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 semiquantitatifs 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 probilités, 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 optimisé 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.

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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 20-199 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 prevalenc-
ces of existing nephropathy, simulated patients were
distributed at baseline to either no nephropathy, microalbumi-
minuria, 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 preva-
ence of overt nephropathy was 6.5% (0.8-12.2) and 12.2%
(9.0-15.5) respectively. No data were available on the preva-
ence 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 diag-
nosed with nephropathy, and irbesartan 300 mg was added
to their conventional antihypertensive therapy. Sensitivity
and specificity of the test strips were taken from a pub-
lished 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 or DSC
to ESRD (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 screen-
ing 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 inclu-
ded 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 assign-
ing 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 neph-
ropathy [30]. A mean utility value for patients with type 2
diabetes of 0.88 was therefore used in the states of no neph-
ropathy, 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 trans-
plant (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>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35</td>
<td>3</td>
</tr>
<tr>
<td>35-44</td>
<td>1</td>
</tr>
<tr>
<td>45-54</td>
<td>11</td>
</tr>
<tr>
<td>55-64</td>
<td>21</td>
</tr>
<tr>
<td>65-74</td>
<td>38</td>
</tr>
<tr>
<td>75-84</td>
<td>17</td>
</tr>
<tr>
<td>85+</td>
<td>9</td>
</tr>
</tbody>
</table>

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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.
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 DSC 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.

Figure 4
Cost savings over time per 1,000 simulated patients screening for nephropathy and optimal antihypertensive treatment versus no screening and conventional antihypertensive treatment alone.

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 sub-groups has a greater beneficial impact than in older sub-groups.
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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