

## Pharmacoeconomics of angiotensin II antagonists in type 2 diabetic patients with nephropathy: Implications for decision making

Boersma, C; Atthobari, J; Gansevoort, RT; de Jong-Van den Berg, LTW; de Jong, PE; de Zeeuw, D; Annemans, LJP; Postma, MJ

Published in:  
*Pharmacoeconomics*

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from this document. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2006

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

Boersma, C., Atthobari, J., Gansevoort, RT., de Jong-Van den Berg, LTW., de Jong, PE., de Zeeuw, D., Annemans, LJP., & Postma, MJ. (2006). Pharmacoeconomics of angiotensin II antagonists in type 2 diabetic patients with nephropathy - Implications for decision making. *Pharmacoeconomics*, 24(6), 523-535.

### **Copyright**

This document is intended for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

This publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-endment>.

### **Take-down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

# Pharmacoeconomics of Angiotensin II Antagonists in Type 2 Diabetic Patients with Nephropathy

## Implications for Decision Making

Cornelis Boersma,<sup>1</sup> Jarir Atthobari,<sup>1</sup> Ron T. Gansevoort,<sup>2</sup> Lolkje T.W. de Jong-Van den Berg,<sup>1</sup> Paul E. de Jong,<sup>2</sup> Dick de Zeeuw,<sup>3</sup> Lieven J.P. Annemans<sup>4,5</sup> and Maarten J. Postma<sup>1</sup>

- 1 Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy, Groningen University Institute for Drug Exploration (GUIDE), Groningen, The Netherlands
- 2 Department of Internal Medicine, Division of Nephrology, Groningen University Institute for Drug Exploration (GUIDE), Groningen, The Netherlands
- 3 Department of Clinical Pharmacology, Groningen University Institute for Drug Exploration (GUIDE), Groningen, The Netherlands
- 4 Department of Public Health, Ghent University, Ghent, Belgium
- 5 IMS Health/Health Economics and Disease Management (HEDM), Brussels, Belgium

### Abstract

Angiotensin II receptor antagonists (angiotensin II receptor blockers; ARBs) are a class of antihypertensive drugs that are generally considered comparable to ACE inhibitors in the prevention of heart and kidney failure. However, these two classes of agents do interfere in different stages of the renin-angiotensin system. In patients with type 2 diabetes mellitus, advantages for ARBs over conventional (non-ACE inhibitor) therapy on progression from micro- to macroalbuminuria and overt nephropathy and end-stage renal disease have been shown in clinical trials. In patients with type 2 diabetes and end-stage renal disease, the need for dialysis and/or transplantation results in the use of major healthcare resources. This paper reviews the available economic evidence on treatment with ARBs in type 2 diabetic patients with advanced renal disease.

Within-trial analytic and Markov model economic evaluations of the RENAAL (Reduction of Endpoint in Non-insulin dependent diabetes mellitus with Angiotensin II Antagonist Losartan), IDNT (Irbesartan Diabetic Nephropathy Trial) and IRMA (Irbesartan in type 2 diabetes with MicroAlbuminuria)-2 studies suggest that treatment with ARBs in patients with type 2 diabetes with overt or incipient nephropathy confers health gains and net cost savings compared with conventional (non-ACE inhibitor) therapy. For reimbursement and reference pricing decisions, there is a need for a head-to-head comparison of an ACE inhibitor with ARBs to model all possible costs and effects of ACE inhibitors and ARBs. This will result in a proper pharmacoeconomic outcome, where both types of drugs can be compared for healthcare decisions.

---

Angiotensin II receptor antagonists (angiotensin II receptor blockers; ARBs) are a relatively recent class of antihypertensives that are generally considered to have similar, or even greater (based on

mechanism of action), efficacy than ACE inhibitors for two major therapeutic areas: prevention of cardiovascular and renal outcomes.<sup>[1]</sup> With respect to the latter, antihypertensive treatment to delay renal disease progression is most effective when targeting the renin-angiotensin system (RAS), i.e. using ARBs or ACE inhibitors. However, both classes do interfere at different stages of the RAS, clearly separating them from each other pharmacologically. A major advantage for ARBs over ACE inhibitors<sup>[2,3]</sup> is their better adverse drug reaction (ADR) profile.

In patients with type 2 diabetes mellitus, advantages for ARBs (added to standard antihypertensive therapy, excluding ACE inhibitors) over amlodipine and placebo for progression from micro- to macroalbuminuria, overt nephropathy and end-stage renal disease (ESRD) have been reported.<sup>[4-6]</sup> Results of these trials have led to ARBs being incorporated into evidence-based treatment guidelines, such as those by the American Diabetes Association (ADA).<sup>[7]</sup> The ADA states that ARBs, next to ACE inhibitors, are first-choice agents for treating nephropathy in hypertensive diabetic patients.<sup>[7]</sup>

In trials comparing ARBs with ACE inhibitors, hard endpoints are either lacking or do not show significant differences between the two drug classes. In addition, more experience exists with ACE inhibitors, and for some ACE inhibitors patents have expired, making them relatively cheap and enhancing their pharmacoeconomic profile.<sup>[8,9]</sup> Both factors probably contributed to recommendations for ACE inhibitors as first-choice agents in clinical guidelines for the treatment of hypertension in diabetic patients, for example in the Dutch guidelines.<sup>[10]</sup> Such guideline recommendations are equally applicable to patients with type 2 diabetes and advanced renal disease, including macroalbuminuria, proteinuria and overt nephropathy.

Obviously, delay in the progression of renal disease – and ultimately prevention of ESRD – may result in financial benefits and health gains. ESRD implies the need for dialysis and/or kidney transplantation (both costly interventions) with often scarce availability, and waiting list problems. European data suggest that dialysis costs around €60 000 annually and transplantation €25 000–40 000 in the first year (2002 values), with lower costs in the

follow-up years.<sup>[11,12]</sup> US data show that 40% of new ESRD cases are caused by diabetes, with a great contribution to the total annual ESRD costs, estimated at approximately \$US25 billion in 2002.<sup>[13]</sup>

This paper reviews the available pharmacoeconomic evidence on treatment with ARBs in type 2 diabetic patients with advanced renal disease. Our paper links to previous work published in this journal concerning the prevention of such advanced stages of renal disease, and concluding that expensive interventions that have proved to be truly effective may have a favourable pharmacoeconomic outcome.<sup>[8]</sup> We also present some original data on the pharmacoeconomic implications of the RENAAL (Reduction of Endpoint in Non-insulin dependent diabetes mellitus with Angiotensin II Antagonist Losartan) trial in The Netherlands.

## 1. Diabetic Nephropathy

Diabetic nephropathy is characterised by persistent and progressive loss of albumin via the urine. Incipient diabetic nephropathy with microalbuminuria involves the urinary excretion of 30–300 mg of albumin in the urine per day (or 20–200 µg/min). Overt nephropathy with persistent macroalbuminuria involves the excretion of >300 mg/day (>200 µg/min). In overt nephropathy, glomerular filtration rate steadily declines. This stage of overt nephropathy will generally result in progression to renal failure, with its associated need for dialysis and transplantation, but also to increasing cardiovascular risk. It has been shown that elevated albuminuria is associated with a higher risk for cardiovascular morbidity and mortality, independent of other 'classical' risk factors such as hypertension, dyslipidaemia and smoking.<sup>[14]</sup> The association is even stronger for albuminuria than for these classical risk factors.<sup>[15,16]</sup>

## 2. Clinical Trials of Angiotensin II Antagonists (ARBs) in Type 2 Diabetes with Overt Nephropathy

Several randomised clinical trials on ARBs in patients with type 2 diabetes and nephropathy have been published recently.<sup>[4,5,17,18]</sup> Most notably – and already economically evaluated – are RENAAL<sup>[4,19]</sup> and IDNT (Irbesartan Diabetic Nephropathy Tri-

al).<sup>[5,20]</sup> Both these trials have shown that the ARBs confer renoprotective effects beyond what might be expected from the achieved blood pressure lowering. Here we discuss both trials and compare the available information on ARBs with that on ACE inhibitors for the specific patient group of type 2 diabetes with overt nephropathy. In section 3 some additional trials on ARBs, notably IRMA-2 (Irbesartan MicroAlbuminuria diabetes type 2 patients),<sup>[6]</sup> and one major trial in cardiology with a subgroup analysis for type 2 diabetes patients (LIFE [Losartan Intervention For Endpoint reduction in hypertension]) are discussed.<sup>[21]</sup>

### 2.1 RENAAL

RENAAL,<sup>[4]</sup> a randomised placebo-controlled trial in 1513 patients with type 2 diabetes and nephropathy, compared the efficacy of losartan versus placebo (added to conventional antihypertensive therapy [diuretics, calcium channel antagonists,  $\alpha$ - and  $\beta$ -adrenoceptor antagonists, centrally acting agents or any combination, excluding ACE inhibitors]). One of the primary endpoints was ESRD or the need for dialysis. Patients on ACE inhibitors at baseline had this medication withdrawn prior to randomisation. RENAAL was discontinued, slightly earlier than planned, as soon as the results of the HOPE (Heart Outcomes Prevention Evaluation) trial<sup>[22,23]</sup> indicated superiority of ACE inhibitors over placebo (additional to conventional therapy) in averting cardiovascular events in renally impaired patients. Cardiovascular morbidity and mortality was specified as a secondary endpoint in RENAAL.

In RENAAL, a relative risk reduction of losartan for ESRD was estimated at 28% ( $p = 0.002$ ) on the basis of the Cox regression model. Crude absolute risks for ESRD of losartan and placebo were 20% and 26%, respectively. No statistically significant differences between losartan and placebo were found for overall mortality and cardiovascular morbidity and mortality. For RENAAL, cardiovascular morbidity and mortality prognosis was found to be better in patients with higher reductions of albuminuria levels whether in the placebo (conventional therapy) or losartan group.<sup>[24,25]</sup>

### 2.2 IDNT

IDNT involved 1715 patients with type 2 diabetes and nephropathy, and had three trial arms – irbesartan, amlodipine and placebo – with all three being added to conventional therapy.<sup>[5]</sup> All patients were hypertensive (blood pressure  $>135/85$  mm Hg or on antihypertensive treatment). Average patient follow-up was almost 3 years. As in RENAAL, patients receiving ACE inhibitors were switched to other antihypertensive therapy prior to inclusion.

Reported outcomes for irbesartan were relative risk reductions for the composite endpoint (death, ESRD or doubling of serum creatinine level) of 19% and 24% compared with placebo and amlodipine, respectively. The relative risk reduction for ESRD was 23%, for both irbesartan versus amlodipine and versus placebo, although these reductions were not statistically significant. The absolute risks for ESRD of irbesartan, amlodipine and placebo were 14%, 18% and 18%, respectively. There were no significant differences between treatments in the rates of death from any cause or in the cardiovascular composite endpoint (including cardiovascular death, myocardial infarction and heart failure).

Patients in the irbesartan group had significantly fewer adverse events per 1000 days of treatment than those in the placebo and amlodipine groups ( $p = 0.002$ ). However, serious hyperkalaemia resulting in the discontinuation of treatment occurred more often in the irbesartan group ( $p = 0.01$  for both comparisons).

### 2.3 Comments

Both RENAAL and IDNT report positive efficacy for ARBs in delaying ESRD, with fairly similar levels of relative risk reduction at 23–28%. When published, these results were highly relevant, as no previously published studies with hard endpoints on renal disease progression existed for ACE inhibitors in type 2 diabetic patients with nephropathy. Previously, it had been shown that ACE inhibitors were beneficial for type 1 diabetic patients with nephropathy, but this patient group differs in various aspects from type 2 diabetics (for example concerning demographic and metabolic factors).<sup>[26]</sup> In both RENAAL and IDNT,<sup>[4,5]</sup> the advantages of ARBs

exceeded those attributable to reductions in blood pressure.

In both trials, patients who were on ACE inhibitors prior to the study were switched to the studied drugs (ARBs) or placebo. In the literature, it has been suggested that discontinuation of ACE inhibitors for washout before a trial could have potential effects on risk reductions.<sup>[27]</sup> A subgroup analysis of RENAAL patients showed that relative risk reductions were rather similar between patients both previously and not previously receiving ACE inhibitors (close to the 28% average for both groups [29% for those previously on ACE inhibitors vs 27% for those not]).<sup>[28]</sup> This indicates that the switch away from ACE inhibitors will not have influenced the findings relevantly. Ideally, trials will be designed directly comparing both groups of drugs: ARBs versus ACE inhibitors.<sup>[27]</sup>

For newer ARBs – candesartan, olmesartan and eprosartan – large clinical trials in patients with type 2 diabetes are not yet available.<sup>[29-31]</sup>

### 3. Other Trials on ARBs

Other trials, discussed in the following subsections, have evaluated ARBs in patients with type 2 diabetes in stages of renal dysfunction that come prior to overt nephropathy, in particular microalbuminuria.

#### 3.1 Incipient Nephropathy

##### 3.1.1 IRMA-2

In the IRMA-2 study, 590 patients with type 2 diabetes, hypertension and microalbuminuria (urine albumin excretion of 20–200 µg/min) were randomised to receive irbesartan, either 150mg or 300mg, or placebo once daily.<sup>[6]</sup> After 2 years, the endpoint of overt diabetic nephropathy was reached in 14.9% of placebo-treated participants, and in 9.7% and 5.2% of those receiving irbesartan 150mg and 300mg, respectively (relative risk reductions of 39% and 70%, respectively).<sup>[6]</sup>

##### 3.1.2 MARVAL

The MARVAL (MicroAlbuminuria Reduction with VALsartan) study was also performed in type 2 diabetic patients with microalbuminuria.<sup>[32]</sup> This tri-

al included patients with a blood pressure <180/105mm Hg at baseline; i.e. normotensive or moderately hypertensive. Patients (n = 332) were randomised to valsartan or amlodipine. Patients receiving other hypertensive agents were switched to the drugs under investigation. Endpoints in the study were defined by albuminuria levels: percentage change in urinary albumin excretion and proportion of patients returning to healthy albuminuria levels (<20 µg/min). Whereas similar changes in blood pressure were seen between treatments, valsartan lowered albuminuria significantly more than amlodipine (reductions of 44% and 8%, respectively;  $p < 0.001$ ). Further, the proportion of patients returning to normoalbuminuria was greater for valsartan than for amlodipine (30% and 15%, respectively;  $p < 0.001$ ).

#### 3.2 Type 2 Diabetes in General; LIFE Substudy

The LIFE trial was conducted among 9193 participants aged  $\geq 55$  years with hypertension and left ventricular hypertrophy, among whom were 1195 patients with type 2 diabetes, with 11% having clinical albuminuria at baseline.<sup>[21,33]</sup> The trial – with a mean follow-up of 4.8 years – was designed to show the beneficial effects of losartan compared with conventional antihypertensive therapy on left ventricular hypertrophy (a strong independent risk factor for cardiovascular morbidity and mortality). Overall, it was found that losartan prevented more cardiovascular morbidity and mortality than atenolol with, in particular, a statistically significant effect on stroke (risk reduction of 25% for losartan compared with atenolol;  $p = 0.001$ ). In the diabetes substudy,<sup>[33]</sup> the same conclusions were reached; losartan seems to have benefits beyond blood pressure reduction and decreasing albuminuria levels.

Additionally, development of microalbuminuria was reported significantly ( $p = 0.002$ ) less often in the losartan group than in the atenolol group. The prevalence of microalbuminuria in the diabetes substudy fell in the losartan group from 11% at baseline to 8% after approximately 5 years versus only a small reduction from 12% to 11% in the atenolol group.<sup>[33]</sup>



#### 4. ACE Inhibitors in Type 2 Diabetes

HOPE and EUROPA (EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease)<sup>[23,34]</sup> showed that ACE inhibitors provide significant reductions in cardiovascular morbidity and mortality versus placebo among patients with cardiovascular risk factors. Both studies included a large group of type 2 diabetes patients.

A subanalysis of the HOPE study on patients with type 2 diabetes has been published.<sup>[22]</sup> It showed that ramipril protects against nephropathy compared with placebo, when added to standard antihypertensive (other blood pressure-lowering drugs) therapy. In addition, a beneficial effect of ramipril was detected for diabetic patients on the composite endpoint of myocardial infarction, stroke and death from cardiovascular causes, with a relative risk of approximately 0.76 (95% CI 0.65, 0.92).<sup>[22]</sup> As such, the HOPE study adequately combined nephrological and cardiovascular endpoints in type 2 diabetes patients.

A further substudy of HOPE among diabetic patients explicitly investigated cardiovascular risks in relation to the nephrological marker albuminuria.<sup>[35]</sup> The results indicated that the risk for cardiovascular events increases with increasing albuminuria levels. Therefore, the authors concluded that screening for albuminuria identifies people at high risk for cardiovascular complications.

The BENEDICT (The BERgamo NEphrologic Diabetes Complications Trial) study<sup>[36]</sup> examined whether ACE inhibitors and non-dihydropyridine calcium channel antagonists, alone or in combination, prevented microalbuminuria (20–200 µg/min) in patients with hypertension, type 2 diabetes, and healthy albuminuria levels. Results showed that patients using ACE inhibitors were less likely to progress to microalbuminuria than those receiving calcium channel antagonists.

Further subanalyses for type 2 diabetes are planned, e.g. the PERTINENT (PERindopril-Thrombosis, Inflammation, Endothelial dysfunction and neurohormonal Activation Trial), a substudy of the EUROPA data.<sup>[37,38]</sup>

#### 5. Pharmacoeconomic Analyses

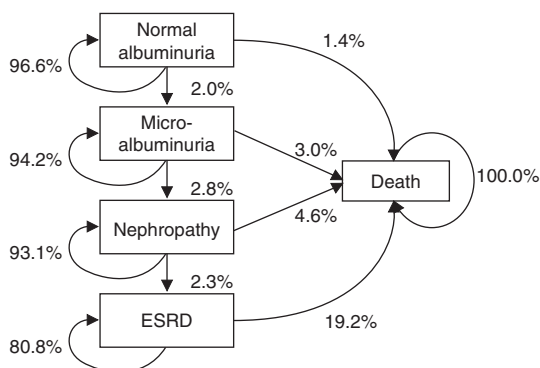
The methodology for economic evaluation of clinical trials is developing quickly. Various methods are now available, including the application of Fieller's method, bootstrap approaches and assuming a bivariate normal distribution for mean costs and effects.<sup>[39]</sup> Even short-term Markov models may be applied to the economic evaluation of clinical trials.<sup>[40]</sup> The advantages are that the data used are all trial-based and only a limited number of assumptions may be required. Some of the clinical trials described in sections 2–4 have been subject to such trial-based economic analysis. A major limitation of such analyses is the relatively short time frame, which does not extend beyond the clinical trial period. For reimbursement studies, long-term analyses are often required.<sup>[41]</sup> For that purpose, long-term Markov models are used.<sup>[40]</sup> An example of such a model is provided in figure 1.

In the following sections, we take a closer look at the economics of the RENAAL, IDNT and IRMA-2 studies. These results are summarised in table I.

##### 5.1 RENAAL

###### 5.1.1 USA

RENAAL<sup>[4]</sup> has been economically evaluated from a US healthcare perspective.<sup>[19]</sup> The analysis included all direct costs related to the study medication and direct benefits of delayed dialysis costs (although a few transplantations occurred in the



**Fig. 1.** General Markov model (1-year cycle) for the progression of renal disease in type 2 diabetic patients. Transition probabilities were estimated based on the UKPDS (United Kingdom Prospective Diabetes Study).<sup>[40,42]</sup> ESRD = end-stage renal disease.

**Table 1.** Results of published pharmacoeconomic evaluations of clinical trials for angiotensin II receptor antagonists (ARBs) in patients with type 2 diabetes mellitus and renal disease

Study and country	ARB	Maximum follow-up (y)	Discount rate (% per annum)		Net cost savings per patient [year of value]
			costs	effects	
<b>RENAAL</b>					
US <sup>[19]</sup>	Losartan	4	3	NM	\$US3522 vs placebo <sup>a</sup> (3.5y follow-up) [2001]
The Netherlands <sup>[43]</sup>	Losartan	3.5	4	4	€4540 vs placebo <sup>a</sup> [2003]
<b>IDNT</b>					
US <sup>[20]</sup>	Irbesartan	25	3	3	\$US23 817 vs amlodipine \$US16 026 vs placebo <sup>a</sup> (10y follow-up) \$US26 290 vs amlodipine \$US15 607 vs placebo <sup>a</sup> (25y follow-up) [2000]
Belgium <sup>[12]</sup>	Irbesartan	10	3	3	€15 000 vs amlodipine €9000 vs placebo <sup>a</sup> [2002]
France <sup>[12]</sup>	Irbesartan	10	3	3	€20 000 vs amlodipine €13 000 vs placebo <sup>a</sup> [2002]
Germany <sup>[44]</sup>	Irbesartan	10	5	5	€14 000 vs amlodipine €9000 vs placebo <sup>a</sup> [2001]
UK <sup>[45]</sup>	Irbesartan	10	6	1.5	£5125 vs amlodipine £2919 vs placebo <sup>a</sup> [2003]
<b>IRMA-2</b>					
US <sup>[46]</sup>	Early and late irbesartan <sup>b</sup>	25	3	3	Early irbesartan treatment: \$US11 922 vs control <sup>a</sup> Late irbesartan treatment: \$US3252 vs control <sup>a</sup> [2000]
Spain <sup>[47]</sup>	Early irbesartan	25	3	3	Early irbesartan treatment: €11 082 vs control <sup>a</sup> [2002]

a Conventional therapy but not ACE inhibitors.

b Based on IRMA-2 linked to IDNT.

**IDNT** = Irbesartan Diabetic Nephropathy Trial; **IRMA** = Irbesartan in type 2 diabetes with MicroAlbuminuria; **RENAAL** = Reduction of Endpoint in Non-insulin dependent diabetes mellitus with Angiotensin II Antagonist Losartan; **NM** = not mentioned in the paper.

trial, all days with ESRD were assumed as dialysis costs). Additionally, health effects were considered in terms of avoided ESRD days during the trial. For the initial analysis, dialysis costs, losartan treatment and ESRD days were evaluated at various periods of patient follow-up. Monetary amounts in \$US, year 2001 values, were discounted at 3%, according to the US guidelines.<sup>[48]</sup>

The study indicated clear potentials for cost savings to be achieved with losartan, increasing with longer periods of patient follow-up. Net cost savings through averted ESRD days were achieved after losartan treatment for 2–2.5 years (break-even point). After 4 years of patient follow-up, net savings were estimated at \$US5300 per patient (95% CI 950, 9600;  $p = 0.017$ ). Additionally, the authors calculated that the addition of losartan to the treatment of 100 patients with type 2 diabetes and ne-

phropathy could be expected to lead to a reduction of 9.2 person-years with ESRD over 3.5 years.<sup>[19]</sup>

The authors concluded that “Treatment with losartan in patients with type 2 diabetes and nephropathy, thus also resulted in substantial cost savings,” which corresponds with findings in the study of Alexander et al.<sup>[49]</sup> and the European study of Gerth et al.<sup>[50]</sup> The authors of RENAAL propose that this holds for the US situation and for patient groups that are comparable to those in RENAAL. To be relevant, we add that cost savings should also persist within an analysis that uses a longer time frame than the within-trial analysis allows. All these limitations are discussed in section 6.

### 5.1.2 Europe

Information was obtained from the manufacturer of losartan<sup>[28]</sup> and local health economics sources, enabling the investigation of the pharmacoeconomic

implications of RENAAL on European, Asian, South American and Canadian markets.

The within-trial analysis conducted from the Dutch healthcare perspective showed potential for cost savings with losartan. These cost savings increased with longer patient follow-up to €4540 per patient after 3.5 years (2003 values; discount rate 4% according to Dutch guidelines;<sup>[51]</sup> annual losartan costs approximately €400; annual dialysis costs €63 000).<sup>[43]</sup>

Further analysis for The Netherlands was conducted by our group, developing a Markov model describing the crucial transitions between disease states and using the cost data for losartan and dialysis as specified above. Our model was an adaption of one used previously,<sup>[52]</sup> which focused on the outcome parameters nephropathy, ESRD and death. As previously stated, the primary advantage of a Markov model is that it enables investigation of potential developments beyond the limited trial horizon (for example, development of ESRD in patients in whom ESRD was successfully delayed beyond the trial horizon and who survived long enough to still develop ESRD). Furthermore, it provides a more flexible tool to vary assumptions than the within-trial analysis.

Annual transition probabilities for albuminuria stages were derived from the RENAAL trial by counting person-years in stages and relating these to annual transitions. These rates were reported in the original publication.<sup>[4]</sup> Death rate in ESRD was taken from van Os et al.<sup>[11]</sup> Transition probabilities for progression to ESRD on losartan and placebo were inserted in the model (derived from both arms of RENAAL). The difference between both options determined potential cost savings. In RENAAL, the mean number of days with ESRD was 31% lower in the losartan-treated group than in the placebo-treated group after approximately 3.5 years. Next to this, the during-trial progression to ESRD was 37%. This is relatively high compared with previous estimates at 0.5–4% per year for progression to ESRD in type 2 diabetes patients with nephropathy.<sup>[53,54]</sup> Also, in the framework of clinical treatment guideline development, this lower rate was previously suggested for Dutch type 2 diabetic patients with nephropathy.<sup>[10]</sup> Therefore, a lower annual transition rate without losartan at 1.6% was assumed for progressing to

ESRD for secondary analysis. Simulations were run for a cohort of 1000 type 2 diabetes patients with nephropathy over their remaining lifetime. Half-cycle corrections were made.<sup>[40]</sup>

Table II shows that application of the Markov model with RENAAL assumptions indicates increasing net savings with increasing period of analysis. Long-term savings are almost 4-fold those in the short term. For validating the Markov model we note that predicted short-term per patient savings are similar to those measured in the within-trial analysis. Finally, the table illustrates that the Markov model did not reproduce short-term net savings if Dutch clinical guideline<sup>[10]</sup> assumptions were inserted into the model. However, in the long-term, net savings were also estimated using these assumptions, which were previously assumed to best reflect the progression of the Dutch type 2 diabetes patient. It should be noted that the current model lacks the inclusion of renal transplantation. Inclusion of these data might alter the results slightly, though we do not expect major changes in results and conclusions.

## 5.2 IDNT

### 5.2.1 USA

A specific within-trial analysis has not been published for the IDNT. However, such an analysis from the healthcare perspective has been performed as a part of a longer term Markov model analysis for the US (\$US, year 2000 values), including three treatment strategies (irbesartan, amlodipine and pla-

**Table II.** Estimated cost savings per patient, calculated from the healthcare perspective, of adding losartan (vs placebo) to standard antihypertensive therapy in overt diabetic nephropathy type 2 diabetes patients, using a Markov Model (1-year cycle) with transition probabilities from (i) RENAAL<sup>[19]</sup> or (ii) the Dutch Clinical Guidelines<sup>[10]</sup>

Time horizon (y)	Cost savings <sup>a</sup> (€ <sup>b</sup> )	
	RENAAL <sup>[19,43]</sup>	CBO <sup>[10]</sup>
3.5	4 540	-330
7	11 400	780
25	16 800	4 260

a Negative cost savings indicate net costs.

b Year 2003 values.

**CBO** = Centraal Begeleidings Orgaan voor de intercollegiale Toetsing, Utrecht, The Netherlands (clinical guideline for Dutch medical specialists); **RENAAL** = Reduction of Endpoint in Non-insulin dependent diabetes mellitus with Angiotensin II Antagonist Losartan.



cebo) and five outcome parameters: (i) nephropathy; (ii) doubling of serum creatinine level; (iii) ESRD managed with dialysis; (iv) ESRD managed with transplantation; or (v) death.<sup>[20]</sup> Transition probabilities within the Markov model were taken from the clinical trial; US values were used and discounted at 3%. The short-term analysis based on the Markov model and limited to the mean period of patient follow-up of approximately 3 years indicated cost savings for irbesartan treatment compared with both amlodipine and placebo. Compared with placebo, irbesartan conferred health gains in terms of days or years of life gained. Health effects for amlodipine and irbesartan over placebo were very similar, with a slight benefit for amlodipine.

Extension of the time horizon of the Markov model changed this slight benefit in health gains for amlodipine and increased health gains for irbesartan. Table I illustrates that cost savings for irbesartan reach their maximum somewhere between 10 and 25 years (in fact at 15 years), while health gains keep improving (not shown in table I).

The authors concluded that "this Markov model predicted that irbesartan would increase life expectancy and decrease costs of care in patients with type 2 diabetic nephropathy. Based on these results, irbesartan could have the potential to substantially reduce the clinical and economic burdens of patients with type 2 diabetic nephropathy."

### 5.2.2 Europe

Three studies have been published – based on the IDNT and using the Markov model developed for the US using the healthcare perspective – providing evidence for the favourable pharmacoeconomic impact of irbesartan in European settings. These studies pertain to Belgium and France,<sup>[12]</sup> Germany<sup>[44]</sup> and the UK.<sup>[45]</sup>

For Belgium and France, country-specific prices (2002 values), a 10-year time horizon and 3% discounting were employed. Onset of ESRD was delayed an additional 1.5 years for irbesartan versus amlodipine and placebo. During the 10-year period, this delay in ESRD translated into gains of 0.13 life-years for irbesartan versus amlodipine and 0.26 life-years versus placebo. Irbesartan provided cost savings of €15 000 and €9000 per patient in Belgium, and €20 000 and €13 000 in France, versus

amlodipine and placebo, respectively, over the 10-year period. These results were found robust under a large range of plausible assumptions in the sensitivity analysis.

The German study employed country-specific prices (2001 values), a time horizon of 10 years and discounting at 5% per annum. It was found that for German 'IDNT-like' patients, the cumulative incidence of ESRD would be lower on irbesartan (36%) than on amlodipine (49%) or placebo (45%). Additionally, irbesartan was estimated to save costs of €14 000 and €9000 per patient versus amlodipine or placebo, respectively, over the 10-year period.

For the UK, a time horizon of 10 years and discount rates for costs (2003 values) and effects of 6.0% and 1.5%, respectively, were used. Delay in onset of ESRD with irbesartan led to cost savings of £5125 and £2919 per patient and improvements in discounted life expectancy of 0.07 and 0.21 over 10 years versus amlodipine and control, respectively.<sup>[45]</sup>

In short, applications of the Markov model to European countries reaffirms the findings for the US: irbesartan appears to save costs and confer health gains for type 2 diabetes patients with nephropathy.

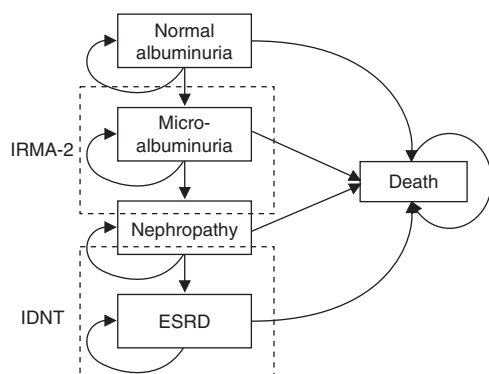
## 5.3 IRMA-2

### 5.3.1 USA

Cost effectiveness for RAS intervention in the phase of incipient nephropathy (IRMA-2) has been studied in relation to the IDNT study (PRIME; Program for Irbesartan Mortality and morbidity Evaluations) using 2002 cost levels.<sup>[5,6,8,46]</sup> Through linking these studies it could be investigated whether it is more cost effective to start with irbesartan at the stage of overt nephropathy or prior to that stage, in particular in incipient nephropathy. The initial problem was that IDNT and IRMA-2 did not link directly to each other. In particular, patients leaving IRMA-2 because of the diagnosis of nephropathy had a median urinary albumin excretion of 700 mg/day versus almost 2000 mg/day for patients entering IDNT. In terms of progression of disease, this means that there is a gap of approximately 2–3 years between the two trials.

To close the gap between the two studies, a state of early nephropathy was created in a Markov model (figure 2). Baseline transition probabilities in the Markov model were directly derived from the placebo arms of IRMA-2 and IDNT and corrected for the estimated relative risks of treatment with irbesartan 300mg daily: 0.30 (95% CI 0.14, 0.61) in IRMA-2 and 0.83 (95% CI 0.62, 1.11) in IDNT.<sup>[46]</sup> The confidence intervals were used in probabilistic analysis using Monte-Carlo methods with a period of analysis of 25 years in each simulation.

Results were calculated for the US healthcare payer perspective with dialysis costs of \$US60 133 and costs of irbesartan at \$US573.05 annually.<sup>[46]</sup> Starting with irbesartan in the microalbuminuric stage would avert >2 years spent with ESRD per patient compared with conventional treatment (other antihypertensive drugs excluding ACE inhibitors). However, starting irbesartan treatment during nephropathy would only avert 146 days spent with ESRD per patient. The mean life expectancies would be 13 years on conventional therapy, 15 years for starting irbesartan in early nephropathy, and 13 years for late treatment. Cumulative incidence of ESRD over 25 years would be 20% on conventional therapy, 7% with early intervention of irbesartan, and 16% if irbesartan was applied later, i.e. only during overt nephropathy. Additionally, cost savings were estimated for early treatment with irbesartan. Total costs per patient were (discounted



**Fig. 2.** Markov model for the analyses of IRMA-2 (Irbesartan in type 2 diabetes with MicroAlbuminuria) and IDNT (Irbesartan Diabetic Nephropathy Trial).<sup>[13]</sup> The estimated transition probabilities from IRMA-2 and IDNT changed from year to year, thus no single value could be indicated in this model.<sup>[20,46]</sup> ESRD = end-stage renal disease.

at 3%): \$US28 782 for conventional therapy, \$US16 859 for early irbesartan and \$US25 529 for late treatment. Cost savings were as follows: \$US11 922 for early irbesartan, \$US3252 for late irbesartan versus conventional treatment and \$US8670 for early versus late irbesartan. The break-even point for early and late irbesartan versus conventional treatment was reached after approximately 10 and 5 years, respectively.<sup>[46]</sup>

### 5.3.2 Europe

Three studies based on IRMA-2 have also provided evidence for the favourable pharmacoeconomic impact of irbesartan in the for Spanish, Swedish and Swiss settings.<sup>[47,55]</sup> In patients with hypertension, microalbuminuria and type 2 diabetes, early treatment with irbesartan reduced the incidence of ESRD, extended life and led to cost savings in these three different European settings. Only the analysis for Spain was published as a full research article. For that reason, only the Spanish results are further described below.

The same Markov model as used for the US (see section 5.3.1) was used to simulate and analyse the situation in Spain. For the analyses from the third-party healthcare payer perspective, country-specific costs, a 25-year time horizon and 3% discounting were used. Early treatment with irbesartan led to 0.88 avoided years of ESRD. During the 25-year period, discounted life expectancy was improved by 0.84 years, with corresponding per patient cost-savings of €11 082 versus conventional therapy.

## 6. Discussion

Recent clinical trials have presented the first evidence on hard endpoints with respect to significant reductions in progression to ESRD with ARBs in type 2 diabetes patients with nephropathy (RENAAL and IDNT).<sup>[4,5]</sup> These trials were evaluated economically in both the short- and the long-term, using within-trial analytic and Markov model techniques for the US and European settings.<sup>[12,19,20,43-47,49,50,52-55]</sup> Results and conclusions were unequivocal: these drugs appear to confer both health gains and net cost savings compared with conventional (non-ACE inhibitor) therapy, i.e. they are dominant therapies. Additionally, the economic evaluation of the IRMA-2 study suggested that it

would be cost effective to start ARB treatment even prior to the overt nephropathy stage.

Whether ACE inhibitors confer similar benefits in these patient groups is as yet unknown, but not unlikely given the related pharmacological properties of the two drug classes and circumstantial evidence. Apart from the DETAIL (Diabetics Exposed to Telmisartan And enalapril) trial, in which telmisartan was found to be not inferior to enalapril in providing renoprotection in type 2 diabetes patients, there are hardly any head-to-head trials comparing ARBs and ACE inhibitors.<sup>[56]</sup>

Despite the absence of hard endpoint measurements on renal function for ACE inhibitors in type 2 diabetes, pharmacoeconomic analysis has been performed based on clinical trials with intermediate endpoints.<sup>[57,58]</sup> These clinical trials were used by Golan et al.<sup>[52]</sup> to estimate progression rates in a Markov model developed to investigate the cost effectiveness of ACE inhibitors in the treatment and screening of type 2 diabetes. The additional net costs for treating all hypertensive diabetic patients with ACE inhibitors would be \$US7500 per QALY gained compared with screening for microalbuminuria first and treating only those in whom it was detected.

Further evidence has been published on favourable cardiovascular outcomes for ARBs, among both type 2 diabetes patients and non-diabetics. For example, the recent LIFE trial showed that losartan was associated with a significant reduction in cardiovascular mortality among almost 1200 patients with type 2 diabetes included in the trial, and provided a significant reduction in the incidence of diabetes among 8000 participants with hypertension.<sup>[33,59]</sup> In economic evaluations of studies such as LIFE, ARBs have been shown to be potentially cost effective in type 2 diabetic patients with nephropathy. Comparable studies also exist for ACE inhibitors, for example the economic evaluation of HOPE for Germany<sup>[60]</sup> and Sweden.<sup>[61]</sup> However, none of these studies explicitly addressed cost effectiveness in patients with type 2 diabetes in relation to albuminuria levels.

In the systematic review by Strippoli et al.,<sup>[62]</sup> similar effects on renal outcomes were found for ARBs and ACE inhibitors. There is a point of discussion in this meta-analysis suggesting a cardio-

vascular and survival benefit with ACE inhibitors but not with ARBs in patients with diabetic nephropathy. The trials with ACE inhibitors were placebo controlled without equal blood pressure control, resulting in a blood pressure difference in favour of ACE inhibitor treatment, whereas the ARB trials were actively controlled (vs standard therapy) with the objective being to obtain equal blood pressure control. This indirect comparison of ACE inhibitors with ARBs also raises the need for a head-to-head comparison and possibly a combination of two different agents from each class to study effects on renal and cardiovascular outcomes, adverse effects<sup>[63,64]</sup> (i.e. dry cough and angio-oedema) and mortality. If effects of ACE inhibitors and ARBs do not differ significantly, costs of drugs involved become more important for reimbursement decisions.<sup>[65]</sup> As the first ACE inhibitors are now off patent, this would favour this class of drugs. The DETAIL study<sup>[56]</sup> showed equivalence in renal protection between ACE inhibitors and ARBs in patients with early diabetic nephropathy. This would suggest lower costs for ACE inhibitor treatment in type 2 diabetic patients with nephropathy. Unfortunately, the DETAIL study<sup>[56]</sup> lacks pharmacoeconomic evidence and is not completely transferable to all patients with type 2 diabetes and nephropathy. There is a need for further investigation on the impact of patent expiries and subsequent cost consequences.

Long-term 'real-world' analyses are often required in national guidelines for 'good pharmacoeconomic practice' in supporting clinical guideline development or reimbursement decisions.<sup>[14,15]</sup> Despite sophisticated methods having been developed for analysing economic data in clinical trials (including Fieller's method, bootstrapping and power calculations for economic outcomes), such analyses are increasingly considered non-optimal given the lack of long-term and 'real-world' perspectives.<sup>[2]</sup> On the other hand, decision makers feel uncomfortable with making healthcare payment decisions based on models with time horizons up to 25 years. Also, in the IRMA-2/IDNT model, break-even is obtained 'only' after 6 years, which may still be considered longer than the typical time horizon of some decision makers.

Positive results from the IRMA-2/IDNT model<sup>[46]</sup> have been published or presented now for about ten countries.<sup>[66]</sup> The same conclusions are found in all ten countries. Yet, it was also shown that the results were sensitive to the number of ESRD patients treated by dialysis and the yearly cost of dialysis. If there is a reduction in the latter cost in the future, the net savings obtained with irbesartan must be revised. Another issue in the transferability of such results over various countries is that the rate of progression from nephropathy to doubling of serum creatinine level, or the earlier progression from microalbuminuria to nephropathy, may be different among countries, because of not only ethnic aspects but also current management of patients, which is often less optimal than the management in the placebo and active arms of the IRMA-2/IDNT study.<sup>[46]</sup> In summary, multi-country adaption models based on existing (multi-country) trials are a good opportunity to calculate cost effectiveness based on sophisticated models and can be easily used by several countries. Despite this advantage, there are still local imperfections for such models that are mostly related to demographic factors and differences in populations (i.e. race). Reimbursement agencies often require analyses that are specifically tailored to their own country, e.g. evaluations of national screening programmes.<sup>[67]</sup>

## 7. Conclusions

Economic evaluations of RENAAL, IDNT and IRMA-2 using different time horizons suggest ARBs versus conventional therapy to be cost saving in type 2 diabetes patients with nephropathy, largely because of the high costs of dialysis and transplantation. Cost savings are seen within about 6 years. It is unusual to have an effective new treatment that may also be cost saving. Even in secondary prevention trials such as the 4S (Scandinavian Simvastatin Survival Study) on simvastatin in a group of high-risk patients, only a quarter of the treatment costs were earned back through cost savings.<sup>[68]</sup>

The economic profile of ACE inhibitors in this particular patient group has still to be elucidated. For reimbursement decisions and reference pricing classifications, a head-to-head trial comparing ACE inhibitors with ARBs is needed, next to building a pharmacoeconomic model with a proper time hori-

zon taking all costs and effects (renal and cardiovascular, mortality and adverse effects) into account.

## Acknowledgements

All authors participated in the concept and design of the paper; analysis and interpretation of data; drafting or revision of the manuscript. The authors have no conflicts of interest to declare.

The authors acknowledge the work of G.W. Carides and W.C. Gerth (Merck & Company, Blue Bell, Pennsylvania, USA) on adapting the RENAAL trial-based pharmacoeconomic model for losartan to the Dutch situation. M.J. Postma and L.J.P. Annemans previously received grant support for economically evaluating ARBs by MSD (Haarlem, The Netherlands), and Sanofi-Synthelabo (Paris, France), respectively.

No sources of funding were used to assist in the preparation of this study.

## References

1. Laverman GD, Remuzzi G, Ruggenenti P. ACE inhibition versus angiotensin receptor blockade: which is better for renal and cardiovascular protection? *J Am Soc Nephrol* 2004; 15: S64-70
2. Postma MJ, Kruidhof H, de Jong-van den Berg LT, et al. Pharmacoeconomic aspects of losartan treatment to delay progression of renal disease in patients with type 2 diabetes. *Expert Opin Pharmacother* 2003; 4 (9): 1543-50
3. Coyle JD, Gardner SF, White CM. The renal protective effects of angiotensin II receptor blockers in type 2 diabetes mellitus. *Ann Pharmacother* 2004; 38: 1731-8
4. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345 (12): 861-9
5. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345 (12): 851-60
6. Parving HH, Lehnert H, Bröchner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; 345 (12): 870-8
7. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2005; 28 Suppl. 1: S4-36
8. Rippin JD, Barnett AH, Bain SC. Cost-effective strategies in the prevention of diabetic nephropathy. *Pharmacoeconomics* 2004; 22 (1): 9-28
9. van Hout B, Simeon GP, McDonnell J, et al. Economic evaluation of benazepril in chronic renal insufficiency. *Kidney Int* 1997; 52 (63): S159-62
10. van Ballegooie E, van Everdingen JJE. CBO guidelines on diagnosis, treatment, and prevention of complication in diabetes mellitus, retinopathy, foot ulcers, nephropathy and cardiovascular diseases: Dutch Institute for Quality Assurance [in Dutch]. *Nederlands Tijdschrift voor Geneeskunde* 2000; 144 (9): 413-8
11. van Os N, Niessen LW, Bilo HJ, et al. Diabetes nephropathy in the Netherlands: a cost-effectiveness analysis of national clinical guidelines. *Health Policy* 2000; 51: 135-47
12. Palmer AJ, Annemans L, Roze S, et al. An economic evaluation of irbesartan in the treatment of patients with type 2 diabetes, hypertension and nephropathy: cost-effectiveness of Irbesartan



- in Diabetic Nephropathy Trial (IDNT) in the Belgian and French settings. *Nephrol Dial Transplant* 2003; 18: 2059-66
13. USRDS annual data report 2004. Bethesda (MD): National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases, 2004
  14. Hillege HL, Fidler V, Diercks GFH, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; 106: 1777-82
  15. Diercks GFH, Hillege HL, van Boven AJ, et al. Microalbuminuria modifies the mortality risk associated with electrocardiographic ST-T segment changes. *J Am Coll Cardiol* 2002; 40 (8): 1401-7
  16. Asselbergs FW, Hillege HL, van Gilst WH. Framingham score and microalbuminuria: combined future targets for primary prevention? *Kidney Int* 2004; 66 Suppl. 92: S111-4
  17. Ruilope LM, Segura J, Losartan and other angiotensin II antagonists for nephropathy in type 2 diabetes mellitus: a review of the clinical trial evidence. *Clin Ther* 2003; 25 (12): 3044-64
  18. Zanella MT, Ribiero AB. The role of angiotensin II antagonism in type 2 diabetes mellitus: a review of renoprotection studies. *Clin Ther* 2002; 24 (7): 1019-34
  19. Herman WH, Shahinfar S, Carides GW, et al. Losartan reduces the costs associated with diabetic end-stage renal disease: the RENAAL study economic evaluation. *Diabetes Care* 2003; 26: 683-7
  20. Rodby RA, Chiou CF, Borenstein J, et al. The cost-effectiveness of irbesartan in the treatment of hypertensive type 2 diabetic nephropathy. *Clin Ther* 2003; 25 (7): 2102-19
  21. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002; 359: 995-1003
  22. Gerstein HC, Yusuf S, Mann JFE, et al. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICROHOPE substudy. *Lancet* 2000; 355: 253-9
  23. Yusuf S, Sleight P, Dagenais G, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342 (3): 145-53
  24. de Zeeuw D, Remuzzi G, Parving HH, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 2004; 110: 921-7
  25. de Zeeuw D, Remuzzi G, Parving HH, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int* 2004; 65: 2309-20
  26. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; 329 (20): 1456-62
  27. Huston P, Peterson R. Withholding proven treatment in clinical research. *N Engl J Med* 2001; 345: 912-4
  28. Data on file, Merck & Co., Inc. 2003
  29. Easthope SE, Jarvis B. Candesartan cilexetil: an update of its use in essential hypertension. *Drugs* 2002; 62 (8): 1253-87
  30. Warner GT, Jarvis B. Olmesartan medoxomil. *Drugs* 2002; 62 (8): 1345-53
  31. Ruilope L, Jäger B. Eprosartan for the treatment of hypertension. *Expert Opin Pharmacother* 2003; 4: 107-14
  32. Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: the MicroAlbuminuria Reduction With VALsartan (MARVAL) study investigators. *Circulation* 2002; 106: 672-8
  33. Lindholm LH, Ibsen H, Dahlöf B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention for Endpoint reduction hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359: 1004-10
  34. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). The EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease investigators. *Lancet* 2003; 362: 782-8
  35. Gerstein HC, Mann JFE, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; 286: 421-6
  36. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004; 351 (19): 1941-51
  37. Gomma AH, Fox KM. The EUROPA trial: design, baseline demography and status of the substudies. The EUROPA investigators. *Cardiovasc Drugs Ther* 2001; 15: 169-79
  38. Ferrari R, Arbustini E, Blann A, et al. PERTINENT (PERindopril-Thrombosis, Inflammation, Endothelial dysfunction and Neurohormonal activation Trial): a sub-study of the EUROPA Study. *Cardiovasc Drugs Ther* 2003; 17: 83-91
  39. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. *Annu Rev Public Health* 2002; 23: 377-401
  40. Briggs A, Sculpher M. An introduction to markov modelling for economic evaluation. *Pharmacoeconomics* 1998; 13 (4): 397-409
  41. International Society for Pharmacoeconomics & Outcomes Research (ISPOR). Pharmacoeconomic guidelines around the world [online]. Available from URL: <http://www.ispor.org/PEguidelines/index.asp> [Accessed 2005 Jun 30]
  42. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003; 63: 225-32
  43. Postma MJ, Bartstra J, Annemans LJP. Angiotensin-II antagonists in diabetes mellitus type 2 [in Dutch]. *Pharm Weekbl* 2004; 139 (33): 1060-3
  44. Palmer AJ, Annemans L, Roze S, et al. Health economic consequences of the use of irbesartan in patients in Germany with type 2 diabetes, nephropathy and hypertension [in German]. *Dtsch Med Wochenschr* 2004; 129: 13-8
  45. Palmer AJ, Annemans L, Roze S, et al. An economic evaluation of the Irbesartan in Diabetic Nephropathy Trial (IDNT) in a UK setting. *J Hum Hypertens* 2004; 18 (10): 733-8
  46. Palmer AJ, Annemans L, Roze S, et al. Cost-effectiveness of early irbesartan treatment versus control (standard antihypertensive medications excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers) or late irbesartan treatment in patients with type 2 diabetes, hypertension, and renal disease. *Diabetes Care* 2004; 27: 1897-903
  47. Palmer AJ, Annemans L, Roze S, et al. Irbesartan is projected to be cost and life saving in a Spanish setting for treatment of patients with type 2 diabetes, hypertension, and microalbuminuria. *Kidney Int* 2005; 67 Suppl. 93: S52-54
  48. Gold MR, Siegel JE, Russel LB, et al., editors. Cost-effectiveness in health and medicine. New York: University Press, 1996
  49. Alexander CM, Lyle PA, Keane WF, et al. Losartan and the United States costs of end-stage renal disease by baseline albuminuria in patients with type 2 diabetes and nephropathy. *Kidney Int* 2004; 66 Suppl. 92: S115-7
  50. Gerth WC, Remuzzi G, Viberti G, et al. Losartan reduces the burden and cost of ESRD: public health implications from the RENAAL study for the European Union. *Kidney Int* 2002; 62 (82): S68-72
  51. College voor zorgverzekeringen (CvZ). Guidelines for pharmacoeconomic research [in Dutch]. Amstelveen: College voor zorgverzekeringen, 1999



52. Golan L, Birkmeyer JD, Welch HG. The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. *Ann Intern Med* 1999; 131 (9): 660-7
53. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM: I. Model construction and assumptions. *Diabetes Care* 1997; 20 (5): 725-34
54. Eastman RC, Javitt JC, Herman WH, et al. Model of complications of NIDDM: II. Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. *Diabetes Care* 1997; 20 (5): 735-44
55. Palmer AJ, Roze S, Valentine WJ, et al. Irbesartan is projected to be cost and life saving compared to standard blood pressure control alone for treatment of patients with type 2 diabetes, hypertension, and microalbuminuria in Spanish, Swedish and Swiss settings [abstract]. *Value Health* 2004; 7 (6): 655
56. Barnett AH, Bain SC, Bouter P, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; 351 (91): 1952-61
57. Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993; 118: 577-81
58. Ravid M, Brosh D, Levi Z, et al. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus: a randomized controlled trial. *Ann Intern Med* 1998; 128: 982-8
59. Lindholm LH, Dahlöf B, Edelman JM, et al. Effect of losartan on sudden cardiac death in people with diabetes: data from the LIFE study. *Lancet* 2003; 362: 619-20
60. Schädlich PK, Brecht JG, Rangoonwala B, et al. Cost-effectiveness of ramipril in patients at high risk for cardiovascular events: economic evaluation of the HOPE (Heart Outcomes Prevention Evaluation) study for Germany from the statutory health insurance perspective. *Pharmacoeconomics* 2004; 22 (15): 955-73
61. Björholt I, Andersson FL, Kahan T, et al. The cost-effectiveness of ramipril in the treatment of patients at high risk of cardiovascular events: a Swedish sub-study to the HOPE study. *J Intern Med* 2002; 251: 508-17
62. Strippoli GFM, Craig M, Deeks JJ, et al. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ* 2004; 329: 828-31
63. Pylypchuk GB. ACE-inhibitor versus angiotensin II blocker induced cough and angioedema. *Ann Pharmacother* 1998; 32: 1060-6
64. Fuchs SA, Meyboom RHB, van Puijenbroek EP, et al. Use of angiotensin receptor antagonists in patients with ACE-inhibitor induced angioedema. *Pharm World Sci* 2004; 26: 191-2
65. Mitch WE. Treating diabetic nephropathy: are there only economic issues? *N Engl J Med* 2004; 351 (19): 1934-6
66. Palmer AJ, Rodby RA. Health economics studies assessing irbesartan use in patients with hypertension, type 2 diabetes, and microalbuminuria. *Kidney Int* 2004; 66 Suppl. 92: S118-120
67. Atthobari J, Asselbergs FW, Boersma C, et al. Cost-effectiveness of screening for albuminuria and subsequent treatment with ACE-inhibitor to prevent cardiovascular events: a pharmacoeconomic analysis linked to the PREVEND and PREVEND-IT studies. The PREVEND-IT study group. *Clin Ther* 2006; 28 (3): 432-44
68. Johannesson M, Jönsson B, Kjerkhus J, et al. Cost-effectiveness of simvastatin treatment in lower cholesterol levels in patients with coronary heart disease. *N Engl J Med* 1997; 336: 332-6

---

Correspondence and offprints: *Cornelis Boersma, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands.*  
E-mail: *C.Boersma@rug.nl*