# The Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitor Empagliflozin Lowers Blood Pressure Independent of Weight or $HbA_{1c}$ Changes

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## INTRODUCTION

- Hypertension is a common comorbidity in patients with diabetes and contributes to morbidity and mortality[1]
- Empagliflozin is a potent and selective inhibitor of sodium glucose cotransporter-2 (SGLT-2)[2] in development as a treatment for type 2 diabetes mellitus (T2DM)
- Empagliflozin has been shown to increase urinary glucose excretion (UGE) and reduce plasma glucose levels in patients with T2DM[3,4]
- Treatment with empagliflozin resulted in clinically meaningful reductions in $HbA_{1c}$ and body weight and demonstrated good overall safety and tolerability in patients with T2DM in Phase IIb trials[5,6]

## OBJECTIVE

- To evaluate the effects of empagliflozin on blood pressure (BP) and the correlations between changes in weight or $HbA_{1c}$ and changes in BP using pooled data from two Phase IIb trials

## METHODS

### Design

- A pooled analysis of systolic BP (SBP), diastolic BP (DBP), pulse rate data (all measured as part of safety assessment), $HbA_{1c}$ and body weight data (efficacy endpoints) from patients with T2DM treated with empagliflozin 10 mg, empagliflozin 25 mg or placebo for 12 weeks

### Outcomes

- Change in SBP and DBP from baseline to week 12 in all patients with T2DM treated with empagliflozin 10 mg, empagliflozin 25 mg or placebo
- Change in SBP from baseline to week 12 in patients with T2DM and with hypertension at baseline (SBP >140 mmHg) treated with empagliflozin 10 mg, empagliflozin 25 mg or placebo
- Change in pulse rate from baseline to week 12
- Correlation coefficients between change in SBP from baseline and change in $HbA_{1c}$ or change in body weight from baseline
- Number of patients from each treatment group achieving the composite endpoint of a reduction in $HbA_{1c}$ of ≥0.5%, a reduction in SBP of ≥3 mmHg, and a reduction in body weight of ≥2% from baseline at week 12

### Statistical analyses

- Changes in BP from baseline to week 12 (last observation carried forward [LOCF]) were analysed using an ANCOVA model with study, treatment, and baseline BP as fixed effects and country as a random effect (changes in BP medication were not accounted for). Changes in BP from baseline to week 12 in patients with hypertension at baseline were analysed as a sub-group
- Change in pulse rate from baseline to week 12 was analysed using an ANCOVA model with study, treatment, and baseline pulse rate as fixed effects and country as a random effect
- Pearson correlation coefficients were calculated between change in SBP and change in $HbA_{1c}$, and between change in SBP and change in body weight

### Population

- Data pooled from two Phase IIb, multicentre, randomised, parallel group, placebo-controlled, double-blind dose-finding studies in which patients with T2DM were treated with placebo or empagliflozin 10 mg or 25 mg (*i.e.* doses investigated in Phase III trials):
  - Monotherapy study (NCT00789035): 408 patients (treatment-naïve or treated with a single oral antidiabetic agent other than a thiazolidinedione) treated with empagliflozin (5, 10, or 25 mg qd), placebo, or open-label metformin IR (1000 mg bid or maximum tolerated dose)
  - Add-on to metformin study (NCT00749190): 495 patients treated with metformin alone or metformin plus one other antidiabetic agent (except a thiazolidinedione, GLP-1 analogue, or insulin), randomised to receive empagliflozin (1, 5, 10, 25, or 50 mg qd), placebo, or open-label sitagliptin (100 mg qd) in addition to continuing metformin therapy (≥1500 mg/day or maximum tolerated dose)

## RESULTS

### Patient disposition

- Patients from both trials who were randomised to empagliflozin 10 mg (n=152), empagliflozin 25 mg (n=152), or placebo (n=153), who received ≥1 dose of study medication and who had a baseline $HbA_{1c}$ measurement were included in the pooled analysis
- Baseline characteristics were balanced across groups **(Table 1)**

**Table 1:** *Baseline characteristics*

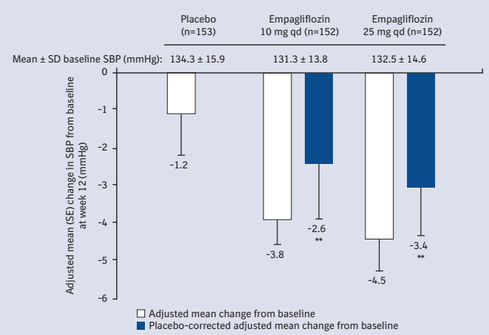
| | Treatment | | |
|---|---|---|---|
| | Placebo | Empagliflozin 10 mg | Empagliflozin 25 mg |
| Patients, n | 153 | 152 | 152 |
| Male, n (%) | 78 (51.0) | 73 (48.0) | 78 (51.3) |
| Age, years, median (min to max) | 59.0 (28–80) | 59.5 (30–78) | 58.0 (30–79) |
| Weight, kg, median (min to max) | 84.2 (49–152) | 82.9 (46–127) | 85.5 (49–132) |
| BMI, kg/m², mean (SD) | 30.3 (4.8) | 29.9 (4.4) | 30.1 (5.0) |
| $HbA_{1c}$, %, mean (SD) | 7.9 (0.8) | 8.0 (0.8) | 7.9 (0.8) |
| SBP, mmHg, mean (SD) | 134.3 (15.9) | 131.3 (13.8) | 132.5 (14.6) |
| DBP, mmHg, mean (SD) | 80.8 (8.4) | 79.1 (9.1) | 80.9 (9.2) |
| Pulse rate, bpm, mean (SD) | 72.3 (9.4) | 72.9 (10.0) | 72.6 (9.6) |
| Antihypertensive medications, n (%) | | | |
| 0 | 43 (28.1) | 49 (32.2) | 55 (36.2) |
| 1 | 58 (37.9) | 51 (33.6) | 50 (32.9) |
| 2 | 34 (22.2) | 41 (27.0) | 31 (20.4) |
| >2 | 18 (11.8) | 11 (7.2) | 16 (10.5) |

### BP changes

- Empagliflozin treatment at both doses significantly reduced SBP from baseline to week 12 compared with placebo **(Figure 1A)**
- Reductions in SBP from baseline to week 12 after treatment with empagliflozin 10 mg and 25 mg in patients with hypertension at baseline (baseline SBP >140 mmHg) appeared to be greater than in the overall population. However, due to the limited number of patients in this subpopulation (n=33 with placebo, 27 with empagliflozin 10 mg, and 38 with empagliflozin 25 mg), differences versus placebo did not reach statistical significance **(Figure 1B)**

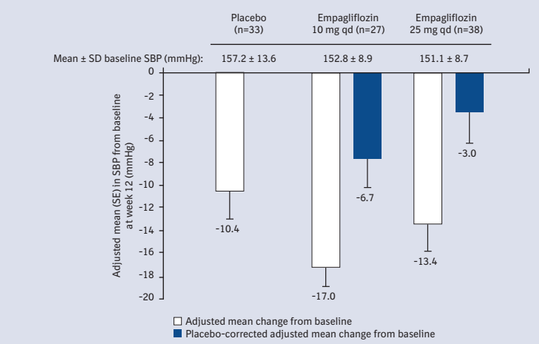
**Figure 1:** *Adjusted mean (+SE) changes in SBP from baseline to week 12 in all patients (A) and in patients with hypertension at baseline (baseline SBP >140 mmHg) (B)*

**A: All patients**




**p<0.05 difference vs. placebo (LOCF, ANCOVA with baseline BP, study and treatment as fixed effects and country as a random effect)

**B: Patients with hypertension at baseline (baseline SBP >140 mmHg)**



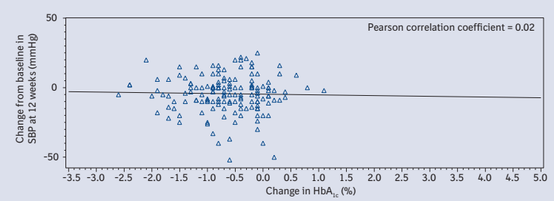

- Reductions in DBP from baseline to week 12 were not significantly different from placebo in either empagliflozin group (data not shown)
- Including the number of antihypertensive medications at baseline in the ANCOVA model did not alter the effect of empagliflozin on BP versus placebo (data not shown)
- Adjusted mean (SE) changes in pulse rate from baseline to week 12 with empagliflozin 10 mg (-0.35 [0.68] bpm) and empagliflozin 25 mg (-0.31 [0.68] bpm) were not significantly different from the change from baseline with placebo (-0.25 [0.68] bpm)

### Pearson correlation analysis

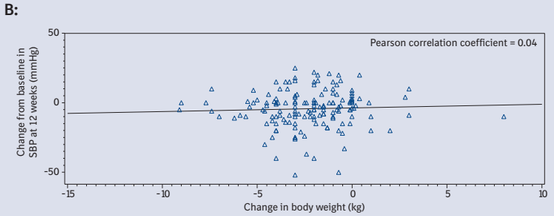
- Change in SBP from baseline to week 12 did not correlate with either change in $HbA_{1c}$ or change in body weight in any group (p>0.14) **(Figure 2A** and **2B** for empagliflozin 25 mg)

**Figure 2:** *Correlation between change in SBP and change in $HbA_{1c}$ (A) or body weight (B) from baseline to week 12 with empagliflozin 25 mg*

**A:**




**B:**




### Composite endpoint

The composite endpoint of a reduction in $HbA_{1c}$ of ≥0.5%, a reduction in SBP of ≥3 mmHg, and a reduction in body weight of ≥2% at week 12 occurred in 9 patients (5.9%) in the placebo compared with 32 (21.1%) in each empagliflozin group (p<0.001 vs. placebo for both groups)

### Safety and tolerability

- The proportion of patients experiencing any AE was comparable between treatment groups: 34.2% of patients on empagliflozin 10 mg, 31.6% on empagliflozin 25 mg, and 34.6% of patients on placebo
- All AEs were mild or moderate in intensity except for one severe adverse event (nausea) in the 10 mg empagliflozin group
- No cases of hypoglycaemia were reported in empagliflozin groups. One case was reported on placebo
- Urinary tract infections (special search of MedDRA preferred terms consistent with urinary tract infections, including cystitis, excluding signs and symptoms) were reported in 4 patients (2.6%) on empagliflozin 10 mg, 5 patients (3.3%) on empagliflozin 25 mg, and 3 patients (2.0%) on placebo
- Genital infection (special search of MedDRA preferred terms consistent with genital infections, including signs and symptoms) occurred in 10 patients (6.6%) on empagliflozin 10 mg, 2 patients (1.3%) on empagliflozin 25 mg and no patients on placebo

## CONCLUSIONS

- Empagliflozin treatment (10 mg or 25 mg qd) for 12 weeks resulted in statistically significant reductions in placebo-corrected adjusted mean change in SBP from baseline without increases in pulse rate
- Change in SBP from baseline to week 12 was not correlated with change in body weight or change in $HbA_{1c}$, suggesting that the antihypertensive effects of empagliflozin are independent of its ability to reduce plasma glucose and body weight. Osmotic diuresis associated with inhibition of renal glucose reabsorption may contribute to the antihypertensive effects of empagliflozin, although no significant increase in urine volume compared with placebo has been observed in Phase I studies[7,8]
- The number of patients who reached the composite endpoint of a reduction in $HbA_{1c}$ of ≥0.5%, a reduction in SBP of ≥3 mmHg, and a reduction in body weight of ≥2% at week 12 was significantly higher in empagliflozin groups compared with placebo
- Overall, empagliflozin demonstrated a good safety and tolerability profile

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