Original Paper

To Treat or Not to Treat? Cost-Effectiveness of Ace Inhibitors in Non-Diabetic Advanced Renal Disease – a Dutch Perspective

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Key Words

Advanced renal disease • Angiotensin-converting enzyme inhibitors • Cost-effectiveness • Decision modeling • Markov model

Abstract

Background: Treating non-diabetic proteinuric patients with advanced renal disease with an angiotensin-converting enzyme (ACE) inhibitor is still subject to discussion. This study aims to determine the cost-effectiveness of ACE inhibitor therapy in this patient population in the Netherlands. **Methods:** We compared two strategies: first, treating patients with advanced renal disease with an ACE inhibitor and no-treatment. A lifetime Markov decision model was developed simulating the progression of renal disease and using published data on costs and health outcomes. A health care perspective was adopted. **Results:** In the base-case analysis, treatment with ACE inhibitors leads to higher benefits and lower costs and dominates the no-treatment strategy. Sensitivity analysis shows that the probability of savings is 83%. **Conclusion:** ACE inhibitor treatment for non-diabetic patients with advanced renal disease in the Netherlands is highly cost-effective and should therefore be considered.

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Introduction

End stage renal disease (ESRD) can be defined by the need for renal transplantation or long-term dialysis [1]. It is a final outcome of advanced renal disease, which is defined as a serum creatinine ≥ 3.0 mg per deciliter. An increasing prevalence of patients in renal replacement therapy in the Netherlands is notable within the last 15 years [2] as it almost

doubled within this period. Currently, more than 15 000 patients require renal-replacement therapy (RRT) and it is remarkable that the proportion of transplanted patients has been continuously increasing and now represents almost 60% of all patients requiring RRT [2].

ESRD costs represent a significant burden for the health care system, with a proportion of the national expenditures in European countries ranging from 0.7% in the UK to 1.8% in Belgium [3, 4], and with a proportion in the Netherlands of about 1.3%. To state that prevention of ESRD is important from a medical perspective, it becomes clear that this also accounts for an economic viewpoint as the costs of ESRD treatment amount to €42 000 per patient per year in the Netherlands [3, 5, 6].

Angiotensin-converting enzyme (ACE) inhibitors decelerate the progression from mild-to-moderate chronic kidney disease (CKD, with a serum creatinine level of 1.5 to 3.0 mg per deciliter) to ESRD in non-diabetic patients with hypertension [7-10]. ACE inhibitors have also shown to be cost-effective in this patient population. In the U. S., eg, benazepril treatment improves health and lowers costs as modelled over a 7-year period [11]. The cost-effectiveness of ACE inhibitors in mild-to-moderate renal disease has also been shown for the Dutch setting [3, 12].

In patients with advanced renal disease (serum creatinine levels of 3.0 mg per deciliter or more) physicians might be reluctant to use ACE inhibitors because of concern that potassium levels or serum creatinine will rise [13, 14]. Several side effects and risks of ACE inhibitor therapy are well described in patients with chronic renal disease. Those risks include cough, hyperkalemia, mild reduction in glomerular filtration rate in patients with parenchymal renal disease, and acute renal failure in patients with bilateral renal artery stenosis or volume depletion [15-18]. A placebo-controlled randomized controlled trial (RCT) by Hou et al. [1] showed that ACE inhibitors can be used safely in this patient population: in the 8-week run-in period only 4 out of 281 patients with a serum creatinine above 3 mg/ml had to be excluded because of hyperkalemia; in the 224 patients who underwent randomization the incidence of hyperkalemia was similar among patients who received an ACE inhibitor and those who received placebo.

The RCT by Hou et al. [1] also showed that ACE inhibitor therapy has a renoprotective effect in this patient population, thus confirming the result of a small prior RCT [19]. Hou et al. demonstrated that the renal protective effect of ACE inhibitors in patients with advanced chronic kidney disease is not only due to their antihypertensive action as the reduction in the rate of progression changed little after correction for blood pressure [1]. Although more than 90% of patients in this study population suffered from hypertension (baseline blood pressure of >150/85 mm Hg), these patients did not suffer from hypertensive kidney disease as the main cause for their renal failure. In about 60% glomerular disease was found to be the main cause [1].

A cost-effectiveness model conducted in Germany by Adarkwah et al. (2011) [20] suggests that ACE inhibitor treatment in this patient population is cost-effective, at least in the German setting. Currently, no data are available on the cost-effectiveness of ACE inhibitor therapy in non-diabetic patients with advanced nephropathy in the Dutch setting. However, results of the German study may not be transferable to the Netherlands. Different factors such as epidemiology of the disease, demography, the, availability of health care resources and differences in reimbursement systems between countries hinder transferability of economic evaluation studies between countries, in particularly due to variances in absolute and relative costs/prices. Other cost effectiveness models on renal disease even in the Dutch setting did include patients with less severe stages or renal disease, i.e. a serum creatinine level of 1.5 to 3.0 mg per deciliter [3, 12]. This also applies to other European cost-effectiveness models [21, 22].

Fig. 1. Schematic representation of the Markov decision models. ESRD = end-stage renal disease.

The goal of this paper was to determine the cost-effectiveness of ACE inhibitor therapy in non-diabetic patients with advanced renal disease (serum creatinine above 3.0 mg/dl) and proteinuria in the Netherlands, based on a meta-analysis of RCTs by Ihle et al. [19] and Hou et al. [1].

Materials and Methods

Overview and model design

A Markov decision model previously developed for the German setting [20] was adapted and also proven suitable for the prevention of diabetic nephropathy [23, 24] in the Dutch and German setting.

Based on the results of the RCTs by Ihle et al. [19] and Hou et al. [1], the progression of a cohort of 1000 patients aged 44 years with advanced renal insufficiency (serum creatinine: > 3.0 mg/dl, glomerular filtration rate (GFR): 15-26 ml/min/1.73 m²), proteinuria, and hypertension (> 150/85 mm Hg), but without severe heart failure (New York Heart Association III or IV) was simulated.

In order to simulate costs and effectiveness over lifetime, a Markov model was constructed. A Markov model is an iterative process where patients stay in one cycle (ie, a defined health state) for a certain time (here: 1 year) and then make a transition to another cycle.

Markov models are useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when important events may happen more than once. A half-cycle correction was used to allow for transition events occurring midway through each 12-month cycle. A cycle length of one year was chosen because most data were given in units per year. The age of 100 was chosen as a cut-off as there are no mortality data available beyond this age. Regardless, more than 99% of patients in the simulation are dead at this age so that the model represents a lifetime horizon. The model was built in Microsoft Excel® 2010.

Our model contains the following 3 health states (figure 1), which represent the occurrence of events after model entry:

1. Advanced renal disease (serum creatinine: >3.0 mg/dl, GFR: 15-26 ml/min/1.73 m², CKD stage 4)
2. ESRD and
3. Death

We performed a cost-utility analysis and health outcomes were measured in terms of quality-adjusted life years (QALYs). QALYs are the product of life years and a measure of health-related quality of life (preference weight or score) and allow comparing cost-effectiveness across diseases. Preference weights are anchored on a scale from 0 to 1, where 0 and 1 represent death and full health, respectively [25]. Economic outcomes were set in relation to clinical outcomes by dividing the incremental (ie, additional) costs of providing ACE inhibitors compared to no therapy by the incremental QALYs gained. The analysis is conducted from a health care perspective instead of choosing a societal perspective in order to increase comparability our previous model on this topic [20].

Table 1.

Baseline characteristics of patients with chronic kidney disease

Characteristics	Hou et al. [1]		Ihle et al. [19]	
	ACE inhibitor (n = 112)	Placebo (n = 112)	ACE inhibitor (n = 36)	Placebo (n = 34)
Age – years	44	45	41	48
Male sex – no. (%)	56 (50)	55 (49)	23 (64)	13 (38)
Blood pressure – mm Hg				
Systolic	153	152	147	154
Diastolic	87	85	87	88
Renal function				
Serum creatinine – mg/dl	4.0	3.9	5.2	4.4
GFR – ml/min/1.73m ²	26.3	25.8	14.6	15.8
Urine protein excretion – g/day	1.6	1.7	2.3	1.9

Doubling of the serum creatinine level (an outcome in the RCT by Hou [1]) was not included as a separate Markov state, as this is a surrogate for and shortly followed by ESRD. After each cycle, a specified proportion of patients move from advanced renal insufficiency to ESRD. This transition is delayed by ACE inhibitors. Simultaneously, a specified proportion of patients die. During each cycle, patients accumulate utilities (measured by QALYs) and costs.

Combining both states – dialysis and transplant – to ESRD is a common course of action when modelling renal disease [26, 27]. We pooled individual data for transplantation and dialysis as well as prevalences according to the national register in order to assess valid costs for the stage ESRD.

Clinical strategies

Two treatment strategies were considered. In the “ACE inhibitor treatment” strategy, patients are treated with benazepril 10 mg twice a day. Patients in the control group receive no ACE inhibitor. In addition, both groups receive other antihypertensive agents (diuretics, alpha- or beta-blockers, calcium-channel antagonists, or some combination of these medications), but no other renin-angiotensin-system agents.

Transition probabilities

In order to identify placebo-controlled RCTs on the effect of ACE inhibitors on the progression of advanced renal insufficiency to ESRD we used a literature review until July 2001 by Terajima et al. [28] as a starting point. This paper found one placebo-controlled RCT [19]. In order to identify additional placebo-controlled RCTs published after July 2001 we searched in the PubMed database (date: September 05, 2012) using the following search strategy:

Renal Insufficiency, Chronic AND creatinine AND antihypertensives AND end-stage renal disease AND angiotensin-converting-enzyme NOT(type-2-diabetes), Limits: Randomized Controlled Trial, All Adult: 19+ years.

We obtained 43 hits. Thereof, 41 papers were excluded because they did not compare ACE inhibitors to placebo, did not consider advanced renal insufficiency, or did not include ESRD as an outcome. The above mentioned REIN study [9, 10] including amongst other Dutch nephropathy patients was excluded because the overall patient population suffered from mild-to-moderate renal disease and therefore also did not meet our inclusion criteria. The only 2 studies left were by Ihle et al. [19] and Hou et al. [1] and therefore used as the source of our effectiveness data. Both studies [7, 8] were double-blinded (see table 1 for baseline characteristics). To combine effectiveness data from both studies and estimate the common odds ratio, we used the Mantel-Haenszel test [29].

In order to determine the annual transition probability from advanced renal disease to ESRD without ACE inhibitor therapy, we first calculated a total probability for each of the two trials, by dividing the number of events (ESRD) during the trial period in the control arm by the number of patients. Second, we determined the annual transition probability by assuming a constant annual hazard rate over the study time horizon [30]. And third, we determined a weighted average rate, with the number of individuals included in each study as weights. In the study by Hou et al. [1] the number of events was obtained by directly contacting the authors and does not include death.

Table 2. Data used to determine the cost-effectiveness of angiotensin-converting enzyme inhibitor treatment

Variable	Base-case estimate	Range *	References
<i>Annual transition probabilities</i>			
Advanced renal insufficiency to ESRD without ACE inhibitor	0.14	0.08 – 0.19	[1,19]
Advanced renal insufficiency to death	Age- and gender dependent	0.003 – 0.54	[61]
ESRD to death	0.09	---	[2]
<i>Effectiveness of ACE inhibitor</i>			
Relative risk of advanced renal insufficiency to ESRD	0.61	0.39 – 0.95	[1,19]
<i>Utilities (health states)</i>			
General population (age-dependent)	0.83 – 0.94	---	[33]
Disutility of chronic kidney disease	0.056	-0.045 – 0.156	[32]
Disutility of ACE inhibitor treatment	0.00	0.00 – 0.05	[34]
ESRD	0.62	0.39 – 0.84	[35]
<i>Annual costs, €</i>			
General health care expenditures by age group	3.140,58 – 23.456,58	---	[39,42,47]
Per-patient cost of chronic kidney disease compared to non-CKD population	Age-dependent	---	[39-36,42,47]
ACE inhibitor	240,92	28,70 – 240,92	[43]
(20 mg benazepril daily; 5 mg enalapril daily in the SA)			
ESRD	42 110	33 688 – 50 532	[2,6]
Transplantation	14 387		[2,6]
Dialysis	79 122		[2,6]
Home/in-center hemodialysis	83 217		[2,6]
CAPD	54 067		[2,6]
CCPD	69 546		[2,6]
SMR of chronic kidney disease	3.42	2.84 – 4.11	[31]
Discount rate of costs	0.04	0.00 – 0.10	[42,47,48]
Discount rate of benefits	0.015	0.00 – 0.10	[42,47,48]

ESRD = end-stage renal disease; ACE = angiotensin-converting enzyme; CKD = chronic kidney disease; SA = sensitivity analysis; CAPD = Continuous ambulatory peritoneal dialysis; CCPD = Continuous cycling peritoneal dialysis; SMR = standardized mortality ratio; *Tested in sensitivity analysis: Based on 95% confidence intervals of the mean except for ESRD (estimate)

Transition probabilities with and without an ACE inhibitor therapy are shown in table 2. In patients without ESRD mortality was regarded as a function of age. Specifically, we used age-specific mortality rates of non-diabetic patients. To calculate the latter, age-specific mortality rates of the general population were multiplied with a standardized mortality ratio for patients with advanced renal disease compared to the general population, which was derived from a large community-based cohort study [31]. For patients with ESRD we assumed that mortality was age-independent.

Preference weights

For patients in the health state “advanced renal disease” we considered a utility loss according to a survey using the time tradeoff (TTO) method in 65 patients [32]. This population had a mean age of 66 years and a GFR between 15 and 30 ml/min/1.73 m². Furthermore, we considered an age-dependent loss of utility [33]. For patients treated with an ACE inhibitor a disutility of 0.05 from all side effects was considered in a sensitivity analysis [34]. The preference weight for ESRD was derived from a systematic review of empirical studies in which TTO weights were provided by patients [35]. The TTO can be regarded as the most commonly used method to derive quality-of-life weights for QALYs [36, 37]. The TTO technique determines the proportion of remaining life years in poor health which patients are willing to give up or trade in exchange for perfect health. Based on patient responses utility scores are calculated. Those utility measures in economic evaluations are becoming more and more important given the fact that decision makers are asked to optimize the allocation of scarce health care resources across disease areas and patient groups [38]. Notably, the values are similar to EQ-5D scores (baseline value 0.61) reported by de Wit et al. [6]. We tested a rather broad range of TTO weights in sensitivity analysis.

Costs

The analysis was conducted from the health care perspective. Therefore, only direct health effects–defined as life years gained – and direct costs and were considered. Making use of data on the consumer

Table 3. Parameters used for calculating the cost of end-stage renal disease (see cost section under “Methods”)

variable	meaning
1	home/center hemodialysis
2	CAPD*
3	CCPD**
β_1	0.82
β_2	0.106
β_3	0.074
x_1	€ 83 217
x_2	€ 54 067
x_3	€ 69 546
p	0.43
X	€ 79 112
Y	€ 14 387

* continuous ambulatory peritoneal dialysis;

**continuous cycling peritoneal dialysis

include 6% value-added tax as well as a 3-monthly pharmacists' prescription fee of €7.50 [45].

The annual costs of patients with ESRD were calculated as a weighted average of the costs of renal transplantation as well as different types of dialysis as based on a Dutch study [6] and prevalence data available from the national register [2].

In detail, the following calculations were made (see table 3 in the appendix for details):

- 1) cost of dialysis = $\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 = X$, where x_n = annual cost of dialysis treatment $n = 1, 2, 3$; β_n = prevalence weight of the dialysis treatment, and $\beta_1 + \beta_2 + \beta_3 = 1$
- 2) cost of ESRD = $pX + (1-p)Y$, where Y = cost of renal transplantation and p = proportion of ESRD treated by dialysis treatment.

We assumed a transplant survival of 10 years and a distinction was made between the first year of transplantation and the years following [46]. Costs were inflated to 2010 Dutch prices.

As our study population is mainly hypertensive (91.5%) and no valid data on CKD treatment costs per se are available, we included the costs for hypertension treatment as an approximation. Costs were discounted at an annual rate of 4% whereas benefits were discounted at an annual rate of 1.5% in accordance with the CVZ recommendations [42, 47, 48].

Sensitivity analysis

In order to address uncertainty around mean incremental costs and effectiveness, we conducted univariate sensitivity analyses, where we varied one variable at a time while keeping all other variables constant at their mean or base-case value. We ran analyses using the upper and lower bound of the 95% confidence intervals of the mean whenever possible. For transplantation costs we did not have information on the 95% CI and thus varied costs by 20% (see table 2 for uncertainty ranges).

To assess how a simultaneous change of several variables affects the incremental cost-effectiveness ratio (ICER), we performed a Monte Carlo simulation, a type of multivariate sensitivity analysis. This method runs a large number of simulations (here: 1000) by repeatedly drawing samples from probability distributions of input variables. Therefore, it provides a probability distribution for the output variables (incremental costs, incremental effectiveness, and ICERs). Cost data were assumed to follow a gamma distribution $\text{Gamma}(a, b)$, which reflects the long right tail and restriction to positive values. Probabilities

price index, costs were inflated to year 2010 euros [39]. Costs of health care expenditures unrelated and related to CKD as well as costs for ACE inhibitors and treatment of ESRD were accounted for. To determine the health care expenditures related and unrelated to CKD, we took resource consumption into account, based on international guidelines for the treatment of CKD [40, 41]. The recommendations of the Dutch guidelines for pharmacoeconomic research were followed [42].

In the base case, the cheapest generic of benazepril 10 mg daily was used twice daily [43]. We included costs of ACE inhibitor therapy for patients who had to be excluded in the 8-week run-in period as these patients would be treated in the real world. In a sensitivity analysis we applied the price of the cheapest generic of enalapril 5 mg once daily as used in the RCT by Ihle et al. [19]. This is, for instance, the most frequently prescribed ACE inhibitor in the Netherlands [44]. The costs of benazepril and enalapril were based on 2010 Dutch prices and

Table 4. Results of the base-case analysis, based on mean estimates of input variables

Strategy	Costs (€)	Undiscounted LYs	Discounted QALYs	ICER (€/QALY)
No ACE inhibitor treatment	220 942	13.38	9.32	
ACE inhibitor treatment	183 535	14.66	11.11	Dominates

ACE = angiotensin-converting enzyme; LYs = life-years; QALY = quality-adjusted life-years; ICER = incremental cost-effectiveness ratio

were assumed to follow a beta distribution $\text{Beta}(\alpha, \beta)$ because they are normally distributed but restricted to take on values between 0 and 1. The standard error of a probability or proportion was calculated according to the following formula [49]:

$$\sigma = \sqrt{\frac{p(1-p)}{n}}$$

Where p = probability and n = sample size. Relative risks and odds ratios were assumed to follow a lognormal distribution.

Based on the Monte-Carlo simulation we generated a cost-effectiveness acceptability curve (CEAC). A CEAC allows a decision-maker to consider whether a prevention strategy is cost-effective in relation to the maximum amount a decision-maker is willing to pay for a QALY. At each ceiling value for the willingness to pay for a QALY, the cost-effectiveness acceptability curve shows the probability that the treatment is cost-effective.

Results

Base case

The base-case analysis, which had a lifetime horizon, shows domination of the ACE inhibitor treatment strategy over the no treatment strategy (table 4). Treatment was therefore associated with lower costs and larger health benefit. Even shorter-term simulations over 3 and 10 years revealed the same finding, ie, lower costs and larger benefits.

Sensitivity analysis

Variables with the largest impact on incremental costs and effectiveness in the univariate sensitivity analysis are the effectiveness of ACE inhibitor treatment, the costs of ESRD, and the discount rates of costs and effects (table 5). Figure 2 shows the cost-effectiveness acceptability curve, considering uncertainty in cost-effectiveness. Replications with lower effectiveness of the “ACE inhibitor treatment” strategy compared to the “no treatment” strategy (1.6%) were categorized as not cost-effective (regardless of concurrent savings). This is because it would be unethical to accept treatment that is less effective than no treatment. Hence, the maximum probability of cost-effectiveness independent of the willingness to pay is 98.4%. The probability of savings is 83%. A scatter plot is presented in figure 3.

Discussion

The study shows that treating non-diabetic patients with advanced renal insufficiency in the Netherlands with ACE inhibitors saves both money and lives. Despite the considerable costs of dialysis treatment, preventing ESRD does not necessarily lead to savings [50], thus necessitating a detailed calculation of costs and benefits. This result is consistent with a previous cost-effectiveness analysis conducted in the German setting [20]. Treating patients with more advanced renal disease (creatinine ≥ 3.0 mg per deciliter) with an ACE inhibitor to delay disease progression is still subject to discussion and no clear guideline statement regarding this aspect is available to date [51-53]. Therefore results could be helpful to adjust current guideline recommendations.

Table 5. Univariate sensitivity analyses from a health care perspective: effects of varying base-case estimates on the incremental cost-effectiveness ratio of treating all patients with advanced renal insufficiency with an ACE inhibitor vs no ACE inhibitor treatment (reference strategy). “Lower bound” and “higher bound” refer to the limits of the 95% confidence interval or estimate thereof

	Lower bound		ICER	Higher bound		ICER
	Incremental costs	Incremental QALYs		Incremental costs	Incremental QALYs	
<i>Annual transition probabilities from advanced renal insufficiency to ESRD</i>						
Without ACE inhibitor	- €36 685	1.76	D	- €32 842	1.62	D
<i>Effectiveness of ACE inhibitor</i>						
Relative risk of advanced renal insufficiency to ESRD	- €72 134	3.39	D	- €2 673	0.17	D
<i>Utilities (health states)</i>						
Chronic kidney disease	- €37 407	1.63	D	- €37 407	1.86	D
ESRD	- €37 407	2.01	D	- €37 407	1.58	D
Disutility of ACE inhibitor treatment	- €37 407	1.79	D	- €37 407	1.57	D
<i>Costs</i>						
ACE inhibitor	- €36 680	1.79	D	- €37 407	1.79	D
ESRD	- €28 400	1.79	D	- €46 415	1.79	D
SMR	- €37 307	1.88	D	- €37 521	1.69	D
Base case	- €37 407	1.79	D			
<i>Discount rate of costs</i>						
0%	- €49 072	1.79	D			
5%	- €35 105	1.79	D			
7%	- €31 066	1.79	D			
10%	- €26 158	1.79	D			
<i>Discount rate of effects</i>						
0%	- €37 407	2.31	D			
5%	- €37 407	1.07	D			
7%	- €37 407	0.84	D			
10%	- €37 407	0.60	D			

QALYs = quality-adjusted life years; ESRD = end-stage renal disease; SMR = standardized mortality ratio; ICER = incremental cost-effectiveness ratio; D = Dominance

Fig. 2. Cost-effectiveness acceptability curve.

Still, our model is subject to some limitations. In modeling studies this is usually the case due to constraints of resources, time, and information availability. The cost-effectiveness by treating non-diabetic progressed chronic kidney disease with ACE inhibitors may be even underestimated for several reasons. First, we did not model that ACE inhibitors reduce the risk for cardiovascular events [54, 55], which leads to additional savings. As our study does not consider savings from avoiding cardiovascular events, it does, however, consider that

Fig. 3. Cost-effectiveness plane showing 1000 replications from a distribution of cost and quality-adjusted life year (QALY) differences (angiotensin-converting enzyme inhibitor vs no treatment).

patients with chronic kidney disease have a higher risk of to die because of cardiovascular reasons. We captured this by the mortality ratio for patients with chronic kidney disease compared to the general population. Second, effectiveness (and thus savings) of benazepril may have been underestimated as ESRD treatment may have been initiated earlier than necessary in the ACE inhibitor arms of the RCTs by Hou et al. [1] and Ihle et al. [19] due to a drug-induced GFR decrease. Third, we did not consider on the cost side that some patients may discontinue ACE inhibitor therapy and therefore incur no drug costs. The reason is that information on compliance was unavailable in the two RCTs [1, 19]. Treatment discontinuation was only considered on the effect side, as the rate of compliance is implicitly incorporated in clinical trial results, ie, efficacy data refer both to adherers and non-adherers. Therefore the Markov model includes patients who discontinue ACE inhibitor treatment in the ACE inhibitor arm. And forth, for patients who receive dialysis we were not able to consider health care costs unrelated to dialysis due to a lack of available data.

On the other hand, the savings might be smaller than estimated by our model. This is because some elderly patients may have a preference against replacement therapy and hence do not incur the associated costs. The bias seems small, however, given that the percentage of elderly patients requiring RRT is small (eg, less than 3% at the age of 80 years and above) according to the register. Further limitations of the model relate to its data sources.

First, the two trials considered as the source of our effectiveness data used for ACE inhibition enalapril and benazepril, respectively. Whether other types of ACE inhibitors can achieve the results reported in these studies is not clear. ACE inhibitors have potentially important differences in plasma protein binding, their affinity for ACE, and pharmacokinetics [56]. To date, there is no convincing evidence that generic long-acting ACE inhibitors (such as lisinopril and enalapril) are inferior to brand-name ACE inhibitors [56, 57].

Second, our preference weights for patients with advanced renal disease were taken from a U. S. study [32] as no similar data for Dutch patients were available.

Third, the model also uses some epidemiological data from Western countries other than the Netherlands. One of the two studies we used as the source of our effectiveness data [1] was conducted in China. There is a debate on whether a significant difference between white and Asian populations exists due to ACE gene polymorphism, which might lead to a difference in the efficacy of ACE inhibitors. In fact, studies examining the association between differences in ACE gene polymorphism and the efficacy of ACE inhibitors have had contradictory results [58]. In a controlled trial performed among Japanese patients with

non-diabetic chronic kidney disease whose blood pressure was maintained at an average of 126/72 mm Hg with ACE inhibitors, no significant correlation was observed between the type ACE gene polymorphism (DD, ID, or II) and the efficacy of the intervention or renal outcome [59]. On the other hand, a controlled trial among 212 whites showed that ACE inhibitor therapy was protective against progression to ESRD only in patients with the DD genotype [60]. But even if this small trial is confirmed, treating whites regardless of ACE genotype may not have a smaller impact than treating Asians as whites with the DD genotype may have a stronger response than the average Asian patient. Furthermore, the study by Ihle et al. [19], which was conducted in Australia, shows a similar result as the study by Hou et al. [1].

Forth, quality of life values were derived from non-Dutch populations due to a lack of availability. Hence, we tested a broad range of TTO values in sensitivity analysis.

And fifth, longitudinal studies that have examined long-term outcomes of ACE inhibitor treatment in patients with advanced chronic kidney disease are not available for model validation. This is a common limitation of models on the prevention of renal failure.

In addition, the costs of dialysis treatment will likely continue to rise in the future, and therefore increase the potential for savings by preventing ESRD. Dialysis costs have significantly increased within the last years [5]. We expect this trend to continue due to stricter regulations concerning dialysis safety, better-tolerated dialysis solutions and technological advancement of dialysis machines. On the other hand, prices of erythropoietin and reimbursement of physicians may drop.

Conclusion

For patients with non-diabetic proteinuric advanced renal disease, treatment with an ACE inhibitor is highly cost-effective and should therefore be considered. A societal perspective will likely lead to even larger savings than a health care perspective as ACE inhibitor treatment avoids productivity loss due to renal failure. Yet, the transferability of the conclusion of this study to other countries is limited given differences in costs, clinical management (eg, treatment of ESRD), and epidemiology.

Conflict of Interests

There are no potential conflicts of interest.

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