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Glycaemic, weight, and blood pressure changes associated with early versus later treatment intensification with dapagliflozin in United Kingdom primary care patients with type 2 diabetes mellitus

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ABSTRACT

Aims: Early treatment intensification for type 2 diabetes mellitus (T2DM) is often required to achieve glycaemic control and avoid longer-term complications. We assessed associations between early versus later dapagliflozin initiation with changes in glucose control, weight, and blood pressure using UK Clinical Practice Research Datalink (CPRD) data.

Methods: People with T2DM aged ≥18 years, initiating dapagliflozin between November 2012 and August 2016 and with prior oral T2DM therapy (N = 3774), were included. The relationship between early (first intensification after metformin or sulfonylurea monotherapy) and later (second or higher-order intensification) dapagliflozin use and baseline changes in glycated haemoglobin A1c (HbA1c; ≥1.0% absolute reduction), weight (≥5.0% relative loss), and systolic blood pressure (SBP; ≥2 mmHg absolute reduction) after 6–12 months were assessed.

Results: Overall, 25% of patients (951 of 3774) were early users and 75% (2823 of 3774) were later users. Later users were older, more likely to be men, and had longer disease duration. Early and later users had similar baseline mean HbA1c levels. For early versus later users, respectively, baseline-adjusted mean (95% confidence interval [CI]) reductions were 1.54% (−1.65, −1.44) versus 1.02% (−1.08, −0.97) in HbA1c, 3.31% (−4.37, −2.25) versus 4.06% (−5.05, −3.07) in weight, and 2.50 mm Hg (−3.89, −1.11) versus 2.84 mm Hg (−3.67, −2.01) in SBP. Early versus later use was associated with a greater likelihood of adjusted HbA1c reduction of ≥1% (odds ratio: 1.68, 95% CI: 1.15–2.45).

Conclusions: Glycaemic benefits were greater with early versus later dapagliflozin intensification. These results support broader and earlier dapagliflozin use.

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1. Introduction

Good glycaemic control, particularly in the early years after diagnosis, is a cornerstone of type 2 diabetes mellitus (T2DM) treatment [1]. Due to the progressive nature of the disease, most people with T2DM require treatment intensification following metformin monotherapy to achieve and maintain recommended glycaemic targets [2]. Patients receiving early treatment intensification demonstrate greater glycated haemoglobin A1c (HbA1c) reductions and a higher probability of achieving or maintaining target HbA1c levels compared with those receiving later treatment intensification [1,3,4]. Clinical inertia may delay treatment intensification not only in patients failing metformin monotherapy [4] but also in those receiving second-line pharmacologic therapies [5].

Dapagliflozin is a sodium–glucose cotransporter-2 (SGLT2) inhibitor, which reduces glucose levels by decreasing the kidney's reabsorption of glucose and also reduces body weight [6]. Dapagliflozin improves blood glucose control relative to placebo in treatment-naïve patients with T2DM [7], and in patients with inadequate glycaemic control on metformin [8,9], sitagliptin, sulfonylureas [10,11], and high-dose insulin [12]. In the Dapagliflozin Effect on CardiovascuLAR Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) cardiovascular outcome trial (CVOT) conducted in 17,160 people (aged ≥40 years) with T2DM (followed for a median 4.2 years) who were at risk for, or had established atherosclerotic cardiovascular disease (CVD), dapagliflozin treatment resulted in a lower rate of hospitalisation for heart failure versus placebo (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.61–0.88), including individuals without atherosclerotic CVD. However, dapagliflozin did not result in a significantly lower rate of CVD than placebo (HR, 0.98; 95% CI, 0.82–1.17). In addition, dapagliflozin-treated patients were less likely to develop end-stage renal disease or die from a renal cause, although such effects were hypothesis generating due to the hierarchical statistical analysis [13]. The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program showed that, apart from hospitalisation for heart failure, canagliflozin also significantly reduced the composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke and exerted renal benefits (again on a hypothesis-generating basis) [14]. The EMPA-REG OUTCOME trial showed that, in addition to hospitalisation for heart failure, empagliflozin also significantly reduced CVD death, all-cause mortality, and the composite of death from CV causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke; renal benefits (such as incident or worsening nephropathy, which were significant and not hypothesis-generating) were also shown [15,16]. Directionally consistent results on CV outcomes have also been observed for the SGLT2-inhibitor class in large observational comparative cohort studies [17–20].

Dapagliflozin could offer similar glycaemic and body weight benefits in the United Kingdom (UK) primary care setting [21]. There remains a need to better characterise the effects of dapagliflozin in people with T2DM when used at different stages in the treatment pathway in the real-world setting. We therefore assessed whether early compared with later dapagliflozin initiation is associated with greater reductions in HbA1c, weight, and systolic blood pressure (SBP) in patients with T2DM in the UK.

2. Materials and Methods

2.1. Study design and patients

This non-interventional retrospective cohort study assessed whether early versus later dapagliflozin initiation is associated with greater reductions in HbA1c, weight, and SBP in adult patients with T2DM with prior oral therapy who remained on dapagliflozin for at least 6 months. The study used patient-level data from the April 2017 version of the UK Clinical Practice Research Datalink (CPRD) GOLD database. CPRD GOLD contains anonymised longitudinal patient-care records of more than 11.3 million patients collected from general practices across the UK [22].

Patients initiating dapagliflozin were followed for as long as they were on treatment up to a maximum of 15 months post-initiation. The study protocol was approved by the Independent Scientific Advisory Committee for CPRD Research (14_236AMn).

Key inclusion criteria were initiation of dapagliflozin (index date) between November 1, 2012, and August 31, 2016; aged ≥18 years at the index date; and diagnosed with T2DM at any time prior to the index date. For assessment of clinical outcomes, patients had to be on dapagliflozin for ≥6 months, have metformin or sulfonylurea as first (ever) T2DM therapy prior to the index date, and have ≥12 months of history prior to the index date and ≥6 months of follow-up after the index date. Key exclusion criteria were diagnosis of type 1 diabetes mellitus or gestational diabetes and use of injectable therapy (glucagon-like peptide-1 receptor agonists [GLP-1 RAs] or insulin) or SGLT2 inhibitors (canagliflozin or empagliflozin) prior to the index date.

Patients were categorised as "early" (second-line) dapagliflozin users if dapagliflozin was the second anti-hyperglycaemic medication prescribed after first-line use of either metformin or sulfonylurea (second-line use after other medications excluded). Patients were categorised as "later" dapagliflozin users if dapagliflozin represented a second or higher-order intensification. This was assessed in the database by looking at the class of initial anti-hyperglycaemic medication and in the 6-month period preceding dapagliflozin initiation. The switch or add-on could have occurred anytime in the treatment pathway prior to dapagliflozin initiation.

2.2. Outcome measures

Baseline characteristics were presented for demographics, body mass index (BMI), weight, HbA1c, SBP, estimated glomerular filtration rate (eGFR; measured according to the Chronic Kidney Disease Epidemiology Collaboration

[CKD-EPI]) equation) [23], smoking status, previous diabetes and blood pressure medications, major comorbidities, including those related to T2DM (nephropathy, retinopathy and neuropathy) and CVD (unstable angina, atrial fibrillation, heart failure, myocardial infarction, stroke and peripheral arterial disease), and time since T2DM diagnosis and since initiation of T2DM therapy.

Primary outcome measures included changes from baseline in HbA1c (%; absolute change and % of patients with ≥1.0% [approximately 8 mmol/mol] absolute reduction), weight (kg; absolute change and % of patients with ≥5.0% relative loss), and SBP (mm Hg; absolute change and % of patients with ≥2.0 mm Hg absolute reduction) for early versus later dapagliflozin initiation. Changes in clinical measures were derived from the nearest to index date reading (within 6 months) and the earliest reading 6–12 months (±30-day window) after the index date. Only measurements in patients on dapagliflozin treatment during follow-up were included for analyses.

2.3. Statistical analyses

All baseline characteristics were reported as frequency and percentage for categorical variables and as mean (standard deviation [SD]) and median for continuous variables. Time on dapagliflozin was estimated via the Kaplan-Meier method, and the probability of being on treatment after the index date is presented up to 15 months. For early versus later dapagliflozin initiation, unadjusted mean changes in clinical measures from baseline with standard errors are presented. Adjusted mean changes (with 95% CIs) in clinical measures were estimated using analysis of covariance, with adjustments for age, sex, time since T2DM diagnosis, baseline HbA1c, BMI, and SBP. Logistic regression was used to assess the relationship between early and later dapagliflozin initiation and the achievement of target reductions in the primary outcome measures. Adjusted odds ratios (ORs) are presented for early versus later dapagliflozin initiation with adjustments for age, gender, time since T2DM diagnosis, baseline HbA1c, BMI, diabetes complications, CVD, and anti-hyperglycaemia medication. Additional adjustments were made specific to BP: baseline BP and differences in the presence or absence of hypertension medications. During follow-up, if there were multiple clinical measures, the first recorded outcome measure was used. All statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patient demographics and baseline characteristics

A total of 3774 patients met the inclusion criteria, of which approximately one quarter were early dapagliflozin users (N = 951) and approximately three quarters were later dapagliflozin users (N = 2823). Early initiation of dapagliflozin generally increased over the study period (21% in 2012–2013 versus 31% in 2016; Table 1). Early versus later dapagliflozin users were younger (mean [SD] 56 [11] versus 60 [10] years), less likely to be men (55% versus 62%), had T2DM for a shorter duration (median of 4 versus 8 years), and were less likely to have diabetes complications (32% versus 51%) and CVD (11% versus 14%; Table 2). Early and later dapagliflozin users, respectively, had similar baseline HbA1c levels (mean [SD] 9.2% [1.7] versus 9.3% [1.5]) and SBP (mean [SD] 135 [15] versus 134 [14] mm Hg; Table 2). Compared with early users, later dapagliflozin users had lower BMIs and slightly lower mean eGFRs (Table 2). The median time on therapy was similar for early and later dapagliflozin users and was approximately 13 months (Fig. 1).

Overall, 52% of patients were on therapy and had an HbA1c measurement at baseline and 6–12 months post-dapagliflozin initiation. A slightly lower percentage of patients had weight (45%) and SBP (44%) measurements at both time points. Later dapagliflozin users were slightly more likely to have clinical measurements than early users (later versus early users: HbA1c, 53% versus 49%; weight, 45% versus 43%; SBP, 44% versus 42%).

3.2. Primary outcomes

Early dapagliflozin users experienced unadjusted mean (standard error) reductions of 1.6% (0.07; n = 470), 3.8% (0.25; n = 410), and 3.0 (0.82; n = 401) mm Hg in HbA1c, weight, and SBP, respectively, versus 1.0% (0.04; n = 1486), 4.6% (0.21; n = 1277), and 3.1 (0.43; n = 1246) mm Hg in later users, respectively.

Early dapagliflozin users experienced baseline-adjusted mean (95% CI) reductions of 1.54% (−1.65, −1.44, p < 0.0001),

Table 1 – Initiation of dapagliflozin by year and position in treatment pathway.

Year of dapagliflozin initiation	Dapagliflozin initiation (n, %)		
	Early use	Later use	Total
2012[†]–2013	79, 21%	289, 79%	368
2014	276, 24%	886, 76%	1162
2015	370, 25%	1140, 75%	1510
2016[§]	226, 31%	508, 69%	734
Total	951	2823	3774

[†] Patients were included if initiation of dapagliflozin was between November 1, 2012 and
[§] August 31, 2016.

Table 2 – Baseline demographics and comorbidities.

Characteristic	Early use (N = 951)	Later use (N = 2823)
Sex, male, n (%)	526 (55)	1738 (62)
Age, years, mean (SD), median	56 (11), 56.0	60 (10), 60.0
Time since T2DM diagnosis, years, mean (SD), median	5.0 (4.2), 4.0	8.8 (5.3), 8.1
HbA1c, %, mean (SD), median, n	9.2 (1.7), 8.8, 937	9.3 (1.5), 9.0, 2809
BMI, kg/m^2, mean (SD), median, n	36.5 (6.8), 35.4, 889	33.6 (6.3), 32.7, 2654
Weight, kg, mean (SD), median, n	106 (22), 103, 894	97 (21), 95, 2660
Systolic BP, mm Hg, mean (SD), median, n	135 (15), 135, 863	134 (14), 134, 2483
Diastolic BP, mm Hg, mean (SD), median, n	80 (9.2), 80, 863	78 (9.0), 79, 2483
eGFR, mL/min/1.73 m^2, mean (SD), median, n	93 (15), 94, 926	88 (16), 90, 2779
Comorbidities, n (%)		
CVD[†]	106 (11)	393 (14)
Atrial fibrillation	25 (2.6)	81 (2.9)
Heart failure	17 (1.8)	48 (1.7)
Myocardial infarction	32 (3.4)	135 (4.8)
Peripheral arterial disease	20 (2.1)	85 (3.0)
Stroke	32 (3.4)	107 (3.8)
Unstable angina	6 (0.6)	30 (1.1)
Diabetes complications	303 (32)	1429 (51)
Nephropathy	64 (6.7)	295 (10)
Neuropathy	115 (12)	591 (21)
Retinopathy	190 (20)	967 (34)

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; SD, standard deviation; T2DM, type 2 diabetes mellitus.
Note: For each measure, the "n" of early and later users represents the number of patients with the clinical measure.
[†] CVD includes myocardial infarction, stroke, unstable angina, heart failure, atrial fibrillation and peripheral arterial disease.

3.31% (−4.37, −2.25), and 2.50 mm Hg (−3.89, −1.11, p = 0.6689) in HbA1c, weight, and SBP, respectively, versus 1.0% (−1.08, −0.97), 4.06% (−5.05, −3.07), and 2.84 mm Hg (−3.67, −2.01) in later users, respectively (Fig. 2).

Early dapagliflozin use was associated with a greater likelihood of HbA1c reductions of ≥1.0% than later use (OR [95% CI] 1.68 [1.15–2.45, p = 0.0073]; Table 3). Compared with patients aged <55 years, patients aged >70 years were less likely to achieve HbA1c reductions (OR [95% CI] 0.64 [0.45–0.90, p = 0.0112]). Patients with a lower baseline HbA1c were less likely to attain reductions than those with a higher baseline HbA1c (HbA1c <8.5% versus >10.0%; OR [95% CI] 0.08 [0.06–0.10], p < 0.0001; Table 3).

No differences in the likelihood of achieving weight and SBP reductions were observed for early versus later dapagliflozin users (OR [95% CI] 0.79 [0.54–1.14, p = 0.2079] and 0.87 [0.58–1.30, p = 0.4870], respectively; Table 3). The main predictors of weight reduction were higher baseline BMI (patients with a BMI >30 and ≤40 kg/m^2 were more likely to achieve a weight reduction of ≥5.0% compared with those with a BMI <30 kg/m^2; [OR (95% CI) 1.56 (1.23–1.98, p = 0.0003)]), lower baseline HbA1c (HbA1c <8.5% versus ≥10%; OR [95% CI] 1.74 [1.34–2.26], p < 0.0001), and female sex (OR [95% CI] 1.64 [1.33–2.02], p < 0.0001). Baseline SBP was the only predictor of reductions in SBP. The higher the baseline SBP, the more likely patients were to achieve reductions of ≥2 mm Hg while on dapagliflozin. For each unit increase in baseline SBP, the odds of a subsequent reduction ≥2 mm Hg are increased by 8% (OR [95% CI] 1.08 [1.07–1.10], p < 0.0001; Table 3).

4. Discussion

Although evidence suggests that people with T2DM could have improved glycaemic control if treatment is intensified quickly after failure of metformin therapy, the potential effects of dapagliflozin use at varying stages in the treatment pathway in real-world clinical practice have not been systematically investigated previously. This study assessed, in the UK primary care setting, treatment intensification in patients initiating dapagliflozin, and its association with glycaemic control, weight, and SBP. Results showed that compared with later use, early dapagliflozin use might lead to slightly greater glycaemic benefits in this patient population. This may reflect the clinical characteristics of people who initiate dapagliflozin treatment later, including advanced age and higher rates of renal impairment, neuropathy, and retinopathy, versus those who initiate treatment early. Both weight and SBP reductions, however, were achieved with similar likelihood among early and later dapagliflozin users.

Individual, anonymised patient data were extracted from the CPRD, a well-validated, clinically representative database frequently used for pharmaco-epidemiological research [22,24,25]. The results therefore represent real-world clinical practice in the UK primary care setting. Another retrospective study using the CPRD database for patients with T2DM receiving first-line metformin monotherapy (N = 9097) reported a higher likelihood of achieving glycaemic and weight reduction goals for patients receiving second-line SGLT2 inhibitors versus those receiving second-line sulfonylureas or dipeptidyl peptidase-4 inhibitors; treatment persistence was also

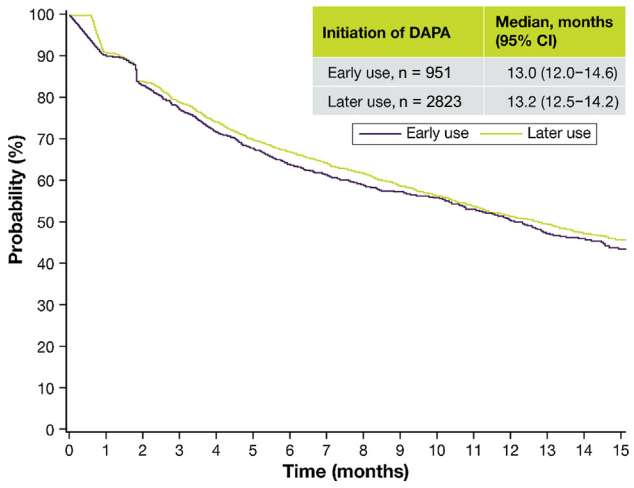

Fig. 1 – Time on dapagliflozin in early versus later users. CI, confidence interval; DAPA, dapagliflozin.

highest in those receiving metformin and an SGLT2 inhibitor [26]. A retrospective study using the CPRD database of patients with T2DM (N = 93,515) found benefits to early treatment intensification in terms of time to subsequent glycaemic control [27]. Three quarters of the patients did not receive intensified treatment for more than a year after the first signs of monotherapy failure. The time from intensification to attainment of glycaemic control was approximately 6 months longer among late intensifiers than among early intensifiers. These and similar findings in a United States population [4] illustrate the common and serious problem of clinical inertia in the treatment of people with T2DM, which occurs when treatment is delayed or not intensified despite failure to achieve glycaemic goals [28]. This phenomenon motivates recommendations of the current position statement of the American Diabetes Association and the European Association for the Study of Diabetes, which recommends a review of treatments every 3–6 months to avoid clinical inertia [2]. However, because SGLT2 inhibitors have been shown to have durable glucose-lowering efficacy up to at least 2 years, with weight loss increasing progressively with treatment duration [6], the timing of treatment intensification may be just as important as avoiding clinical inertia. Moreover, treatment decisions that stratify patients by risk may be a promising approach towards initiating SGLT2 inhibitors at any stage in the treatment paradigm [29], especially at an early rather than a later stage for dapagliflozin, as suggested by the results of the present study.

In clinical practice, new classes of anti-hyperglycaemic drugs (e.g., SGLT2 inhibitors and GLP-1 RAs) tend to be more frequently used at advanced stages of the disease (i.e., at later points in the treatment pathway) and recommended for specific subgroups (e.g., in those with obesity) [30]. Our data corroborate these clinical observations, although the pattern is slowly evolving over time.

Recent guidelines for T2DM [2] recommend, for people with a history of established atherosclerotic CVD or chronic kidney disease, early intensification with any of the drugs that have shown CV benefits, i.e., SGLT2 inhibitors or GLP-1 RAs. In addition, our results suggest that greater benefits can be achieved by using dapagliflozin earlier in the T2DM treatment pathway, because this is associated with better glycaemic control. The increase in dapagliflozin prescribing over the study period combined with recently reported results of a dapagliflozin CVOT [13] and directionally consistent results from large, observational, global cohort studies of dapagliflozin and other SGLT2 inhibitors [17–20] support a growing evidence base for dapagliflozin use early in the treatment pathway. Results from other CVOTs [14,16] similarly provide evidence supporting the use of other SGLT2 inhibitors. For example, a recent meta-analysis [31] of the three CVOTs provides evidence that supports the use of SGLT2 inhibitors in people with T2DM regardless of their history of heart

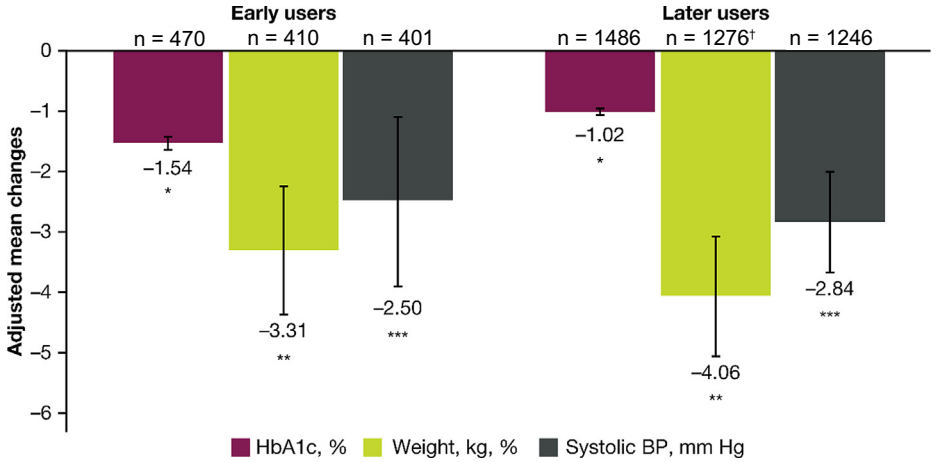

Fig. 2 – Adjusted mean changes (with 95% confidence intervals) from baseline in clinical measures at 6–12 months. BP, blood pressure; HbA1c, glycated haemoglobin. Data have been adjusted for age, sex, and time since type 2 diabetes mellitus diagnosis. Other adjustments specific to measure are baseline values of HbA1c, weight, and BP. *p < 0.0001; **p = 0.0097; ***p = 0.6689. †One extreme outlier was removed for calculations of adjusted weight changes. For each measure, the "n" of early and later users represents the number of patients with the clinical measure.

Table 3 – Likelihood of achieving reductions in HbA1c, weight, and systolic BP while on dapagliflozin treatment (6–12 months post-initiation).

Characteristic	Reduction in HbA1c ≥1.0%			Reduction in weight ≥5.0%			Reduction in systolic BP ≥2 mm Hg		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Early versus later use of dapagliflozin	1.68	1.15–2.45	0.0073	0.79	0.54–1.14	0.2079	0.87	0.58–1.30	0.487
HbA1c, % (reference: >10)									
<8.5 (69 mmol/mol)	0.08	0.06–0.10	<0.0001	1.74	1.34–2.26	<0.0001	0.91	0.68–1.20	0.4933
8.5–10 (69–86 mmol/mol)	0.37	0.28–0.49	<0.0001	1.50	1.16–1.95	0.0023	0.84	0.63–1.11	0.2187
Baseline systolic BP, mm Hg	N/A	N/A		N/A	N/A		1.08	1.07–1.10	<0.0001
Time since T2DM diagnosis, years (reference: <4)									
4–8	0.87	0.65–1.17	0.3525	1.24	0.93–1.66	0.1473	1.04	0.76–1.42	0.8268
8–12	0.99	0.72–1.37	0.9489	1.28	0.93–1.77	0.1281	0.97	0.69–1.37	0.8707
>12	0.95	0.66–1.37	0.7766	1.36	0.94–1.95	0.1007	0.94	0.64–1.39	0.7684
Age, years (reference: <55)									
55–70	0.83	0.66–1.06	0.1324	0.90	0.71–1.13	0.3714	0.99	0.76–1.28	0.9285
>70	0.64	0.45–0.90	0.0112	0.84	0.59–1.21	0.3501	0.94	0.64–1.37	0.7465
Sex, female	0.91	0.74–1.13	0.4038	1.64	1.33–2.02	<0.0001	1.16	0.92–1.46	0.2038
BMI, kg/m^2 (reference: <30)									
>30–40	1.06	0.83–1.34	0.6587	1.56	1.23–1.98	0.0003	1.01	0.77–1.30	0.9682
>40	0.84	0.60–1.17	0.2909	1.72	1.25–2.37	0.0010	1.09	0.76–1.57	0.6314
Missing	0.89	0.55–1.46	0.6533	0.39	0.04–3.46	0.3967	0.98	0.54–1.80	0.9594
[†]Diabetes complications	0.95	0.77–1.18	0.6632	1.15	0.93–1.42	0.1921	0.98	0.78–1.23	0.8486
[§]CVD	0.86	0.64–1.17	0.3408	0.90	0.66–1.21	0.483	1.20	0.86–1.68	0.2942

BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; N/A, not applicable; OR, odds ratio; T2DM, type 2 diabetes mellitus.
Note: Additional adjustments were made across all models for prior use of dipeptidyl peptidase-4 inhibitors and sulfonylureas. Additional adjustments were also made for BP: baseline differences in the presence or absence of hypertension medications.
[†] Diabetes complications include diabetic retinopathy, neuropathy and nephropathy.
[§] CVD includes myocardial infarction, stroke, unstable angina, heart failure, atrial fibrillation and peripheral arterial disease.

failure or atherosclerotic CVD [32]; however, the benefit is largely related to reductions in heart failure hospitalisation and the number needed to treat is high for low-risk populations.

Several limitations of the present study should be acknowledged. Since this is a descriptive study focusing only on patients initiating dapagliflozin, we did not assess the effectiveness of early treatment intensification with dapagliflozin versus other T2DM treatments. Adjustments in models were based on baseline characteristics and any changes observed during follow-up may not relate to dapagliflozin alone. Furthermore, as patients had to be on treatment and have clinical measurements for at least 6 months after initiation of dapagliflozin, the study may reflect a bias whereby patients who are responding well are more likely to persist with treatment. The CPRD records that a prescription was issued, not whether it was dispensed or taken by the patient. Adherence was thus not assessed. Because many people with T2DM are non-adherent to oral glucose-lowering therapy [33], this could bias the results, especially if adherence was different between the groups. Although the study captured patients initiating dapagliflozin up to the end of August 2016 and therefore does not reflect current prescribing practices, the results are not expected to change dramatically over the course of a couple of years. Safety was not assessed. Finally, the results of this study should be interpreted with caution because of missing clinical information and possible bias due to lack of randomisation.

5. Conclusions

Results of this large retrospective observational study show that most people with T2DM in a UK clinical practice setting are initiated on dapagliflozin later in the treatment pathway. The proportion of patients initiated early on dapagliflozin progressively increased over time. The glycaemic benefits of dapagliflozin might be greater in people who receive it early versus later.

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Declaration of Competing Interest

UR, BTB, STN, PF, and JM are employees of AstraZeneca. JPHW, outside the submitted work, has grants, personal fees, and consultancy fees (paid to his institution) from AstraZeneca, Novo Nordisk, and Takeda; personal fees and consultancy

fees (paid to his institution) from Boehringer Ingelheim, Janssen, Lilly, Mundipharma, Napp, and Sanofi; and consultancy fees (paid to his institution) from Wilmington Healthcare. All authors have approved the final article.

Ethical approval

All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki 1964 and its later amendments or comparable ethical standards. The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines, and followed applicable regulatory requirements, including AstraZeneca's policy on bioethics. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Author contributions

JPHW, UR, PF, and JM contributed to the study design. UR, BTB, and JM were involved in data acquisition. All authors were involved in data analysis and interpretation. All authors contributed to the drafting and critical review of the manuscript and approved the final draft.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107791.

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