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

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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 initiated dapagliflozin in 2015-2016 and 14,801 patients who initiated 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 initiated 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.

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 United Kingdom reported that 9-12% of patients initiating second or more advanced line of therapy permanently discontinued treatment by 3 months, reaching >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 sulphonylureas 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 glycaemic and extra-glycaemic endpoints 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, 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 initiated treatment, we recorded whether there was a follow-up visit within the study data collection period (ending 31th 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 2 groups: those who initiated dapagliflozin and those who initiated 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 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 initiated dapagliflozin or comparators, by comparing the average characteristics of patients who discontinued the drug versus patients who persisted on drug. Continuous variables were compared using 2-tail 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 complete case are 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 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 initiated new GLM, of whom 2484 patients initiated dapagliflozin and 14,801 initiated 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 initiated 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 initiated comparators for whom a follow-up visit was available, 6464 patients persisted on treatment and 4617 discontinued treatment (41.7%). Clinical characteristics of these patients are summarized in table 1.

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 10 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.

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 (Figure 2).

Upon a logistic regression analysis on 10 imputed datasets with all covariates entered as a block, the relative risk of discontinuation associated with dapagliflozin versus comparators was 1.32 (95% C.I. 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 effect. Rather, common reasons for discontinuing other GLM are gastrointestinal symptoms (GLP-1RA and, rarely, DPP4i) or hypoglycemia (sulphonylureas). 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 characteristics recorded at the time patients received 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 initiated dapagliflozin was extremely different from those of patients who initiated other GLM. Despite 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 initiated dapagliflozin and those who initiated a comparator (especially DPP-4i and gliclazide) prevented us to perform 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 or early GLM discontinuation, likely because the newly initiated drug could not afford the desired glycemic effect in patients with HbA1c far from target, leading to need to further intensification with a change in the treatment regimen. In this regards, 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 sulphonylureas. 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 complains. Yet, hyperfiltration is expected to result in stronger glycemic effect of SGLT2i and, indeed, higher eGFR was among 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 not 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 side effects, lack of efficacy, and other reasons. Finally, updated clinical data of patients who discontinued treatment were not available, preventing any further consideration on 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 indicators, as well as the therapeutic trajectories of patients.

In conclusion, we found no evidence that any baseline characteristics recorded at the time patients received 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.

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Conflict of interest disclosure

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

Author contribution

Study design: GPF, and 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.

Composition of the DARWIN-T2D database

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

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, mm Hg	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
Calcum 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

Table 2. Results of the multivariate analysis. 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.

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

Figure 1. Study flowchart. GLM, glucose lowering medications.

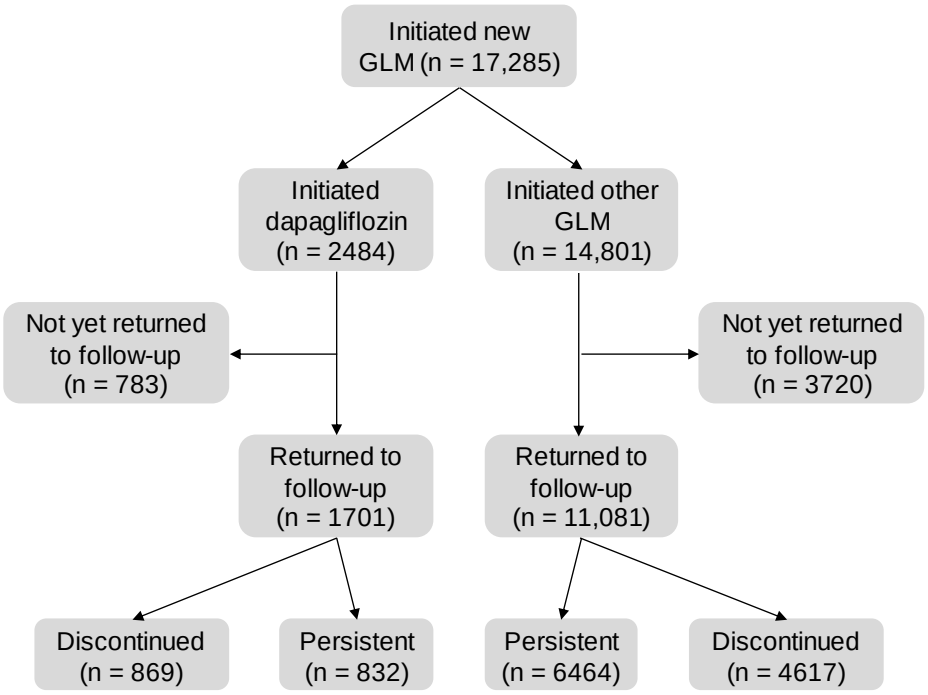

Figure 2. **Possible scenarios of common and drug-specific predictors of discontinuation**. Var stands for variable. The example graphically represented at the bottom corresponds to the findings of the present study, wherein drug 1 is dapagliflozin and drug 2 are comparators.