Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-019-01110-w

ORIGINAL ARTICLE

Predictors of early discontinuation of dapagliflozin versus other glucose-lowering medications: a retrospective multicenter real-world study

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Received: 27 June 2019 / Accepted: 3 September 2019

Abstract

Background and aims In routine clinical practice, early discontinuation of newly initiated glucose-lowering medications (GLM) is relatively common. We herein evaluated if the clinical characteristics associated with early discontinuation of dapagliflozin were different from those associated with early discontinuation of other GLM.

Methods The DARWIN-T2D was a multicenter retrospective study conducted at diabetes specialist outpatient clinics in Italy. We included 2484 patients who were initiated on dapagliflozin in 2015–2016 and 14,801 patients who were initiated on other GLM (DPP-4 inhibitors, GLP-1 receptor agonists, or gliclazide) in the same period. After excluding patients who had not (yet) returned to follow-up, we compared the characteristics of patients who persisted on drug versus those who were no longer on drug at the first available follow-up after at least 3 months.

Results As compared to those who persisted on drug, patients who discontinued dapagliflozin (51.7%) were more often female, had higher baseline fasting plasma glucose (FPG), HbA1c, and eGFR, and less common use of metformin. Upon multiple regression, higher HbA1c, higher eGFR, and lower metformin use remained independently associated with early discontinuation. Among patients who had been initiated on other GLM, 41.7% discontinued. Variables independently associated with discontinuation were older age, longer diabetes duration, higher HbA1c, eGFR, and albumin excretion, more common use of insulin and less metformin.

Conclusion In routine clinical practice, all variables associated with dapagliflozin discontinuation were also associated with discontinuation of other GLM. Thus, despite a distinctive mechanism of action and a peculiar tolerability profile, no specific predictor of dapagliflozin discontinuation was detected.

Keywords Adherence · Pharmacotherapy · Real-world · Observational · Type 2 diabetes

Members of the DARWIN-T2D Network are listed in Acknowledgement section.

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Published online: 12 September 2019

Introduction

Type 2 diabetes (T2D) is a progressive disease needing stepwise pharmacologic intensification in most cases [1]. Thus, initiation of new glucose-lowering medications (GLM) can occur multiple times for each patient during the natural history of T2D. Among the many classes of GLM available, drugs vary in their efficacy, safety, and tolerability profile [1]. Since it is hard to predict which GLM will be most effective and best tolerated in individual patients, early discontinuation of GLM is relatively common. An analysis conducted in the UK reported that 9–12% of patients initiated on second or more advanced line of therapy permanently discontinued treatment by 3 months, resulting in > 20% by 12 months [2].

By virtue of their unique mechanism of action [3], sodium–glucose cotransporter-2 inhibitors (SGLT2i), can cause adverse events (AEs) not shared by other GLM, such as genital tract symptoms and infections, dehydration, and hypovolemia [4, 5]. Much rarer AEs associated with SGLT2i include diabetic ketoacidosis [6], pyelonephritis, amputations [7], and Fournier's gangrene [8]. In contrast, AEs associated with metformin, acarbose, pioglitazone, and GLP-1 receptor agonists (GLP-1RA) are mostly gastrointestinal, while the most common AE during therapy with insulin or sulfonylureas is hypoglycemia [9]. Except for pioglitazone [10], no other specific AE is commonly observed with these GLM, and most trials with DPP-4 inhibitors (DPP-4i) showed less common AEs compared with placebo [11]. Patients' satisfaction with treatments is not only the result of eventual AEs, but is also determined by the delivery route (oral versus parenteral), treatment schedule (e.g., number of injections), and additional treatment benefits, with body weight reduction being the most appreciated [12].

Based on these diversified efficacy, safety, and tolerability profiles, it may be hypothesized that determinants of treatment discontinuation are different for SGLT2i versus other GLM. We therefore asked if initiation of the SGLT2i dapagliflozin was associated with any drug-specific predictor of discontinuation. To address this issue, we re-analyzed the database of a multicenter study that collected retrospective data on T2D patients who received new prescription of dapagliflozin, GLP-1RA, DPP-4i, or gliclazide.

Methods

Data source

The DARWIN (DApagliflozin Real World evIdeNce)-T2D was a multicenter retrospective real-world study collecting electronic chart data from 46 diabetes specialist outpatient clinics in Italy in 2015–2016. The study design has been published in late 2017 [13]. The primary objective was to describe the baseline clinical characteristics of T2D patients at the time they received a new prescription of dapagliflozin, a DPP-4i (all available but linagliptin), a GLP-1RA (liraglutide or exenatide once weekly), or gliclazide. The study also evaluated effectiveness of these treatments on glycemic and extra-glycemic end points at the first available follow-up visit, 3–12 months after baseline. Results of the primary analysis, published elsewhere [14], indicated that patients receiving dapagliflozin had very different baseline clinical characteristics than patients receiving other GLM, especially DPP-4i and gliclazide.

The baseline date was set as the date patients received a first prescription of the above-mentioned medications, without being treated with the same drugs or another drug of the same class before, as recorded in the electronic chart. We collected the following baseline data: age, sex, diabetes duration, body weight and height for the calculation of BMI, systolic and diastolic blood pressure, fasting plasma glucose and HbA1c, lipid profile, serum creatinine for the calculation of eGFR, urinary albumin excretion, prescribed GLM and other medications, and presence or absence of microangiopathy or macroangiopathy. Definitions of the variables and of complication status have been previously described in detail [13–19].

For each of the patients who had been initiated treatment, we recorded whether there was a follow-up visit within the study data collection period (ending 31 Dec 2016). For patients who had a follow-up visit, we recorded whether or not the prescription was confirmed for the new medication initiated at baseline. Thus, we defined discontinuation when the prescription was not confirmed at the first available visit 3–12 months after baseline. Updated clinical variables were recorded only for patients who continued therapy at follow-up. We had not information on whether the patients actually took the prescribed medications and for how long, nor which were the reasons for discontinuation, and which different GLM regimen were the patients prescribed in case of discontinuation.

The objective of the study was to evaluate whether there was any clinical variable associated with discontinuation of dapagliflozin that was not associated with discontinuation of other medications. To this end, patients were divided into two groups: those who had been initiated on dapagliflozin and those who had been initiated on a comparator (DPP-4i, GLP-1RA or gliclazide). Within each group, we compared the clinical characteristics of patients who discontinued treatment to those who persisted on treatment at the first follow-up. The lists of variables predicting early discontinuation within each group were then compared.

Statistical analysis

Continuous data are presented as mean and standard deviation. Normality of continuous data was checked using the Kolmogorov–Smirnov test. Non-normal variables were log transformed for statistical analysis. Categorical variables are presented as percentage. We first performed a univariate analysis in each group of patients who were initiated dapagliflozin or comparators, by comparing the average characteristics of patients who discontinued the drug versus patients who persisted on the drug. Continuous variables were compared using two-tailed Student's *t* test, whereas categorical variables were compared using the Chi square test. To identify variables independently associated with discontinuation, we performed multiple logistic regression analyses. Since some data were missing for several variables in the database and the complete case is needed to run multiple regressions, we performed multiple imputation (MI) using the Markov chain Monte Carlo (MCMC) method. Ten imputed datasets were obtained for each group. Within each imputed dataset, we performed logistic regression analyses, which were then pooled to obtain the final estimates. We used two different models. Model 1 included as covariates only variables that were significantly associated with discontinuation upon univariate analysis in each group. To avoid the fact that two different sets of covariates were used for the two groups, in model 2 we entered all clinical variables as covariates. A variable was considered specific for dapagliflozin discontinuation if it was significantly and independently associated with discontinuation in the dapagliflozin, but not in the comparator group. SPSS version 24 was used and statistical significance was accepted at $p < 0.05$.

Results

Patient disposition

Figure 1 shows the study flowchart. The study retrospectively collected data from a total of 17,285 patients who were initiated on new GLM, of whom 2484 patients were initiated on dapagliflozin and 14,801 initiated on a comparator drug. The primary study results published elsewhere already described the baseline differences among patients who received for the first time dapagliflozin or other GLM [14]. In general, such comparison suggested that, during the study period, dapagliflozin was used in difficult-to-treat patients. The common support between patients in the dapagliflozin group and those in the comparator group was very low, especially for DPP-4i and gliclazide [14]. We herein compared, within each of the two groups (dapagliflozin and comparators), those who discontinued treatment versus those who persisted on treatment at the first follow-up visit. Among the 1701 patients who were initiated on dapagliflozin for whom a follow-up visit was available, 832 persisted on treatment and 869 discontinued treatment (51.1%). Among the 11,081 patients who were initiated on comparators for whom a follow-up visit was available, 6464 patients persisted on treatment and 4617 discontinued treatment (41.7%). The clinical characteristics of these patients are summarized in Table 1.

Fig. 1 Study flowchart. *GLM* glucose-lowering medications

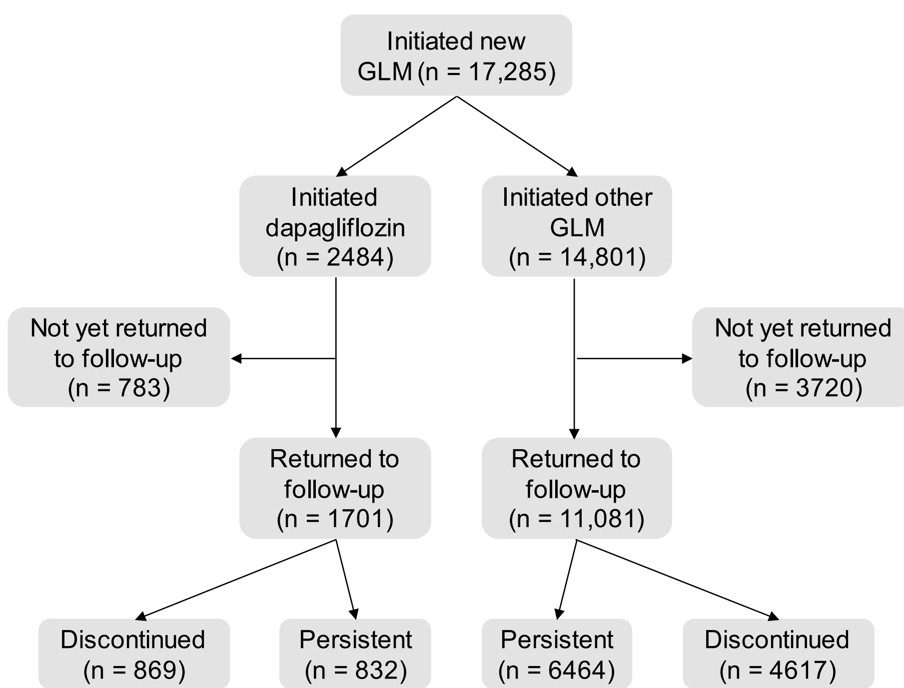

Table 1 Comparisons of patients who persisted on treatment versus those who discontinued treatment

Variable	Dapagliflozin		Comparators	
	Persistent	Discontinued	Persistent	Discontinued
Number	832	869	6464	4617
Age, years	60.2 ± 9.3	59.9 ± 9.6	66.5 ± 9.4	65.9 ± 9.9*
Sex male, %	61.3	55.5*	58.5	58.3
Diabetes duration, years	12.4 ± 8.2	12.3 ± 8.0	11.3 ± 7.6	11.2 ± 7.8
Body weight, kg	92.5 ± 18.8	92.3 ± 18.4	83.3 ± 17.2	84.7 ± 18.6*
BMI, kg/mq	33.1 ± 6.0	33.1 ± 5.9	30.3 ± 5.5	30.7 ± 6.0*
SBP, mm Hg	139.0 ± 18.3	141.1 ± 20.4	138.4 ± 18.8	138.4 ± 19.4
DBP, mmHg	80.5 ± 10.4	80.8 ± 11.2	79.0 ± 9.4	79.4 ± 9.9
FPG, mg/dl	175.0 ± 53.1	185.5 ± 60.9*	160.7 ± 42.5	168.4 ± 52.6*
HbA1c, %	8.6 ± 1.4	8.9 ± 1.5*	7.9 ± 1.1	8.2 ± 1.4*
Total cholesterol, mg/dl	174.5 ± 39.6	179.1 ± 40.3	171.9 ± 37.7	176.4 ± 40.8*
HDL cholesterol, mg/dl	45.8 ± 13.1	45.5 ± 12.5	47.9 ± 13.4	47.4 ± 13.5
Triglycerides, mg/dl	167.5 ± 123.6	185.0 ± 167.9	148.7 ± 93.1	156.3 ± 94.0*
LDL cholesterol, mg/dl	96.0 ± 32.1	98.9 ± 33.9	94.6 ± 32.2	97.9 ± 35.3*
eGFR, ml/min/1.73 mq	88.6 ± 16.1	116.9 ± 27.7*	82.2 ± 21.1	110.1 ± 31.1*
AER, mg/g	110.9 ± 369.3	180.5 ± 1392.2	75.4 ± 251.4	96.7 ± 432.2
Glucose-lowering medications				
Insulin, %	55.6	54.9	16.7	22.3*
Metformin, %	99.2	91.2*	81.3	76.5*
Other therapies				
Anti-platelet agents, %	48.3	44.1	55.0	55.5
Statin, %	63.3	61.5	53.2	44.2*
ACEi/ARBs, %	71.4	69.7	71.0	72.6
Calcium channel blockers, %	22.9	22.8	19.1	17.4*
Beta blockers, %	30.4	30.2	25.3	22.5*
Diuretics, %	9.4	9.5	24.4	29.5*
Microangiopathy	37.3	36.1	30.5	28.0*
Macroangiopathy	32.1	33.2	37.1	35.7

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HDL* high density cholesterol, *eGFR* estimated glomerular filtration rate, *AER* albumin excretion rate, *ACEi* angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers

*$p < 0.05$ versus persistent (not adjusted for multiple comparison)

Univariate analyses

Upon direct group comparison, patients who discontinued treatment with dapagliflozin, as compared to those who persisted on dapagliflozin, were more often female, had a higher fasting plasma glucose and HbA1c, higher eGFR, and less frequent use of metformin. Patients who discontinued comparators, as compared to those who persisted on drug, were slightly younger, had a slightly higher body weight and BMI, higher fasting plasma glucose, HbA1c, total and LDL cholesterol, triglycerides and eGFR, more frequent use of insulin and less of metformin, some differences in medications for the treatment of risk factors, and a lower prevalence of microangiopathy.

Multivariate analyses

Logistic regressions were performed in ten imputed datasets (Table 2). In model 1, where covariates were those identified by univariate comparison, higher HbA1c and eGFR and less common use of metformin were significant independent predictors of dapagliflozin discontinuation. The same variables were identified in model 2, including all possible covariates.

For comparator GLM, model 1 identified older age, higher body weight, HbA1c, triglycerides, eGFR, use of insulin and not use of metformin, as well as use of diuretics and predictors of discontinuation. In model 2, the same variables were selected except that diabetes duration replaced body weight as an independent predictor of discontinuation.

Table 2 Results of the multivariate analysis

Variable	Dapagliflozin				Comparators			
	Model 1		Model 2		Model 1		Model 2	
	B ± SE	*p*	B ± SE	*p*	B ± SE	*p*	B ± SE	*p*
Age			0.00 ± 0.01	0.591	0.01 ± 0.00	0.006	0.01 ± 0.00	0.035
Sex	− 0.06 ± 0.10	0.360	− 0.19 ± 0.14	0.280			0.14 ± 0.06	0.065
Diabetes duration			0.00 ± 0.01	0.572			0.01 ± 0.00	0.025
Weight			0.01 ± 0.01	0.330	0.01 ± 0.00	0.004	0.00 ± 0.00	0.164
BMI			− 0.02 ± 0.02	0.312	− 0.02 ± 0.01	0.101	0.00 ± 0.01	0.629
SBP			0.00 ± 0.00	0.447			0.00 ± 0.00	0.254
DBP			0.00 ± 0.00	0.214			0.00 ± 0.00	0.526
FPG	0.00 ± 0.00	0.382	0.00 ± 0.00	0.442	0.00 ± 0.00	0.358	0.00 ± 0.00	0.373
HbA1c	0.11 ± 0.04	0.037	0.13 ± 0.04	0.019	0.08 ± 0.02	< 0.001	0.08 ± 0.02	< 0.001
Total cholesterol			0.00 ± 0.00	0.629	0.00 ± 0.00	0.346	0.00 ± 0.00	0.197
HDL cholesterol			0.00 ± 0.00	0.380			0.00 ± 0.00	0.246
Triglycerides			0.00 ± 0.00	0.325	0.00 ± 0.00	0.030	0.00 ± 0.00	0.165
eGFR	0.01 ± 0.00	< 0.001	0.01 ± 0.00	< 0.001	0.01 ± 0.00	< 0.001	0.02 ± 0.00	< 0.001
AER			0.00 ± 0.00	0.300			0.00 ± 0.00	0.037
Insulin			− 0.25 ± 0.12	0.060	0.29 ± 0.05	< 0.001	0.25 ± 0.05	< 0.001
Metformin	− 2.53 ± 0.38	< 0.001	− 2.61 ± 0.38	< 0.001	− 0.42 ± 0.05	< 0.001	− 0.43 ± 0.05	< 0.001
Anti-platelet			− 0.06 ± 0.12	0.606			0.01 ± 0.05	0.631
Statin			0.02 ± 0.12	0.700	− 0.28 ± 0.04	< 0.001	− 0.29 ± 0.04	< 0.001
ACEi/ARBs			− 0.06 ± 0.12	0.595			0.07 ± 0.05	0.354
CCB			0.00 ± 0.13	0.793	− 0.03 ± 0.05	0.537	− 0.05 ± 0.05	0.412
Beta blockers			0.03 ± 0.12	0.703	− 0.07 ± 0.05	0.198	− 0.08 ± 0.05	0.152
Diuretics			0.06 ± 0.17	0.661	0.37 ± 0.05	< 0.001	0.36 ± 0.05	< 0.001
Microangiopathy			0.08 ± 0.12	0.464	− 0.15 ± 0.05	0.101	− 0.19 ± 0.05	0.055
Macroangiopathy			0.15 ± 0.11	0.220			0.13 ± 0.04	0.164

For each treatment group separately, two logistic regression models were used. Model 1 only included variables identified in the univariate analyses, whereas model 2 included all covariates. For each model, the regressions coefficient B and its standard error are presented along with the respective *p* values

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HDL* high density cholesterol, *eGFR* estimated glomerular filtration rate, *AER* albumin excretion rate, *ACEi* angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *CCB* calcium channel blockers

When predictors of discontinuation were compared between the two groups, we detected no variable specifically associated with dapagliflozin discontinuation that was not associated with discontinuation of comparators (Fig. 2).

Upon a logistic regression analysis on ten imputed datasets with all covariates entered as a block, the relative risk of discontinuation associated with dapagliflozin versus comparators was 1.32 (95% CI 1.17–1.47; $p < 0.001$).

Discussion

In this exploratory, non-prespecified, analysis of the DARWIN-T2D study, we examined if early discontinuation of dapagliflozin could be predicted by any specific baseline patient characteristic that was not a predictor of discontinuing other GLM. The rationale was that SGLT2i have a mode of action completely different from that of other GLM. The tolerability profile of SGLT2i is also different from that of other GLM: reasons for discontinuing SGLT2i are most often genitourinary tract infections and, less frequently, dehydration or other rarer side effects. The common reasons for discontinuing other GLM are gastrointestinal symptoms (GLP-1RA and, rarely, DPP4i) or hypoglycemia (sulfonylureas). In addition, lack of efficacy is a common reason for discontinuing any medication. We found that all baseline clinical variables identified as independent predictors of early dapagliflozin discontinuation were also detected as independent predictors of discontinuing comparator GLM. Thus, it appears that discontinuation of dapagliflozin at the first follow-up could not be predicted by any specific baseline characteristic. In other words, among clinical

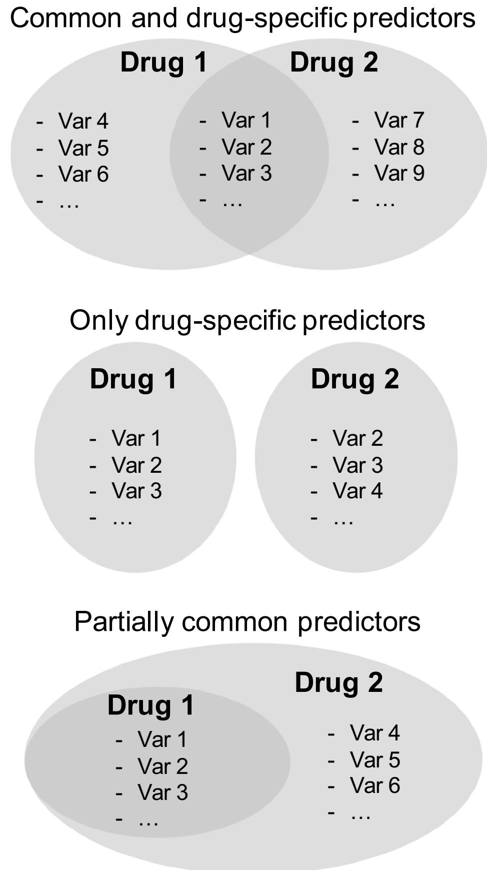

Fig. 2 Possible scenarios of common and drug-specific predictors of discontinuation. Var stands for variable. The example graphically represented at the bottom corresponds to the findings of the present study, wherein drug 1 is dapagliflozin and drug 2 are comparators

characteristics recorded at the time patients received the first prescription of dapagliflozin, those independently associated with drug discontinuation at the first follow-up were also associated with early discontinuation of other classes of GLM, and thus not specific for dapagliflozin. This finding is reassuring against the risk of dapagliflozin discontinuation in a population of difficult-to-treat patients.

The percentage of patients discontinuing dapagliflozin was apparently higher than the percentage of patients discontinuing other GLM. Although the analysis identified a 32% higher relative risk of discontinuing dapagliflozin versus other medications, this comparison was biased by the fact that the phenotype of patients who had been initiated on dapagliflozin was extremely different from those of patients who had been initiated on other GLM. Despite that we adjusted the between-group comparison of discontinuation rates for baseline confounders, it is not surprising that discontinuation of a drug for which less clinical experience exists is more frequent than discontinuation of drugs for which extensive clinical experience is available. The aim of the study was, however, to evaluate whether any specific predictor of discontinuation emerged. Indeed, it could be anticipated that the different mode of action, together with the different clinical profile of treated patients, drove specific patterns of predictors of early discontinuation in the dapagliflozin group. By analyzing the two groups separately, we detected similar patterns of discontinuation predictors, despite very different baseline characteristics. Therefore, it was decided that, in this circumstance, adjusting for between-group differences at baseline was not necessary. In addition, the low common support between patients who were initiated on dapagliflozin and those who were initiated on a comparator (especially DPP-4i and gliclazide) prevented us from performing propensity score matching [14].

It should be noted that, in the absence of information on tolerability, side effects, and efficacy in patients receiving new GLM prescriptions, interpreting predictors of discontinuation can only lead to speculations. With this limitation in mind, variables identified as independent predictors of discontinuation portray the phenotype of a patient slightly older and more obese, with a worse glycemic and lipid control, more frequent use of insulin and less frequent use of metformin, statin, and blood pressure-lowering medications. More frequent use of diuretics among patients who discontinued may identify frail patients with or at risk for heart failure. An elevated baseline HbA1c was a strong predictor of early GLM discontinuation, likely because the newly initiated drug could not afford the desired glycemic effect in patients with HbA1c far from the target, leading to need further intensification with a change in the treatment regimen. In this regard, it should be mentioned that, during the study period, dapagliflozin was reimbursed only in combination with metformin and/or insulin, whereas many other combinations were possible for comparator GLM. This was likely the major reason driving the more frequent discontinuation of a dapagliflozin-based regimen, which could not be intensified with add-on therapy with, e.g., DPP-4i, GLP-1RA, or sulfonylureas. Nonetheless, this important difference in reimbursement criteria between dapagliflozin and comparators did not lead to drug-specific predictors of discontinuation.

Less apparent is the reason why an elevated eGFR, which may identify hyperfiltration, was a consistent predictor of discontinuation of dapagliflozin as well as of other GLM. It can be speculated that, among patients treated with SGLT2i, hyperfiltration leads to higher urinary glucose excretion, in turn causing more genitourinary complaints. Yet, hyperfiltration is expected to result in stronger glycemic effect of SGLT2i and, indeed, higher eGFR was among the characteristics of dapagliflozin responders in a longitudinal, prospective, nationwide dapagliflozin surveillance study in Korea [20]. For other GLM, however, why hyperfiltration was associated with discontinuation of other GLM is unclear.

The study has important limitations. First, we only collected data at the first follow-up visit, such that there was no information on long-term persistence on treatment. Discontinuation was defined when the prescription was not confirmed at the first follow-up and we had no information on whether the patients ever took the drugs, when discontinuation occurred between baseline and follow-up, and whether it was decided by the physician, the patient, or both. In addition, data on adherence and pharmacy refill rates were not available. Second, reasons for discontinuation were not known, limiting the possibility to distinguish between the side effects, lack of efficacy, and other reasons. Finally, updated clinical data of patients who discontinued treatment were not available, preventing any further consideration of their clinical and therapeutic trajectory. For example, no information was available on how the prescription of other GLM changed in patients who discontinued a recently initiated drug. Future studies addressing the issue of discontinuation should take into account adherence, compliance, side effects, change in efficacy variables, as well as the therapeutic trajectories of the patients.

In conclusion, we found no evidence that any baseline characteristics recorded at the time patients received the first dapagliflozin prescription predicted early discontinuation in a drug-specific manner. All predictors of dapagliflozin discontinuation were also predictors of discontinuation of other GLM. Thus, despite a different mode of action and tolerability profile, SGLT2i may not be associated with specific predictors of discontinuation.

Acknowledgements We wish to thank Alessia Russo, Italian Diabetes Society, for the invaluable technical support. Composition of the DARWIN-T2D database: Agostino Consoli and Gloria Formoso (Dipartimento di Medicina e Scienze dell'Invecchiamento - Università Degli studi G. D'Annunzio di Chieti-Pescara); Giovanni Grossi (Ospedale San Francesco di Paola - Azienda Sanitaria Provinciale di Cosenza); Achiropita Pucci (Azienda Sanitaria Provinciale di Cosenza); Giorgio Sesti and Francesco Andreozzi (Azienda Ospedaliero Universitaria di Catanzaro); Giuseppe Capobianco (Azienda Sanitaria Locale Napoli 2 Nord); Adriano Gatti (Ospedale San Gennaro dei Poveri - Azienda Sanitaria Locale Napoli 1 Centro); Riccardo Bonadonna, Ivana Zavaroni and Alessandra Dei Cas (Azienda Ospedaliero Universitaria di Parma); Giuseppe Felace (Ospedale di Spilimbergo - Azienda per l'Assistenza Sanitaria n.5 Friuli Occidentale); Patrizia Li Volsi (Ospedale di Pordenone - Azienda per l'Assistenza Sanitaria n.5 Friuli Occidentale); Raffaella Buzzetti and Gaetano Leto (Ospedale Santa Maria Goretti - Azienda Sanitaria Locale di Latina); Gian Pio Sorice (Fondazione Policlinico Universitario A. Gemelli, Roma); Paola D'Angelo (Ospedale Sandro Pertini - Azienda Sanitaria Locale Roma 2); Susanna Morano (Azienda Ospedaliera Universitaria Policlinico Umberto I, Roma); Antonio Carlo Bossi (Ospedale di Treviglio - Azienda Socio Sanitaria Territoriale Bergamo Ovest); Edoardo Duratorre (Ospedale Luini Confalonieri di Luino - Azienda Socio Sanitaria Territoriale Sette Laghi); Ivano Franzetti (Ospedale Sant'Antonio Abate di Gallarate - Azienda Socio Sanitaria Territoriale Valle Olona); Paola Silvia Morpurgo (Ospedale Fatebenefratelli - Azienda Socio Sanitaria Territoriale Fatebenefratelli Sacco); Emanuela Orsi (Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico di Milano); Fabrizio Querci (Ospedale Pesenti Fenaroli di Alzano Lombardo - Azienda Socio Sanitaria Territoriale Bergamo Est); Massimo Boemi† and Federica D'Angelo (Presidio Ospedaliero di Ricerca INRCA-IRCCS di Ancona); Massimiliano Petrelli (Azienda Ospedaliero Universitaria Ospedali Riuniti di Ancona); Gianluca Aimaretti and Ioannis Karamouzis (Azienda Ospedaliero Universitaria Maggiore della Carità di Novara); Franco Cavalot (Azienda Ospedaliero Universitaria San Luigi Gonzaga, Orbassano); Giuseppe Saglietti† (Ospedale Madonna del Popolo di Omegna - Azienda Sanitaria Locale Verbano Cusio Ossola); Giuliana Cazzetta (Casa della Salute, Ugento - Distretto Socio Sanitario Gagliano del Capo - Azienda Sanitaria Locale di Lecce); Silvestre Cervone (Presidio ospedaliero San Marco in Lamis - Distretto Socio Sanitario San Marco in Lamis - Azienda Sanitaria Locale di Foggia); Eleonora Devangelio (Distretto Socio Sanitario di Massafra - Azienda Sanitaria Locale di Taranto); Olga Lamacchia (Azienda Ospedaliero Universitaria Ospedali Riuniti di Foggia); Salvatore Arena (Ospedale Umberto I - Azienda Sanitaria Provinciale di Siracusa); Antonino Di Benedetto (Azienda Ospedaliera Universitaria Policlinico G. Martino di Messina); Lucia Frittitta (Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi di Catania); Carla Giordano (Azienda Universitaria Policlinico Paolo Giaccone di Palermo); Salvatore Piro (Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi di Catania); Manfredi Rizzo, Roberta Chianetta and Carlo Mannina (Azienda Universitaria Policlinico Paolo Giaccone di Palermo); Roberto Anichini (Ospedale San Jacopo di Pistoia - Azienda USL Toscana Centro); Giuseppe Penno (Azienda Ospedaliero Universitaria Pisana); Anna Solini (Azienda Ospedaliera Universitaria Pisana); Bruno Fattor (Comprensorio Sanitario di Bolzano - Azienda Sanitaria della Provincia Autonoma di Bolzano); Enzo Bonora and Massimo Cigolini (Azienda Ospedaliero Universitaria Integrata di Verona); Annunziata Lapolla and Nino Cristiano Chilelli (Complesso Socio Sanitario Ai Colli - Azienda ULSS n.6 Euganea); Maurizio Poli (Ospedale Girolamo Fracastoro di San Bonifacio - Azienda ULSS n.9 Scaligera); Natalino Simioni and Vera Frison (Ospedale di Cittadella - Azienda ULSS n.6 Euganea); Carmela Vinci (Azienda ULSS n.4 Veneto Orientale).

Author contributions Study design: GPF, AA. Data collection and analysis: GPF, PLV, ED, MP, GX, GF. Manuscript writing: GPF, AA. Manuscript revision: GPF, PLV, ED, MP, GC, GF AA. All authors approved the final version of the manuscript.

Funding The study was partly supported by the Italian Diabetes Society, through a grant from AstraZeneca. The external sponsor had no role in the study design, data analysis and interpretation, and the decision to publish.

Compliance with ethical standards

Conflict of interest GPF received grant support, lecture or advisory board fees from AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Novo-Nordisk, Sanofi, Genzyme, Abbott, Mundipharma, Novartis, and Merck Sharp & Dohme. ED received grant support, lecture or advisory board fees from AstraZeneca, Eli Lilly, Lifescan, and NovoNordisk, Sanofi. GC received, lecture or advisory board fees from AstraZeneca, Lilly/Boehringer, Menarini, and Servier. AA received research grants, lecture or advisory board fees from Merck Sharp & Dome, AstraZeneca, Novartis, Boeringer-Ingelheim, Sanofi, Mediolanum, Janssen, and NovoNordisk. PLV, MP, and GF have nothing to disclose.

Ethical approval The study has been conducted in compliance with ethical standards for research involving human participants. The study was approved by local ethical committees at each participating center.

Informed consent The study was conducted on retrospectively collected anonymous patient records. Therefore, based on national regulations on retrospective studies, informed consent was not required.

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