COMPARISON OF THE ADHERENCE AND PERSISTENCE TO INHALED CORTICOSTEROIDS AMONG ADULT PATIENTS WITH PUBLIC AND PRIVATE DRUG INSURANCE PLANS

Marie-Christyne Cyr[1], Marie-France Beauchesne[1,3], Catherine Lemière[2,3], Lucie Blais[1,3]

[1]Faculty of Pharmacy, Université de Montréal, Montreal, Quebec, Canada; [2]Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada; [3]Research Center, Hôpital du Sacré-Cœur de Montréal, Montreal, Quebec, Canada

Corresponding Author: *lucie.blais@umontreal.ca*

ABSTRACT

Background
Despite important differences in reimbursement procedures between private and public drug insurance plans in Quebec (Canada), no study has evaluated the impact of the type of drug insurance on the use of essential medications such as inhaled corticosteroids (ICS). The lack of data might be attributable, at least in part, to the absence of a provincial medication database for patients with private drug insurance.

Objectives
To compare patient's adherence and persistence to ICS between Quebec residents (Canada) with private and public drug insurance.

Methods
A matched cohort design with patients selected from the database of the *Régie de l'assurance maladie du Québec* (RAMQ) and from reMed, a database that we have put in place for Quebec residents covered by a private drug insurance, was used. ICS users with private drug insurance were selected from reMed between 2008 and 2010 and matched to ICS users with public drug insurance selected from the RAMQ database. Patient's adherence, measured with the proportion of prescribed days covered (PPDC) and persistence over one year, was compared between patients privately and publicly insured using linear regression and Cox regression models.

Results
This study included 330 and 1,109 ICS users with private and public drug insurance, respectively. Patients privately insured were significantly less adherent than patients publicly insured (adjusted mean difference of PPDC: -9.7%; 95% CI: -13.2% to -6.5%). Moreover, patients privately insured were found to be 52% more likely to stop ICS during the first year than patients publicly insured (adjusted HR=1.5; 95% CI: 1.2 to 2.0).

Conclusions
Although adherence and persistence were rather low in both groups, patients with public drug insurance appeared to have greater adherence and persistence to ICS than patients with private drug insurance. Differences in reimbursement policies might explain the observed differences.

Key Words: *Administrative database, inhaled corticosteroids, persistence, adherence, private drug insurance*

Asthma is one of the most common chronic diseases worldwide. In Canada, the prevalence of asthma is estimated to be 14.1%.[1] Inhaled corticosteroids (ICS) are recommended by Canadian and international guidelines as first line therapy for persistent asthma.[2-4]

Unfortunately, sub-optimal adherence to ICS in monotherapy or in combination with a long-acting beta2-agonist (LABA) in the treatment of asthma is well documented and ranges from less than 20% to 50%.[5-11] Persistence to ICS therapy among asthma patients is also very low, with rates ranging between 4 and 18% at one year.[12-15] Poor adherence and persistence to ICS have been shown to contribute to the deterioration of disease control and lung function, an increase in costs of healthcare services, and a reduction of quality of life.[10,16]

In the province of Quebec, Canada, under the Quebec Universal Drug Insurance program, all residents are required by law to have drug insurance coverage by either a private insurer or by the province's public drug insurance plan managed by the Régie de l'assurance maladie du Québec (RAMQ). In 2009, 3.2 million Quebecers (41%) were covered by the RAMQ's public drug plan, 4.3 million (56%) were covered by a private drug plan available through their employers or their professional associations, and the others were covered by a federal public drug plan.[17,18] Persons covered by a private drug plan are required to obtain coverage under that plan for their spouse and children, unless they are already covered by another private drug plan. Medication claims data of patients covered by the RAMQ public drug insurance plan are recorded in a database administered by the RAMQ, while there is no such provincial database for Quebec residents with private drug plans. Using the RAMQ database, studies on the use of ICS have been conducted among patients covered by the public drug insurance.[5,14,15] No studies have estimated the adherence and the persistence to ICS among patients privately insured in Quebec mainly due to the absence of computerized medication databases that can easily be linked to other health databases for said patients. Consequently, the public and private sub-populations of the Quebec Universal Drug Insurance Plan have never been formally compared on the use of ICS, despite important differences between the private and public drug plans, and the fact that plan characteristics have been shown to influence patient's adherence and persistence.[19] Moreover, only one study, performed in the United States, has evaluated the impact of the type of drug insurance on the use of prescribed medications to treat asthma. They found that patients under the Medicaid program (publicly insured) were more likely to use medications to treat asthma than those with private drug insurance.[20] However, this study did not measure adherence and persistence per se, and it is difficult to generalize its results to Canadians due to major differences between the health care systems between the two countries.

The aim of this study was to compare the adherence and persistence to ICS between Quebec residents with private and public drug insurance. This study was based on data retrieved from the RAMQ database, covering patients with public drug insurance, and from reMed, a database that was put in place by our group to circumvent the lack of a provincial database for patients with private drug insurance.

METHODS

Sources of Data

RAMQ databases

The RAMQ Prescription Medications database is a provincial database that contains claims data on prescriptions filled at community pharmacies (e.g. name, dose, form, quantity of medication dispensed, date and duration of prescription, and so on) for Quebec residents insured by the RAMQ public drug plan. The RAMQ databases also contain the patient's birth date, gender, date of death, as well as the type of drug beneficiary (adherents (1,710,176 workers aged less than 65 years and their family[18]), elderly, and social welfare recipients) and dates of coverage for the drug insurance plan. The RAMQ databases have been extensively used for epidemiological studies and the information related to medications has been proven valid.[21-23]

reMed database and recruitment of patients with private drug insurance

reMed is a computerized database that we developed to record data related to prescribed medications filled at community pharmacies for residents of Quebec who are less than 65 years old and are covered by a private drug plan. Participants were recruited by research assistants in community pharmacies, medical clinics, or blood sampling centres in the province of Quebec between April 2007 and March 2011. Each participating patient signed an informed consent form and completed a questionnaire relative to the study. Socio-demographic variables and information relative to the drug plan were collected at enrolment (patient's healthcare insurance number, private insurance number (PIN), date of birth, postal code, drug co-payment and deductible, the average number of filled medications over the past year, weight, height as well as information pertaining to smoking). Using the PIN and the date of birth, we obtained data relative to filled prescriptions through the community pharmacies' computer services providers (drug identification number (DIN) assigned by Health Canada, prescription identification number, quantity of the prescribed medication, date at which the prescription was dispensed, number of days supply, number of authorized refills remaining, whether the prescription is new or is an authorized refill, pharmacy and prescriber encoded identifier, cost of medications and amount paid by the insurer). The DIN allowed to make the link with the Drug Products Database managed by Health Canada to obtain further data relative to the prescribed medications such as the Anatomical Therapeutic Chemical (ATC) code, active ingredient(s), strength, route(s) of administration, pharmaceutical form(s), etc.[24,25]

Data related to medications have been recorded in reMed since March 15th, 2008 and have been updated bi-weekly ever since. For each patient, we also obtained data relative to their prescribed medications filled in the year prior to their enrolment in reMed. The drug related variables recorded in reMed are similar to those recorded in the RAMQ Prescription Medications database. As of March 1st, 2011, 7,931 patients were enrolled in reMed and the participation rate was 76%. This sample represents less than 1% of the Quebec residents with private drug insurance.

Study Population and Design

We used a matched cohort design. We first selected users of ICS patients with private drug insurance from the reMed database between March 15, 2008, and December 31st, 2010. To be included in the cohort, patients had:

1. to fill at least one prescription of ICS (ICS only or in combination with a LABA in the same inhaler) with a duration of more than 14 days after enrolment in reMed (the 14 days criteria was applied to exclude ICS prescribed for non chronic diseases such as respiratory infections);
2. to be aged between 20 and 64 years; and
3. to be insured under a private drug plan in the year preceding and at least 90 days after cohort entry.

Patients were excluded if they filled a prescription for an antibiotic in the 14 days preceding the prescription of ICS (to exclude ICS prescribed for respiratory infections); if they were taking treatment for chronic obstructive pulmonary disease (COPD) such as theophylline, ipratropium or tiotropium in the year prior to cohort entry; and if they were registered in reMed for less than 90 days. Since ICS could be prescribed for several indications and indication is not recorded in the database, inclusion and exclusion criteria were selected to include patients with asthma and exclude patients with COPD and respiratory infections. Cohort entry was defined as the date of the first prescription of ICS that fulfilled the inclusion and exclusion criteria after enrolment in reMed. Follow-up was stopped when the earliest of the following events occurred: 12 months of follow-up, March 1st, 2011, a switch to the public drug plan, 65th birthday, or the first prescription of theophylline, ipratropium or tiotropium after cohort entry. In addition, for a minority of patients, follow-up was terminated because their medications stopped to be recorded in reMed, either because they went to a pharmacy not covered by reMed, switched to an insurance company that did not process the reimbursement of the medications directly at the pharmacy, or

they died. In these cases, the follow-up was terminated if the gap without any prescription recorded in reMed was larger than two times the mean number of days between filled prescriptions in the year prior to cohort entry. The end of follow-up occurred at the end of the gap or six months after the last filled prescription, if the gap was greater than six months.

Similarly, a cohort of users of ICS publicly insured and not receiving social assistance, i.e. workers and their family who are not admissible to a private drug plan at their workplace, was selected from the RAMQ Prescription Medications database between March 15, 2008, and July 31st, 2010. The same inclusion and exclusion criteria as for the reMed cohort were applied except that patients had to be covered by the RAMQ Public Drug Plan and not receiving social assistance in the year preceding and at least 90 days after cohort entry. Cohort entry was defined by the date of the first prescription of ICS that fulfill the inclusion and exclusion criteria after March 15, 2008. For each patient privately insured selected from reMed, up to four patients publicly insured were matched on sex, age at cohort entry, number of days of follow-up, whether or not the patient filled a prescription of oral corticosteroids, ICS, or LABA in the year preceding cohort entry, the number of doses of short-acting β2-agonists (SABA) per week on average in the year before cohort entry, and whether LABA were added to ICS at cohort entry.

These matching criteria allowed the inclusion of patients with similar level of asthma severity and control at cohort entry between the groups. Follow-up was stopped when the earliest of the following events occurred: 12 months of follow-up, July 31st, 2010, a switch to a private drug plan, started to receive social welfare, 65th birthday, or death. It is worth noting that the period of patient's selection was longer for patients with private drug insurance (until March 1st, 2011) than for patients with public insurance (until July 31st, 2010), to increase the sample size of the privately insured cohort. The study was approved by the ethic committee of the Hôpital du Sacré-Coeur de Montréal.

Drug Plans

For patients included in the cohort and covered by the RAMQ public drug insurance (i.e. not receiving social assistance and aged less than 65 years), the premium is collected annually via income taxes and the amount varies between 0 and $563 per year according to family income. The deductible is fixed at $16 per month, the co-payment is fixed at 32% of the cost of the medications and the maximal monthly contribution is $80.25 ($963 per year).[26] Private plans vary from one workplace to the other with premiums negotiated with the insurer and usually taken in the form of payroll deductions throughout the year. The deductible is usually applicable to a one year period representing the first portion of a person's drug costs, while the co-payment varies between 0 and 32%, depending on the plan. The private plans should cover at least all medications covered by the public plan and the maximal contribution is also set at $963 per year for all plans. Reimbursement with private plans can be made at the time of purchase or differed, while patients on the public plan are always reimbursed at the time of purchase. Further details can be found in appendix 1.

Adherence Assessment

Adherence to ICS was assessed in each cohort using the Proportion of Prescribed Days Covered (PPDC), defined as the number of days' supply dispended over the number of days' supply prescribed during the follow-up period.[5] The number of day's supply dispensed is equal to the sum of the duration of all prescriptions (including new prescriptions and refills) of ICS filled by the patient during the follow-up. The number of day's supply prescribed is the sum of the duration of all new prescriptions and allowed refills prescribed by any physician during the follow-up (whether or not the patient get the refills).[5] This measure was chosen to reflect the quantity of ICS dispensed that takes into account the variability in the prescription patterns. A more classical measure of adherence, the Proportion of Days Covered (PDC), defined as the number of days' supply dispensed during the follow-up over the number of days of follow-up,[27] was also used to compare our results to those found in previous studies.

Persistence Assessment

Persistence was defined as having any ICS prescription filled at least every 60 days. The discontinuation date was defined as the end date of the last filled prescription (date of delivery plus the number of day's supply) plus 60 days.

Potential Confounders

Potential confounders included sex, age (< 45 years versus 45-64 years), area of residence (rural versus urban, postal codes with a number ranging from 1 to 9 in the second position represent urban areas and postal codes with a 0 represent rural areas), and the receipt of ICS in monotherapy, ICS and LABA in the same inhaler or ICS and LABA in two different inhalers at cohort entry. They also included markers of asthma severity and control in the year preceding cohort entry: filled prescription of oral corticosteroids (yes/no), LABA (yes/no), and average number of doses of SABA per week (none, > 0 to 3, or > 3). The use of intra-nasal corticosteroids (yes/no) and anti-leukotrienes (yes/no) in the year preceding cohort entry was also considered. Finally, confounders included markers of co-morbidity based on filled prescriptions of non-steroids anti-inflammatory/ antirheumatic drugs, anxiolytics, antidepressants, acid related disorders drugs, antihypertensive agents, cardiovascular disorders (yes/no, based on the ATC classification)[24] and the total number of different medication classes filled in the year prior to cohort entry (based on the ATC classification).[24]

Statistical Analysis

Characteristics were compared between patients privately and publicly insured using descriptive statistics. The mean and 95% CI of the PPDC and the PDC were estimated for each cohort. The PPDC and the PDC were compared between patients privately and publicly insured using linear regression models for all patients and for new users of ICS (no prescription of ICS in the year preceding cohort entry). For each cohort, persistence was estimated using Kaplan-Meier curves among new users of ICS. ICS discontinuation rates between patients privately and publicly insured were compared using Cox regression models. A backward selection strategy was used to find reduced models starting with full models that comprehend all potential confounders listed above, removing at each step the least significant variable, and reintroducing in the models variables that acted as confounders (i.e. if the rate ratio or the mean difference associated with the type of drug insurance was changed by 5% or more).[28,29] Variables that were not found to be confounders but were significantly associated with the outcome (p-value < 0.05) were also kept in the model. A sub-analysis was also performed among patients receiving ICS/ LABA in the same inhaler.

RESULTS

A total of 415 users of ICS with private drug insurance met the inclusion and exclusion criteria and were initially selected from reMed. From the RAMQ database, a total of 9,961 users of ICS were also initially selected. As shown in Figure 1, we were able to match 330 users of ICS with private drug insurance to 1,109 users of ICS with public drug insurance. The remaining unmatched patients were excluded from the analyses. Among patients privately insured included in the study, 116 (35.1%) were followed for 12 months, 185 (56.1%) reached the last day of the study (March 1st 2011), 5 (1.5%) filled a prescription of ipratropium after cohort entry and 24 (7.3%) were censored because their filled prescriptions stopped to be recorded in reMed, switched to a public drug plan or reached their 65th birthday. In the publicly insured cohort, 391 (35.3%) were followed for 12 months, 713 (64.3%) were censored because they were matched to a patient privately insured who had a follow-up of less than 12 months, 5 (0.5%) reached the last day of the study (July 31st 2010) or switched to a private drug plan.

Table 1 presents the patients' characteristics. ICS users privately insured were comparable to patients publicly insured in terms of demographic variables and length of follow-up, except that a larger proportion of patients privately insured were living in an urban area. Patients privately and publicly insured used similar asthma medications except for the use of ICS and LABA in the same inhaler, which was lower for privately insured patients (37.3% versus 45.3%, p = 0.01) and the use of intra-nasal corticosteroids in the year preceding cohort entry, which was higher for privately insured patients (34.6% versus 25.6%, p < 0.01). Markers of co-morbidity were also

comparable between the two cohorts, except for the use of antihypertensive agents and anxiolytics. Patients privately insured filled slightly more different molecules on average in the year before cohort entry than patients publicly insured (6.8 versus 6.0). At cohort entry, fluticasone (Flovent ®) was the most prescribed ICS in both groups, but the distribution of the type of ICS was significantly different ($p<0.01$) between the groups.

As shown in Table 2, the mean PPDC (48.5% versus 58.1%) and PDC (36.1% versus 41.4%) were lower among patients privately than publicly insured. We also observed that new users of ICS therapy and users of ICS in monotherapy were less adherent than users of ICS in combination with LABA in both cohorts. The difference in adherence between patients with private and public drug insurance remained significant after adjustment for confounders (Table 3 adjusted mean difference of PPDC=-9.7%; 95% CI: -13.2% to -6.5%). This model revealed that men and patients taking a greater number of medications were significantly more adherent to their ICS treatment. The difference in PPDC increased to -13.7% (95% CI:-20.2% to -7.2%) in favour of publicly insured patients when the analysis was restricted to new users of ICS.

We also found similar results when the analysis was restricted to patients who were taking ICS and LABA in the same inhaler at cohort entry (adjusted mean difference of PPDC = -7.9%; 95% CI: -13.7% to -2.1%). In the analysis using the PDC as the measure of adherence, we found similar results (adjusted mean difference of PDC = -6.2%; 95% CI: -13.7% to -2.1%). In the analysis in using PDC as the measure of adherence, we found similar results (adjusted mean difference of PDC = -6.2%; 95% CI: -10% to -2.5%).

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FIG. 1 Selection of patients with public and private drug insurance

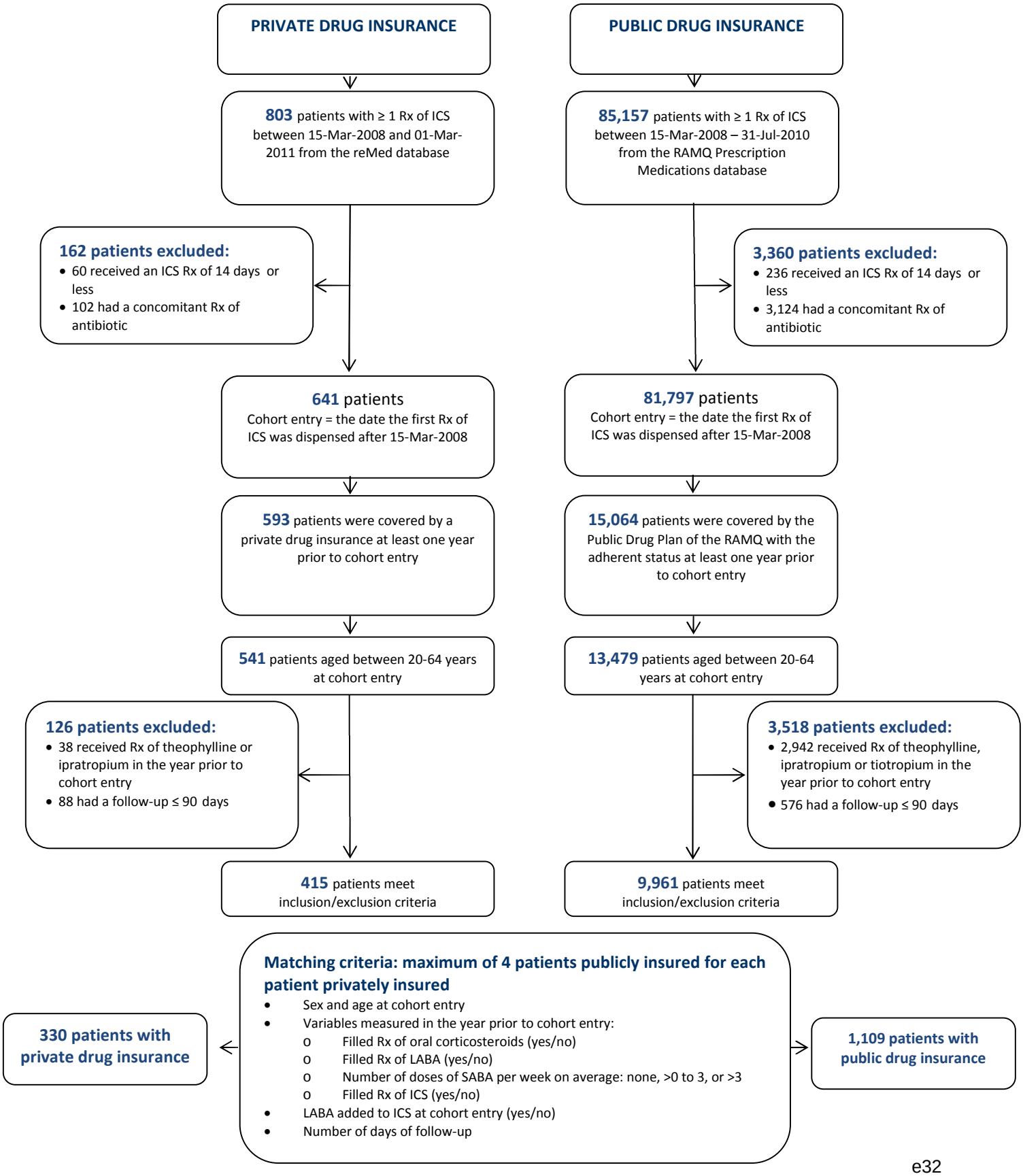

TABLE 1 Characteristics of ICS users comparing patients with private and public drug insurance

	Private drug insurance n=330	Public drug insurance n=1,109	p-value
Variables measured at cohort entry			
Women, n (%)	224 (67.9)	734 (66.2)	0.57
Age in years, n (%)			
20-44	143 (43.3)	459 (41.4)	0.53
45-64	187 (56.7)	650 (58.6)	
Urban area of residence, n (%)	320 (97.0)	798 (72.0)	< 0.01
Follow-up (days), mean ± s.d.	309.3 ± 180.4	309.1 ± 180.2	0.98
Treatment at cohort entry, n (%)			
ICS monotherapy	186 (56.4)	553 (49.9)	0.01
ICS and LABA in the same inhaler	123 (37.3)	502 (45.3)	
ICS and LABA in two different inhalers	21 (6.4)	54 (4.9)	
Type of ICS (excluding ICS/LABA combination in the same inhaler) at cohort entry	**n=207**	**n=607**	
Fluticasone, n (%)	137 (66.2)	443 (73.0)	0.01
Budesonide, n (%)	44 (21.3)	118 (19.4)	
Ciclesonide, n (%)	22 (10.6)	27 (4.5)	
Béclométhasone, n (%)	4 (1.9)	19 (3.1)	
Type of ICS/LABA combination in the same inhaler at cohort entry	**n=123**	**n=502**	
Fluticasone/salmeterol, n (%)	50 (40.6)	240 (45.3)	0.15
Budesonide/formoterol, n (%)	73 (59.4)	262 (52.3)	
In the year preceding cohort entry			
ICS, n (%)	205 (62.1)	728 (65.6)	0.24
LABA, n (%)	118 (35.8)	447 (40.3)	0.13
Oral corticosteroids, n (%)	52 (15.8)	174 (15.7)	0.97
Intra-nasal corticosteroids, n (%)	114 (34.6)	284 (25.6)	< 0.01
Leukotriene-receptor antagonist, n (%)	34 (10.3)	93 (8.4)	0.28
SABA doses/week, n (%)			
≤ 3	222 (67.3)	691 (62.3)	0.10
> 3	108 (32.7)	418 (37.7)	
≥ 1 filled prescription for, n (%)			
Chronic inflammation	103 (31.2)	293 (26.4)	0.09
Anxiety	83 (25.2)	208 (18.8)	0.01
Depression	78 (23.6)	211 (19.7)	0.07
Acid related disorders	68 (20.6)	248 (22.4)	0.50
Hypertension	58 (17.6)	250 (22.5)	0.05
Cardiovascular disorders	64 (19.4)	232 (20.9)	0.55
Diabetes	22 (6.7)	78 (7.0)	0.82
Number of different prescribed molecules, mean ± s.d.	6.8 ± 4.1	6.0 ± 4.3	< 0.01

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TABLE 2 Adherence to ICS between patients with private and public drug insurance

	Private drug insurance Mean in %± s.d	Public drug insurance Mean in % ± s.d	Mean difference in % (IC 95%)	p-value	Private drug insurance Mean in % ± s.d	Public drug insurance Mean in % ± s.d	Mean difference in % (IC 95%)	p-value
All types of ICS	**n=330**	**n=1109**			**n=125**	**n=381**		
PPDC*	48.5 ± 27.7	58.1 ± 29.0	-9.6 (-13.2; -6.1)	<0.01	43.0 ± 30.6	57.3 ± 32.6	-14.4 (-20.9; -7.9)	<0.01
PDC†	36.1 ± 24.4	41.4 ± 25.1	-5.3 (-8.4;-2.2)	<0.01	21.4 ± 15.6	28.8 ± 19.2	-7.4 (-11.2; -3.7)	<0.01
ICS in monotherapy	**n=186**	**n=553**			**n=96**	**n=270**		
PPDC*	46.7 ± 28.1	57.8 ± 29.2	-11.0 (-15.8; -6.2)	<0.01	43.4 ± 30.4	58.6 ± 31.9	-15.2 (-22.5; -7.8)	< 0.01
PDC†	31.0 ± 22.1	36.6 ± 22.1	-5.4 (-9.2; -1.8)	<0.01	21.0 ± 15.1	30.3 ± 19.2	-9.3 (-13.6; -5.1)	<0.01
ICS/LABA in the same inhaler	**n=123**	**n=502**			**n=26**	**n=102**		
PPDC*	51.2 ± 27.9	58.3 ± 28.8	-7.1 (-12.8; -1.4)	0.01	43.1 ± 33.2	55.3 ± 34.6	-12.2 (-27.1; 2.8)	0.11
PDC†	42.9 ± 26.3	46.0 ± 27.0	-3.2 (-8.4 2.2)	0.25	22.4 ± 18.2	25.5 ± 19.0	-3.1 (-11.3; 5.09)	0.45
ICS/LABA in two different inhalers	**n = 21**	**n = 54**			**n = 3**	**n = 9**		
PPDC*	48.1 ± 23.2	60.5 ± 27.9	-12.4 (-26.1; 1.3)	0.07	26.3 ± 10.9	42.7 ± 30.4	-16.4 (-57.4; 22.9)	0.39
PDC†	40.9 ± 23.0	47.6 ± 27.2	-6.7 (-20.1; 6.7)	0.32	26.3 ± 10.9	22.5 ± 12.8	3.8; (-15.3; 24.5)	0.67

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TABLE 3 Impact of the type of drug insurance on patient's adherence (n=1439)

	Crude mean difference of PPDC (95% CI)	Final model: Adjusted mean difference of PPDC (95 % CI)
Private versus public drug insurance	-9.6 (-13.2; -6.1)	-9.7 (-13.2; -6.5)
Variables measured at cohort entry		
Gender (male versus female)	3.3 (0.1; 6.5)	3.6 (0.4; 6.8)
Age (45-64 years versus < 45 years)	2.8 (-0.2; 5.8)	NR
Area of residence (rural versus urban)	3.2 (-0.4; 6.8)	NR
Treatment at cohort entry (ICS monotherapy reference)		
ICS and LABA in the same inhaler	1.9 (-1.1; 5.0)	NR
ICS and LABA in 2 different inhalers	2.1 (-4.8; 8.9)	
In the year preceding cohort entry		
Treatment for respiratory diseases		
ICS, (yes/no)	3.3 (0.2; 6.4)	NR
LABA, (yes/no)	3.1 (0.0; 6.1)	NR
Oral corticosteroids, (yes/no)	3.4 (-0.7; 7.6)	NR
Intra-nasal corticosteroids, (yes/no)	-1.7 (-5.1; 1.6)	-3.1 (-6.6; 0.4)
Leukotriene-receptor antagonist, (yes/no)	0.9 (-4.4; 6.2)	NR
Doses of SABA/week (≤ 3 reference) :	3.4 (0.3; 6.5)	NR
≥ 1filled prescription for:		
Chronic inflammation, (yes/no)	-2.1 (-5.5; 1.3)	-4.0 (-5.9; -0.3)
Anxiety, (yes/no)	-0.7 (-4.4; 3.0)	-3.2 (-7.3; 0.9)
Depression, (yes/no)	0.8 (-2.9; 4.5)	NR
Acid related disorders, (yes/no)	2.4 (-1.2; 6.0)	NR
Hypertension, (yes/no)	2.9 (-0.7; 6.6)	NR
Cardiovascular disorders, (yes/no)	2.9 (-0.8; 6.6)	NR
Diabetes, (yes/no)	2.3 (-3.6; 8.2)	NR
Number of different prescribed molecules (difference of 1 molecule)	0.4 (0.0; 0.7)	0.9 (0.4; 1.3)

* NR = Not retained in the final model

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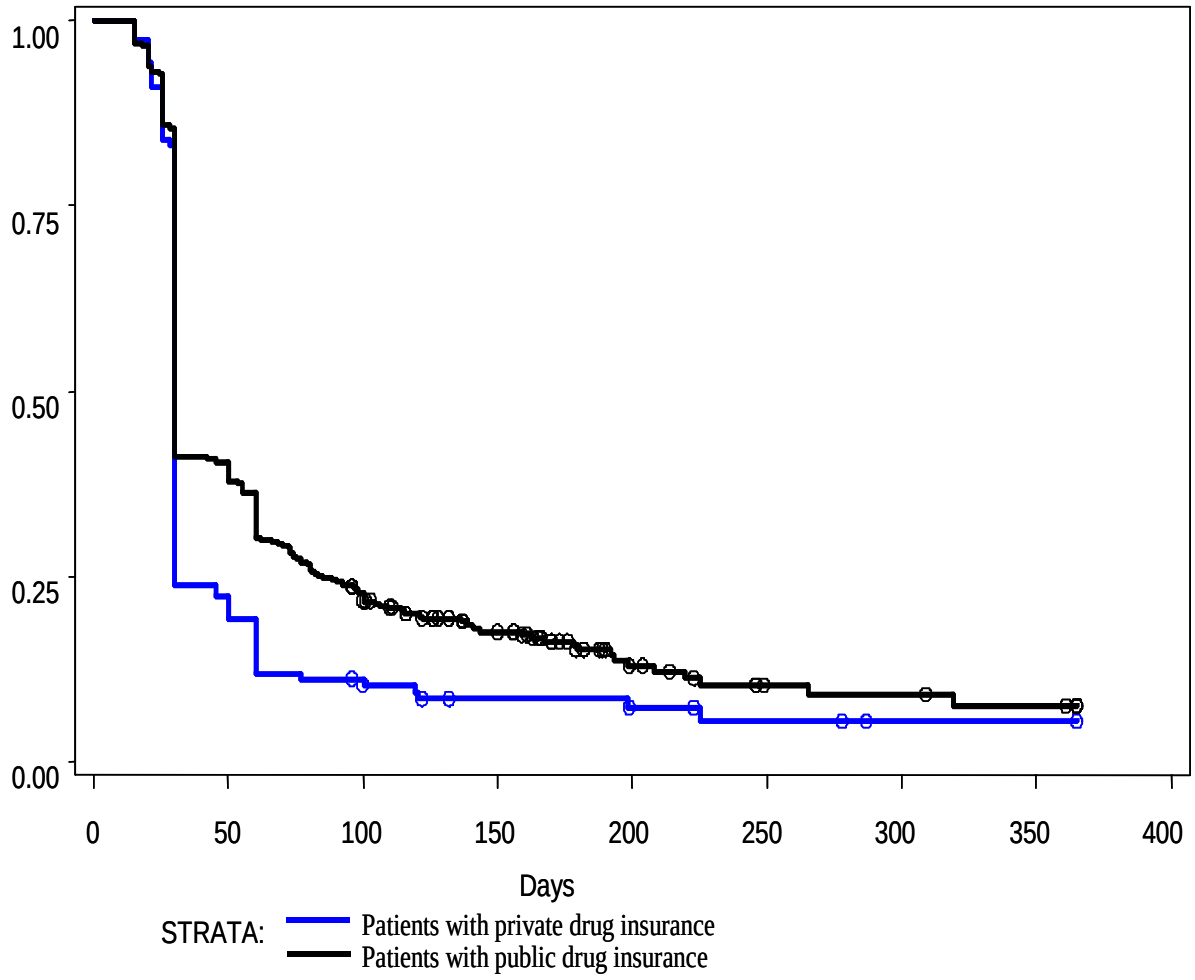
FIG. 3 Kaplan-Meier curves comparing persistence to ICS over one-year between patients with public and private drug insurance



DISCUSSION

The present study is the first to investigate whether there are differences in adherence and persistence to ICS between patients with private and public drug insurance in Canada. Levels of adherence and persistence to ICS therapy were found to be low in both cohorts, but our data showed that patients privately insured were less adherent and persistent than patients publicly insured.

The low level of adherence and persistence to ICS therapy observed in this study are concordant with the results of other studies.[5-15] Among new users of ICS in monotherapy with private drug insurance, adherence was estimated at 21.0% with the PDC and at 43.4% with the PPDC in our study, and at 30.4% with the medication possession ratio (MPR, a measure similar to the PDC) in the American study published by Ivanova et al.[8] Moreover, Delea et al. report

adherence rate of 52% estimated with the MPR among users of ICS and LABA combination identified in an outpatient pharmacy claims database from more than 30 private health benefit plans across the United States, which is similar to what we found among Quebec residents privately insured.[7] Our study results related to persistence to ICS among patients publicly insured are also similar to those found by Dorais et al. who reported that only 7.5% of patients insured by the RAMQ Drug Insurance Plan were still persistent one year after the initiation of the therapy.[14]

The significant difference in adherence found in our study between patients with private and public drug insurance is consistent with the American study published by Rice et al. reporting that patients publicly insured were 56% more likely to be taking medications for asthma than those with private insurance.[18] As suggested by Rice and al., the differences observed between our two cohorts may be explained by the fact that patients with public drug insurance pay only the deductible and the co-insurance at the pharmacy, while a large proportion of patients with private drug insurance pay the full cost of the prescription and receive a deferred payment. There is evidence that a higher prescription drug cost paid at the pharmacy is associated with a reduction in adherence or more frequent discontinuation.[19] Despite the fact that there was, a larger proportion of patients using ICS and LABA in the same inhaler at cohort entry among patients publicly insured, this factor was not found to act as a confounder for the association between the type of drug insurance and the adherence to ICS in the regression analysis, and is unlikely to explain the observed difference between the 2 cohorts. Moreover, a similar difference in adherence to ICS was found between patients privately and publicly insured when the analysis was restricted to patients using an ICS and a LABA in the same inhaler.

One of the main strengths of this study is that it is the first to compare Quebec residents with private and public drug insurance treated with ICS and to show the differences that can exist between these two sub-populations. The analyses performed were adequately powered and reflect ICS use in real clinical practice. Other strengths are related to the use of the reMed and RAMQ databases that provide prospectively collected data on filled prescriptions, avoiding the need to interview patients to measure drug exposure and eliminating recall bias.

In addition, from the results of a pilot study that we conducted in 2007, we concluded that reMed participants were representative of Quebecers with private drug insurance and were similar to non-participants, which minimize selection bias. During the pilot study, 34% of reMed participants were male and the mean age was 43.8 years, while corresponding figures were 32% and 44.3 years among non-participants.[30] Moreover, smoking habits and obesity were found to be comparable between reMed participants and the general population of Quebec. Among reMed participants, 22% were current smokers and 49% were overweight or obese.[30] Corresponding figures were 25% and 47% among Quebecers who participated in the Canadian Community Health Survey 2005.[31,32] We also observed in the pilot study that the distribution of medication classes was similar between reMed participants and Quebec's residents with private drug insurance according to data retrieved from the 2007 Drug Trend Report of the health claims management company ESI Canada Inc. that manages over 65 million medication prescriptions per year dispensed to Canadians.[30,33,34] The overall average claim cost was found to be similar between the two compared groups with an average of $47.93 for reMed participants and $45.76 for patients covered by the ESI Canada's Report.[30,33,34]

On the other hand, our study has some limitations inherent to the use of medication claims databases. Despite matching and adjustment for well known markers of asthma severity and control,[2,6,9,15] we cannot completely rule out the possibility of residual confounding due to unmeasured variables. Indeed, clinical measures of the level of asthma severity and control, such as pulmonary function tests, and the use of acute care for asthma were not available in the databases. In addition, even if the study was restricted to workers and their family members, patients publicly insured might have had lower level of income and education, more co-morbidity and might have had different health habits than patients privately insured. Given that patients with lower socio-economic level have been found to be less adherent to medications,[35] not adjusting for this characteristic could have led to an

underestimation of the true difference in adherence between patients privately and publicly insured. However, we learned from the results of the pilot that smoking habits and obesity were found to be comparable between reMed participants and the general population of Quebec and consequently probably comparable to patients publicly insured.[30]

Another weakness of the study is the fact that dispended medications might not coincide exactly with the actual intake of the medications, potentially resulting in non-differential drug use misclassification, again if present, leading to an underestimation of the effect of the type of drug insurance.[36] Finally, the indication for which ICS were prescribed was not available in the databases, and despite our inclusion and exclusion criteria chosen to select patients with asthma, we might have included patients with other conditions such as COPD or respiratory infections. However, there is no reason to believe that the proportion of patients with other diseases would differ between the two cohorts.

Our results show that the type of drug insurance plan has an impact on adherence and persistence to ICS among asthmatic adults, patients privately insured being less adherent and persistent than patients publicly insured. Given that adherence and persistence to ICS is very low, we should make sure that the type of drug insurance and reimbursement policies are not additional barriers to the optimal use of medications that are highly effective. On the basis of these results, it is now important to investigate whether or not the differences observed in the use of ICS have an impact on patients' health and on the use of health care services. Also, further studies will be necessary to evaluate the impact of the type of drug insurance on the adherence and persistence to therapy for other chronic diseases.

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APPENDIX 1
KEY FEATURES OF THE QUEBEC UNIVERSAL DRUG INSURANCE PROGRAM: PUBLIC DRUG PLAN VERSUS PRIVATE DRUG PLAN IN 2011

	The public drug plan	Private drug plan
Universal Drug Insurance Program	The RAMQ covers all Quebecers who do not have access to private insurance from their workplace, including about 1.7 million workers and dependents aged less than 65 years, elderly, and social welfare recipients and their dependents.	All Quebecers eligible for a private drug insurance plan from their workplace or their spouse workplace must register.
Financing of benefits	The public plan is financed by general taxes and user fees (premiums, deductibles and co-payments).	Private plans are financed by user fees (premiums, deductibles and co-payments) and employer contributions.
Limits for out-of-pocket Spending • The Premium	‡ The premium is collected annually via income taxes and the amount varied between 0 and $563 per year per adult in 2011, according to family income.[1] The public plan exempts the socially assisted, low-income seniors, and children from payment of the premium.	Premiums are not regulated for private plan beneficiaries. Persons insured under a private plan must pay a premium, whether or not they purchase prescription drugs. In most cases, they pay the premium in the form of regular payroll deductions throughout the year and the premium is negotiated between the policyholder (employer, professional association, etc.) and insurer.
• The contribution 1. Deductible	‡ The deductible was fixed at $16 per month.[1]	The deductible is generally a yearly amount that represents the first x dollars spent on medications. Certain private plans do not require a deductible.
2. The co-payment	‡ The co-payment was fixed at 32% of the cost of the medication.[1]	The co-payment varied between private plans but could not be greater than 32%.
3. Maximal contribution	‡ After reaching the maximal monthly contribution of $80.25 (co-payment + deductible), medications were entirely paid by the RAMQ for the month and after reaching the maximal annual contribution of $963, medications were entirely paid by the RAMQ for the year.[1]	After reaching the maximal annual contribution that could not be higher than $963, medications were entirely paid by the private drug plan for the year.
Type of reimbursement	The insured pay only the amount of their contribution when purchasing their prescribed medications.	Depending on the plan, the insured pay only the amount of their contribution when purchasing their prescribed medications, pay for their prescribed medication in full at the time of purchase and get reimbursed by the insurer, or pay for their prescribed medication in full at the time of purchase and send a claim to the insurer with the receipt of the prescribed medications purchased to received a reimbursement from the insurer.
Drug formularies	The public drug plan covers over 5000 prescribed medications listed on the List of Medications periodically published by the RAMQ under the recommendation of a pharmacological advisory board from Quebec's Minister of Health and Social Services. Public plan is requiring prior authorization for prescribed medications listed on the list of medications of exception.	Private drug plans must cover at least the medications listed on the RAMQ's List of Medications with or without applying the restrictions required by the RAMQ.

1. Régie de l'assurance maladie du Québec. Amount to pay for prescription drugs. Régie de l'assurance maladie du Québec, 2011 (Accessed April 15, 2011) http://www.ramq.gouv.qc.ca/en/citoyens/assurancemedicaments/regimesprives/lescouts_contributionannuellemaximale.shtml).

‡ The costs were applicable for persons insured under the RAMQ drug insurance plan receiving no social assistance, i.e. workers and their dependents that are not admissible to a private drug plan from their workplace.

REFERENCES

1. Braman SS. The global burden of asthma. Chest 2006;130:4S-12S.
2. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008;31:143-178.
3. Lougheed MD, Lemiere C, Dell SD, et al. Canadian Thoracic Society Asthma Management Continuum--2010 Consensus Summary for children six years of age and over, and adults. Can Respir J 2010;17:15-24.
4. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
5. Blais L, Kettani FZ, Beauchesne MF, Lemiere C, Perreault S, Forget A. New measure of adherence adjusted for prescription patterns: the case of adults with asthma treated with inhaled corticosteroid monotherapy. Ann Pharmacother 2011;45:335-341.
6. Bukstein DA, Henk HJ, Luskin AT. A comparison of asthma-related expenditures for patients started on montelukast versus fluticasone propionate as monotherapy. Clin Ther 2001;23:1589-1600.
7. Delea TE, Hagiwara M, Stanford RH, Stempel DA. Effects of fluticasone propionate/salmeterol combination on asthma-related health care resource utilization and costs and adherence in children and adults with asthma. Clin Ther 2008;30:560-571.
8. Ivanova JI, Birnbaum HG, Hsieh M, et al. Adherence to inhaled corticosteroid use and local adverse events in persistent asthma. Am J Manag Care 2008;14:801-809.
9. Stempel DA, Mauskopf J, McLaughlin T, Yazdani C, Stanford RH. Comparison of asthma costs in patients starting fluticasone propionate compared to patients starting montelukast. Respir Med 2001;95:227-234.
10. Williams LK, Pladevall M, Xi H, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol 2004;114:1288-1293.
11. Williams LK, Peterson EL, Wells K, et al. A cluster-randomized trial to provide clinicians inhaled corticosteroid adherence information for their patients with asthma. J Allergy Clin Immunol 2010;126:225-31, 231.
12. Breekveldt-Postma NS, Gerrits CM, Lammers JW, Raaijmakers JA, Herings RM. Persistence with inhaled corticosteroid therapy in daily practice. Respir Med 2004;98:752-759.
13. Cramer JA, Bradley-Kennedy C, Scalera A. Treatment persistence and compliance with medications for chronic obstructive pulmonary disease. Can Respir J 2007;14:25-29.
14. Dorais M, Blais L, Chabot I, LeLorier J. Treatment persistence with leukotriene receptor antagonists and inhaled corticosteroids. J Asthma 2005;42:385-393.
15. Marceau C, Lemiere C, Berbiche D, Perreault S, Blais L. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. J Allergy Clin Immunol 2006;118:574-581.
16. Rand C, Bilderback A, Schiller K, Edelman JM, Hustad CM, Zeiger RS. Adherence with montelukast or fluticasone in a long-term clinical trial: results from the mild asthma montelukast versus inhaled corticosteroid trial. J Allergy Clin Immunol 2007;119:916-923.
17. Institut de la statistique du Québec (ISQ). Population du Québec, 1971-2012. Statistique Canada, Estimation de la population, 2012 (Accessed February 4, 2010 http://www.stat.gouv.qc.ca/donstat/societe/demographie/struc_poplt/qc_1971-20xx.htm).
18. Régie de l'assurance maladie du Québec. Statistiques annuelles RAMQ - 2009. Tableau AM.6. Régie de l'assurance maladie du Québec, 2009. Available from: https://www.prod.ramq.gouv.qc.ca/IST/CD/CDF_DifsnInfoStats/CDF1_CnsulInfoStatsCNC_iut/RappPDF.aspx?TypeImpression=pdf&NomPdf=CCB3R01A_AM06_2009_0_O.PDF
19. Goldman D, Joyce G, Zheng Y. Prescription drug cost sharing association with medication and medical utilization and spending and health. JAMA 2007;298:61-69.
20. Rice T, Lavarreda SA, Ponce NA, Brown ER. The impact of private and public health insurance on medication use for adults with chronic diseases. Medical Care Research and Review 2005;62:231-249.
21. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995;48:999-1009.
22. Pilote L, Lavoie F, Ho V, Eisenberg MJ. Changes in the treatment and outcomes of acute myocardial infarction in Quebec, 1988-1995. CMAJ 2000;163:31-36.

23. Martel MJ, Rey E, Beauchesne MF, et al. Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study. BMJ 2005;330:230.
24. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2011. 14th ed ed. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology; 2010.
25. Health Canada. Drug Product Database. Drugs and Health Products, Health Canada, 2010 (Accessed April 4, 2010 http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php).
26. Régie de l'assurance maladie du Québec. Amount to pay for prescription drugs. Régie de l'assurance maladie du Québec, 2011 (Accessed April 15, 2011 http://www.ramq.gouv.qc.ca/en/citoyens/assurancemedicaments/regimesprives/lescouts_contributionannuellemaximale.shtml).
27. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother 2006;40:1280-1288.
28. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79:340-349.
29. Rothman KJ, Greenland S, Last TL. Modern epidemiology. 3rd ed ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2008.
30. CYR MC, Blais L, Beauchesne MF, et al. The use of prescribed medications among residents of Quebec covered by a private drug insurance plan: results from the reMed pilot study. Pharmacoepidemiol Drug Saf 2009;18:184.
31. Bernèche F, Dumitru V. Données sociale du Québec, Chapitre 2 Santé: perceptions et comportements. Satistique Canada, Enquête sur la santé dans les collectivités canadiennes, cycle 3 1 (2005-2006), Fichier de microdonnées à grande diffusion(FMGD) Compilation Institut de la statistque du Québec (ISQ), 2009. Available from: http://www.stat.gouv.qc.ca/publications/conditions/pdf2009/donn_sociale09c2.pdf
32. Indice de masse corporelle (norme internationale), population de 20 à 64 ans excluant les femmes enceintes, Québec et régions sociosanitaires. Satistique Canada, Enquête sur la santé dans les collectivités canadiennes, cycle 3 1 (2005-2006), Fichier de microdonnées à grande diffusion(FMGD) Compilation Institut de la statistque du Québec (ISQ), 2008. Available from: http://www.bdso.gouv.qc.ca/pls/ken/p_afch_tabl_clie?p_no_client_cie=FR&p_param_id_raprt=908
33. ESI Canada. ESI Canada 2007 Drug Trend Report. ESI CANADA, 2008. Available from: http://www.esi-canada.com/aboutus/outcomes/2008/ESI_Canada_2007_Drug_Trend_Report.pdf
34. ESI Canada. Health Newsflash-Therapeutic Class Ranking (Top 100 Ranked by Claim Cost) Prescriptions filled from 01/2006 through 12/2006 compared to 01/2007 through 12/2007 Quebec. No. 2. 2008.10. Available from: http://www.esi-canada.com/aboutus/news/health_newsflashes/Volume_10_Issue2_TherapyClasses_Qc.pdf
35. Janson SL, Earnest G, Wong KP, Blanc PD. Predictors of asthma medication nonadherence. Heart Lung 2008;37:211-218.
36. Lynd LD, Guh DP, Pare PD, Anis AH. Patterns of inhaled asthma medication use: a 3-year longitudinal analysis of prescription claims data from British Columbia, Canada. Chest 2002;122:1973-1981.