Cost-effectiveness of ACE inhibitor therapy to prevent dialysis in nondiabetic nephropathy
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Introduction  End-stage renal disease is associated with high health-care costs and low quality of life compared with chronic kidney disease. The renoprotective effectiveness of angiotensin-converting enzyme inhibitors (ACEi) is largely determined by the ACE insertion/deletion (I/D) polymorphism. We determined the cost-effectiveness of ACEi therapy in nondiabetic nephropathy for the ACE II/ID and for the ACE DD genotype separately. Furthermore, we considered a selective screen-and-treat strategy in which patients are prescribed alternative, more effective, therapy based on their ACE (I/D) polymorphism.

Methods  Time-dependent Markov models were constructed; cohorts of 1000 patients were followed for 10 years. Data were mainly gathered from the Ramipril Efficacy in Nephropathy trial. Both univariate and probabilistic sensitivity analyses were performed.

Results  ACEi therapy dominated placebo in both the ACE II/ID group (€15 826, and 0.091 quality-adjusted life years gained per patient) and the ACE DD group (€105 104 and 0.553 quality-adjusted life years gained). Sensitivity analyses showed 30.2% probability of ACEi being not cost-effective in the ACE II/ID group, against an almost 100% probability of cost-effectiveness in the ACE DD group. A selective screen-and-treat strategy should incorporate an alternative therapy for patients with the ACE II/ID genotype with an at least 9.1% increase in survival time compared with ACEi therapy to be cost-effective.

Conclusion  ACEi therapy is a cost-saving treatment compared with placebo in nondiabetic nephropathy, irrespective of ACE (I/D) genotype. However, ACEi therapy saved more costs and more health gains were achieved in the ACE DD genotype than in the ACE II/ID genotype. An alternative treatment featuring a modest increase in effectiveness compared with ACEi therapy for patients with the ACE II/ID genotype can be incorporated in a cost-effective or even cost-saving screen-and-treat strategy.

Keywords: angiotensin-converting enzyme inhibitors, chronic kidney failure, cost-effectiveness analysis, end-stage renal disease, genetic polymorphism

Reference


as nondiabetic nephropathy [5,6]. However, individual differences in therapy response are large [7]. An important factor influencing ACEi efficacy is a polymorphism located in the ACE gene. This polymorphism was first described by Rigat et al. in 1990 [8] and is based on the presence (insertion, I) or absence (deletion, D) of a 287 base pair element in intron 16 of the ACE gene. A recent review presented an overview of the main studies evaluating the relationship between the ACE genotype and response to ACEi in nondiabetic renal disease [9]. The Ramipril Efficacy In Nephropathy (REIN) trial was the largest trial in terms of patient numbers and duration, and crucially was the only study that has used a hard endpoint, namely ESRD [5]. Patients with the ACE DD genotype showed increased susceptibility for ACEi therapy [10,11]. The finding that the ACE (I/D) polymorphism influences treatment efficacy in nondiabetic nephropathy has boosted research efforts for a treatment with increased effectiveness for patients with the ACE II/ID genotype. Such a treatment, incorporated in a selective screen-and-treat strategy, would have a high probability of being cost-effective or even cost saving, as the ACE II/ID genotype is common and the costs and disease burden associated with ESRD are high [12,13].

**Study objectives**

The importance of pharmacoconomics for decision making is increasing in all fields of health-care, in particular regarding drug treatments. In that context it is useful to know the cost-effectiveness of ACEi therapy for the separate ACE (I/D) genotypes. Citing a checklist from our group on performing pharmacoeconomic analyses on pharmacogenetic screening interventions, an important starting point of such analyses is a comprehensive review of the evidence for the assumed association between genotype and phenotype [12]. No selective screen-and-treat strategy in nondiabetic nephropathy based on the ACE (I/D) polymorphism existed at the time, nor were studies found with conclusive evidence for such a strategy. Therefore, our first study objective was to understand the magnitude of difference in cost-effectiveness of ACEi therapy in association with the ACE genotype. In particular, we determined the cost-effectiveness of ACEi therapy versus non-renin–angiotensin system acting antihypertensive drugs in nondiabetic nephropathy separately for those with the ACE DD genotype and those with the ACE II/ID genotype. Our second study objective was to estimate cost-effectiveness of a selective screen-and-treat strategy involving an alternative treatment modality. By employing a threshold analysis, we determined the increase in effectiveness of an alternative treatment would require compared with the existing ACEi treatment to justify a screen-and-treat strategy, taking into account expected additional costs and health effects. This analysis should provide valuable information to researchers considering new treatment modalities for nondiabetic nephropathy and to decision makers considering research budgets for such research.

**Methods**

**Data**

Data from the REIN trial were used for this economic analysis. The REIN trial was a randomized controlled trial in nondiabetic nephropathy aimed at determining the efficacy of the ACEi ramipril compared with placebo, at the same level of blood pressure control [5]. The REIN investigators found that the ACE (I/D) polymorphism was a strong predictor of ACEi efficacy; progression to ESRD was considerably and significantly reduced in ACEi-treated compared with placebo-treated patients with the ACE DD genotype (36% in placebo vs. 14% in ACEi), whereas a much smaller reduction was found in those with the ACE II/ID genotype (23% in placebo vs. 21% in ACEi) [10,11].

**Models**

Time-dependent Markov models were constructed with three health-states: CKD, ESRD and death. Cohorts of 1 000 patients entered the model and were followed for a time period of 10 years, and the health states were determined on monthly cycles. Given this short cycle time in the Markov model, no half-cycle correction was used. Patients were not allowed to recover from ESRD by reentering the CKD state.

**Cost-effectiveness analysis of ACEi therapy**

For the first study objective, the cost-effectiveness of ACEi therapy was determined as compared with placebo therapy. Cost-effectiveness was determined for patients with the ACE II/ID and with the ACE DD genotype separately.

**Threshold analysis for the selective screen-and-treat strategy**

For our second study objective, we compared a selective screen-and-treat strategy with the absence of screening. For this goal, the Markov model was embedded in a decision-tree analytical framework (Fig. 1). In the nonscreening strategy, all patients received ACEi therapy. In the screening strategy, the ACE (I/D) genotype of all patients was screened; those with the ACE DD genotype received ACEi therapy, whereas those with the ACE II/ID genotype received an alternative renoprotective treatment. As no preferred treatment over ACEi for patients with ACE II/ID genotype currently exists, no prespecified effectiveness for this treatment was assumed. Instead, a threshold analysis was performed in which the effectiveness of the alternative treatment was varied. The increase in effectiveness of the alternative treatment compared with ACEi therapy needed for a screen-and-treat strategy to become cost-effective was determined.
Five parametric survival distributions (Weibull, exponential, lognormal, loglogistic and Gaussian) were fitted on the REIN data by maximizing the likelihood ratio; the Akaike information criterion (lower value indicates better fit) was calculated for each distribution [14]. The effectiveness of ACEi compared with placebo in our model was based on the parameters of the best-fit distribution.

Mortality rates of patients with CKD were calculated using data from the REIN and a similar trial in nondiabetic nephropathy, REIN-2 [15]. In these trials, nine deaths occurred over a cumulative follow-up of 1700 patient-years, resulting in an annual mortality rate of 0.53% per year [5,15]. Patients in the REIN trial were followed until ESRD development or death [5]; therefore no data on ESRD mortality were available. Mortality rates of ESRD patients were instead derived from the Dutch End-Stage Renal Disease Registry (RENINE), using data from 1998 to 2008 [2]. No differences in mortality rates between the ACE polymorphisms or treatment arms were assumed.

ACE (I/D) polymorphism prevalences were derived from several clinical trials in nondiabetic nephropathy [10,11,16–20], all described in a systematic review by Ruggenenti et al. [9]. QoL estimates were obtained by examining a recently published systematic review [3], in which one study was reported with QoL estimates for CKD and ESRD based on community preferences, using the Health Utilities Index-3 [21]. In economic evaluations, community or societal preferences are preferred over patient preferences [22].

A third-party payer perspective for the cost estimates was adopted. Costs of ESRD were based on a weighted average of Dutch cost estimates for active haemodialyses, passive haemodialyses and peritoneal dialysis, adjusted for inflation to 2008 values [23]. Costs of ramipril treatment were based on 2008 Dutch prices [24], including 6% value-added tax and a 3-monthly pharmacists’ prescription fee of €6.10. In the REIN trial, ACEi therapy was compared with placebo treatment; both treatment arms received similar additional blood pressure lowering drugs and health-care services [5]. Associated health-care costs were equal in both groups and therefore not included in our analysis. The costs of an alternative treatment modality in the screening strategy were based on Dutch prices for the new renin inhibitor aliskiren [24], to reflect costs for a new treatment modality; these costs were varied in sensitivity analyses. The price of a genetic screening test for the ACE (I/D) polymorphism was based on polymerase chain reaction and included staff costs [25]. Costs and health effects were discounted at 3% per annum, following recommendations by Gold et al. [22] and Drummond et al. [26]. An overview of all parameters is shown in Table 1.

### Sensitivity analysis

Univariate and probabilistic sensitivity analyses were performed for both the cost-effectiveness analysis and the threshold analysis. In the univariate sensitivity analyses, all model parameters were varied by 25% to determine the main cost and effect drivers in our model. Discount rates were varied based on Dutch guidelines for pharmacoeconomic research recommending differential discounting for costs and health effects, at 4 and 1.5%.
respectively [27,28]. Results of the univariate sensitivity analysis are presented in a tornado diagram [29]. In the probabilistic sensitivity analyses, triangular distributions were used for all cost parameters; beta distributions for ACE (I/D) genotype prevalences and QoL estimates; and Poisson distributions for mortality probabilities. Variation in ACEi effectiveness was captured by nonparametric bootstrapping, in which a random sample of the same size as the original data is drawn with replacement. This procedure is performed a large number of times. Bootstrapping is used to estimate the true distribution of a sample regardless of the distribution of the original data [29]. The probabilistic sensitivity analysis was run 10 000 times.

### Statistics
Fitting and bootstrapping of the REIN data were performed in the statistical package R, version 2.5.1 [30]. The models and sensitivity analyses were constructed in Microsoft Office Excel 2003.

### Results
Five parametric distributions (Weibull, exponential, lognormal, loglogistic and Gaussian) were fitted on the REIN data. Akaike information criterion values and visual assessment showed that the lognormal distribution provided the best fit for both genotype groups and both treatment arms. This distribution was therefore selected for use in the Markov model.

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**Table 1 Parameters used in the analyses**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline value</th>
<th>Univariate sensitivity range</th>
<th>Probabilistic sensitivity distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype prevalences</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE DD prevalence</td>
<td>32.87%</td>
<td>24.65–41.08%</td>
<td>Beta</td>
<td>[10,11,16–20]</td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis (per year)</td>
<td>€72 354</td>
<td>€54 265–690 443</td>
<td>Triangular</td>
<td>[23]</td>
</tr>
<tr>
<td>ACEi therapy (per month)</td>
<td>€3.03</td>
<td>€2.27–€3.79</td>
<td>Triangular</td>
<td>[24]</td>
</tr>
<tr>
<td>Alternative therapy (per month)</td>
<td>€23.67</td>
<td>€17.75–€29.59</td>
<td>Triangular</td>
<td>[24]</td>
</tr>
<tr>
<td>Genetic screening test</td>
<td>€50.00</td>
<td>€37.50–€62.50</td>
<td>Triangular</td>
<td>[25]</td>
</tr>
<tr>
<td>Health effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QoL chronic kidney disease</td>
<td>0.67</td>
<td>0.50–0.84</td>
<td>Beta</td>
<td>[21]</td>
</tr>
<tr>
<td>QoL dialysis</td>
<td>0.54</td>
<td>0.41–0.68</td>
<td>Beta</td>
<td>[21]</td>
</tr>
<tr>
<td>Annual mortality rate – CKD</td>
<td>0.53%</td>
<td>0.40%–0.66%</td>
<td>Poisson</td>
<td>[5,15]</td>
</tr>
<tr>
<td>Annual mortality rate – ESRD</td>
<td>9.95%</td>
<td>7.46%–12.44%</td>
<td>Poisson</td>
<td>[1]</td>
</tr>
<tr>
<td>ACEi effectiveness in ACE II/ID (days)*</td>
<td>15.3</td>
<td>11.5–19.1</td>
<td>Bootstrapping</td>
<td>[11]</td>
</tr>
<tr>
<td>ACEi effectiveness in ACE DD (days)*</td>
<td>106.1</td>
<td>79.6–132.6</td>
<td>Bootstrapping</td>
<td>[11]</td>
</tr>
</tbody>
</table>

Ranges for univariate sensitivity analysis were ± 25% for all parameters.

ACEi, angiotensin-converting enzyme inhibitor; CKD, chronic kidney disease; ESRD, end-stage renal disease; QoL, quality of life.

*Effectiveness of ACEi therapy was defined as prolongation of median time to ESRD compared with placebo.

*Effectiveness of the alternative treatment was defined as increase in effectiveness compared with ACEi therapy.

**Table 2 Cost-effectiveness at baseline and probabilistic sensitivity analysis**

<table>
<thead>
<tr>
<th>Cost-effectiveness of ACEi therapy</th>
<th>ACEi therapy</th>
<th>Placebo</th>
<th>Cost-effectiveness of ACEi therapy</th>
<th>Probability of cost-effectiveness (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs/QAL Ys</td>
<td>Costs QAL Ys</td>
<td>Costs QAL Ys</td>
<td>Costs QAL Ys</td>
<td>Costs QAL Ys</td>
</tr>
<tr>
<td>All patients</td>
<td>€115 826</td>
<td>5.130</td>
<td>€160 789</td>
<td>4.887</td>
</tr>
<tr>
<td>ACE II/ID genotype group</td>
<td>€125 786</td>
<td>5.078</td>
<td>€141 612</td>
<td>4.988</td>
</tr>
<tr>
<td>ACE DD genotype group</td>
<td>€94 860</td>
<td>5.235</td>
<td>€199 963</td>
<td>4.682</td>
</tr>
</tbody>
</table>

Threshold analysis for the selective screen-and-treat strategy

<table>
<thead>
<tr>
<th>Screening strategy</th>
<th>Costs QAL Ys</th>
<th>Costs QAL Ys</th>
<th>Costs QAL Ys</th>
<th>Costs QAL Ys</th>
<th>Costs QAL Ys</th>
<th>Costs QAL Ys</th>
</tr>
</thead>
<tbody>
<tr>
<td>No increase in effectiveness</td>
<td>€ – 44 221</td>
<td>0.243</td>
<td>€ – 45 198</td>
<td>0.243</td>
<td>€977</td>
<td>0.000</td>
</tr>
<tr>
<td>9.1% increase in effectiveness</td>
<td>€ – 45 102</td>
<td>0.248</td>
<td>€ – 45 198</td>
<td>0.243</td>
<td>€96</td>
<td>0.005</td>
</tr>
<tr>
<td>25% increase in effectiveness</td>
<td>€ – 46 606</td>
<td>0.256</td>
<td>€ – 45 198</td>
<td>0.243</td>
<td>€ – 1 408</td>
<td>0.013</td>
</tr>
</tbody>
</table>

The term ‘dominance’ denotes that a strategy saves costs as well as QALYs compared with its comparator strategy (which is then said to be ‘dominated’).

ACEi, angiotensin-converting enzyme inhibitor; QALY, quality-adjusted life year.

aThe probability of cost-effectiveness was determined in the probabilistic sensitivity analysis.

bEffectiveness of the alternative treatment was defined as increase in effectiveness compared with ACEi therapy, which was defined as prolongation of median time to ESRD compared with placebo.
Cost-effectiveness of ACEi therapy
In the baseline analysis (Table 2), ACEi therapy dominated placebo in both genotype groups, that is, resulted in clinical benefits as well as cost-savings. In the 10-year time frame, cost savings for a patient with the ACE II/ID genotype was €15,826 and €105,104 for a patient with the ACE DD genotype. Overall, ACEi therapy resulted in cost savings of €45,198. Quality-adjusted life years (QALYs) gained per patient were 0.091 for a patient with the ACE II/ID genotype and 0.553 for ACE DD. Overall, ACEi therapy gained 0.243 QALYs per patient in the 10-year time frame.

Univariate sensitivity analysis showed that dialysis costs and ACEi effectiveness had the largest influence on the cost savings of ACEi therapy in both genotype groups (Fig. 2a). The main drivers of health gains were QoL of CKD and ESRD patients, followed by ACEi effectiveness.

(a and b) Univariate sensitivity analysis for net cost savings (a) and health gains (b) of angiotensin-converting enzyme inhibitors (ACEi) therapy; the dashed line represents the baseline analysis. Black bars denote influence of the high end of the sensitivity range and grey bars denote influence of the low end of the sensitivity range. Discounting rate was varied to 0% for both costs and health gains on the low end and 4 and 1.5% on the high end for costs and health gains, respectively. CKD, chronic kidney disease; ESRD, end-stage renal disease; QALY, quality-adjusted life year; QoL, quality of life.
(Fig. 2b). Probabilistic sensitivity analysis (Fig. 3; Table 2) showed that in the ACE II/ID genotype, ACEi therapy has a 30.2% probability of resulting in an unfavourable outcome (no health benefits or cost-effectiveness of more than €20 000 /QALY). In the ACE DD genotype, however, there was only a 0.2% probability of an unfavourable cost-effectiveness outcome.

**Threshold analysis for the selective screen-and-treat strategy**

A selective screen-and-treat strategy was based on the decision-tree analytical framework and Markov model (Fig. 1). The effectiveness of the alternative treatment for ACE II/ID patients in the screening arm of this strategy was varied in a threshold analysis. Results are presented in Table 2. This analysis showed that an alternative treatment should increase effectiveness compared with ACEi therapy by 9.1% for a screening strategy to be cost-effective compared with a nonscreening strategy. Probabilistic sensitivity analysis showed that the chance of cost-effectiveness under this assumption is 72.3%. With an increase in effectiveness of the alternative treatment of 25%, a screening strategy would save €1 408 and 0.013 QALY per patient, thus resulting in a dominating strategy compared with nonscreening. The chance of cost-effectiveness under this assumption was 89.8%. When no increase in effectiveness of the alternative treatment was assumed, a screening strategy would generate extra costs and no health gains, thus causing the screening strategy to be dominated by the nonscreening strategy.

Univariate sensitivity analyses showed that the costs of dialysis and of the alternative therapy were the most influential factors on the variability of the cost-effectiveness
estimates. Two-way analyses were performed for these two variables and the effectiveness of the alternative treatment (Figs 4 and 5). Lower costs of dialysis and higher costs of the alternative treatment decreases the cost-effectiveness of a screening strategy.

Discussion
This study showed that ACEi therapy is a cost-saving treatment modality to prevent ESRD in nondiabetic nephropathy irrespective of ACE genotype, based on the Caucasian population of the REIN trial. However, although ACEi is cost saving for all patients, there are considerable differences in cost-effectiveness in the different ACE (I/D) genotypes. ACEi therapy, compared with non-renin–angiotensin system acting antihypertensive drugs, resulted in more costs-savings and more health gains in the ACE DD group than in the ACE II/ID group. In addition, in the ACE II/ID genotype, there was a 30.2% probability of ACEi therapy resulting in an unfavourable cost-effectiveness outcome, while the chance of ACEi therapy being cost-effective or even cost saving in the ACE DD genotype was almost 100%. Although separate analyses for the different polymorphisms have not been performed before, the finding that ACEi therapy is a cost-effective treatment in nondiabetic nephropathy has been reported in other studies. Van Hout et al. [31] analyzed ACEi cost-effectiveness based on the ACE Inhibition in the Progressive Renal Insufficiency trial, and found ACEi therapy to save $28 014 per patient, using a time frame of 10 years (in 1996 US$, equivalent to €30 272 in 2008 price levels). Ruggenenti et al. [32] performed a cost-effectiveness analysis based on the REIN trial and found ACEi therapy to save between $16 605 and $23 894 per lifetime (in 2000 US$, equivalent to €20 887 and €30 056 in 2008 price levels). Schädlich et al. [33] reported cost savings between 76 700 and 81 900 Deutschemarks per patient-year of chronic dialysis avoided, using a time frame of 1–3 years (in 1999 Deutschemarks, equivalent to €51 168 and €54 637 in 2008 price levels). Our model demonstrated cost savings of ACEi therapy compared with placebo of €45 198 per patient using a 10-year time frame (ACE II/ID and ACE DD combined). Overall, cost savings per patient-year of chronic dialysis avoided were €60 597. The larger cost savings in our study compared with previous studies can be explained by lower discounting rates and higher costs of dialysis assumed in our model compared with the other studies.

The main limitation of this study is the assumption of an association between the ACE (I/D) polymorphism and ACEi therapy response, which is still disputed. In fact, several studies reported that the D allele is associated with ACEi therapy resistance [16,19], contrary to our model assumptions. The trial used for our analyses was the only trial evaluating a hard endpoint, namely ESRD. A recent analysis in one of the contradicting trials [19] showed that the preintervention rate of renal function loss (measured as creatinine clearance) was significantly higher in the ACE DD group compared with the other genotype groups [34]. Taking this preintervention rate
into account, ACEi therapy did in fact benefit patients with the ACE DD genotype, but not those with ACE II/ID genotype [34]. Therefore, although the REIN trial was the largest trial on the subject, other studies seem to confirm the findings. However, environmental factors should also be considered when determining the association between ACE genotype and ACEi response. ACEi therapy response is also dependent on sodium status, with more effective response on low sodium excretion in the ACE DD genotype [17].

We employed a third-party perspective for our cost estimates as opposed to a societal perspective. Although many guidelines recommend adoption of a societal perspective, for a first assessment of the cost-effectiveness of genetic screening interventions, there are limitations in performing this in our case because of a lack of data in developmental stages and data being based on efficacy as opposed to real-life effectiveness [12]. In addition, the third-party focus is often of prime interest to payer decision makers. However, for full understanding of the economic impact, indirect costs should be considered before final decisions on implementations of screening strategies are made [12].

The models and parameters used in this economic analysis have been kept as relevant and transparent as possible. However, as in all economic analyses, several assumptions and estimates were made. Sensitivity analyses showed that mortality rates had a minor influence of the cost-effectiveness of the treatment modalities. Mortality rates in CKD were estimated from data obtained from the REIN and REIN-2 study combined. Mortality rates in ESRD were assumed to be similar in both ACE genotype groups. There is evidence that mortality is higher in dialysis patients with the ACE DD genotype [35]; however no information on ACEi therapy versus other antihypertensive drugs was reported. The most influential factor in sensitivity analyses was the cost of dialysis. When higher dialysis costs were assumed, ACEi therapy became more cost-effective in both ACE genotypes. Cost-effectiveness of the selective screen-and-treat strategy also increased with higher dialysis costs, but was also dependent on the assumed effectiveness and costs of the alternative treatment; these factors should therefore be taken into account when developing an alternative treatment to be employed in a selective screen-and-treat strategy.

**Conclusion**

The ACE (I/D) polymorphism is a large determinant of response to ACEi therapy not only in terms of health outcomes but also of cost-effectiveness. This study showed that ACEi therapy compared with placebo both reduces costs and improves QALYs more in the ACE DD group than in the ACE II/ID group, although ACEi treatment remains cost saving in both genotypes. A selective screen-and-treat strategy based on a treatment modality, which produces a modest increase in effectiveness in patients with the ACE II/ID genotype, can result in large cost savings and clinical benefits. Unfortunately, clinical evidence for such a selective screen-and-treat strategy has been scarce and no such strategy has yet been implemented in clinical practice. Before this, ACEi therapy should be given to non-diabetic nephropathy patients irrespective of ACE genotype. Still, the large potential cost savings and clinical benefits associated with a selective screen-and-treat strategy should ensure that studies and trials in this field remain appealing for both researchers and decision makers.

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