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Original Article

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

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Abstract

Background. In the Irbesartan in Diabetic Nephropathy Trial (IDNT), treatment with irbesartan demonstrated 23 and 20% reductions in the combined endpoint of doubling of serum creatinine (DSC), end-stage renal disease (ESRD) or death in patients with hypertension, type 2 diabetes and overt nephropathy compared with amlodipine and control, respectively. A simulation model was developed to project long-term cost consequences of the IDNT in Belgium and France.

Methods. A Markov model simulated progression from nephropathy to DSC, ESRD and death in patients with hypertension, type 2 diabetes and overt nephropathy. Treatment-specific probabilities were derived from IDNT. Country-specific ESRD-related data were retrieved from published sources. Delay in onset of ESRD, life expectancy and mean lifetime costs were calculated for patients with a baseline age of 59 years. Future costs were discounted at 3% per annum (p.a.), and clinical benefits were discounted at 0 and 3% p.a.. Extensive sensitivity analyses were performed.

Results. Onset of ESRD was delayed with irbesartan by 1.41 and 1.35 years *vs* amlodipine and control, respectively. When a 10-year time horizon was considered, delay in ESRD onset led to anticipated improvements in life expectancy of 0.13 years *vs* amlodipine and 0.26 years *vs* control. Irbesartan was associated with cost savings of €14 949 and €9205/patient in Belgium, and €20 128 and €13 337 in France, *vs* amlodipine and control, respectively. The results were robust under a wide range of plausible assumptions.

Conclusions. Treating patients with hypertension, type 2 diabetes and overt nephropathy using irbesartan was both cost- and life-saving compared with amlodipine and control.

Keywords: amlodipine; hypertension; irbesartan; nephropathy; type 2 diabetes

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Introduction

There has been an explosive increase in the incidence and prevalence of end-stage renal disease (ESRD) with type 2 diabetes as the major underlying cause over the last decade in the western world [1]. Between 1993 and 1999 there was an annual increase of 5% in the prevalence of ESRD in France [1]. With the prevalence of diabetes among renal replacement therapy patients ~21% the scale of this problem is clear. Moreover, renal replacement therapy patients with type 2 diabetes have high morbidity and mortality rates. In France, the median survival time is ~2.7 years and cardiovascular mortality the main cause of death [2].

The Irbesartan in Diabetic Nephropathy Trial (IDNT) was a multicentre, double-blind, placebo controlled study assessing the effect of irbesartan (angiotensin II-receptor blocker) *vs* amlodipine (dihydropyridine calcium channel blocker) or placebo on the progression of diabetic renal disease and all-cause mortality in hypertensive patients with type 2 diabetes and proteinuria [3]. Irbesartan treatment resulted in a reduction of ~23% in the combined endpoint of death, ESRD and doubling of serum creatinine (DSC) compared with amlodipine ($P = 0.006$) and a 20% reduction compared with the control group ($P = 0.02$). We developed a

Markov model (a common approach to simulate long-term progressive diseases [4]) to extrapolate the results of the IDNT and project long-term clinical and cost outcomes. This article provides a description of the methodology used and reports the findings of this long-term simulation. While other treatment agents like ACE inhibitors are also used in this patient group, and health-economic comparisons with ACE inhibitors and other medications would be interesting if appropriate clinical data were available, we restricted the analysis to the treatments assessed in the IDNT due to lack of direct clinical comparisons between angiotensin II-receptor blockers and ACE inhibitors.

Subjects and methods

Model structure

A computer-based Markov simulation software program was developed to model the clinical course of disease of a population with type 2 diabetes, overt nephropathy and hypertension as they progressed to DSC, onset of ESRD (treated with either dialysis or renal transplantation) and death. Markov models are made up of a set of distinct states, with transitions between the states occurring according to probabilities, which are usually derived from published studies. When a simulation is run, simulated patients can remain in any particular state or switch to another state in each cycle of the simulation (usually representing 1 year) until they reach a terminal state (for example death) or the time horizon is reached.

In this analysis, the model consisted of five primary health states (Figure 1), with all patients starting in the 'no progression' state:

(i) Initial or 'no progression state': IDNT patient at inclusion with type 2 diabetes and proteinuria ($\geq$900 mg/24 h).
(ii) Progression of diabetic nephropathy with DSC.
(iii) ESRD treated with dialysis.
(iv) ESRD receiving transplant.
(v) Death.

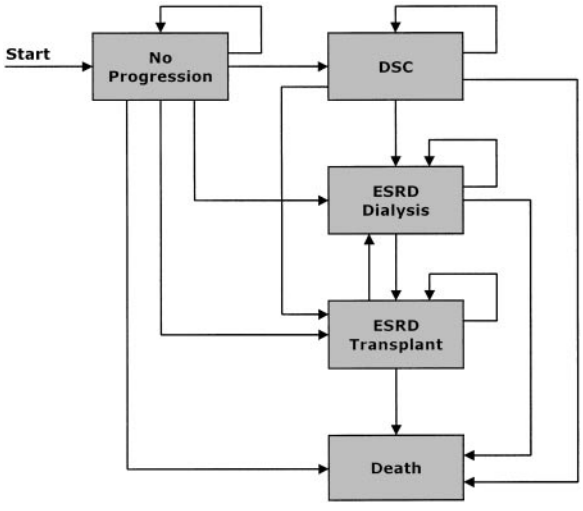

Fig. 1. The simulated cohort started in the 'no progression' state. Patients may remain in a given state, or progress to another state. The state of 'no progression' represents the cohort state at the start of the IDNT.

Cohort and treatment groups

The model simulated a hypothetical cohort of patients with type 2 diabetic nephropathy similar to those in the IDNT. The baseline characteristics of this cohort have been described previously [5]. Three treatment choices were simulated based on treatments in the IDNT: irbesartan titrated from 75 to 300 mg/day, amlodipine titrated from 2.5 to 10 mg/day, or control (standard antihypertensive therapy, excluding ACE inhibitors, angiotensin-receptor blockers or calcium channel blockers). Other antihypertensive drugs were permitted to achieve target blood pressure ($\leq$135/85 mmHg).

Clinical data inputs (transition probabilities)

Probabilities from the states 'no progression' and 'DSC' are summarized in Table 1. The duration of the IDNT was up to 5 years with 2.9 years as the mean length of total patient follow up. Transitional probabilities for the first 3 years of the model were obtained from the actual number of annual events in the IDNT clinical trial. For the remainder of the model, an average of probabilities across those first 3 years was used for each arm.

Once a patient progressed to the 'DSC' state, the transition probability to ESRD increased in comparison with the 'no progression' state. Rodby *et al.* [6] showed that the median time from DSC to ESRD, based on IDNT data, varied between treatment arms: 328 days with irbesartan, 301 days with amlodipine and 273 days with control. The data, together with an assumption of a constant hazard rate function, were applied to estimate the annual probability of transition from DSC to ESRD in each treatment arm.

Table 1. Overview of probabilities derived from the IDNT

Year	Probability		
	Irbesartan	Amlodipine	Control
Probability of moving from 'no progression' to 'DSC'			
1	0.0069	0.0141	0.0141
2	0.0454	0.0507	0.0486
3	0.0423	0.0872	0.0644
4+	0.0315	0.0507	0.0424
Probability of moving from 'no progression' to 'ESRD'			
1	0.0311	0.0264	0.0246
2	0.0207	0.0487	0.0447
3	0.0249	0.0410	0.0396
4+	0.0256	0.0388	0.0363
Probability of moving from 'DSC' to 'ESRD'			
1+	0.537606	0.568517	0.604156

Probabilities were calculated from the following sample sizes (first, second and third years, respectively) for irbesartan: 579, 529 and 430 patients; for amlodipine: 567, 513 and 390 patients; and for the control group: 569, 514 and 404 patients. For year 4 and beyond, the average of the first 3 years was used for each treatment arm. Probability = annual transition probability; 'year' refers to year of model simulation. Distinction was made between the Belgian and French probabilities of transplantation and dialysis due to differences in country-specific ESRD management practices.

Mortality rates for patients in the 'no progression' and 'DSC' states were assumed to be equal as there is no evidence that patients with DSC (and not progressing to ESRD) have a higher mortality rate than those without DSC. To calculate the annual probabilities of dying, the mean annual death rates in each treatment arm over the 2.9-year follow up period were converted to transition probabilities using the 'RatetoProb' function of the DATA software. For the first 10 years of the model, mortality data from the IDNT were used [3].

Age was taken into account from year 10, based on the published evidence that mortality doubles every 10 years in type 2 diabetes patients [7]. Mortality was age-adjusted by doubling it with every 10-year increase in age (after the first 10 years of simulation).

When a simulated patient developed ESRD, the probabilities of death or changing between the dialysis and renal transplant states were assumed to be independent of treatment arm. The model outcome was adapted to the French and Belgian settings by incorporation of country-specific ESRD management and outcomes data for Belgium and France where available (Table 2) [8–10]. There were two main exceptions to this:

(i) In Belgium, the transition from transplant to dialysis was high in the first year but much lower in subsequent years [8]. For France, the transitions from dialysis to transplant and from transplant to dialysis (transplant failure) were only available for 1 year. Therefore, the Belgian data were used as a proxy for these transitions for all subsequent years in France.

(ii) Reliable mortality rates for patients receiving renal transplants were not found for either France or Belgium. It was assumed that mortality rates would not differ widely in Western countries, and US figures for transplant patients (not specific to gender or race) were applied [10].

Table 2. Country-specific transition probabilities from ESRD states

Belgium		France	
Year	Probability	Year	Probability
Probability of moving from 'dialysis' to 'transplant'			
1	0.0460	1	0.0415
2	0.0340	2	0.0415
3	0.0230	3	0.0415
4	0.0130	4	0.0415
5+	0.0080	5+	0.0415
Probability of moving from 'transplant' to 'dialysis'			
1	0.1000	1	0.1000
2+	0.0193	2+	0.0193
Probability of moving from 'dialysis' to 'death'			
1+	0.1897	1+	0.1937
Probability of moving from 'transplant' to 'death'			
1	0.0737	1	0.0737
2–6	0.0932	2–6	0.0932
7–11	0.1140	7–11	0.1140
12–21	0.1664	12–21	0.1664
22+	0.1876	22+	0.1876

Probability, annual transition probability; 'year' refers to year of model simulation; distinction was made between the Belgian and French probabilities of transplantation and dialysis due to differences in country-specific ESRD management practices.

Cost inputs

The perspective of a third party payer [i.e. social security in France, Institut National d'Assurance de Maladie et Invalidité (INAMI) in Belgium] was taken. Costs of medications and ESRD were assessed for patients in all three treatment arms. Costs of cardiovascular events and management (e.g. visits to the general practitioner, urinary albumin monitoring and other investigations that were similar in each treatment arm) were not considered, as we wanted to determine the incremental costs between each treatment arm. Therefore, costs for patients in the states 'no progression' and 'DSC' were based on study drugs and concomitant antihypertensive agents, and for patients in with ESRD costs of dialysis or transplant were also included.

To determine study drug medication costs (irbesartan 75, 100 and 300 mg, and amlodipine 2.5, 5 and 10 mg), exposure time by dose was calculated for all patients in the IDNT study. The cost of each dose was calculated from the INAMI tariffs for Belgium and the VIDAL database for France. The cost of study medication was calculated by dividing the number of days exposed to each dose by the number of patients, multiplied by the mean duration of follow up, multiplied by the cost of that dose (Table 3).

The average annual costs of concomitant medications (Table 3) were based on the same sources. Exposure to antihypertensive medication classes and adjunctive hypertensive medications was calculated for each treatment arm. For each therapeutic class, the price of the drug which is currently most used was utilized.

Cost estimates for transplant or dialysis due to ESRD were based on total third party reimbursement (Table 4) [8,11–15]. Cost figures specific to ESRD of diabetic aetiology (or better still, type 2 diabetes aetiology) were not available for Belgium. However, Lins has reported full annual costs of managing patients with ESRD in Belgium based on reports from nephrology centres, which were used for this analysis [8,12]. These figures related to all patients treated with renal replacement therapy. Cost estimates for France were derived from several sources. Jungers *et al.* [11] reported the following distribution of dialysis patients for Ile-de-France: 68.3% in-centre; 31.7% out-centre (self-care haemodialysis 18.5%, home haemodialysis 1.7%, or peritoneal dialysis 11.6%). Engel *et al.* [14] published the specific cost of diabetic ESRD patients. Taking into account the relative weights of the different types of dialysis [11], a cost of €56 768 per year was estimated. Average length of hospital stay was estimated to be 13.4 days at a cost per day of €327.72 [15,16]. Taking the cost of hospitalization into account, the total cost for dialysis in France was €61 159. These figures relate to diabetes patients (not subdivided by

Table 3. Country-specific parameters used to calculate the costs of treatment and other management costs for each treatment arm

Annual costs of medications	Belgium (€ per year)	France (€ per year)
Irbesartan costs	353.66	232.50
Irbesartan concomitant medications	140.35	123.21
Amlodipine costs	243.43	204.09
Amlodipine concomitant medications	136.07	120.77
Control costs	–	–
Control concomitant medications	153.12	135.60

Table 4. Country-specific total costs for end-stage renal disease treatment

Treatment	Annual costs (€)		Reference
	Year 1	Years 2+	
Belgium			
Kidney transplant	21 647	2959	[8,12]
Dialysis	44 638	44 520	[8,12]
France			
Kidney transplant	24 102	6725	[13]
Dialysis	61 159	61 159	[14–16]

Costs given include cost of dialysis/transplants and cost of hospitalizations for comorbidities and complications.

type of diabetes); Cogny *et al.* [13] described transplantation costs for a single centre in France. Costs of transplantation in the first, second and third years were calculated to be €19 026, €6306 and €5309, respectively. These costs did not include the costs of more recent immunosuppressive therapy like tacrolimus. The addition of tacrolimus to the immunosuppressive regimen may not necessarily increase the total costs associated with transplantation, as the acquisition costs of the medications are offset by reductions in hospitalizations and rejections. It is therefore unclear if the exclusion of tacrolimus from the cost analysis following transplantation leads to an under- or over-estimation of the total costs following transplantation [17]. Costs were converted to 2002 values based on a 3% annual actualization rate.

Discounting

Discounting is the process by which the future costs and/or benefits (beyond 12 months) are converted to equivalent present values. Discounting is commonly used in health economic analyses to adjust for the diminished value of future costs and benefits. The reasons for discounting are the time preference (costs and benefits in the future are not as highly valued as costs or benefits that can be realized immediately) and other diseases or medical advances may intervene, thereby fully or partially negating the expected future benefits of any given intervention. In the present study, future costs and future clinical benefits where discounted at a rate of 3% per annum (p.a.) [4].

Sensitivity analysis

One-way sensitivity analyses were performed on total costs and life expectancy to assess the impact of different assumptions on the results. The impact of discount rates for costs and life expectancy was evaluated by varying discount rates between 0 and 6%. Sensitivity analysis was performed on the extrapolation of transition probabilities beyond the 3-year trial period. In the base case analysis, transitional probabilities for the first 3 years of the model were obtained from the actual number of annual events in the IDNT clinical trial. For the remainder of the model, an average of probabilities across those first 3 years for each treatment arm was used. As an extremely conservative assumption for sensitivity analysis, it was assumed that the probabilities would return to those of the control group after the 3-year trial period in all treatment arms (i.e. only the within-trial effects of irbesartan and amlodipine were considered).

Results

Irbesartan was associated with delayed onset of ESRD compared with amlodipine and control. Mean time to development of ESRD in the irbesartan-treated cohort was 8.23 years, compared with 6.82 years for amlodipine and 6.88 for control, corresponding to delays of 1.41 (*vs* amlodipine) and 1.35 years (*vs* control). Moreover, simulated long-term treatment with irbesartan was associated with a lower incidence of ESRD than amlodipine or placebo. At 10 years, the cumulative incidence of ESRD was 36, 49 and 45% in the irbesartan, amlodipine and control treatment arms, respectively. The 25-year (lifetime) cumulative incidence of ESRD was 47% in the irbesartan cohort, compared with 59% with amlodipine and 55% with control. This corresponds to lifetime reductions in the cumulative incidence of ESRD with irbesartan of 12 and 8% *vs* amlodipine and control, respectively (Figure 2).

Life expectancy and total lifetime costs

Both life expectancy and total lifetime costs differed between the Belgian and French settings due to different dialysis and transplant rates, survival rates following the onset of ESRD, and unit costs.

In the Belgian setting life expectancy was improved in the irbesartan group compared with the amlodipine and control groups, as anticipated from the delayed onset of ESRD. Non-discounted life expectancy (discounted at 3% p.a. shown in brackets) was 10.59 (8.57) years with irbesartan, 9.88 (8.11) years with amlodipine and 9.68 (7.95) years in the control group. This corresponds to improvements with irbesartan of 0.71 (0.46) years *vs* amlodipine and 0.91 (0.62) years *vs* control. When a 10-year time horizon was used, improvements in undiscounted life expectancy (discounted shown in brackets) with irbesartan were 0.13 (0.10) and 0.26 (0.22) years *vs* amlodipine and control, respectively. In addition, total lifetime costs were lower in the irbesartan cohort than in the other treatment groups. Total lifetime costs (discounted 3% p.a.) were €76 777 with irbesartan, €97 940 with amlodipine and €88 662 with control (cost savings of €21 163 and €11 885 for irbesartan *vs* amlodipine and control, respectively). After 10 years, cost savings of €14 949 and €9205 *vs* amlodipine and control, respectively, were projected (Figure 3).

A similar pattern of results was observed in the French setting. Life expectancy (discounted at 3% shown in brackets) was improved with irbesartan compared with amlodipine or control, with values of 10.61 (8.58) years in the irbesartan group, 9.92 (8.13) years in the amlodipine group and 9.71 (7.97) years in

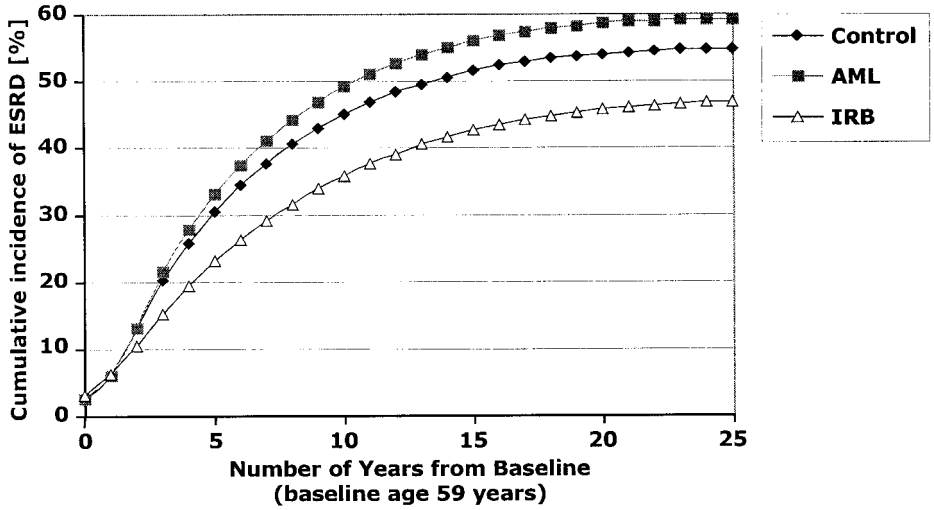

Fig. 2. The cumulative incidence of ESRD after 25 years was 44.7, 57.1 and 52.9% for irbesartan, amlodipine and control, respectively. AML, amlodipine; IRB, irbesartan.

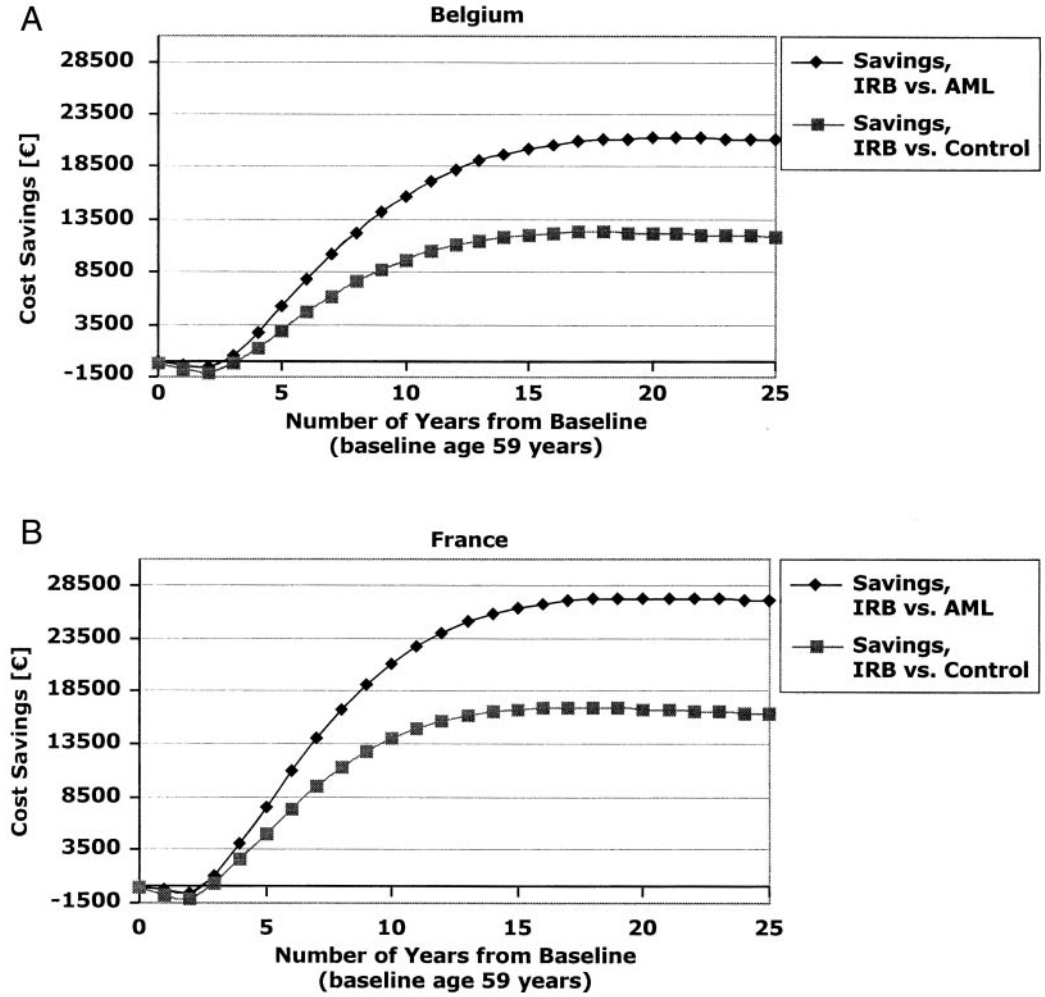

Fig. 3. Graphs show the cost savings per patient over time for irbesartan compared with amlodipine or control in the Belgian setting (**A**), or the French setting (**B**). In both settings, cost savings become evident after 3 years of treatment with irbesartan. Eighty per cent of the total cost savings were achieved after 9–11 years of therapy. IRB, irbesartan; AML, amlodipine.

the control group. This translated into improvements of 0.69 (0.45) and 0.90 (0.61) years *vs* amlodipine and control, respectively. Ten-year differences in life expectancy were similar in the French and Belgian settings. Irbesartan also proved to be cost saving in the French setting. Total lifetime costs were €93 240 with irbesartan, €120 284 with amlodipine and €109 585 in the control group, which corresponds to cost savings of €27 044 and €16 345 for irbesartan *vs* amlodipine and control, respectively. Again, important cost savings in the irbesartan treatment arm were observed after 10 years in the French setting (€20 128 *vs* amlodipine and €13 337 *vs* control).

Breakdown of the per patient costs revealed that the cost of irbesartan and amlodipine made up 2–4% of the total costs considered in this analysis, whereas ESRD costs contributed to 94–99%. Reduction in ESRD costs in the irbesartan treatment arm was one of the major factors that led to overall cost savings in the irbesartan treatment arm (Table 5). The cost savings were due mainly to ESRD avoided with irbesartan and became evident after 3 years of treatment. In the Belgian setting, after only 5 years, costs savings were €5180 and €2973 *vs* amlodipine and control, respectively. In the French setting after 5 years, cost savings were €7557 and €5058 *vs* amlodipine and control, respectively. Eighty per cent of the overall savings were achieved within 9–11 years of treatment (Figure 3).

Sensitivity analysis

Using different combinations of discount rates for costs and clinical outcomes had no impact on the relative outcomes, with irbesartan remaining both life and cost saving under all combinations of discount rates (discount rates from 0 to 6% on costs and clinical benefits).

The parameter with the greatest single impact on life expectancy was the annual probability of death in the state 'no progression' (taken from the IDNT), closely followed by the annual probability of death in the state 'ESRD treated with dialysis' (taken from country-specific published sources). It was calculated that irbesartan would remain life saving compared with amlodipine with up to a 14% increase in the probability of dying in the 'no progression' state in the irbesartan treatment arm. In comparison with placebo, irbesartan remained life saving with up to a 21% increase in this probability.

The parameter with the greatest single impact on total lifetime costs was the annual costs of dialysis. In the unlikely case that the costs of dialysis in Belgium fell below €3220 (compared with €44 580 used in the base case analysis), irbesartan would no longer be cost saving compared with amlodipine. The annual cost of irbesartan had the fourth greatest impact on total lifetime costs. The annual cost of irbesartan treatment would have to be higher than €1680 per patient (compared with the current cost of €353.66) to lead to an overall cost increase compared with no treatment (or €2764 compared with amlodipine).

Under the conservative assumption that only the within-trial (first 3 years) effects of irbesartan and amlodipine were considered (after which transition probabilities corresponded to those of the control arm), non-discounted life expectancies (discounted at 3% shown in brackets) in the Belgian setting were 9.98 (8.17) years for irbesartan, 9.76 (8.02) years for amlodipine and 9.68 (7.95) years for the control arm. Total lifetime costs were €88 213 in the irbesartan group, €93 697 for amlodipine and €88 662 in the control group. Thus, even with very conservative assumptions about the long-term effectiveness of the medications, irbesartan remained both cost and life saving compared with amlodipine and control.

Table 5. Breakdown of mean total lifetime costs per patient

	Mean total lifetime costs per patient (€)		
	Irbesartan	Amlodipine	Control
Belgium			
Total	76 777 (100%)	97 940 (100%)	88 662 (100%)
Drug costs	3029 (4%)	1974 (2%)	0
Adjuvant medications	1202 (2%)	1103 (1%)	1218 (1%)
ESRD	72 546 (94%)	94 863 (97%)	87 444 (99%)
France			
Total	93 204 (100%)	120 284 (100%)	109 585 (100%)
Drug costs	1995 (2%)	1659 (1%)	0
Adjuvant medications	1057 (1%)	982 (1%)	1081 (1%)
ESRD	90 188 (97%)	117 643 (98%)	108 504 (99%)

Drug costs, medication costs specific to treatment arm; %, percentage of total costs. The costs associated with dying in the ESRD states were included in the ESRD costs.

Discussion

Patients with hypertension, type 2 diabetes and overt nephropathy are at extremely high risk of developing ESRD, which is associated with high morbidity, mortality and treatment costs. Any intervention that can reduce or delay the progression from nephropathy to ESRD is likely to have a large impact on cost and clinical outcomes in this patient group.

This is confirmed by the present modelling study, which demonstrated that a reduction in progression to DSC and ESRD associated with irbesartan treatment leads to an important improvement in life expectancy and reduction in total lifetime costs of medications and ESRD per patient compared with treatment with amlodipine or control. The anticipated gains in non-discounted life expectancy (due to delay in the onset of ESRD) compare very well with other established interventions in health care [18]. Cost savings with irbesartan treatment instead of amlodipine or standard blood pressure control alone begin to occur after ~3 years of therapy (the within-trial period of the analysis).

The results of the model were robust under a wide range of plausible assumptions about the long-term effectiveness of drug therapy and costs of complications and medications, even in the extreme case assuming no effect of irbesartan or amlodipine after the 3-year trial period. This sensitivity analysis indicates that the conclusion of the study would probably not change in a real-life setting, even taking into account the difference between efficacy in the clinical trial situation (as in the IDNT) and real-life effectiveness.

There were some limitations in this modelling study. Data derived from the IDNT were applied whenever possible in the model. Some of these probabilities, although different within treatment arms, were not statistically significant. This is often the case when a clinical trial is used as a basis for an economic analysis, as the trial is powered to show a difference only in the primary endpoint, which is not the only relevant endpoint used in an economic analysis. For example, the probability of death from any cause was not significantly different between treatment arms after the within-trial follow up period, but the IDNT was not powered for an analysis of this secondary outcome [5]. However, the significant delay in the onset of ESRD seen with irbesartan during the trial period was projected to lead to important improvements in life expectancy, primarily due to avoidance of the excess mortality associated with the onset of ESRD. The sensitivity analyses revealed that those probabilities, which were significantly different in the IDNT (for example progression to DSC) had a large impact on the outcomes, and variation of these probabilities within plausible ranges did not alter the relative outcomes. The mortality probabilities following transplantation were taken from US figures, and included racial subgroups with higher mortality rates. This may have led to a slight over-estimation of the mortality, although the impact on the results is minimal due to the low rates of transplantation in Belgium and France. On the other hand, we assumed that there was no increase in mortality when patients progressed to DSC. Because irbesartan delayed progression to DSC, this may have led to an under-estimation of the associated improvements in life expectancy.

The ESRD treatment costs used in the model were not type 2 diabetes-specific. In the US setting, costs of renal replacement therapies are typically higher for diabetes patients than other patients [10]. Additionally, the costs for transplant maintenance in France were derived from a period when the use of tacrolimus and other expensive immunosuppressive agents was not common. These two factors led to a possible under-estimation of the costs of renal replacement therapy compared to the current approach with more expensive immunosuppressants, in turn leading to an under-estimation of the cost savings to be expected with irbesartan.

It should be noted that the population of the IDNT represented patients with advanced diabetic nephropathy, and as such these results should only be taken in the context of these patients and not in those with microalbuminuria. Moreover, the purpose of the IDNT was to investigate the effects of irbesartan, amlodipine or placebo on the progression to DSC, ESRD or death from any cause, independent of blood pressure control. In all three treatment arms, blood pressure at baseline was similar. During the study follow up, there was no significant difference in mean arterial blood pressure between the amlodipine and the irbesartan groups, but the control group had a mean arterial blood pressure 3.3 mmHg higher than the two active groups. The differences in outcomes between the active groups cannot, therefore, be explained by differences in blood pressure control, but instead may lie in the different mechanisms of action irbesartan and amlodipine. When the disparity in blood pressure control between the irbesartan and placebo groups was adjusted for, the magnitude of renal benefit afforded by irbesartan did not decrease significantly [3].

One of the main limitations of the study relates to the fact that the model does not consider ACE inhibitors, beta-blockers or other angiotensin 2-receptor blockers as treatments for type 2 diabetes patients with hypertension and nephropathy. In this analysis we attempted to model the health economic outcomes of the IDNT and were therefore limited to the treatment arms included in this particular trial. In fact, no head-to-head clinical comparisons of irbesartan and ACE inhibitors, beta-blockers or other angiotensin 2-receptor blockers have been published in this population at the time of writing, making direct comparison in the modelling setting difficult. The cost-effectiveness of angiotensin-receptor blockers *vs* ACE inhibitors would be particularly interesting when appropriate clinical data become available. Data from a study of ACE inhibitors in non-diabetic renal patients has indicated that benazepril is cost saving in the US setting [19]. Treatment of patients with chronic renal insufficiency with benazepril was associated with a total cost saving of more than USD 4000 ($\sim$ €3692) per patient over 3 years and USD 23 500 ($\sim$ €21 690) per patient when extrapolated to 10 years. The data suggest that ACE inhibitor treatment has a significant impact on costs for renal patients and highlight the need for clinical studies comparing antihypertension therapies in patients with type 2 diabetes, hypertension and nephropathy to form the basis of an economic investigation.

In conclusion, this modelling study demonstrated that the delay in progression to DSC and ESRD by treating patients with type 2 diabetes, hypertension, and overt nephropathy with irbesartan led to both reductions in overall costs and anticipated improvements in life expectancy compared with treatment with amlodipine or antihypertensive therapy alone.

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