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Research: Treatment

Intensive monitoring of adverse drug events associated with the use of new glucose-lowering drugs: results from an inception cohort study in Portugal

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Abstract

Aims To determine the frequency and the time-course profile of adverse drug events associated with new glucose-lowering drugs in daily practice and to explore factors potentially associated to these events.

Methods An inception cohort study was implemented. Adults with type 2 diabetes mellitus initiating a dipeptidyl peptidase-4 inhibitor, a glucagon-like peptide-1 receptor agonist or a sodium-glucose co-transporter-2 inhibitor were eligible for inclusion. Data were collected through baseline and follow-up telephone questionnaires, administered at 2 weeks, 3 months and 6 months. Kaplan–Meier curves and log-rank were computed to compare the time to adverse drug event onset. Cox models were used to explore potential factors associated with adverse drug events.

Results A total of 1328 participants were recruited to the study. In all, 1118 adverse drug events were reported (of which 36% were not listed in the summary of product characteristics) by 41% of participants. The median latency time of adverse drug events reported in ≥1% of participants ranged from 0 to 2 days. Glucagon-like peptide-1 receptor agonist and sodium-glucose co-transporter-2 inhibitor subgroups were associated with an increased likelihood of adverse drug event reporting when compared with the dipeptidyl peptidase-4 inhibitor subgroup. A total of 328 glucose-lowering drugs were withdrawn, more than half as a result of an adverse drug event.

Conclusions More than two-fifths of participants reported an adverse drug event; dipeptidyl peptidase-4 inhibitors led to the highest proportion of unlabelled adverse drug events. Adverse drug event latency time data show that counselling and adverse drug event management should be proactively addressed from treatment initiation. There should be greater focus on prevalent new users of glucose-lowering drugs, who were more complex participants in this study in terms of type 2 diabetes disease, as they were more likely to report an adverse drug event than the incident new users.

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Introduction

The number of people with type 2 diabetes is growing globally and the disease has become a major public health concern. Over the last 15 years, the number of people living with diabetes has more than doubled, from 194 million in 2003 to 451 million in 2017 [1]. In this period, novel glucose-lowering drugs have been marketed, including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors having all demonstrated sufficient efficacy through randomized clinical trials [2].

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In clinical practice, despite the broad range of treatment options and the existence of comprehensive clinical guidelines [2], the recommended glycaemic targets are achieved by less than half of people with type 2 diabetes. This has been attributed to, among other reasons, poor levels of adherence to treatment and tolerability concerns [3,4]. In order to target use of these novel agents in an effective and safe manner, real-world evidence is needed [5], especially in the non-responders to metformin for whom care and management of type 2 diabetes has become increasingly complex [2].

Very little attention has been given to the assessment of non-serious symptomatic adverse drug events (ADEs), although it has been shown that the occurrence of these events, including hypoglycaemic episodes, compromises

What's new?

- Despite their relevance to clinical practice, there has been a paucity of data on the frequency and time-course profile of adverse drug events related to the use of new glucose-lowering drugs.
- More than two-fifths of participants in this study reported at least one adverse event, with the overall median latency time being < 2 days.
- A total of 36% adverse events were not listed in the summary of product characteristics; gliptins were associated with the highest proportion of these events.
- Continuous attention should be given to adverse drug events, since such events led to half of the glucose-lowering drug withdrawals that occurred in this study.

adherence to treatment and represents limiting factors in the management of type 2 diabetes [6–8]. To improve medication use behaviour and address early discontinuation rates, information on the frequency, time course and outcomes of ADEs is needed as this could be used proactively to provide tailored advice to people who initiate these new drugs [8,9].

With this background, and given that Portugal is one of the European countries with the highest uptake of recently launched glucose-lowering drugs [10], we implemented an intensive monitoring study focused on gathering longitudinal information since the first day of drug use. An observational inception cohort study of adults with type 2 diabetes initiating one of the new glucose-lowering drugs was conducted between November 2015 and November 2016. The medication-taking behaviour (persistence and adherence levels) [11] and health-related quality of life [12] associated with use of these drugs have been described in previous papers. The present paper focuses on the real-world safety data reported in an inception cohort study, in which we determined the frequency and the time-course profile of ADEs and explored the factors potentially associated with their occurrence.

Methods

The data presented in this paper were retrieved from a nationwide observational inception cohort study of people with type 2 diabetes, recruited by Portuguese community pharmacies, initiating one of the novel glucose-lowering drugs that were reimbursed at the time of enrolment: DPP-4 inhibitors (linagliptin, saxagliptin, sitagliptin and vildagliptin) alone or in fixed-dose combination with metformin, GLP-1 receptor agonists (exenatide and liraglutide) or an SGLT2 inhibitor (dapagliflozin) [11,12]. As described by Suissa *et al.* [13], the study cohort was divided into two subgroups on the basis of participants' treatment experience: incident new users (participants who were using one of the monitored glucose-lowering drugs for the first time and had no current or prior experience with DPP-4 inhibitors, GLP-1 receptor agonists or SGLT2 inhibitors) and prevalent new users (participants who had previously used at least one glucose-lowering drug of the monitored drug classes, but not the inception drug).

Pharmacies' and participants' study recruitment procedures have been described in depth elsewhere [11,12]. In brief, at cohort entry, a trained pharmacist administered a face-to-face structured questionnaire to participants, comprising sociodemographic, anthropometric and self-reported clinical characteristics. Follow-up data covered up to three structured telephone questionnaires, conducted 2 weeks, 3 months and 6 months after the reported index date of the monitored glucose-lowering drugs, where possible ADEs, namely, those considered to be conceivably associated with the monitored glucose-lowering drugs by participants, real pattern of use and hypoglycaemic episodes were collected. If a participant reported an ADE, date of onset (and if applicable, end date), description, management (treatment and action taken: withdrawal/suspension/dose reduction/continuation), outcome (recovered/recovering/not recovered/unknown) and seriousness according to the International Conference on Harmonization of Good Clinical Practice guidelines [14] were collected. ADEs were first recorded according to how the participant described the event (verbatim) and then reviewed and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 terminology, by pharmacovigilance assessors. All ADEs were grouped by MedDRA system organ classification and then by preferred term. Hypoglycaemic episodes were categorized as described elsewhere [15]: very severe (requiring assistance from medical personnel); severe (requiring assistance from non-medical personnel to manage symptoms, e.g. with food/drink); moderate (some interruption of activities and no assistance needed to manage symptoms); and mild (little/no interruption of activities and no assistance needed to manage symptoms). Follow-up ceased whenever the participant confirmed that the monitored glucose-lowering drug was withdrawn. In those cases, the motives for withdrawing the glucose-lowering drug were collected.

Statistical analysis

Data were reported as absolute and relative counts and measures of dispersion and central tendency. The age and gender distribution of participants and refusals were compared using Wilcoxon or Kruskal–Wallis tests for continuous variables and chi-squared or Fisher's tests for categorical variables. The chi-squared goodness-of-fit test was used to compare the regional distribution, rural/suburban/urban setting and staff of those pharmacies that recruited participants with the national distribution of pharmacies.

Incidence proportions were calculated for all ADEs and illustrated according to three different time-to-onset interval periods: 0–14 days; 15–90 days; and 91–180 days. Although a participant could report the same ADE through different questionnaires, one specific ADE was counted only once when calculating incidences. The self-reported ADEs were divided into 'labelled' if the event was listed in the summary of product characteristics with the exact MedDRA® term, 'related' and 'not labelled'. The outcome and the action taken with the inception glucose-lowering drugs after the occurrence of each ADE was determined. Whenever a participant reported different actions across follow-up questionnaires, only the action with the highest relevance was counted (with 'drug withdrawal' considered the most relevant and 'continuing drug use' the least relevant). The same rationale was used for the ADE outcome, with 'recovered' considered the most relevant and 'unknown' as the least relevant.

The ADE latency time adverse drug events reported in >= 1% of all participants was calculated using the monitored glucose-lowering drugs index date and the ADE start date. In cases where participants reported more than one ADE falling into the same preferred term, the latency of the first ADE was used. Chi-squared/Fisher's test for categorical variables and Wilcoxon/Kruskal–Wallis tests for continuous variables were used to compare ADE proportions and the latency time of the ADE among the cohort subgroups. Kaplan–Meier curves and log-rank tests were computed to compare the time to ADE onset among cohort subgroups. Participants who were lost to follow-up (defined as those who withdrew consent or could not be reached by telephone), who were hospitalized or who withdrawn for a reason other than an ADE, were censored in the survival analysis.

Potential factors associated with ADEs were explored using Cox models. Univariable and multivariable hazard ratios (HRs) were computed and Wald's 95% CIs presented. In the multivariable model building strategy, Kaplan–Meier curves for all covariates considered relevant to study the potential association or confounding (age, gender BMI, treatment cohort subgroup, type 2 diabetes duration and related conditions, chronic diseases, comedication, current insulin use and hypoglycaemic episodes) were plotted univariably. Afterwards, a stepwise selection (significance level of 0.20 for a variable to enter and 0.25 to stay) was implemented. Model diagnoses comprised the computation of likelihood ratios, Wald chi-squared statistics, and the variance inflation factor. Residuals analysis included plots with the scaled Schoenfeld residuals. The statistical significance level adopted was 5%. All statistical analysis was conducted using SAS® Enterprise Guide v4.2.

Ethics and data protection

This study was approved by the Portuguese Data Protection Authority and by the Ethics Committee of the Institute of Public Health of the University of Porto, complying with the national ethical requirements and legal procedures. A written signed consent form was obtained from all participants. This study was registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance E-register (ENCEPP/SDPP/8433).

Results

Participant characteristics and study flow

A total of 385 of 1979 invited pharmacies (19%) recruited at least one participant. The proportion of pharmacies in urban/suburban/rural locations (P=0.372) and the regional (P=0.097) distribution of those pharmacies that participated in this study was similar to the national distribution of pharmacies; however, the participating pharmacies included more pharmacists among their staff (P<0.001). Additional information concerning pharmacy participation is available in Table S1. Of the 1579 people invited to participate, 231 (15%) declined. Those who declined had a similar gender and age distribution (P>0.05) when compared to those who participated. In all, 58 and 327 participants were lost to follow-up and withdrawn the glucose-lowering drugs, respectively. The most frequently reported motives for discontinuing the glucose-lowering drug were physician decision (61%), followed by ADEs (54%) and poor glycaemic control (23%). A study flow chart is provided in Fig. S1.

Table 1 presents the participants' baseline characteristics. The median (interquartile range) age and type 2 diabetes duration were 65 (57–72) and 8 (3–15) years, respectively. More than two-thirds (n=884; 67%) of participants were receiving type 2 diabetes medication other than the monitored glucose-lowering drugs and one-fifth (n=248; 19%) was currently taking insulin. More than two-thirds (n=905; 68%) changed type 2 diabetes medication prior to enrolment, one-fifth of whom (n=169; 19%) did so because of an ADE occurrence.

Adverse drug event occurrence

A total of 1118 ADEs, corresponding to 146 different MedDRA preferred terms, were reported by 537 participants (41%; one ADE led to hospitalization, and was therefore classified as serious). The mean number of different preferred terms per participant was 2.1 (95% CI 2.0–2.2). ADE occurrence was very common (≥1/10), with nausea, diarrhoea, dizziness, pollakiuria (increase in urinary frequency) and constipation being the most frequently reported. Overall, significant differences (P<0.001) between cohort subgroups were observed: prevalent new users (47.9%; 95% CI 43.6–52.3) and GLP-1 receptor agonist inception users (67.3%; 95% CI 59.8–74.8) presented the highest ADE proportions when compared to incident new users (37.2%; 95%

Table 1 Participants baseline demographic, anthropometric and clinical characteristics

		DPP-4 inhibitors* (*n*=848; 63.9%) *n* (%)	GLP-1 receptor agonists (*n*=147; 11.1%) *n* (%)	SGLT2 inhibitors (*n*=308; 23.2%) *n* (%)	≥2 inception glucose-lowering drugs (*n*=25; 1.9%) *n* (%)
Exposure experience: incident new users		658 (77.6)	48 (32.7)	99 (32.1)	9 (36.0)
Gender (male)		437 (51.5)	71 (48.3)	150 (48.7)	15 (60.0)
Age	< 55 years	130 (15.5)	55 (37.9)	72 (23.8)	7 (28.0)
	55–64 years	218 (26.0)	49 (33.8)	102 (33.7)	10 (40.0)
	65–74 years	291 (34.6)	32 (22.1)	103 (34.0)	6 (24.0)
NR=15	≥ 75 years	201 (23.9)	9 (6.2)	26 (8.6)	2 (8.0)
BMI	< 25.00 kg/m^2	129 (15.6)	4 (2.8)	33 (10.9)	1 (4.0)
	25.00– 29.99 kg/m^2	344 (41.5)	18 (12.4)	111 (36.8)	5 (20.0)
NR=27	≥ 30.00 kg/m^2	356 (42.9)	123 (84.8)	158 (52.3)	19 (76.0)
Chronic diseases	0	86 (10.1)	15 (10.2)	44 (14.3)	5 (20.0)
	1–2	547 (64.6)	89 (60.5)	214 (69.7)	16 (64.0)
	≥ 3	214 (25.3)	43 (29.3)	49 (16.0)	4 (16.0)
Number of different drugs in addition to type 2 diabetes medication	0	45 (5.4)	5 (3.5)	17 (5.6)	2 (8.3)
	1–2	201 (24.3)	35 (24.3)	99 (32.7)	7 (29.2)
	3–4	266 (32.2)	40 (27.8)	97 (32.0)	7 (29.2)
	≥ 5	315 (38.1)	64 (44.4)	90 (29.7)	8 (33.3)
Type 2 diabetes duration	<1 year	101 (13.1)	5 (3.6)	19 (6.5)	3 (12.5)
	1–5 years	231 (30.0)	28 (20.0)	73 (25.1)	8 (33.3)
	6–9 years	107 (13.9)	17 (12.1)	43 (14.8)	1 (4.2)
NR=103	≥ 10 years	331 (43.0)	90 (64.3)	156 (53.6)	12 (50.0)
Type 2 diabetes-related complications	Yes	199 (23.7)	44 (30.1)	71 (23.3)	3 (12.0)
	Retinopathy	134 (16.0)	32 (21.9)	57 (18.7)	2 (8.0)
	Nephropathy	88 (10.5)	16 (11.0)	15 (4.9)	1 (4.0)
NR=12	Diabetic Foot	49 (5.8)	10 (6.8)	24 (7.9)	0 (0.0)
Current use of insulin		110 (13.0)	72 (49.0)	60 (19.5)	6 (24.0)

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; NR, non-respondents; SGLT2, sodium-glucose co-transporter-2 inhibitors.
*Alone or fixed-dose with metformin.

CI 33.8–40.6) and to DPP-4 (34.6%; 95%CI 31.4–37.8) or SGLT2 inhibitor inception users (48.4%; 95% CI 43.0–53.9), respectively. The ADEs reported by >1% of all participants are shown in Table S2.

A total of 403 (36%) reported ADEs were identified as unlabelled (not listed in the summary of product characteristics). Liraglutide (10%) and exenatide (15%) were associated with the lowest proportion of unlabelled ADEs, whereas vildagliptin (60%) and linagliptin (92%) were associated with the highest. A list of unlabelled ADEs according to the summary of product characteristics for each glucose-lowering drug is provided in Table S3.

With regard to hypoglycaemic episodes, 22% of participants (95% CI 19–24) experienced at least one episode, with the majority of episodes classified as mild to moderate (21%; 95% CI 19–23). Severe/very severe episodes were reported by 1.6% of participants (95% CI 0.9–2.3).

Time-course profile, outcome and management of adverse drug events

Kaplan–Meier curves (Fig. 1) and the calculation of cumulative incidence of the 10 most frequently reported ADEs (Fig. 2) showed that these occur in early treatment, reaching a plateau at ~1 month after the index date. An overview of detailed latency times according to MedDRA preferred terms is available in Table S4. Overall, the median latency time for ADEs reported in at least 1% of all participants ranged from 0 to 2 days.

When participants withdrew, suspended or reduced the dose of the monitored glucose-lowering drugs, 79%, 91% and 65% had recovered, respectively. However, differences were observed. For example, for nausea, diarrhoea or dizziness, more than two-thirds of participants had recovered/were recovering when continuing the use of the inception glucose-lowering drugs, indicating that these events were transient and, in most cases, resolved spontaneously. This was much less pronounced for pollakiuria or constipation, where the majority of participants reported that they had recovered/were recovering from these events only after they had withdrawn the drug, suggesting that the ADE outcome experienced was more dependent on drug cessation. Following the experience of ADE, almost one-quarter of participants (*n*=126; 24%) reported having undergone treatment to recover (74% of whom received pharmacological treatment).

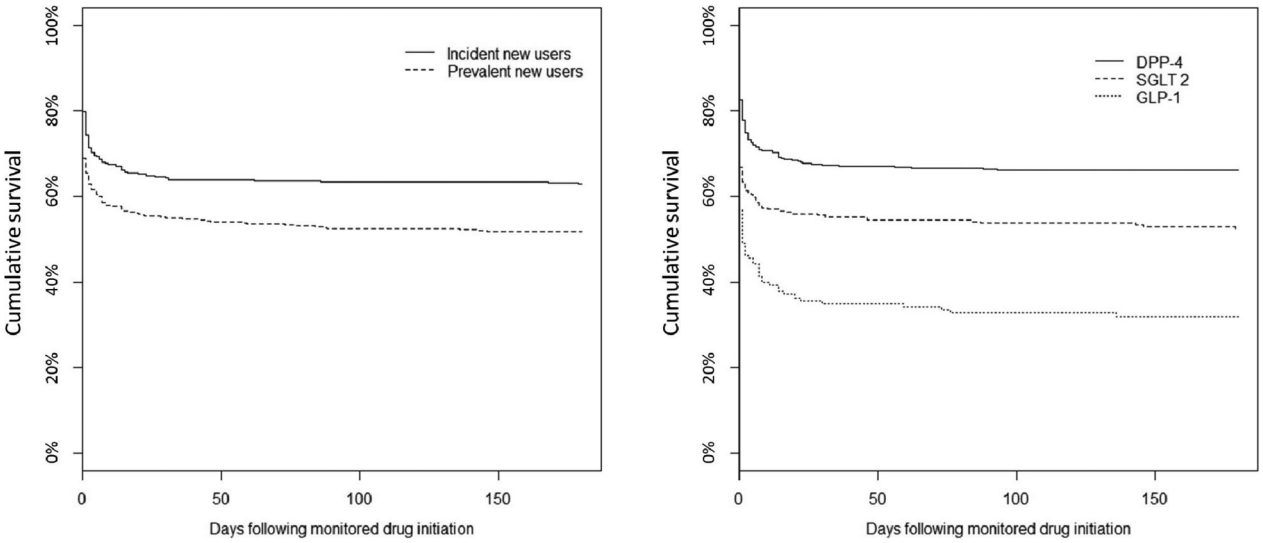

FIGURE 1 Kaplan–Meier curves illustrating the cumulative incidence of all adverse drug events, according to cohort subgroups. DPP-4, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1 receptor agonists; SGLT-2, sodium-glucose co-transporter-2 inhibitors.

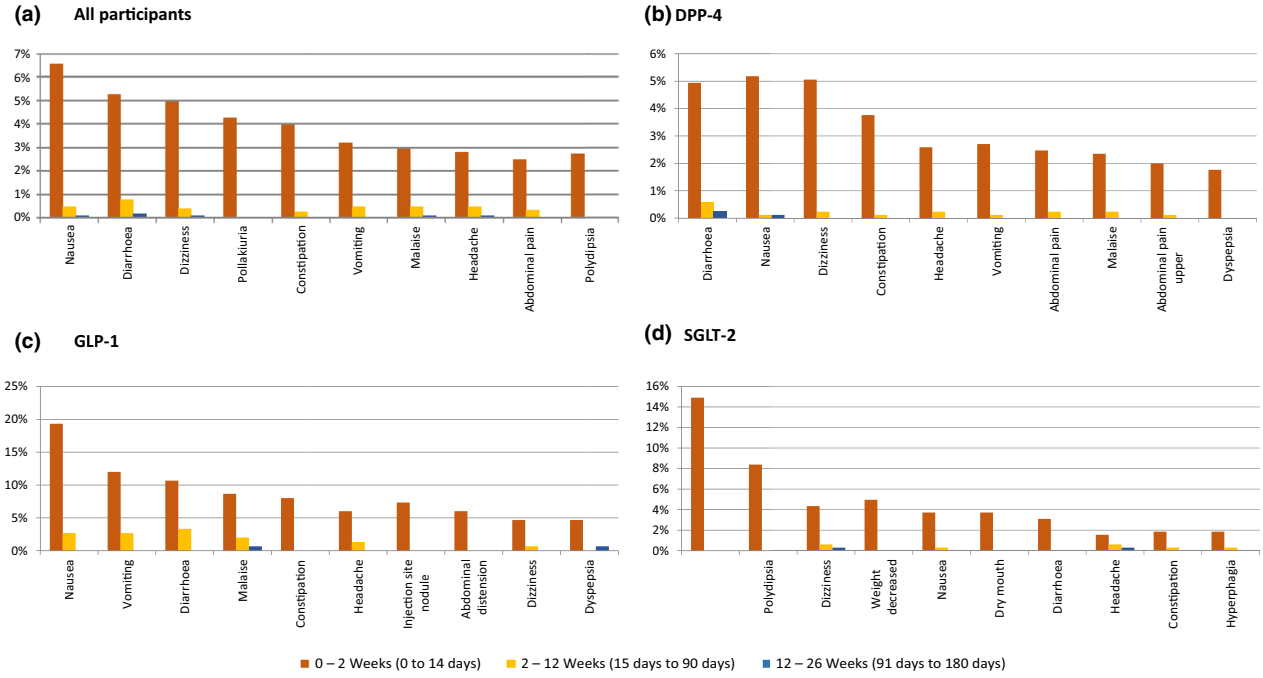

FIGURE 2 Ten most frequently reported adverse drug events per preferred term, according to specific time to onset intervals (all participants and per cohort subgroups). DPP-4, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1 receptor agonists; SGLT-2, sodium-glucose co-transporter-2 inhibitors.

Factors potentially associated with adverse drug event reporting

In the multivariable analysis (Table 2), GLP-1 receptor agonist (HR 2.11, 95% CI 1.63–2.73) and SGLT2 inhibitor inception treatment subgroups (HR 1.38, 95% CI 1.11–1.72) were associated with an increased likelihood of reporting at least one ADE when compared with the DPP-4 inihibitor subgroup. Furthermore, with the exception of hypoglycaemic episodes, which were marginally associated with ADE reporting, no other variable was significantly associated with time to first ADE.

Discussion

The present study provides insight into the occurrence and time-course information of ADEs related to the use of new glucose-lowering drugs in adults with type 2 diabetes in daily

Table 2 Factors associated with reported adverse drug events

		Univariable HR (95% CI)	Multivariable* HR (95% CI)
Exposure experience subgroup	Incident new users	Reference	
	Prevalent new users	1.366 (1.149–1.623)	
Gender	Female	Reference	Reference
	Male	0.831 (0.699–0.987)	0.845 (0.703–1.015)
Age (years)		0.988 (0.980–0.995)	0.991 (0.982–1.000)
BMI (kg/m^2)		1.022 (1.006–1.039)	
Inception monitored drug treatment group	DPP-4	Reference	Reference
	GLP-1 receptor agonists	2.420 (1.921–3.048)	2.110 (1.630–2.732)
	SGLT2 inhibitors	1.530 (1.250–1.872)	1.380 (1.109–1.718)
Chronic diseases	0	Reference	
	≥1	0.821 (0.636–1.059)	
Number of different medicines	0	Reference	
	≥1	1.126 (0.753–1.683)	
Diabetes duration (years)		1.011 (1.001–1.021)	1.009 (0.998–1.020)
Diabetes-related conditions†	No	Reference	
	Yes	1.067 (0.876–1.300)	
Number of other different substances taken for type 2 diabetes treatment	0	Reference	
	≥1	1.259 (1.042–1.521)	
Current use of insulin	No	Reference	
	Yes	1.367 (1.115–1.675)	
Hypoglycaemic episodes	No	Reference	Reference
	Yes	1.405 (1.156–1.707)	1.236 (1.004–1.522)

DPP-4, dipeptidyl peptidase-4 inhibitors alone or fixed dose with metformin; HR: hazard ratio.
*Wald test: P value < 0.001; variation inflation factor ≤ 1.1. Twenty-five participants were excluded from the analysis (participants ≥ 2 different inception monitored glucose-lowering drugs).
†Diabetes-related conditions included: eye disease (retinopathy); kidney disorders (nephropathy); foot complications (diabetic foot); and other(s).

practice. Such information could be used proactively to help manage adherence to treatment; however, despite this clinical relevance, there has been a paucity of data on this issue. We found that ADE occurrence was very common (≥1/10), with nausea, diarrhoea, dizziness, pollakiuria and constipation being the most frequently reported. The majority of ADEs were experienced at the beginning of treatment (the median latency time of the most common ADE ranged from 0 to 2 days), which is consistent with these events being a direct pharmacological effect of the drug.

This study could not establish any association between the reporting of at least one ADE and factors such as gender, presence of other comorbidities and co-medication in the multivariable analysis, despite such associations being reported previously [7]. The DPP-4 inhibitor subgroup (the subgroup with the highest proportion of incident new users), was less likely to report an ADE when compared to the remaining treatment subgroups. In the multivariable analysis, results were validated and compared with models using the full set of variables and models including only the significant associations in the univariable analysis. Results were similar and the influence of excluded variables was considered not relevant as confounders/effect modifiers. Furthermore, the results were very similar when adjusting for incident/prevalent new users (data not shown). The differences observed in ADE proportions between monitored glucose-lowering drug subgroups, however, require careful interpretation as prescribing is not a random behaviour and differences among participants in baseline characteristics were found; thus, we cannot rule out the existence of channelling bias.

Overall, prevalent new users which accounted for a significant number of users of novel glucose-lowering drugs in daily practice (approximately two-thirds of the GLP-1 receptor agonist and SGLT2 inhibitor treatment subgroups) experienced a significantly higher frequency of ADEs as compared to incident new users. This was to be expected because this subgroup was more complex in terms of type 2 diabetes disease (e.g. higher prevalence of diabetes complications and disease duration). The differences found between incident and prevalent new users reinforce the need for prevalent new users also to be taken into consideration when conducting comparative drug effect studies. Although methodologically challenging because of potential confounding bias, excluding prevalent new users (i.e. population who withdrew from previous drugs, possibly because of lack of theurapeutic response or tolerability issues) might compromise the ability to fully characterize the real-world setting. Notwithstanding, this subset of the population has been frequently excluded [13], not only from randomized clinical trials [5]), but also from observational studies [16], which are often based on selective populations (i.e. treatment-naïve/those with limited treatment experience).

Most of the ADEs that occurred did not require withdrawal and were resolved without additional treatment. These findings indicate that participants were willing to

accept or deal with a wide range of symptomatic events without discontinuing treatment, which was in line with a recent study that assessed ADE patterns experienced by people with type 2 diabetes [17].

The proportion of participants who withdrew the monitored glucose-lowering drugs is in line with existing literature, where withdrawal rates of 31.4% [18] and 33.5% [19] were reported. In the present study, inability to tolerate an ADE was cited as the second reason for inception glucose-lowering drug withdrawal. As reported in previous studies [6,8,20,21], experience of non-serious symptomatic ADEs, although frequently neglected by healthcare professionals, compromises adherence to treatment and represents a limiting factor in type 2 diabetes management. Measures of education and closer monitoring by healthcare providers, which should encompass counselling, active follow-up and adequately prompt management of ADE, should be secured in order to minimize the risk of failure to adhere to treatment [22]. A greater effort should be put into those with previous withdrawals related to ADEs because this population might have an increased susceptibility to ADEs [6].

Approximately one-fifth of participants reported at least one hypoglycaemic episode. To date, data on hypoglycaemia are inconsistent and heterogeneous due to different study designs/data collection methods, hence it is difficult to compare our results with previous studies. However, a similar prevalence was observed in the Portuguese HIPOS-PHARMA study [23]. Although it has been reported that the risk of hypoglycaemia is not a significant concern with new glucose-lowering drugs, attention is needed when combining these agents with secretagogues or insulin therapy [24,25], which was the case in the present study (a higher frequency of hypoglycaemic episodes was observed in the GLP-1 receptor agonist subgroup, half of whom used insulin at cohort entry).

The primary source of data collected was people with type 2 diabetes. This has advantages because the ADEs were self-reported by the individual experiencing the event, but also drawbacks as the ADEs were not medically confirmed. However, although comparative studies of ADE reporting between people with disease and healthcare professionals found results conflicted [26], recent studies have suggested that the level of relevant clinical information was similar [27]. Additionally, since people with disease do not have a healthcare professional view of what to expect to report, they can add information and provide other perspectives on ADEs, which might increase the chance of finding new events [28]. In a recent review of studies on glucose-lowering drugs, it was stated that person-oriented methods seem to be more appropriate for assessing non-serious symptomatic ADEs than reports from healthcare providers, given the latter often underestimate these type of events [20]. This might have played a role in the present study, which was one of the first to include people with type 2 diabetes as the primary information source for assessing the safety of new glucose-lowering drugs. We identified a high proportion (36%) of ADEs not listed in the corresponding summary of product characteristics, which, given the only recent availability of the monitored drugs, are largely based on randomized clinical trial data. This finding appears consistent with the results of other studies which showed that consumer reports have the potential to identify new ADEs that were not previously included in the summary of product characteristics, and that the ADEs are sometimes reported earlier by consumers than by healthcare professionals [28–30]. Nevertheless, surprising differences among the monitored glucose-lowering drugs were found in the present study, with the highest proportions of unlabelled ADEs being reported by new users of DPP-4 inhibitors alone. We did not use a standard checklist to collect ADEs, but rather an open question, given that this methodology is based on event monitoring [31]. Although underreporting may have occurred [20,32], we have no reason to believe that the level of ADE reporting differed among glucose-lowering drugs. As in other intensive monitoring studies worldwide [8,33], no causality assessment was conducted. These unlabelled events merit further investigation on a case-by-case basis and lay the ground for larger comparative real-world safety studies.

The present study had several strengths. The data presented were collected through a non-interventional study with no limiting inclusion or exclusion criteria as compared with randomized clinical trials and other observational studies. Given that community pharmacies were the inclusion points for eligible participants, this study encompassed prescriptions from both primary and secondary care settings, which increased the representativeness of the cohort. Furthermore, because the study was based on an event monitoring methodology, it had the potential to identify unrecognized/unsuspected ADEs. Finally, the proportion of participants lost to follow-up was very low.

Potential limitations of this study include pharmacy self-selection, although participating pharmacies were representative of Portuguese pharmacies, with similarities found with regard to the regional and setting distribution of pharmacies that did and did not participate. Secondly, potential selection bias could have occurred. However, unlike other intensive monitoring systems worldwide, information about eligible participants who did not participate was collected, which indicated that those who declined to participate were similar to participants in terms of age group and gender distribution. Thirdly, although the baseline questionnaire was administered by the pharmacist and studies have previously demonstrated substantial agreement for some type 2 diabetes characteristics [34], clinical data were self-reported, hence could be associated with some degree of inaccuracy. Even though participants were asked to only report events that were associated with the use of the inception glucose-lowering drug, we cannot exclude the possibility that some events were not caused by the monitored drug. Finally, many comparisons were conducted and there might be an increased chance of a type I error.

In conclusion, contributing to the real-world framework for evidence generation data, this study adds knowledge related to the use of new glucose-lowering drugs, regarding ADE latency time, frequency, outcome and management. More than two-fifths of participants reported a non-serious ADE, with nausea, diarrhoea, dizziness, pollakiuria and constipation, being the most frequent. ADE latency time data show that counselling and ADE management should be proactively addressed from treatment initiation. Although the highest proportion of unlabelled events found were non-serious, especially those reported by the DPP-4 inhibitor group, these events merit further investigation, and lay the ground for larger comparative glucose-lowering drugs safety studies in real-life settings.

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Competing interests

C.T. was working at Centre for Health Evaluation & Research/Portuguese National Association of Pharmacies when the study was performed and is currently employed by the Faculty of Pharmacy, University of Lisbon and has no conflict of interest to declare. A.P.M., J.G. and P.L. declare that they have no conflict of interest. H.L. reports being past-chairman of the Dutch Medicines Evaluation Board and a past-member of the European Medicines Agency's Committee for Medicinal Products for Human Use, and Scientific Director of the Utrecht WHO Collaborating Centre for Pharmaceutical Policy and Regulation. This centre accepts no direct funding or donations from the pharmaceutical industry or other private parties. J.F.R. has received honoraria for consultancy/lectures from Merck Sharp & Dohme, Lilly, Novo Nordisk over the last year.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Distribution of pharmacies with recruited participants and the national universe of pharmacies according to region, setting and number of pharmacists in their staff.
Table S2. Reported adverse drug events that occurred in more than 1% of all participants.
Table S3. Reported adverse drug events classified as 'not-labelled' according to the Summary of Product Characteristics.
Table S4. Latency time of reported adverse drug events that occurred in more than 1% of all participants.
Figure S1. Study flow diagram.