Health economic implications of irbesartan plus conventional antihypertensive medications versus conventional blood pressure control alone in patients with type 2 diabetes, hypertension, and renal disease in Switzerland

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Summary

Objectives: The aim of this health economic modelling study was to investigate the effect of irbesartan combined with conventional antihypertensive medications compared to conventional antihypertensive therapy alone on the progression of nephropathy in patients with hypertension, type 2 diabetes and microalbuminuria in a Swiss setting.

Methods: In simulated patients with hypertension and type 2 diabetes, treatment of microalbuminuria with irbesartan 300 mg daily plus conventional antihypertensive medications was compared to a control regimen (conventional medications excluding angiotensin converting enzyme inhibitors, other angiotensin-2-receptor antagonist and dihydropyridine calcium channel blockers). Progression from microalbuminuria to nephropathy, doubling of serum creatinine, ESRD, and all-cause mortality was simulated over a 25-year time horizon using a published Markov model adapted to a Swiss setting. Transition probabilities were based on the Irbesartan in Reduction of Microalbuminuria-2 Study, Irbesartan in Diabetic Nephropathy Trial and other sources. Costs and clinical outcomes were discounted at 5% annually according to Swiss guidelines, and a third party payer perspective was taken.

Results: Treatment with irbesartan was projected to improve mean life expectancy by 0.57 years compared to conventional antihypertension treatment (undiscounted 1.22 years). Irbesartan treatment was associated with cost savings of CHF 21,488 per patient over the 25-year time horizon. Sensitivity analysis showed that irbesartan therapy remained dominant to conventional antihypertension treatment over a range of plausible assumptions.

Conclusions: Addition of irbesartan to conventional antihypertension therapy was projected to improve life expectancy and reduce costs in hypertensive patients with type 2 diabetes and microalbuminuria in a Swiss setting.

Key words: irbesartan; costs; microalbuminuria; nephropathy; modelling; Switzerland

Introduction

End-stage renal disease (ESRD) has a huge impact on health and represents a substantial burden for healthcare payers. Within the last five years evidence has been published demonstrating that type 2 diabetes is the major underlying cause of ESRD, defined as chronic renal failure requiring dialysis or renal transplant, in the western world, with nephropathy developing in approximately 40% of type 2 diabetes patients [1, 2]. In Switzerland, it has been estimated that there are around 285 000 patients with type 2 diabetes, and approximately 2300 patients receiving renal dialysis [3, 4]. As the incidence of type 2 diabetes continues to increase worldwide and the population ages, the bur-

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den represented by type 2 diabetes and associated ESRD is likely to continue to grow [5].

In 1998, Lundman and Engstrom published evidence of a link between type 2 diabetes, hypertension and nephropathy [6]. In a Swedish cohort of type 2 diabetes patients, 50% had concurrent hypertension and 13% had signs of nephropathy. Encouragingly, recent studies have reported blood pressure-independent renoprotective effects of angiotensin receptor antagonist treatment on the progression of various stages of renal disease in patients with hypertension and type 2 diabetes [7–9]. Data from these studies suggest that timely treatment of nephropathy and hypertension in patients with type 2 diabetes may help to reduce the health and economic burden of renal failure.

Irbesartan is an angiotensin-2-receptor antagonist for the treatment of hypertension that has been shown to have additional blood pressure independent renoprotective effects [7, 8]. In 2001, Parving et al. reported results from the Irbesartan in Reduction of Microalbuminuria-2 (IRMA-2) study, which demonstrated that in an international cohort of 590 patients with type 2 diabetes and microalbuminuria, treatment with irbesartan was associated with protection against the progression from microalbuminuria to overt nephropathy, independently of its blood pressure lowering effect [7]. The international Irbesartan in Diabetic Nephropathy Trial (IDNT) [8], published in the same year, showed that irbesartan was renoprotective in a cohort of 1715 patients with hypertension, type 2 diabetes and advanced overt nephropathy, reducing the incidence of doubling serum creatinine (DSC) and onset of ESRD. These studies have shown that appropriate treatment can delay the progression of renal complications in patients with type 2 diabetes, a fact which could have substantial benefits in terms of improving life expectancy and reducing health care costs.

We have performed a cost-consequence analysis using a decision analytic cost-effectiveness model to investigate the effect of irbesartan treatment versus conventional blood pressure control in patients with type 2 diabetes and microalbuminuria in the Swiss setting. A peer-reviewed, previously published computer simulation model was adapted to project the progression to ESRD, impact on life expectancy and associated costs over the long-term (25 years), based on data from the IDNT and IRMA-2 studies [10].

Methods

Model structure

The structure of the model used in the present analysis has been previously published and described in detail by Palmer et al. [10]. In summary, it is a computer simulation Markov model developed using DATA Pro software (TreeAge Software Inc., Williamstown, Massachusetts, USA). The Markov structure is made up of seven disease states designed to simulate the progression of renal disease in patients with type 2 diabetes. It models progression from *microalbuminuria* (urinary albumin excretion (UAE) 20–199 µg/min) to *early overt nephropathy* (UAE 200 µg/min to median UAE 1,900 mg/24 h); *advanced overt nephropathy* (median UAE on entry ≥1,900 mg/24 h); doubling of serum creatinine *(DSC); ESRD treated with dialysis; ESRD treated with renal transplant; and Death* as outlined in figure 1. For the purposes of continuity in the model, a distinction was made between early and advanced overt nephropathy to compensate for the differences between patients reaching the endpoint of the IRMA-2 study (UAE 200 µg/min with minimum of 30% increase in UAE from baseline) [7], and those included in the IDNT (median UAE 1,900 mg/24h) [8]. A deterministic approach was used, taking point estimates of probabilities and costs to calculate mean values for the outcomes generated by the model.

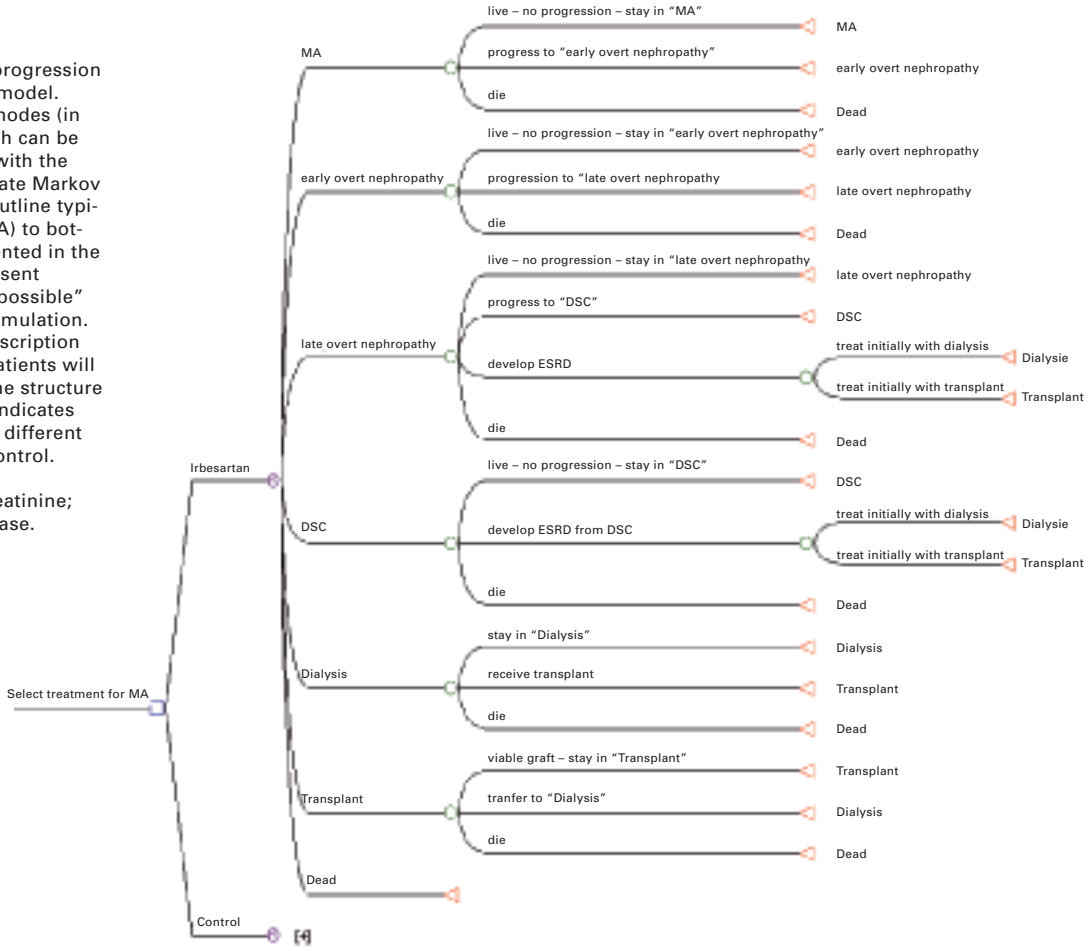
Transition probabilities

Data from the IRMA-2 study were used to calculate transition probabilities for progression from *microalbuminuria* to *early overt nephropathy* in the model and have been previously published [10]. Annual probabilities for the progression from *early overt nephropathy* to *advanced overt nephropathy* were calculated using linear extrapolation of the rate of increase of UAE in all patients in the IRMA-2 trial reaching the endpoint (UAE >200 µg/min with minimum 30% increase from baseline), and evaluating the conditional probability of reaching the threshold for entry into the IDNT (advanced overt nephropathy) stage of the model. A UAE rate of 1,100 mg/24 h was set as a threshold value to reproduce the baseline characteristics of the IDNT population. Using this value, the median UAE of patients crossing this threshold at any given time corresponded to the median baseline value in IDNT (UAE 1,900 mg/24 h) [8]. As there were no suitable published data on the progression from early to advanced overt nephropathy, it was conservatively assumed that the rate of progression from *early overt nephropathy* to *advanced overt nephropathy* in the model was the same in both treatment arms. After the development of ESRD, subsequent transitions (to account for mortality and changing between the states representing kidney transplantation and modes of renal replacement therapy) were also assumed to be independent of treatment arm. As no data for these transitions were available for the Swiss setting, data from Germany were used as a substitute. The published data reported that 0.35% of patients diagnosed with ESRD received renal transplantation [11]. Approximately 95.2% of patients start haemodialysis and 4.8% receive peritoneal dialysis [11]. The proportion of patients receiving other forms of dialysis (such as autodialysis or home haemodialysis) was considered negligible. Although these figures refer specifically to the global population of ESRD patients, they are likely to be similar for patients with diabetes mellitus.

Transition probabilities for the switch from dialysis to transplantation were based on German data from the year 2000, which showed an annual rate of 4.2% for dialysis patients receiving transplants [11]. This rate refers to all dialysis patients, but no data have been published for patients with diabetes alone. The fact that the dialysis patients with type 2 diabetes are older and have a higher mortality rate than the average dialysis patients suggest

Figure 1

Model Structure.
The diagram illustrates the progression of simulated patients in the model. Squares represent decision nodes (in this case for treatment) which can be defined by the user. Circles with the letter 'M' in the middle indicate Markov nodes in the model, which outline typical progression from top (MA) to bottom (Dead) states as represented in the diagram. Green circles represent chance nodes which allow "possible" events to occur during the simulation. Red triangles with a state description afterwards indicate where patients will be sent at each cycle end. The structure is shown for irbesartan. [+] indicates same tree structure but with different transition probabilities for control.
MA = microalbuminuria;
DSC = doubling of serum creatinine;
ESRD = end-stage renal disease.



that these transition probabilities may differ, but literature search revealed no published information on the effect of duration of dialysis on the transition from dialysis to transplantation. Therefore the same transition probability has been used in each cycle of the model, even though it is generally accepted that transplant rates increase with duration of dialysis. Calculation of probabilities for the transition from transplant to dialysis was based on data from the European transplant register which reported the transplant to dialysis as 17.1% in the first year decreasing to 5% in subsequent years [12].

Table 1

Costs of ESRD treatment in Switzerland.

Treatment	Annual costs (CHF)		Reference(s)
	Year 1	Years 2+	
Renal transplant	95,000	25,000	[19]
Dialysis	71,000	71,000	[20]

Mortality calculations

In the states of *microalbuminuria*, *early overt nephropathy*, *advanced overt nephropathy*, and DSC, mortality was calculated using age- and gender-specific all-cause mortality tables and values adjusted by state-dependent RRs. Mortality was independent of treatment arm and was dependent on the level of renal disease reached by a simulated patient. In the state *microalbuminuria* the RR for all-cause mortality was based on data from the Danish Steno-2 study versus age- and gender-matched mortality in the general Danish population [13, 14]. RR of mortality for patients with type 2 diabetes, hypertension and microalbuminuria was calculated to be 2.03. The RR of mortality in both overt nephropathy states was calculated in a similar way based on data published by Stehouwer et al. [15]. The RR for mortality in patients with type 2 diabetes, hypertension and overt nephropathy was calculated to be 4.4 compared to the general population. In the absence of published data, RRs for all-cause mortality in the *early*

Table 2

Summary of results.

	Control	Irbesartan
Life expectancy (years) [undiscounted / discounted at 5% p.a.]	14.39	15.61
Life years gained versus control (years), undiscounted	–	1.22
Life expectancy (years), discounted at 5% p.a.]	9.80	10.37
Life years gained versus control (years), discounted at 5% p.a.	–	0.57
Years free of ESRD*	12.90	15.04
Cumulative incidence of ESRD (%)	26.6	10.7
25-year costs** (CHF)	46,956	25,469
Cost savings versus control	–	21,487

* = mean outcome per patient; ** costs discounted at 5% p.a.; Control = conventional antihypertensive medications excluding ACE-Is, other angiotensin-2-receptor antagonists and dihydropyridine calcium channel blockers with equivalent blood pressure control.

Figure 2

Number of life years gained per 1000 patients treated with irbesartan versus control.

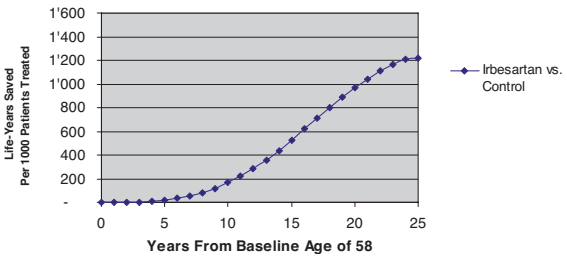


Figure 3

Number of ESRD cases avoided per 1000 patients treated with irbesartan versus control.

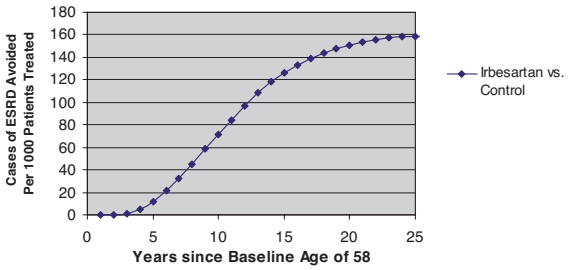
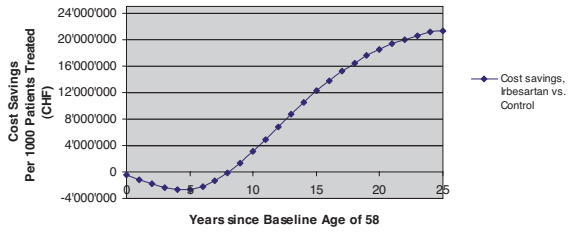


Figure 4

Cost savings over time per 1000 patients treated for irbesartan versus control.



overt nephropathy, *advanced overt nephropathy* and *DSC* states were conservatively assumed to be the same. In the *ESRD* state, mortality was dependent on the type of renal replacement therapy received (i.e. dialysis or transplantation). Annual mortality in dialysis patients in Switzerland was 16.91% [16]. For transplant patients, mortality was calculated based on data from the European transplant register [12]. Comparable mortality rates have been reported in two other recent publications [17, 18].

Simulated cohort and treatments

The model simulated a hypothetical cohort with type 2 diabetes, hypertension and microalbuminuria (UAE 20–199 µg/min on two out of three consecutive occasions), with characteristics similar to those of the baseline cohort of the IRMA-2 study [7]. The simulated cohort was treated with either irbesartan 300 mg daily plus conventional antihypertensive therapy (irbesartan group), or conventional antihypertensive treatment alone (including diuretics, beta blockers, alpha/beta blockers, peripheral vasodilators, peripheral adrenergic blockers, and central adrenergic blockers, but excluding angiotensin converting enzyme inhibitors [ACE-I], other angiotensin-2-receptor antagonists and dihydropyridine calcium channel blockers) to achieve a target blood pressure of <135/85 mm Hg, and started when patients were in the state of microalbuminuria. In both treatment groups, therapy was initiated when patients had developed microalbuminuria.

Costs

All the costs retrieved have been updated to 2003 values according to the consumer price index, and are reported as 2003 Swiss Francs (CHF). The perspective of a third party Swiss health insurance payer was taken. The analysis focused on the incremental costs of the addition of irbesartan to otherwise conventional blood pressure control, and on the costs associated with the treatment of ESRD in the simulated cohort. The annual costs of irbesartan 300 mg daily were CHF 788 per patient. Regarding the costs of other medications, it was assumed that these did not differ between treatment groups, and were therefore not included in the present analysis. It could be argued that this was a conservative assumption which perhaps biases the study against the irbesartan treatment arm, given that the cost of conventional antihypertensive therapy in the control group is not included in the analysis.

Costs of ESRD, dialysis or transplant were included as previously reported for Switzerland (table 1) [19, 20]. Cost estimates for renal transplant and follow-up treatment due to ESRD were estimated based on national insurance data [19]. The cost of transplantation in the first year was derived by calculating a weighted average determined by the number of patients who received either a cadaveric or living donor transplant. The unit cost of haemodialysis was based on the Schweizerischer Dialysetarifvertrag and the cost of peritoneal dialysis was calculated using data reported in the literature and expert interviews, as exact figures were not available elsewhere [19–21].

Sensitivity analysis

To assess the robustness of the study findings, several sensitivity analyses were performed. One such analysis was on the level of UAE at which patients would enter the IDNT part of the model (i.e. *the advanced overt nephropathy* state). In the base-case analysis, median UAE for those patients who progressed to advanced overt nephropathy was 1900 mg/24 h, using a threshold of 1100 mg/24 h for entering the IDNT state, chosen to reflect the baseline characteristics of patients in the IDNT study [8]. We tested the effect of changing the threshold value to 585 mg/24 h (the minimum UAE required for inclusion in the IDNT) on projected costs and life expectancy. Sensitivity analysis was also performed on assumptions of annual mortality rates in the model. The annual probabilities of dying for the newly-diagnosed patients with type 2 diabetes and either no renal disease, microalbuminuria, or overt nephropathy have recently been assessed in the United Kingdom; these were 1.4%, 3.0%, and 4.6%

Table 3

Sensitivity analysis.

	Undiscounted life expectancy (years)		25-year costs* (CHF)	
	Control	Irbesartan	Control	Irbesartan
Base case	14.39	15.61	46,866	25,505
UAE threshold for advanced over nephropathy set to 585 mg/24 h	14.31	15.59	54,242	28,391
UKPDS mortality data for no renal disease, microalbuminuria, or overt nephropathy	15.17	16.56	50,698	27,458
RR of mortality in the states leading up to ESRD set to 1.0, simulating only effects of treatment on delaying ESRD onset ESRD and associated mortality	18.65	19.61	67,487	35,898

* costs discounted at 5% p.a.; Control = conventional antihypertensive medications excluding ACE-Is, other angiotensin-2-receptor antagonists and dihydropyridine calcium channel blockers with equivalent blood pressure control.

respectively [22]. These values were applied as constant age- and gender-independent mortality rates to assess the impact on costs and life expectancy. An additional sensitivity analysis was performed by varying the RR of mortality in the states leading up to ESRD by setting them to a value of 1.0. As such, the model only simulated the effects of treatment on delaying the onset of ESRD and its associated increase in mortality.

Results

Life expectancy

Irbesartan treatment was associated with improvements in life expectancy compared to conventional antihypertension treatment (table 2). Mean discounted (5% per annum) life expectancy was 10.37 years in the irbesartan group and 9.80 years in the control group, corresponding to an incremental gain in discounted life expectancy of 0.57 years with irbesartan. Undiscounted life expectancy in the irbesartan treatment group was 15.61 years compared to 14.39 years with control. Irbesartan was associated with an improvement in undiscounted life expectancy of 1.22 years versus control. Analysis of life years saved with irbesartan versus control indicated that the benefits in terms of survival could be observed after 7 years of irbesartan treatment (figure 2).

Cumulative incidence and years free of ESRD

The cumulative incidence of ESRD after 25 years was 10.7% in the irbesartan group compared to 26.6% in the control group (table 2). Plotting the number of cases of ESRD avoided with irbesartan treatment versus control showed that after 3–4 years of simulation, cases of ESRD avoided were evident for irbesartan versus control (figure 3). After 10 years of the simulation, more than 60 cases of ESRD per 1000 patients were avoided with irbesartan versus control. Irbesartan was estimated to delay the onset of ESRD by a mean of 2.14 years, corresponding to 255 fewer days of ESRD treatment compared to conventional antihypertension treatment.

Costs

Irbesartan treatment was associated with cost savings of CHF 21,487 per patient compared to conventional antihypertension treatment over the 25-year simulation. Projected costs per patient, discounted at 5% *per annum* were CHF 25,469 with irbesartan treatment and CHF 46,956 in the control treatment group. Analysis of cost savings with irbesartan versus control showed that over the first 8-9 years of treatment, irbesartan was more expensive than control, but cost savings became evident after around 10 years of treatment (figure 4).

Sensitivity analysis

Variation in the UAE rate threshold values for patients entering the state of *advanced overt nephropathy* in the model (i.e. entering the IDNT portion of the model) had no effect on the relative outcomes. With the threshold value set to the minimum (UAE of 585 mg/24 h) inclusion level for the IDNT, irbesartan treatment was projected to be both cost- and life-saving compared to control. Undiscounted life expectancy was 1.3 years greater with irbesartan than with control and irbesartan was associated with cost savings of over CHF 25,000 (table 3).

When the impact of using different assumptions on the annual probability of dying in the states of *microalbuminuria*, *early overt nephropathy*, and *advanced overt nephropathy* was assessed, the relative results remained stable under all conditions tested. When UKPDS-derived constant age- and gender-independent annual mortality rates for the state-specific mortality rates were applied (3.0% in *microalbuminuria*, and 4.6% in *early* and *advanced overt nephropathy* and *DSC*), treatment with irbesartan still improved undiscounted life expectancy by 1.22 years versus control treatment and reduced 25-year costs by approximately CHF 19,700 (table 3).

When only the effects of treatment on delaying the onset of ESRD and its associated increase in mortality were assessed by setting the RR of mortality in the states *microalbuminuria*, *early overt nephropathy*, *advanced overt nephropathy* and *DSC* to 1.0, treatment with irbesartan led to incremental cost savings of approximately CHF 31,588 and an improvement in undiscounted life expectancy of 0.96 years compared to control (table 3).

Discussion

Treatment with irbesartan in hypertensive type 2 diabetes patients with microalbuminuria was projected to extend life and reduce costs when compared to conventional antihypertension treatment. Given the substantial burden associated with ESRD, the most common underlying cause of which is type 2 diabetes, these data suggest that irbesartan represents an attractive treatment option in patients with hypertension and type 2 diabetes in Switzerland. Sensitivity analysis demonstrated that these findings were robust under variation in a range of assumptions, including mortality rates. Setting the RR of mortality in the states leading up to ESRD to 1.0, to produce results that

only reflect the impact of treatment on onset of ESRD and associated mortality, had the greatest impact on the absolute values of undiscounted life expectancy and 25-year costs, but had no impact on the relative results (i.e. treatment with irbesartan resulted in reduced costs and was life-saving). The RRs of mortality in the base case analysis were 2.03 for patients in the *microalbuminuria* state (based on the Steno-2 trial [13], and supported by data from the UK [23]) and 4.4 in the *overt nephropathy* and DSC states (based on Stehouwer et al.) [15]. When these values were replaced with RRs values derived from the UKPDS, the relative results also remained unchanged, with irbesartan treatment started in the state of *microalbuminuria* leading to life- and cost-savings in comparison to control.

It is worthy of note that only the incremental costs of irbesartan and ESRD treatment were included in the present study. This could be considered a conservative approach, as the non-inclusion of the costs of concomitant conventional antihypertensive therapy should bias against irbesartan. However, it is unlikely that this would be a major driver of overall costs in this population. Previously published data indicates that "other costs", such as those associated with additional concomitant medications and cardiovascular disease events, only have a relatively small impact compared to the costs of developing ESRD on total costs in patients with overt nephropathy [24].

The model used in the analysis has been validated by comparing results generated from the model to results of the IDNT and IRMA-2 studies, with a close correlation noted between observed and predicted results.

Perhaps the primary limitation of the analysis was that, due to the lack of direct clinical comparisons, we were unable to compare the projections for irbesartan treatment with those of ACE-Is or other angiotensin-2-receptor antagonists. In the IRMA-2 and IDNT studies, the control arms included commonly used antihypertensive treatment like diuretics, beta blockers, calcium channel blockers (except dihydropyridines) and central alpha antagonists to achieve the target blood pressure of <135/85 mm Hg, but excluded ACE-Is and angiotensin receptor blockers [7, 8]. It currently remains unclear whether ACE-Is are associated with renoprotective effects, i.e. a beneficial effect of ACE-Is on kidney function beyond blood pressure control in hypertensive patients with type 2 diabetes and microalbuminuria, since the nine published studies to date have provided conflicting evidence [25–32]. So far, one very recent study did not find a difference between the angiotensin receptor blocker telmisartan and the ACE inhibitor enalapril with respect to change in glomerular filtration rate, urinary albumin excretion and blood pressure in type 2 diabetics with nephropathy [33]. Interestingly, modeling studies have shown that treatment of nephropathy with ACE-Is in patients with type 1 diabetes and non-diabetic nephropathy in a number of different countries may lead to long-term cost savings [34–39]. Future head-to-head clinical studies comparing ACE-Is and angiotensin-2-receptor antagonists would provide valuable data, not least in facilitating health economic comparisons between the two.

One may question the generalisability of results of an intervention taken from a clinical trial and translated into a "real life" setting. It is usually assumed that effectiveness of an intervention will be lower in a real-life population compared to efficacy observed in a clinical trial, primarily due to factors such as lower adherence to- or compliance with medications. This may have an impact on the cost-effectiveness of an intervention outside the clinical trial setting, with decreased costs of medications and a lesser clinical impact of the intervention due to lower adherence. If results of studies in a non-clinical trial setting (e.g. post-marketing/phase 4 studies) become available which more closely reflect the effectiveness of irbesartan, it will be interesting to feed these results into the cost-effectiveness model and observe the impact on projected long term costs and clinical outcomes.

Another limitation of this analysis is the lack of published data regarding the distribution of treatment of ESRD with hemodialysis, CAPD or transplant in Switzerland, which meant that we had to use German data as a substitute in this analysis. This highlights an area of limited research in Switzerland - data of this nature would be welcome in the Swiss setting.

Conclusions

In the majority of cases, advances in technology leading to improvements in healthcare are associated with increased costs. Limited budgets mean that healthcare payers are often faced with difficult decisions when selecting which interventions to fund. The findings of this health economic analysis indicate that irbesartan treatment of type 2 diabetes patients with hypertension and microalbuminuria is both cost- and life-saving in the Swiss setting. These data suggest that use of irbesartan will not only improve outcomes in this patient population, but will result in cost savings to healthcare payers in Switzerland.

Acknowledgements

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References

1 Ritz E, Rychlik I, Locatelli F, Halimi S. End-stage renal failure in type 2 diabetes: A medical catastrophe of worldwide dimensions. Am J Kidney Dis 1999;34:795–808.
2 Vora JP, Ibrahim HA, Bakris GL. Responding to the challenge of diabetic nephropathy: the historic evolution of detection, prevention and management. J Hum Hypertens 2000;14:667–85.
3 Golshayan D, Paccaud F, Wauters JP. Epidemiology of end-stage renal failure: comparison between 2 Swiss cantons. Nephrologie 2002;23:179–84.
4 Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabet Med 1997;14(Suppl 5):S1–85.
5 The DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care 2003;26:61–9.
6 Lundman B, Engström L. Diabetes and its complications in a Swedish county. Diabetes Res Clin Pract 1998;39:157–64.
7 Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:910–2.
8 Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–60.
9 Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–9.
10 Palmer AJ, Annemans L, Roze S, Lamotte M, Lapuerta P, Chen R, 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.
11 Palmer AJ, Annemans L, Roze S, Lamotte M, Rodby RA, Ritz E. Gesundheitsökonomische Aspekte der Anwendung von Irbesartan in Deutschland. Health economic consequences of irbesartan treatment of type 2 diabetes patients with hypertension and nephropathy in Germany. Dtsch Med Wochenschr 2004; 129:13–8.
12 QuaSi-Niere GmbH. Quasi-Neire Annual Report 2000.
13 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–93.
14 World Health Organization. Life tables for 191 countries. World mortality in 2000. http://www3.who.int/whosis/life_tables/life_tables.cfm?path=evidence,life_tables&language=english. 2002.
15 Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH. Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. Diabetes 2002;51:1157–65.
16 Arzneimittelkompendium der Schweiz. Basel: Documed AG, 2003.
17 Wenying Y, Lixiang L, Jinwu Q, Guangwei L, Zhiqing Y, Xiaoren P. The preventive effect of acarbose and metformin on the IGT population from becoming diabetes mellitus: a 3 year multicentral prospective study. Chinese Journal of Endocrinology and Metabolism 2001;17:131–4.
18 Boucek P, Saudek F, Pokorna E, Vitko S, Adamec M, Koznarova R, et al. Kidney transplantation in type 2 diabetic patients: a comparison with matched non-diabetic subjects. Nephrol Dial Transplant 2002;17:1678–83.
19 Schweizerische Unfallversicherungsanstalt (SUVA). Schweizerischer Verband für Gemeinschaftsaufgaben der Krankenversicherer SVK. Geschaftsbericht 2001. 2002. Solothurn.
20 Schweizerischer Verband für Gemeinschaftsaufgaben der Krankenversicherer SVK. Schweizerischer Verband für Gemeinschaftsaufgaben der Krankenversicherer SVK und H+ die Spitäler der Schweiz. Schweizerischer Dialsyevertrag, Anhang Tarif. 1998. Aarau and Solothurn, 1998.
21 Verband der Nierenpatienten Aargau VPN. 2004.
22 Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003;63:225–32.
23 Walters DP, Gatling W, Houston AC, Mullee MA, Julious SA, Hill RD. Mortality in diabetic subjects: an eleven-year follow-up of a community-based population. Diabet Med 1994;11: 968–73.
24 Rodby RA, Chiou CF, Borenstein J, Smitten A, Sengupta N, Palmer AJ, et al. The cost-effectiveness of irbesartan in the treatment of hypertensive patients with type 2 diabetic nephropathy. Clin Ther 2003;25:2103–19.
25 Lacourciere Y, Nadeau A, Poirier L, Tancrede G. Captopril or conventional therapy in hypertensive type II diabetics. Three-year analysis. Hypertension 1993;21:786–94.
26 Lebovitz HE, Wiegmann TB, Cnaan A, Shahinfar S, Sica DA, Broadstone V, et al. Renal protective effects of enalapril in hypertensive NIDDM: role of baseline albuminuria. Kidney Int Suppl 1994;45:S150–S155.
27 Trevisan R, Tiengo A. Effect of low-dose ramipril on microalbuminuria in normotensive or mild hypertensive non-insulin-dependent diabetic patients. North-East Italy Microalbuminuria Study Group. Am J Hypertens 1995;8:876–83.
28 Agardh CD, Garcia-Puig J, Charbonnel B, Angelkort B, Barnett AH. Greater reduction of urinary albumin excretion in hypertensive type II diabetic patients with incipient nephropathy by lisinopril than by nifedipine. J Hum Hypertens 1996;10: 185–92.
29 Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, et al. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998;21: 597–603.
30 Gaede P, Vedel P, Parving H-H, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomiised study. Lancet 1999;353:617–22.
31 Chan JC, Ko GT, Leung DH, Cheung RC, Cheung MY, So WY, et al. Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. Kidney Int 2000;57:590–600.
32 Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care 2000;23(Suppl 2):B54–B64.
33 Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med 2004;351:1952–61.
34 Rodby RA, Firth LM, Lewis EJ. An economic analysis of captopril in the treatment of diabetic nephropathy. The Collaborative Study Group. Diabetes Care 1996;19:1051–61.
35 Schadlich PK, Brecht JG, Brunetti M, Pagano E, Rangoonwala B, Huppertz E. Cost effectiveness of ramipril in patients with non-diabetic nephropathy and hypertension: economic evaluation of Ramipril Efficacy in Nephropathy (REIN) Study for Germany from the perspective of statutory health insurance. Pharmacoeconomics 2001;19:497–512.
36 Ruggenenti P, Pagano E, Tammuzzo L, Benini R, Garattini L, Remuzzi G. Ramipril prolongs life and is cost effective in chronic proteinuric nephropathies. Kidney Int 2001;59:286–94.
37 Hendry BM, Viberti GC, Hummel S, Bagust A, Piercy J. Modelling and costing the consequences of using an ACE inhibitor to slow the progression of renal failure in type I diabetic patients. QJM 1997;90:277–82.
38 Clark WF, Churchill DN, Forwell L, Macdonald G, Foster S. To pay or not to pay? A decision and cost-utility analysis of angiotensin-converting-enzyme inhibitor therapy for diabetic nephropathy. CMAJ 2000;162:195–8.
39 Le Pen C, Petitjean P, Levy P, Hannedouche T. Economic evaluation of the contribution of captopril in the treatment of diabetic nephropathy:a cost-benefit approach. Nephrologie 1996; 17:321–6.

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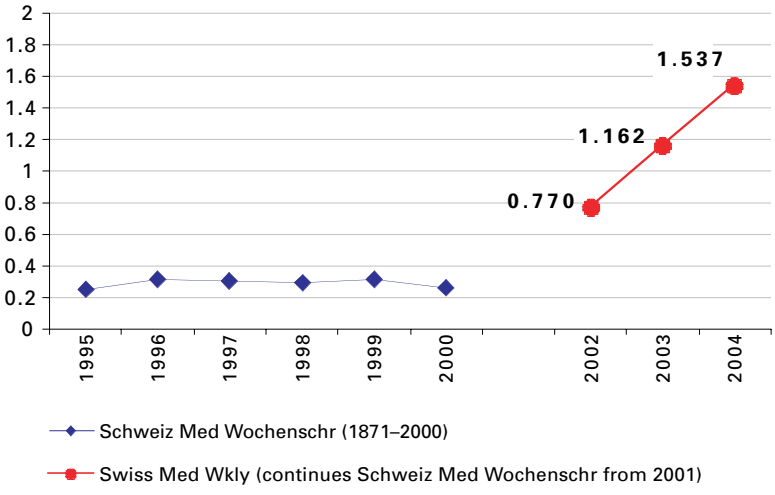

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