

Changes in HbA1c, body weight, and systolic blood pressure in type 2 diabetes patients initiating dapagliflozin therapy: a primary care database study

Markus F Scheerer¹
Roland Rist¹
Orm Proske¹
Annika Meng²
Karel Kostev²

¹Medical Department, AstraZeneca GmbH, Wedel, Germany; ²IMS Health GmbH & Co. OHG, Frankfurt am Main, Germany

Aims: To investigate changes in glycated hemoglobin (HbA1c), body weight (BW), and systolic blood pressure (SBP) in type 2 diabetes (T2D) primary care patients initiating dapagliflozin treatment.

Methods: T2D patients who started dapagliflozin in 985 general and 32 diabetologist practices (Disease Analyzer, Germany: December 2012–October 2014) were analyzed (3- and 6-month follow-up). Multivariate linear regression analyses were used to identify clinical characteristics and comorbidity associated with changes in HbA1c, BW, and SBP.

Results: The study included 1,169 T2D patients (age: 62.5 years; men: 59.3%; diabetologist care: 23%) with newly initiated dapagliflozin therapy. At the 3-month stage, dapagliflozin significantly reduced HbA1c ($-0.8\% \pm 1.4\%$) compared to the baseline ($8.5\% \pm 1.5\%$) ($P < 0.001$). Changes were maintained after 6 months ($-0.8\% \pm 1.5\%$) ($P < 0.001$). Patients with high baseline HbA1c values ($>9\%$) showed greater reductions in HbA1c than the overall sample (3 months -1.8% , 6 months -1.8% ; both $P < 0.05$). BW and SBP also showed statistically significant reductions with dapagliflozin over 3 and 6 months (-2.2 kg, $P < 0.001$; -2.2 mmHg, $P = 0.003$ and -2.5 kg, $P < 0.001$; -2.3 mmHg, $P = 0.011$, respectively). After 3 months, 53% of patients achieved a reduction in both HbA1c and BW; the same holds true for 45% of patients at the 6-month mark. Similar results were observed both in general and diabetologist practices. In multivariate analyses, baseline HbA1c (parameter estimate: -0.6479) and diabetologist care (-0.2553) were independent predictors of HbA1c change (6 months) (all $P < 0.05$).

Conclusion: T2D patients treated with dapagliflozin therapy achieved statistically significant reductions in HbA1c, BW, and SBP in a real-world primary and diabetologist care setting. The changes were comparable to the results of the dapagliflozin clinical trial program.

Keywords: type 2 diabetes, dapagliflozin, HbA1c, body mass index, systolic blood pressure

Introduction

Renal glucose production increases with insulin resistance, the hallmark of type 2 diabetes (T2D).¹ Approximately 40% of the increased endogenous glucose release in patients with T2D has been attributed to renal gluconeogenesis.¹ Furthermore, the capacity for renal glucose reabsorption is higher in patients with T2D, thus perpetuating hyperglycemia.² SGLT2 is located in the proximal tubule and is involved in the reabsorption of glucose ($\sim 90\%$) in the kidney.³ As the action of SGLT2 is independent of insulin, its inhibition should not be influenced by the degree of insulin resistance or insulin secretion.⁴ Therefore, SGLT2 inhibitors have the potential to be effective in reducing hyperglycemia by stimulating urinary glucose excretion at any stage and duration of T2D. In 2015, the

Correspondence: Karel Kostev
Epidemiology & Evidence-Based Medicine,
Real-World Evidence Solutions, IMS
Health GmbH & Co. OHG, Darmstädter
Landstraße 108, 60598 Frankfurt am
Main, Germany
Tel +49 69 6604 4878
Email kkostev@de.imshealth.com

American Diabetes Association and European Association for the Study of Diabetes issued an update to their joint position statement on the management of hyperglycemia in T2D.⁵ SGLT2 inhibitors are mentioned among the options for second-line therapy after treatment with metformin and as alternative first-line options in patients with contraindications to metformin in an oral triple therapy or as add-on to insulin therapy.⁵

Dapagliflozin was the first approved selective SGLT2 inhibitor in Europe that reduces hyperglycemia through the reduction of glucose reabsorption into the kidney.⁶ Previous randomized clinical studies on dapagliflozin have demonstrated reductions in glycated hemoglobin (HbA1c) at all stages of T2D progression, favorable effects on body weight (BW), and a moderate lowering of blood pressure. These benefits have been observed when dapagliflozin was used as monotherapy or in combination with metformin (normal and extended release formulations), sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, or insulin.⁷⁻¹⁶ However, there is a paucity of data on the efficacy of dapagliflozin in a real-world setting, eg, in primary care patients with T2D. Furthermore, studies to determine baseline characteristics that could be used to predict which patients would benefit most from dapagliflozin treatment are lacking.

The first aim of this study was to investigate changes in treatment outcomes (HbA1c, BW, systolic blood pressure [SBP]) for T2D patients initiating dapagliflozin therapy using a large database representative of practices in Germany. The second aim was to evaluate baseline clinical predictors of changes in HbA1c, weight, and SBP after dapagliflozin initiation.

Methods

The Disease Analyzer database (IMS Health GmbH & Co. OHG) collects drug prescriptions, diagnoses, and basic medical and demographic data directly obtained from the computer system of a representative sample of general practitioners and internal medicine practices throughout Germany.¹⁷ For such studies based on anonymous data in Germany no special ethic approval or patient consent is required and hence it was not sought for this study. The analyzed database period for the current study was from December 2012 to October 2014 (985 general and 32 diabetologist practices). Patients with T2D who were initiated on dapagliflozin therapy during the study period (index date) were included. Two cohorts with ≥ 3 - or ≥ 6 -month follow-up after index date were analyzed, respectively. The practice visit records were used to determine baseline demographic characteristics 6 months prior to the index date.

Macrovascular complications were determined based on primary care diagnoses (ICD-10 codes) for coronary heart

disease (I24, I25), myocardial infarction (I21, I22, I23, I25.2), stroke (I63, I64, G45), and peripheral vascular disease (I739, E105, E115, E145). Microvascular complications included retinopathy (E113, E143, H360), neuropathy (E114, E144), and nephropathy (N18, N19, E112, E142, Z49, Z992). Treatment with antidiabetic drugs prior to the index date was also assessed. Finally, the recorded HbA1c values and the documented BW and SBP before and after the index date were included in the analyses.

Descriptive statistics were provided and changes in HbA1c, BW, and blood pressure were assessed using paired *t*-tests. Two-sided tests were used and a *P*-value of <0.05 was considered as statistically significant. Scatter plots were used to visualize changes in BW and changes in HbA1c. Multivariate linear regression model was fitted to investigate the associations between clinical variables or comorbidity and changes in HbA1c, BW, and SBP, respectively. All analyses were carried out in accordance with the Good Practice of Secondary Data Analysis (GPS): guidelines and recommendations of the German Society¹⁸ using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Upon patient selection, 1,169 new users of dapagliflozin (age: 62.5 years; male: 59.3%) were included. The baseline clinical characteristics are shown in Table 1. Approximately 25% of the T2D patients who received dapagliflozin were treated by diabetologists. There was a high prevalence of privately insured patients. Approximately 10% of the patients received dapagliflozin monotherapy, whereas biguanides were the antidiabetic drug most frequently prescribed in combination with dapagliflozin, followed by insulin (Table 1).

Macrovascular complications and related risk factors were frequently found in the T2D patients initiating dapagliflozin therapy (Table 1). Coronary heart disease, peripheral vascular disease, history of myocardial infarction, or stroke was diagnosed in 47% of the patients prior to onset of dapagliflozin treatment. Microvascular diabetes complications were observed in 22% of the study population (Table 1).

At 3 months, a statistically significant reduction in mean HbA1c from baseline (8.5%) was observed with dapagliflozin (-0.8%) ($P<0.001$) (Table 2). The reduction in HbA1c with dapagliflozin treatment was maintained at 6 months (-0.8% : standard deviation [SD]: 1.4) ($P<0.001$) (Table 3). Greater HbA1c decreases were observed with dapagliflozin in 466 patients with higher baseline HbA1c $>8.0\%$ (-1.3% ; SD: 1.5) ($P<0.001$) and 251 patients with

>9.0% (−1.8%; SD: 1.7) ($P<0.001$) at 3 months, and these greater reductions were still evident at 6 months (data not shown).

A statistically significant reduction in mean BW was observed in patients treated with dapagliflozin at 3 months (−2.3 kg) (Table 2) and was maintained through 6 months (−2.5 kg) (Table 3) (both $P<0.001$). The mean reduction in SBP was statistically significant at 3 months (−2.2 mmHg) and was also maintained at 6 months (−2.3 mmHg) (both

$P<0.05$) (Tables 2 and 3). The effects of dapagliflozin on HbA1c and BW were largely comparable in both T2D patients treated in general practices and diabetologist care (Tables 2 and 3). The reductions in SBP at both 3 and 6 months were somewhat greater in patients treated by diabetologists compared to patients in general practices.

Scatter plots representing the relationship between reductions in HbA1c and BW after 3 and 6 months of treatment are shown in Figures 1 and 2, respectively. Approximately 50% of patients receiving dapagliflozin responded simultaneously to the two-item endpoint of combined HbA1c (>0% HbA1c%) and BW (>0 kg) reductions at 3 months (Figure 1). The combined endpoint reductions were achieved in 45% of new dapagliflozin patients after 6 months (Figure 2). Furthermore, ~19% of patients treated with dapagliflozin achieved an HbA1c reduction at 3 months despite an increase in BW (Figure 1). At 6 months, this proportion increased to 25% (Figure 2). After 3 months of dapagliflozin treatment, only 8.5% failed to exhibit reductions in both HbA1c and BW. After 6 months, the corresponding proportion was 12.4%.

The correlations of baseline clinical variables with changes in HbA1c after onset of dapagliflozin treatment were investigated using linear regression. Only baseline HbA1c was statistically significantly inversely related to change in HbA1c after both 3 and 6 months, indicating that higher HbA1c values were related to a greater decrease after onset of dapagliflozin treatment ($P<0.0001$). Furthermore, age was positively correlated with the HbA1c decrease observed at 3 months, indicating that HbA1c increased with age after the index date (Table 4). Finally, diabetologist treatment

Table 1 Baseline characteristics of type 2 diabetes patients who received newly prescribed dapagliflozin in primary care practices in Germany (Disease Analyzer)

Variables	
N	1,169
Age (years)	62.5 (11.2)
Male (%)	59.3
Private health insurance coverage (%)	12.9
Diabetologist care (%)	22.7
Dapagliflozin therapy (%)	
Monotherapy	10.9
Dapagliflozin + metformin	37.1
Dapagliflozin + insulin (±metformin)	33.5
Dapagliflozin + DPP-4i (±metformin)	9.7
Other combinations	8.9
Comorbidity (%)	
Macrovascular complications	47.1
Microvascular complications	22.8
Hypertension	78.8
Hyperlipidemia	62.0

Notes: Data are mean (SD) or proportions (%) DPP-4i. Macrovascular complications include coronary heart disease, myocardial infarction, peripheral vascular disease, and stroke. Microvascular complications include retinopathy, nephropathy, and neuropathy.

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; SD, standard deviation.

Table 2 Three-month (after the ID) changes in HbA1c, body weight, and systolic blood pressure in type 2 diabetes patients initiating dapagliflozin therapy in primary care practices in Germany

Variables	N	Baseline ≤6 months before ID	3 months after ID	Difference (before-after ID)	P-value
Total patients					
HbA1c (%)	826	8.5 (1.5)	7.8 (1.2)	−0.8 (1.4)	<0.001
Body weight (kg)	268	102.7 (22.1)	100.4 (21.6)	−2.3 (4.8)	<0.001
Systolic blood pressure (mmHg)	471	137.0 (14.5)	134.8 (17.3)	−2.2 (17.6)	0.003
Patients treated by general practitioners					
HbA1c (%)	682	8.6 (1.5)	7.8 (1.2)	−0.8 (1.4)	<0.001
Body weight (kg)	180	99.7 (22.2)	97.4 (21.4)	−2.3 (4.9)	<0.001
Systolic blood pressure (mmHg)	326	136.9 (17.4)	135.1 (17.2)	−1.8 (17.2)	0.046
Patients treated by diabetologists					
HbA1c (%)	144	8.4 (1.3)	7.8 (1.2)	−0.6 (1.3)	<0.001
Body weight (kg)	88	108.9 (20.9)	106.4 (20.9)	−2.5 (4.8)	<0.001
Systolic blood pressure (mmHg)	145	137.2 (17.7)	134.2 (17.6)	−3.0 (18.6)	0.016

Note: Data are mean (SD).

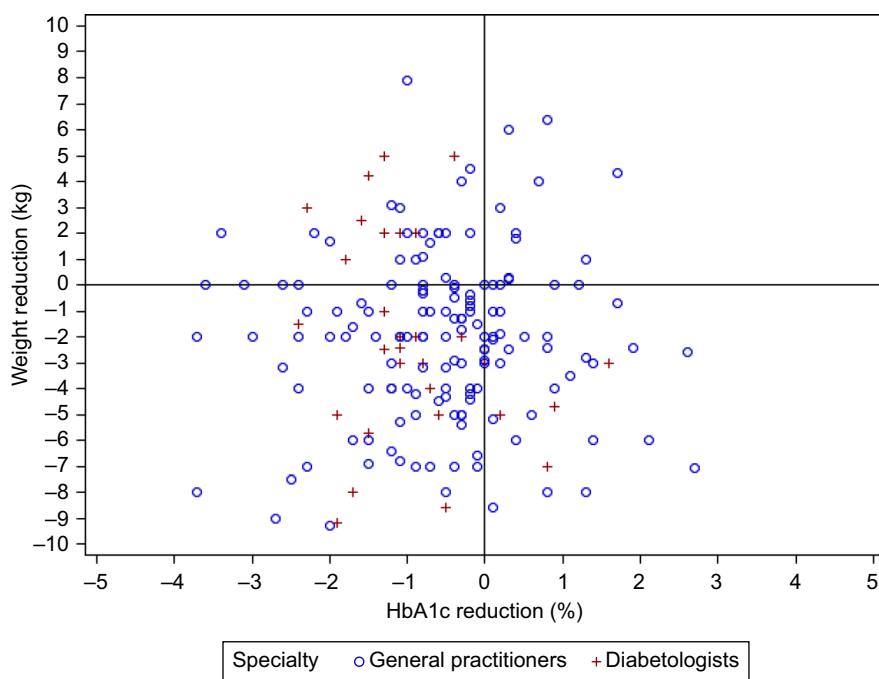
Abbreviations: ID, index date; SD, standard deviation; HbA1c, glycated hemoglobin.

Table 3 Six-month (after the ID) changes in HbA1c, body weight, and systolic blood pressure in type 2 diabetes patients initiating dapagliflozin therapy in primary care practices in Germany

Variables	N	Baseline ≤ 6 months before ID	6 months after ID	Difference (before-after ID)	P-value
Total patients					
HbA1c (%)	645	8.5 (1.6)	7.8 (1.2)	-0.8 (1.5)	<0.001
Body weight (kg)	239	102.3 (22.5)	99.8 (22.1)	-2.5 (7.1)	<0.001
Systolic blood pressure (mmHg)	388	137.7 (16.7)	135.4 (16.2)	-2.3 (16.7)	0.011
Patients treated by general practitioners					
HbA1c (%)	530	8.5 (1.6)	7.8 (1.2)	-0.7 (1.5)	<0.001
Body weight (kg)	167	98.9 (21.7)	96.4 (21.3)	-2.5 (5.4)	<0.001
Systolic blood pressure (mmHg)	265	137.6 (16.9)	135.7 (16.5)	-2.0 (15.9)	0.064
Patients treated by diabetologists					
HbA1c (%)	115	8.6 (1.5)	7.7 (1.2)	-0.9 (1.3)	<0.001
Body weight (kg)	72	110.1 (22.6)	107.7 (22.2)	-2.5 (9.9)	0.031
Systolic blood pressure (mmHg)	123	137.8 (16.4)	134.8 (15.5)	-2.9 (18.3)	0.073

Note: Data are mean (SD).

Abbreviations: ID, index date; SD, standard deviation; HbA1c, glycated hemoglobin.

**Figure 1** Scatter plot representing the relationship between the change in HbA1c (%) and body weight (kg) after 3 months in type 2 diabetes patients initiating dapagliflozin treatment in primary care practices.

Abbreviation: HbA1c, glycated hemoglobin.

was related to a significantly greater decrease in HbA1c at 6 months compared to treatment in general practices.

Baseline BW was inversely related to weight change (kg) both at 3 and 6 months, indicating that higher BW was related to a greater change after onset of dapagliflozin treatment (Table 5). Furthermore, diabetologist care was related to a greater weight change at 3 months after onset of dapagliflozin therapy compared to treatment in general practices.

With respect to changes in SBP at 3 months, only baseline systolic values (negative) and age (positive) were statistically

significantly related (data not shown). Thus, higher baseline SBP was related to a greater decrease. At 6 months, only baseline SBP was negatively related to its change; this change was statistically significant.

Changes in HbA1c, BW, and SBP in various subgroups of patients treated with antidiabetic combination therapies, including dapagliflozin, are shown in Tables S1 and S2. After 3 months of treatment, both dapagliflozin monotherapy and combination therapy with metformin, insulin, or DPP-4 inhibitors yielded statistically significant decreases of HbA1c

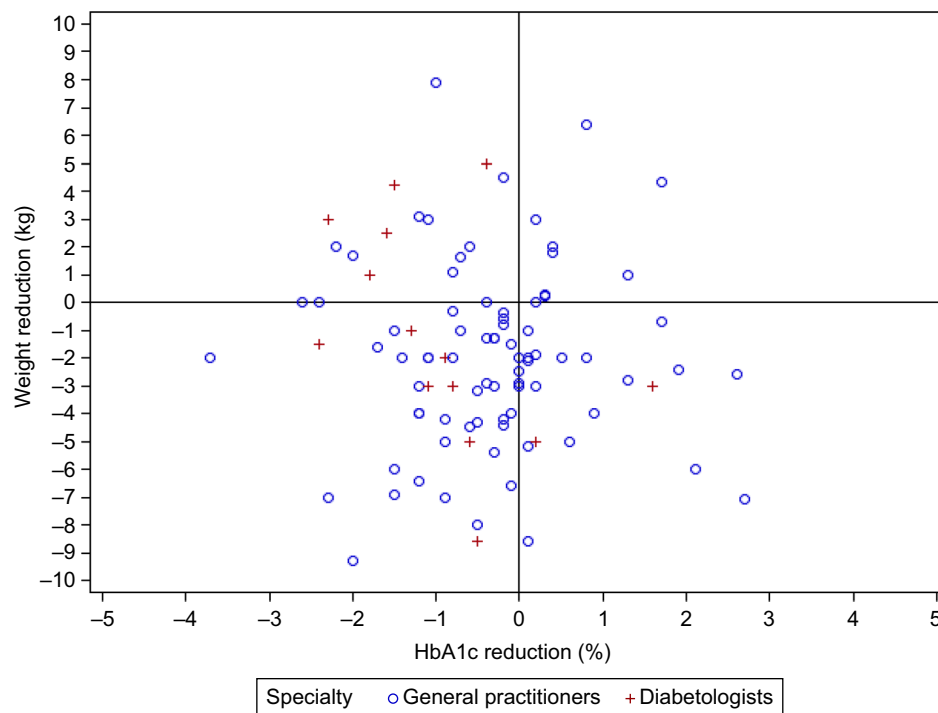


Figure 2 Scatter plot representing the relationship between the change in HbA1c (%) and weight (kg) after 6 months in type 2 diabetes patients initiating dapagliflozin treatment in primary care practices.

Abbreviation: HbA1c, glycated hemoglobin.

Table 4 Variables associated with HbA1c (%) change after 3 and 6 months in type 2 diabetes patients initiating dapagliflozin in primary care practices: multivariate linear regression models

Variables	Change (3 months) beta-coefficients	P-value	Change (6 months) beta-coefficients	P-value
Age (per year)	0.0073	0.0381	0.0055	0.1995
HbA1c (baseline) (%)	-0.6124	<0.0001	-0.6479	<0.0001
Male gender	-0.0493	0.5169	-0.1023	0.2619
Private health insurance coverage	-0.1487	0.1983	0.0605	0.6600
Diabetologist care	-0.0024	0.9817	-0.2553	0.0391
Dapagliflozin monotherapy	0.1096	0.5269	0.0834	0.6701
Dapagliflozin + insulin (\pm metformin)	0.0773	0.5774	0.1021	0.5104
Dapagliflozin + DPP-4i (\pm metformin)	-0.1287	0.3450	-0.1260	0.4143
Other combinations	0.0237	0.8892	-0.0227	0.9060
Macrovascular complications	-0.0180	0.8135	-1.6027	0.0929
Microvascular complications	-0.0990	0.2845	-0.0912	0.3844
Hypertension	-0.1217	0.1964	0.0935	0.4158
Hyperlipidemia	-0.0247	0.7512	0.0513	0.5879

Note: Bold text indicate that the effect is significant.

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; HbA1c, glycated hemoglobin.

and BW (Table S1). A statistically significant reduction of SBP was also observed in patients treated with dapagliflozin and DPP-4 inhibitors. After 6 months of treatment, similar statistically significant reductions of HbA1c and BW were found for dapagliflozin monotherapy (Table S2). Moreover, a statistically significant decrease in HbA1c and BW was observed for dapagliflozin combination therapy with insulin or DPP-4 inhibitors. A statistically significant HbA1c reduction was maintained in patients with dual treatment with metformin, whereas a borderline statistical significance

was found for BW ($P=0.06$). With respect to SBP, no statistically significant decrease was observed in all four treatment subgroups after 6 months of treatment. However, patient numbers are small in several of these groups, thus limiting statistical power.

Discussion

For the first time, a real-world study evaluated the short-term changes in HbA1c, BW, and SBP in T2D patients initiating dapagliflozin treatment in primary care and

Table 5 Variables associated with body weight change (kg) after 3 and 6 months in type 2 diabetes patients initiating dapagliflozin in primary care practices: multivariate linear regression model

Variables	Change (3 months) parameter estimate	P-value	Change (6 months) beta-coefficients	P-values
Age (per year)	0.0055	0.1995	-0.0147	0.7682
Body weight baseline (per kg)	-0.6479	<0.0001	-0.0847	0.0003
Male gender	-0.1023	0.2619	0.6923	0.4843
Private health insurance coverage	0.0605	0.6600	-1.4899	0.3785
Diabetologist care	-0.2553	0.0391	-0.3018	0.7790
Dapagliflozin monotherapy	0.0834	0.6701	-2.9286	0.1779
Dapagliflozin + insulin (\pm metformin)	0.1021	0.5104	1.0618	0.5308
Dapagliflozin + DPP-4i (\pm metformin)	-0.1259	0.4143	-0.7029	0.6894
Other combinations	-0.0227	0.9060	-0.1178	0.9575
Macrovascular complications	0.3595	0.5658	-1.6027	0.0929
Microvascular complications	0.3971	0.5529	0.9438	0.3827
Hypertension	0.1935	0.4158	1.3511	0.2697
Hyperlipidemia	0.0513	0.5879	-1.6202	0.0999

Note: Bold text indicate that the effect is significant.

Abbreviation: DPP-4i, dipeptidyl peptidase-4 inhibitor.

diabetologist practices. Overall, T2D patients treated with dapagliflozin exhibited statistically significant reductions in HbA1c (-0.8%), BW (-2.5 kg), and SBP (-2.3 mmHg) after 6 months of treatment. In addition, HbA1c reductions were greater in patients with poor glycemic control. These real-world treatment effects are comparable to results of dapagliflozin randomized clinical trials.^{7-15,18-21,26}

Changes in HbA1c

In the dapagliflozin clinical trial program, monotherapy yielded a statistically significant HbA1c reduction of 0.66% after 24 weeks when compared to placebo (-0.89% vs -0.23%, $P < 0.0001$).⁷ As an add-on to metformin, dapagliflozin consistently improved HbA1c (placebo-corrected) by 0.54% after 24 weeks (-0.84% vs -0.30%, $P < 0.0001$).⁸ In third-line therapy, when dapagliflozin was used concomitant with the DPP-4 inhibitors sitagliptin or saxagliptin, HbA1c reductions of -0.5% (-0.5% vs 0.0%, $P < 0.0001$) and -0.72% (-0.82% vs 0.10%, $P < 0.0001$), respectively, were observed compared with placebo after 24 weeks.^{10,16} In third-line therapy with metformin and sulfonylureas, dapagliflozin led to placebo-corrected HbA1c reductions of -0.69% ($P < 0.0001$).¹⁵ Moreover, addition of dapagliflozin in T2D patients receiving high doses of insulin (≥ 30 IU/day) and up to two other antidiabetic agents effectively reduced HbA1c by 0.57% compared with placebo after 24 weeks (-0.96 vs -0.39%, $P < 0.001$)¹¹ and by 0.35% over a period of 2 years (-0.78% vs -0.43%, $P < 0.0007$) with stable insulin doses over the entire study period and a net increase of placebo by 19.2 IU at 2 years when compared to the study drug.¹⁹

In the present study, the HbA1c reduction of 0.8% achieved with dapagliflozin after 3 and 6 months was

commensurate with most HbA1c reductions over 24 weeks found in the dapagliflozin arm of clinical trials, rather than their placebo-corrected margin.

Similar results were obtained for the second largest cohort of patients using dapagliflozin as an add-on to insulin (33%). This cohort exhibited an HbA1c reduction of 0.8% after 6 months. Identical numerical reduction of HbA1c at 6 months was shown for the oral triple therapy adding dapagliflozin to a preexisting treatment with metformin and a DPP-4 inhibitor. This observation in real-life yielded reductions similar to the recently published clinical trial using dapagliflozin as a third-line drug add-on to metformin and saxagliptin.¹⁶

This analysis also indicated clinical variables that are independently related to change in HbA1c after initiation of dapagliflozin treatment. Most important, the baseline HbA1c was inversely related to both the changes in HbA1c at 3 and 6 months. This result is in accordance with a recent clinical trial with statistically significantly greater HbA1c reductions observed with dapagliflozin treatment in patients with baseline HbA1c $\geq 8.0\%$ (-0.56%) and $\geq 9.0\%$ (-0.99%) at 6 months compared to the overall sample (-0.46%).²⁰

In this real-world study, a greater HbA1c reduction was found in patients treated in diabetologist practices. This outcome most likely reflects the fact that diabetologists are more familiar with the relatively new dapagliflozin therapy. The positive correlation with age found in the present study ostensibly indicates that older patients have a more advanced stage of the disease along with declining kidney function, which makes it more difficult to achieve a reduction in HbA1c using dapagliflozin.

Taken together, dapagliflozin usage in real life favorably reflected the HbA1c reductions previously measured in the

dapagliflozin clinical trial program. Higher baseline HbA1c values led to greater reductions and if higher age is associated with decreasing kidney function, smaller reductions are well explainable due to dapagliflozin's mechanism of action.

Changes in body weight

The weight loss observed in the present study was consistent with the weight loss observed across RCTs in clinical trials.²¹ Twelve RCTs, including 2,005 participants in the intervention groups and 2,003 participants in the control groups with follow-up durations ranging from 12 to 104 weeks, were included in a meta-analysis.²¹ BW decreases ranged from -3.33 to -1.54 kg after treatment with dapagliflozin.²¹ The overall mean difference between the intervention and control groups was -2.10 kg ($P < 0.001$).²¹ In another network meta-analysis of RCTs, the mean change in weight associated with dapagliflozin was statistically significant compared with the other antidiabetic agents: -2.74 kg relative to DPP-4 inhibitors, and -4.67 kg relative to sulfonylureas.²² The results from the present real-world study demonstrate that similar reductions in BW (-2.5 kg at 6 months) can be achieved in primary care patients. This weight loss has been attributed to the ~200–300 cal of glucose excreted per day as a result of treatment with dapagliflozin.²³ Although the impact of this amount of weight loss on mortality and cardiovascular events is debatable, even small weight decreases in T2D have been shown to improve treatment satisfaction and quality of life.^{24,25}

Similar to HbA1c, baseline BW was negatively correlated with weight change at 3 months. The BW reduction observed in clinical trials for dapagliflozin was primarily caused by a reduction in body fat mass, as shown by dual energy X-ray absorptiometry and calorie loss.²⁶ A subgroup analysis using magnetic resonance imaging showed a reduction of visceral adipose tissue mass greater than 9% compared to the baseline during treatment with dapagliflozin. Furthermore, consistent with the changes in HbA1c, diabetologist care was associated with a greater change in BW at 3 months. This most likely reflects more intensive care and/or a more motivated patient population.

Changes in systolic blood pressure

A recent meta-analysis of 27 RCTs involving dapagliflozin ($n=12$) reported that SGLT2 inhibitor use was associated with a statistically significant reduction in SBP from baseline (-4.0 mmHg).²⁷ This real-world study also showed statistically significant reductions in SBP (-2.3 mmHg) at 6 months. The impact of the blood pressure reductions achieved with dapagliflozin on cardiovascular outcomes requires further investigation. The underlying mechanisms of a dapagliflozin-specific

reduction of SBP must be identified. In the present investigation, baseline blood pressure (inverse association) was the only relevant variable associated with changes in SBP.

Strength and limitations of the study

The present study provides an illustration of prescriptions and diagnoses in primary care and diabetologist practices in Germany. The strength of the study is the use of a large nationwide database and the unbiased assessment of prescriptions and outcomes. As this study used primary care records, a number of limitations should be mentioned: First, no valid information regarding onset of diabetes was provided. Additionally, assessment of comorbidities solely relied on ICD codes filled in by physicians. Moreover, measurements of HbA1c and body mass index values were not standardized. Finally, data on socioeconomic status and lifestyle-related risk factors were also unavailable. It must also be mentioned that, in this study, the adherence to the dapagliflozin administration was not assessed. No investigation was also performed about the change of other antihyperglycemic drugs during the study period. Both adherence and therapy change might affect the findings.

Conclusion

This is the first report of real-world outcomes concerning the effect of dapagliflozin on HbA1c, BW, and systolic blood pressure in T2D patients in primary care and diabetologist practices. The absolute reductions in HbA1c (-0.8%), BW (-2.5 kg), and SBP (-2.3 mmHg) observed in patients inadequately controlled with other antidiabetic agents and insulin were similar to results from the dapagliflozin clinical trial program.

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Disclosure

MF Scheerer, R Rist, and O Proske are employees of AstraZeneca GmbH, Germany. Karel Kostev and Annika Meng are employees of IMS Health GmbH & Co. OHG. The authors report no other conflicts of interest in this work.

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Supplementary materials

Table S1 Three-month changes (after the ID) in HbA1c, body weight, and systolic blood pressure in type 2 diabetes patients initiating dapagliflozin therapy in primary care practices in Germany

Variables	N	Baseline ≤6 months before ID	3 months after ID	Difference	P-value
Dapagliflozin monotherapy					
HbA1c (%)	72	8.1 (1.7)	7.7 (1.4)	-0.4 (1.2)	0.010
Body weight (kg)	24	110.0 (27.6)	105.3 (25.7)	-4.7 (7.5)	<0.001
Systolic blood pressure (mmHg)	45	137.1 (15.3)	136.0 (18.6)	-1.1 (17.6)	0.499
Dapagliflozin + metformin					
HbA1c (%)	73	8.3 (1.6)	7.7 (1.2)	-0.6 (1.5)	<0.001
Body weight (kg)	17	99.9 (21.4)	96.7 (22.3)	-3.2 (3.7)	0.002
Systolic blood pressure (mmHg)	37	135.4 (18.1)	134.5 (14.8)	-0.9 (20.3)	0.964
Dapagliflozin + insulin					
HbA1c (%)	305	8.7 (1.5)	8.0 (1.2)	-0.8 (1.4)	<0.001
Body weight (kg)	133	105.7 (22.8)	103.8 (22.5)	-1.9 (5.0)	<0.001
Systolic blood pressure (mmHg)	223	137.0 (17.8)	135.4 (18.1)	-1.6 (18.1)	0.070
Dapagliflozin + DPP-4 inhibitors					
HbA1c (%)	298	8.5 (1.5)	7.6 (1.1)	-0.9 (1.4)	<0.001
Body weight (kg)	68	96.9 (18.1)	94.7 (17.0)	-2.1 (3.6)	<0.001
Systolic blood pressure (mmHg)	128	139.0 (18.1)	135.4 (17.2)	-3.6 (17.0)	0.018

Note: Data are presented as mean (SD). Bold text indicate that the effect is significant.

Abbreviations: DPP-4, dipeptidyl peptidase-4; ID, index date; SD, standard deviation; HbA1c, glycated hemoglobin.

Table S2 Six-month changes (after the ID) in HbA1c, body weight (kg), and systolic blood pressure in type 2 diabetes patients initiating dapagliflozin therapy in primary care practices in Germany

Variables	N	Baseline ≤6 months before ID	6 months after ID	Difference	P-value
Dapagliflozin monotherapy					
HbA1c (%)	62	8.3 (1.7)	7.8 (1.5)	-0.6 (1.3)	0.001
Body weight (kg)	20	108.3 (30.8)	102.2 (29.2)	-6.1 (16.3)	0.042
Systolic blood pressure (mmHg)	40	137.1 (15.3)	136.0 (18.6)	-1.1 (17.6)	0.518
Dapagliflozin + metformin					
HbA1c (%)	69	8.3 (1.6)	7.7 (1.4)	-0.6 (1.6)	0.001
Body weight (kg)	21	102.7 (20.9)	100.6 (21.2)	-2.1 (4.3)	0.058
Systolic blood pressure (mmHg)	31	139.7 (15.2)	135.4 (12.6)	-4.4 (17.2)	0.129
Dapagliflozin + insulin					
HbA1c (%)	233	8.7 (1.6)	7.9 (1.2)	-0.8 (1.6)	<0.001
Body weight (kg)	118	104.6 (22.5)	102.8 (22.3)	-1.9 (6.4)	0.007
Systolic blood pressure (mmHg)	180	137.2 (16.7)	135.0 (17.3)	-2.2 (17.0)	0.508
Dapagliflozin + DPP-4 inhibitors					
HbA1c (%)	298	8.5 (1.5)	7.7 (1.2)	-0.8 (1.5)	<0.001
Body weight (kg)	68	95.9 (19.2)	93.4 (18.3)	-2.5 (3.7)	<0.001
Systolic blood pressure (mmHg)	128	138.5 (18.2)	136.2 (16.4)	-2.3 (16.8)	0.227

Note: Data are presented as mean (SD). Bold text indicate that the effect is significant.

Abbreviations: DPP-4, dipeptidyl peptidase-4; ID, index date; SD, standard deviation; HbA1c, glycated hemoglobin.

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