Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Early drug use of dapagliflozin prescribed by general practitioners and diabetologists in Germany

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ARTICLE INFO

Article history:
Received 23 June 2016
Received in revised form
12 October 2016
Accepted 30 October 2016
Available online 9 November 2016

Keywords:
Dapagliflozin
Diabetes
Anti-diabetic

ABSTRACT

Objectives: Dapagliflozin is an inhibitor of the human sodium-glucose co-transporter 2 (SGLT2) that has been shown to improve glycaemic control in patients with type 2 diabetes mellitus (T2DM). This study aimed to evaluate the characteristics and treatment patterns of dapagliflozin users in comparison to users of other anti-diabetic (AD) treatments in Germany.

Methods: Data from patients with T2DM initiating at least one prescription for dapagliflozin or other AD therapy between November 2012 and April 2014 were collected from the IMS German Disease Analyzer database.

Results: The use of dapagliflozin combination therapy ($n = 1034$; 74%) was more common than monotherapy ($n = 371$; 26%). In comparison with other AD therapy users, a higher percentage of dapagliflozin users were ⩽64 years of age (62.3% vs. 36.4%), and a higher proportion were male (59.1% vs. 53.6%). The average duration of diabetes was comparable between dapagliflozin patients and other AD therapy users (5.7 years vs. 5.5 years), however higher levels of HbA1c were found in dapagliflozin users (8.2% (66 mmol/mol) vs. 7.5% (58 mmol/mol). For the vast majority (71.5% of 10 mg dapagliflozin users and 88.9% of 5 mg users), dapagliflozin was prescribed in combination with other AD therapy.

Conclusions: Patients starting on dapagliflozin differed in several demographic and health-related respects to patients starting another AD therapy during the same period. Dapagliflozin was predominantly used as a component of combination therapy, adding on to existing therapy. After initiation, switching to other AD treatments or adding to therapy was comparatively rare during the first year.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a global public health concern affecting 387 million people world-wide and 52 million people in Europe. By the year 2035, these numbers are expected to increase to 592 million and 69 million respectively. In Germany alone, 7.3 million people have T2DM, equating to one in nine adults affected by the disease [1].

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http://dx.doi.org/10.1016/j.diabres.2016.10.025
0168-8227/

T2DM is a metabolic disorder characterised by hyperglycaemia and an increased risk of both microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) and macrovascular complications (coronary artery disease, peripheral arterial disease, and stroke). While improved glycaemic control can reduce diabetes-related complications, especially microvascular, almost four in ten patients with T2DM in Germany fail to reach their target blood glucose and haemoglobin HbA1c levels [2].

There are today several available therapies for glycaemic control including insulin, metformin, thiazolidinediones, sulphonylureas, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and most recently sodium-glucose co-transporter 2 (SGLT-2) inhibitors. SGLT-2 is a major transporter of glucose responsible for renal glucose reabsorption. Dapagliflozin is a highly potent and selective SGLT2 inhibitor of, with a mechanism of action that is different from and complementary to the mechanisms of currently available in other anti diabetic medicine classes. It improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption, resulting in the direct, insulin-independent, elimination of excess glucose by the kidney. SGLT2 is selectively expressed in the kidney minimising the risk of off-target (i.e. non-kidney) effects [3].

Dapagliflozin is the first agent of its class to be approved in the European Union for the treatment of T2DM in adults. It received marketing approval in November 2012 as a monotherapy to improve glycaemic control in adults with T2DM, when adequate glycaemic control was not achieved through diet and exercise alone and metformin was considered inappropriate due to intolerance. Dapagliflozin has also been approved in combination therapy with other glucose-lowering products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control [3]. In January 2014, a combination product of dapagliflozin and metformin received marketing approval for use in adults with T2DM as an adjunct to diet and exercise to improve glycaemic control.

In 2013, the German Institute for Quality and Efficiency in Health Care (IQWiG) carried out a dapagliflozin benefit assessment and reported that the incremental benefit of dapagliflozin over standard therapy could not be demonstrated given the lack of real-world data from which to form a comparison [4]. This study aimed to show dapagliflozin use in a real-world setting by evaluating demographic and clinical characteristics of dapagliflozin users in comparison to users of other antidiabetic (AD) treatments in Germany, and identifying dapagliflozin treatment patterns. The study should provide a basis for understanding how the medical community perceives dapagliflozin and how it can be used to meet unmet treatment needs.

2. Methods

2.1. Study design and source population

This study adhered to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidance [5]. Data were obtained from the IMS German Disease Analyzer (DA), an electronic healthcare database with anonymised, individual-level information on more than 13 million patients and about 77 million prescriptions identified from over 3000 general practitioner (GP) practices and specialists [6]. Compared with other patient databases, DA is unique, being the only database available to include and combine all information on physicians, patients, diagnoses, and courses of therapy relevant for the decision-making process. The data within the DA are obtained directly from GP and specialist practice computers through standardised interfaces used in day-to-day practice [7]. The German DA represents 2% of all practices in Germany and is indicative of the larger general German population in the health assurance fund with respect to age, region, prescriptions and diagnoses [6]. The longitudinal nature of the data provides the ability to track changes in drug utilisation over time. Becher et al. (2009) found no indication of lack of representativeness or validity of the DA database. In principle, the database appears suitable for pharmacoepidemiological and pharmacoeconomic studies [7].

As with all electronic medical record (EMR) datasets, information is limited by the level of detail and quality of information recorded by the physician. The low response rate among physicians is certainly a point of concern and warrants a thorough investigation of the potential for bias when using the DA database in a study [7].

The study time period began from the time of first licensing of dapagliflozin in Germany (12 November 2012), until 30 April 2014. The index date was defined as the first-time use of either dapagliflozin or other AD therapy within the study time period (new user design). The observation period was defined as the period between the index date and the end of data capture (end of the study time period, death or lost to follow-up). The cohort for this study was defined as patients who were either: (i) prescribed dapagliflozin or (ii) prescribed other AD therapies. The primary exposure of interest in this study was dapagliflozin. Patients prescribed other AD therapies were considered a comparator group. To be included in the study patients must have had at least one prescription for dapagliflozin or other AD therapy during the study time period, at least one recorded diagnosis of T2DM prior to or on the index date, and a minimum of 6 months of continuous enrolment within IMS German DA prior to the index prescription. Subjects were excluded from the study if they had a diagnosis of type 1 diabetes mellitus. Covariates measured at the time of the index date are reported to cover information on demographic characteristics (age and sex), diabetes history (duration of T2DM before first AD therapy prescription), comorbid conditions, concomitant medications, laboratory parameters and prescriber information.

2.2. Statistical methods

Descriptive analysis was performed using counts and proportions (n, %) for categorical variables; means and medians (SD, 95% CI) were estimated for continuous variables. Variables were categorised into quartiles as required. Interquartile range (IQR) and range of data (min, max) were reported. All statistical analysis was performed using SAS (Cary, North Carolina). Graphical display of information was derived from MS Excel.

Demographic and clinical characteristics of patients initiating a new AD therapy (incident users) were reported at the time of the index date. In particular, patient age, gender, insurance type and residence, diabetes history, comorbid conditions, concomitant medications and laboratory parameters were reported. Incident users of dapagliflozin and other AD therapies were analysed separately. Patterns of prescribing by age and sex were not formally compared between cohorts due to the heterogeneity of the 'other AD therapy' cohort. The dapagliflozin user cohort was stratified further into monotherapy users and combination therapy subgroups. Dapagliflozin prescriber information was characterised by prescriber practice type (general practice or diabetologist), age category of practitioner and number of patients in practice.

To quantify drug utilisation, data on the average daily dose (ADD) was obtained. ADD of dapagliflozin was defined as the average dose prescribed over a treatment episode and was calculated by dividing the total quantity prescribed by the number of days in the treatment period. Analysis associated with dose calculations only considered standard dosing available for dapagliflozin (i.e., 5 mg or 10 mg). Data was also obtained on subsequent use of insulin or other additional AD therapy (the proportion of AD therapy users who subsequently use insulin vs. those who subsequently use other additional AD therapies).

Analyses of the treatment patterns of dapagliflozin utilisation were conducted. Identification of switch in therapy was defined as the discontinuation of the existing therapy coupled with a new prescription for an alternative AD therapy. Switching in therapy from dapagliflozin to other AD therapies as well as switching in therapy from other AD therapies to dapagliflozin was examined. The presence/absence of a switch, the time to switch and the drug class involved were reported. The date of switch was the day immediately preceding the prescription date of the new product. Add-on therapy for dapagliflozin users was defined as the addition of a new AD prescription that overlaps with the existing dapagliflozin prescription, were examined. The number of dapagliflozin users with add-on therapy, the time to add-on and the drug classes added were reported.

Dose adjustment for dapagliflozin was defined as the recorded change in starting dosage (i.e. 5 mg or 10 mg) from the index treatment. The number of patients affected and the average time to dose adjustment were reported.

The compliance of dapagliflozin use was examined. Compliance of dapagliflozin was defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen [8]. Compliance was quantified by the medication possession ratio (MPR), which measured the percentage of time that medication was available for use during the period the patient was persistent with dapagliflozin. MPR was calculated by dividing the number of prescribed therapy units (i.e., daily doses) for dapagliflozin by the number of assumed therapy units needed according to the physician's individual dose recommendation for the observational period. A maximum of 100% compliance was assumed for prescription periods that extended beyond the end of the study period. MPR was calculated only for patients with more than one prescription available. Patients with MPR >80% were considered to be compliant [9]. Average compliance was reported and sensitivity analysis performed by evaluating compliances as MPR > 50%, MPR > 60%, MPR > 70% and MPR > 90%.

3. Results

3.1. Demographic characteristics

A total of 82,868 patients were included in the study; 1405 were identified as dapagliflozin users and 81,463 received other anti-diabetic medication. Among the dapagliflozin users 1234 patients used the 10 mg dose (88%) and 171 patients used the 5 mg dose (12%). Overall, 371 patients (26%) received dapagliflozin monotherapy and 1034 patients (74%) received dapagliflozin as in combination therapy.

Table 1 outlines the demographic characteristics of dapagliflozin and other AD therapy users. Overall patients on dapagliflozin tended to be younger, with a mean age of 61.3 years (SD 10.8, range 19.0–92.0) compared to other AD therapy users [mean age of 68.2 years (SD 12.2, range 18.0–103.0)]. Furthermore, 62.3% (n = 875/1405) of dapagliflozin users were ⩽64 years of age compared to 36.4% (n = 29,687/81,463) of other AD therapy users. A higher proportion of patients on dapagliflozin were male compared to other AD therapy users (59.1%, n = 830/1405 vs. 53.6%, n = 43,661/81,463 respectively).

Private insurance was utilised by 14.9% (n = 210/1405) of patients receiving dapagliflozin therapy compared to 5.7% (n = 4659/81,463) of other AD therapies users. As expected from the population of the respective regions, 75% of the dapagliflozin and other AD therapies users resided in West Germany.

The average duration of diabetes was comparable between dapagliflozin patients and other AD therapy users (5.7 years, SD 4.0 vs. 5.5 years, SD 4.5 respectively).

The majority of patients on dapagliflozin monotherapy were aged between 55 to 64 years (39.6%, n = 147/371), followed by those aged 6574 years (22.9%, n = 85/371) and 4554 years (20.8%, n = 77/371). Among dapagliflozin monotherapy users, men (59.6%, n = 221/371) were more frequently being prescribed with dapagliflozin than were women (40.4%, n = 150/371). Similar age and gender trends were seen for the 1034 patients on dapagliflozin combination therapy.

Dapagliflozin users were reported to have higher levels of HbA1c (8.2% (66 mmol/mol), SD 1.5, N = 902), fasting plasma glucose (172.7 mg/dl, SD 59.0, N = 677) and glomerular filtration rate (80.8 ml/min, SD 22.0, N = 174) compared to other AD therapy users (7.5% (59 mmol/mol), SD 1.4, N = 47,097; 156.9 mg/dl, SD 62.6, N = 38,872 and 74.6 ml/min, SD 25.95, N = 7997 respectively) (Table 2). There was substantial missing data for BMI and smoking status; therefore no comparisons between the two treatment groups was analysed.

3.2. Comorbid conditions and concomitant medications

Comorbid conditions were grouped into three categories: those indicative of disease progression (retinopathy, diabetic neuropathy, nephropathy, and diabetes ketoacidosis), those related to cardiovascular diseases (myocardial infarction, chronic heart failure, stroke, arrhythmia and heart valve disorders) and for those associated with hepatic disease and

Table 1 – Demographic characteristics for dapagliflozin (overall, monotherapy, combination therapy) and other AD therapy users.

Variables	Dapagliflozin			Other AD therapy
	Overall N = 1405	Monotherapy N = 371	Combination N = 1034	Overall N = 81463
Age, n (%)				
18–34	16 (1.1)	6 (1.6)	10 (1.0)	592 (0.7)
35–44	75 (5.3)	19 (5.1)	56 (5.4)	2213 (2.7)
45–54	277 (19.7)	77 (20.8)	200 (19.3)	8746 (10.7)
55–64	507 (36.1)	147 (39.6)	360 (34.8)	18,136 (22.3)
65–74	358 (25.5)	85 (22.9)	273 (26.4)	23,829 (29.3)
75+	172 (12.2)	37 (10.0)	135 (13.1)	27,947 (34.3)
Mean age, years (SD)	61.3 (10.8)	60.4 (10.5)	61.6 (10.9)	68.2 (12.2)
Gender, n (%)				
Male	830 (59.1)	221 (59.6)	609 (58.9)	43,661 (53.6)
Female	575 (40.9)	150 (40.4)	425 (41.1)	37,802 (46.4)
Weight, kg (N, SD)	100.3 (441, 21.7)	99.4 (106, 18.5)	100.6 (335, 22.6)	90.5 (19,126, 20.0)
Insurance type, n (%)				
Statutory	1195 (85.1)	309 (83.3)	886 (85.7)	76.804 (94.3)
Private	210 (14.9)	62 (16.7)	148 (14.3)	4659 (5.7)
Residence, n (%)				
West Germany	1049 (74.7)	289 (77.9)	760 (73.5)	61,084 (75.0)
East Germany	356 (25.3)	82 (22.1)	274 (26.5)	20,379 (25.0)
Duration of diabetes				
Mean, years (SD)	5.7 (4.0)	5.2 (3.9)	5.9 (4.1)	5.5 (4.5)

Table 2 – Laboratory parameters for dapagliflozin (overall, monotherapy, combination therapy) and other AD therapy users.

Variables	Dapagliflozin			Other AD therapy
	Overall	Monotherapy	Combination	Overall
HbA1c, mean% (mmol/mol) (SD, N)	8.2 66 (1.5, 902)	8.1 65 (1.6, 233)	8.2 66 (1.4, 669)	7.5 59 (1.4, 47,097)
Fasting plasma glucose, mean mg/dl (SD, N)	172.7 (59.0, 677)	169.3 (60.5, 178)	173.9 (58.5, 499)	156.9 (62.6, 38,872)
Glomerular filtration rate, mean ml/min (SD, N)	80.8 (22.0, 174)	78.1 (19.3, 51)	81.9 (23.0, 123)	74.6 (26.0, 7997)
Serum creatinine mean mg/dL, (SD, N)	0.90 (0.28, 886)	0.90 (0.23, 231)	0.90 (0.29, 655)	1.00 (0.42, 46,073)
HDL Cholesterol, mean mg/dL (SD, N)	45.9 (12.3, 678)	47.2 (12.4, 179)	45.4 (12.2, 499)	48.8 (14.6, 33,043)
LDL Cholesterol, mean mg/dL (SD, N)	119.5 (39.2, 673)	122.8 (39.6, 175)	118.4 (39.0, 498)	118.2 (39.0, 32,423)

hypertension. The incidence of conditions indicative of diabetes progression was similar for dapagliflozin and other AD therapy users although dapagliflozin users were slightly less likely than other AD therapy users to show signs of nephropathy (15.2%, $n = 214/1405$ vs. 18.6%, $n = 15,191/81,463$) (Table 3). Dapagliflozin users experienced a history of cardiovascular disease less frequently than other AD therapy users, in particular in relation to chronic heart failure (9.7%, $n = 136/1405$ vs. 15.8%, $n = 12,877/81,463$), stroke (3.3%, $n = 46/1405$ vs. 6.2%, $n = 5081/81,463$), and arrhythmia (10.7%, $n = 151/1405$ vs. 16.7%, $n = 13,610/81,463$). However, patients on dapagliflozin suffered more frequently from hepatic disease than other AD therapy users (19.1%, $n = 268/1405$ vs. 14.8%, $n = 12,060/81,463$). A high incidence of hypertension was seen in all patients regardless of therapy (69.3–75.1%), however, dapagliflozin monotherapy users showed a slightly lower risk compared to those on combination therapy (69.3%, $n = 257/371$ vs. 74.1%, $n = 766/1034$) and other AD therapies (75.1%, $n = 61,153/81,463$). There were no distinct differences between dapagliflozin monotherapy and combination therapy users in these respects.

Among the concomitant medications prescribed for dapagliflozin users immediately prior to the index date (during the 6 months before index) (Appendix A), a high proportion of

Table 3 – Comorbid conditions among dapagliflozin (overall, monotherapy, combination therapy) and other AD therapy users.

Variables	Dapagliflozin			Other AD therapy
	Overall N = 1405 n (%)	Monotherapy N = 371 n (%)	Combination N = 1034 n (%)	Overall N = 81463 n (%)
Marker of diabetes disease progression and complications				
Retinopathy	120 (8.5)	17 (4.6)	103 (10.0)	5620 (6.9)
Diabetic neuropathy	292 (20.8)	66 (17.8)	226 (21.9)	17,322 (21.3)
Nephropathy	214 (15.2)	47 (12.7)	167 (16.2)	15,191 (18.6)
Diabetic ketoacidosis	2 (0.1)	0 (0)	2 (0.2)	164 (0.2)
Cardiovascular disease				
Myocardial infarction	47 (3.3)	14 (3.8)	33 (3.2)	3154 (3.9)
Chronic heart failure	136 (9.7)	37 (10.0)	99 (9.6)	12,877 (15.8)
Stroke	46 (3.3)	9 (2.4)	37 (3.6)	5081 (6.2)
Arrhythmia	151 (10.7)	49 (13.2)	102 (9.9)	13,610 (16.7)
Heart valve disorders	36 (2.6)	13 (3.5)	23 (2.2)	3945 (4.8)
Hypertension	1023 (72.8)	257 (69.3)	766 (74.1)	61,153 (75.1)
Other				
Hepatic disease	268 (19.1)	66 (17.8)	202 (19.5)	12,060 (14.8)

patients on dapagliflozin were prescribed metformin (67.6%, $n = 950/1405$) and dipeptidyl peptidase-4 (DPP-4) inhibitors (44.9%, $n = 631/1405$) respectively. Prescriptions for insulin and analogues were also common (35.9%, $n = 505/1405$). A large number of dapagliflozin users (53.2%) were prescribed an angiotensin converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (ARB).

3.3. *Prescription patterns of dapagliflozin*

The uptake of dapagliflozin has grown steadily since its launch in Germany in 2012 (Fig. 1). The greatest increase in prescription volume was observed between the first and second quarter of 2013, with the majority of prescriptions being made for 10 mg dapagliflozin. Uptake slowed slightly from the third quarter of 2013 onwards. After a low uptake of 5 mg dapagliflozin, a noticeable increase in prescription volume was observed, from 74 in the third quarter of 2013 to 171 in the second quarter of 2014.

For most patients, dapagliflozin and other AD therapies were prescribed by a GP, but a higher proportion of patients had dapagliflozin prescribed by a specialist diabetologist (26.3%, $n = 369/1405$) compared to other AD therapies (18.7%, $n = 15{,}244/81{,}463$). The age distribution of prescribing practitioners was similar for dapagliflozin and other AD therapy users, however, it should be noted that in practices with multiple doctors, only the age group of the lead doctor was given (Appendix B).

Table 4 outlines the therapy type (monotherapy/combination) and drug classes used in combination with dapagliflozin for the 10 mg and 5 mg populations at index date. Only 28.5% ($n = 325/1234$) of patients who were using 10 mg dapagliflozin and 11.1% ($n = 19/171$) of patients using 5 mg dapagliflozin had been prescribed this treatment alone at the index date. Patients using 10 mg dapagliflozin were most commonly prescribed in combination with either biguanide alone (12.3%, $n = 152/1234$), biguanide plus a DPP-4 inhibitor (13.2%, $n = 163/1234$), or insulin alone (10.1%, $n = 125/1234$). Of those

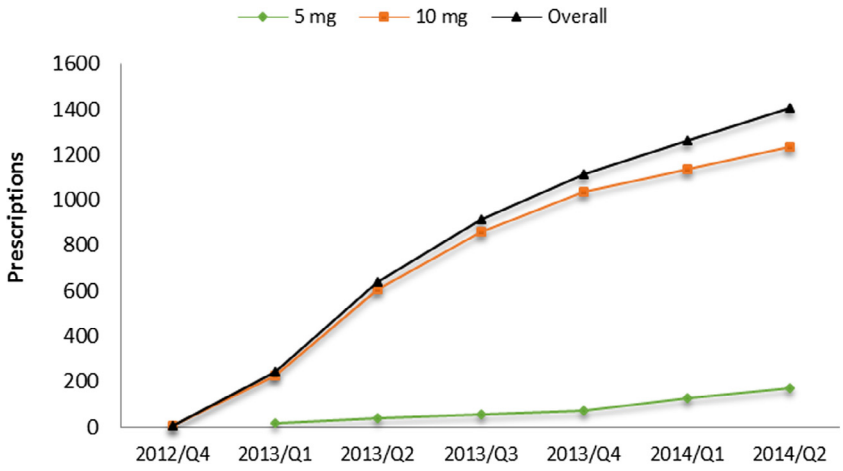

Fig. 1 – Cumulative prescription pattern of dapagliflozin over time.

Table 4 – Therapy type (monotherapy/combination) and drug classes for dapagliflozin combination therapy users at index date.

Therapy type	Dapagliflozin dose	
	10 mg (N = 1234) n (%)	5 mg (N = 171) n (%)
Monotherapy dapagliflozin	352 (28.5)	19 (11.1)
Combination therapies	882 (71.5)	152 (88.9)
Dapagliflozin + biguanide + DPP-4 inhibitor	163 (13.2)	14 (8.2)
Dapagliflozin + biguanide	152 (12.3)	56 (32.7)
Dapagliflozin + insulin	125 (10.1)	10 (5.8)
Dapagliflozin + biguanide + insulin	104 (8.4)	22 (12.9)
Dapagliflozin + biguanide + DPP-4 inhibitor + insulin	54 (4.4)	10 (5.8)
Other combination	284 (23.0)	40 (23.4)
Including insulin	49 (4.0)	10 (5.8)

who were using 5 mg dapagliflozin, combination therapy with biguanide alone (32.7%, $n = 56/171$), biguanide plus insulin (12.9%, $n = 22/171$) or biguanide plus DPP-4 inhibitor (8.2%, $n = 14/171$) were the most common regimens prescribed. A large proportion of patients who initiated on dapagliflozin did so in combination with insulin (27.3%, $n = 384/1405$).

Overall, 62 (4.4%) dapagliflozin patients had their dose adjusted, with a mean adjusting time of 36 days (SD 33, range 1–219). 12 patients (0.9%) given the 10 mg dapagliflozin formulation had their dose adjusted after a mean period of 61 days (SD 60, range 1–219) and 50 patients (3.6%) given the 5 mg formulation had their dose adjusted after a mean period of 30 days (SD 16, range 7–106).

At the time of the index prescription, in total, 85.1% ($n = 1196/1405$) of users were not switched to dapagliflozin from a previous therapy but either had no previous AD medication or added dapagliflozin to another AD compound. For those that were switched to dapagliflozin, the most common previous therapies were DPP-4 inhibitors (5.4%, $n = 76/1405$), insulin (2.5%, $n = 35/1405$), and GLP-1 inhibitors (2.1%, $n = 30/1405$).

During the observation period, only a small proportion of the total population of dapagliflozin users (6.3%, $n = 89/1405$) were switched onto another therapy (after a mean of 134 days, SD 108, range 5–452). Overall, the most common drug classes that dapagliflozin users switched to were found to be insulin (30.3%, $n = 27/89$), DPP-4 inhibitors (15.7%, $n = 14/89$), and sulfonylureas (14.6%, $n = 13/89$) (Appendix C).

Overall, add-on therapy was prescribed for a moderate number of patients on dapagliflozin during the observation period (13.4%, $n = 188/1405$) after a mean of 105 days (SD 91, range 1–410) (Appendix D).

A high rate (80%) of patient compliance was observed at the $\geqslant$90% threshold. As per sensitivity analyses, for thresholds of MPR $\geqslant$ 70%, MPR $\geqslant$ 60% and MPR $\geqslant$ 50%, the compliance proportions were 92%, 95% and 97%, respectively.

4. Discussion

Within a German population, patients on dapagliflozin differed in important characteristics to patients using other AD medicine. This study shows that patients on dapagliflozin tended to be younger and a higher proportion were male (3:2 ratio of male to female). The average duration of diabetes was comparable between dapagliflozin and other AD therapy users but patients on dapagliflozin were on average heavier and had higher levels of HbA1c and fasting plasma glucose.

The majority of patients on dapagliflozin were aged from 45–74 years with a mean age of around 61 years, whereas the highest proportion of other AD therapy users were over 75 years. The much lower proportion of dapagliflozin users over 75 years may be due to prescription guidelines suggesting that initiation of dapagliflozin therapy is not recommended in patients over 75 years due to the limited therapeutic experience in this age group [3].

Patients on dapagliflozin had less glycaemic control than patients on other AD therapies. The recommended daily target for HbA1c levels for people with diabetes is 6.5% (48 mmol/mol). The recommended level for those at greater risk of hypoglycaemia is 7.5% (59 mmol/mol) [10–12]. In this study, dapagliflozin users averaged 8.2% (66 mmol/mol) compared to 6.9% (52 mmol/mol) for other AD therapy users. The higher HbA1c and fasting plasma glucose levels found in dapagliflozin users in this study may be a result of the dapagliflozin treatment pathway rather than a consequence of its use. The preference to use dapagliflozin as a second or third-line treatment option, generally when other therapies have not provided adequate glycaemic control, would suggest that higher HbA1c and fasting plasma glucose levels were evident prior to initiation of the therapy.

A higher proportion of patients using dapagliflozin had private insurance and had their therapy prescribed by a specialist diabetologist compared to other AD therapy users. Approximately 10% of the German population are privately insured [13]. Approximately 15% of dapagliflozin users had private insurance compared to only 6% of other AD therapy users. This is consistent with a recent study on the treatment patterns of T2DM patients in Germany, which found those who were privately insured had a higher probability of being prescribed newer anti-hyperglycaemic drugs (AHD) than patients on statutory insurance [13].

Patients on dapagliflozin were more likely to be suffering from comorbid liver disease but less likely to suffer from comorbid kidney disease than patients on other AD therapies. The prescription guidelines report that the efficacy of dapagliflozin is reduced in patients with renal impairment and suggests that dapagliflozin should not be prescribed for patients with moderate to severe renal impairment [3]. Our findings are consistent with these guideline recommendations.

Patients on dapagliflozin were less likely to experience a history of cardiovascular (CV) disease, including heart failure, stroke and arrhythmia, than those on other AD therapies. This would indicate that prescribing of dapagliflozin was more restrictive in patients with a history of cardiovascular disease. Notably, the recent findings of the EMPA-REG clinical trial showed a reduction in hospitalization for heart failure and cardiovascular mortality in patients randomized to empagliflozin compared to placebo on top of standard of care [14]. It is yet unclear to what extent these effects are also present for other SGLT2 inhibitors. A cardiovascular outcome trial for dapagliflozin (the DECLARE study) is ongoing.

During the 6 months before the index date a high proportion of patients on dapagliflozin were prescribed metformin (a biguanide), especially those initiated on dapagliflozin combination therapy. Metformin is the most widely prescribed first-line drug for T2DM in Germany and accounted for 63% of newly prescribed OADs in 2003 and more than 80% in 2009 [15]. The high proportion of dapagliflozin users who were previously prescribed metformin reflect these high prescriptions figures. It can be assumed that in patients previously prescribed metformin, glycaemic control was inadequate or an intolerance to metformin was evident, thus necessitating the use of additional treatment. Studies where dapagliflozin was added onto metformin therapy show improvements to HbA1c levels and body weight and validate the use of dapagliflozin as a next line treatment option [16–19]. Approval in January 2014 of the combination dapagliflozin/metformin therapy may see a further increase in metformin users being prescribed this combination therapy.

A review of treatment guidelines for T2DM suggests that if metformin is not tolerated or contraindicated then the second choice of first-line drug therapy is generally monotherapy with DPP-4 inhibitors, insulin, sulfonylureas/glinides, glucosidase inhibitors or SGLT2 inhibitors [12]. Furthermore, if HbA1c targets were not reached using metformin monotherapy then the treatment could be amplified with the addition of a second antidiabetic drug (combination therapy) or else metformin could be discontinued and insulin used alone. In this study, in addition to metformin, prescriptions for DPP-4 inhibitors and insulin were common in the 6 months prior to dapagliflozin use, again with those initiated on dapagliflozin combination therapy showing a greater percentage. This study also found that in the 6 months prior to dapagliflozin treatment there were no instances of patients who were drug- naïve or off-therapy, suggesting that dapagliflozin was only prescribed as a second or third-line treatment option when glycaemic control was not achieved using alternative therapies.

Patients were not usually switched from other therapies onto dapagliflozin (Appendix B). Since most patients had progressive diabetes with a mean average diabetes duration of 5.7 years and were unlikely to be treatment-naïve or off-therapy, it may be assumed that in the majority of these cases dapagliflozin was added-on to existing therapy. A moderate number of patients used dapagliflozin as monotherapy however, for the vast majority of patients it was prescribed as a component of combination therapy with either biguanide alone, biguanide plus a DPP-4 inhibitor, insulin alone, biguanide plus insulin or biguanide plus a DPP-4 inhibitor and insulin. This supports evidence of dapagliflozin use as a second or third-line treatment option, which is in-line with current treatment guidelines [12].

Almost a third of patients who initiated on dapagliflozin did so in combination with insulin (28%, $n = 396/1405$). Often over time, therapies that depend on insulin run the risk of hypoglycaemia, weight gain, decreased insulin sensitivity and eventual loss of effectiveness. This is especially true in patients with late-stage T2DM who require escalating insulin doses, often with oral agents such as metformin to maintain glycaemic control. In these cases dapagliflozin may be used as a strategy for controlling glycaemia independently of insulin. Studies supporting the use of dapagliflozin as an add-on to insulin therapy include a 2012 European and North American randomised trial that found dapagliflozin improved glycaemic control, stabilised insulin dosing and reduced weight without increasing major hypoglycaemic episodes in patients inadequately controlled with insulin alone or with up to 2 oral antidiabetic drugs [20]. An extension to this study found this control could be maintained for over 104 weeks [21]. A Dutch study into the cost effectiveness of adding dapagliflozin to insulin for the treatment of T2DM concluded that dapagliflozin in combination with insulin was a cost-effective treatment option for patients with T2DM whose insulin treatment regimen did not provide adequate glycaemic control in a Dutch healthcare setting [22].

There were some limitations to this study. The German healthcare system is provided through statutory health insurance, which means that GP's are not involved in the allocation of healthcare resources. Consequently, right truncation and early censoring of longitudinal records may be an issue since patients can readily move between primary care practices and do not require GP referrals in order to receive specialist care.

Diabetes therapy may be initiated either in the primary or secondary care setting. However, given the absence of linkage information between the German DA and other healthcare settings, concurrent use of healthcare resources may lead to a distortion in the utilisation pattern of diabetes care.

Continuous enrolment is not explicit in the German DA but rather inferred from utilisation of services. As a result, gaps in care may be overlooked and the precise date of

follow-up cannot be estimated. Censoring due to death cannot be established due to the absence of linkage with national mortality data. In addition, measures of liver function or damage (e.g. ALT, AST) were not reported.

Given the nature of real-world data, there is a possibility of missing data. However, missing data on diabetes-specific parameters is less likely. For instance, approximately 70% of patients are expected to have available information on HbA1c, although this will be reduced following the start of diabetes treatment. In this study there was a substantial proportion of missing data for several of the laboratory variables and for BMI. This limits the interpretation of differences between starters of dapagliflozin and starters of other AD agents in this study.

5. Conclusions

Since its launch in Germany in 2012, dapagliflozin uptake has increased rapidly, mainly as a combination treatment with biguanide, DPP-4 inhibitors or insulin. In comparison to users of other AD therapy, patients on dapagliflozin differed in several demographic as well as health related respects. All patients on dapagliflozin therapy were prescribed concomitant AD medication prior to initiating dapagliflozin, supporting evidence for its use as a second or third-line treatment option. During a 12 month follow-up, few patients were switched to other anti-diabetic treatments and few had add-on therapy after dapagliflozin initiation. Compliance with treatment was high. These early findings indicate that dapagliflozin is an important complement to traditional anti-diabetic drugs, including insulin, in the treatment of diabetic patients.

Funding sources

These findings are the result of work supported by AstraZeneca.

Appendix A.

Appendix A – Concomitant medications prescribed for dapagliflozin users immediately prior to the index date (overall, monotherapy, combination therapy).

Concomitant medications	Overall *N* = 1405 *n* (%)	Monotherapy *N* = 371 *n* (%)	Combination *N* = 1034 *n* (%)
Diabetic drugs			
Metformin	950 (67.6)	200 (53.9)	750 (72.5)
DPP-4 inhibitors	631 (44.9)	138 (37.2)	493 (47.4)
Insulin and analogues	505 (35.9)	82 (22.1)	423 (40.9)
Sulphonylureas	184 (13.1)	32 (8.6)	152 (14.7)
GLP-1 agonists	179 (12.7)	46 (12.4)	133 (12.9)
Thiazolidinediones	24 (1.7)	4 (1.1)	20 (1.9)
Non-diabetic drugs			
ACE-I	396 (28.2)	90 (24.3)	306 (29.6)
ARB	380 (27.0)	93 (25.1)	287 (27.8)
ACE-I/ARB	747 (53.2)	174 (46.9)	573 (55.4)

Appendix B.

Appendix B – Age category of practitioners prescribing dapagliflozin and other AD therapies.

Age group	Dapagliflozin *N* = 1405 n (%)	Other AD therapy *N* = 81463 n (%)
<40	5 (0.4)	556 (0.7)
41–50	259 (18.4)	17,507 (21.5)
51–60	617 (43.9)	30,825 (37.8)
>60	514 (37.3)	32,575 (40.0)

Appendix C.

Appendix C – Therapies by drug class dapagliflozin users switched from and to (overall and by dose).

Drug class	Switch from other therapies			Switch to other therapies		
		Dapagliflozin dose			Dapagliflozin dose	
	Overall N = 1405 n (%)	10 mg N = 1234 n (%)	5 mg N = 171 n (%)	Overall N = 1405 n (%)	10 mg N = 1234 n (%)	5 mg N = 171 n (%)
No switch	1196 (85.1)	1063 (86.1)	133 (77.8)	1316 (93.7)	1159 (93.9)	157 (91.8)
Switch	209 (14.9)	171 (13.9)	38 (22.2)	89 (6.3)	75 (6.1)	14 (8.2)
DPP-4 inhibitor	76 (5.4)	53 (4.3)	23 (13.5)	14 (1.0)	10 (0.8)	4 (2.3)
Insulin	35 (2.5)	30 (2.4)	5 (2.9)	27 (1.9)	25 (2.0)	2 (1.2)
GLP-1 inhibitor	30 (2.1)	25 (2.0)	5 (2.9)	11 (0.8)	11 (0.9)	–
Sulfonylurea	19 (1.4)	17 (1.4)	2 (1.2)	13 (0.9)	11 (0.9)	2 (1.2)
Biguanide	15 (1.1)	15 (1.2)	–	8 (0.6)	6 (0.5)	2 (1.2)
Biguanide + DPP-4 inhibitor	13 (0.9)	13 (1.1)	–	3 (0.2)	1 (0.1)	2 (1.2)
Thiazolidinediones	6 (0.4)	6 (0.5)	–	4 (0.3)	4 (0.3)	–
Glinide	5 (0.4)	5 (0.4)	–	2 (0.1)	2 (0.2)	–
Alpha glucose inhibitor	4 (0.3)	3 (0.2)	1 (0.6)	–	–	–
Biguanide + insulin	3 (0.2)	3 (0.2)	–	1 (0.1)	1 (0.1)	–
Biguanide + GLP-1 inhibitor	1 (0.1)	1 (0.1)	–	–	–	–
DPP-4 inhibitor + insulin	1 (0.1)	–	1 (0.6)	–	–	–
GLP-1 inhibitor + insulin	1 (0.1)	–	1 (0.6)	1 (0.1)	–	1 (0.6)
Glinide + DPP-4 inhibitor	–	–	–	1 (0.1)	–	1 (0.6)
Biguanide + sulfonylurea	–	–	–	1 (0.1)	1 (0.1)	–
Canagliflozin	–	–	–	3 (0.2)	3 (0.2)	–

Appendix D.

Appendix D – Therapies by drug class added-on to dapagliflozin users (overall and by starting dose).

Drug class		Dapagliflozin dose	
	Overall N = 1405 n (%)	10 mg N = 1234 n (%)	5 mg N = 171 n (%)
No add-on	1217 (86.6)	1063 (86.1)	154 (90.1)
Add-on	188 (13.4)	171 (13.9)	17 (9.9)
Insulin	64 (4.6)	56 (4.5)	8 (4.7)
DPP-4 inhibitor	35 (2.5)	35 (2.8)	–
GLP-1 inhibitor	24 (1.7)	22 (1.8)	2 (1.2)
Biguanide	22 (1.6)	21 (1.7)	1 (0.6)
Sulfonylurea	19 (1.4)	16 (1.3)	3 (1.8)
Glinide	6 (0.4)	6 (0.5)	–
Biguanide + DPP-4 inhibitor	4 (0.3)	4 (0.3)	–
Alpha glucose inhibitor	4 (0.3)	3 (0.2)	1 (0.6)
Biguanide + insulin	4 (0.3)	3 (0.2)	1 (0.6)
DPP-4 inhibitor + insulin	2 (0.1)	1 (0.1)	1 (0.6)
Biguanide + DPP-4 inhibitor + insulin	1 (0.1)	1 (0.1)	–
Biguanide + thiazolidinediones	1 (0.1)	1 (0.1)	–
GLP-1 inhibitor + insulin	1 (0.1)	1 (0.1)	–
Thiazolidinediones	1 (0.1)	1 (0.1)	–

Appendix E. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2016.10.025.

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