Efficacy and safety of empagliflozin in patients with type 2 diabetes from Asian countries: pooled data from four Phase III trials

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Abstract

We investigated the efficacy and safety of empagliflozin over 24 weeks in Asian patients with type 2 diabetes (T2DM) using pooled data from four Phase III trials. In these trials, patients were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo as monotherapy or add-on to metformin, metformin plus sulphonylurea, or pioglitazone ± metformin. In total, 1326 patients from Asia received ≥1 dose of study drug. At week 24, adjusted mean (95% CI) differences versus placebo in change from baseline in HbA1c were −0.66 (−0.76, −0.56) % and −0.73 (−0.83, −0.64) % and in weight were −1.6 (−1.9, −1.3) kg and −1.8 (−2.1, −1.5) kg with empagliflozin 10 mg and 25 mg, respectively (all $p<0.001$). Empagliflozin significantly reduced systolic and diastolic blood pressure. The proportion of patients reporting ≥1 adverse event was similar across treatment groups, but events consistent with genital infection were more common in patients treated with empagliflozin 10 mg (3.4%) or 25 mg (2.3%) than placebo (0.9%). Thus in Asian patients with T2DM, empagliflozin reduced HbA1c, weight and blood pressure, and was well tolerated.

Keywords: SGLT2 inhibitor, blood glucose, blood pressure, body weight, clinical trial, Asia

Introduction

Projections for the prevalence of diabetes suggest that increased urbanisation may drive the number of people with diabetes in the Asia-Pacific region to over 320 million by 2035 [1]. The majority of Asian patients with type 2 diabetes (T2DM) do not achieve HbA1c targets despite receiving pharmacotherapy [2,3].

By inhibiting renal glucose reabsorption, the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin increases urinary glucose excretion and so improves glycaemic control. Data from international Phase III trials showed that in patients with T2DM, empagliflozin 10 mg and 25 mg as monotherapy or add-on therapy reduced HbA1c, weight and blood pressure (BP) versus placebo [4–11]. Empagliflozin was well tolerated, with a low risk of hypoglycaemia, but an increased risk of genital infections and an increased risk of urinary tract infections in female patients.

The objective of this *post-hoc* analysis was to assess the efficacy and safety of empagliflozin over 24 weeks in Asian patients with T2DM using pooled data from four randomized, placebo-controlled, Phase III trials [4–7].

Methods

Study Design and Patients

Data were pooled from patients with T2DM from Asian countries who were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily for 24 weeks in one of four Phase III trials as monotherapy [4], or add-on to metformin [5], metformin plus sulphonylurea [6] or pioglitazone (with or without metformin) [7]. The designs and overall results of these trials have been described [4–11].

Endpoints

In this *post-hoc* analysis, efficacy endpoints included changes from baseline at week 24 in HbA1c, fasting plasma glucose (FPG), weight, systolic BP (SBP) and diastolic BP (DBP). Adverse events (AEs) were coded according to preferred terms in the Medical Dictionary for Drug Regulatory Activities [MedDRA] version 15.0. Confirmed hypoglycaemic AEs were defined as events with plasma glucose ≤3.9 mmol/L and/or requiring assistance. AEs of special interest included events consistent with urinary tract infection, genital infection, or volume depletion, which were identified from AEs reported by investigators using searches of 70, 89, and 8 MedDRA preferred terms, respectively.

Statistical Analyses

Changes from baseline in HbA1c, FPG, weight, SBP and DBP at week 24 versus placebo were analysed using an analysis of covariance (ANCOVA) model in the full analysis set (FAS), with the respective baseline value and baseline HbA1c as linear covariates, and baseline eGFR (MDRD), study and treatment as fixed effects. The FAS comprised randomized patients who received ≥1 dose of study drug and had a baseline HbA1c value. Values observed after a patient started anti-diabetes rescue therapy were set to missing and a last observation carried forward (LOCF) approach used to impute missing data. Safety analyses were undertaken in the treated set (randomized patients who received ≥1 dose of study drug) and were descriptive, except for changes in lipids.

Results

Patients

A total of 1326 (53.5%) patients treated in the trials were from countries in Asia (China, India, Japan, Korea, Philippines, Taiwan, Thailand), mainly China (n=580) and India (n=332) (Table S1). The FAS comprised 447, 443 and 436 patients receiving placebo, empagliflozin 10 mg and

empagliflozin 25 mg. The treated set comprised 446, 443 and 437 patients in these groups, respectively.

Baseline characteristics were balanced across groups, except for higher proportions of males in the empagliflozin 10 mg (59.1%) and 25 mg (58.3%) groups compared with the placebo group (48.1%) (Table S2). Discontinuation rates were 11.4%, 6.5 and 8.7% in the placebo, empagliflozin 10 mg and empagliflozin 25 groups, respectively.

Glycaemic Parameters

In the pooled data, adjusted mean changes (standard error [SE]) from baseline in HbA1c at week 24 were −0.10% (0.04), −0.76% (0.04) and −0.84% (0.04) in the placebo, empagliflozin 10 mg and empagliflozin 25 mg groups, respectively. Adjusted mean differences versus placebo in changes from baseline were −0.66% with empagliflozin 10 mg (95% CI −0.76, −0.56%; p<0.001) and −0.73% with empagliflozin 25 mg (95% CI −0.83, −0.64%; p<0.001) (Figure 1A).

Adjusted mean changes (SE) from baseline in FPG at week 24 were 0.4 mmol/L (0.1), −1.1 mmol/L (0.1) and −1.3 mmol/L (0.1) in the placebo, empagliflozin 10 mg and empagliflozin 25 mg groups, respectively. Adjusted mean differences versus placebo in changes from baseline were −1.5 mmol/L with empagliflozin 10 mg (95% CI −1.7, −1.3 mmol/L; p<0.001) and −1.7 mmol/L with empagliflozin 25 mg (95% CI −1.9, −1.5 mmol/L; p<0.001) (Figure 1B).

Weight

In the pooled data, adjusted mean changes (SE) from baseline in weight at week 24 were −0.1 kg (0.1), −1.7 kg (0.1) and −1.9 kg (0.1) in the placebo, empagliflozin 10 mg and empagliflozin 25 mg groups, respectively. Adjusted mean differences versus placebo in changes from baseline were −1.6 kg with empagliflozin 10 mg (95% CI −1.9, −1.3 kg; p<0.001) and −1.8 kg with empagliflozin 25 mg (95% CI −2.1, −1.5 kg; p<0.001) (Figure 2A).

Blood Pressure

In the pooled data, adjusted mean changes (SE) from baseline in SBP at week 24 were −0.2 mmHg (0.5), −3.7 mmHg (0.5) and −4.1 mmHg (0.5) in the placebo, empagliflozin 10 mg and empagliflozin 25 mg groups, respectively. Adjusted mean differences versus placebo in changes from baseline were −3.5 mmHg with empagliflozin 10 mg (95% CI −4.9, −2.0 mmHg; p<0.001) and −3.9 mmHg with empagliflozin 25 mg (95% CI −5.3, −2.4; p<0.001) (Figure 2B). Data on DBP are shown in Figure S1 .

Mean ± standard deviation changes from baseline in pulse rate at week 24 were 0.2 ± 8.4 bpm with placebo, -0.9 ± 8.3 bpm with empagliflozin 10 mg, and -0.8 ± 9.0 bpm with empagliflozin 25 mg.

Safety and Tolerability

The proportion of patients reporting ≥1 AE was similar across treatment groups (Table S3). Serious AEs were reported in 3.1%, 4.1% and 1.1% of patients in the placebo, empagliflozin 10 mg and empagliflozin 25 mg groups, respectively. AEs leading to discontinuation occurred in 2.2%, 1.6% and 3.2% of patients in these groups, respectively.

Confirmed hypoglycaemic AEs were reported in 3.6%, 6.1% and 3.4% of patients in the placebo, empagliflozin 10 mg and 25 mg groups, respectively; none required assistance. Events consistent with urinary tract infection were reported in 7.0%, 7.7% and 7.8% of patients in these groups, respectively. Most events consistent with urinary tract infection were mild in intensity (Figure S2A) and occurred in females. Events consistent with genital infection were reported in 0.9%, 3.4% and 2.3% of patients in the placebo, empagliflozin 10 mg and empagliflozin 25 mg groups, respectively; most events were mild (Figure S2B) and occurred in females. Events consistent with volume depletion were reported in 0.2% of patients per treatment group. Data on

adverse events of decreased renal function and hepatic injury are reported in Table S3. Laboratory measurements are reported in Table S4.

Discussion

In this *post-hoc* analysis of trial data from Asian patients with T2DM, empagliflozin given as monotherapy or add-on therapy for 24 weeks led to significant and clinically meaningful improvements in glycaemic control. The results were consistent with those of the overall study populations [4–7].

Empagliflozin was also associated with weight loss, likely due to loss of calories in urine and mild osmotic diuresis [12]. A previous analysis of data from these four trials showed that 24 weeks' treatment with empagliflozin reduced visceral adiposity, regardless of age, sex, or degree of abdominal obesity [13]. This effect may be particularly important in Asian patients who, at a given BMI, have more visceral adiposity than Caucasians [14]. Further, empagliflozin was associated with a significant reduction in blood pressure, which might reflect improvements in glucose control, weight loss, and mild osmotic diuresis [15].

Empagliflozin was well tolerated, with a low risk of hypoglycaemia. In this analysis, the proportion of patients with events consistent with urinary tract infection was similar across treatment groups, but empagliflozin has been associated with an increased risk of urinary tract infection in some trials, particularly in female patients. Events consistent with genital infection were more common in patients treated with empagliflozin and more common in women. A greater proportion of patients treated with empagliflozin experienced volume depletion, consistent with its diuretic effect. Small changes in eGFR were observed with empagliflozin, which likely reflect haemodynamic changes due to its effects on tubular-feedback mechanisms [16].

In summary, in Asian patients with T2DM, empagliflozin given as monotherapy or add-on therapy for 24 weeks improved glycaemic control, reduced weight and BP, and was well tolerated.

Author Contributions

All authors contributed to the interpretation of data and writing of the article.

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Conflict of Interest

K-HY has served on advisory boards for AstraZeneca, Eli Lilly, Merck and Pfizer, has received research support from Merck, AstraZeneca and Bayer, and has received speaker fees from Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Merck, Takeda and Novartis.

RN has received research support from Japan Diabetes Foundation, Boehringer Ingelheim, Daiichi-Sankyo and Astellas, has participated in speaker's bureau/advisory panels for Novo Nordisk, Eli Lilly, Sanofi, Kissei, Astellas, Boehringer Ingelheim, Daiichi-Sankyo, Tanabe- Mitsubishi, AstraZeneca, Kowa, Ono, Johnson & Johnson, Medtronic, Takeda and Astellas, and served as a consultant for Boehringer Ingelheim and Eli Lilly and Company.

JL, AS and HJW are employees of Boehringer Ingelheim. TH and SC were employees of Boehringer Ingelheim at the time this analysis was conducted.

References

1. Guariguata L, Whiting D, Hambleton I, Beagley J, Linnenkamp U, Shaw J. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014; **103**: 137–149.
2. Ji LN, Lu JM, Guo XH et al. Glycemic control among patients in China with type 2 diabetes mellitus receiving oral drugs or injectables. BMC Public Health 2013; **13**: 602.
3. So WY, Raboca J, Sobrepena L et al. Comprehensive risk assessments of diabetic patients from seven Asian countries: The Joint Asia Diabetes Evaluation (JADE) program. J Diabetes 2011; **3**: 109–118.
4. Roden M, Weng J, Eilbracht J et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 2013; **1**: 208–219.

5. Häring H-U, Merker L, Seewaldt-Becker E et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2014; **37**: 1650–1659.
6. Häring H-U, Merker L, Seewaldt-Beck E et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week randomized, double-blind, placebo-controlled trial. Diabetes Care 2013; **36**: 3396–3404.
7. Kovacs CS, Seshiah V, Swallow R et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. Diabetes Obes Metab 2014; **16**: 147–158.
8. Häring H-U, Merker L, Christiansen AV et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes. Diabetes Res Clin Pract 2015; **110**: 82–90.
9. Roden M, Merker L, Christiansen AV et al. Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naïve patients with type 2 diabetes: a double-blind extension of a phase III randomized controlled trial. Cardiovasc Diabetol 2015; **14**: 154.
10. Merker L, Häring H-U, Christiansen AV et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes. Diabet Med 2015; **32**: 1555–1567.
11. Kovacs CS, Seshiah V, Merker L et al. Empagliflozin as add-on therapy to pioglitazone with or without metformin in patients with type 2 diabetes mellitus. Clin Ther 2015; **37**: 1773–1788.
12. Barnett AH. Impact of sodium glucose cotransporter 2 inhibitors on weight in patients with type 2 diabetes mellitus. Postgrad Med 2013; **125**: 92–100.
13. Neeland IJ, McGuire DK, Chilton R et al. Empagliflozin reduces body weight and indices of adipose distribution in patients with type 2 diabetes mellitus. Diab Vasc Dis Res 2016; **13**: 119–126.
14. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci 2013; **1281**: 64–91.

15. Cherney DZ, Perkins BA, Soleymanlou N et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol 2014; **13**: 28.

16. Cherney DZ, Perkins BA, Soleymanlou N et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014; **129**: 587–597.

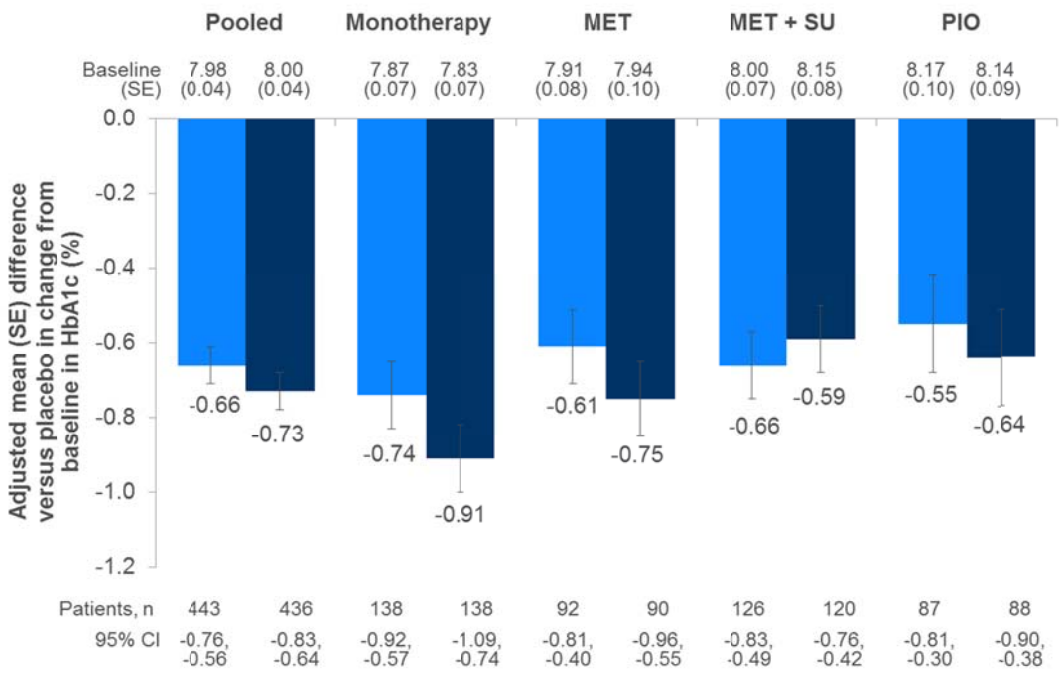

Figure 1. Effect of empagliflozin on glycaemic parameters. (A) Adjusted mean differences versus placebo in changes from baseline in HbA1c at week 24 (FAS, ANCOVA, LOCF), p<0.001 versus placebo for all.

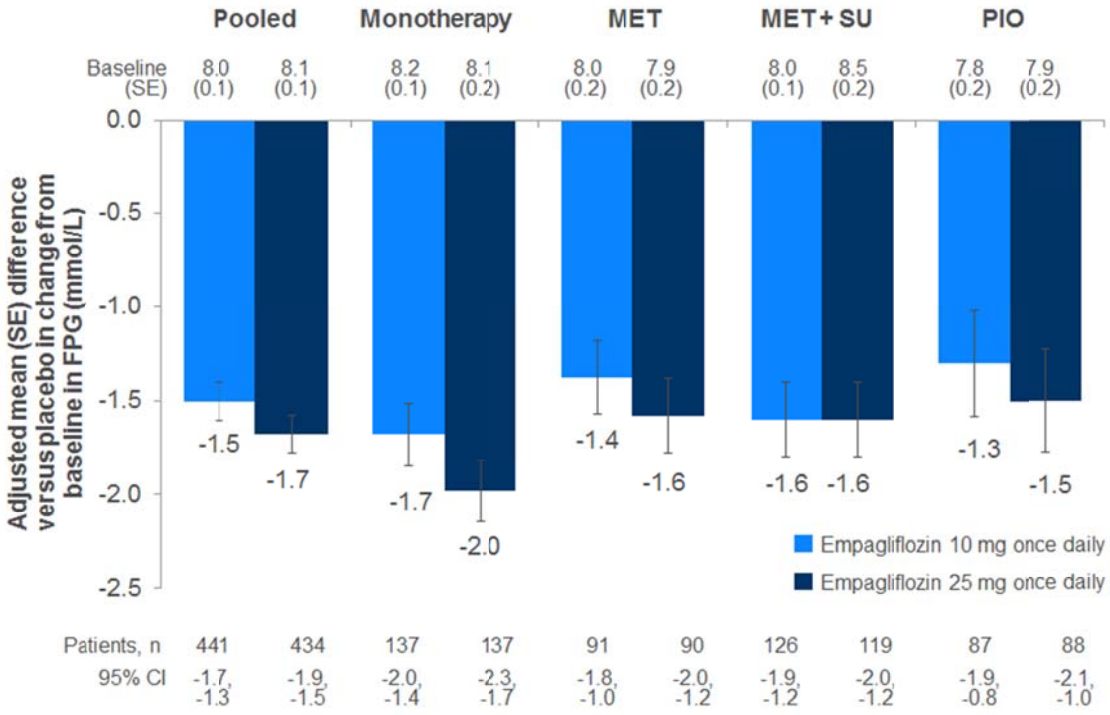

Figure 1. Effect of empagliflozin on glycaemic parameters. (A) Adjusted mean differences versus placebo in changes from baseline in HbA1c at week 24 (FAS, ANCOVA, LOCF), p<0.001 versus placebo for all. (B) Adjusted mean differences versus placebo in changes from baseline in FPG at week 24 (FAS, ANCOVA, LOCF), p<0.001 versus placebo for all. FAS, full analysis set; ANCOVA, analysis of covariance; LOCF, last observation carried forward; FPG, fasting plasma glucose; SE, standard error; MET, add-on to metformin trial; MET + SU, add-on to metformin plus sulphonylurea trial; PIO, add-on to pioglitazone trial.

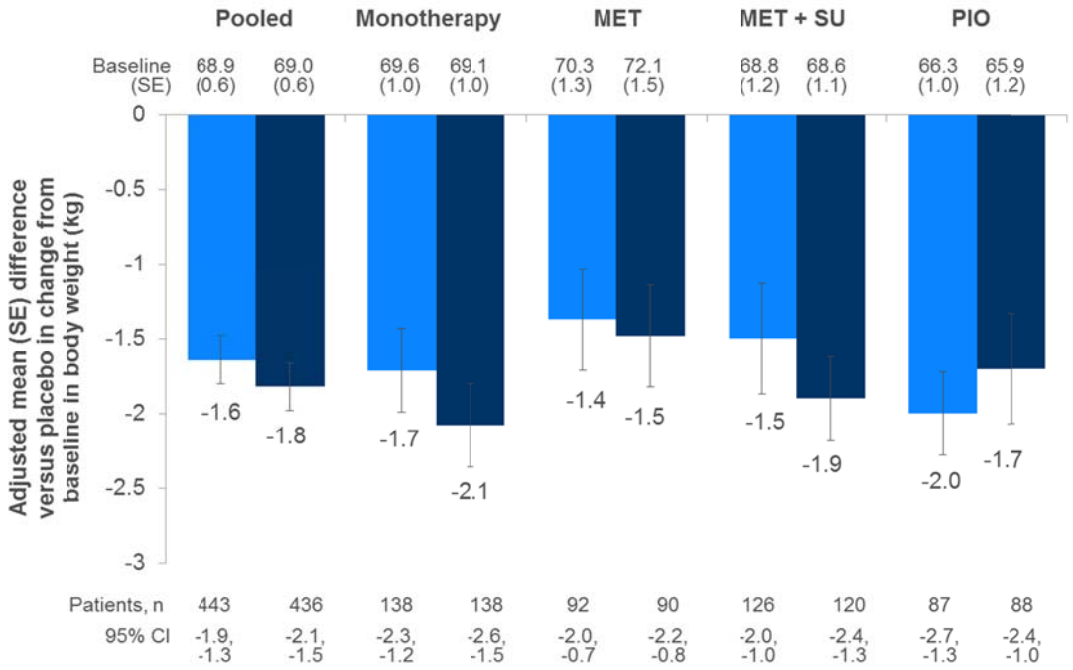

Figure 2. Effect of empagliflozin on weight and systolic blood pressure. (A) Adjusted mean differences versus placebo in changes from baseline in weight at week 24 (FAS, ANCOVA, LOCF), $p<0.001$ versus placebo for all.

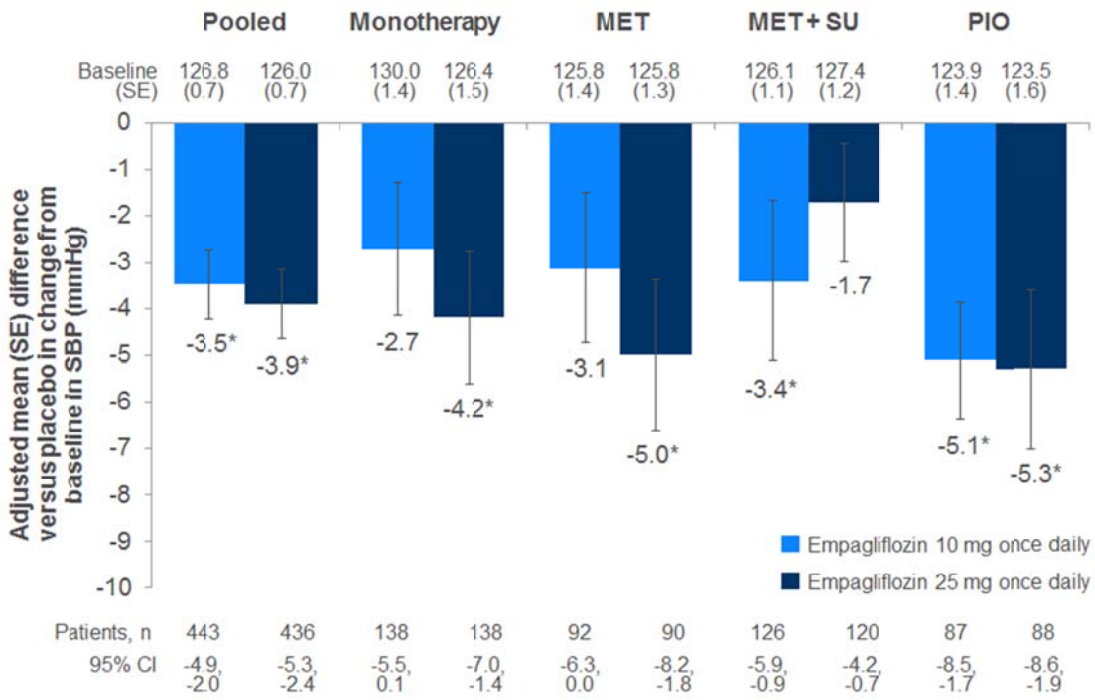

Figure 2. Effect of empagliflozin on weight and systolic blood pressure. (A) Adjusted mean differences versus placebo in changes from baseline in weight at week 24 (FAS, ANCOVA, LOCF), p<0.001 versus placebo for all. (B) Adjusted mean differences versus placebo in changes from baseline in SBP at week 24 (FAS, ANCOVA, LOCF), *p<0.05 versus placebo. FAS, full analysis set; ANCOVA, analysis of covariance; LOCF, last observation carried forward; SBP, systolic blood pressure; SE, standard error; MET, add-on to metformin trial; MET + SU, add-on to metformin plus sulphonylurea trial; PIO, add-on to pioglitazone.