The DIVE/DPV registries: evolution of empagliflozin use in clinical practice in Germany

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ABSTRACT

Introduction Empagliflozin reduced morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) in clinical trials. A registry study was undertaken to describe evolution of patient characteristics and assess the real-world effectiveness/safety of empagliflozin.

Research design and methods Data from the Diabetes Patienten Verlaufsdokumentation (DPV)/Diabetes Versorgungsevaluation (DIVE) registries on 9571 adults with T2DM (registered in 2014–2019) receiving empagliflozin were used. Patients were grouped according to the following: early users (group 1; n=505) received empagliflozin before the EMPA-REG OUTCOME study publication (mid-September 2015); intermediate users (group 2; n=2961) started empagliflozin after the EMPA-REG OUTCOME publication but before the European Medicines Agency label change (from mid-September 2015 to mid-January 2017); and late users (group 3; n=6105) started empagliflozin after mid-January 2017. Data on clinical and treatment characteristics were collected.

Results Over time, the proportion of recipients aged <65 years decreased (71.1% vs 54.4% among early and late adopters), male patients increased (from 50.9% to 66.5%), body mass index (mean±SD) decreased (from 35.5±6.7 to 32.7±6.6 kg/m^2), proportion with cardiovascular morbidities increased (from 20.4% to 26.4%), and mean estimated glomerular filtration rate decreased (from 83.2±19.5 to 78.5±21.1 mL/min/1.73 m^2) (all p<0.001). Patients increasingly received empagliflozin in combination with metformin (60.8% vs 68.6% of early and late adopters; p<0.001), glucagon-like peptide-1 (GLP-1) agonists (11.0 vs 14.1%; p<0.001) or insulin (34.3% vs 49.9%; p<0.001). Empagliflozin was generally added to existing antidiabetic regimens. Six months after empagliflozin initiation, the mean glycated hemoglobin (HbA1c) decreased by 0.4%, the proportion of patients with HbA1c <6.5% increased (19.2% vs 12.8%), and the mean fasting plasma glucose decreased (155.8±49.7 vs 168.0±55.1 mg/dL) (all p<0.001). No significant changes in rates of severe hypoglycemia and no cases of diabetic ketoacidosis were seen.

Conclusions Over time, empagliflozin is being prescribed to a broader patient range in routine practice, is usually added to existing antidiabetic regimens, and is increasingly used in combination with metformin, GLP-1 agonists and/or insulin. Empagliflozin had a beneficial effect on glycemic control, with no increase in hypoglycemia.

Significance of this study

What is already known about this subject?

► Clinical trials have shown that empagliflozin reduces morbidity and mortality in patients with type 2 diabetes mellitus (T2DM).

What are the new findings?

► This registry study, which was undertaken to describe evolution of patient characteristics and assess the real-world effectiveness and safety of empagliflozin, has shown that empagliflozin is increasingly being used in a broader patient population than the ones in the clinical trials.

► This is particularly true for older patients, patients with cardiovascular morbidities, patients with lower body mass index and patients with lower estimated glomerular filtration rate, which were less often included in the clinical trials.

► Our findings show that empagliflozin had a beneficial effect on glycemic control, with no increase in hypoglycemia and no cases of diabetic ketoacidosis rates in an all-comers patient population.

How might these results change the focus of research or clinical practice?

► The findings of this registry have the potential to increase the number of patients with T2DM who could be considered for treatment with empagliflozin and will reassure clinicians that empagliflozin has a beneficial effect on glycemic control and does not increase the rates of hypoglycemia.

BACKGROUND

Empagliflozin is a recently introduced antidiabetic drug of the sodium-glucose cotransporter-2 (SGLT-2) inhibitor drug class which has been shown to reduce morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) was the first specific outcome study to show cardiovascular and renal benefits for a

non-insulin glucose-lowering drug versus placebo, when added to standard of care.[1 2] It has high bioavailability, high selectivity for SGLT-2 over SGLT-1 and a relatively long half-life of 13.2 hours compared with other SGLT-2 inhibitors.[3]

While the clinical trial-based development of empagliflozin for the treatment of T2DM may be regarded as complete, further data are necessary to understand the real-world implications of its use. This not only includes the description of its use in patients who may not have been eligible for one of the pivotal studies, but also the real-world effectiveness and safety of the drug. For this purpose, we evaluated registry data on recipients of empagliflozin, divided into three groups based on when they started treatment with the drug. Group 1 included patients in whom treatment with empagliflozin was initiated before the EMPA-REG OUTCOME study results were reported (ie, before mid-September 2015). Group 2 included patients who were initiated on the drug between mid-September 2015 and the time when the European Medicines Agency (EMA) changed the label wording from 'improvement of glycaemic control' to the more general 'treatment of adults with insufficiently controlled T2DM', with reference to 'effects on glycaemic control and cardiovascular events' (mid-January 2017). Group 3 included all patients started on empagliflozin thereafter, that is, from mid-January 2017 onwards.

We aimed to describe the evolution of patient characteristics over time, to assess the real-world effectiveness of empagliflozin, and to describe the rates of adverse effects such as hypoglycemia and ketoacidosis.

METHODS
Study design and data sources
This analysis used combined data from the Diabetes Patienten Verlaufsdokumentation (DPV) and Diabetes Versorgungsevaluation (DIVE) registries. Their design has been described previously.[4 5] Briefly, the DPV initiative collects data on patients with diabetes mellitus from centers predominantly in Germany. Data are collected every 6 months using DPV software and then sent anonymized to the University of Ulm for aggregation into the cumulative database.

The DIVE registry was established in 2011.[6 7] Consecutive patients with diabetes mellitus, regardless of disease stage, were enrolled from centers across the country, and continue to be followed up. Data are entered into an online database using DPV software. All patients included in the DIVE registry provided written informed consent.

A total of 216 centers from Germany, Austria, Switzerland and Luxemburg were included in the present analysis. Patients were sampled in September 2019 and included in the current analysis if they had T2DM, were at least 18 years old, were initially registered between 2014 and 2019, and received empagliflozin either as a single-drug pill or in combination with other drugs.

Documentation
For the current analysis, data regarding age, sex, body mass index (BMI), blood pressure, renal parameters, antidiabetic and antihypertensive drug treatment, and current comorbidities were collected. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[8] Chronic kidney disease (CKD) was defined as eGFR $<60\,mL/min/1.73\,m^2$ or eGFR $\geq 60\,mL/min/1.73\,m^2$ plus albuminuria (urinary albumin to creatinine ratio $\geq 30\,mg/g$).[9 10] Severe hypoglycemia was defined as the need of assistance from another person, a self-monitoring of blood glucose value of $\leq 56\,mg/dL$ ($\leq 3.0\,mmol/L$) or hospitalization.

Analysis
The analysis describes the real-life treatment of adult patients with T2DM receiving empagliflozin, comparing the characteristics of patients starting empagliflozin in three time periods. The first analysis group included patients who were receiving empagliflozin before the EMPA-REG OUTCOME study was published (ie, before mid-September 2015; 'Group 1', early adopters). The second analysis group included patients who started receiving empagliflozin after the EMPA-REG OUTCOME study results were published but before EMA label change (ie, between mid-September 2015 and mid-January 2017; 'Group 2', intermediate adopters). The third analysis group included those patients who started receiving empagliflozin between mid-January 2017 and the last available data cut in September 2019 ('Group 3', late adopters).

Statistics
Data from all patients within a group were combined and analyzed as a single data set. Categorical variables are presented as percentages. Continuous variables are presented as mean with SD. Unadjusted comparisons were conducted using χ^2 or Kruskal-Wallis test. The Bonferroni stepdown method was used to correct p values for multiple testing. A p value <0.05 was considered statistically significant. Statistical analysis was performed using SAS V.9.4.

RESULTS
A total of 9571 patients with T2DM who received empagliflozin treatment were included in the analysis (figure 1). A marked increase in the number of patients treated with empagliflozin was seen over time: 505 patients were classified as early adopters (ie, started the drug before mid-September 2015), 2961 as intermediate adopters (ie, started between mid-September 2015 and mid-January 2017), and 6105 as late adopters (ie, started after mid-January 2017).

Patient characteristics
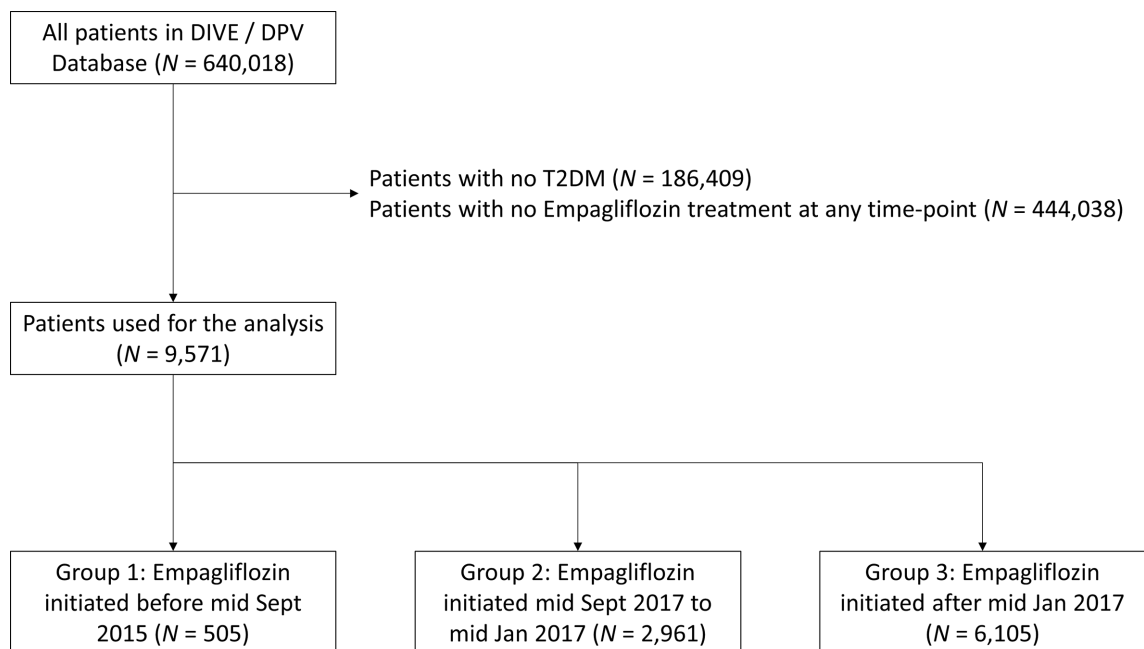Baseline patient characteristics are summarized in table 1. In all three time periods, empagliflozin was

Figure 1 Patient population (as of September 2019). DIVE, Diabetes Versorgungsevaluation; DPV, Diabetes Patienten Verlaufsdokumentation; T2DM, type 2 diabetes mellitus.

most commonly initiated in younger patients, but over time it was increasingly prescribed to older patients, with the proportion of recipients aged <65 years decreasing from 71.1% among early adopters to 54.4% among late adopters (p<0.001). The proportion of male patients increased over time, from 50.9% to 66.5% (p<0.001).

BMI (mean±SD) decreased from $35.5 \pm 6.7\,\mathrm{kg/m^2}$ among early adopters to $32.7 \pm 6.6\,\mathrm{kg/m^2}$ among late adopters (p<0.001). The proportion of patients with cardiovascular morbidities increased over time (from 20.4% to 26.4%; p<0.001), and the mean eGFR decreased from $83.2 \pm 19.5\,\mathrm{mL/min/1.73\,m^2}$ in early adopters to $78.5 \pm 21.1\,\mathrm{mL/min/1.73\,m^2}$ in late adopters (p<0.001).

Drug treatment

Concomitant drug treatment is summarized in table 2. Over time, empagliflozin was increasingly used in patients being treated with different cardiovascular drugs, including antihypertensive drugs, lipid-lowering agents and antiplatelets/anticoagulants (all p<0.001).

The proportion of patients receiving concomitant sulfonylurea treatment decreased over time (p<0.001), as did the proportion receiving acarbose (although this did not achieve statistical significance), whereas an increasing number of patients received empagliflozin in combination with metformin (60.8% of early adopters vs 68.6% of late adopters; p<0.001). There was a marked increase in the proportion of patients receiving empagliflozin in conjunction with insulin (from 34.3% of early adopters to 49.9% of late adopters; p<0.001).

Switch analysis

The results of a switch analysis of glucose-lowering treatments are shown in table 3. The data suggest that, in general, empagliflozin did not replace other drugs, but

was added to the antidiabetic regimen. This was seen for non-insulin-based antidiabetic therapy, where an increase in two-drug and three-drug combinations was observed (p<0.001), as well as for insulin-based regimens, where there was an increase from 23.1% of patients prior to empagliflozin initiation to 42.4% after initiation of empagliflozin (p<0.001).

Effectiveness and safety

A comparison of effectiveness and safety parameters prior to empagliflozin initiation and at 6 months after initiation of empagliflozin is provided in table 4. The mean glycated hemoglobin (HbA1c) significantly decreased by 0.4% points (from 7.8% to 7.4%; p<0.001) at the 6-month timepoint compared with the value prior to empagliflozin initiation (p<0.001), and the proportion of patients with HbA1c <6.5% was significantly greater at the 6-month timepoint (19.2% vs 12.8%; p<0.001). The mean fasting plasma glucose also decreased significantly, from 168.0 ± 55.1 to $155.8 \pm 49.7\,\mathrm{mg/dL}$ (p<0.001). There was no increase in the rate of severe hypoglycemia after starting empagliflozin treatment. No case of diabetic ketoacidosis occured after start of empagliflozin during the study follow-up. No significant effect on the rate of CKD was seen.

DISCUSSION

The principal findings of this analysis investigating the use of empagliflozin in routine clinical practice were as follows. In recent years, older patients, more male patients, and more patients with substantial cardiovascular comorbidity are being treated with empagliflozin. Empagliflozin is usually being added to an antidiabetic regimen, rather than replacing other antidiabetic drugs.

Table 1 Patient characteristics according to period of empagliflozin treatment initiation

	Total	Group 1 (early adopters)	Group 2 (intermediate)	Group 3 (late adopters)	P value
Age, years, mean (SD)	62.4 (11.5)	59.2 (11.3)	61.2 (11.5)	63.2 (11.4)	<0.001
<65, %	57.3	71.1	60.8	54.4	<0.001
65–<75, %	27.9	20.0	27.4	28.9	0.001
75–80, %	10.1	6.5	8.3	11.3	<0.001
>80, %	4.7	2.4	3.6	5.4	<0.001
Gender, male, %	64.2	50.9	61.8	66.5	<0.001
BMI, kg/m^2, mean (SD)	33.3 (6.8)	35.5 (6.7)	33.9 (7.1)	32.7 (6.6)	<0.001
Height, cm, mean (SD)	172.1 (9.7)	170.5 (9.5)	171.8 (9.9)	172.3 (9.6)	<0.001
Weight, kg, mean (SD)	98.6 (22.2)	103.2 (21.4)	100.3 (23.1)	97.3 (21.7)	<0.001
Diabetes management program participants, %	38.2	53.5	48.6	31.8	<0.001
Duration of diabetes, years, mean (SD)	11.0 (8.4)	10.7 (7.8)	10.8 (8.2)	11.2 (8.5)	0.475
HbA1c, %, mean (SD)	8.3 (1.8)	8.2 (1.7)	8.3 (1.7)	8.4 (1.9)	0.475
mmol/mol, mean (SD)	67.4 (19.8)	65.7 (18.4)	66.6 (18.7)	67.8 (20.4)	0.475
FPG, mg/dL, mean (SD)	181.7 (78.3)	186.0 (85.6)	182.3 (76.5)	181.1 (78.5)	1.000
Cardiovascular comorbidities, %	24.6	20.4	21.6	26.4	<0.001
Myocardial infarction, %	6.7	3.0	4.5	8.1	<0.001
Stroke, %	3.6	1.8	3.0	4.1	0.031
Coronary artery disease, %	14.3	11.3	12.0	15.7	<0.001
Peripheral arterial disease, %	11.3	10.7	10.8	11.6	1.000
Congestive heart failure, %	1.1	0.0	0.7	1.4	0.123
Diabetes late complications, %	59.1	59.6	57.6	59.8	0.835
Neuropathy, %	40.4	43.6	39.8	40.4	1.000
Nephropathy, %	38.7	36.1	39.1	38.8	1.000
Chronic kidney disease, %	38.7	36.1	39.1	38.8	1.000
Microalbuminuria, %	36.0	37.5	40.1	34.1	0.002
Macroalbuminuria, %	5.5	1.1	4.5	6.4	0.001
eGFR, mL/min/1.73 m^2, mean (SD)	79.6 (21.0)	83.2 (19.5)	81.4 (20.6)	78.5 (21.1)	<0.001
Diabetic foot syndrome, %	7.0	10.1	7.5	6.6	0.072
Retinopathy, %	8.4	5.4	6.5	9.7	0.060
Proliferative, %	1.7	0.5	1.5	1.9	1.000
Non-proliferative, %	6.6	4.8	4.9	7.7	0.118

BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

It is increasingly being used in dual and triple combinations with metformin or glucagon-like peptide-1 (GLP-1) agonists or together with insulin. Empagliflozin provides a beneficial effect on glycemic control, with no increase in the rates of severe hypoglycemia.

Patient characteristics

The comparably low number of empagliflozin patients is surprising, especially when considering that in the Arzneimittelmarkt-Neuordnungsgesetz (AMNOG) Health Technology Assessment (HTA) procedure in September 2016 the Federal Joint Committee (G-BA) granted empagliflozin a considerable additional benefit for the treatment of patients with T2DM with established cardiovascular disease (eCVD). Generally, there are no specific prescribing limitations for specialists in Germany. Indeed, the National Association of Statutory Health Insurance Physicians in collaboration with the Drug Commission of the German Medical Association recommended empagliflozin use prior to sitagliptin and saxagliptin in patients with T2DM/eCVD. However, there are different drug agreements on a regional level with lead substances, minimum and maximum quotas that can impact specialists' prescription behavior.

The results of the study, however, suggest that the population of patients being prescribed empagliflozin is broadening over time and that it is being prescribed

Table 2 Concomitant drug treatment according to period of empagliflozin initiation

	Total	Group 1 (early adopters)	Group 2 (intermediate)	Group 3 (late adopters)	P value
Antihypertensive drugs, %	55.8	45.4	49.5	59.8	<0.001
ACEi, %	27.9	21.2	24.7	30.0	<0.001
ARB, %	19.2	16.8	17.7	20.1	0.083
Beta-blockers, %	31.4	19.6	25.8	35.1	<0.001
Diuretics, %	25.5	17.8	21.9	27.9	<0.001
Calcium antagonists, %	17.9	12.5	15.4	19.5	<0.001
Lipid-lowering agents, %	42.1	28.3	36.4	46.0	<0.001
Statins, %	39.9	26.1	34.2	43.8	<0.001
Ezetimibe, %	2.9	1.4	2.1	3.4	0.004
Other non-statin LLT, %	2.9	3.4	2.8	2.9	0.803
Antiplatelet, anticoagulant drugs, %	22.1	11.7	17.4	25.3	<0.001
Platelet aggregation inhibitors, %	19.0	11.7	15.1	21.5	<0.001
Oral anticoagulants, %	5.1	0.0	4.2	5.8	<0.001
Glucose-lowering therapies, %	87.7	80.2	83.1	90.6	<0.001
Insulin, %	45.1	34.3	37.2	49.9	<0.001
Metformin, %	65.4	60.8	59.7	68.6	<0.001
Acarbose, %	0.6	1.0	0.9	0.4	0.157
Sulfonylurea, %	5.8	9.3	6.8	5.0	<0.001
DPP-4 inhibitors, %	31.2	25.2	31.1	31.8	0.071
GLP-1 agonists, %	13.2	12.1	12.2	13.9	0.317
SGLT2 inhibitors other than empagliflozin, %	2.9	7.9	2.3	2.7	<0.001

ACEi, ACE inhibitor; ARB, angiotensin-receptor blocker; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; LLT, lipid-lowering therapy; SGLT-2, sodium-glucose transport protein-2.

Table 3 Glucose-lowering treatment prior to versus post empagliflozin initiation: switch analysis

	Prior to empagliflozin initiation	After empagliflozin initiation	P value
Drug classes			
Metformin, %	51.1	62.2	<0.001
Acarbose, %	0.5	0.5	0.781
Sulfonylurea, %	7.4	6.1	0.055
DPP-4 inhibitors, %	25.8	28.3	0.035
GLP-1 agonists, %	11.0	14.1	<0.001
SGLT2 inhibitors, %	6.3	100	<0.001
Empagliflozin, %	0	100	<0.001
Any other, %	6.3	3.8	<0.001
Insulin, %	29.3	42.4	<0.001
Drug–drug combination therapy			
Single drug, %	27.3	26.1	0.602
Two-drug combinations without insulin, %	16.6	28.3	<0.001
Three-drug combinations without insulin, %	2.9	14.5	<0.001
Combinations including insulin, %	23.1	42.4	<0.001

DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose transport protein-2.

Table 4 Real-world effectiveness and safety

	Within 1 year prior to empagliflozin initiation	3–9 months after empagliflozin initiation	P value
HbA1c, %, mean (SD)*	7.8 (1.3)	7.4 (1.1)	<0.001
mmol/mol, mean (SD)	61.9 (14.5)	57.3 (11.8)	<0.001
HbA1c <6.5%, %	12.8	19.2	<0.001
HbA1c ≥6.5% and <7.0%, %	15.4	19.8	<0.001
HbA1c ≥7.0% and <7.5%, %	19.0	22.1	0.013
HbA1c ≥7.5% and <8.0%, %	17.1	16.3	0.635
HbA1c ≥8.0%, %	35.8	22.7	<0.001
FPG, mmol/mol, mean (SD)	168.0 (55.1)	155.8 (49.7)	<0.001
Severe hypoglycemia, %	0.6	0.4	0.430
Chronic kidney disease, %	43.6	40.3	0.070
Diabetic ketoacidosis, %	0.03	0.0 (n=0)	0.635

*The HbA1c differs from table 1 as only a subgroup of patients available for this analysis were considered.
FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

earlier in the treatment algorithm. This could be a consequence of prescribers gaining greater experience with the drug, and the availability of clinical trial results supporting its beneficial effects on major cardiovascular and renal outcomes in patients with T2DM, leading to updates of the product label, as well as respective treatment guidelines worldwide.

Although empagliflozin is most commonly prescribed to younger patients (aged <65 years), it is increasingly being used in older patients, too. The proportion of recipients having cardiovascular comorbidities, such as a history of myocardial infarction, coronary artery disease or stroke, has also increased. These two findings may be related, as comorbidity tends to increase with age. Use of empagliflozin in older patients and those with comorbidities increased after the publication of the results of the EMPA-REG OUTCOME study, which showed that empagliflozin treatment was associated with a reduced risk of adverse cardiovascular outcomes and death compared with placebo, when added to standard care in patients with T2DM who were at high cardiovascular risk.[1]

The mean eGFR decreased between early and late adopters of empagliflozin in the current study, suggesting that an increasing number of patients with low eGFR are being treated with empagliflozin. Prescribers may have been reassured by data from the EMPA-REG OUTCOME study showing that the beneficial renal effects (ie, slower progression of kidney disease) of empagliflozin were independent of renal function and HbA1c. Furthermore, the safety profile was consistent across the eGFR spectrum down to $30\,mL/min/1.73\,m^2$.[2]

Empagliflozin treatment is known to lead to a reduction in bodyweight.[11] The decrease in mean BMI seen between early and late adopters suggests that empagliflozin was initially used in patients with high BMI but is now also being used in patients with lower BMI.

Drug–drug combinations

The study shows that in recent years, empagliflozin is increasingly often being prescribed in conjunction with metformin. Metformin is the first-line oral glucose-lowering medication for most patients with T2DM; however, as the disease progresses, many patients need combination therapy to maintain adequate reductions in glucose levels. The combination of metformin and empagliflozin has been shown to improve glycemic control compared with either agent alone, with a low risk of hypoglycemia.[12–14] It has also been shown to be superior to the combination of metformin and glimepiride in HbA1c change from baseline in a 2-year study, while reducing non-severe hypoglycemia by more than 20% (>90% relative risk reduction).[15]

A switch analysis of previous glucose-lowering treatment showed that empagliflozin was generally not introduced as a replacement for other drugs but was usually added to the antidiabetic regimen. Actually more than a quarter of patients received triple combination therapy, which is in line with the German Diabetes Guideline[16] recommending the oral triple combination of metformin, a dipeptidyl peptidase-4 inhibitor and SGLT-2 inhibitor as a safe, effective and simple treatment regimen based on clinical trial evidence.[17 18 19] The triple combination offers sustained reductions in HbA1c, fasting blood glucose, weight and blood pressure with a low rate of hypoglycemia, but at the costs of known side effects of each of these drugs.

In patients with T2DM in whom glycemic targets cannot be achieved with oral agents, basal insulin therapy can be added.[20] It has been shown that the addition of empagliflozin to basal insulin improves glycemic control with no increased risk of hypoglycemia.[21] This was confirmed in a trial published by Rosenstock et al. where the addition of empagliflozin to multiple daily injections of insulin in obese patients with T2DM improved glycemic control and reduced weight without increasing the risk of hypoglycemia

and with lower insulin requirements.[22] The current study found a marked increase in the use of empagliflozin in combination with insulin in more recent time periods.

Consequently, increases in two-drug and three-drug oral/GLP-1-receptor antagonist-based combination regimens, and in combinations involving insulin, were seen after patients started empagliflozin treatment.

Effectiveness and safety

Clinical trials established that empagliflozin improves glycemic control with a low risk of hypoglycemia.[15 23–26] The current study provides evidence of the effectiveness and safety of empagliflozin when used in routine clinical practice. Empagliflozin treatment was associated with significant reductions in mean HbA1c and mean fasting plasma glucose levels, and a significant increase in the proportion of patients achieving an HbA1c <6.5%, compared with the status prior to initiation. There was no increase in the rates of severe hypoglycemia. The risk of diabetic ketoacidosis could not be evaluated due to the low number of events. In fact, no such event occured after start of empagliflozin within the study follow-up. There was also no increase in the rate of CKD after initiation of empagliflozin; in fact, a non-significant trend toward a reduced rate of CKD was seen after 6 months.

Germany-specific aspects

One aspect to be considered when evaluating the changing use of empagliflozin in Germany is its adoption in the German 'disease management program (DMP) type-2 diabetes (T2D)'. At the end of April 2017, the Federal Joint Committee (G-BA), Germany's highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds, decided to add empagliflozin as a drug 'with proven benefit on clinical outcomes' recommended for patients with eCVD. This resolution became effective July 1, 2017.

G-BA's decision to grant empagliflozin a considerable additional benefit in the AMNOG HTA procedure in September 2016 is a further aspect to be considered. Because of this we assume some beneficial effect on empagliflozin real-world use in Germany. However, the Germany-wide so-called practice specialty, exempting physicians' empagliflozin prescriptions for patients with T2D/eCVD from budget restrictions, is considered to impact physicians' prescribing behavior even more than the G-BA decision itself. This practice specialty became effective only in January/February 2017.

Clinical implications

The results of this study support the effectiveness and safety of empagliflozin in daily clinical practice. The findings are consistent with the known profile of empagliflozin from clinical trials, which necessarily involved a more restricted patient population.

Major guidelines recommend adding an SGLT-2 inhibitor or GLP-1 agonist with proven cardiovascular benefits to metformin in patients with T2DM and atherosclerotic cardiovascular disease (ASCVD), with empagliflozin and liraglutide, respectively, favored over other drugs from these classes because they have been shown to reduce both major adverse cardiovascular events and cardiovascular mortality.[20 27 28] SGLT-2 inhibitors are recommended as add-on therapy for patients with ASCVD, heart failure or CKD.[20] It should be noted that, although there is some evidence of a class effect on cardiovascular outcomes for SGLT-2 inhibitors, individual studies have produced varying results.[29] Nonetheless, several observational studies support SGLT-2 inhibitors having a beneficial effect on cardiovascular outcomes in 'real-world' practice.[30 31] It is likely that the use of this drug class will continue to increase in the future. The current study does not provide long-term outcome data for empagliflozin, but it does provide reassurance that the drug can be safely used in patients with T2DM, including those with cardiovascular comorbidity, who are managed in a routine practice setting.

Limitations

The main limitation of the study is that patients were recruited from specialized centers that were participating in diabetes registries, which could bias the results toward patients requiring specialist care. The cross-sectional nature of the study precludes the identification of causal links between findings. The strengths include the large number of patients that were enrolled and the routine practice setting, which means that the study provides evidence from 'real-world' clinical practice.

CONCLUSIONS

This study shows that in routine practice, empagliflozin is being prescribed to a broader range of patients and earlier in the treatment regimen over time. It is usually being added to an existing antidiabetic regimen and is increasingly being used in combination with metformin, GLP-1 A and/or insulin. In a 'real-world' setting, empagliflozin has a beneficial effect on glycemic control, with no increase in the rates of severe hypoglycemia.

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