

# Effect of different methods for estimating persistence and adherence to new glucose-lowering drugs: results of an observational, inception cohort study in Portugal

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**Purpose:** Several methods have been developed for assessing medication-taking behavior; understanding the determinants and variability in estimates obtained is crucial in interpreting results. We estimated persistence and adherence levels to new glucose-lowering drugs (GLDs) in type 2 diabetes mellitus (T2DM) patients using different methods: through the collection of pharmacy records and combining pharmacy records with self-reported data.

**Methods:** We conducted a prospective observational cohort study of T2DM patients initiating a new GLD. Data were collected at baseline through interviews (demographic and clinical data). Follow-up data included pharmacy records (refill dates and medication possession) and telephone questionnaires (self-declared monitored GLD refill in another pharmacy, reasons for drug withdrawal). The cohort was divided into incident and prevalent new users. Persistence and adherence (proportion of days covered) were estimated for patients using pharmacy records exclusively (Method 1) and  $\geq 1$  self-declared statement of being persistent (Method 2). Log-rank tests were used to compare Kaplan–Meier curves of time to nonpersistence.

**Results:** A total of 1,328 patients were recruited. When considering Method 1, 38.7% (95% confidence interval [95% CI]: 36.0–41.5) of patients were persistent, whereas combining with self-reported information, this estimate increased to 65.6% (95% CI: 62.9–68.2). Using Method 1, the risk of persistence failure was associated with using an oral GLD, living alone and living in a suburban/urban setting. Three hundred and twenty-seven (24.8%) patients stopped to use the inception GLD.

**Conclusion:** Regardless of the method used, results indicated low levels of persistence and adherence to a new GLD; however, when combining self-reported information, higher estimates were obtained. Considering pharmacy records exclusively, prevalent new users, who were more complex patients in terms of T2DM disease but more likely to be pharmacy-loyal patients, were significantly more adherent than the incident new users. Barriers and reasons leading to GLD withdrawal, namely adverse drug event management, should be addressed, since they represent half of the reasons for treatment switching or discontinuation.

**Keywords:** type 2 diabetes mellitus, medication use behavior, discontinuation, daily practice

## Introduction

Type 2 diabetes mellitus (T2DM) is a serious illness, leading to severe complications<sup>1,2</sup> and increased mortality.<sup>3</sup> Considering the demographic trends, diabetes prevalence is expected to rise to >690 million people by 2,045, posing a major health concern to many countries worldwide.<sup>4</sup> Portugal is no exception,<sup>5</sup> and according to the International

Diabetes Federation figures, is one of the countries with the highest prevalence of this condition in Europe.<sup>6</sup>

Achieving and maintaining glycemic control as a primary treatment goal is challenging. In general, T2DM treatment is carried out in a stepwise manner, initially with lifestyle modifications, followed by metformin, and subsequently by adding another glucose-lowering drug (GLD).<sup>7,8</sup> Although it is recognized that persistence and adherence to medication is crucial to obtain optimal clinical outcomes,<sup>9,10</sup> studies have shown that recommended glycemic goals are achieved by <50% of patients, suggesting poor levels of these metrics.<sup>11</sup>

Several new GLDs, such as dipeptidyl peptidase-4 inhibitor (DPP-4), glucagon-like peptide-1 (GLP-1) and sodium-glucose co-transporter 2 inhibitors, have recently been marketed, enabling physicians to tailor therapy through a range of combination strategies. In order to target these new agents to T2DM patients in actual clinical practice, it is essential to monitor and understand the use behavior outside of a clinical trial setting.<sup>12</sup> This is especially relevant among treatment-experienced patients<sup>13</sup> where information is scarce, as published studies usually come from treatment-naïve or selective T2DM patients' groups with strict eligibility criteria, which represent only a small part of the real-life user population.<sup>14</sup>

Efforts to accurately measure and improve persistence and adherence have received increased attention from health systems. Several methods and measures have been proposed using different data sources and definitions analysis; hence, understanding the variability in obtained estimates is crucial in interpreting the results.<sup>15–17</sup> Unlike much of the existing GLD persistence and adherence studies, which used secondary data known to be often poor in covariates, namely large claims databases,<sup>11,18,19</sup> we used primary data originally collected for this research purpose, thus taking increased control over available information.<sup>20–23</sup>

We estimated persistence and adherence levels using two methods (the collection of pharmacy records and their combination with self-reported information on medication use behavior), within 6 months of initiating treatment with a new GLD. Additionally, we examined reasons for switching or discontinuation and identified potential factors associated with nonpersistence and nonadherence among different GLD user profiles. This study was conducted in Portugal, which is one of the European countries with the highest consumption rate of novel GLD,<sup>24</sup> and where, unlike many other countries, pharmacy records are not centralized.

## Methods

### Study design, setting and population

An intensive monitoring design, defined as an observational, prospective cohort study of adult T2DM patients initiating one of the recently launched GLDs (inception cohort), recruited by community pharmacies, was conducted between November 15, 2014 and November 30, 2015. Invitation letters were sent to all pharmacies from the National Association of Pharmacies that satisfied the inclusion criteria (ie, required software, participation in at least one research study in the previous 4 years and had an average daily sale of  $\geq 1$  DPP-4/GLP-1 package) ( $n=1,979$ ; 67.8% of all Portuguese pharmacies). The pharmacists who agreed to participate were invited to attend a training session in which the study was explained.

The eligible study population consisted of first users of the new GLD (defined as users who did not take the inception-monitored drug within the 6 months prior to recruitment, as self-reported by the patients) that were that were reimbursed in Portugal at the time of enrollment: DPP-4 (sitagliptin, vildagliptin, saxagliptin and linagliptin) alone or in fixed-dose combination with metformin, GLP-1 (liraglutide and exenatide) or SLGT-2 (dapagliflozin). In this context, the inception drug corresponded to the GLD within the monitored therapeutic classes (DPP-4, GLP-1 or SLGT-2) which the patient was identified with at cohort entry. As previously proposed by Suissa et al,<sup>13</sup> our study cohort was divided into two subgroups on the basis of participants' T2DM treatment experience: subgroup 1 – incident new users (patients who used one of the monitored drugs for the first time [inception drug] and had no prior experience with DPP-4, GLP-1 or SLGT-2) and subgroup 2 – prevalent new users (patients who had previously used at least one GLD of the monitored antidiabetic drug classes [DPP-4, GLP-1 or SLGT-2], but not the inception-monitored drug). For the eligible subjects who did not wish to participate, information regarding age group and gender was collected through a refusal log form.

### Data collection

Data were collected through three different sources. At baseline, patients had a structured face-to-face interview with a pharmacist to collect the sociodemographic (birth date, gender, highest educational level completed, co-residence status and number of people living in the subject's household), anthropometrics (weight and height were measured at enrollment by pharmacy staff in order to calculate the body mass index [BMI] which was categorized as underweight: <18.50 kg/m<sup>2</sup>, normal: 18.50–24.99 kg/m<sup>2</sup>,

overweight: 25.0–29.9 kg/m<sup>2</sup> and obese:  $\geq 30$  kg/m<sup>2</sup>) and clinical characteristics (age at time of T2DM diagnosis, usual diabetes outpatient clinical care [eg, primary care, hospital-specialized diabetes care appointments, private practice], T2DM treatment [dose and prescribed posology of inception GLD and other current and past treatments], diabetes-related complications [eg, retinopathy, nephropathy, diabetic foot], comorbidities and concomitant therapy).

Over the study period, data regarding persistence and adherence (eg, refill dates and medication possession) were collected by an electronic data capture system developed for the electronic extraction of pharmacy records, from the pharmacy where the participant was recruited. Follow-up data also included structured telephone questionnaires conducted 2 weeks, 3 months and 6 months after the reported index date (starting date of the inception-monitored GLD), where information about the real pattern of use was asked. When the subjects were identified as potentially nonpersistent through the pharmacy records database (which was checked prior to each telephone questionnaire administration), the questions for confirmation of nonpersistence status (eg, acquisition of inception GLD from a different pharmacy, and if yes, the number of packages refilled and the corresponding refill dates) were asked. If the patients confirmed inception GLD withdrawal, reasons for drug discontinuation or switching (defined as withdrawal of monitored drug and initiation of another GLD) were collected (eg, adverse drug events conceivably considered to be associated with the use of inception drug, physician's decision, economic reasons and poor glycemic control, among other reasons). In the case of switching, information about the new GLD prescribed was recorded. To minimize the potential recall bias, a maximum 4-week period was allowed to obtain responses from the telephone questionnaires. However, the patient would still be invited to complete the following questionnaire if a response was not obtained within this period. Follow-up ceased whenever a patient confirmed switching or discontinuation of the inception GLD.

## Data analysis

Discrete variables were summarized by absolute and relative counts. Continuous variables were summarized using central tendency measures and dispersion (mean and standard deviation [SD]; median and interquartile range [IQR]). Chi-square test or Fisher's exact test was used to compare the characteristics between subgroups, as well as the distribution of refusals with the distribution of participants.

Overall persistence and adherence were calculated through two different methods: Method 1 – using pharmacy records exclusively and Method 2 – using pharmacy records and their combination with patients' self-reported data on persistence collected during the telephone follow-up questionnaires (inception GLD refilled in a different pharmacy). The proportion of pharmacy-loyal patients, defined as those who always refilled the inception GLD at the same pharmacy, was calculated.

Persistence was defined as the accumulation of time from initiation to withdrawal (switching or discontinuation) of the monitored treatment, based on the number of consecutive days of inception GLD dispensed to the subject through pharmacies within a grace period of 30 days (after the supply from the previous prescription was exhausted). A nonpersistent subject was defined as one who missed prescription cycles according to the definition of persistence and was considered nonpersistent for the remainder of the study period, regardless of whether the subject had refilled the inception GLD for the subsequent months. In Method 2, self-reported information on the number of packages refilled and the refill dates was used. Time to nonpersistence was calculated as the time in days between the index date and the last day the patient was still classified as persistent. The refill interval considered in the analysis was calculated using the baseline information of the real prescribed posology, when available. Whenever that information was missing, we used the information provided by the drug's summary of product characteristics. Patients were censored in the survival analysis if they were lost to follow-up (subjects who could not be reached by telephone or those who withdrew consent), died or were hospitalized.

Kaplan–Meier (KM) curves, 95% confidence interval (CI) and log-rank test were computed to compare the time to nonpersistence between subgroups. A sensitivity analysis was conducted for both methods using a grace period of 14 days. Cox models were used to explore potential factors that could contribute to time to nonpersistence. Univariate and multivariate hazard ratios (HRs) were computed and Wald's 95% CI presented. In the multivariate model-building strategy, KM curves for all covariates were plotted univariately, as the first step. Subsequently, a stepwise selection was implemented (significance levels of 0.20 and 0.25 for a variable to enter and to stay in the model, respectively). Model diagnoses comprised the computation of likelihood ratio, Wald and score Chi-square statistics and the variance inflation factor (VIF). In-depth residuals analysis, including plots with the scaled Schoenfeld residuals, was performed, the latter to assess proportional hazards assumption.

Adherence was computed for each participant based on the proportion of days covered (PDC). PDC was calculated as the number of days of medication supplied within the refill interval divided by the number of days of the observation period. By calculating the PDC, the proportion of days for which the inception GLD was available during the observation period was assessed. Overlapping refill days were moved forward to the first day that the patient would not have medication from the previous dispensing. In Method 2, self-reported information on the number of packages refilled and refill dates was used to estimate adherence. A patient was classified as adherent when PDC was  $\geq 80\%$ .<sup>15,25,26</sup> Patients were excluded from the analysis if they were lost to follow-up, died, were hospitalized or stopped the inception GLD after a physician's decision. Adherence level estimates were compared between subgroups. A sensitivity analysis was performed to take into consideration patients who stopped the inception GLD by physician decision, and new estimates of adherence levels were obtained including these patients. Logistic regression was used to explore the factors associated with nonadherence. Univariate and multivariate odds ratio (OR) and Wald's 95% CI were estimated. In the model-building strategy, all variables were evaluated univariately, as the first step. Subsequently, a stepwise selection was implemented (significance levels of 0.20 and 0.25 for a variable to enter and to stay in the model, respectively). Model diagnoses comprised the calculation of Hosmer and Lemeshow goodness-of-fit test and VIF. In-depth residuals analysis including plots with deviance residuals was performed.

All tests were two-sided and the statistical significance level adopted was 5%. Data analysis was performed using SAS® software.

## Ethics and data protection

This study was approved by the Portuguese Data Protection Authority (5339/2014) and by the Ethics Committee of the Institute of Public Health of the University of Porto (CE14021), and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. A written, signed informed consent form was obtained from all participants prior to initiation of any study procedures. This study was registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance E-register of studies (ENCEPP/SDPP/8433).

## Results

### Pharmacies and patients flow

A total of 670 (33.9%) pharmacies agreed to participate in the study, out of which 385 (19.5%) pharmacies recruited at

least one patient. Regional ( $p=0.0974$ ) and urban/suburban/rural setting ( $p=0.3716$ ) distribution of pharmacies with recruited patients was similar to the national distribution of pharmacies, but participating pharmacies had significantly more pharmacists, in their staff ( $p<0.0001$ ). A total of 1,569 patients were invited to participate, of whom 231 (14.7%) refused to participate and 10 were excluded because they did not satisfy the eligibility criteria. Compared to the study participants, refusals had similar ( $p>0.05$ ) age and gender distributions. A total of 1,328 eligible patients were considered: 61.3% were incident new users and 38.7% were prevalent new users. Patient flow and the respective response rate per questionnaire are available in the Supplementary material.

## Baseline population characteristics

Participants' demographic and clinical characteristics are depicted in Table 1. Slightly more than half of the cohort were male ( $n=673$ ; 50.7%) and the mean age was 64.1 ( $SD=11.4$ ) years. Approximately two-thirds (66.7%;  $n=865$ ) had only completed 9 years of education, and 84.3% were living in household with at least two people ( $n=1,115$ ). At cohort entry, the median BMI and T2DM duration were 30.1 ( $IQR=26.8-33.7$ )  $kg/m^2$  and 8.0 years ( $IQR=3.0-15.0$ ), respectively. About one-quarter ( $n=317$ ; 24.1%) of patients self-reported having at least one diabetes-related complication, with retinopathy ( $n=225$ ; 17.1%) being the most frequent. Prevalent new users reported a significantly higher T2DM duration, prevalence of diabetes-related complications and follow-up by a specialist diabetes physician at hospital, compared with incident new users.

In addition to T2DM, 88.7% ( $n=1,176$ ) self-reported having chronic illnesses, with hypertension (71.8%;  $n=952$ ) and dyslipidemia (55.9%;  $n=741$ ) being the most frequent. No statistically significant differences were found between subgroups regarding the most common chronic illnesses and the number of different medicines taken in addition to T2DM treatment.

Results showed that 9.7% ( $n=128$ ) of patients were treatment-naïve for T2DM, 66.6% ( $n=884$ ) were receiving other antidiabetic therapy than the inception GLD and 18.7% ( $n=248$ ) were currently taking insulin. Overall, prevalent new users were significantly more likely to receive another antidiabetic therapy, including insulin, compared with incident new users. A total of 905 (68.2%) patients reported having changed (including switching, discontinuation or intensification with a fixed-dose combination) T2DM medication prior to recruitment.



**Table 1** Participants' baseline demographic, anthropometric and self-reported clinical characteristics

Characteristic	Incident new users n (%)	Prevalent new users n (%)	p-value
Gender (male)	420 (51.60)	253 (49.22)	0.3991
Age (years)			0.2548
< 55	159 (19.83)	105 (20.55)	
55–64	225 (28.05)	154 (30.14)	
65–74	259 (32.29)	173 (33.86)	
≥ 75	159 (19.83)	79 (15.46)	
NR=15			
Diabetes duration (years)			<0.0001
< 1	116 (15.87)	12 (2.43)	
1–5	224 (30.64)	116 (23.48)	
6–9	102 (13.95)	66 (13.36)	
≥ 10	289 (39.53)	300 (60.73)	
NR=103			
BMI (kg/m <sup>2</sup> )			0.0215
< 25.00	104 (13.07)	63 (12.48)	
25.00–29.99	314 (39.45)	164 (32.48)	
≥ 30.00	378 (47.49)	278 (55.05)	
NR=27			
Chronic diseases			0.1627
0	86 (10.58)	64 (12.48)	
1–2	547 (67.28)	319 (62.18)	
≥ 3	180 (22.14)	130 (25.34)	
Number of different medicines			0.2645
0	46 (5.82)	23 (4.53)	
1–2	218 (27.59)	124 (24.41)	
3–4	250 (31.65)	160 (31.50)	
≥ 5	276 (34.94)	201 (39.57)	
Diabetes-related complications			
Yes	166 (20.54)	151 (29.72)	0.0001
Retinopathy	112 (13.86)	113 (22.24)	<0.0001
Nephropathy	70 (8.66)	50 (9.84)	0.4694
NR=12			
Diabetic foot	42 (5.20)	41 (8.07)	0.0369
Current use of insulin	111 (13.64)	137 (26.65)	<0.0001

**Abbreviations:** BMI, body mass index; NR, nonrespondents.

## Persistence and potential factors associated with time to nonpersistence

KM analysis (Figure 1) showed that overall persistence to the inception GLD, which was estimated exclusively with electronic data from pharmacy records (Method 1), was 38.70% (95% CI: 35.98–41.40), whereas including patient self-reported information on persistence (Method 2) was 65.61% (95% CI: 62.91–68.16). In both estimates, persistence rates were similar between cohort subgroups ( $p>0.05$ ). Sensitivity analysis using a 14-day grace period revealed lower levels of persistence estimates; however, no differences were observed between subgroups irrespective of the method used. Differences were found in the level of pharmacy loyalty, whereas

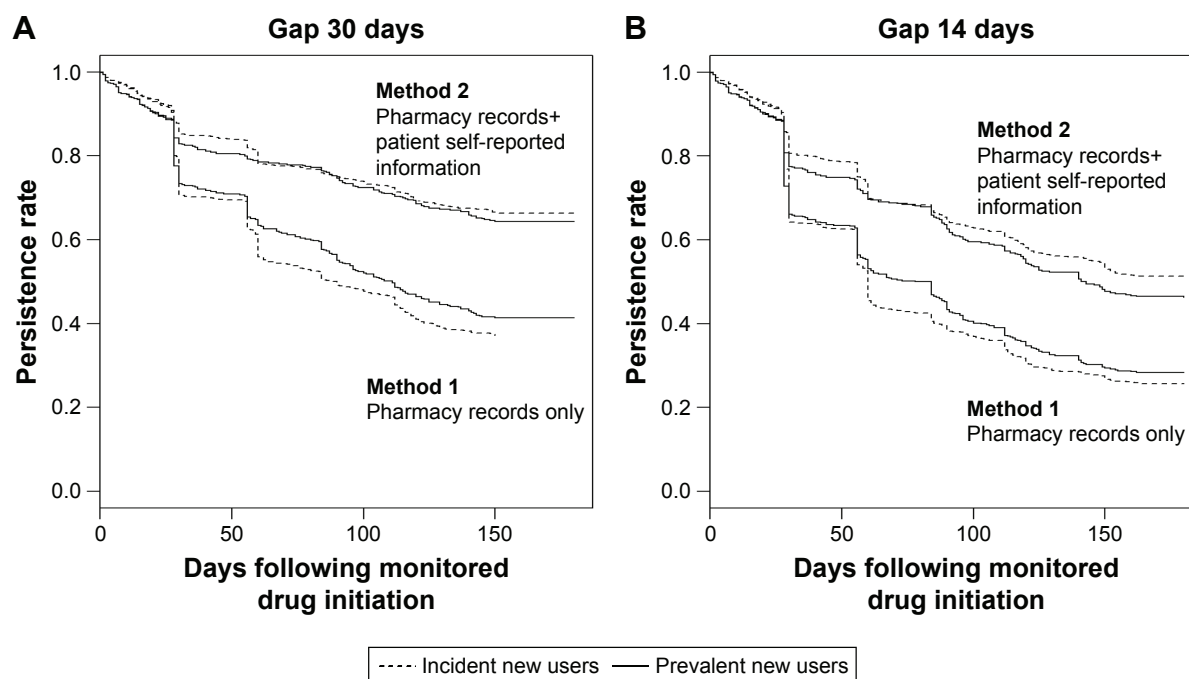
significantly ( $p=0.0035$ ) higher proportion of loyal patients was found within the prevalent new users subgroup (67.5% of prevalent new users and 32.6% of incident new users were considered loyal patients).

In the multivariate Cox analysis, differences were found between the two methods regarding the factors associated with the risk of persistence failure (Table 2). When considering pharmacy records exclusively, patients living alone (HR=1.302; 95% CI: 1.058–1.602) and living in urban/suburban setting (HR=1.580; 95% CI: 1.134–2.203) had a significantly higher risk of persistence failure. Conversely, subgroup with GLP-1 inception-monitored treatment patients had a significantly lower risk of persistence failure than patients using an inception oral GLD. Analysis combining both pharmacy records and self-reported information showed that increasing age was the only factor significantly associated with the risk of persistence failure (1.6% increase in risk of persistence failure for every 1-year increase in age).

Over the study period, a total of 327 (24.8%) patients stopped using the inception GLD: 186 (22.9%) incident and 141 (27.4%) prevalent new users. Withdrawal rates were similar ( $p=0.0591$ ) between subgroups. The most reported reasons given for inception GLD withdrawal were physician decision (61.5%), followed by adverse drug event (ADE) (53.5%), poor glycemic control (23.2%) and patient decision (7.3%). One ADE met the criteria of seriousness (hospitalization) and was reported to the national spontaneous reporting system, where it was handled according to the regulations regarding serious reports. Treatment switching recommended by physician was recorded for 137 (41.8%) cases who stopped inception GLD (93 DPP-4 alone or in fixed-dose combination with metformin, 31 dapagliflozin, eight exenatide and five liraglutide). Among patients administered DPP-4 alone or in fixed-dose combination with metformin, it was noted that 50.5% ( $n=47$ ) switched within the same drug class, whereas among dapagliflozin inception users, 29.0% ( $n=9$ ) and 25.8% ( $n=8$ ) switched to fixed-dose combinations of DPP-4 with metformin and insulin, respectively.

## Adherence and potential factors associated with nonadherence

At the end of the study, when adherence estimates considered patient self-reported information (Method 2), 73.6% (95% CI: 70.9–76.3) of participants were adherent (PDC  $\geq 80\%$ ). No significant differences were observed between subgroups ( $p=0.1614$ ). However, when adherence rates were estimated exclusively considering electronic data from pharmacy records (Method 1), a significant higher proportion



		Total	Incident new users	Prevalent new users	p-value*
<b>Method 1 – pharmacy records only</b>	<b>Gap 30 days</b>	38.70% [35.98–41.40]	36.96% [33.52–40.41]	41.37% [36.98–45.69]	0.1523
	<b>Gap 14 days</b>	25.74% [22.66–28.92]	25.74% [22.66–28.92]	28.55% [24.59–32.61]	0.3404
<b>Method 2 – pharmacy records+patient self-reported information</b>	<b>Gap 30 days</b>	65.61% [62.91–68.16]	66.42% [62.96–69.64]	64.36% [59.97–68.40]	0.3919
	<b>Gap 14 days</b>	49.27% [46.47–52.00]	51.22% [47.61–54.70]	46.25% [41.79–50.59]	0.0775

**Figure 1** Persistence and KM curves to inception-monitored glucose-lowering drug at 6 months of follow-up.

**Notes:** \*p-value of the log rank test for the comparison between groups. (A) Gap 30 days. (B) Gap 14 days.

of nonadherents was found among incident new users ( $p=0.0112$ ; Table 3). Adherence sensitivity analysis (patients who stopped the inception drug due to physician decision were included) revealed lower levels of adherence estimates (Method 1: 35.9% [95% CI: 33.8–39.2]; Method 2: 63.9% [95% CI: 63.5–64.6]), yet no differences were observed between subgroups irrespective of the method used. In the multivariate regression analysis, although differences were found between the two methods, factors associated with nonadherence (Table 4) were overall similar with those found in the risk of persistence failure analysis. In both methods, living alone and using an oral inception GLD were factors associated with nonadherence.

## Discussion

Contrasting with most published studies that use claims databases to measure persistence and adherence, we used an

intensive monitoring design that collected information from the first day of drug use and explored the differences between two methods, namely pharmacy records and their combination with patient self-reported data, each yielding different estimates. The use of patient self-reports also allowed us to explore the important features of medication-taking behavior, namely reasons for treatment switching or discontinuation, which are not often captured in administrative databases. As with other chronic diseases, low persistence rates for new GLD were found: 38.7% considering information exclusively from pharmacy records and 65.6% in combination with self-reported information. Almost two-thirds of patients were identified as nonadherent when considering pharmacy records exclusively, which decreased to almost one-quarter of patients, when including patient self-reported data.

Overall, considering the persistence and adherence estimates obtained in this study, together with sensitivity analysis

**Table 2** Factors associated with time to nonpersistence to the inception monitored glucose lowering drug (Method 1: pharmacy records exclusively and Method 2: combination of pharmacy records and self-reported information)

Variable	Method 1: pharmacy records exclusively		Method 2: pharmacy records+patient self-reported information	
	Univariate, HR (95% CI)	Multivariate,* HR (95% CI)	Univariate, HR (95% CI)	Multivariate,** HR (95% CI)
Exposure experience subgroup				
Incident new users	Reference		Reference	
Prevalent new users	0.899 (0.777–1.041)		1.082 (0.894–1.310)	
Gender				
Female	Reference		Reference	
Male	0.992 (0.861–1.143)		1.052 (0.872–1.270)	
Age (years)	0.997 (0.991–1.004)	0.995 (0.988–1.002)	1.013 (1.005–1.022)	1.016 (1.007–1.025)
BMI (kg/m <sup>2</sup> )	0.996 (0.982–1.010)		0.990 (0.972–1.009)	
Educational level				
No degree and basic education ( $\leq 9$ years)	Reference		Reference	
Secondary and university degree ( $> 9$ years)	1.032 (0.868–1.228)		0.955 (0.755–1.208)	
Living alone				
No	Reference	Reference	Reference	
Yes	1.256 (1.042–1.514)	1.302 (1.058–1.602)	1.269 (0.994–1.619)	
Setting of residence				
Rural	Reference	Reference	Reference	
Urban/suburban	1.490 (1.112–1.995)	1.580 (1.134–2.203)	1.162 (0.807–1.674)	
Inception-monitored drug treatment group				
GLP-I	Reference	Reference	Reference	
Others	1.393 (1.096–1.771)	1.389 (1.074–1.797)	1.274 (0.927–1.752)	
Chronic diseases				
No	Reference	Reference	Reference	
Yes	0.773 (0.628–0.953)	0.788 (0.620–1.001)	0.955 (0.715–1.276)	
Diabetes duration (years)	0.996 (0.987–1.005)		1.004 (0.992–1.015)	
Diabetes-related complications				
No	Reference		Reference	
Yes	0.982 (0.832–1.160)		0.963 (0.771–1.202)	
Current use of insulin				
No	Reference		Reference	Reference
Yes	0.781 (0.645–0.945)		0.851 (0.663–1.093)	0.841 (0.646–1.095)

Notes: \*Wald test:  $p=0.0002$ ; VIF $\leq 1.12$ . \*\*Wald test:  $p=0.0014$ ; VIF $\leq 1.01$ .

Abbreviations: BMI, body mass index; CI, confidence interval; GLP-I, glucagon-like peptide-I; HR, hazard ratio; VIF, variance inflation factor.

**Table 3** Adherence to inception-monitored glucose-lowering drug

			Total	Incident new users	Prevalent new users	p-value
Method 1 – pharmacy records exclusively	Adherent (PDC $\geq 80\%$ )	% [95% CI]	41.29% [38.27–44.31]	38.23% [34.45–42.02]	46.27% [41.32–51.23]	0.0112
	PDC classes	[0–20]	11.64%	11.22%	12.34%	0.0570
		[20–40]	12.04%	13.43%	9.77%	
		[40–60]	12.62%	12.95%	12.08%	
		[60–80]	22.41%	24.17%	19.54%	
		[80–100]	41.29%	38.23%	46.27%	
Method 2 – pharmacy records+patient self-reported information	Adherent (PDC $\geq 80\%$ )	% [95% CI]	73.57% [70.87–76.26]	72.06% [68.57–75.54]	76.02% [71.79–80.25]	0.1614
	PDC classes	[0–20]	5.25%	4.71%	6.12%	0.2317
		[20–40]	4.08%	4.08%	4.08%	
		[40–60]	3.30%	3.61%	2.81%	
		[60–80]	13.80%	15.54%	10.97%	
		[80–100]	73.57%	72.06%	76.02%	

Abbreviations: CI, confidence interval; PDC, proportion of days covered.

**Table 4** Factors associated with nonadherence to inception-monitored glucose-lowering drug (Method 1: pharmacy records exclusively and Method 2: combination of pharmacy records and self-reported information)

Variable	Method 1: pharmacy records exclusively		Method 2: pharmacy records+patient self-reported information	
	Univariate, OR (95% CI)	Multivariate,* OR (95% CI)	Univariate, OR (95% CI)	Multivariate,** OR (95% CI)
Exposure experience subgroup				
Incident new users	Reference	Reference	Reference	
Prevalent new users	0.719 (0.556–0.928)	0.802 (0.604–1.066)	0.813 (0.609–1.086)	
Gender				
Female	Reference		Reference	
Male	1.031 (0.804–1.323)		1.168 (0.885–1.542)	
Age (years)	0.981 (0.970–0.993)	0.968 (0.955–0.981)	1.013 (1.000–1.026)	
BMI (kg/m <sup>2</sup> )	1.004 (0.980–1.028)		0.997 (0.970–1.025)	
Educational level				
No degree and basic education ( $\leq 9$ years)	Reference		Reference	
Secondary and university degree ( $> 9$ years)	1.013 (0.747–1.374)		0.897 (0.635–1.268)	
Living alone				
No	Reference	Reference	Reference	Reference
Yes	1.677 (1.166–2.412)	2.020 (1.345–3.033)	1.600 (1.114–2.297)	1.645 (1.117–2.424)
Setting of residence				
Rural	Reference		Reference	
Urban/suburban	1.360 (0.871–2.122)		0.753 (0.466–1.216)	
Inception-monitored drug treatment group				
GLP-I	Reference	Reference	Reference	Reference
Others	1.845 (1.252–2.719)	1.697 (1.082–2.661)	1.980 (1.186–3.305)	1.859 (1.093–3.161)
Chronic diseases				
No	Reference		Reference	
Yes	0.664 (0.439–1.005)		1.061 (0.679–1.659)	
Diabetes duration (years)	0.986 (0.971–1.001)		0.995 (0.978–1.012)	
Diabetes-related complications				
No	Reference	Reference	Reference	
Yes	1.030 (0.771–1.376)	1.356 (0.983–1.870)	0.969 (0.701–1.341)	
Current use of insulin				
No	Reference	Reference	Reference	
Yes	0.576 (0.419–0.792)	0.713 (0.494–1.029)	0.716 (0.489–1.047)	

**Notes:** \*Hosmer and Lemeshow goodness-of-fit test,  $p=0.9914$ ; VIF $\leq 1.196$ . \*\*Hosmer and Lemeshow goodness-of-fit test,  $p=0.8785$ ; VIF $\leq 1.004$ .

**Abbreviations:** BMI, body mass index; CI, confidence interval; GLP-I, glucagon-like peptide-I; OR, odds ratio; VIF, variance inflation factor.

results, we believe that the “true” persistence/adherence rates reported for the new GLD might possibly be between the lower limit of estimates retrieved from pharmacy records exclusively and the upper limit of estimates retrieved from the combination of pharmacy records and patient self-reported information. From this perspective, it is assumed that, on the one hand, patient self-reported information on medication-taking behavior could overestimate the results. On the other hand, over a 6-month period, given that, in Portugal, patients can go to more than one pharmacy and there is no single database that records all prescription refills from different pharmacies at an individual patient level, estimates retrieved exclusively from pharmacy records could be underestimated. More than one-third of patients who started the monitored GLD self-declared at least one refill in a different pharmacy where they were recruited.

Regardless of these assumptions, at 6 months from therapy initiation, persistence and adherence rates observed, although very low, were in line with, or to some extent lower than, the existent literature. A recent systematic review of observational studies revealed a persistence mean rate to T2DM medication of 56.2% (95% CI: 46.1–66.3).<sup>27</sup> However, it should be noted that the included studies in the review had a longer follow-up period than our study, and pharmacy or prescription records data used in the studies were centralized. Concerning adherence, in another recent systematic review of 27 studies published between 2003 and 2014,<sup>28</sup> it was found that the levels ranged from 38.5% to 93.1%, based on surveys on specific instruments or on claims databases. When considering only studies that used the medication possession ratio methodology (in general, for a follow-up duration of 12 months), the prevalence of adherence ranged between 46.0% and 89.8%.



With regard to factors that could contribute to nonpersistence and nonadherence, irrespective of the differences found between each method, they were broadly in line with what has been described in previous studies elsewhere. When combining pharmacy records with patient self-reported information, it was observed that increasing age was the only factor associated with persistence failure risk.<sup>11</sup> Yet, when analyzing pharmacy records only, patients living alone,<sup>29</sup> living in a suburban/urban setting<sup>30,31</sup> and using an oral inception GLD had a higher risk of persistence failure. The later disputes findings from previous studies,<sup>32,33</sup> although comparison studies using the new GLD for persistence and adherence, are scarce due to its recent availability in the market.

The overall clinical demographics of our study participants were generally similar to a large Portuguese T2DM patient cohort analyzed in 2013, in a primary care setting. From the data available, we found that our study population had comparable gender distribution, mean age and similar distribution regarding the most frequent comorbidities.<sup>34</sup> The prevalent new users subgroup, representing almost two-fifths of all participants, had a significant higher T2DM duration, a higher prevalence of diabetes complications, use of insulin and use of specialist care visits, compared with incident new users. This was not surprising, as T2DM is a progressive condition, and therefore, prevalent new users are more likely to be complex patients.<sup>35,36</sup>

Given the differences observed in T2DM characteristics between incident and prevalent new user subgroups, we would expect dissimilar persistence and adherence results. However, rates estimated through the two methods were comparable overall. Only adherence estimates considering pharmacy records exclusively showed that prevalent new users (46.3%; 95% CI: 41.3–51.2) were significantly ( $p=0.0112$ ) more adherent than incident new users (38.23%; 95% CI: 34.5–42.0). This could be explained partially by the fact that a significantly higher proportion (almost double: 67.5% versus 32.6%) of pharmacy-loyal patients was found among the prevalent new user subgroup. Our findings are consistent with the literature. In a recent study conducted in the Canadian province of Quebec, it was observed that pharmacy-loyal patients were more likely to be adherent (PDC $\geq$ 80%) with T2DM medication (OR=1.22; 95% CI: 1.19–1.26).<sup>37</sup> The positive association between pharmacy loyalty and persistence or adherence has also been demonstrated with other therapeutic groups, such as that including antipsychotic treatment<sup>38</sup> and cardiovascular medication.<sup>39</sup> Similarly, a study from the USA that included older adults with Medicare Part D demonstrated that filling prescriptions

at multiple pharmacies, which was a prevalent phenomenon (38.1% of beneficiaries), was associated with lower medication adherence across a range of chronic medications.<sup>40</sup>

Over the study period, almost one-quarter of participants stopped using the inception GLD. These results are slightly lower than some reports from other studies, where a higher stopping rate of 31.4% was found.<sup>27</sup> Our study adds information on commonly reported reasons for discontinuation from the patients' perspective, which are not frequently captured in database studies. Physician decision, followed by ADE and reported poor glycemic control, was the most frequent reason stated for interrupting the inception GLD. It should be emphasized that among patients who stopped the inception GLD due to physician decision, only 67% switched to another antidiabetic drug, commonly the drug they were taking prior to recruitment. In these cases, conflicting decisions between doctors (primary care versus specialists) were frequently the reason, as some patients in our study declared. Addressing early risk of treatment failure for the new GLD should be put in place, and improvements in patient–health care provider communication as well as between health care providers are required. Furthermore, proactive management of ADE, including those which are expected and transient, but which may lead to unnecessarily early therapy discontinuation, should be a priority. In particular, clinicians should closely monitor patients with previous discontinuations related to ADE, because it is assumed that these patients might have an increased susceptibility to ADE compared to others.<sup>41</sup>

The results of the present study should be viewed in light of the following limitations. First, although it has been demonstrated that patients' self-reported GLD utilization patterns are reliable,<sup>42</sup> the use of self-reported information to ascertain medication-taking behavior could be biased by a reluctance to admit inappropriate behavior (social desirability bias); hence, a potential misclassification bias of patients being classified as persistent should be considered. Notwithstanding, inaccuracies in self-reported information are believed to be minimized, since independent research interviewers and not patients' health care providers were responsible for conducting the follow-up interviews.<sup>43,44</sup> Even when including patient self-reported information, the rates found were still very low; that is to say, the majority of patients did not show reluctance to declare they had stopped taking the medication. Second, persistence estimates were calculated on an individual drug level, and the impact of switching to other antidiabetic medication during the study period was not assessed.

Despite the mentioned limitations, this study has several strengths. Data presented were collected through a

pharmacy-based intensive monitoring model, which is a noninterventive inception cohort study mirroring the real use of new GLD, prescribed by both general practitioners and specialists, with no limiting inclusion (with the exception of a T2DM treatment indication) or exclusion criteria compared with clinical trials. Further, although self-selection of pharmacies could have occurred since participation was not mandatory, it seems reasonable to assume that the study sample is representative of the overall country population of T2DM patients taking new GLD, given the similarities found with the reference population and since pharmacies included were representative of the Portuguese pharmacies. Also, refusals had a similar age and gender distribution as compared to the study participants, and several strategies to minimize patients' nonsystematic selection were put in place during the enrollment period (namely pop-up reminders at the pharmacy software whenever a new GLD was dispensed). Finally, this study provided a good source for persistence/adherence investigation because, on the one hand, data were collected directly from pharmacy dispensing, rather than physicians' prescriptions that may never be dispensed. This is of relevance, as primary nonadherence is a frequent phenomenon: it was identified in almost a quarter of patients in both the USA<sup>45</sup> and Portugal.<sup>46</sup> On the other hand, as previously highlighted, patient self-reported usage data may well collect and explore the important features of medication use and behavior, namely reasons for treatment discontinuation, which are not captured in claims databases.<sup>47</sup>

## Conclusion

Regardless of the method used, in case of pharmacy records or their combination with patient self-reported information, low levels of new GLD persistence and adherence were found. The combination of pharmacy records with self-reported information yielded higher estimates, even though they were in line with existent literature. Adherence estimates considering pharmacy records exclusively showed that prevalent new users, who were more complex in terms of T2DM disease but more likely to be pharmacy-loyal patients, were significantly more adherent than incident new users. Strategies to improve adherence and persistence should be implemented right from the commencement of therapy, and continuous attention should be given to nonserious ADE, since they represent half of the reported reasons for treatment switching or discontinuation.

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## Author contributions

CT was responsible for the implementation of the study, data analysis and drafting the manuscript. APM and HL had the original idea for the manuscript; they conducted and supervised the study and helped drafting the manuscript. JG and PL participated in data collection, analysis and revision of the manuscript. JFR participated in the collection of additional literature, contributed to the writing of the manuscript and revised it critically for important intellectual content. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

## Disclosure

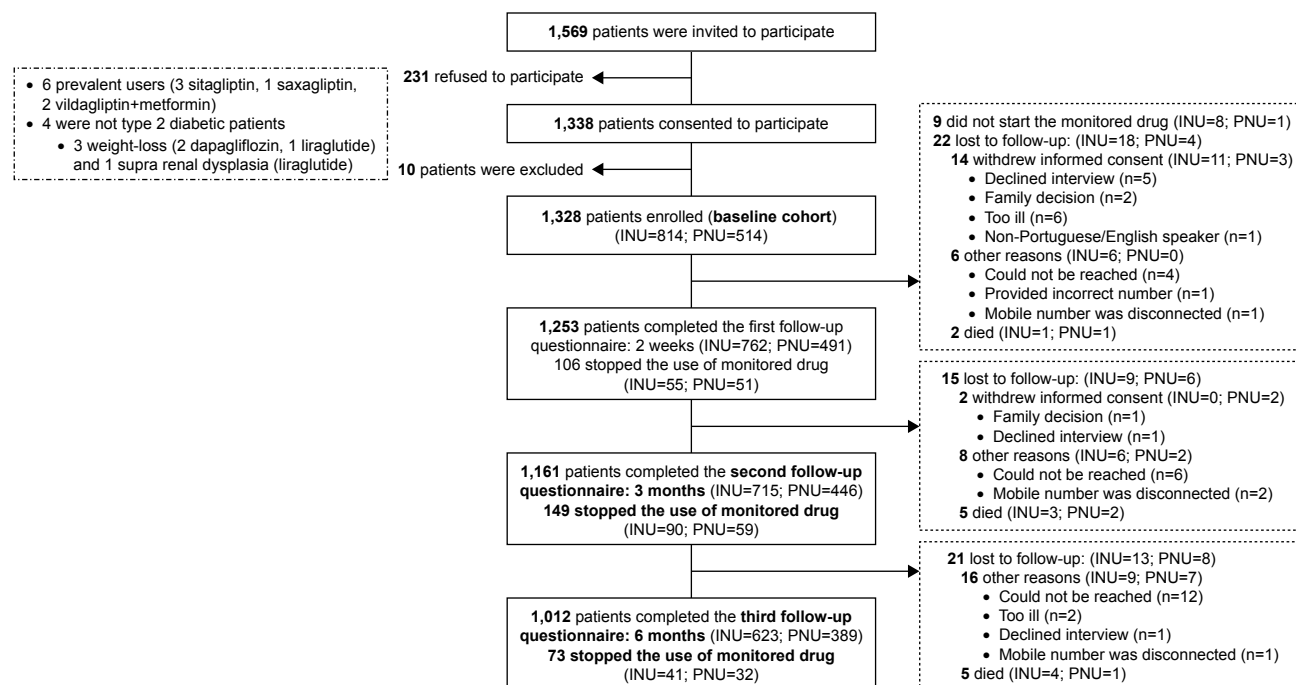
CT was working at CEFAR/National Association of Pharmacies (ANF) when the study was performed and is currently employed by the Portuguese Pharmaceutical Society and has no conflict of interest to declare. JFR has received honoraria for consultancy or giving lectures from Merck Sharp & Dohme, Lilly and Novo Nordisk over the last year. All costs associated with the development and implementation of this study were fully supported by the Portuguese ANF. ANF had no role in study protocol, data analysis or interpretation of this study. The authors report no other conflicts of interest in this work.

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# Supplementary material



**Figure S1** Study flow diagram.

**Notes:** Patients were allowed to fill in a questionnaire even if they had not completed the previous one. Among the eligible patients (1,328), 63.86% (n=848) started one DPP-4 alone or in fixed-dose combination with metformin, 11.07% (n=147) one GLP-I and 23.19% (n=308) dapagliflozin. For 25 participants, two different inception GLDs were prescribed simultaneously (17 out of 25 started dapagliflozin with DPP-4 [alone or in fixed-dose combination with metformin]); these patients could stop the inception GLD in different moments. A total of 328 inception-monitored GLDs were stopped (24.4% [n=207] DPP-4 alone or in fixed-dose combination with metformin, 28.9% [n=89] dapagliflozin and 21.8% [n=32] GLP-I).

**Abbreviations:** DPP-4, dipeptidyl peptidase-4 inhibitor; GLD, glucose-lowering drug; GLP-I, glucagon-like peptide-I; INU, incident new user; PNU, prevalent new user.

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