Screening for the alpha-adducin Gly460Trp variant in hypertensive patients: a cost-effectiveness analysis

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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 study compared screening for the alpha-adducin gene variant in hypertensive patients with no screening (standard care). In the study, if patients in the screening group tested positive for the alpha-adducin variant, a portion of those patients had a diuretic added to their therapy.

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of hypertensive patients not receiving diuretics. In the base-case, the cohort consisted of 65-year-old Caucasian men and women being treated for hypertension. The risk factors in this cohort were proportion of alpha-adducin variants (37%), average systolic blood pressure (141.1 mmHg), cholesterol level (227.9 mg/dl), proportion of diabetic patients (16%) and proportion of patients who were smokers (11%).

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1991 and 2002. The price year was 2004.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies. The results of the review were supplemented with authors' assumptions.

Modelling
A Markov model was added to a decision tree to compare the screening and no screening strategies. The Markov model consisted of six health states corresponding to a treated hypertension patient with no cardiovascular events, MI, post-MI, stroke, post-stroke and death. Patients moved between health states in yearly cycles according to defined transitions. The transition probabilities varied, depending on whether the patient was non variant, alpha-adducin variant without diuretic, or alpha-adducin variant with diuretic.

Outcomes assessed in the review
The clinical parameters included in the model were:

- The probabilities of stroke-attributable mortality, MI-attributable mortality, switching after screening and genotype frequency of the alpha-adducin variant;
- The odds ratios of MI and stroke (non variant patients compared with those on diuretics, variant patients on diuretics compared with those not taking diuretics, and variant patients on diuretics compared with those on diuretics); and
- The utility of the health states, specifically, hypertension treatment with diuretic, stroke and MI during the first year, and stroke and MI after the first year.

**Study designs and other criteria for inclusion in the review**
Not applicable.

**Sources searched to identify primary studies**
Not applicable.

**Criteria used to ensure the validity of primary studies**
Not applicable.

**Methods used to judge relevance and validity, and for extracting data**
Not applicable.

**Number of primary studies included**
Approximately 9 studies were included in the review.

**Methods of combining primary studies**
Not applicable.

**Investigation of differences between primary studies**
Single studies were identified for each parameter.

**Results of the review**
The probability of stroke-attributable mortality was 0.24.

The probability of MI-attributable mortality was 0.35.

The probability of switching after screening was 0.7.

The probability of genotype frequency of the alpha-adducin variant was 0.37.

The odds ratios of MI and stroke, respectively, were:

- For non variant patients compared with those on diuretics, 1 and 1;
- For variant patients on diuretics compared with those not taking diuretics, 1.53 and 1.62; and
- For variant patients on diuretics compared with those on diuretics, 0.66 and 1.
Methods used to derive estimates of effectiveness
The authors made several key assumptions in their analysis.

Estimates of effectiveness and key assumptions
The authors’ main assumptions were:

- 70% of patients screening positive for the alpha-adducin variant had a diuretic added to their therapy;
- the addition of a diuretic to antihypertensive therapy for patients with the non variant alpha-adducin received no additional benefit;
- the medical side effects from diuretics were negligible;
- there were no negative consequences for patients screening negative for the variant;
- no patient would be switched from their current antihypertensive medication to a diuretic, but instead a diuretic would be added to current therapy; and
- all other hypertensive medications were identical between alpha-adducin variant and non variant patients.

Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs). The utilities were derived from the literature and were all based on time trade-off methods.

Direct costs
The direct costs to the third-party payer were included in the analysis. These were the costs of alpha-adducin screening, diuretics, and stroke and MI during the first and subsequent years. All costs, except for the cost of alpha-adducin screening, were obtained from the literature. The costs of alpha-adducin screening were based on currently available direct to consumer single nucleotide polymorphism DNA test costs. As costs could be incurred in the future, future costs were discounted at a rate of 3%. The study reported the average costs. All costs were updated to 2004 prices using the Consumer Price Index for medical care.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
The authors conducted a variety of one-way sensitivity analyses to evaluate the effect of uncertainty in the model parameters. Each parameter in the model was varied over a specified range (e.g. 95% confidence intervals, ranges published in the literature, or +/- 25% of the base-case estimate).

Probabilistic sensitivity analyses were also performed to evaluate the effect of overall parameter uncertainty in the model. A probability distribution for each parameter was specified. In general, the authors used logistic normal
distributions for odds ratios, triangular distributions for utilities and probabilities, and normal distributions for costs. The authors also performed a series of scenario analyses.

**Estimated benefits used in the economic analysis**
The number of (discounted) QALYs gained was 14.19 (95% confidence interval, CI: 11.8 to 17.9) for the strategy of screening to add diuretic, and 14.05 (95% CI: 11.7 to 17.7) for no screening and no diuretic.

Consequently, the difference in QALYs gained when the no screening strategy was compared with the screening strategy was -0.14 (95% CI: -0.36 to -0.05).

**Cost results**
The discounted costs were $17,311 (95% CI: 12,332 to 24,154) for the strategy of screening to add diuretic, and $19,145 (95% CI: 13,663 to 27,938) for no screening and no diuretic.

Compared with no screening, screening resulted in savings per patient of $1,834 (95% CI: 505 to 5,174).

**Synthesis of costs and benefits**
The costs and benefits were not combined as the screening strategy was found to be both more effective (i.e. more QALYs gained) and less costly than the no screening strategy. The results from the one-way sensitivity analysis showed that the most influential parameters were:

- the effect of the alpha-adducin gene variant on diuretics and not on diuretics with regard to stroke;
- the effect of the alpha-adducin gene variant on diuretics and not on diuretics with regard to MI;
- the probability that a diuretic would be added to the patient’s hypertensive medication regimen;
- the proportion of patients with the variant; and
- the discount rate.

**Authors’ conclusions**
Screening for the alpha-adducin gene variant may be a useful mechanism to identify those patients most likely to benefit from diuretic therapy and to improve compliance with current treatment guidelines.

**CRD COMMENTARY - Selection of comparators**
A justification was given for using no screening as the comparator. It represented current practice in the authors’ settings. You should decide if the comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The clinical data were taken from published studies. However, the authors did not report that a systematic review of the literature was undertaken to identify all relevant research and minimise biases. It was unclear if the best evidence was used. The authors supplemented the results from the review with their own assumptions, which they reported and justified explicitly and in detail. Further, exhaustive sensitivity analyses were undertaken to evaluate uncertainty in the results.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled using a Markov model, which was appropriate for the study question. As benefits could be incurred over the lifetime of the patient, all future benefits were appropriately discounted.
Validity of estimate of costs
All the categories of cost relevant to the third-party payer perspective adopted were included in the analysis. No major costs appear to have been omitted. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The unit costs were derived from published sources. An exhaustive sensitivity analysis was undertaken to evaluate uncertainty in the results. Since costs could be incurred over the lifetime of the patients, future costs were appropriately discounted. The price year was reported, which will aid any future inflation exercises.

Other issues
The authors reported that other academic detailing strategies for improving antihypertensive adherence were also found to be cost-saving. The issue of generalisability to other settings was partly addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported a number of further limitations to their study. First, they had to make numerous assumptions in their model, which always tended to be conservative. Second, there was uncertainty in several model parameters. Finally, several of the estimates used for some model parameters were based on single trials or simplified assumptions.

Implications of the study
The authors reported that further studies are needed to confirm the relationship between alpha-adducin variants, diuretics and cardiovascular outcomes.

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None stated.

Bibliographic details

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16424826

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Calmodulin-Binding Proteins /genetics; Cohort Studies; Cost-Benefit Analysis; Diuretics /pharmacology; Female; Genetic Testing /economics /methods; Genetic Variation; Humans; Hypertension /genetics; Male; Markov Chains; Mass Screening /methods; Odds Ratio; Pharmacogenetics /methods; Quality-Adjusted Life Years; Sensitivity and Specificity; Treatment Outcome

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