A health economic analysis of screening and optimal treatment of nephropathy in patients with type 2 diabetes and hypertension in the USA

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Abstract

Background. Nephropathy is an indicator of end-organ damage and is a strong predictor of an increased risk of cardiovascular disease and death in patients with diabetes. Screening can lead to early identification and treatment, both of which incur costs. However, identification and treatment may slow or prevent progression to a more expensive stage of the disease and thus may save money. We assessed the health economic impact of screening for nephropathy (microalbuminuria and overt nephropathy) followed by optimal renoprotective-based antihypertensive therapy in a US setting.

Methods. A Markov model simulated the lifetime impact of screening with semi-quantitative urine dipsticks in a primary care setting of hypertensive patients with type 2 diabetes and subsequent treatment with irbesartan 300 mg in patients identified as having nephropathy. Progression from no nephropathy to end-stage renal disease (ESRD) was simulated. Probabilities, utilities, medication and ESRD treatment costs came from published sources. Clinical outcomes and direct medical costs were projected. Second order Monte Carlo simulation was used to account for uncertainty in multiple parameters. Annual discount rates of 3% were used where appropriate.

Results. Screening, followed by optimized treatment, led to a 44% reduction in the cumulative incidence of ESRD and improvements in non-discounted life expectancy of 0.25 ± 0.22 years/patient (mean ± SD). Quality-adjusted life expectancy was improved by 0.18 ± 0.15 quality-adjusted life years (QALYs)/patient and direct costs increased by $244 ± 3499/patient. The incremental cost-effectiveness ratio was $20 011 per QALY gained for screening and optimized therapy versus no screening. There was a 77% probability that screening and optimized therapy would be considered cost effective with a willingness to pay a threshold of $50 000.

Conclusion. In patients with type 2 diabetes and hypertension, screening for nephropathy and treatment with a renoprotective-based antihypertensive agent was projected to improve patient outcomes and represent excellent value in a US setting.

Keywords: angiotensin receptor blocker; cost-effectiveness; costs; hypertension; nephropathy; type 2 diabetes mellitus

Introduction

The prevalence of microalbuminuria, defined as a urinary albumin excretion rate (UAE) of 20–200 µg/min, in patients with diabetes and hypertension has been estimated to be 31%, and the prevalence of overt nephropathy (UAE > 200 µg/min) 11% in the USA [1]. Hypertension is present in ~50% of patients with type 2 diabetes at diagnosis, with hypertension developing later in the course of the disease in the majority of remaining patients [2,3]. Diabetes has been identified as the leading cause of end-stage renal disease (ESRD) in Europe and the United States [3,4]. The average annual total healthcare cost for a patient receiving dialysis is ~$60 000 and ~$28 000 for patients with a functioning renal transplant. Disconcertingly, the ESRD population increases by 6%/year and Medicare ESRD-related expenditures have been projected to be around $28 billion/year in 2010 [5]. Microalbuminuria and overt nephropathy are associated with progressively increasing risks of cardiovascular disease and all-cause mortality [6–8].

Since ~40% of the 21 million patients with diabetes in the United States (16 million diagnosed and an estimated 5 million undiagnosed) are likely to develop diabetic
nephropathy, the projected ESRD-related costs for this population are staggering (American Diabetes Association; Facts & Figures: http://www.diabetes.org). In this context, early identification and appropriate treatment of diabetic nephropathy may have the potential to have a huge impact on health outcomes and costs associated with patients with type 2 diabetes and hypertension. The American Diabetes Association recommends that patients with type 2 diabetes, hypertension and microalbuminuria are treated with an angiotensin receptor blocker or an angiotensin converting enzyme inhibitor [9]. Both angiotensin receptor blockers and angiotensin converting enzyme inhibitors are generally very well tolerated by most individuals, but the incidence of cough is less frequent with angiotensin receptor blockers, with as much as 5–35% of patients on angiotensin converting enzyme inhibitor reporting dry cough [10]. Studies have reported that angiotensin receptor blockers slow the progression of diabetic nephropathy by mechanisms that are independent of their effects on blood pressure. This property, entitled ‘renoprotection’ treatment, has been shown to delay the development of diabetic nephropathy at various stages of this disease [11–13]. The results of these studies indicate that if diabetic nephropathy is treated in a timely and ordered manner, great economic savings could be made with substantial clinical gains [14]. To ensure that this occurs, screening is required so that microalbuminuria and overt nephropathy can be identified early and thus optimal renoprotective treatment with angiotensin receptor blockers can be initiated [14,15].

Unfortunately in the USA, nephropathy (microalbuminuria and overt nephropathy) screening rates and optimal treatment of hypertension are well below recommendations. A recent survey of adherence to the 2002 American Diabetes Association guidelines for the management of diabetic nephropathy [9] revealed that in a managed care setting only 30% of patients with diabetes and hypertension had a claim indicator for a protein urine check or a diagnosis of nephropathy in the 12-month analysis period. Moreover, 31.3% did not have a claim for an angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, and of those diagnosed with nephropathy, only 25% were receiving an angiotensin receptor blocker as per ADA guidelines [16]. Limited healthcare budgets and the fact that healthcare policy makers sometimes take a short-term view may present an obstacle to the implementation of a new medical intervention. Interventions such as improving screening rates, while generally more costly than commonly accepted practice, usually provide greater clinical benefit. This benefit may be seen in the short term or it may not be apparent until the medium to long term. Health policy decision makers take costs and benefits into account and adopt a long-term view to assess the overall economic impact of an intervention. In patients with type 2 diabetes and hypertension, we hypothesize that some of the huge costs associated with ESRD could be avoided by screening these patients for early nephropathy and treating those affected with timely and optimal antihypertensive therapy resulting in net clinical gain as well as representing good value for money.

To test this hypothesis we performed cost-utility analysis [calculating incremental 25-year direct medical costs per quality-adjusted life year (QALY) gained] as well as calculating other important clinically relevant outcomes (projected life expectancy, cumulative incidence of ESRD, ESRD-free survival, days of renal replacement therapy avoided) using computer-based Markov modelling techniques to project long-term outcomes for patients with type 2 diabetes and hypertension.

Methods

Overview

Two interventions were modelled. Subjects in one intervention arm were screened for nephropathy (microalbuminuria and overt nephropathy) and if detected received irbesartan 300 mg daily in addition to other conventional antihypertensive agents. In the other arm, subjects were not screened for nephropathy, and equivalent blood pressure control was achieved with conventional medications alone. The computer model simulated progression from no renal disease to ESRD over a 25-year horizon.

Model structure

TreeAge Pro decision analysis software (TreeAge Software Inc., Williamstown, MA, USA) was used to develop a Markov/Monte Carlo simulation model. The progression of renal disease in patients with type 2 diabetes was simulated with eight progressive disease states: (1) no nephropathy (24 h UAE <20 µg/min); (2) microalbuminuria (24 h UAE 20–199 µg/min); (3) early overt nephropathy (UAE 200 µg/min to median UAE 1900 mg/24 h); (4) advanced overt nephropathy (median UAE on entry ≥1900 mg/24 h); (5) DSC (doubling of serum creatinine levels); (6) ESRD treated with dialysis; (7) ESRD treated with renal transplant and (8) death (Figure 1). There were additional states in the ‘screening’ arm. If subjects were correctly diagnosed as having nephropathy (microalbuminuria or overt nephropathy), as determined by the sensitivity of the screening test, they were given irbesartan 300 mg daily in addition to any other antihypertensive medication they were taking. Subjects could be wrongly diagnosed as having nephropathy (determined by screening test specificity) and commence irbesartan 300 mg daily. In this case, we did not assume a benefit from a potential reduction in the rate of development of microalbuminuria (as no clinical data currently exist that support a reduction in the development of microalbuminuria with irbesartan) but only to incur the costs of irbesartan treatment.

Transition probabilities

The probability of microalbuminuria development in the absence of renal disease was derived from the control arm of the BENEDICT study in patients with type 2 diabetes and hypertension [17]. Subjects were treated with conventional antihypertensive medication to achieve a target blood pressure of 120/80 mmHg; ∼15% developed microalbuminuria within a 4-year period. Transition probabilities for the ‘no screening arm’ were taken from the control arms
of the IRMA-2 and IDNT studies and have been reported extensively by Palmer et al. [11,12,14,17]. If nephropathy was detected in the screening arm of the model, treatment with irbesartan commenced and further transition probabilities were obtained from the irbesartan 300 mg daily treatment arms of the IRMA-2 and IDNT studies [14]. Transition probabilities from microalbuminuria to early overt nephropathy and from early overt nephropathy to advanced overt nephropathy were derived from the IRMA-2 study. Estimates from the IDNT trial were used to calculate transition probabilities from advanced overt nephropathy to DSC or ESRD and have been previously published by Palmer et al. [14].

Once a subject progressed to the state of ESRD, future transition probabilities for mortality and for switching between alternative states of renal replacement became independent of treatment, and therapy with irbesartan was assumed to cease. These probabilities have been documented previously by Palmer et al. [18].

**Mortality calculations**

Mortality probabilities were dependent solely on the level of renal disease reached by simulated subjects. In the states of no nephropathy, microalbuminuria, early overt nephropathy, advanced overt nephropathy and DSC, mortality was calculated using US age- and gender-specific all-cause mortality tables [19] and values adjusted by state-dependent multipliers. In the state of no nephropathy, a multiplier was drawn from a triangular distribution defined by a minimum value 1.17, a most likely value 1.76 and a maximum value 2.66 [20]. In the state of microalbuminuria, a multiplier of 2.21 relative to no nephropathy was used, based on data from the Danish Steno-2 study [19,21]. The risk multiplier for mortality in patients with type 2 diabetes, hypertension and overt nephropathy was calculated to be 3.29 relative to no nephropathy [22]. In the absence of published data, it was conservatively assumed that the risk multipliers for all-cause mortality in the early overt nephropathy, advanced overt nephropathy and DSC states were the same.

Once simulated patients reached the states relating to ESRD, mortality was dependent on the type of renal replacement therapy received (i.e. dialysis or transplantation). ESRD outcomes data, including mortality rates in the ESRD states, were taken from published US sources and have been described previously [4,23].

**Simulated cohort and interventions compared**

A hypothetical cohort of patients with type 2 diabetes and hypertension was simulated by the model and cohort definition reflected important demographic characteristics including the age-dependent prevalences of microalbuminuria and overt nephropathy found in diabetic patients with hypertension in the USA [1]. Baseline age was drawn from the distribution of ages of US patients with type 2 diabetes taking oral hypoglycaemic agents, as reported in an IMS survey (Table 1) [24]. Subjects were allocated at the beginning of the simulation to either no nephropathy, microalbuminuria or overt nephropathy according to age-dependent prevalences reported in US patients with diabetes and hypertension (Table 2) [1]. In the absence of data it was assumed that of those subjects with overt nephropathy, 85% had early overt nephropathy and 15% had advanced overt nephropathy (personal communication, Hans-Henrik Parving, Steno Diabetes Center, Denmark).
Screening for nephropathy was assumed to take place in a primary care setting using the semi-quantitative Micral II urine test strips once every 12 months during routine physician visit. It was assumed that if patients were tested negative on their first test, they would be tested again within 12 months. If they were tested positive on the first test, however, two confirmatory tests would be performed (also using Micral II test strips). If two out of three of these tests were positive, the subjects would be deemed to have nephropathy, and have irbesartan 300 mg added to their current treatment regimen. This annual testing regimen would continue for each subject unless they had nephropathy diagnosed. The sensitivity and specificity of the Micral II test strips were taken from figures reported by the University of Sheffield with sensitivities ranging between 70 and 97% and specificities ranging between 71 and 98% [25].

Second order Monte Carlo simulation

To account for multiple parameter uncertainty in health economic analyses, second order Monte Carlo simulation is a well-accepted mathematical technique that is commonly employed [26]. In the present analysis, baseline age, baseline prevalence of microalbuminuria and overt nephropathy, and the sensitivity and specificity of screening were all sampled from distributions utilizing this method. Furthermore, transition probabilities for the irbesartan treatment arms of the model were determined by values sampled from distributions of the relative risk (RR) of progression between health states in the irbesartan treatment arms of the IRMA-2 trial and the IDNT [11,12].

Costs

All costs used in the model were reported in US dollars ($), referenced to year 2000. The perspective of a US third-party health insurance payer was taken, so indirect costs were not included. In the screening arm of the model, the costs of screening for nephropathy in the primary care setting were accounted for. Differentiation in the costs of screening was made between negative screening tests and positive screening. Each screening episode was assumed to include the cost of a general practitioner consultation, and the cost of the test strip. The costs of screening that turned out to be negative included one screening test with Micral II test strips, and one general practitioner consultation. Note that this could be considered to be a conservative assumption since patients would likely be seeing their practitioner for reasons in addition to those of performing a screening test. If the initial test was positive, additional costs of two confirmatory test strips and two general practitioner consultations were added. If screening was positive for nephropathy, the cost of irbesartan 300 mg daily was also added. Annual costs of irbesartan 300 mg daily were taken from the Drug Topics Red Book [27], using the average wholesale price, and amounted to $573.05/patient/year. The costs of ESRD treatment (dialysis and transplantation) were taken from the US Renal Data Service [4]. For dialysis, these costs amounted to ~$60 100/patient/year. In the first year following transplantation, costs per patient were $62 442. In maintenance years, costs following transplantation were $27 600/patient/year.

Health state utilities and quality-adjusted life expectancy

Health state utility values were assigned to each health state in the model to enable quality-adjusted life expectancy to be calculated. The utility used in the states of no nephropathy, microalbuminuria, early and advanced overt nephropathy was 0.88, and accords with to one published by Brown et al. who reported that no difference in health state utility was notable in patients with diabetes regardless of whether or not they had nephropathy [28]. The state of DSC, which represents renal function shortly before onset of renal failure, was assigned a utility value of 0.70 representing chronic renal disease (pre-dialysis) with no anaemia [29]. Health state utilities for ESRD treated with either transplant (0.762) or dialysis (0.462) have been reported by Tengs and Wallace and were used for subjects receiving either renal transplantation or renal dialysis [29].

Discounting and time horizon

In accordance with current US guidelines, costs were discounted at 3% annually [30]. Whilst life expectancy was calculated in natural units (non-discounted years), it was also discounted at 3% annually. This discount rate was varied between 0 and 7% in a sensitivity analysis. Outcomes
were projected for time horizons ranging between 0 and 25 years, with a 25-year time horizon used in the base case.

Sensitivity analyses
In the base-case analysis, second order Monte Carlo simulation was utilized to assign baseline age for simulated subjects. Two further simulations were run where sampling of age did not occur for subjects with baseline ages of 40 or 75 years. Furthermore, in the base case, it was assumed that 85% of subjects with overt nephropathy had early overt nephropathy and 15% had advanced overt nephropathy. A sensitivity analysis was performed where the proportion of subjects with advanced overt nephropathy was varied from 0 to 30%.

Results
Cumulative incidence of ESRD and ESRD-free survival
The cumulative incidence of ESRD was reduced by 44% from 8.4 ± 8.0% without screening to 4.7 ± 2.3% with screening and optimal antihypertensive treatment. The first cases of ESRD began to be avoided as early as 2 years after implementation of screening and optimal antihypertensive therapy versus no screening (Figure 2). Mean ESRD-free survival was increased from 10.8 ± 5.1 to 11.2 ± 5.4 years, with 45 ± 52.8 days of renal failure avoided per simulated patient with screening and optimized therapy versus no screening.

Life expectancy
Non-discounted life expectancy increased by 0.25 ± 0.22 years/patient with screening and optimal treatment. Life expectancy (not discounted) was improved from 10.71 ± 4.97 years/patient without screening to 10.96 ± 5.18 years/patient with screening and optimal antihypertensive treatment. Discounted life expectancy was improved by 0.16 ± 0.12 years/patient. Gains in life expectancy were noted after a period of 3 years (Figure 3).

Quality-adjusted life expectancy
An improvement of 0.18 ± 0.15 QALYs was seen for screening versus no screening. Quality-adjusted life expectancy (discounted at 3% annually) improved from 7.57 ± 3.13 QALYs/patient without screening to 7.75 ± 3.28 QALYs/patient with screening and optimal antihypertensive treatment.

Costs
Total 25-year costs per patient (discounted at 3% annually) increased marginally from $11 200 ± 11 534/patient without screening to $11 444 ± 8278/patient with screening and optimal antihypertensive treatment, an increase in costs of $244 ± 3499/patient. The measures of dispersion of costs and differences in costs per patient were large, due to the typically skewed distribution of the costs in each treatment arm (Figure 4) [31,32].

Incremental costs per quality-adjusted life-year gained
A median incremental cost-effectiveness ratio of $20 011 per QALY gained was calculated. The acceptability curve, generated from the second order Monte Carlo simulation [31], demonstrated that with a willingness-to-pay (WTP) threshold of $50 000, there was a 77% probability that screening and optimal antihypertensive therapy would be considered good value for money versus no screening. With a WTP threshold of $100 000, there was a 93% probability of acceptance (Figure 5).

Sensitivity analysis
When the 10-year time horizon was used, screening and optimal antihypertensive treatment still led to improvements
in patient outcomes. After 10 years, cumulative incidence of ESRD was reduced from 3.7 ± 2.3% to 2.2 ± 1.4%, non-discounted life expectancy was improved by 0.04 ± 0.01, discounted life expectancy by 0.03 ± 0.01, discounted quality-adjusted life expectancy by 0.04 ± 0.01 QALYs/patient and increased costs of $1922/patient were projected, with a median incremental cost-effectiveness ratio of $51 544 per life-year gained. Acceptability analysis determined that at 10 years, there was a 48% probability of acceptance with a WTP threshold of $50 000 per QALY gained and an 87% probability of acceptance with a WTP threshold of $100 000 per QALY gained.

Using annual discount rates of 0% for both costs and quality-adjusted life expectancy resulted in the screening and optimal screening strategy becoming dominant to no screening, i.e. improvements in quality-adjusted life expectancy as well as overall cost savings. Mean quality-adjusted life expectancy was projected to improve from 9.70 ± 4.52 QALYs with no screening to 10.00 ± 4.78 QALYs with screening and optimal treatment. Mean costs were reduced from $16 622 ± 19 593 to $15 745 ± 13 661. Using annual discount rates of 7% for both costs and quality-adjusted life expectancy resulted in an incremental cost-effectiveness ratio of $24 162 per QALY gained. With a WTP threshold of $50 000, there was a 73% probability of acceptance of screening and optimal therapy versus no screening. With a WTP threshold of $100 000, this increased to 86%.

Varying the proportion of all patients with nephropathy who were assumed to have advanced overt nephropathy at
baseline had no substantial impact on the qualitative results (screening and optimal antihypertensive therapy always led to improved patient outcomes and remained excellent value for money). When this percentage was varied between 0% and 30%, improvements in discounted quality-adjusted life expectancy with screening versus no screening varied from 0.19 ± 0.16 to 0.17 ± 0.15 QALYs, and cost increases varied from $201 ± 3589/patient to $401 ± 3502/patient, with costs per QALY gained of $19 266 and $21 105 respectively.

Screening and optimal antihypertensive therapy had the greatest impact in younger patient groups. In patients with mean baseline age of 40 years, improvements in discounted quality-adjusted life expectancy increased in 0.45 ± 0.05 QALYs, and overall cost savings of $6234 ± 1717 were projected (compared to the base-case improvements in life expectancy of 0.18 ± 0.15 years and increased costs of $244 ± 3499/patient calculated on a distribution of baseline ages with a mean age of 61 years). When a subgroup of patients with baseline age of 70 years was simulated, quality-adjusted life expectancy was increased by 0.06 ± 0.02 years and costs by $2529 ± 2026/patient, with an incremental cost-effectiveness ratio of $42 616 per QALY gained.

Discussion

Our modelling analysis demonstrated that annual screening for nephropathy in a typical population of patients with type 2 diabetes and hypertension followed by renoprotective-based antihypertensive treatment in a US setting may lead to substantial improvements in long-term patient outcomes, with only minor increases in costs. Screening and optimal treatment represent excellent value for money by current US standards due to a reduced incidence of ESRD. Screening and treatment with irbesartan may also represent good value for money in Europe, where ESRD-related costs are substantial contributors to healthcare expenditure [33,34]. However, further country-specific analyses are required to confirm the cost-effectiveness in European settings. Improvements in patient outcomes were seen after 2 years. Sensitivity analysis demonstrated the robustness of the results—screening and optimal treatment always led to improved patient outcomes and represented excellent value for money, or even led to overall cost savings in some circumstances. Subgroup analysis revealed that screening in younger patient subgroups has a greater beneficial impact, leading to overall improvements in patient outcomes as well as cost savings.

It is likely that our estimates of only minor increases in costs associated with screening and irbesartan are conservative, with some screening expenses overstated and potential cost savings not fully quantified. Whereas we attributed the full cost of a visit to a clinician for the initial screening evaluation, in practice screening for nephropathy would more likely represent just one component of a routine healthcare visit. Also, the cost offset associated with concomitant antihypertensive medication was not included in our calculations. Had these cost offsets been incorporated screening would have been associated with a smaller increase in lifetime costs versus the base case or even cost savings. Subjects who were not screened were assumed to have received antihypertensive medication with a target blood pressure of <135/85 mmHg. In practice, it would be unlikely that patients not screened would receive such adequate blood pressure control, so the analysis may have underestimated the clinical improvements and overestimated the increase in costs associated with screening and optimal treatment with irbesartan [16].

A number of previous studies have investigated the cost-effectiveness of screening for nephropathy in patients with type 1 or type 2 diabetes [35–40]. Our study, however, is the first to investigate the health economic implications of screening for nephropathy and managing it optimally with antihypertensive medication including an angiotensin receptor blocker in hypertensive patients with type 2 diabetes in a US setting. Our study is based directly on recent clinical trials that provided information on health state transition probability across the broad spectrum of nephropathy from normoalbuminuria to ESRD. Only one published study to date [40] has examined the cost-effectiveness of screening for nephropathy and angiotensin-converting enzyme inhibition in patients with type 2 diabetes, but a number of key assumptions about the progression of nephropathy had to be made due to clinical data being unavailable. The findings of our analysis support screening for nephropathy in patients with type 2 diabetes who are hypertensive by demonstrating that screening in this high-risk group can improve clinical outcomes substantially and be cost saving. We do not feel that short-term financial concerns should act as a barrier to the implementation of screening for nephropathy in this group of patients.

Conclusions

Limited healthcare budgets require policy decision makers to identify interventions that are cost effective before considering which to implement or promote. Our modelling analysis indicated that screening for nephropathy followed by optimal antihypertensive therapy with renoprotective agents in patients with type 2 diabetes and hypertension may improve clinical outcomes while only marginally increasing overall costs, and representing an excellent value for the money spent.

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