Cost-consequence analysis in a French setting of screening and optimal treatment of nephropathy in hypertensive patients with type 2 diabetes

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SUMMARY
Aim: Forty percent of hypertensive type 2 diabetes patients develop nephropathy (microalbuminuria/overt nephropathy), indicating end organ damage, increased risk of cardiovascular disease (CVD), and death. In France, screening rates and nephropathy treatment are sub-optimal. We assessed the health economic impact of nephropathy screening in hypertensive patients with type 2 diabetes followed by optimal antihypertensive/nephroprotective therapy in those who have nephropathy in France.

Methods: A Markov/Monte Carlo model simulated lifetime impacts of screening for albuminuria (microalbuminuria/overt nephropathy) using semi-quantitative urine dipsticks in a primary care setting, and subsequent addition of irbesartan 300 mg to conventional therapy in hypertensive type 2 diabetes patients identified as having nephropathy. Progression from no renal disease to end-stage renal disease (ESRD) was simulated. Probabilities, utilities and costs of CVD events, medications and ESRD treatment came from published sources. Cumulative incidence of ESRD, life expectancy, quality-adjusted life years (QALYs) and direct costs were projected. Second-order Monte Carlo simulation accounted for uncertainty in multiple parameters. Costs and QALYs were discounted at 3% annually.

Results: Screening and optimized treatment led to a 42% reduction in the cumulative incidence of ESRD from 10.1 ± 9.9% without screening to 5.8 ± 5.7%, improvements in life expectancy of 0.38 ± 0.59 years, improvements of 0.29 ± 0.32 QALYs, and decreased costs of €4,812 ± 7,882/patient over 25 years. Sensitivity analysis showed that the results were robust. Screening was most beneficial when performed in younger patients.

Conclusion: In hypertensive patients with type 2 diabetes, screening for albuminuria followed by optimal antihypertensive/nephroprotective treatment improves patient outcomes and leads to cost savings in France.

Key-words: Type 2 diabetes mellitus · Hypertension · Nephropathy · Screening · Cost-effectiveness.

RÉSUMÉ
Analyse des conséquences sur les coûts, dans un cadre français, du dépistage et du traitement optimal de la néphropathie chez l’hypertendu diabétique de type 2

Objectif : Quarante pour cent des hypertendus diabétiques de type 2 développent une néphropathie (microalbuminurie/néphropathie avérée), indicateur d’une atteinte organique, d’un risque accru de maladie cardiovasculaire (CV), et d’un décès. En France, les taux de dépistage et de traitement de la néphropathie sont sous-optimaux. Nous avons évalué l’impact économique du dépistage de la néphropathie chez l’hypertendu diabétique de type 2 suivi d’une thérapie antihypertensive/néphroprotectrice chez les patients atteints de néphropathie en France.

Méthodes : Un modèle de Markov/Monte-Carlo a simulé l’impact sur la durée de vie du dépistage de l’albuminurie (microalbuminurie/néphropathie avérée), utilisant des sticks urinaires semi-quantitatifs en médecine générale, et l’addition ultérieure d’irbesartan 300 mg à la thérapie conventionnelle de l’hypertendu diabétique de type 2, chez les patients identifiés comme étant atteints de néphropathie. La progression de l’absence de maladie rénale vers la maladie rénale en stade terminal (MRST) a été simulée. Les probabilities, les utilités et les coûts des événements CV, les médicaments et le traitement de la MRST proviennent de sources publiées. L’incidence cumulée de MRST, l’espérance de vie, les années de vie ajustées sur la qualité de vie (QALY) et les coûts directs furent projetés. Une simulation de Monte-Carlo de second ordre a pris en compte l’incertitude de multiples paramètres. Les coûts et les QALYs ont été ajustés sur une base annuelle de 3 %.

Résultats : Le dépistage, suivi d’un traitement optimal a conduit à une réduction de 42 % de l’incidence cumulée de MRST de 10,1 ± 9,9 % sans dépistage à 5,8 ± 5,7 %, à une amélioration de l’espérance de vie de 0,38 ± 0,59 ans, de 0,29 ± 0,32 QALYs, et une réduction des coûts de 4 812 ± 7 882 €/patient sur 25 ans. L’analyse de sensibilité a montré que les résultats sont robustes. Le dépistage apporte un bénéfice plus important chez les patients jeunes.

Conclusion : Chez l’hypertendu atteint de diabète de type 2, le dépistage de l’albuminurie suivi d’un traitement optimal anti-hypertenseur/néphroprotecteur améliore le pronostic des patients et conduit à des économies de coûts en France.

Mots-clés : Diabète de type 2 · Hypertension · Néphropathie · Le dépistage · Cost-effectiveness.
Introduction

The 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension recognize microalbuminuria (MA) as a sign of target organ damage [1]. The combination of inadequately-treated hypertension, nephropathy and type 2 diabetes places patients at increased risk of morbidity and death, mainly due to cardiovascular causes [2]. The prevalence of microalbuminuria in hypertensive patients with diabetes is high at ~31%, and the prevalence of overt nephropathy is ~11% [3]. Hypertension is present in around 50% of type 2 diabetes patients at diagnosis, and develops later in the course of the disease in the majority of remaining patients [4,5]. Optimal antihypertensive/nephroprotective treatment may reduce the progression of nephropathy, but the current rates of screening for and treatment of hypertension and nephropathy are currently well below recommended levels [1,6,7].

Most of the costs of type 2 diabetes in France and other European countries are attributable to the management of complications, including end-stage renal disease (ESRD) [8]. Type 2 diabetes is the leading cause of ESRD in the Western world [4,5]. In France, between 1993 and 1999 the prevalence of ESRD due to diabetic nephropathy rose annually by approximately 5% [9]. The impact of ESRD on health and healthcare budgets is of significant concern to healthcare decision makers. With the prevalence of type 2 diabetes increasing in France [7,10-12], the cost of medical care for diabetes patients is expanding rapidly [11].

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 [13-15]. These data 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 [16]. Budgetary concerns may represent a theoretic barrier to implementation of adequate screening and subsequent treatment programs. We therefore performed a cost-consequence analysis to quantify the health economic impact of screening for nephropathy in hypertensive patients with type 2 diabetes, and subsequent optimal treatment of nephropathy with irbesartan 300 mg daily added to conventional therapy versus no screening and equivalent blood pressure control with conventional medications alone.

Methods

Model structure

A Markov/Monte Carlo simulation model was developed using TreeAge Pro® software (TreeAge Software Inc., Williamstown, Massachusetts, USA). In the “no screening” arm of the model, the Markov structure was made up of eight basic disease states designed to simulate the progression of renal disease in patients with type 2 diabetes. Progression from no nephropathy (24-hour urinary albumin excretion (UAE) < 20 µg/min) to; microalbuminuria (24-hour UAE 0.30-200 µg/min); early overt nephropathy (UAE 200 µg/min to median UAE 1,900 mg/24-hours); advanced overt nephropathy (median UAE on entry ≥ 1,900 mg/24-hours); doubling of serum creatinine (DSC); ESRD treated with dialysis; ESRD treated with renal transplant; and Death was simulated (figure 1). In the “screening” arm of the model, additional states accounted for patients who were screened, correctly diagnosed as having nephropathy (determined by the sensitivity of the screening tests), and subsequently had irbesartan 300 mg daily added to their treatment regimen. Other states accounted for patients wrongly diagnosed as having nephropathy (1-specificity) and subsequently also started on irbesartan. In these states, the additional costs of irbesartan 300 mg daily were considered, but no reduction in the rate of progression from no nephropathy to microalbuminuria was assumed.

Transition probabilities

The probability of progression from no nephropathy to microalbuminuria was taken from the control arm of the BENEDICT study [17], which investigated progression from no renal disease (UAE < 30 mg/24 hours) to microalbuminuria in hypertensive patients with type 2 diabetes. In the placebo arm, with target blood pressure of 120/80 mmHg and treatment with conventional antihypertensives, approximately 15% of hypertensive patients with type 2 diabetes with UAE < 20 µg/minute at baseline developed microalbuminuria within a 4-year period [17].

In the “no screening” arm of the model, probabilities of progression were taken from the control arms of the BENEDICT, IRMA-2 and IDNT studies [13,14,17] and have been extensively reported by Palmer et al [16]. In the screening arm of the model, if nephropathy was detected and consequently irbesartan was added, transition probabilities were taken from the irbesartan 300 mg daily treatment arms of the IRMA-2 and IDNT studies [16]. Data from IRMA-2 were used to calculate transition probabilities for progression from microalbuminuria to early overt nephropathy, from early overt nephropathy to advanced overt nephropathy, and from advanced overt nephropathy to DSC or ESRD and have been previously published [16].

Once a patient had progressed to ESRD, it was assumed that further transitions (mortality and switching between renal transplantation and alternative methods of renal replacement therapy) were independent of treatment arm, and that irbesartan treatment would cease once patients were determined to have developed ESRD. The inclusion
of French ESRD therapeutic and outcomes data (transplant and dialysis mortality, and changes between renal replacement therapy modes), where available, enhanced the setting specificity of the model. These probabilities have been previously documented and the interested reader is referred to Palmer et al. [18].

**Mortality Calculations**

Mortality was independent of treatment arm but dependent on the level of renal disease reached by a simulated patient. In the states of no nephropathy, microalbuminuria, early overt nephropathy, advanced overt nephropathy and DSC, mortality was calculated using French age- and gender-specific all-cause mortality tables [19] and values were 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, most likely value 1.76, and a maximum value 2.66 [20]. In the state of microalbuminuria mortality was further increased by a factor of 2.21 versus no nephropathy was based on data from the Danish Steno-2 study [19,21]. The relative risk (RR) of mortality in both overt nephropathy states was calculated in a similar way based on data published by Stehouwer et al. [22]. The RR for mortality in patients with type 2 diabetes, hypertension and overt nephropathy was calculated to be 3.29 compared to those with no nephropathy. In the absence of published data, RRs for all-cause mortality in the early overt nephropathy, advanced overt nephropathy and DSC states were conservatively assumed to be the same.

In the ESRD-related states, mortality was dependent on the type of renal replacement therapy received (i.e. dialysis or transplantation). In the French setting, an average mortality rate of 19.37% per year for dialysis was used, based on rate of 24.4% at 2 years in non-diabetic patients, adjusted for a diabetic population by a factor of 1.588 ([1-(1-(24.4%*1.588))/2]) [23]. No reliable mortality rates were identified for type 2 diabetes patients in France receiving renal transplantation. Consequently, assuming that the mortality rates in Western countries would not differ substantially, US data for transplant patients were used [24].

**Simulated cohort and interventions compared**

The model simulated a hypothetical cohort of patients with type 2 diabetes and hypertension. Baseline age was drawn from the distribution of ages of French patients with type 2 diabetes taking oral hypoglycemic agents, as reported in an IMS survey (table I) [25]. To reflect the prevalen-
ces of existing nephropathy, simulated patients were distributed at baseline to either no nephropathy, microalbuminuria, or overt nephropathy, according to published data on hypertensive diabetes patients in the US [3]. Prevalences of microalbuminuria in subjects aged 20-49 and ≥ 50 years were 35.5% (21.3-49.7) and 29.9% (25.8-34.0) respectively (mean values with 95% confidence intervals). The prevalence of overt nephropathy was 6.5% (0.8-12.2) and 12.2% (9.0-15.5) respectively. No data were available on the prevalence of early overt nephropathy versus advanced overt nephropathy, so it was assumed that of those with overt nephropathy, 85% had early and 15% had advanced overt nephropathy (personal communication, Prof. Hans-Henrik Parving, Steno Diabetes Center, Denmark).

Screening was assumed to be performed annually in a primary care setting using Micral II semi-quantitative urine dipstick test strips. Patients who tested negative on the first test, would be tested again 12 months later. Patients who tested positive on the first test, had two confirmatory tests. If two out of three were positive, the patient was diagnosed with nephropathy, and irbesartan 300 mg was added to their conventional antihypertensive therapy. Sensitivity and specificity of the test strips were taken from a published review reporting sensitivities ranging between 70 and 97%, and specificities between 71 and 98% [26].

Second order Monte Carlo simulation

Second order Monte Carlo simulation is a well accepted, and commonly used approach in health economics analyses to take into account uncertainty in multiple parameters [27]. In the present analysis, transition probabilities for the irbesartan treatment arms were calculated by applying the placebo arm probabilities and multiplying them with a value drawn from the distribution of RR of progression from microalbuminuria to early overt nephropathy (RR 0.30; 95% CI 0.14 to 0.61; P < 0.001); from advanced overt nephropathy to DSC (RR 0.71; 95% CI 0.54 to 0.92; P = 0.009); and from advanced overt nephropathy to DSC (RR 0.83; 95% CI 0.62 to 1.11; p = 0.19) taken from the irbesartan 300 mg treatment arms of IRMA-2 and the IDNT [13,14]. Additionally, distributions of baseline age and baseline prevalence of microalbuminuria and overt nephropathy, and sensitivity and specificity of screening as previously outlined were also sampled.

Costs

All the costs used in the model were reported in euros (€), year 2002 values. The perspective of a French third party health insurance payer was taken. In the screening arm of the model, the costs of screening for nephropathy in the primary care setting were accounted. 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 (20€), and the cost of the test strip (0.52€). The costs of screening that turned out to be negative included one test with Micral II test strips, and one general practitioner consultation. If the initial test was positive, additional costs of 2 confirmatory test strips and 2 general practitioner consultations were added. If screening was positive for nephropathy, the costs of irbesartan 300 mg daily were also added (288.35€ per patient per year) [28]. The French-specific costs of treatment of ESRD (dialysis and transplantation costs) were used. The total cost per patient with diabetes receiving dialysis was calculated to be 61,159€ per year and included hospital day costs, medical costs for dialysis, erythropoietin, dietician consultations, laboratory tests, blood pressure monitoring, and blood transfusions. Costs of transplantation in the first, second and third years were calculated to be 19,026€, 6,306€ and 5,309€ respectively [29].

Health state utilities and quality-adjusted life expectancy

Quality-adjusted life expectancy was calculated by assigning health utilities to each state in the model. Years alive in each state was weighted by the severity of nephropathy complications, thus taking into account patient quality of life as well as length of life. The utilities used in the states of no nephropathy, microalbuminuria, early and advanced overt nephropathy corresponded to utilities published by Brown et al. who reported that there were no differences in utility between diabetes patients with and without nephropathy [30]. A mean utility value for patients with type 2 diabetes of 0.88 was therefore used in the states of no nephropathy, microalbuminuria, early and advanced overt nephropathy. For the state of DSC, the utility was taken from Tengs and Wallace [31], who reported a value of 0.70 for chronic renal disease, pre-dialysis (no anemia). Utilities in the states of ESRD treated with either transplant (0.762) or dialysis (0.462) were taken from the same study [31].

Table I

Distribution of age at baseline for the French diabetes population taking oral hypoglycaemic agents (25).

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Percentage of patients with type 2 diabetes in age group (%)</th>
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<tbody>
<tr>
<td>&lt;35</td>
<td>3</td>
</tr>
<tr>
<td>35-44</td>
<td>1</td>
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<tr>
<td>45-54</td>
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<td>55-64</td>
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<td>65-74</td>
<td>38</td>
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<td>75-84</td>
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<td>85+</td>
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Discounting and time horizon

Costs were discounted at 3% annually in accordance with current French guidelines published by the International Society for Pharmacoeconomic Outcomes Research [32]. Life expectancy was calculated both in natural (undiscounted) form and discounted at 3% annually. The base-case time horizon was 25 years (lifetime).

Sensitivity analysis

In the base-case analysis, baseline age was drawn from a distribution of ages of patients with type 2 diabetes receiving oral antidiabetic agents. Sensitivity analysis was performed by simulating distinct sub-groups based on baseline age. Separate simulations were run for baseline ages 40 and 75 years. Further sensitivity analysis was performed on the assumption that 85% of patients with overt nephropathy at baseline would be categorized as having early overt nephropathy, with 15% having advanced overt nephropathy. Sensitivity analysis was also performed on base case discount rates and time horizon.

Results

Cumulative incidence of ESRD

Cumulative incidence of ESRD was reduced from 10.1 ± 9.9% without screening to 5.8 ± 5.7% with screening and optimal antihypertensive treatment. The first cases of ESRD began to be avoided after 2 years for screening versus no screening (figure 2).

Life expectancy and quality-adjusted life expectancy

Life expectancy (not discounted) improved from 11.50 ± 6.64 years without screening to 11.87 ± 7.17 years with screening and optimal antihypertensive treatment, an improvement of 0.38 ± 0.59 years. Discounted life expectancy was improved by 0.20 ± 0.24 years. Life-years gained were noted after a period of 4 years (figure 3). Quality-adjusted life expectancy (discounted at 3% annually) was improved from 8.58 ± 3.73 quality-adjusted life years (QALYs) without screening to 8.87 ± 4.02 QALYs with screening and optimal antihypertensive treatment, an improvement of 0.29 ± 0.32 QALYs.

Costs

Total 25-year costs per patient (discounted at 3% annually) decreased from 17,968€ ± 21,047€ without screening to 13,155€ ± 13,283€ with screening and optimal antihypertensive treatment, a decrease in costs of 4,812€ ± 7,882€ per patient. Cost savings first occurred after 8 years, and increased from 8 to 25 years (figure 4).

Sensitivity analysis

When a shorter time horizon of 10 years was used, screening and optimal antihypertensive treatment still led to improvements in patient outcomes as well as cost savings. After 10 years, the cumulative incidence of ESRD was reduced from 4.1% ± 2.1% to 2.5% ± 1.3%, discounted life expectancy was improved by 0.02 ± 0.01 years, quality-adjusted life expectancy was improved by 0.04 ± 0.01 QALYs, and cost savings of 71€ ± 690€ were projected. Using discount rates of 0-7% had no impact on the relative outcomes after 25 years: screening and optimal antihypertensive therapy improved clinical outcomes and led to cost savings.
savings. Varying the percentages of patients with overt nephropathy and advanced overt nephropathy at baseline between 0% and 25%, did not notable affect the relative results. Improvements in non-discounted life expectancy with screening versus no screening varied from 0.25 ± 0.21 to 0.23 ± 0.19 years, and cost savings varied from 2,819€ ± 4,396€ to 3,320€ ± 4,905€.

Screening and optimal antihypertensive therapy had the greatest impact in younger patient groups. In patients with mean baseline age of 40 years, improvements in non-discounted life expectancy increased to 0.43 ± 0.05 years, and cost savings were increased to 13,053€ ± 1,948€. In patients with mean baseline age of 75 years, improvements in non-discounted life expectancy decreased to 0.04 ± 0.01 years, and costs increased by 761€ ± 102€ per patient.

**Discussion**

Our modeling analysis demonstrated that annual screening for nephropathy in a typical population with a mixture of no renal disease, microalbuminuria and overt nephropathy in hypertensive patients with type 2 diabetes, and optimal antihypertensive/nephroprotective treatment may lead to substantial improvements in long-term patient outcomes, with the added benefit of overall cost savings in the French setting. Improvements in patient outcomes were seen after 2-3 years, and cost savings were noted after a period of 7-8 years. Sensitivity analysis demonstrated the robustness of the results: variations in key assumptions had no substantial impact on the relative outcomes. Sub-group analysis revealed that screening in younger patient subgroups has a greater beneficial impact than in older sub-groups.

It should be noted that our estimates of cost savings are likely to be conservative because: 1) we attributed the full cost of a healthcare visit to the initial screening evaluation, whereas in practice, screening for proteinuria would represent just one of many recommended preventive measures in managing a patient with type 2 diabetes; and 2) we have not included the cost offset associated with concomitant antihypertensive medications that might be used in place of irbesartan 300 mg. These factors would favor the screening strategy and reduce its costs primarily in the short-term. In addition, we did not assume that patients in the states of advanced overt nephropathy or DSN would receive erythropoietin (with its associated annual costs) used to treat anemia associated chronic diabetic renal disease [33] and thereby possibly underestimating to the full costs attributable to the development of advanced diabetic nephropathy. Finally, we assumed that if patients were not screened, they would receive antihypertensive therapy with a target blood pressure of <135/85 mmHg. Given the relatively low proportion of patients who actually receive adequate blood pressure treatment in France, this is likely to be an assumption that will lead to an underestimation of the clinical improvements and cost savings associated with screening and optimal treatment.

Other studies have investigated the cost-effectiveness of screening strategies in type 1 diabetes patients and support the findings of the present analysis, reporting screening to be dominant (cost and life saving) or cost-effective [34,35,36]. Notable observations were made by Kilberd et al. in a study which suggested that screening for microalbuminuria was not cost-effective compared to treating all patients with ACE inhibitors five years after the onset of type 1 diabetes [37]. This raises an intriguing question: what would be the health economic implications of screening all patients with type 2 diabetes and hypertension without screening? To answer this question is outside the scope of the current study, but is the subject of currently ongoing modeling analyses (personal communication, A.J. Palmer).

The present study is the first to report the health economic implications of screening and optimal antihypertensive treatment including an angiotensin 2 receptor antagonist in hypertensive patients with type 2 diabetes. It is directly based on recent clinical trial results that inform transition probabilities across the progression of disease from normoalbuminuria to ESRD. In contrast, previous studies that examined cost-effectiveness of screening in patients with diabetes often required a number of assumptions on renal disease progression to inform key transition probabilities, since clinical data were not always available across the disease spectrum at the time. The results of our analysis are encouraging, suggesting that screening in this high risk patient group, particularly when performed in younger patients, has the potential to substantially improve patient outcomes, with cost savings as an added bonus. Financial concerns should not be a barrier to implementation of improved screening programs in this patient group.
Conclusions

Restricted healthcare budgets require that decision and policy makers must identify interventions that are cost-effective. Our modeling analysis indicated that screening for nephropathy and optimal antihypertensive treatment may improve patient outcomes, and lead to overall cost savings in the long-term, particularly in younger patients.

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