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3 **Title: Association between interpersonal continuity of care and medication adherence in**  
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5 **type 2 diabetes**  
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**ABSTRACT**

**Background:** Higher interpersonal continuity of care (ICoC) is associated with better health outcomes. The extent to which ICoC could also be associated with medication adherence has not been well established. We sought to determine whether higher ICoC is associated with medication adherence among patients who initiated an oral antidiabetes drug (AD) treatment.

**Methods:** We conducted a cohort study of new users of oral AD aged 18 or more years. Patients were categorized according to tertiles of their ICoC index measured during the 1<sup>st</sup> year after oral AD initiation. ICoC index is based on the number of different physicians seen and the number of visits to each physician in this period. Tertiles of ICoC index were used to categorize individuals into low, intermediate and high level of ICoC. Two constructs of medication adherence were assessed during the 2<sup>nd</sup> year: 1) persistence with AD, 2) compliance among those considered persistent. The association between ICoC and medication persistence and compliance was assessed using Generalized linear models.

**Results:** A total of 60,924 patients were included in the initial cohort. Compared to individuals with a high ICoC, those with intermediate and low ICoC were less likely to be persistent (adjusted prevalence ratio (aPR) 0.97, 95% confidence interval [CI] 0.96-0.98 and 0.96, 0.95-0.97, respectively) and compliant with their AD (aPR 0.98, 95% CI 0.97-0.99 and 0.95, 0.94-0.97, respectively).

**Interpretation:** Our results suggest that a higher ICoC is associated with a higher likelihood of persistence and compliance with AD although the magnitude of this association is weak.

Key words: Continuity of care; Medication adherence; Diabetes Mellitus, Type 2

## INTRODUCTION

Interpersonal continuity of care (ICoC) refers to the ongoing relationship between a patient and an individual physician<sup>1</sup>. There is good evidence from a systematic review that a high ICoC is associated with decreased hospitalization and emergency department visits, and improved patient satisfaction<sup>2</sup>. To what extent a high ICoC is associated with a higher likelihood of medication adherence is less clear<sup>2</sup>.

Medication adherence is made of two main constructs: persistence (consistently refilling prescriptions for the prescribed length of time) and compliance (taking the drug in accordance with the prescribed dosage and schedule)<sup>3</sup>. To our knowledge, the relationship between ICoC and medication adherence has been assessed in six studies<sup>4-9</sup>. In four of these studies<sup>4,7-9</sup>, a positive relationship between ICoC and medication adherence was observed. For example, a high ICoC was associated with higher persistence with statins<sup>8</sup>, and higher compliance with oral antidiabetes drugs (AD)<sup>7</sup>, statins<sup>9</sup> and drugs used in heart failure<sup>4</sup>. Five of these studies<sup>4,6-9</sup> were however limited by the fact that their design was cross-sectional. Therefore, the temporal relationship between ICoC and medication adherence could not be established.

Type 2 diabetes is a chronic condition usually necessitating long-term use of drugs to control hyperglycemia. However, to a large extent the use of those drugs is not optimal. In one study conducted in Quebec, less than 79% of patients persisted with the oral AD one year after initiation and among them, only 78% were compliant as they obtained drug supplies for at least 80% of days during the year<sup>10</sup>.

As type 2 diabetes patients may have to consult many physicians during their therapeutic journey<sup>11</sup>, we hypothesized that higher ICoC could translate in a higher medication adherence. We

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3 conducted a study aiming to assess the association between ICoC and each of the two main  
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5 constructs of medication adherence among new users of oral AD: 1) persistence with AD; 2)  
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7 compliance with AD among those persistent.  
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## 10 11 **METHODS**

### 12 13 14 **Study design and data sources**

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17 We conducted a cohort study among patients insured by the Quebec public drug plan using  
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19 medico-administrative data from the Quebec Health Insurance Board (*Régie de l'Assurance*  
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21 *Maladie du Québec* [RAMQ]) and the Quebec registry of hospitalisations (*Maintenance et*  
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23 *exploitation des données pour l'étude de la clientèle hospitalière* [Med-Écho]). The RAMQ  
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25 databases contain information on individual characteristics (age, sex, guaranteed income  
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27 supplement (GIS) status, public drug plan eligibility), use of outpatient medical services (date,  
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29 primary diagnosis and the identification number of the physician consulted), drugs claimed (drug  
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31 identification, date, quantity supplied, number of days' supply, and the pharmacy identification  
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33 number). Med-Écho is the source of data for hospital admissions (dates, primary and secondary  
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35 diagnoses). With a unique identifier, it is possible to link at individual level, the information  
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37 contained in these databases.  
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45 ICoC was measured during the first year while medication adherence was assessed in the  
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47 second year of follow-up (Figure 1). It was then possible to assess the temporal relationship  
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49 between the two variables <sup>2</sup>.  
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### 53 **Patients**

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56 We included patients aged 18 or more years who were newly dispensed an oral AD between Jan.  
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3 1, 2000 and Dec. 31, 2006 (Figure 2). To identify new users, we excluded patients who had not  
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5 been continuously eligible for the public drug plan, and who had no AD claim throughout the  
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7 entire year before the first AD claim registered on or after Jan. 1, 2000. Those for whom we did  
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9 not have a follow-up period of at least 730 days were also excluded. This was done to allow the  
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11 measurement of ICoC and medication adherence in the first and the second year of follow-up,  
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13 respectively. To obtain a measurement of outpatient drug compliance over a period of at least 90  
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15 days, we excluded patients who had 275 days or more of hospitalization in the first or in the  
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17 second year after oral AD initiation. Moreover, to ensure a valid measurement of ICoC, as  
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19 recommended by Bice<sup>12</sup>, we excluded patients who had less than 3 or more than 50 outpatient  
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21 visits in the 12 months after oral AD initiation.  
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## 28 **Variables**

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31 We measured ICoC with an index proposed by Bice<sup>12</sup>. This index measures the extent to which  
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33 ambulatory visits for a specific patient are dispersed among different physicians. This index takes  
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35 into account the contribution of each physician in the continuity of the patients care. This index is  
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37 calculated as follows: 
$$= \frac{[\sum_{i=1}^M n_i^2] - N}{N(N-1)}$$
 (N= total number of outpatients visits; ni= number of visits to  
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39  $i^{\text{th}}$  different physician;  $i=1,2,\dots M$ ; M= number of physicians within the follow-up time). The  
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41 values of the index range from 0 to 1, 1 indicating the highest level of ICoC. The highest level of  
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43 ICoC means that the patient visits are concentrated among only one physician<sup>12</sup>. Since index  
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45 scores have no validated thresholds, we categorized ICoC in three categories (low, intermediate  
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47 and high) using tertiles, as did previous researchers<sup>5,7,13</sup>.  
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54 We assessed medication adherence during the second year after oral AD initiation. Patients were  
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56 considered persistent with their AD treatment if they had any oral AD or insulin available 730  
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3 days after oral AD initiation. This was estimated based on the number of days supplied at the  
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5 most recent dispensing before the second anniversary date plus a permissible gap of 0.5 times the  
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7 days' supply for oral ADs. The number of oral AD days' supply was derived directly from the  
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9 RAMQ database. As the use of insulin may vary on a daily basis, the number of days' supply was  
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11 beforehand defined as 90 for all insulin claims<sup>10,14</sup>. Patients hospitalized on day 730 were  
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13 considered persistent if they had filled any oral AD or insulin in the period prior to the date of  
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15 their most recent hospital entry along the same lines as those defined above.  
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21 We measured compliance with AD among those who persisted with their treatment using the  
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23 proportion of days covered (PDC)<sup>15</sup>. The PDC was calculated as the total number of days  
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25 covered by either any oral AD or insulin divided by the number of days in the second year after  
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27 oral AD initiation i.e. 365. For oral ADs, the number of days' supply was derived directly from  
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29 the RAMQ database and number of days' supply was beforehand defined as 90 for insulin claims  
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31<sup>14</sup>. As information on drugs taken in hospital is not recorded in Med-Écho, we removed the  
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33 number of days spent in hospital from both the PDC numerator and denominator. Patients with a  
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35 PDC of 80% or more were considered compliant. It has been shown that a PDC <80% predicts  
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37 subsequent hospitalization in diabetes<sup>16</sup>.  
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43 Covariates included socio-demographic, healthcare use characteristics, and those related to the  
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45 first oral AD claim. We used socio-demographic characteristics at oral AD initiation: age  
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47 (continuous), sex (men, women) and socioeconomic (no/partial/maximum GIS) status. We  
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49 assessed the presence of healthcare use variables in the first year after oral AD initiation.  
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52 Healthcare use variables included loyalty to a pharmacy (1; > 1 different pharmacies visited) and  
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54 number of hospitalizations for any cause (continuous). In addition, we considered the number of  
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56 distinct drugs claimed (continuous) as a co-morbidity indicator<sup>17</sup>. Characteristics related to the  
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3 initial oral AD claim included the type of treatment (metformin monotherapy, sulfonylurea  
4 monotherapy, other oral AD monotherapy, AD bi-therapy, AD tri-quadri-and penta-therapy),  
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8 specialty of the prescriber (general practitioner, endocrinologist or internist, other) and calendar  
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10 year (2000 to 2006).  
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### 12 13 14 **Statistical analysis**

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17 We conducted two generalized linear models with a log link and a Poisson working model<sup>18</sup>. The  
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19 first model assessed the association between ICoC index and persistence with AD, and the second  
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21 the association between ICoC and compliance with AD among those persistent. In both models,  
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23 potential confounders included age, sex, socioeconomic status, number of distinct drugs claimed,  
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25 loyalty to a pharmacy, hospitalization for any cause, initial oral AD treatment type, calendar year  
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27 of oral AD initiation and specialty of the initial oral AD prescriber. Adjusted prevalence ratios  
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29 (APR) with their 95% confidence intervals (CI) were computed. We assessed multicollinearity  
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31 using the procedure described by Belsley et al.<sup>19</sup>. We tested the sensitivity of our results to the  
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33 80% PDC threshold for compliance by repeating the analysis using 70% and 90% as cut-off  
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35 points. Analyses were performed using SAS, version 9.4 [SAS Institute Inc., Cary, NC, USA].  
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### 41 42 **RESULTS**

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45 A total of 60,924 patients were included in the study population. Their characteristics are  
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47 displayed in Table 1. The median ICoC value (first quartile - third quartile) was 0.14 (0.04-0.33).  
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49 The patients were categorized into low (0.00-0.06), intermediate (0.07-0.24) and high (0.25-1.00)  
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51 level of ICoC.  
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56 A total of 49,007 (80.4%) patients were persistent with their AD treatment two years after oral  
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3 AD initiation (Table 2). Compared to patients with high ICoC (0.25-1.00), those with  
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5 intermediate (0.07-0.24) and low ICoC (0.00-0.06) were 3% and 4% less likely to be persistent  
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7 with their AD, respectively (adjusted prevalence ratio (aPR) 0.97, 95% confidence interval [CI]  
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9 0.96-0.98 and 0.96, 0.95-0.97, respectively) (Table 3). Among persistent patients, 39,246 (80.1%)  
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11 complied with their AD (Table 2). Compared to patients with high ICoC, those with intermediate  
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13 and low ICoC were 2% and 5% less likely to be compliant with their AD, respectively (aPR 0.98,  
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15 95% CI 0.97-0.99 and 0.95, 0.94-0.97, respectively) (Table 3). The association between ICoC  
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17 and compliance with AD was not sensitive to change in the PDC cut-off points (data not shown).  
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## 22 23 INTERPRETATION

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26 One main result emerges from our study: as the ICoC decreases, patients are less likely to persist  
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28 and comply with their AD but the magnitude of those associations is low. The decreased  
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30 likelihood to persist and be compliant with AD as the ICoC decreases is in line with results  
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32 observed in four studies conducted among users of oral ADs<sup>7</sup>, statins<sup>8,9</sup> and antihypertensive  
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34 drugs<sup>4</sup>. For example, in a study by Chen et al.<sup>7</sup>, compared to new users of oral ADs with a low  
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36 index (0.00-0.22) of continuity of care, those with a medium (0.23-0.43) and a high index (0.44-  
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38 1.00) were 1.8 fold and 3.4 fold more likely to have a one-year medication possession ratio  $\geq$   
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40 80%, respectively. In this latter study<sup>7</sup>, associations were of a higher magnitude than those we  
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42 observed. It is likely due to the fact that those researchers used odds ratios as measures of  
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44 association whereas we used prevalence ratios. Odds ratios, as opposed to prevalence ratios,  
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46 overestimate the risk ratio when the prevalence of the studied outcome in a study population is  
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48 higher than 10%<sup>18</sup>. This is the case in our study: the prevalence of persistence and compliance  
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50 was around 80%.  
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3 In contrast, our results are different from those observed in two studies, one conducted among  
4 patients treated for hypertension <sup>5</sup> and the other among patients treated for multiple chronic  
5 diseases <sup>6</sup>. In the first of those studies, Kerse et al. did not observe an association between ICoC  
6 and medication adherence. However, both ICoC and medication adherence were self-reported as  
7 opposed to being measured using physicians visits and pharmacy dispensing data as we did <sup>6</sup>.  
8 Self-reported measures of adherence exhibit poor agreement with those based on pharmacy data  
9 <sup>20</sup>. In addition, adherence was assessed with no attempt to distinguish persistence and compliance  
10 constructs from each other as we did <sup>6</sup>. Likewise, Robles et al. found no association between  
11 ICoC and compliance with antihypertensive drugs as measured by a 1-year PDC of 80% or more  
12 <sup>5</sup>. However, in this latter study, when patients who had been hospitalized or had a cardiovascular  
13 event were excluded, a positive association was observed between higher levels of ICoC and  
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33 The decreased likelihood of persistence and compliance we have observed among patients with  
34 lower ICoC suggests that the ICoC might have a small but positive effect on both persistence and  
35 compliance with AD. According to findings from previous studies on patients' preferences,  
36 patients reported to believe that ICoC improves their trust in their physician as well as their  
37 physician's ability to communicate health issues to them <sup>21</sup>. Although further research is needed  
38 to confirm the link between those latter attributes and ICoC, in prior studies, better physician  
39 communication skills <sup>22</sup> and patients' trust in the provider <sup>23,24</sup> were associated with self-reported  
40 medication adherence.  
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53 Our study has some limitations. First, we assumed that drugs claimed were all taken and we made  
54 no distinction between mono and polytherapy. As a result, we may have overestimated  
55 persistence and compliance with AD, thus leading to a non-differential misclassification with an  
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3 effect estimate biased toward the null. In addition, the RAMQ databases lack information on  
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5 psychosocial variables (e.g. patient's perception of risk of disease and benefits of the treatment)  
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7 that are likely to influence medication persistence and compliance<sup>25</sup>. Therefore, we were not able  
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9 to adjust effect estimates for those potential confounding variables. Moreover, to get a valid ICoC  
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11 measure we had to exclude patients who had less than three physicians visits in the 1-year period  
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13 during which ICoC was assessed. To what extent these excluded patients are less sick or do not  
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15 have an as good access to a physician as those included in the study is unknown. Finally, we  
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17 assessed ICoC in the first year of treatment and persistence and compliance in the year after.  
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19 Therefore we cannot assume that the association we have observed between ICoC and persistence  
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21 and compliance would remain the same if those outcomes were assessed in subsequent years.  
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## 27 28 **CONCLUSION**

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31 Prior studies have shown that patients with a high ICoC as opposed to those with a low ICoC  
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33 have a lower likelihood of hospitalization and emergency department visits, and a higher  
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35 likelihood of patient satisfaction<sup>26</sup>. Our results suggest that it may also be associated with better  
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37 persistence and compliance with the AD among patients newly treated for type 2 diabetes,  
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39 although the magnitude of this association is low.  
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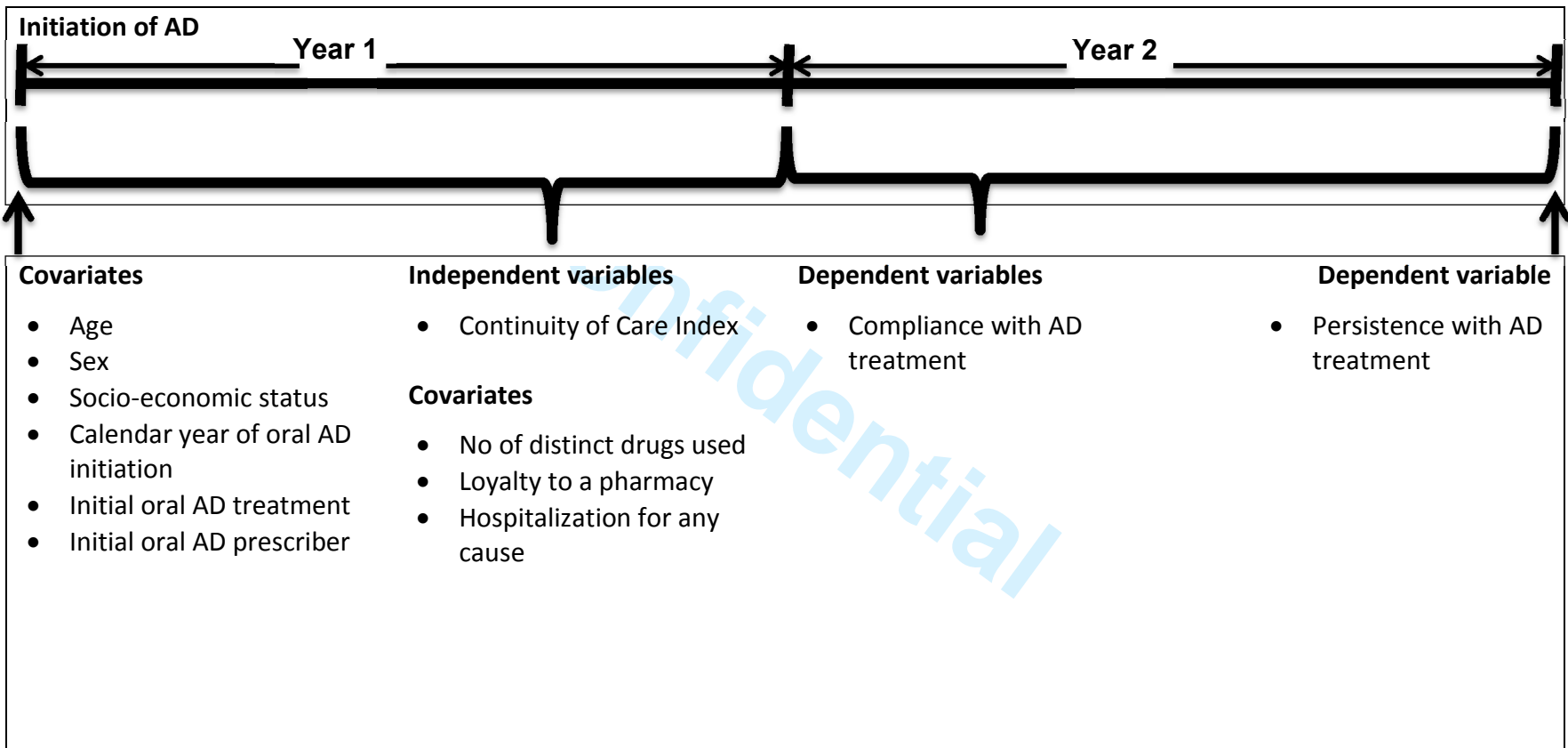
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Note: AD= Antidiabetes drugs

Figure 1. Study design and timeline for measurement of variables

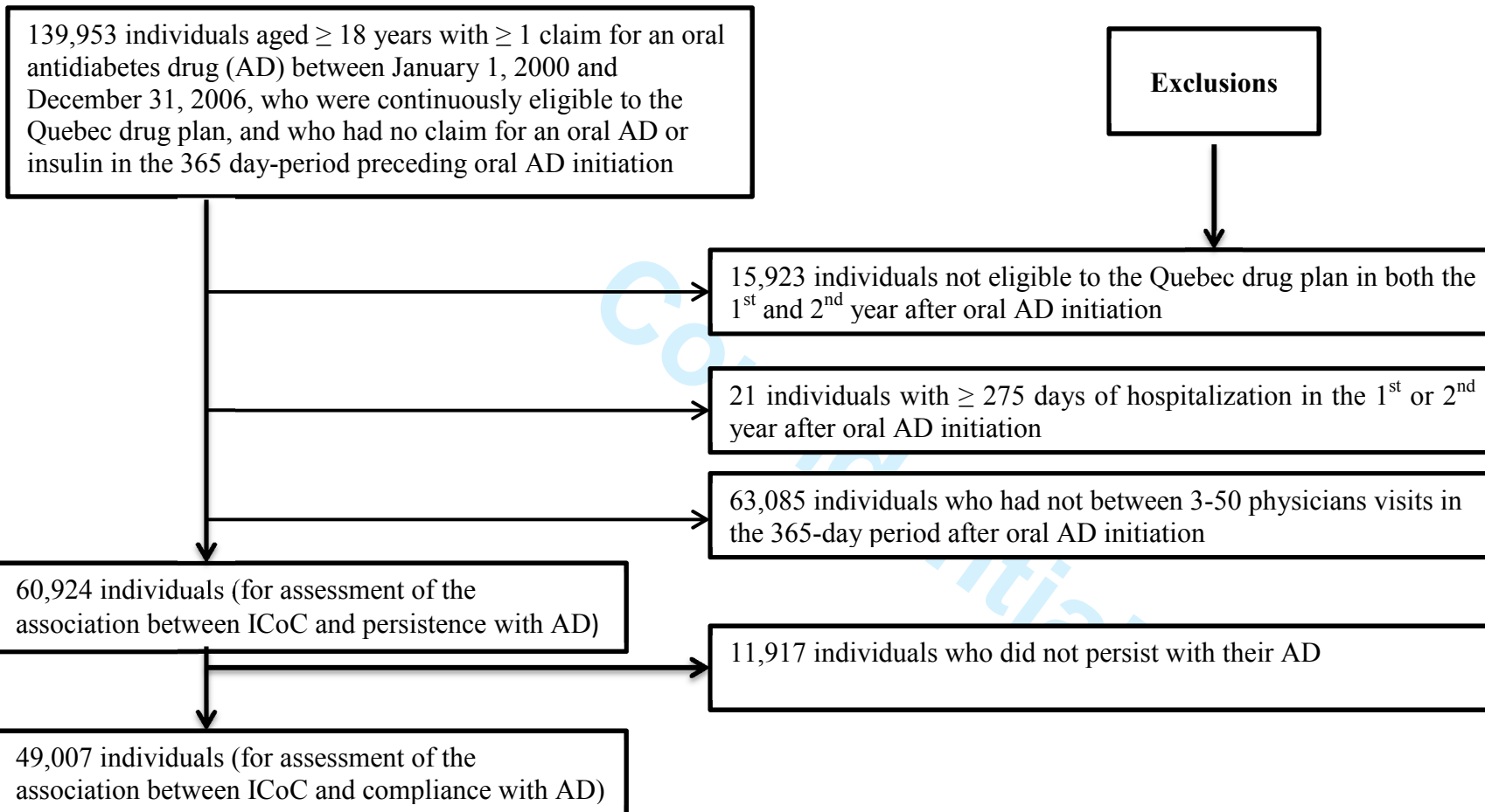


Figure 2. Selection of the study population

Table 1 Characteristics of patients at or in the year after oral antidiabetes drug initiation according to interpersonal continuity of care (ICoC) levels (n= 60,924)

Characteristics	Levels of ICoC						P-value
	High (0.25–1.00) N = 20,305		Intermediate (0.07-0.24) N = 19,898		Low (0.00-0.06) N = 20,721		
	N	%	N	%	N	%	
<b>Sociodemographic variables</b>							
Age in years (mean) (median) (Q1- Q3)	(64.2)	(67)	(65.1)	(67)	(65.0)	(67)	<0.0001*
		(57-74)		(58-74)		(57-74)	
Sex							0.031
Men	9,730	47.9	9,486	47.7	9,675	46.7	
Women	10,575	52.1	10,412	52.3	11,046	53.3	
Socio-economic status at oral antidiabetes drug initiation							<0.0001
No guaranteed income supplement (GIS)	10,921	53.8	10,645	53.5	10,477	50.6	
Partial GIS	4,936	24.3	5,108	25.7	5,473	26.4	
Welfare or maximum GIS	4,448	21.9	4,145	20.8	4,771	23.0	
<b>Healthcare use variables†</b>							
Loyalty to a pharmacy							<0.0001
Yes	12,118	59.7	10,767	54.1	11,092	53.5	
No	8,187	40.3	9,193	45.9	9,629	46.5	
Hospitalization for any cause							<0.0001
Yes	3,863	19.0	7,877	39.6	9,038	43.6	
No	16,442	81.0	12,021	60.4	11,683	56.4	
Number of distinct drugs claimed (mean) (median) (Q1- Q3)	(10.5)	(10)	(13.0)	(12)	(13.3)	(12)	<0.0001*
		(7-13)		(9-16)		(9-17)	
<b>Initial oral AD related characteristics</b>							
Initial oral AD treatment							<0.0001
Monotherapy with metformin	16,069	79.1	15,089	75.8	15,844	76.4	
Monotherapy with sulfonylurea	2,897	14.3	3,294	16.5	3,494	16.9	
Monotherapy with another oral AD	190	0.9	291	1.5	293	1.4	
Bitherapy	1,140	5.6	1,210	6.1	1,085	5.2	
Tri-quadri-and pentatherapy	9	0.1	14	0.1	5	0.1	
Initial oral antidiabetes drug prescriber							<0.0001
General practitioner	16,728	82.5	15,671	78.8	17,415	84.2	
Endocrinologist or internist	2,380	11.7	2,957	14.9	2,274	11.0	



Table 1 Characteristics of patients at or in the year after oral antidiabetes drug initiation according to interpersonal continuity of care (ICoC) levels (n= 60,924)

Characteristics	Levels of ICoC						P-value
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	N	%	N	%	N	%	
Other	1,167	5.8	1,242	6.3	996	4.8	
Calendar year of oral antidiabetes drug initiation							<0.0001
2000	2,212	10.9	2,529	12.7	2,705	13.1	
2001	2,236	11.0	2,429	12.2	2,672	12.9	
2002	2,286	11.3	2,523	12.7	2,754	13.4	
2003	2,625	12.9	2,657	13.3	2,895	13.9	
2004	3,407	16.8	3,107	15.6	3,198	15.4	
2005	3,543	17.4	3,179	15.9	3,282	15.8	
2006	3,996	19.7	3,474	17.6	3,215	15.5	

\* Chi-square test for proportions and Wilcoxon test for medians

† Variables measured in the 1<sup>st</sup> year following oral antidiabetes drug initiation (day of initiation and 365<sup>th</sup> day included)

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Table 2 Persistence and compliance with antidiabetes drug treatment according to levels of interpersonal continuity of care (ICoC)

Medication adherence construct*	Levels of ICoC		
	High <i>N in category</i> (n with the adherence construct; %)	Intermediate <i>N in category</i> (n with the adherence construct; %)	Low <i>N in category</i> (n with the adherence construct; %)
Persistence with antidiabetes drug treatment among the 60,924 study patients	20,305 (16,820; 82.8)	19,898 (15,886; 79.8)	20,721 (16,301; 78.7)
Compliance with antidiabetes drug treatment among the 49,007 patients who were persistent	16,820 (13,592; 80.8)	15,886 (12,817; 80.7)	16,301 (12,837; 78.7)

\* Medication adherence was measured in the 2<sup>nd</sup> year after oral antidiabetes drug initiation

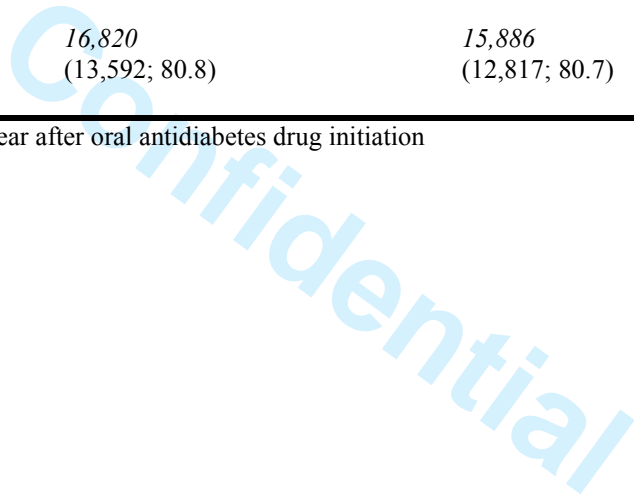


Table 3 Adjusted prevalence ratios (APR) and 95% confidence intervals (CI) of persistence and compliance with antidiabetes drug treatment according to levels of interpersonal continuity of care (ICoC)

Medication adherence*	Levels of ICoC		
	High ICoC	Intermediate ICoC	Low ICoC
	APR	APR (95% CI)	APR (95% CI)
Persistence with antidiabetes drug treatment among the 60,924 study patients	1.00 <sup>†</sup>	0.97 <sup>†</sup> (0.96-0.98)	0.96 <sup>†</sup> (0.95-0.97)
Compliance with antidiabetes drug treatment among the 49,007 patients who were persistent	1.00 <sup>†</sup>	0.98 <sup>†</sup> (0.97-0.99)	0.95 <sup>†</sup> (0.94-0.97)

\* Medication adherence (persistence and compliance) was measured in the 2<sup>nd</sup> year after oral antidiabetes drug initiation

<sup>†</sup> Adjusted for: age, sex and socioeconomic status at oral antidiabetes drug initiation, calendar year of oral antidiabetes drug initiation, number of distinct drugs used, hospitalization for any cause and loyalty to a pharmacy in the year following oral antidiabetes drug initiation, initial oral antidiabetes drug treatment and the initial oral antidiabetes drug prescriber.