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Editorial Review

The economic benefits of preventing end-stage renal disease in patients with type 2 diabetes mellitus

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The burden of renal disease

The incidence of end-stage renal disease [ESRD; stage 5 chronic kidney disease (CKD)] continues to increase in Europe, particularly due to type 2 diabetes, hypertensive renovascular disease or atherosclerosis [1–3]. Indeed, across nine European countries (Austria, Belgium, Denmark, Finland, Greece, Norway, Scotland, Spain and the Netherlands) from 1990 to 1999, the adjusted incidence of renal replacement therapy to treat ESRD increased by ∼5% per year [4]. Moreover, the adjusted overall incidence of ESRD cases in treatment approximately doubled over this 9-year period, from 12.7 to 23.6 per million population due to diabetes, from 6.3 to 11.5 per million due to hypertension, and from 3.6 to 7.6 per million population due to renovascular disease [4]. The global prevalence of ESRD is 280 cases per million and is subject to regional variations; the prevalence is lower in Europe (585 cases per million) than in North America (1505 cases per million) and Japan (2045 cases per million) [5].

In addition to the information on the incidence and prevalence of ESRD, multiple studies have shown a considerable number of individuals in the general population with a slight-to-moderate decrease in renal function. This population may have an increased risk of ESRD compared with those without renal impairment. Prevalence data from the USA [6] and Europe [7,8] are consistent, with ∼10% of the general population having stage 1–3 CKD.

Risk factors for the development of ESRD include diabetes, hypertension, obesity, dyslipidaemia, history of smoking, anaemia and proteinuria/albuminuria. Diabetic nephropathy occurs in up to 40% of diabetic subjects with microalbuminuria and is currently the major cause of ESRD in many regions of the world [9–13]. Worldwide, more than 180 million people are estimated to have diabetes, and this number is projected to more than double by 2030 [14].

Clearly, we need an armamentarium of intervention, as well as prevention measures, to reduce the burden of renal disease now and in the near future. Several such risk management strategies have been tested, targeting risk factors such as hyperglycaemia, hypertension, dyslipidaemia and albuminuria/proteinuria in addition to lifestyle changes [15–20]. Intensive management of all risk factors in diabetes is clearly important in preventing or slowing nephropathy progression [11,21–23]. This armamentarium is needed not only to improve the health of the population concerned, but also to provide lifetime net cost savings with long-term financial benefits offsetting the potential high initial investment costs in preventive strategies.

The increasing incidence of ESRD presents a considerable financial burden. Renal dysfunction (decreased eGFR) and ESRD are associated with high morbidity and mortality, and high treatment costs [9,11,24,25]. The primary objective of this paper is to provide an overview of the economic value, from a European perspective, of various pharmacotherapeutic interventions, in slowing renal progression in type 2 diabetic nephropathy.

Drug treatment in diabetic renal disease

Pro-active encouragement of life-style changes and drug treatment to prevent or reduce the progression of cardiovascular and renal disease is currently the main approach to treating type 2 diabetes. The benefits of tight blood pressure and glycaemic control, and anti-dyslipidaemic (e.g. statins) and anti-platelet (e.g. aspirin) interventions are now firmly established with regard to reduced progression of cardiac and renal events [26–30]. These studies show that the risk of these events is best reduced by effectively controlling high blood pressure, although it is also beneficial to initiate antihypertensive therapy in nonhypertensive patients with type 2 diabetes [31]. The choice of the exact antihypertensive agent is important, since the classes of antihypertensive

agents that intervene in the renin–angiotensin system may be more effective than the other classes [32,33]. Additionally, safety differences between agents may prove to be even more prominent than potential efficacy differences. This applies to late intervention as well as early intervention strategies [34]. The current (artificial) staging of prevention and intervention therapies deals with the following criteria: (i) prevention of the development of diabetes; (ii), when the disease is present, prevention of switching from normoalbuminuria to microalbuminuria and (iii) switching from microalbuminuria to overt nephropathy. These strategies may be labelled prevention and/or early intervention, whereas late intervention could be defined as postponing or preventing dialysis or transplantation in patients with overt nephropathy.

Genetic polymorphisms of the angiotensin-converting enzyme (ACE) gene are thought to be involved in the response to treatment. A recent subanalysis of the RENAAL (Reduction of Endpoints in Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan) study in proteinuric patients with type 2 diabetes showed that, unlike the ACE II allele, the D allele of the *ACE* gene [insertion (I)/deletion (D) and D/D] was associated with an unfavourable renal prognosis, which was improved with losartan therapy [35]. Similar findings from the REIN trial in non-diabetics led to one specific economic analysis on whether or not to genetically screen prior to treatment initiation [36].

Prevention of diabetes

Data from secondary analyses of several studies reveal that ACE inhibitors and angiotensin receptor blockers (ARBs), administered to patients without diabetes, but with various cardiovascular conditions, can reduce the risk of new-onset type 2 diabetes by up to 25% [37]. Examples are the DREAM study (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication) and the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study. The first showed that ramipril therapy significantly increased regression to normoglycaemia compared with placebo ($P = 0.001$) [38]. The second showed that new-onset diabetes occurred significantly less frequently ($P = 0.001$) in the losartan- than in the atenolol-treated group (13.0 versus 17.4 per 1000 patient-years of follow-up) [39].

Prevention of microalbuminuria

ACE inhibitors have been shown to prevent or delay the development of microalbuminuria in normoalbuminuric patients with type 2 diabetes. The BENEDICT (Bergamo Nephrologic Diabetes Complication Trial) study showed that treatment with trandolapril slowed the onset of persistent microalbuminuria by 53%. Interestingly, in the control arm of this study where the antihypertensive verapamil was used alone, there was no reduction in the development of microalbuminuria. This clearly shows that, although blood pressure control is important in diabetes, using an intervention in the renin–angiotensin–aldosterone system (RAAS) is of important additive value in protective prevention of renal disease [40].

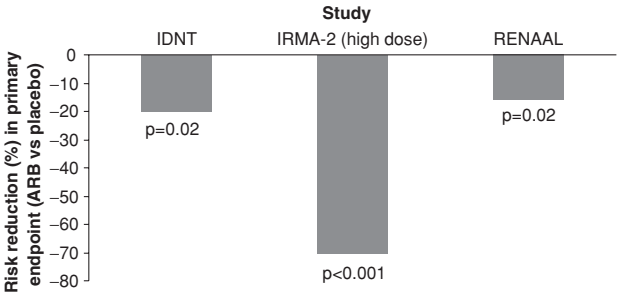

Fig. 1. ARBs reduce the risk of diabetic nephropathy progression: data shown (relative risk reductions versus placebo) are for the primary composite endpoint of doubling of serum creatinine, onset of ESRD or death from any cause (IDNT [50] and RENAAL [49] trials); or for the primary outcome of time to the onset of diabetic nephropathy (IRMA-2 trial [41]). ARB, angiotensin receptor blocker; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA-2, irbesartan in reduction of microalbuminuria-2; RENAAL, Reduction of Endpoints in Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan.

Early intervention

The IRMA-2 (Irbesartan in Reduction of Microalbuminuria-2) study was the first to demonstrate that ARBs can prevent the further development of albuminuria in hypertensive type 2 diabetic patients with microalbuminuria, and delay progression to overt nephropathy (Figure 1) [41]. Over a 2-year period, irbesartan effectively maintained low levels of microalbuminuria and exerted an independent renoprotective effect that was sustained after the cessation of treatment. Overt diabetic nephropathy was reached in 14.9% of placebo-treated participants, and in 9.7% and 5.2% of those receiving low- (150 mg) and high-dose (300 mg) irbesartan, respectively [41].

That RAAS inhibition could prevent transition from microalbuminuria to overt nephropathy was confirmed in the randomized, double-blind INNOVATION (INcipient to OVert: Angiotensin II blockers, Telmisartan, Investigation On type 2 diabetic Nephropathy) study [42] in hypertensive and also in normotensive Japanese patients with type 2 diabetes. With a mean follow-up time of 1.3 years, the transition rates to overt nephropathy were 16.7% and 22.6% with telmisartan 80 mg/day and 40 mg/day, respectively, compared with 49.9% with placebo ($P < 0.0001$ for both telmisartan doses versus placebo) [42].

Even at very low levels, microalbuminuria is strongly correlated with cardiovascular risk in diabetes patients [43]. The HOPE (Heart Outcomes Prevention Evaluation) study showed that, over a 4.5-year period, ACE inhibitor therapy reduced the risk of cardiovascular events by 25% in patients with type 2 diabetes and microalbuminuria [44].

In the Steno-2 study, patients with type 2 diabetes and microalbuminuria received either conventional antihypertensive therapy ($n = 80$) or intensive antihypertensive therapy with either ACE inhibitors or ARBs ($n = 80$) for a mean treatment duration of 7.8 years [22]. At follow-up (mean 13.3 years), intensive early intervention with ACE inhibitors or ARBs reduced the risk of cardiovascular

disease, nephropathy and death by 59%, 56% and 46%, respectively [45].

Recently, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation) study considered the impact of antihypertensive therapy for early to late-phase prevention in patients with type 2 diabetes regardless of hypertensive or renal status [28]. ADVANCE investigated the effect of an ACE inhibitor and diuretic in combination on major macrovascular and microvascular events. After a mean 4.3 years' follow-up, active therapy reduced the relative risk of a major event by 9% ($P = 0.04$), and the relative risk of death from cardiovascular disease was reduced by 18% ($P = 0.03$) [28].

Late intervention

Patients with type 2 diabetes and overt nephropathy are at high risk of cardiovascular events and progression to ESRD; therefore, prompt initiation of antihypertensive treatment is recommended [46]. ACE inhibitors and ARBs markedly reduce the risk of cardiovascular events in these patients [44,47,48]. Large, double-blind, multicentre, placebo-controlled studies such as RENAAL [49] and IDNT (Irbesartan Diabetic Nephropathy Trial) [50] have suggested that ACE inhibitors and ARBs are able to slow the rate of progression of diabetic nephropathy via blockade of RAAS constituents (Figure 1).

ACE inhibitors have been studied with particular respect to their effect on the progression of cardiovascular disease, whereas the effects of ARBs in patients with type 2 diabetes have been assessed against specific endpoints reflecting kidney performance, with some consideration given to competing cardiovascular events [51]. Although this creates a sound rationale for combination therapy with an ACE inhibitor and an ARB in patients with overt nephropathy, recent data from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) question the value of such an approach. Combined treatment with the ARB telmisartan and the ACE inhibitor ramipril appeared to worsen major renal outcomes, compared with either agent alone [52]. Currently, at least two studies have been started that further study the effect of combination therapy on renal hard outcomes: the LIRICO (Long-term Impact of RAS Inhibition on Cardiorenal Outcomes study [53]) and the VA-NEPHRON-D study [54].

Unfortunately, direct comparisons between ACE inhibitors and ARBs are generally limited to small studies, and are often not based on rigorously defined renal endpoints. The DETAIL study showed that telmisartan was not inferior if directly compared to enalapril on the primary endpoint of glomerular filtration [55]. Also, the effects of both drugs on the secondary endpoints (inclusive rates of ESRD and cardiovascular events) were not significantly different after 5 years. The ROAD (Renoprotection of Optimal Antiproteinuric Doses) study in non-diabetic nephropathy patients clearly showed similar effects of ACEi and ARB intervention on hard renal outcome [56]. In diabetes, no such studies have been reported yet.

Pharmacoeconomic studies in type 2 diabetic renal disease

The management costs associated with albuminuria and cardiovascular complications of kidney disease are substantial [57]. Caro and colleagues estimated that, of the total costs involved in the care of patients with type 2 diabetes, the costs of managing macrovascular complications comprise the largest component, accounting for 85% of the cumulative costs over the first 5 years and 77% over the first decade [58]. In the USA, the total annual cost of ESRD in patients with type 2 diabetes is projected to increase to more than $39 billion by 2010 [25]. Data from France and Belgium suggest that ESRD dialysis costs the health services ∼€44 000–61 000 per patient annually [59]. Annual costs of transplantation per ESRD patient from Dutch, French and Belgian studies have been estimated to be €25 000–50 000 in the first year [59,60]. Other data have shown the average cost of treating ESRD in the UK to be ∼£20 802 (∼€25 000) per patient per year [61] and the annual cost of dialysis to be £30 000 (∼€35 500) [62], whereas ESRD costs in Germany in 1999 were estimated at €40 414 per patient per year [63] and, in France, the estimated annual expenditure per ESRD patient in 2003 was ∼€41 000 [24]. Finally, in their economic analysis on the REIN trial, Costa-Scharplatz [36] analysed a range for dialysis costs for European Union countries from €20 000 to €80 000, with €48 170 as the most likely value (representing the German situation).

Halting the progression to ESRD would appear to be the obvious goal in type 2 diabetic renal disease, thus saving on costs of dialysis care or transplantation for patients who have no remaining kidney function. Intervention at the microalbuminuria and overt nephropathy stages can prevent or slow the progression to ESRD. A lot of effort, in terms of time and cost of treatment, in patients with a relatively low chance of reaching ESRD (i.e. all those with microalbuminuria) would appear at first sight to be costly due to the high numbers needed to treat. However, analyses comparing early and late interventions have demonstrated that early treatment with irbesartan in hypertensive patients with type 2 diabetes and microalbuminuria is likely to improve life expectancy and reduce overall costs compared to later treatment in patients who had already progressed to overt nephropathy [64,65].

Late intervention

A number of European pharmacoeconomic studies have quantified the cost savings that can be attained by intervening with ARB therapy to slow renal disease progression in type 2 diabetic patients with overt nephropathy (urinary albumin excretion >300 mg/24 h) (Table 1) [66]. Analyses using Markov modelling on data from IDNT revealed projected cost savings, over 10–25 years, of up to €27 611 per patient treated with irbesartan versus amlodipine, due to slowing of the progression from overt nephropathy to ESRD; corresponding cost savings for irbesartan versus control were up to €16 688 per patient (Table 2) [59,67,68].

Table 1. Pharmacoeconomic analyses of pharmacotherapy for slowing of renal disease progression in type 2 diabetic patients with overt nephropathy

Reference	Pharmacotherapy	Base study data	Countries	Projected time frame of analysis	Parameters evaluated	Reduction in relative risk of progression to ESRD	Key findings	Estimated ESRD-related cost savings per patient
Palmer *et al*. 2005 [68]	IRB AML	IDNT [50]	Belgium, France, Germany, Hungary, Italy, Spain, UK, USA	4 years	Clinical and cost outcomes (over a 25-year timeframe) from 7 studies	23%*	IRB improved DLE by up to 0.65 years versus AML, and by 0.36–0.76 years versus control	€10 158–€27 611 for IRB versus AML, and €5336–€16 688 for IRB versus control
Palmer *et al*. 2004 [67]	IRB AML	IDNT [50]	UK	4 years	Mean 10-year costs and changes in DLE	23%*	IRB improved DLE by 0.07 years versus AML, and by 0.21 years versus control	£5125 for IRB versus AML, and £2919 for IRB versus control
Palmer *et al*. 2003 [59]	IRB AML	IDNT [50]	Belgium, France	4 years	Mean 10-year costs and changes in DLE	23%*	IRB improved DLE by 0.13 years versus AML, and by 0.26 years versus control	€14 949–€20 128 for IRB versus AML, and €9205–€13 337 for IRB versus control
Gerth *et al*. 2002 [63]	LOS	RENAAL [49]	EU	4 years	Burden and costs of ESRD	29%	51 800 fewer ESRD cases; 89 900 ESRD person-years avoided	€3.6 billion[a]
Jonsson *et al*. 2005 [69]	LOS	RENAAL [49]	Nordic region (Denmark, Finland, Norway, Sweden)	4 years	Costs associated with ESRD	29%	Mean medical costs per patient during the first year of treatment = €53 235	€5591–€7025 per patient
Souchet *et al*. 2003 [70]	LOS	RENAAL [49]	France	4 years	Cost savings associated with reduced ESRD days	29%		€7438 per patient
Szucs *et al*. 2004 [71]	LOS	RENAAL [49]	Switzerland	4 years	Number of ESRD days saved	29%	33.6 ESRD days saved	CHF10 086 per patient
Vora *et al*. 2005 [62]	LOS	RENAAL [49]	UK	4 years	Life-years saved	29%	Projected mean life-years saved = 0.44	£7390 per patient

[a]Total, not per patient.
AML, amlodipine; CHF, Swiss Francs; DLE, discounted life expectancy; ESRD, end-stage renal disease; EU, European Union; IDNT, Irbesartan Diabetic Nephropathy Trial; IRB, irbesartan; LOS, losartan; RENAAL, Reduction in Endpoints in Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan.
*Relative to placebo, but also amlodipine.

Table 2. Irbesartan improves discounted life expectancy and saves costs relative to amlodipine and conventional antihypertensive therapy in patients with type 2 diabetes, hypertension and overt nephropathy: data from a systematic review of seven published cost-effectiveness analyses [68]

	Increase in discounted life expectancy (years/patient)[a]		Cost savings (€/patient)[b]	
Country	IRB versus AML	IRB versus CAT	IRB versus AML	IRB versus CAT
Belgium	0.46	0.62	21 798	12 241
France	0.45	0.61	27 611	16 688
Germany	–	–	15 445[c]	9338[c]
Hungary	0.15	0.36	10 158	5336
Italy	0.30	0.46	17 003	9418
Spain	0.21	0.37	14 083	7861
UK	0.31	0.58	13 457	7300
USA	0.65	0.76	21 585	12 810

Adapted from Palmer AJ *et al*. Cost-effectiveness of irbesartan in diabetic nephropathy: a systematic review of published studies. *Nephrol Dial Transplant* 2005; 20: 1103–1109, by permission of Oxford University Press on behalf of ERA-EDTA.
[a]25-year time frame; discount rate 1.5–6%.
[b]25-year time frame; discount rate 3–6%.
[c]10-year time frame; discount rate 5%.
AML, amlodipine; CAT, conventional antihypertensive therapy; IRB, irbesartan.

Palmer *et al*. performed a systematic review of seven cost-effectiveness analyses that applied IDNT data to Belgium, France, Germany, Hungary, Italy, Spain, the UK and the USA [68]. Within the framework of a Markov model, the mean time to the onset of ESRD was estimated to be 8.23 years for irbesartan, 6.82 years for amlodipine and 6.88 years for placebo, respectively; moreover, the corresponding mean cumulative incidences of ESRD were 36%, 49% and 45%. Irbesartan improved discounted life expectancy, projected over a 25-year period, by up to 0.65 years relative to amlodipine and by 0.36–0.76 years versus control (Table 1). In addition to these benefits, irbesartan was estimated to produce major cost savings over 25 years (up to €27 611 per patient; Tables 1 and 2); the latter savings generally manifested within 2–3 years of starting treatment [68].

Several pharmacoeconomic evaluations have applied RENAAL study data to European regions (Table 2) [62,63,69–71]. One analysis reported that treatment with losartan, to delay the progression of overt nephropathy to ESRD, would save an estimated €3.6 billion over 4 years throughout the European Union; these savings were associated with a predicted decrease of more than 50 000 cases of ESRD and 89 900 person-years living with ESRD avoided [63]. Other analyses—using costing designs or decision analytic techniques—documented per-patient cost savings of ∼€2687–7500 in Nordic countries [69], France [70] and Switzerland [71]. From the UK National Health Service payer perspective, losartan was estimated to statistically significant save overall health-care costs if compared with conventional antihypertensive therapy [62]. Sensitivity analyses revealed that losartan therapy remained cost saving in all cases, even if the costs of renal replacement therapy for ESRD were halved. Furthermore, losartan versus conventional antihypertensive therapy was associated with a projected mean number of life-years saved of 0.44 ($P = 0.002$) due to a reduction in the relative risk for ESRD [62].

To date, there have been no direct comparisons between ARBs and ACE inhibitors in terms of cost-effectiveness. Using indirect comparisons, ACE inhibitors are far more economic in terms of pricing, whereas ARBs have advantages on safety [72]. Obviously, such comparisons are highly sensitive to the exact assumptions applied.

In summary, results from economic studies have shown that late intervention with RAAS-inhibiting agents, to delay the progression of overt nephropathy to ESRD, provides substantial cost savings versus conventional antihypertensive therapy [73]. In strict pharmacoeconomic terminology, this would mean that such treatments represent 'dominant' interventions.

Early intervention

The high residual risk—and the high residual treatment costs—of type 2 diabetic patients with overt nephropathy during consequential ARB or ACE inhibitor treatment, as observed in RENAAL, IDNT and other studies, suggests a need to intervene earlier in the course of this progressive condition, for example, upon detection of microalbuminuria in patients with type 2 diabetes or earlier. Indeed, the IRMA-2 study showed that ARBs could delay the progression of microalbuminuria to overt nephropathy [41]. Several cost-effectiveness analyses have been performed using these data [60,74–77].

In one analysis, a Markov model was used to assess the health economic impact of screening for albuminuria using urinary dipstick testing in a primary care setting in French type 2 patients with hypertension [74]. In patients with microalbuminuria or overt nephropathy, treatment with irbesartan 300 mg/day was added to conventional antihypertensive therapy. Screening, and subsequently optimized therapy, for albuminuria reduced the cumulative incidence of ESRD by 42%, improved life expectancy by 0.38 years, produced an improvement of 0.29 quality-adjusted life years (QALYs) and reduced ESRD-related costs by €4812 per patient, over a projected time frame of 25 years [74]. Similar favourable results were found by the same investigators in a US setting [78].

An economic analysis in the Netherlands showed the cost-effectiveness of recommendations, in national clinical guidelines, for the prevention of type 2 diabetic nephropathy

[60]. Treatment of patients with type 2 diabetes according to clinical guidelines produced a gain of 0.2 complication-free life years, with a cost-effectiveness ratio of ∼€14 000 per QALY. With over half a million of diabetes patients in the Netherlands, strict adherence to guidelines may therefore gain ∼100 000 complication-free life years [60].

Several other analyses support the benefits of early pharmacological intervention in patients with hypertension, type 2 diabetes and microalbuminuria (Table 3) [75–77]. All these studies indeed found the dominant situation of cost savings combined with favourable health effects for ARB therapy.

A recently published economic analysis of Steno-2 from a Danish healthcare payer perspective also found acceptable pharmacoeconomics of intensive early intervention in patients with type 2 diabetes and microalbuminuria [79]. Intensive antihypertensive treatment increased life expectancy with a corresponding discounted incremental cost-effectiveness ratio of €2538 per QALY gained compared with conventional treatment, which, as a conservative estimate, is well within accepted cost-effectiveness limits. A sensitivity analysis showed that intensive therapy became dominant if all patients were treated in a primary care setting.

Prevention of diabetes

There are no published pharmacoeconomic analyses of preventing new-onset diabetes through RAAS treatment. Of note, the PREVEND cohort has shown that microalbuminuria levels (and even high normal levels of albuminuria) are associated with increased risk for developing new-onset diabetes [80]. Prospective studies of looking into the cost-effectiveness of preventing diabetes could be interesting, particularly in light of the finding that early intervention is potentially more cost-effective than late.

Prevention of microalbuminuria in patients with diabetes

At present, there are no data on the cost-effectiveness of preventing the development of microalbuminuria in patients with diabetes in clinical practice. Whether albuminuria lowering will reduce the rate of new-onset diabetes and subsequent economic burden would be an interesting focus of future research.

Early or late intervention: which is best?

Recently, Palmer and colleagues conducted a cost-effectiveness analysis in the French setting, in which early or late intervention with ARB therapy was compared with conventional antihypertensive therapy in hypertensive patients with type 2 diabetes and microalbuminuria or overt nephropathy [65]. A Markov model was used to simulate the progression from microalbuminuria to overt nephropathy, doubling of serum creatinine, ESRD and total mortality over a 25-year period. Transition probabilities were derived from IDNT, IRMA-2 and other sources. Relative to conventional antihypertensive therapy, early versus late ARB therapy added 0.94 versus 0.04 life years per patient, 1.03

Table 3. Pharmacoeconomic studies of pharmacotherapy for slowing renal disease development and progression, in patients with hypertension, type 2 diabetes and microalbuminuria

Reference	Pharmacotherapy	Base study data	Countries	Projected timeframe of analysis	Parameters evaluated	Reduction in relative risk of progression to ESRD	Other key findings[a]	Estimated ESRD-related cost savings[a]
Palmer *et al.* 2006 [75]	IRB CAT	IDNT [50]; IRMA-2 [41]	Switzerland	25 years	Progression of microalbuminuria to death (from any cause) through the following stages: early overt nephropathy; advanced overt nephropathy; DSC; ESRD with dialysis; and ESRD with transplant	15%	Increased mean DLE by 0.57 years	CHF 21 487 per patient
Palmer *et al.* 2005 [76]	IRB CAT	IDNT [50]; IRMA-2 [41]	Spain	25 years		15%	Saved 1.4 life-years per patient	€11 082 per patient
Palmer *et al.* 2007 [77]	IRB CAT	IDNT [50]; IRMA-2 [41]	Hungary	25 years		7.5%	Increased ULE by 0.98 years	HUF 519 993 per patient (lifetime cost savings)

[a]IRB versus CAT.

CAT, conventional antihypertensive therapy; CHF, Swiss Francs; DLE, discounted life expectancy; DSC, doubling of serum creatinine; ESRD, end-stage renal disease; HUF, Hungarian Florins; IDNT, Irbesartan Diabetic Nephropathy Trial; IRB, irbesartan; IRMA-2, irbesartan in reduction of microalbuminuria-2; ULE, undiscounted life expectancy.

versus 0.06 QALYs and saved €22 314 versus €6619 per patient. Thus, although late intervention with ARB therapy was clearly beneficial, earlier intervention had advantages in terms of markedly greater life expectancy and improved quality of remaining life, and considerably greater cost savings [65]. These findings reinforced previous findings by the same authors [56].

Golan *et al*. performed a cost-effectiveness analysis of prescribing ACE inhibitors to all patients aged 50 years or older with newly diagnosed type 2 diabetes [81]. Conducted from a societal perspective over a lifetime horizon, and based on 1999 US prices, they estimated an incremental cost-effectiveness ratio of $7500 per QALY gained when compared with routine prescription of ACE inhibitors for all patients who were screened for microalbuminuria. Screening for proteinuria (i.e. identifying patients with overt diabetic nephropathy) had the highest cost and the lowest benefit [82].

Conclusion

In Europe, although some progress has been made against ESRD caused by glomerulonephritis, urological interstitial nephritis or type 1 diabetes, the incidence of ESRD caused by hypertensive renovascular disease or type 2 diabetes continues to increase [1]. ESRD related to type 2 diabetes is associated with increased cardiovascular morbidity and mortality [9,11], and with a relevant financial burden to third party payers [82,83]. These high ESRD costs, coupled with World Health Organization projections for future increased prevalence rates of type 2 diabetes [14], clearly outline the need for improved preventive strategies designed to target various ESRD 'precursors'.

Several strategies for intervention are available; however, the effectiveness of such strategies leaves many patients with a high residual risk. Early intervention strategies appear more effective in reducing the risk, and moreover, the pharmacoeconomic profiles of early intervention clearly outweigh those of late intervention, despite the fact that many more patients need to be treated. In that respect, our findings are in line with those in a previous review [66]. Whether prevention of type 2 diabetes itself should be attempted is a major question and a challenge for the patients at risk, for clinicians, in terms of choice of drugs to use and for pharmacoeconomists, in terms of the complexities involved in the construction of pharmacoeconomic models for cost analysis and comparison.

Despite the availability of consistent clinical data on the prevention of renal complications in patients with type 2 diabetes [46,84], these drugs are greatly underutilized according to treatment guidelines [85]. Our economic evidence on favourable cost-effectiveness supports further increased efforts to enhance adhering to diabetes management guidelines.

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