: fatal myocardial infarction (MI), non-fatal MI, sudden death, heart failure, angina, fatal stroke, non-fatal stroke, death from peripheral vascular disease, amputation, death from renal failure, renal failure, retinal photocoagulation, vitreous haemorrhage, blindness in one eye, cataract extraction, death from hyperglycaemia, death from hypoglycaemia, fatal accident, death from cancer, death from any other specified cause, and death from unknown cause. Survival function estimates were calculated using the Kaplan-Meier method. The study groups were comparable at baseline with respect to demographics and blood pressure.

**Effectiveness results**
The effectiveness results were not presented in the economic paper and have been taken from the paper reporting on the parent clinical trial. In the captopril (c) and atenolol (a) groups:

- Fatal MIs were 35 (c) and 24 (a) (relative risk (RR) for captopril: 1.31; 99% confidence interval (CI): 0.66 - 2.59; p=0.31);
- Non-fatal MIs were 30 (c) and 21 (a) (RR: 1.30; 99% CI: 0.63 - 2.71; p=0.35);
- Sudden deaths were 8 (c) and 3 (a) (RR: 2.42; 99% CI: 0.42 - 13.82; p=0.18);
- Heart failures were 12 (c) and 9 (a) (RR: 1.21; 99% CI: 0.39 - 3.78; p=0.66);
- Episodes of angina were 20 (c) and 25 (a) (RR: 0.72; 99% CI: 0.33 - 1.56; p=0.27);
- Episodes of fatal stroke were 4 (c) and 5 (a) (RR: 0.72; 99% CI: 0.13 - 4.04; p=0.62);
- Non-fatal strokes were 17 (c) and 12 (a) (RR: 1.28; 99% CI: 0.49 - 3.38; p=0.51);
- Deaths from peripheral vascular disease were 1 (c) and 0 (a);
- Amputations were 5 (c) and 3 (a) (RR: 1.48; 99% CI: 0.23 - 9.71; p=0.59);
- Deaths from renal failure were 0 (c) and 2 (a);
- Cases of renal failure were 4 (c) and 4 (a) (RR: 0.91; 99% CI: 0.15 - 5.64; p=0.59);
- Episodes of retinal photocoagulation were 37 (c) and 24 (a) (RR: 1.40; 99% CI: 0.71 - 2.74; p=0.20);
- Vitreous haemorrhages were 2 (c) and 1 (a) (RR: 1.83; 99% CI: 0.08 - 42.98; p=0.62);
- Cases of blindness in one eye were 10 (c) and 8 (a) (RR: 1.12; 99% CI: 0.33 - 3.79; p=0.82);
cataract extractions were 19 (c) and 17 (a) (RR: 1.01; 99% CI: 0.43 - 2.39; p=0.98);  

deads from hyperglycaemia and from hypoglycaemia were 0 in both groups;  
  
fatal accidents were 1 (c) and 0 (a);  
  
deaths from cancer were 11 (c) and 18 (a) (RR: 0.55; 99% CI: 0.21 - 1.48; p=0.12);  
  
deaths from any other specified cause were 13 (c) and 5 (a)(RR: 2.33; 99% CI: 0.60 - 9.02; p=0.099); and  
  
deaths from unknown cause were 2 (c) and 2 (a) (RR: 0.89; 99% CI: 0.07 - 11.73; p=0.91).  

Clinical conclusions  
Captopril and atenolol were equally effective in reducing hypertension in type-2 diabetic patients.  

Modelling  
A modelling approach was used to estimate the difference in life expectancy between patients allocated to the two study drugs on the basis of the assumption that the two groups had similar hazard rates beyond the trial period. The effectiveness data on the occurrence of clinical endpoints were used as model inputs. Details of the model were published in a separate article (see "Other Publications of Related Interest"). The authors stated that a non-parametric bootstrap process was used to deal with the issue of uncertainty: captopril and atenolol patients were sampled with replacement from the study population.  

Measure of benefits used in the economic analysis  
The summary benefit measure was life expectancy (LE) associated with captopril or atenolol. LE was calculated from the analytic model. In the base case, a discount rate of 6% was applied.  

Direct costs  
An annual discount rate of 6% was used as costs were incurred over a period of time greater than two years. Unit costs were reported separately from quantities of resources used. The categories of costs considered in the cost analysis were captopril, atenolol, other drugs, hospital-based clinic visits, hospital stay (in general surgery, ophthalmology, ENT, or cardiothoracic surgery), haemodialysis, retinal photocoagulation, outpatient attendances, general practitioner (GP), diabetes specialist nurse, practice nurse, and several diagnostic tests. The cost/resource boundary was that of the health care purchaser. Resource use was estimated alongside the clinical trial through the use of questionnaires and hospital charts. Unit costs were based on United Kingdom Prospective Diabetes Study centres data, British National Formulary, Department of Health, the Diabetes Control and Complications Trial Research Group, and Personal Social Services Research Unit. The price year was 1997.  

Statistical analysis of costs  
Estimated costs were reported as average values and standard deviations. Mean differences were reported with 95% CIs. The authors stated that, in 19% of the admissions, length of stay was not recorded and multiple imputation methods were used to replace the missing data.  

Indirect Costs  
Indirect costs were not included.  

Currency  
UK pounds sterling (£).
Sensitivity analysis
The issue of uncertainty was investigated by conducting sensitivity analyses on three model inputs: the cost of providing care in a standard practice setting; variations in the cost of captopril, and modelling of non-hospital costs.

Estimated benefits used in the economic analysis
The estimated discounted LE was 10.5 years (95% CI: 9.9 - 11 years) with captopril and 10.6 years (95% CI: 10.1 - 11.2 years) with atenolol. Thus the same LE was gained with both study treatments.

Cost results
The discounted total costs of therapy per patient were 6,485 +/- 6,107 with captopril and 5,550 +/- 4,292 with atenolol. The use of atenolol resulted in cost-savings of 935 (95% CI: 188 - 1,682).

The sensitivity analysis showed that the inclusion of an additional annual GP visit reduced the cost-savings of atenolol to 854 (95% CI: 108 - 1,601), while a significant difference in mean costs was maintained until the price of captopril was reduced by 50%.

Variations in non-hospital costs had no impact on the estimated costs of treatment.

Synthesis of costs and benefits
Costs and benefits were not combined because a cost-minimisation analysis was conducted due to the fact that there was no statistically significant difference between captopril and atenolol with respect to LE.

Authors' conclusions
The authors concluded that their analysis showed no difference in effectiveness between captopril and atenolol. However, costs of treatment were significantly lower for atenolol patients, due to lower drug costs and fewer hospitalisation episodes (with lower length of stay) in comparison with captopril patients.

CRD COMMENTARY - Selection of comparators
The authors did not provide any specific justification for the choice of the comparators, which were selected on the basis of the interventions evaluated in the previous randomised trial. You should decide whether they represent valid comparators in your own setting.

Validity of estimate of measure of effectiveness
A randomised, multicentre trial was conducted to estimate the effectiveness evidence and this was appropriate for the study question. Most of the details of the analysis were reported in separate papers. The methods of sample selection and randomisation were described. Study groups were balanced at baseline. The sample size was quite large, but power calculations were not reported. Statistical tests were conducted to estimate the effectiveness endpoints and to evaluate the potential impact of confounding factors. The internal validity of the original trial is likely to be high.

Validity of estimate of measure of benefit
The summary benefit measure was LE, which was appropriate to assess the impact of the study intervention on patient's health. The LE was modelled using effectiveness outcomes as model inputs, full details of the model were not reported and as such it is difficult to assess. Appropriate discounting was conducted and analysis using different discount rates was conducted. The measure chosen is comparable with the benefits of other health care interventions.

Validity of estimate of costs
The authors reported the perspective adopted in the study and all relevant categories of costs were included in the
analysis. A breakdown of costs was provided. Unit costs and quantities of resources used were analysed separately and the price year was reported. These facts aid reproducibility in other settings. Different discount rates were applied to total costs. The source of cost data was reported for each cost item. Statistical tests were conducted to calculate confidence intervals and sensitivity analyses were performed to assess the impact of variations of costs and resources used. Overall the economic analysis appears to have been conducted satisfactorily.

**Other issues**
The authors compared their findings with those from other studies that reported direct comparisons between ACE inhibitors and beta-blockers, although it was stated that such comparisons were sparse. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were carried out only for some items.

**Implications of the study**
The authors suggest that atenolol is more efficient than captopril in type-2 diabetes patients requiring hypertension control, despite a similar clinical and safety profile.

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**Other publications of related interest**


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