IMPACT OF THE SOCIOECONOMIC STATUS ON THE PROBABILITY OF RECEIVING FORMULARY RESTRICTED THIAZOLIDINEDIONES (TZDS)

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ABSTRACT

Background
In the province of Quebec, Canada, the reimbursement of thiazolidinediones (TZDs) is limited to patients who do not respond to doses of metformin and a sulfonylurea.

Objectives
The objective of this research project was to study, in a real-life setting, the "risk factors" for receiving these restricted drugs among patients who meet the reimbursement criteria.

Methods
Among patients eligible for drug coverage under the RAMQ between May 2000 and June 2005, we selected those who received six consecutive dispensations of high doses of both metformin and a sulfonylurea. The date of the sixth dispensation was set as the index date. The proportion of patients who received a TZD in the year following the index date was calculated and a logistic regression was used to estimate the impact of several factors on the probability of receiving a TZD.

Results
There were 4,836 patients in the cohort. A TZD was dispensed to 24.9% (95% CI: 23.7%;26.2%) of the patients. Compared to the oldest group of patients (65 years and more), the probability to receive a TZD was higher for patients aged 51 to 64 years (OR=1.33 95% CI: 1.11;1.59) and patients aged 19 to 50 years [OR=1.81 (95% CI: 1.40;2.33)]. Patients with the highest income were more likely to receive a TZD (OR=1.55 95% CI: 1.21;1.98) compared to patients with the lowest income.

Conclusions
These findings suggest that the restricted access to TZDs probably results in social inequities, as individuals with lower incomes are less likely to receive these drugs.

Key words: *Restricted drugs, TZDs, diabetes*

In an effort to contain ever-increasing drug costs, payers have applied a series of restrictions to the reimbursement of some of the newer, more expensive drugs.

In the province of Quebec (Canada) every person aged 65 or more, every income security recipient, and all those who do not have access to a private drug plan (and their dependents), benefit from the provincial drug plan for prescribed drugs, which is administered by the "Régie de l'assurance maladie du Québec" (RAMQ).

In this public drug plan, 158 drugs are currently reimbursed through a special authorization process.[1] The procedure requires the physician to complete a special authorization form and fax it to the Quebec prescription drug insurance plan for approval. On this form, the physician must demonstrate that the patient meets

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the reimbursement criteria. If the reimbursement criteria have been adequately met, pre-authorized reimbursement approval is then sent to the pharmacist. Failure to fulfill all requirements results in rejection of the request, and the patient can only obtain the medication by paying the full amount out of pocket.

Diabetes is a chronic, progressive disease, which causes a variety of microvascular and macrovascular complications. Several oral drugs are available to treat patients with type 2 diabetes. Used in monotherapy or combination therapy, these oral drugs are effective in lowering blood glucose to achieve glycaemia goals and in reducing diabetes-related end-organ disease.

Two of these drugs, rosiglitazone and pioglitazone, belong to the class called thiazolidinediones (TZDs). Both rosiglitazone and pioglitazone are indicated as either monotherapy or in combination with a sulfonylurea, metformin, or when diet, exercise, and a single agent do not result in adequate glycaemia. In addition to lowering blood glucose, both drugs may benefit cardiovascular parameters, such as lipids, blood pressure, inflammatory biomarkers, endothelial function and fibrinolytic status.[2] However, these drugs have been associated with heart failure and are contra-indicated in this condition.[3] TZDs are significantly more expensive than other oral agents, which have been generic for a long time. Consequently, RAMQ has restricted the use of these drugs. One of the conditions for reimbursement is "patients who do not respond to maximal doses of first line oral hypoglycaemic agents".

The objective of this research project was to study, in a real-life setting, the degree of under use of TZDs among patients who meet the reimbursement criteria, and the "risk factors" for receiving these restricted drugs.

METHODS

Data Sources

The study was carried out using the computerized medical and pharmaceutical services databases of the RAMQ. These databases contain information on medical services provided to all Quebec residents and information on prescribed medications dispensed to the elderly (65 years and older), income security recipients, and since January 1997, all Quebec residents not covered by a private drug insurance plan. In 2004, 3,167,999 beneficiaries were covered by the RAMQ drug plan. Information on medical services includes diagnosis (ICD-9 codes), date of service provision, and site where the service was provided (hospital, emergency department or clinic). Information on dispensation of prescribed medication includes the date the medication was dispensed, drug code, drug dose, quantity of medication dispensed and prescription duration.

Cohort Selection

Using a computerized random number generator, a random sample of 25% of all beneficiaries who received at least one prescribed dispensation of insulin or an oral hypoglycaemic agent between May 1998 and June 2005 was obtained from RAMQ. If consistent with the aims of the project, RAMQ usually provides investigators with random samples to better preserve the confidentiality of their data. The oral hypoglycaemic agent group was composed of metformin, acarbose, acetohexamide, chlorpropamide, glicazide, glimepiride, glyburide, tolbutamide, rosiglitazone, and pioglitazone. Repaglinide and nateglinide were not included because they are not listed in the Quebec formulary.

From this random sample, the study cohort was created selecting all beneficiaries who received at least 6 consecutive combinations of high doses of both metformin and a sulfonylurea (chlorpropamide, glyburide or tolbutamide) between May 2000 and June 2004. The above-mentioned sulfonylureas were the only ones included in the sample because they represent 98% of the sufonylureas reimbursed by RAMQ. The high doses were defined as follows: metformin $\geq$1,250 mg/day, chlorpropamide $\geq$625 mg/day, glyburide $\geq$12.5 mg/day, and tolbutamide $\geq$1,250 mg/day. Beneficiaries with an incomplete coverage in the RAMQ database for the year preceding and the year following the 6th combination of high doses were excluded from the study. The index date was defined as the day of the 6th combination of high doses.

Measure of the Economic Status

A code is assigned by RAMQ to each beneficiary covered by the public drug plan according to income. This code establishes the maximal

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monthly contribution that the beneficiary has to pay to RAMQ to be covered by the public plan. There are 4 categories of maximal monthly contribution: high, medium, low, and none. The maximal monthly contribution variable is determined by the income (i.e., a higher income leads to a higher category of contribution to the RAMQ drug plan).

Measures of Co-morbidity

Co-morbidity was assessed by chronic disease score (CDS), using a technique originally developed and validated by Von Korff et al.[4], that provides a measure of a patient's chronic disease status over a period of time through prescription patterns. To quantify this parameter, medications for the treatment of specific diseases were assigned a weighting factor based on the seriousness of the condition for which they were employed; and a patient's CDS was determined by adding up the appropriate weighting factors for each medication taken for a chronic condition. Medications that were frequently used only for symptom management (analgesics, anti-inflammatory, antidepressant agents, etc.) were not included in the score. The overall score ranged from 0 to 35, 0 being the minimum score for co-morbidity.

In the present study, CDS was based on an assessment of the selected patient's prescription claim pattern in the year preceding the index date. Medications for diabetes (insulin and oral antidiabetic agent) were excluded from the calculation of CDS.

Statistical Analyses

The proportion of beneficiaries who received at least 1 dispensation of TZDs in the year following the index date and the associated 95% confidence interval were calculated.The impact of factors on the probability of receiving a dispensation of TZDs in the year following the index date was estimated using a logistic regression. Variables included in the model were age, gender, chronic disease score, health care services use per person in the year preceding the index date, year of the index date, visit to an endocrinologist in the year following the index date and the maximal monthly contribution.

The Kaplan-Meier method was employed to illustrate the adjusted proportion of beneficiaries treated with TZDs in time. This analysis was stratified by maximal monthly contribution categories and the differences between categories were measured by log-rank analysis. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

From the 78,335 beneficiaries present initially in the RAMQ databases, 4,836 received 6 consecutive combinations of high doses of both metformin and a sulfonylurea between May 2000 and June 2004 and were covered by the RAMQ drug plan for the year preceding and the year following the index date. The characteristics of beneficiaries at the index date are presented in Table 1. A majority of beneficiaries were at least 65 years of age (64%), and 49% were male. Forty-seven percent of beneficiaries were in the highest category of maximal monthly contribution to RAMQ, 31% in the medium category, 11% in the low category, and 11% in the no contribution category.

The proportion of beneficiaries who received at least 1 dispensation of TZDs during the year following the index date was 24.9% (95% CI: 23.7%; 26.2%). The mean length of time between the index date and the first dispensation of TZDs was 168 days (SD=101) among beneficiaries treated with TZDs.

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TABLE 1 Characteristics of Beneficiaries at the Index Date

	(n = 4,836)
Age (years) – mean ± SD	67 ± 11
Age group – no. (%)	
19 to 50 years	434 (9)
51 to 64 years	1,303 (27)
65 years and +	3,099 (64)
Men – no. (%)	2,392 (49)
Chronic disease score – mean ± SD	4.5 ± 3.1
Resource use/ Person in the year prior to the index date – mean ± SD	
Number of hospitalizations	0.4 ± 1.0
Number of days of hospitalization	1.2 ± 3.6
General practitioner visits	5.4 ± 4.6
Specialist visits	4.0 ± 4.8
Emergency room visits	0.7 ± 1.6
Visit to an endocrinologist in the year following the index date – no. (%)	810 (17)
Year of the index date – no. (%)	
2000*	2,967 (61)
2001	635 (13)
2002	563 (12)
2003	459 (10)
2004**	212 (4)
Maximal monthly contribution to the RAMQ drug plan – no. (%)	
High	2,279 (47)
Medium	1,489 (31)
Low	528 (11)
No contribution	540 (11)

* Beginning of the study: May 1, 2000
** End of the study: June 30, 2004

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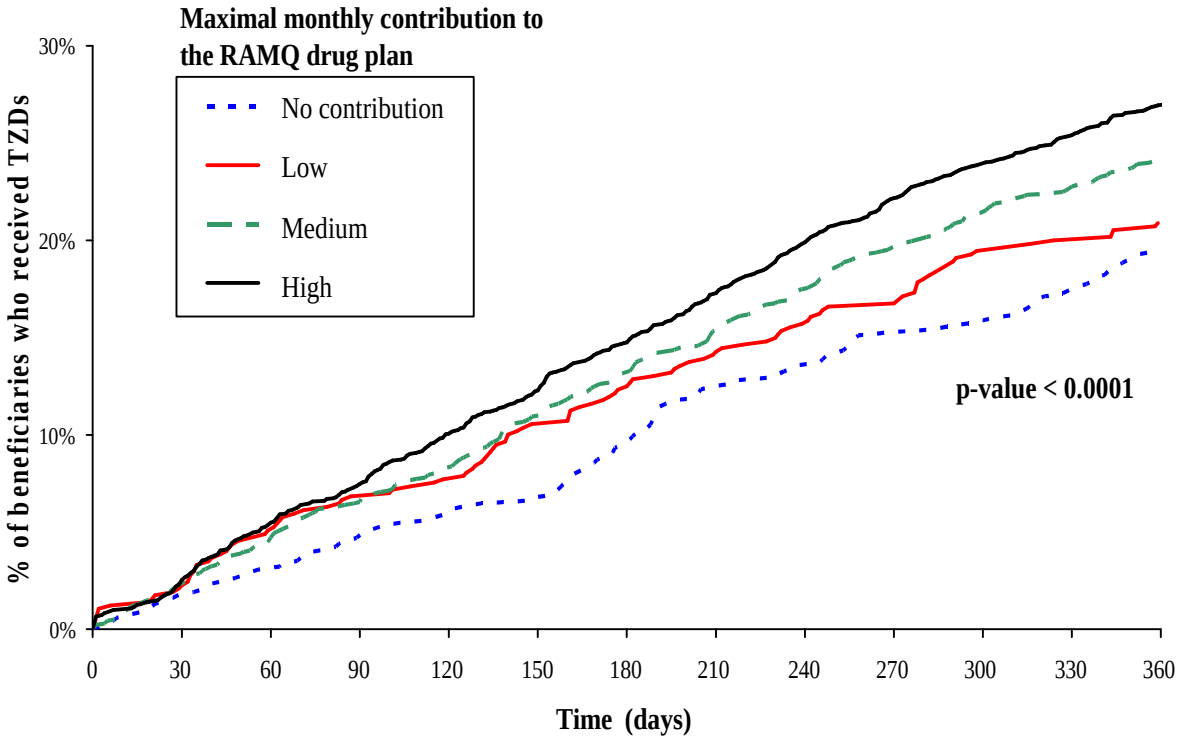
Kaplan-Meier survival curves adjusted for covariates were plotted to assess the rates of beneficiaries treated with TZDs in time (Figure 1). The analysis was stratified by maximal monthly contribution. Beneficiaries in the high category were significantly more likely to receive a TZD ($p<0.0001$). At the 360th day, 27% of beneficiaries in the high category received TZDs, compared to 19% of beneficiaries in the no contribution category. The probability of receiving TZDs decreased as the monthly contribution decreased.

Figure 1. Proportion of beneficiaries who received TZDs according to RAMQ contribution in time



The adjusted logistic regression model was used to measure the influence of factors on the likelihood of receiving TZDs in the year following the index date (Table 2). Beneficiaries in the high category of the maximal monthly contribution had a significantly higher probability of receiving TZDs compared to those in the no contribution category [OR=1.55 (95% CI: 1.21; 1.98)]. Beneficiaries aged 19 to 50 years were significantly more likely to receive TZDs compared to patients aged 65 years and more [OR=1.81 (95% CI: 1.40; 2.33)].

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TABLE 2 Factors which Influence the Probability of Receiving TZDs

	Odds Ratio (95%CI)
Maximal monthly contribution to the RAMQ drug plan	
No contribution	1.00 (reference)
Low	1.09 (0.81-1.46)
Medium	1.32 (0.99-1.77)
High	1.55 (1.21- 1.98)
Age group	
65 years and +	1.00 (reference)
51 to 64 years	1.33 (1.11-1.59)
19 to 50 years	1.81 (1.40-2.33)
Men	0.97 (0.85 -1.11)
Chronic disease score	1.03 (1.00-1.05)
Year of the index date	0.94 (0.89-0.99)
Resource use/ Person in the year prior to the index date	
Number of hospitalizations	0.95 (0.87-1.04)
Number of days of hospitalization	1.00 (0.97-1.02)
General practitioner visits	1.01 (0.99-1.03)
Specialist visits	1.00 (0.98-1.01)
Emergency room visits	0.98 (0.93-1.03)
Visit to an endocrinologist in the year following the index date	0.84 (0.70-1.01)

DISCUSSION

Our results show that about 25% of the patients selected on the basis of our high doses algorithms actually received these drugs. However, the fact that some of the patients identified by our algorithms might have contraindications to TZDs, or have a good control of their diabetes at the selected doses, or have been started on insulin has to be taken under consideration. Most importantly, the patients' income has an important influence on the probability of receiving these drugs. The poorer patients are less likely to receive them than those who are richer. There is no reason to believe that the contraindications to the drugs, or better diabetes control at high doses of the usual hypoglycaemic agents, might be differentially distributed between the rich and the poor. While older age is a factor, it should not bias our results since this parameter has been adjusted for in the regression. Furthermore, it is highly unlikely that co-payments might be a factor in our results, since by definition the poorer patients do not have to make a co-payment.

Our study has several strengths. It is based on a large, well–validated administrative database[5], which is considered to be of epidemiological quality by several major medical journals.[6-8] Since

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this was a retrospective database study, the physicians and patients behaviour was not affected by the fact that they knew they were being observed (Hawthorne effect). Furthermore, the information about the drug being dispensed is factual and does not rely on the patients' memory.

The main weakness of our study is the absence of biochemical information on glycaemia control or clinical information that might determine a contraindication to TZDs. The criteria to establish the fact that the patient was a candidate for TZDs, after receiving high doses of the usual oral hypoglycaemic agents for 6 consecutive months, had to be based on the opinion of expert committees. These committees, which were composed of academic and community endocrinologists, internists and general practitioners, found that at least 90% of the patients who received doses superior to those we selected in our study, would be likely to benefit from a TZD. We are aware that some physicians might disagree with this assumption or might prefer a higher dose threshold, which would result in a smaller number of patients being eligible of TZDs. However, it is important to realise that using a more stringent threshold would not have changed the results of the logistic regression we used to establish the risk factors for receiving a TZD. These risk factors constitute, in our opinion, the most important finding of our study. Of particular importance, is the fact that among patients who meet the criteria, the probability of receiving a TZD decreases as the patient's income decreases. It would thus appear that the bureaucratic hurdle to the access of TZDs results in important social inequities.

Given the steady rise in health care costs and expenditures in drugs, it is quite likely that restrictions to drug access are here to stay. Drug plan managers should be aware of the fact that their administrative decisions may result in social inequities. A better collaboration between drug plan managers, academics and industry (the three solitudes) would result in constant experimentation and validation of various administrative mechanisms whose aim should be to improve health and resource allocation through cost-effective drug use.

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