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Diabetes & Metabolism 39 (2013) 250–257

Original article

Difficulty adhering to antidiabetic treatment: Factors associated with persistence and compliance

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Received 20 April 2012; received in revised form 13 December 2012; accepted 13 December 2012

Abstract

Aims. – This study aimed to assess the 1-year treatment persistence and compliance of new oral antidiabetic drug (OAD) users with their treatment, and to identify the factors associated with both persistence and compliance.

Methods. – This population-based cohort study of new OAD users aged 18 years or above used the Quebec health insurance board databases. Those having a prescription filled for antidiabetic treatment during the period leading up to the 1-year anniversary of their first claim were considered to be persistent with their antidiabetic treatment. Of these patients, individuals with a medication possession ratio (MPR) greater or equal to 80% for OAD or insulin were deemed compliant. Also identified were the characteristics associated with both outcomes, using a multivariate logistic regression model.

Results. – Our cohort consisted of 151,173 individuals, 119,832 (79.3%) of whom were considered persistent. Of these, 93,418 (78.0%) were also deemed compliant. Persistence and compliance were associated with older ages, living in a rural region, low socioeconomic status, having the first OAD prescribed by a general practitioner and a history of using five different drugs or more. People were less likely to be persistent and compliant if their initial OAD was a secretagogue and if they had consulted a physician eight times or more during the year prior to starting treatment.

Conclusion. – One year after OAD treatment initiation, 21% had discontinued their treatment and 22% of those still being treated were non-compliant. These results could help to tailor interventions aimed at optimizing the use of OAD treatments.

Keywords: Type 2 diabetes; Oral antidiabetic treatment; Adherence; Persistence; Compliance; Determinants

Résumé

La difficulté à adhérer à un traitement antidiabétique : les facteurs associés à la persistance et à l'observance.

Buts. – Déterminer la persistance au traitement chez les nouveaux utilisateurs d'antidiabétique oral (ADO) un an après l'initiation du traitement. Parmi les persistants, évaluer leur observance du traitement et, enfin, identifier les facteurs associés à la persistance et à l'observance.

Méthodes. – Nous avons effectué une étude de cohorte populationnelle de nouveaux utilisateurs d'ADO âgés de 18 ans ou plus en utilisant les banques de données de la Régie de l'assurance maladie du Québec. Les personnes qui ont acquis une ordonnance pour un traitement antidiabétique dans la période précédant le premier anniversaire de leur première acquisition ont été considérées persistantes à prendre leur traitement antidiabétique. Parmi ces personnes, celles pour qui plus de 80 % des jours étaient couverts par un ADO ou de l'insuline ont été considérées observantes. Nous avons identifié les caractéristiques associées à la persistance et à l'observance en utilisant un modèle de régression logistique multivariée.

Résultats. – Notre cohorte était composée de 151 173 individus dont 119 832 (79,3 %) étaient considérés persistants. De ces individus, 93 418 (78,0 %) ont été jugés observants. La persistance et l'observance étaient associées à l'augmentation de l'âge, au fait de vivre dans une région rurale, à un statut socioéconomique bas, au fait que le premier ADO prescrit l'ait été par un médecin généraliste et au fait d'avoir utilisé cinq médicaments différents ou plus dans l'année précédente. Les individus étaient moins susceptibles d'être persistants et observants si le premier ADO prescrit était une sulfonylurée et s'ils avaient consulté un médecin huit fois ou plus dans l'année précédant l'initiation de leur ADO.

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1262-3636/$ – see front matter
http://dx.doi.org/10.1016/j.diabet.2012.12.005

Conclusions. – Un an après l'initiation d'un traitement ADO, 21 % des individus avaient cessé leur traitement et 22 % de ceux toujours traités n'étaient pas observants. Ces résultats pourront guider le développement d'interventions ciblées visant à favoriser l'usage optimal des antidiabétiques.

Mots clés : Diabète de type 2 ; Antidiabétiques oraux ; Adhésion ; Persistance ; Observance ; Déterminants

1. Introduction

When the dietary therapy and physical activity proposed to individuals with type 2 diabetes fail to achieve adequate glycaemic control, the recommendation is then to use an oral antidiabetic drug (OAD) or, for those with marked hyperglycaemia, insulin [1]. Adherence to the recommended antidiabetic treatment is a major contributor to adequate glycaemic control. Adherence is a broad concept that can be divided into two main components [2]. The first is persistence, defined as continuously refilling prescriptions for the prescribed length of time [3]. However, even if individuals persist with their treatment, those with type 2 diabetes may not be taking their drug in accordance with the prescribed dosage and schedule. This relates to compliance with treatment, the second major component of adherence.

Adherence to OAD treatment has been assessed in many studies. In those specifically examining treatment persistence [4–15], most limited their interest to persistence with the initial OAD [4,5,7–10,13,15] and thus considered those switching to another antidiabetic therapy non-persistent. Moreover, although some individuals initially treated with an OAD are expected to later switch to insulin [16], in only two studies [6,11] were patients considered persistent if they were still using any antidiabetic treatment, including insulin.

On the other hand, some authors [8,9,17–22] have tentatively examined compliance with OADs, but within a mix of persistent and non-persistent users. Also, in many studies of OAD compliance, individuals initially taking more than one OAD were either excluded [11,18,23,24] or the assessment of compliance was restricted to only the initial OAD used [4,8–10,18,19,24–31]. This may not be representative of clinical practice where polytherapy and medication modifications are commonly seen [15] and, in fact, are often desirable if treatment targets are not reached [1].

However, to the best of our knowledge, no studies have assessed factors associated with both persistence and compliance with the overall antidiabetic treatment (including both OADs and insulin) in the same population. It is also known from studies conducted in hypertension [32,33] that the factors associated with persistence may differ from those related to compliance.

The objectives of the present study were:

- to measure the proportion of new OAD users persisting with any antidiabetic treatment after 365 days;
- to measure the proportion of compliant users among patients still taking treatment after 365 days and;
- to identify the factors associated with persistence and with compliance.

2. Research design and methods

This population-based cohort study of new users of OADs was carried out using the Quebec health insurance board (RAMQ) databases and the Quebec registry of hospitalizations (*Maintenance et exploitation des données pour l'étude de la clientèle hospitalière*, the MED-ECHO registry). The RAMQ health insurance plan covers all permanent residents of the province of Quebec, Canada, for both medical services and hospitalizations. Its public drug plan covers all residents aged 65 years or above, welfare recipients and those without access to a private drug group insurance plan. The RAMQ drug plan database is known to be accurate for prescription claims [34]. In 2009–2010, out of a population of 7.6 million, a total of 3.3 million people were beneficiaries of this drug plan.

A unique encrypted number was used to link the databases and the MED-ECHO registry at the patient level. The RAMQ databases served as the data source for patient demographics (age, gender and region of residence [rural or urban, as defined by Canada Post according to the national postal code]), eligibility for guaranteed income supplements or welfare, drug plan eligibility, medical services (date and diagnosis, as defined by the International Classification of Diseases, Ninth Revision [ICD-9]), drugs dispensed (drug name, dispensing date, number of days' supply and prescriber specialty) and death. Hospitalization data (dates, primary and secondary diagnoses) were also drawn from MED-ECHO.

RAMQ supplied these data for all drug plan beneficiaries aged 18 years or above who were newly dispensed an OAD or insulin between 1 January 2000 and 31 December 2008 — in other words, people for whom no OAD or insulin prescription had been dispensed the previous year (here called 'treatment initiation', $n = 188{,}659$). As the focus of our study was type 2 diabetes, those who had insulin only (without an OAD) at treatment initiation ($n = 6{,}858$) were excluded. Furthermore, to ensure that the data for every patient over the 365-day period following OAD treatment initiation were complete, individuals with a follow-up duration of less than 365 days, including those who died ($n = 6{,}120$), those not eligible for the public drug plan ($n = 4{,}831$) and those who initiated their treatment after 1 January 2008 ($n = 19{,}677$), were also excluded.

To guarantee anonymity, RAMQ assigned each patient a unique encrypted number. Data acquisition was authorized by the Quebec Committee for Access to Information (*Commission d'accès à l'information du Québec*), and our institutional ethics committee (*Comité d'éthique à la recherche du Centre hospitalier affilié universitaire de Québec*) gave its approval for the study.

Table 1
Characteristics of patients according to persistence with antidiabetic drug treatment 365 days after treatment initiation ($n = 151,173$).

Characteristics	Persistent				Unadjusted	95% CI	*P* value	Adjusted	95% CI	*P* value
	Yes		No		OR			OR		
	($n = 119,832$)		($n = 31,341$)							
Age (years)										
18–54	21,509	18.8	8069	25.7	1			1		
55–63	25,851	21.6	5850	18.7	1.66	1.60–1.72	< 0.0001	1.62	1.56–1.68	< 0.0001
64–69	24,742	20.6	5718	18.2	1.62	1.56–1.69	< 0.0001	1.62	1.55–1.69	< 0.0001
70–75	24,295	20.3	5728	18.3	1.59	1.53–1.65	< 0.0001	1.58	1.52–1.65	< 0.0001
≥ 76	23,435	19.6	5976	19.1	1.47	1.42–1.53	< 0.0001	1.44	1.39–1.51	< 0.0001
Gender										
Male	57,960	48.4	15,020	47.9	1					
Female	61,872	51.6	16,321	52.1	0.98	0.96–1.01	0.1621	N/A	N/A	N/A
Residential region										
Urban	93,639	78.2	25,465	81.3	1			1		
Rural	25,924	21.6	5777	18.4	1.22	1.18–1.26	< 0.0001	1.67	1.13–1.21	< 0.0001
Undisclosed	269	0.2	99	0.3	0.74	0.59–0.93	0.0101	0.75	0.59–0.94	0.0135
Socioeconomic status										
High	64,252	53.6	18,413	58.8	1			1		
Medium	30,373	25.4	6939	22.1	1.25	1.22–1.29	< 0.0001	1.1	1.07–1.14	< 0.0001
Low	25,207	21	5989	19.1	1.21	1.17–1.25	< 0.0001	1.3	1.26–1.35	< 0.0001
Specialty of initial prescriber										
Endocrinologist or internist	10,301	8.6	3286	10.5	1			1		
General practitioner	104,715	87.4	25,752	82.2	1.3	1.24–1.35	< 0.0001	1.21	1.16–1.26	< 0.0001
Other or undisclosed	4816	4	2303	7.3	0.67	0.63–0.71	< 0.0001	0.69	0.65–0.74	< 0.0001
Initial OAD treatment										
Metformin	95,873	80	23,788	75.9	1			1		
Secretagogue	16,716	14	5740	18.3	0.72	0.70–0.75	< 0.0001	0.74	0.72–0.77	< 0.0001
Other[a]	7243	6	1813	5.8	0.99	0.94–1.05	0.7469	1.15	1.09–1.22	< 0.0001
History of hospitalization[b]										
No	27,413	22.9	7611	24.3	1					
Yes	92,419	77.1	23,730	75.7	0.93	0.90–0.95	< 0.0001	N/A	N/A	N/A
Number of physician visits[b]										
< 7	40,369	33.7	10,574	33.7	1			1		
8–18	39,950	33.3	9861	31.5	1.06	1.03–1.09	0.0002	0.93	0.90–0.96	< 0.0001
≥ 19	39,513	33	10,906	34.8	0.95	0.92–0.98	0.0007	0.79	0.76–0.82	< 0.0001
Number of different drugs[b]										
≤ 4	40,311	33.6	13,180	42.1	1			1		
5–8	38,184	31.9	8727	27.8	1.43	1.39–1.46	< 0.0001	1.41	1.36–1.45	< 0.0001
≥ 9	41,337	34.5	9434	30.1	1.43	1.39–1.48	< 0.0001	1.5	1.45–1.56	< 0.0001

Data are presented as numbers and proportions (%) unless otherwise specified, OR: odds ratio; N/A: not applicable (variable not retained in the adjusted model).
[a] Includes treatment with drugs of other pharmacological classes and treatment with more than one drug from other pharmacological classes or not.
[b] Assessed during the 365-day period prior to OAD treatment initiation.

2.1. Variables

The two dependent variables (persistence and compliance) were assessed using data registered in the prescription-claims database. Individuals were considered persistent with their antidiabetic treatment if they had filled at least one prescription for any OAD in the 45 days before the first anniversary of treatment initiation or one prescription for insulin in the 90 days prior to the first anniversary of starting treatment. Antidiabetic treatment switches were therefore covered by the study definition of persistence [35]. In the province of Quebec, most individuals are supplied OAD prescriptions for a 30-day period [15]. Consequently, this 45-day period allowed them sufficient time to refill their OAD prescriptions at the end of the 1-year follow-up and still be considered persistent. Likewise, it was recently suggested that 90 days would be a permissible gap between insulin prescriptions when assessing adherence to insulin treatment [36].

Next, compliance was measured among those individuals who persisted with their treatment using the 'medication possession ratio' (MPR) [37]. The MPR is the number of days' supply of OAD or insulin during the 365-day period after OAD initiation divided by the number of treatment days (in this case, 365 days). For OADs, the number of days' supply was taken directly from the RAMQ database. However, as a days' supply of insulin provided in the RAMQ databases may have been imprecise because the use of insulin may vary from day to day [35], this number was defined a priori as 90 days, as suggested by Bonafede et al. [36]. Also, as drugs taken in hospital are not registered in the RAMQ databases, the number of days spent in hospital was removed from the MPR denominator [35]. People with an MPR of 80% were deemed compliant. This 80%

Table 2
Characteristics of patients compliant and non-compliant with antidiabetic drug treatment among persistent patients 365 days after treatment initiation ($n = 119,832$).

Characteristics	Compliant[a]				Unadjusted	95% CI	*P* value	Adjusted	95% CI	*P* value
	Yes		No		OR			OR		
	($n = 93,418$)		($n = 26,414$)							
Age (years)										
18–54	17,291	18.5	6239	23.6	1			1		
55–63	18,636	19.9	5194	19.7	1.3	1.24–1.35	< 0.0001	1.33	1.27–1.39	< 0.0001
64–69	19,403	20.8	5339	20.2	1.31	1.26–1.37	< 0.0001	1.35	1.35–1.48	< 0.0001
70–75	19,142	20.5	5153	19.5	1.34	1.29–1.40	< 0.0001	1.35	1.35–1.48	< 0.0001
≥ 76	18,946	20.3	4489	17	1.52	1.46–1.59	< 0.0001	1.44	1.44–1.59	< 0.0001
Gender										
Male	44,689	47.8	13,271	50.2	1					
Female	48,729	52.2	13,143	49.8	1.1	1.07–1.13	< 0.0001	N/A	N/A	N/A
Residential region										
Urban	72,587	22.1	21,052	20.1	1			1		
Rural	20,626	77.7	5298	79.7	1.13	1.09–1.17	< 0.0001	1.12	1.08–1.16	< 0.0001
Undisclosed	205	0.2	64	0.2	0.93	0.70–1.23	0.6075	0.88	0.66–1.17	0.3794
Socioeconomic status										
High	48,586	52	15,666	59.3	1					
Medium	24,312	26	6061	23	1.29	1.25–1.34	< 0.0001	1.08	1.04–1.12	< 0.0001
Low	20,520	22	4687	17.7	1.41	1.36–1.46	< 0.0001	1.45	1.40–1.51	< 0.0001
Specialty of initial prescriber										
Endocrinologist or internist	7912	8.5	2389	9	1			1		
General practitioner	81,739	87.5	22,976	87	1.07	1.02–1.13	0.0035	1.12	1.07–1.18	< 0.0001
Other or undisclosed	3767	4	1049	4	1.08	0.10–1.18	0.054	1.08	0.99–1.17	0.0805
Initial OAD treatment										
Metformin	74,661	79.9	21,212	80.3	1			1		
Secretagogue	12,732	13.6	3984	15.1	0.91	0.87–0.94	< 0.0001	0.89	0.85–0.92	< 0.0001
Other[b]	6025	6.5	1218	4.6	1.41	1.32–1.50	< 0.0001	1.46	1.37–1.56	< 0.0001
History of hospitalization[c]										
No	70,820	75.8	21,599	81.8	1			1		
Yes	22,598	24.2	4815	18.2	1.43	1.38–1.48	< 0.0001	1.28	1.23–1.34	< 0.0001
Number of physician visits[c]										
< 7	30,639	32.8	9730	36.8	1			1		
8–18	30,804	33	9146	34.6	1.07	1.04–1.11	< 0.0001	0.9	0.87–0.93	< 0.0001
≥ 19	31,975	34.2	7538	28.6	1.35	1.30–1.39	< 0.0001	0.88	0.84–0.92	< 0.0001
Number of different drugs[c]										
≤ 4	29,362	31.4	10,949	41.5	1			1		
5–8	29,801	31.9	8383	31.7	1.33	1.28–1.37	< 0.0001	1.3	1.26–1.35	< 0.0001
≥ 9	34,255	36.7	7082	26.8	1.8	1.74–1.87	< 0.0001	1.69	1.62–1.76	< 0.0001

Data are presented as numbers and proportions (%) unless otherwise specified, OR: odds ratio; N/A: not applicable (variable not retained in adjusted model).
[a] At least 80% of follow-up period covered by any antidiabetic drug treatment.
[b] Includes treatment with drugs from other pharmacological classes and with more than one drug from other pharmacological classes or not.
[c] Assessed in the 365-day period prior to OAD treatment initiation;

threshold has been used in the past to assess adherence to OADs [11,14,17,20,25,29,31].

The following variables were considered potential factors associated with persistence and compliance, and were assessed at OAD treatment initiation. From the RAMQ beneficiary demographic database were obtained data on: age (in quintiles); gender; socioeconomic status, as measured by the guaranteed income supplement (GIS), with welfare as a marker (high = no GIS and no welfare; medium = partial GIS and no welfare; and low = maximum GIS or welfare); and region of residence (urban or rural). The RAMQ pharmacy database was also searched for the initial OAD treatment (metformin, secretagogue or other) and the initial prescriber's specialty (endocrinologist or internist, general practitioner, or other or undisclosed).

In addition, the present study looked at data recorded in the MED-ECHO registry over the 365-day period prior to OAD treatment initiation as well as in the RAMQ medical services and pharmacy databases, along with searches in the MED-ECHO registry for hospitalizations (yes/no). The medical services database provided the number of physician visits, and the pharmacy database provided the number of different drugs used by each participant.

2.2. Statistical analysis

The proportion of those who persisted with any antidiabetic therapy for 365 days after OAD treatment initiation was calculated, including the mean and standard deviation (SD) and the

median MPR; the proportion of compliant individuals was also calculated. To identify the characteristics associated with persistence, both unadjusted and adjusted odds ratios (OR) were calculated along with their 95% confidence interval (CI) and two-tailed *P* values, using univariate and multivariate logistic regression models, respectively. Two-tailed *P* values < 0.05 were considered statistically significant. To test the sensitivity of the 80% MPR cut-off point for compliance, the analysis was repeated using two different thresholds (70% and 90%). Analyses were carried out using SAS version 9.2 software (SAS Institute, Cary, NC, USA).

3. Results

A total of 151,173 individuals was included in the analysis. Of these, 119,832 (79.3%) were persistent: they were still using antidiabetic drug treatment 365 days after its initiation. Individuals aged 54 years or above were more likely to persist than those aged between 18 and 53 years, as well as those living in a rural region, having a medium or low socioeconomic status, receiving initial treatment with metformin (rather than a secretagogue), prescribed their initial OAD by a general practitioner rather than an endocrinologist or internist and if, in the year prior to initiating OAD treatment, they had used five or more different drugs compared with those who used four drugs or less and had fewer than seven visits to their physician (Table 1).

Of the 119,832 who persisted with their treatment, 93,418 (78%) were deemed compliant. Their mean MPR was 86.3% (SD: 16.2%; median: 92.9%). Eight variables were found to have a statistically significant relationship with compliance when 80% was used as the MPR cut-off point (Table 2). In fact, all these variables were still associated with compliance when a cut-off of 70% was used, and all but one (initial treatment was with metformin) were statistically associated with compliance when a 90% cut-off point was used. The factors associated with compliance were similar to those associated with persistence, although being hospitalized in the year prior to OAD initiation was a factor associated with compliance but not with persistence (Table 2).

4. Conclusion

The main findings of our study are that, 1 year after initiation of OAD treatment, around 20% of individuals are no longer taking any kind of antidiabetic treatment. Of those still being treated, more than one in five is non-compliant with the treatment. Overall, 38% of our cohort members either did not persist or did not comply during their first year of antidiabetic treatment.

In addition, the proportion (79.3%) of persisting individuals after 1 year in our study was higher than those reported in two other studies focused on any OAD, which found proportions of 63.0% [11] and 68.0% [12], respectively. The lower proportions reported in those studies may be explained by differences in the definition of persistence, the nature of the population studied and the period covered. In the two studies mentioned above, for example, persistence was more strictly defined. In the Hertz et al. study [11], persistent patients were those who continuously refilled a prescription for an OAD within 1.25 times the days' supply of the previous refilling. In the other study [12], persistence in the first year of treatment was defined as the number of days of uninterrupted use of any OAD from the index date onwards, with a permissible gap between dispensation of less than half the period of the given dispensation or 7 days, whichever was longer. In the present study, individuals were considered persistent with their treatment if they had filled at least one prescription for any OAD within 45 days of the first anniversary of treatment initiation or filled one prescription for insulin within 90 days of the first anniversary of starting the treatment.

The discrepancies might also be explained by differences in the nature of the population studied and the time period covered. Hertz et al. [11] selected only patients aged less than 65 years. In contrast, around 60% of our study population was aged 64 years or above. As increased age has been associated with better persistence with antidiabetic treatment [11,13], this might explain why there was a larger proportion of persistent individuals in the present study. Furthermore, in contrast to ours, only one of those studies covered the years of the first decade of the 2000s [12].

Past studies [4,5,7–9,12,15] have reported the probabilities of individuals persisting with their initial OAD after 1 year as ranging from a low of 15% [8] to a high of 76% [4]. Persistence was likely to be lower in studies focusing on initial treatment because individuals discontinuing their initial drug were considered non-persistent even when they had switched to another antidiabetic drug (including insulin) whereas, in our study, this other antidiabetic therapy use was still considered persistence. Variations in the proportion of persistent individuals across drug classes may also be due to differences in the proportion of individuals who experienced drug side effects, as this can vary with drug classes. In past studies, for instance, it has been observed that, among patients using metformin [5,15] or a sulphonylurea [5,15], the probability of persisting after 1 year is greater than 50%, whereas it is less than 50% for patients using repaglinide [5], troglitazone [5] and alpha-glucosidase inhibitors [5,7]. On the other hand, Balkrishnan et al. [4] found a significantly higher proportion of persistent individuals among thiazolidinedione users compared with other OAD users (including metformin and sulphonylurea users). Experiencing side effects with a drug has been associated with lower rates of persistence in hypertension [32].

Our study also found that, among individuals still being treated after a year, 22% were not compliant: the MPR for their antidiabetic treatment was less than 80%. However, the mean MPR observed was 86.3%, a result similar to that reported by Morningstar et al. ($86 \pm 0.4\%$) in a study that measured compliance among individuals persisting with their OAD medication [28]. Apart from this example, as far as we know compliance has never been studied among individuals who were persistent with any antidiabetic drug treatment.

To the best of our knowledge, our study is also the first to identify factors associated with both components of adherence — persistence and compliance — with any antidiabetic treatment in the same population. Although use of the currently available administrative databases limited the number of factors

that could be assessed, it was found that persistence and compliance with antidiabetic treatment were both associated with the same seven factors.

Consistent with the findings of earlier studies, increased age was associated with both better persistence [11,13] and better compliance [30,38,39] with antidiabetic treatment. In fact, individuals aged 54 years or above were more likely to be persistent and compliant compared with those aged from 18 to 53. Venturini et al. [30] have suggested that, although older patients are likely to have more difficulties than younger patients due to the greater complexity of their regimens, they may perceive their health as more dependent on their medications and, as a result, may be more compliant. Our study also found that patients who lived in rural regions were more likely to persist and comply with their antidiabetic treatments compared with those living in urban settings. This result is similar to what has been observed in the field of hypertension [40].

Individuals with low rather than high socioeconomic status were also more likely to be both persistent and compliant. In the province of Quebec, the entire population has access to a drug plan, albeit public or private. Under the Quebec public drug plan, the patient's financial contribution (co-payment) demanded for dispensed prescription drugs is lower for those of low socioeconomic status than for others, and our results suggest that this health policy may be having a favourable effect on adherence to antidiabetic drug treatment. This concurs with earlier studies of antihypertensive drug treatment, in which people of low socioeconomic status were more likely to persist [32], and with studies of antidiabetic drugs [8,17], in which those with low co-payments were more likely to be compliant.

In addition, individuals prescribed their initial OAD by a general practitioner rather than an endocrinologist or internist were more likely to be persistent and compliant with their antidiabetic treatment. With respect to persistence, however, the results reported in the literature are conflicting. Some have reported results similar to ours [10,15] whereas others have reported the opposite [7]. Interpretation of these results is difficult, given that important clinical data are not included in administrative databases. Indeed, the greater adherence among individuals initially treated by general practitioners may simply reflect the fact that these patients have conditions that are less complex to manage than is the case for those who consult an internist or endocrinologist. Also, certain characteristics of these patients not captured in the databases may be associated with both the type of physician consulted and adherence. Further research is needed to better assess whether or not physician specialty is an independent predictor of persistence and compliance with antidiabetic treatment.

Individuals who received metformin as their initial treatment rather than a secretagogue were also more likely to be persistent and compliant with their antidiabetic treatment, and earlier studies of persistence [5,15] have reported similar findings. It has been suggested that OAD-related side effects, such as hypoglycaemic events, are a significant barrier to compliance [41]. Indeed, patients treated with insulin secretagogues are at higher risk of hypoglycaemia compared with patients treated with metformin [1].

Individuals with a history of using five or more different drugs in the year preceding their OAD initiation compared with those using four or fewer drugs were more likely to be persistent and compliant with their antidiabetic treatment. This result is in keeping with what has been reported in some studies where individuals filling a higher number of different prescription drugs per month were more likely to be persistent with their antidiabetic treatment [11]. On the other hand, the opposite has also been noted, with an increase in the number of drugs being associated with a decrease in compliance [8,18,21,30]. Further research in this area is needed to better assess the role of treatment complexity in antidiabetic treatment persistence and compliance.

Individuals who visited their physician fewer than seven times in the year preceding OAD treatment initiation were more likely to persist with their antidiabetic treatment and be compliant than were those individuals with eight or more visits. A large number of physician visits may indicate that patients have concomitant illnesses. The presence of certain conditions, such as depression [11] and mental disorders [15], before the first antidiabetic drug prescription has been associated with non-persistence with antidiabetic treatment, whereas a smaller number of concomitant illnesses is a factor that has been reported to be associated with better compliance [42].

The present study has some limitations that need to be considered when interpreting the results, especially those related to the use of administrative data. Estimates of both persistence and compliance were based on patterns of drugs dispensed, but not necessarily consumed. Consequently, both persistence and compliance might have been overestimated in cases where individuals filled their prescriptions but did not take the drug. Furthermore, the RAMQ databases do not provide medication information for members of the population aged less than 65 that are covered by private drug insurance plans. This resulted in a sample that underrepresented people who are employed, which might limit the generalizability of our findings to all Quebec individuals aged less than 65 years, although our results can be extended to all individuals covered by the Quebec drug plan. Certain characteristics known to have an impact on persistence and compliance to OAD treatment, such as severity of disease, self-perception of health status [30] and other psychosocial variables [25], are also not available in the databases and therefore could not be considered in our analyses. Finally, it was assumed that patients who had not filled a prescription for an antidiabetic treatment in the period prior to the first anniversary of their treatment initiation were not persistent. However, it cannot be assumed that these patients will never again take any such treatment. In fact, it has been reported that around 60% of patients who discontinue their OAD treatment initiate a new course of treatment within the year following discontinuation [15]. Moreover, as persistence was defined as filling a prescription for any OAD treatment or insulin in the period preceding the first anniversary of treatment initiation, those who were hospitalized during this period were considered not persistent, although they might have received their treatment from the hospital pharmacy. Having a high number of physician visits prior to treatment initiation and having been hospitalized in the year prior to treatment initiation might also be associated with an increased risk of

hospitalization in the following year and, therefore, may be associated with non-persistence. However, only the former of these two characteristics was associated with non-persistence. Furthermore, on assessing the history of hospitalization in the 45 days before the first anniversary of starting antidiabetic treatment, it was found that the proportion of individuals who were both hospitalized and persistent with their treatment during that period (4.1%) was similar to the proportion of those observed to be both hospitalized and non-persistent (5.2%).

Despite these limitations, our study has several strengths. Using the RAMQ databases to assess determinants of persistence and of compliance allowed the evaluation of a large cohort of individuals using antidiabetic drugs for up to 365 days. These individuals were studied in a real-life practice setting, thereby preventing any behavioural adjustments as seen in clinical trials [35]. In addition, in contrast to most previous studies that have described persistence or compliance with only the initial OAD prescribed [13,15], our study focused on the overall antidiabetic treatment situation, which may be more representative of the clinical practice of diabetes where treatment switches are common [13,15] and often desirable.

Diabetes is a chronic disease that requires long-term and continuous treatment. Consequently, persistence and compliance with any antidiabetic medication are important factors for achieving adequate glycaemic control, and for preventing diabetes complications and hospitalizations. Several factors associated with persistence and with compliance were identified in our study that may help in the development of interventions designed to prevent adherence problems and to optimize the use of antidiabetic treatments.

5. Author contributions

L.G. contributed substantially to the interpretation of data, the discussion of results, and edited and critically revised the manuscript. J.M. contributed substantially to the conception and design of the study, the analysis and interpretation of the data, and edited and critically revised the manuscript. M.C.B. contributed substantially to the interpretation of data and co-drafted the article. C.S. contributed substantially to the literature research and interpretation of data, and critically revised the manuscript. J.P.G. contributed substantially to the conception and design of the study, the analysis and interpretation of the data and co-drafted the article.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

This study was partly funded by the Chair on Adherence to Treatments of Laval University. This Chair is supported by non-restricted grants from AstraZeneca, Merck Canada, Sanofi-Aventis Canada, Pfizer and the *Prends soin de toi program* (Take-care-of-yourself programme; a Quebec provincial programme for the improvement of public health).

We thank Éric Demers from the statistics department of our research center for assistance in data analysis and Joanne Vidal, a freelance editor, for editing the text.

The study results were presented in part at the Canadian Association for Population Therapeutics Annual Conference, 2011 April 17–19, Ottawa, Ontario, Canada.

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