Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial

R. R. Henry, A. V. Murray, M. H. Marmolejo, D. Hennicken, A. Ptaszynska, J. F. List

SUMMARY

Background: Combining metformin (XR) with dapagliflozin to initiate pharmacotherapy in patients with type 2 diabetes (T2D) and high baseline HbA1c may be advantageous. We conducted two randomised, double-blind, three-arm 24-week trials in treatment-naïve patients to compare dapagliflozin plus metformin, dapagliflozin alone and metformin alone. Methods: Eligible patients had baseline HbA1c 7.5–12%. Each trial had three arms: dapagliflozin plus metformin, dapagliflozin monotherapy and metformin monotherapy. Dapagliflozin in combination and as monotherapy was dosed at 5 mg (Study 1) and 10 mg (Study 2). Metformin in combination and as monotherapy was titrated to 2000 mg. The primary endpoint was HbA1c change from baseline; secondary endpoints included change in fasting plasma glucose (FPG) and weight. Results: In both trials, combination therapy led to significantly greater reductions in HbA1c compared with either monotherapy: −2.05 for dapagliflozin + metformin, −1.19 for dapagliflozin, and −1.35 for metformin (p < 0.0001) (Study 1); −1.98 for dapagliflozin + metformin, −1.45 for dapagliflozin and −1.44 for metformin (p < 0.0001) (Study 2). Combination therapy was statistically superior to monotherapy in reduction of FPG (p < 0.0001 for both studies); combination therapy was more effective than metformin for weight reduction (p < 0.0001). Dapagliflozin 10 mg was non-inferior to metformin in reducing HbA1c (Study 2). Events suggestive of genitourinary infection were reported in 6.7%, 6.9% and 2.0% (Study 1) and 8.5%, 12.8% and 2.4% (Study 2) of patients in combination, dapagliflozin and metformin groups; events suggestive of urinary tract infection were reported in 7.7%, 7.9% and 7.5% (Study 1) and 7.6%, 11.0% and 4.3% (Study 2) of patients in the respective groups. No major hypoglycaemia was reported. Conclusion: In treatment-naïve patients with T2D, dapagliflozin plus metformin was generally well tolerated and effective in reducing HbA1c, FPG and weight. Dapagliflozin-induced glucosuria led to an increase in events suggestive of urinary tract and genital infections.

Introduction

Renal sodium-glucose co-transporter-2 (SGLT2) is a promising target for treating type 2 diabetes. Dapagliflozin, a stable, competitive, reversible and highly selective inhibitor of SGLT2, inhibits renal glucose reabsorption, promotes urinary glucose excretion and lowers hyperglycaemia independently of insulin secretion or action. Previously, dapagliflozin was found to be effective as add-on therapy to metformin (1). Here, we investigated dapagliflozin and metformin, combined or alone, as initial pharmacotherapy for type 2 diabetes.

Achieving optimal glycaemic control early in the course of type 2 diabetes is an important goal for patients. Early intervention may prevent disease progression and minimise long-term microvascular and macrovascular complications. Traditional step-wise pharmacotherapy begins with metformin, which increases insulin sensitivity, reduces hepatic glucose production and enhances peripheral glucose uptake. However, metformin use is limited by gastrointestinal side effects, with 5–10% of patients unable to tolerate metformin at any dose (2,3), and higher percentages who experience dose-limiting effects with rapid titration or high initial dose (4). Immediate
(IR) and extended release (XR) formulations demonstrate similar efficacy (5), although metformin XR may be better tolerated because of slower release and absorption (4–6).

Metformin alone usually fails to maintain long-term glycaemic control. Thereafter, insulin or sulphonylureas may be added to the regimen (7). Although these agents differ mechanistically, each utilises insulin-dependent pathways; consequently, effectiveness is diminished with disease progression, increased β-cell dysfunction and insulin resistance. Furthermore, the step-wise approach to pharmacotherapy is inadequate for patients with delayed diagnosis or severe hyperglycaemia, requiring intensified treatment efforts. These patients may benefit from treatment with two drugs of differing mechanisms to enhance therapeutic outcome. One potentially advantageous regimen combines metformin and dapagliflozin; the former utilises insulin-dependent pathways whereas the latter does not.

We undertook two trials of dapagliflozin and metformin XR (metformin), combined or alone, in treatment-naïve patients with type 2 diabetes.

**Methods**

**Trial design**

Both trials were 24-week, randomised, double-blind active-controlled studies conducted at a combination of clinics and hospital sites in North America, Latin America, Europe and Asia. Study 1 (NCT00643851) compared dapagliflozin 5 mg plus metformin XR (combination), dapagliflozin 5 mg plus placebo (dapagliflozin), and metformin XR plus placebo (metformin) at 105 sites. Study 2 (NCT00859898) compared dapagliflozin 10 mg plus metformin XR (combination), dapagliflozin 10 mg plus placebo (dapagliflozin), and metformin XR plus placebo (metformin) at 131 sites. The trials were conducted pursuant to the Declaration of Helsinki and Good Clinical Practice guidelines, and approved by institutional review boards/independent ethics committees. All participants provided informed consent.

**Patients**

Patients were aged 18–77 years, had haemoglobin A1c (HbA1c) 7.5–12%, body mass index £ 45 kg/m², C-peptide concentration ≥ 0.33 nmol/l and type 2 diabetes uncontrolled by diet and exercise. Exclusion criteria included serum creatinine ≥ 132.60 μmol/l (men) or ≥ 123.76 μmol/l (women) consistent with metformin labelling; urine albumin:creatinine ratio > 1800 mg/g; serum aspartate transaminase or alanine transaminase > 3 times upper limit of normal (ULN); creatine kinase > 3 times ULN; history of diabetes insipidus; symptoms of poorly controlled diabetes (including marked polyuria and polydipsia with > 10% weight loss during 3 months before enrollment); clinically significant renal, hepatic, haematological, oncological, endocrine, psychiatric or rheumatic disease; a cardiovascular event within 6 months or New York Heart Association Class III or IV congestive heart failure; and systolic blood pressure ≥ 180 or diastolic blood pressure ≥ 110 mmHg.

**Trial conduct**

Patients were enrolled by investigators at individual sites and following screening and qualification, entered a 7-day lead-in. A central Interactive Voice Response System (IVRS) assigned patients unique numbers and a single-blind placebo kit to assess compliance. During lead-in and study duration, patients received diet and exercise counselling. Patients eligible for continuation were stratified by site, in blocks of three, and randomly assigned (1:1:1) to double-blind groups of combination therapy, dapagliflozin monotherapy and metformin monotherapy by IVRS.

Drug administration occurred with the evening meal. Metformin was force-titrated in a blinded fashion in 500 mg weekly increments as tolerated, up to 2000 mg daily. Titration was re-evaluated at weeks 4, 6 and 8 in patients not yet up-titrated to 2000 mg. Up-titration was not permitted after week 8 or allowed if patients experienced recurrent episodes of non-major hypoglycaemia. Patients up-titrated at least once could be down-titrated 500 mg for recurrent non-major hypoglycaemia or gastrointestinal intolerance. Down-titration was not permitted after week 12.

Withdrawal from the study was required for any episode of major hypoglycaemia (i.e., symptomatic episode requiring third-party assistance because of severe impairment in consciousness or behaviour, with capillary or plasma glucose < 3.00 mmol/l, and prompt recovery after glucose or glucagon administration). Patients lacking glycaemic control could receive open-label rescue with pioglitazone, sitagliptin or acarbose in addition to double-blind treatment, based on fasting plasma glucose > 14.99 mmol/l (weeks 6–7), > 13.32 mmol/l (weeks 8–11) or > 11.10 mmol/l (weeks 12–20).

**Endpoints and assessments**

The primary efficacy endpoint in both trials was HbA1c change from baseline at week 24. Key secondary endpoints were change from baseline at week 24 in fasting plasma glucose, proportion of patients achieving a therapeutic glycaemic response (HbA1c < 7%), HbA1c for patients with baseline HbA1c ≥ 9%,

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total body weight, and the proportion of subjects discontinued or rescued for failing to achieve pre-specified glycaemic targets based on prespecified rescue criteria. Additional key secondary endpoints in Study 2 included non-inferiority of dapagliflozin 10 mg to metformin XR for changes in fasting plasma glucose (0.83 mmol/L margin) and HbA1c (0.35% margin); if non-inferiority was demonstrated, superiority of dapagliflozin 10 mg was tested. The difference in weight reduction with dapagliflozin 10 mg vs. metformin was also tested for statistical significance.

Safety assessments included vital signs, laboratory measurements and adverse events coded by preferred terms [Medical Dictionary for Regulatory Activities, versions 12 (Study 1) and 13 (Study 2)]. Patients were actively questioned at each visit for signs and symptoms suggestive of urinary tract infection and of vulvovaginitis, balanitis and related genital infection. These assessments were prospectively defined, assessed throughout the study by targeted review, and consisted of patient and physician reports coded by a wide net of definitive and non-specific terms.

Statistical analysis
With 190 patients per group with postbaseline measurements, there was 90% power to detect a difference in HbA1c means of 0.4% between combination vs. monotherapy groups, assuming 1.1% standard deviation. If 5% of subjects per trial had no postbaseline assessment, 600 patients (200 per group) needed to be randomised per study.

Primary efficacy data were derived from randomised patients with ≥1 dose of double-blind medication, and with baseline and ≥1 postbaseline measurements. Measurements after rescue medication were included in safety but not efficacy analyses. Primary and most secondary efficacy analyses were performed by analysis of covariance with treatment group as an effect and baseline value as a covariate. The proportion of patients achieving a therapeutic glycaemic response was analysed using logistic regression based on established methodology (8,9).

A hierarchical closed testing procedure controlled the familywise type I error rate related to primary and secondary endpoints at the two-sided 0.05 level. When testing differences between combination vs. monotherapy groups, combination therapy had to be superior to both monotherapy groups to be considered significant. Secondary endpoints were tested only if combination therapy was statistically significant to both monotherapies (primary endpoint) and if all previous sequential tests for secondary endpoints were significant. Last observation carried forward (LOCF) imputed missing data. Statistical analyses were done with SAS/STAT version 8.2 (SAS Institute Inc., Cary, NC). Summary statistics were calculated for safety parameters.

Results
Study 1 was initiated in June 2008 and completed in August 2009. Study 2 was initiated in April 2009 and completed in November 2010. Of 598 (Study 1) and 638 (Study 2) patients who took ≥1 dose of medication during the double-blind treatment period, 80 (13.4%) and 86 (13.5%) discontinued before study completion; most frequent reasons were withdrawn consent and loss to follow-up. Figure 1 shows the trial profile. Table 1 presents demographic and baseline characteristics.

The median metformin XR dose for combination and metformin monotherapy groups in both studies was 2000 mg. Mean metformin XR doses for combination and metformin groups were 1773.5 mg and 1843.6 mg (Study 1), and 1928.6 mg and 1949.7 mg (Study 2).

In both trials, mean HbA1c reductions from baseline at week 24 were significantly greater with combination than with either monotherapy (Table 2, Figure 2). The proportion of patients with HbA1c < 7% at week 24 was significantly greater with combination vs. either monotherapy; approximately half of patients on combination regimens achieved therapeutic goal (Table 2). In patients with baseline HbA1c ≥ 9.0%, week 24 reductions were significantly greater with combination than with either monotherapy (Table 2).

Significantly greater mean fasting plasma glucose reductions were observed in combination groups than in monotherapy groups (Table 2, Figure 2). Mean weight loss with combination therapy and dapagliflozin monotherapy was more than double the weight loss with metformin monotherapy in both trials (Table 2, Figure 2).

In Study 2, where dapagliflozin monotherapy was specifically compared with metformin monotherapy in prespecified analyses, dapagliflozin 10 mg demonstrated non-inferiority for HbA1c reduction, superiority for fasting plasma glucose reduction and significantly greater weight reduction compared with metformin monotherapy.

Prespecified analyses showed fewer patients on combination or dapagliflozin monotherapy were discontinued or rescued for not achieving fasting plasma glucose targets compared with patients taking metformin. In the respective combination, dapagliflozin and metformin groups, there were 1/194 (0.5%),
15/203 (7.4%) and 26/201 (12.9%) discontinuations or rescues in Study 1, and 3/211 (1.4%), 17/219 (7.8%) and 28/208 (13.5%) discontinuations or rescues in Study 2. According to the protocol, rescue for failing to meet glycaemic targets preceded discontinuation for lack of glycaemic control. Therefore, these data comprise all patients who received rescue medication, plus one metformin patient in Study 2 who discontinued because of lack of glycaemic control prior to rescue. Two dapagliflozin patients (one from each study) discontinued after rescue because of lack of glycaemic control.
**Safety**

Table 3 summarises adverse events. There was no major hypoglycaemia or hypoglycaemia resulting in discontinuation from either study. Most adverse events across all groups were of mild and moderate intensity. Few serious adverse events were reported, with similar proportions of patients reported for all groups. Deaths in these studies were rare. One death from cardiopulmonary failure was reported 19 days postdouble-blind treatment in the dapagliflozin monotherapy group (Study 1), which the investigator considered unlikely to be related to study drug. One death from myocardial infarction was reported on day 65 in the metformin XR group (Study 2), which the investigator considered to be unrelated to study drug.

There were no bladder malignancies in the studies. Breast malignancy was rare; in the dapagliflozin monotherapy group (Study 1), one breast mass found 16 days after randomisation was diagnosed to be a breast cancer.

Diarrhoea and nausea were reported in 2–10% of patients across the groups (Table 3). Diarrhoea was seen more commonly in groups receiving metformin (7.0–9.6%) than in groups receiving dapagliflozin monotherapy (2.7–3.9%). Events suggestive of urinary tract infection and of vulvovaginitis and balanitis were reported in 2–13% of patients. In Study 2, more events suggestive of urinary tract infection were reported in combination and dapagliflozin groups. In both studies, there were no events of pyelonephritis in dapagliflozin combination and monotherapy groups. In Study 1, there was one event of pyelonephritis in the metformin monotherapy group. More events suggestive of vulvovaginitis and balanitis were reported in the combination and dapagliflozin groups in both studies (Table 3).

Marked abnormalities in laboratory measurements were few and generally balanced among groups. Table 4 reports mean changes from baseline in laboratory measurements and blood pressure. At week 24, greater mean reductions were observed in seated systolic/diastolic blood pressure in combination and dapagliflozin groups than in metformin XR groups. These changes occurred without an increase over baseline in the proportion of patients with orthostatic hypotension, dehydration, hypovolaemia or syncope. There was no effect of treatment on serum sodium. Small mean increases in haematocrit observed in combination and dapagliflozin groups appeared to stabilise at weeks 12 (Study 1) and 16 (Study 2). Small changes in lipid parameters were observed in all groups (data not shown).

**Discussion**

These trials demonstrate that SGLT2 inhibition with dapagliflozin can significantly improve glycaemic control when initiating pharmacotherapy in combination with metformin for type 2 diabetes. The rationale for combining two medications as initial treatment has been advanced in Guidelines of the American Association of Clinical Endocrinologists (10) and the Canadian Diabetes Association (11). Initial combination therapy may benefit patients with delayed diagnosis, severe hyperglycaemia or intolerance to gastrointestinal effects of metformin during initial dosing. Aggressive and well-managed treatment early in the course of diabetes may delay onset and progression of complications. The United Kingdom Prospective Diabetes Study demonstrated that early intervention may produce a legacy effect of reducing microvascular risk and improving cardiovascular outcomes in later years (12).
Table 2 Primary and key secondary efficacy measurements

|                       | Study 1 | DAPA 5 mg + MET (n = 194) | DAPA 5 mg + PBO (n = 203) | MET + PBO (n = 201) | Study 2 | DAPA 10 mg + MET (n = 211) | DAPA 10 mg + PBO (n = 219) | MET + PBO (n = 208) |
|-----------------------|---------|----------------------------|---------------------------|---------------------|---------|-----------------------------|---------------------------|---------------------|
| **HbA1c at week 24 (%)** |         |                            |                           |                     |         |                            |                           |                     |
| Baseline              |         | 9.21 (1.31)                | 9.14 (1.37)               | 9.14 (1.32)         |         | 9.10 (1.28)                 | 9.03 (1.27)               | 9.03 (1.30)         |
| Week 24               |         | 7.13 (1.20)                | 7.96 (1.44)               | 7.79 (1.53)         |         | 7.10 (1.00)                 | 7.59 (1.23)               | 7.60 (1.42)         |
| Change from baseline  |         | -2.05 (–2.23, –1.88)       | -1.19 (–1.36, –1.02)      | -1.35 (–1.53, –1.18)|         | -1.98 (–2.13, –1.83)        | -1.45 (–1.59, –1.31)      | -1.44 (–1.59, –1.29)|
| DAPA + MET vs. DAPA   |         | < 0.0001†                 | < 0.0001†                 | < 0.0001†          |         | < 0.0001†                  | < 0.0001†                 | < 0.0001†          |
| p value               |         |                            |                           |                     |         |                            |                           |                     |
| DAPA + MET vs. MET    |         | -0.70 (–0.94, –0.45)       | -0.54 (–0.75, –0.33)      | -0.54 (–0.75, –0.33)|         |                            |                           |                     |
| p value               |         | < 0.0001†                 | < 0.0001†                 | < 0.0001†          |         | < 0.0001†                  | < 0.0001†                 | < 0.0001†          |
| HbA1c at week 24 in patients with baseline HbA1c ≥ 9.0 (%) |         |                            |                           |                     |         |                            |                           |                     |
| Baseline              |         | 10.29 (0.90)               | 10.33 (0.91)              | 10.18 (0.94)        |         | 10.10 (0.84)               | 10.21 (0.86)              | 10.20 (0.84)        |
| Week 24               |         | 7.28 (1.11)                | 8.65 (1.55)               | 8.38 (1.72)         |         | 7.55 (1.00)                | 8.05 (1.35)               | 8.13 (1.66)         |
| Change from baseline  |         | -3.01 (–3.28, –2.74)       | -1.67 (–1.94, –1.40)      | -1.82 (–2.08, –1.56)|         | -2.59 (–2.83, –2.34)        | -2.14 (–2.39, –1.88)      | -2.05 (–2.31, –1.79)|
| DAPA + MET vs. DAPA   |         | < 0.0001†                 | < 0.0001†                 | < 0.0001†          |         | < 0.0001†                  | < 0.0001†                 | < 0.0001†          |
| p value               |         |                            |                           |                     |         |                            |                           |                     |
| DAPA + MET vs. MET    |         | -1.19 (–1.57, –0.82)       | -0.53 (–0.89, –0.18)      | -0.53 (–0.89, –0.18)|         |                            |                           |                     |
| p value               |         | < 0.0001†                 | < 0.0001†                 | < 0.0001†          |         | < 0.0001†                  | < 0.0001†                 | < 0.0001†          |

Notes:
- NT: not tested.
- † Non-inferiority test.
- ‡ Superiority test.
- § Patients with HbA1c < 7.0% at week 24.
|                      | Study 1                      |                      | Study 2                      |                      |
|----------------------|-----------------------------|----------------------|-----------------------------|----------------------|
|                      | DAPA 5 mg + MET             | DAPA 5 mg + PBO     | MET + PBO                   | DAPA 10 mg + MET    |
|                      | \(n = 194\)                 | \(n = 203\)         | \(n = 201\)                 | \(n = 211\)         |
| Total body weight at | \(84.24\) (19.51)           | \(86.20\) (21.13)   | \(85.75\) (19.93)           | \(88.56\) (19.72)   |
| week 24 (kg)         | \(86.12\) (18.88)           | \(83.57\) (20.85)   | \(84.45\) (19.67)           | \(85.21\) (18.86)   |
| Baseline             | \(-2.66\) (−3.14, −2.19)   | \(-2.61\) (−3.07, −2.15) | \(-1.29\) (−1.76, −0.82)   | \(-3.33\) (−3.80, −2.86) |
| Change from baseline | \(-0.05\) (−0.72, 0.61)    | NT                  | NT                          | NT                  |
|                      | 0.8769                       |                      |                             |                     |
| DAPA + MET vs. DAPA  | \(-1.37\) (−2.04, −0.71)   | \(-1.97\) (−2.64, −1.30) | \(< 0.0001\)†             | \(< 0.0001\)†      |
| p value              | \(< 0.0001\)                |                      |                             |                     |
| DAPA vs. MET         | NT                          |                      |                             | −1.37 (−2.03, −0.71) |
| p value              | NT                          |                      |                             | \(< 0.0001\)†      |

DAPA, dapagliflozin; HbA1c, haemoglobin A1C; MET, metformin XR; NT, not tested by study design; PBO, placebo. Data are mean (standard deviation) or mean (95% confidence interval), excluding data after rescue. Non-inferiority and superiority data for DAPA 10 mg vs. MET are not listed in order of statistical sequential testing (see Methods). Changes reported for week 24 are adjusted for baseline values and based on LOCF. *\(n\) = randomised patients who took ≥ 1 dose of double-blind medication and who had both baseline and week 24 (LOCF) values. †Significance tested at \(\alpha = 0.05\) for DAPA + MET superiority over both active controls. ‡Significant after sequential testing procedure at \(\alpha = 0.05\). §Number of responders/number of randomised patients with baseline and week 24 (LOCF) values. *Proportion of patients reported for week 24 (LOCF) are adjusted for baseline values.
Patients who received dapagliflozin plus metformin demonstrated mean HbA1c and fasting plasma glucose reductions significantly greater than those in patients who received either monotherapy. Mean week 24 reductions with combination therapy were approximately 2% in HbA1c and 3.33 mmol/l in fasting plasma glucose. We note that, although metformin IR or metformin XR share similar efficacy (5), only metformin XR was studied here.

Dapagliflozin monotherapy was also effective. Although metformin is the standard for initiating treatment for type 2 diabetes, dapagliflozin 10 mg was as effective in reducing HbA1c and more effective in reducing fasting plasma glucose and weight than metformin.

Other trials have demonstrated glycaemic improvement when combining metformin with various agents of differing mechanisms as initial therapy (13–21). However, sulphonylureas (21) and thiazolidinediones (17) are likely to increase weight, and sulphonylureas, but not thiazolidinediones, are likely to increase the incidence of hypoglycaemia. Co-administration of dipeptidyl peptidase-4 inhibitors and metformin has produced weight stabilisation.
or loss similar to that obtained with metformin alone, with low risk of hypoglycaemia (13,15,16,20).

Dapagliflozin works through a unique mechanism and therefore offers a different therapeutic profile. In these two trials, the incidence of hypoglycaemia was low across treatment groups. Neither dapagliflozin nor metformin is prone to cause hypoglycaemia. This favourable profile was maintained when both drugs were combined. In addition, combination therapy and dapagliflozin monotherapy resulted in greater weight loss compared with metformin monotherapy. Dapagliflozin acts through SGLT2 inhibition to promote urinary glucose excretion; consequently, excess glucose is directly removed from the body rather than stored or metabolised in other tissues. By contrast, metformin increases insulin sensitivity of tissues and, thus, further complements the therapeutic effects of dapagliflozin. Together, both drugs more effectively lower blood glucose, without an increased risk of hypoglycaemia and weight gain, than either drug alone.

Safety and tolerability of dapagliflozin in combination or as monotherapy were confirmed. As previously reported, glucosuria attributable to SGLT2 inhibition may be associated with urinary tract infection (22) or genital infection (1,22). The present studies provided evidence of increased incidence of these infections with dapagliflozin treatment, which is consistent with the emerging safety profile seen in other SGLT2 clinical trials. Events suggestive of urinary tract infection were more common for patients receiving dapagliflozin 10 mg combination or monotherapy than

| Table 3 Adverse events |
|------------------------|
| **Study 1** | **Study 2** |
| | DAPA 5 mg + MET | DAPA 5 mg + PBO | MET + PBO | DAPA 10 mg + MET | DAPA 10 mg + PBO | MET + PBO |
| | (n = 194) | (n = 203) | (n = 201) | (n = 211) | (n = 219) | (n = 208) |
| One or more adverse event | 133 (68.6) | 107 (52.7) | 119 (59.2) | 126 (59.7) | 132 (60.3) | 118 (56.7) |
| One or more related adverse event | 37 (19.1) | 29 (14.3) | 30 (14.9) | 34 (16.1) | 47 (21.5) | 32 (15.4) |
| Adverse event leading to discontinuation | 2 (1.0) | 5 (2.5) | 6 (3.0) | 4 (1.9) | 9 (4.1) | 8 (3.8) |
| One or more serious adverse event | 6 (3.1) | 9 (4.4) | 7 (3.5) | 3 (1.4) | 5 (2.3) | 4 (1.9) |
| Deaths | 0 | 1 (0.5) | 0 | 0 | 0 | 1 (0.5) |

| Adverse events with frequency ≥ 5% in any group (by preferred term) | DAPA 5 mg + MET | DAPA 5 mg + PBO | MET + PBO | DAPA 10 mg + MET | DAPA 10 mg + PBO | MET + PBO |
|------------------------|------------------|-----------------|---------|------------------|-----------------|---------|
| Diarrhoea | 15 (7.7) | 8 (3.9) | 14 (7.0) | 15 (7.1) | 6 (2.7) | 20 (9.6) |
| Nausea | 11 (5.7) | 4 (2.0) | 8 (4.0) | 10 (4.7) | 8 (3.7) | 5 (2.4) |
| Upper respiratory tract infection | 10 (5.2) | 10 (4.9) | 11 (5.5) | 7 (3.3) | 6 (2.7) | 7 (3.4) |
| Urinary tract infection | 10 (5.2) | 9 (4.4) | 10 (5.0) | 6 (2.8) | 17 (7.8) | 4 (1.9) |
| Dyslipidaemia | 9 (4.6) | 11 (5.4) | 8 (4.0) | 8 (3.8) | 3 (1.4) | 3 (1.4) |
| Vulvovaginal mycotic infection | 2 (1.0) | 3 (1.5) | 0 | 7 (3.3) | 11 (5.0) | 1 (0.5) |

| Special interest categories | DAPA 5 mg + MET | DAPA 5 mg + PBO | MET + PBO | DAPA 10 mg + MET | DAPA 10 mg + PBO | MET + PBO |
|------------------------|------------------|-----------------|---------|------------------|-----------------|---------|
| Hypoglycaemia* | 5 (2.6) | 0 | 0 | 7 (3.3) | 2 (0.9) | 6 (2.9) |
| Events suggestive of urinary tract infection‡ | 15 (7.7) | 16 (7.9) | 15 (7.5) | 16 (7.6) | 24 (11.0) | 9 (4.3) |
| Males | 2 (2.6) | 4 (4.3) | 3 (3.2) | 6 (5.7) | 6 (5.7) | 3 (3.1) |
| Females | 13 (11.2) | 12 (10.8) | 12 (11.3) | 10 (9.5) | 18 (15.8) | 6 (5.4) |
| Events suggestive of vulvovaginitis, balanitis and related genital infection§ | 13 (6.7) | 14 (6.9) | 4 (2.0) | 18 (8.5) | 28 (12.8) | 5 (2.4) |
| Males | 4 (5.1) | 1 (1.1) | 0 | 6 (5.7) | 7 (6.7) | 2 (2.1) |
| Females | 9 (7.8) | 13 (11.7) | 4 (3.8) | 12 (11.4) | 21 (18.4) | 3 (2.7) |
| Hypotension or syncope§ | 1 (0.5) | 4 (2.0) | 0 | 0 | 2 (0.9) | 0 |

DAPA, dapagliflozin; MET, metformin XR; PBO, placebo. Data are number (%) of patients, and include data after rescue. *None led to discontinuation from study, and none was major (defined as a symptomatic episode requiring third party assistance because of severe impairment in consciousness or behaviour, with a capillary or plasma glucose value < 3.0 mmol/l, and prompt recovery after glucose or glucagon administration). †Reports of urinary tract infection were based on a predefined list of signs, symptoms and other events suggestive of ‘urinary tract infection’. All such events were of mild or moderate intensity, except for one (metformin group) of severe intensity in Study 1. ‡Reports of genital infection were based on a predefined list of signs, symptoms and other events suggestive of ‘genital infection’. All such events were of mild or moderate intensity except for one (rash in dapagliflozin group) of severe intensity in Study 1. §There was no increase in measured orthostatic hypotension, and no discontinuations because of potentially hypotension-related adverse events.
for patients receiving metformin. Events suggestive of vulvovaginitis and balanitis were more common for patients receiving dapagliflozin 5 or 10 mg combination or monotherapy than for patients receiving metformin. Most of these events were of mild or moderate intensity, easily diagnosed, resolved with self-treatment or conventional interventions, and rarely resulted in discontinuation from the trials. Pyelonephritis was not associated with dapagliflozin treatment. Diarrhoea was more common with combination or metformin than with dapagliflozin monotherapy.

Compared with metformin, greater mean reductions in blood pressure were observed with combination and dapagliflozin treatment, with no increase in measured orthostatic hypotension. These results are consistent with previous dapagliflozin trials (1,22). Blood pressure improvements with dapagliflozin may be caused by natriuresis and osmotic diuresis inherent in its mechanism, as well as to weight loss. Although modest, reduction in blood pressure may potentially improve long-term macrovascular and microvascular outcomes.

Results of these trials suggest that combination or monotherapy may benefit specific patients. More urinary tract and genital infections were seen with dapagliflozin, whereas diarrhoea was more common with metformin. Each monotherapy was effective in lowering hyperglycaemia, but dapagliflozin was better in lowering fasting plasma glucose and body weight. Thus, for patients with moderate hyperglycaemia (HbA1c 7.5% to < 9.0%) and a predisposition to gastrointestinal side effects, dapagliflozin 10 mg monotherapy may be the better treatment choice. For patients predisposed to urogenital infection, metformin may be an appropriate choice. For patients with severe hyperglycaemia (HbA1c ≥ 9%), both drugs combined may be preferable whenever the side effects are tolerated.

Table 4 Changes from baseline in laboratory measurements and seated blood pressure

|                     | Study 1                      | Study 2                      |
|---------------------|------------------------------|------------------------------|
|                     | DAPA 5 mg + MET              | DAPA 5 mg + PBO              |
| Sodium (mmol/l)*    | 169 (138.6 (3.01)            | 167 (138.7 (3.09)            |
| Baseline            | 138.6 (3.01)                 | 138.7 (3.09)                 |
| Change at week 24   | 1.2 (0.24)                   | 0.7 (0.20)                   |
| Potassium (mmol/l)* | 169 (4.37 (0.47)             | 167 (4.38 (0.47)             |
| Baseline            | 4.37 (0.47)                  | 4.38 (0.47)                  |
| Change at week 24   | -0.05 (0.03)                 | 0.01 (0.03)                  |
| Serum creatinine (μmol/l)* | 169 (72.3 (15.4)    | 167 (72.7 (14.3)            |
| Baseline            | 72.3 (15.4)                  | 72.7 (14.3)                  |
| Change at week 24   | -1.59 (0.62)                 | -1.50 (0.71)                 |
| Serum uric acid (μmol/l)† | 193 (293.9 (91.0)  | 200 (301.6 (85.1)            |
| Baseline            | 293.9 (91.0)                 | 301.6 (85.1)                 |
| Change at week 24   | -23.2 (3.6)                  | -24.4 (3.6)                  |
| Haematocrit (%)*    | 164 (42.83 (3.68)            | 166 (42.93 (3.65)            |
| Baseline            | 42.83 (3.68)                 | 42.93 (3.65)                 |
| Change at week 24   | 1.30 (0.18)                  | -0.43 (0.20)                 |
| Seated blood pressure (mm Hg)*,‡ | 171 (126.2 (13.9) | 168 (127.9 (14.1)    |
| Systolic blood pressure baseline | 167 (127.9 (14.1)    | 168 (127.6 (15.6)            |
| Mean change at week 24 | -2.9 (0.9)                  | -1.8 (0.9)                   |
| Diastolic blood pressure baseline | 178 (80.0 (8.6)   | 182 (80.2 (8.3)             |
| Mean change at week 24 | -2.2 (0.5)                  | -0.4 (0.6)                   |

DAPA, dapagliflozin; MET, metformin XR; PBO, placebo. n = number of treated patients with both baseline and week 24 values. *Data are mean baseline [standard deviation (SD)] and mean change at week 24 (standard error), including data after rescue. †Data are mean baseline (SD) and adjusted mean change at week 24 (LOCF) based on analysis of covariance model with treatment group as an effect and baseline value as a covariate, excluding data after rescue. ‡Investigators were permitted to treat blood pressure by usual standard of care.
effect risk is minimal compared with the benefits of greater reductions in HbA1c, fasting plasma glucose and body weight, and modest improvements in blood pressure.

Conclusions

Dapagliflozin or metformin XR improves glycaemic control, and both are generally well tolerated as initial pharmacotherapy for type 2 diabetes. Dapagliflozin-treated patients experienced a greater incidence of events suggestive of urinary tract and genital infections vs. metformin-treated patients; most of these events were clinically manageable. Dapagliflozin 10 mg monotherapy was non-inferior to metformin in lowering HbA1c and superior to metformin in lowering fasting plasma glucose and body weight. Dapagliflozin combined with metformin provided even greater benefits in reducing hyperglycaemia and body weight in treatment-naive patients with inadequate glycaemic control.

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Author contributions

Robert R. Henry was involved in data analysis/interpretation, drafting the article, critical revision, and approval.

Alexander V. Murray and Marisol Herrera Marmolejo were involved in clinical trial site (data collection), data analysis/interpretation, drafting the article, critical revision, and approval.

Delphine Hennicken: Statistics, data analysis/interpretation, critical revision, and approval.

Agata Ptaszynska and James F. List were involved in design/concept, data analysis/interpretation, drafting the article, critical revision, and approval.

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