Efficacy and Renal Safety of Dapagliflozin in Patients with Type 2 Diabetes Mellitus Also Receiving Metformin: A Real-Life Experience

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Received 21 September 2017; Revised 5 March 2018; Accepted 13 March 2018; Published 3 May 2018

Academic Editor: Bernard Portha

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Introduction. This study aimed at evaluating the efficacy and safety of dapagliflozin in patients with type 2 diabetes (T2D) who also received metformin in clinical practice in Italy. Methods. This was a retrospective observational study and it included data from patients who received dapagliflozin 10 mg once daily in conjunction with metformin for 12 months (DAPA + MET). In those with inadequate glycemic control, insulin or glimepiride was added after 30 days (DAPA + MET + other glucose-lowering drugs). Efficacy assessments included glycosylated hemoglobin (HbA1c) levels at 6 and 12 months, as well as body mass index (BMI) and lipid parameters at 12 months. Safety was also assessed. Results. Data on 66 patients were included. In both groups, HbA1c was significantly reduced at 6 and 12 months compared with baseline and significant reductions in HbA1c were observed at 12 months compared with 6 months. Over the 12-month treatment period, dapagliflozin significantly reduced BMI in both groups. No significant changes in lipid parameters were observed in either group and no detrimental effects on renal function were detected. Conclusions. Dapagliflozin is effective and safe in patients with T2D also receiving metformin. Glycemic control was already achieved with dapagliflozin + metformin, and add-on therapy was not associated with further improvements.

1. Introduction

Over the past 20 years, the proportion of Italians with diabetes in the general population increased from 3.4% to 5.5% and the vast majority (91%) have type 2 diabetes. In Italy, the management of diabetes is associated with approximately €10 billion per year in direct and indirect costs [1].

The principal goal of effective treatment of type 2 diabetes is to reduce blood glucose [2]. At the same time, because type 2 diabetes is characterized by systemic dysregulation of metabolism and is strongly associated with obesity [3], glucose-lowering agents that reduce body weight are preferable to those that have no effect on or increase it. Cardiovascular diseases, for which obesity is a major risk factor, are estimated to cause 40% of all deaths attributed to type 2 diabetes [4].

Dapagliflozin is a glucose-lowering agent that acts by inhibiting sodium glucose cotransporter 2 (SGLT2). Located in the proximal tubule of the nephron, SGLT2 is responsible for the reabsorption of most of the previously filtered glucose [5]. SGLT2 inhibition results in glycosuria and represents an insulin-independent method of reducing blood glucose levels. It also results in a reduction in body weight due to the loss of calories contained in excreted glucose [6]. Studies have demonstrated that dapagliflozin reduced serum glycosylated hemoglobin (HbA1c) levels and body weight in patients with type 2 diabetes when used as monotherapy [7], as well as in combination with other glucose-lowering agents [8–11].

The aim of this study was to evaluate the efficacy and safety of dapagliflozin in patients with type 2 diabetes also receiving metformin in clinical practice in Italy.
2. Methods

2.1. Study Design. This retrospective observational study investigated the effectiveness and renal safety of dapagliflozin 10 mg once daily in adults with type 2 diabetes mellitus who were also receiving metformin 1.5–2.5 g/day (DAPA + MET). Data from outpatients treated at the Regional Referral Centre for Insulin Pump Implantation and Diabetes at the Civic Hospital of Palermo, Italy, who initiated dapagliflozin treatment between March 2015 and March 2016 and who had undergone a follow-up visit at 12 months were included in the analysis. We included 66/94 subjects with type 2 diabetes inadequately controlled with metformin who attended our outpatient clinic for the entire period of observation, had never discontinued therapy, had never had side or adverse effects, had normal renal function (estimated glomerular filtration rate over 60 mL/min), modified their dietary habits according to our advice, and since baseline, underwent all blood tests in our outpatient clinic laboratory. If they were not able to perform self-blood glucose testing at home or did not modify according to our advice, they were excluded. In patients whose HbA1c level was ≥7.5%, insulin or glimepiride were added to the treatment regimen at the same time of initiation of dapagliflozin (DAPA + MET + other glucose-lowering drugs), as per normal clinical practice and clinician’s decision.

The ethics committee (Comitato Bioetico Palermo) at the investigational site was notified of the study protocol and the study was conducted in accordance with the Italian law and the Declaration of Helsinki.

2.2. Assessments. Baseline characteristics included age, sex, weight, waist circumference, systolic blood pressure, diastolic blood pressure, and disease duration.

Effectiveness was assessed using the change from baseline in HbA1c at 6 and 12 months as well as changes in body mass index (BMI) and lipid parameters (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides) at 12 months. HbA1c was self-monitored, with outpatient visits performed every three months or when needed. Renal function was assessed by the change in blood creatinine levels at 6 and 12 months, as well as urine microalbumin levels at 12 months.

2.3. Statistical Analyses. Statistical analyses were performed using SPSS Statistics version 21 for Windows. All variables were analyzed by summary statistical methods and the analyses were performed separately in patients who received DAPA + MET and DAPA + MET + other glucose-lowering drugs. For continuous/quantitative variables, descriptive statistics, including the number of available values, arithmetic mean, standard deviation (SD), minimum, median, and maximum were calculated, while for categorical/qualitative variables, frequency tables were generated. Paired sample t-tests were performed using an analysis of covariance (ANCOVA) model with baseline values as a covariate with a significance level set at 5%. General linear models were used to adjust for variation between patients who received DAPA + MET and those who received DAPA + MET + other glucose-lowering drugs. Baseline values, age, and disease duration served as covariates, while sex served as the fixed factor.

3. Results

Data on 66 patients (mean age 56 years; 39% female) were included in the study after database analysis of 235 type 2 diabetic subjects as reported in the Methods. At baseline, mean HbA1c of the entire patient population was 9.2%, while mean eGFR was 95.5 mL/min. Concomitant therapies included angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers for hypertension, and statins for management of dyslipidemia. The baseline demographics and characteristics were not significantly different between patients who received DAPA + MET alone and those who were prescribed additional therapy (DAPA + MET + other glucose-lowering drugs), with the exception of waist circumference and disease duration (Table 1). After 12 months of therapy, 29 (44%) patients had initiated treatment with an additional glucose-lowering agent (glimepiride 2–4 mg/day or insulin) and 12 (18%) patients had discontinued metformin due to intolerance.

3.1. Effectiveness. When added to metformin, dapagliflozin significantly reduced HbA1c levels from baseline in patients who received DAPA + MET, as well as in those who received DAPA + MET + other glucose-lowering drugs (Figure 1). Significant reductions were observed after 6 and 12 months of treatment. Moreover, in all patients significant reductions were observed at 12 months compared with the HbA1c levels at 6 months (Figure 1(b)). After 6 months of treatment, HbA1c levels decreased by 1.4% (95% confidence interval (CI): 1.1% to 1.7%; p < 0.001) and 0.8% (95% CI: 0.5% to 1.1%; p < 0.001) in patients who received DAPA + MET and those who also received other glucose-lowering drugs, respectively. After 12 months of treatment, HbA1c levels decreased by 1.7% (95% CI: 1.5% to 2.0%; p < 0.001) and 1.3% (95% CI 1.0% to 1.6%; p < 0.001), respectively. In patients who received DAPA + MET, the change from baseline in HbA1c levels at 6 months was significantly greater than in patients who received DAPA + MET + other glucose-lowering drugs (p = 0.020); however, no significant between-group difference was observed at 12 months (p = 0.053). Over the 12-month treatment period, dapagliflozin significantly reduced BMI in patients who received DAPA + MET (ΔBMI = −0.7 kg/m², 95% CI: −1.1 to −0.3; p < 0.001) and DAPA + MET + other glucose-lowering drugs (ΔBMI = −0.9 kg/m², 95% CI: −1.3 to −0.5; p < 0.001) (Table 2), with no significant difference between patients. No significant changes in lipid parameters over the study period were observed.

3.2. Renal Function. No detrimental effects on renal function were observed during the study. There were no significant changes from baseline in creatinine levels at 6 and 12 months in all patients (Figure 2). On the other hand, after 12 months, a significant reduction in microalbumin was observed in patients who received DAPA + MET alone (Table 2). The
eGFR values in all patients remained above 60 mL/min throughout the study, in accordance with the prescribing rules of the Italian Medicines Agency (AIFA). No statistically significant variation in eGFR was observed between treatment groups.

### 4. Conclusions

This retrospective observational study investigated the effectiveness and safety of add-on therapy with dapagliflozin in patients with type 2 diabetes treated at a single facility in Italy. The results demonstrate that dapagliflozin is effective and safe. Dapagliflozin significantly reduced HbA1c levels after 12 months of treatment regardless of whether other glucose-lowering agents were received. In both patients, significant reductions were apparent from 6 months. Contrary to expectations, greater reductions were obtained in patients who received DAPA + MET, that is, those who received no additional therapy. We did not find any negative effects on renal function (assessed by blood creatinine and urine microalbumin levels) during the study. Microalbumin reduction was observed in patients who received DAPA + MET alone but we cannot exclude, due to the nature of our study, other potential factors that could explain this exclusive effect.

The results of this study are in line with those of other studies of dapagliflozin conducted in patients with type 2 diabetes inadequately controlled with metformin [8–16].

This study had a number of limitations due to its retrospective observational design. It used data from an unselected sample of patients, which may introduce selection bias. Additionally, the study was observational in nature, and thus, it is not possible to establish causality. Nevertheless, the results provide valuable insights into the potential benefits and safety of add-on therapy with dapagliflozin in patients with type 2 diabetes.
group of patients and the size of the patient population was not as large as in other studies conducted in patients with type 2 diabetes. Furthermore, no measures were taken to control for confounding factors. This, in combination with a lack of a control group, means that this study cannot adequately explain the finding that patients treated with DAPA + MET experienced greater reductions in HbA1c levels compared with those who received additional glucose-lowering drugs. The strengths of this study, on the other hand, included the length of the observational period and the fact that it was conducted in a real-life setting. These factors improve the generalizability of its findings. In conclusion, this

### Table 2: Secondary efficacy and safety parameters.

<table>
<thead>
<tr>
<th></th>
<th>DAPA + MET alone (n = 37)</th>
<th>DAPA + MET + other glucose-lowering drugs (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>33.1 ± 6.2</td>
<td>32.5 ± 6.0</td>
</tr>
<tr>
<td>Δ</td>
<td>-0.7 (-1.1 to -0.3)**</td>
<td>-0.9 (-1.3 to -0.5)*</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>189.5 ± 33.9</td>
<td>184.1 ± 40.1</td>
</tr>
<tr>
<td>Δ</td>
<td>-2.2 (-15.8 to +11.4)</td>
<td>-10.9 (-25.2 to +3.4)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>111.1 ± 32.2</td>
<td>104.9 ± 36.4</td>
</tr>
<tr>
<td>Δ</td>
<td>-4.8 (-17.0 to +7.4)</td>
<td>-9.5 (-22.4 to +3.3)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>47.7 ± 11.9</td>
<td>52.2 ± 13.0</td>
</tr>
<tr>
<td>Δ</td>
<td>+4.8 (+0.6 to +9.1)</td>
<td>+0.8 (-3.8 to +5.3)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>145.8 ± 62.9</td>
<td>135.1 ± 54.2</td>
</tr>
<tr>
<td>Δ</td>
<td>-4.5 (-24.6 to +15.6)</td>
<td>-5.8 (-27.0 to +15.5)</td>
</tr>
<tr>
<td>Microalbumin (µg/mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>119.5 ± 139.6</td>
<td>93.6 ± 103.2</td>
</tr>
<tr>
<td>Δ</td>
<td>-22.9 (-30.6 to -15.2)*</td>
<td>-18.6 (-27.1 to -10.0)</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td></td>
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</tbody>
</table>

Δ = mean (95% confidence interval) change from baseline to 12 months. BMI, body mass index; DAPA, dapagliflozin; HDL, high density lipoprotein; LDL, low density lipoprotein; MET, metformin; SD, standard deviation. *Additional glucose-lowering agents included glimepiride or insulin. *p < 0.001 and **p < 0.01.

![Figure 2: Creatinine (a) at each study visit and (b) change from baseline. DAPA, dapagliflozin; MET, metformin; other, glimepiride or insulin.](image-url)
retrospective observational study demonstrates that dapagli- 
flozin is effective in reducing HbA1c levels and safe 
when administered in a real-life setting in Italy in patients 
with type 2 diabetes also receiving metformin. Glycemic 
control was more likely to be achieved in patients treated 
with dapagliflozin alone or in combination with metformin, 
while add-on therapy with insulin and/or glimepiride was 
not associated with further improvement in HbA1c levels.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest 
regarding the publication of this paper.

**Acknowledgments**

The authors would like to thank Georgii Filatov of Springer 
Healthcare Communications for the preparation of the 
manuscript up to submission, and Valentina Mirisola of 
Mediservice (Italy) who provided statistical analysis of the 
data. Sponsorship for medical writing assistance, statistical 
support, and the article processing charges for this publica-
tion were funded by AstraZeneca (Italy).

**References**

review on diabetes care in Italy,” *Annals of Global Health*, 
vol. 81, no. 6, pp. 803–813, 2015.

of hyperglycemia in type 2 diabetes, 2015: a patient-centered 
approach: update to a position statement of the American Dia-
abetes Association and the European Association for the Study 

diabetes: principles of pathogenesis and therapy,” *The Lancet*, 

The Verona Diabetes Study,” *Diabetes Care*, vol. 22, no. 5, 

“The human kidney low affinity Na+/glucose cotransporter 
SGLT2. Delineation of the major renal reabsorptive mecha-
nism for D-glucose,” *The Journal of Clinical Investigation*, 

“Sodium-glucose cotransport inhibition with dapagliflozin in 
type 2 diabetes,” *Diabetes Care*, vol. 32, no. 4, pp. 650–657, 
2009.

“Dapagliflozin monotherapy in type 2 diabetic patients with 
inadequate glycemic control by diet and exercise: a random-
ized, double-blind, placebo-controlled, phase 3 trial,” *Diabetes 

Mansfield, and J. F. List, “Dapagliflozin add-on to metformin 
in type 2 diabetes inadequately controlled with metformin: a 
randomized, double-blind, placebo-controlled 102-week trial,” 
*BMC Medicine*, vol. 11, no. 1, p. 43, 2013.

“Effect of dapagliflozin in patients with type 2 diabetes who 
have inadequate glycemic control with metformin: a ran-
mised, double-blind, placebo-controlled trial,” *The Lancet*, 

glycaemic response and tolerability of dapagliflozin versus a 
sulphonylurea as add-on therapy to metformin in patients 
with type 2 diabetes: 4-year data,” *Diabetes, Obesity and 
Metabolism*, vol. 17, no. 6, pp. 581–590, 2015.

versus glipizide as add-on therapy in patients with type 2 dia-
betes who have inadequate glycemic control with metformin: a 
randomized, 52-week, double-blind, active-controlled nonin-
feriority trial,” *Diabetes Care*, vol. 34, no. 9, pp. 2015–2022, 
2011.

of glycaemic efficacy over 2 years with dapagliflozin versus gli-
pizide as add-on therapies in patients whose type 2 diabetes 
meellitus is inadequately controlled with metformin,” *Diabetes, 
Obesity and Metabolism*, vol. 16, no. 11, pp. 1111–1120, 2014.

J. Sugg, and S. J. Parikh, “Dapagliflozin added to usual care 
in individuals with type 2 diabetes mellitus with preexisting 
cardiovascular disease: a 24-week, multicenter, randomized, 
double-blind, placebo-controlled study with a 28-week exten-
sion,” *Journal of the American Geriatrics Society*, vol. 62, 

J. Sugg, and S. J. Parikh, “Dapagliflozin’s effects on glycemia 
and cardiovascular risk factors in high-risk patients with type 2 
diabetes: a 24-week, multicenter, randomized, double-blind, 
placebo-controlled study with a 28-week extension,” *Diabetes 

A. Norhammar, and J. W. Eriksson, “Novel oral glucose-
lowering drugs are associated with lower risk of all-cause 
mortality, cardiovascular events and severe hypoglycaemia 
compared with insulin in patients with type 2 diabetes,” *Dia-
betes, Obesity and Metabolism*, vol. 19, no. 6, pp. 831–841, 2017.

ity in patients with diabetes under treatment with dapagliflo-
zin: a population-based, open-cohort study in the health 
improvement network database,” *The Journal of Clinical 
Endocrinology & Metabolism*, vol. 102, no. 5, pp. 1719–1725, 
2017.
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