Cost-effectiveness of pharmacogenetic testing to predict treatment response to angiotensin-converting enzyme inhibitor

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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 authors compared pharmacogenetic testing for the I/D polymorphism to predict treatment response before starting angiotensin-converting enzyme (ACE) inhibitor therapy against a conventional strategy of non-selective treatment of patients with nephropathies. In the group assigned to the pharmacogenetic testing, DD and DI carriers were subsequently treated with ACE inhibitors, while II carriers were assigned to angiotensin-II receptor blockers (ARBs).

Type of intervention
Diagnosis and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with non-diabetic nephropathy and severe persistent proteinuria (>3.0 g/day), whose outcomes in a previous trial were used to inform the current study.

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

Dates to which data relate

Source of effectiveness data
The following data were gathered for use in the decision model and Markov model:

genotype prevalence;

the risk of coughing, angioedema, death from angioedema, and acute renal failure;

the annual probability of ESRD for II and ACE inhibitor treatment, for DD/DI and ACE inhibitor treatment, for all genotypes with ACE inhibitor treatment, for all genotypes with ARB, and for all genotypes without treatment; and

the annual mortality rate for all patients with ESRD.

Modelling
Decision analysis and Markov models were used to estimate cost-effectiveness, combining cost and effectiveness outcomes. The initial decision model took into account testing and associated outcomes, ACE or ARB treatment and associated side effect, and final outcomes over a 3-month period. Then, the outcomes of the short-term decision tree analysis were used as direct input for the Markov model, which considered a 3-year horizon. The Markov model considered the health states of no end-stage renal disease (ESRD), ESRD and death, and explored the annual transition probabilities of moving between these states. A half cycle correction was used for the mortality rate to allow for events that may have occurred mid cycle within the Markov model.

**Sources searched to identify primary studies**
Data were collected from published systematic reviews, where possible, and official reports. Probabilities for the decision analysis were obtained from a literature search that included controlled studies. Some outcome estimates were based on authors’ assumptions.

**Methods used to judge relevance and validity, and for extracting data**
Details of the literature search were not reported. However, the authors did note the bibliographic details of the systematic review that informed some of their data.

**Measure of benefits used in the economic analysis**
The summary measures of health benefit were ESRD-free life-years and years of chronic dialysis avoided. The health benefits were discounted by 4%.

**Direct costs**
The costing was carried out from the perspective of the health care payer. It focused on the direct medical costs associated with the length of time that the cohort of individuals spent within any health state defined by the Markov model. The average costs of dialysis comprised dialysis procedures, medical services, erythropoietin usage, treatment of complications induced by dialysis, treatment of co-morbidity, and transportation. The costs of chronic dialysis were derived from a cost-effectiveness analysis of the data of the REIN (Ramipril Efficacy in Nephropathy) trial. Genotyping and related costs were derived from national sources. The costs of ACE inhibitor or ARB treatment were derived by detailed cost calculation for Switzerland and the Netherlands. A price year of 2005 was used and the costs were discounted by 4%. The costs were adjusted by the German inflation factor of 1.119.

**Statistical analysis of costs**
The authors defined distributions around the cost and effectiveness parameters.

**Indirect Costs**
Productivity costs were not relevant to the perspective adopted.

**Currency**
Euros (EUR).

**Sensitivity analysis**
Probabilistic sensitivity analyses, using 1,000 bootstrap replications, were performed to test the robustness of the results. Cost-effectiveness acceptability curves (CEACs) were also generated.

**Estimated benefits used in the economic analysis**
Over 3 months, life-years without ESRD were 0.25 per patient, both with and without testing. Over 3 years, these were
2.158 per patient with no testing and 2.184 per patient with testing (difference 0.026).

Over 3 years, the number of patients without ESRD was 520 with no testing and 532 with testing (difference 12).

**Cost results**
The costs per patient over 3 months were EUR 60 with no testing and EUR 114 with testing. These costs were EUR 43,905 with no testing and EUR 42,837 with testing over 3 years (difference -EUR 1,068).

**Synthesis of costs and benefits**
The results indicated that pharmacogenetic testing was the dominant strategy.

Using a 0% discount rate and varying cost inputs had no major impact on the results.

The CEAC demonstrated that testing was likely to be cost-effective if the difference in the annual probability of transition to ESRD between genetic sub-groups exceeded 1.4%.

The probability that testing was cost-effective was 81% at a ceiling ratio of zero, rising gradually to 100% at a ceiling ratio of EUR 29,000.

**Authors' conclusions**
“Genetic testing of I/D polymorphism in patients with non-diabetic nephropathies to support treatment management is likely to be beneficial not only from a clinical perspective, but also from a cost-savings point of view.”

**CRD COMMENTARY - Selection of comparators**
The authors compared pharmacogenetic testing with a conventional strategy of no testing and, therefore, non-selective treatment of patients with nephropathy. No testing represented current clinical practice in the authors' setting. Readers must assess whether these are valid comparators within their own setting.

**Validity of estimate of measure of effectiveness**
The parameter inputs to the model were clearly identified, but the methods used to define the review of the literature could have been reported more thoroughly. In particular, it would have been helpful to have had some information relating to which literature was searched, how the authors selected some references in preference to others, and how the data were pooled.

**Validity of estimate of measure of benefit**
ESRD-free life-years and years of chronic dialysis avoided were used as summary measure of health benefits, and were estimated from the models. These measures are disease specific and, whilst they could be compared with other health technologies aimed at reducing ESRD, they could not be used to compare technologies having a broader effect on health.

**Validity of estimate of costs**
The costing was carried out from the perspective of the health care payer. It appears that, for this perspective, all the relevant categories of costs have been included in the analysis. The authors reported that antihypertensive, diuretics and additional drug costs were not valued because they were equal for the two strategies. Therefore, this exclusion was relevant and did not bias the results of the model. Owing to the small actual difference in costs between the comparators, future differences due to changes in clinical practice or the perspective adopted may well influence the overall results and, therefore, the conclusions drawn. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. Since the costs were incurred over a long time, discounting was relevant and was therefore performed. The price year was reported, which will aid any future inflation exercises.
Other issues
The authors were unable to draw comparisons with other studies as they believed this to be the first study to consider testing for ACE genotype before initiating ACE inhibitor therapy. They did, however, acknowledge the results of another study that explored genotype testing before lipid-lowering therapy with statins. The issue of generalisability to other settings was not addressed, although the use of the model and sensitivity analyses improves generalisability. Readers might consider the applicability of the data inputs to their own setting. The results were well presented and easy to understand, although a breakdown of the total cost would have improved the readers' ability to understand the key cost-drivers. The principal limitation of the study was noted as being the remaining uncertainty around the predictive value of the I/D polymorphism for ACE inhibitors-associated renoprotection.

Implications of the study
The authors suggested further work to "corroborate the difference in treatment response between ACE genotypes" and also recommended that this is required before testing can be justified in clinical practice.

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Other publications of related interest
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