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Empagliflozin for Patients with Presumed Resistant Hypertension: a Post Hoc Analysis of the EMPA-REG OUTCOME Trial

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Short title: Empagliflozin for resistant hypertension

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Abstract

Background: Type 2 diabetes (T2D) and resistant hypertension (rHT) often coexist, greatly increasing risk of target-organ damage and death. We explored the effects of empagliflozin in patients with and without presumed resistant hypertension (prHT) in a post hoc analysis of EMPA-REG OUTCOME (NCT01131676).

Methods: Overall, 7020 patients received empagliflozin 10mg, 25mg, or placebo with median follow-up of 3.1 years. We defined baseline prHT as ≥3 classes of antihypertensive drugs including a diuretic and uncontrolled BP (SBP≥140 and/or diastolic BP [DBP]≥90 mmHg), or ≥4 classes of antihypertensive, including a diuretic, and controlled BP. We explored the effect of empagliflozin on CV death, heart failure hospitalization (HHF), 3-point major adverse cardiac events (3P-MACE), all-cause death, and incident/worsening nephropathy by Cox regression and BP over time by a mixed-repeated-measures-model analysis.

Results: 1579 (22.5%) patients had prHT. The mean difference in change in SBP from baseline to week 12 versus placebo was -4.5 (95% CI, -5.9 to -3.1) mmHg (p<0.001) in prHT and -3.7 (-4.5, -2.9) mmHg (p<0.001) in patients without prHT. SBP was more frequently controlled (<130/80 mmHg) with empagliflozin than with placebo. Patients with prHT had 1.5 to 2-fold greater risk of HHF, incident/worsening nephropathy and CV death compared to those without prHT. Empagliflozin improved all outcomes in patients with and without prHT (interaction *P*>0.1 for all outcomes).

Conclusions: Empagliflozin induced a clinically relevant reduction in SBP and consistently improved all outcomes regardless of prHT status. Due to these dual effects, empagliflozin should be considered for patients with hypertension and T2D.

Key-words: resistant hypertension; type 2 diabetes; empagliflozin.

INTRODUCTION

Cardiovascular (CV) risk in patients with diabetes is graded and continuous across the entire range of blood pressure (BP). International recommendations support the start of antihypertensive treatment in persons with diabetes who have high blood pressure with a treatment goal of reducing systolic blood pressure (SBP) to <130 mmHg.[1-3] A subset (5–30%) of patients with high BP may have resistant hypertension (rHT) defined (by European guidelines) as a seated office SBP ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg on maximally tolerated doses of ≥3 antihypertensive agents (including a diuretic) or when BP control is achieved but requires ≥4 medications.[3] Diabetes increases the risk of developing rHT.[4] Furthermore, the concomitant existence of diabetes and rHT is associated with a major increase in the risk of target-organ damage (including heart failure [HF], atrial fibrillation, myocardial infarction [MI], stroke, chronic kidney disease [CKD]) and ultimately death.[3-8]

Spironolactone is recommended as 4th line therapy for rHT; notwithstanding, a large proportion of patients with rHT remain uncontrolled and/or may have a formal contraindication or intolerance (e.g., advanced CKD, hyperkalemia) to spironolactone, therefore additional strategies are urgently needed.[5, 9]

Empagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor, which, compared with placebo, reduced time to first HF hospitalization, incident or worsening nephropathy, and death (CV and all-cause) in patients with type 2 diabetes mellitus (T2D) and CV disease in the EMPA-REG OUTCOME trial.[10] SGLT2-inhibitors also reduce blood pressure,[11] and in the EMPA-REG BP trial empagliflozin (compared with placebo) reduced mean SBP by 3–5 mmHg and DBP by 1–2 mmHg at week 12.[12, 13] However, the effect of empagliflozin in patients with rHT is yet to be studied.

The aim of the present study is to assess the BP-lowering effects of empagliflozin in patients with and without rHT (rHT versus no-rHT), and whether the treatment effect of empagliflozin on CV, renal and HF outcomes are consistent in those with and without rHT; as rHT was a presumptive post-hoc diagnosis in this population, we refer to it as presumed resistant hypertension (prHT) throughout the manuscript (please see also the methods section).

METHODS

The methods of the EMPA-REG OUTCOME trial have been previously described.[10] In short, 7020 patients with T2D and established CV disease were assigned to receive either 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from CV causes, nonfatal MI, or nonfatal stroke (3P-MACE), as analyzed in the pooled empagliflozin group versus the placebo group. Other outcomes were CV death, hospitalization for HF, the composite of CV death or hospitalization for HF, incident/worsening nephropathy, and all-cause death. These outcomes were also assessed in the present analysis. The median follow-up time was 3.1 years.

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance.

Definition of Resistant Hypertension and Blood Pressure Assessment

In this post hoc analysis, we defined prHT at baseline as the use of ≥3 classes of antihypertensive drugs, including a diuretic, and uncontrolled BP (SBP ≥140 and/or DBP ≥90 mmHg), or use of ≥4 classes of antihypertensive drugs, including a diuretic, and SBP <140 and DBP <90 mmHg. "True" rHT definition requires a BP that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes, with (ideally) one of the 3 agents being a diuretic, with all agents prescribed at maximally tolerated doses; and (ideally) also requires ambulatory confirmation of high BP.[3] Typically, a clinic BP of 140/90 mmHg corresponds to home BP values of 135/85 mmHg and to ambulatory blood pressure monitoring values defined as a daytime SBP/DBP of 135/85 mmHg, a night-time SBP/DBP of 120/70 mmHg, and a 24-hour SBP/DBP of 130/80 mmHg[2]. For this reason, we used the 140/90 mmHg cutoff in our rHT definition, as it may better reflect "true" rHT (i.e., be more specific). As our study is a post hoc analysis of an outcome trial, we cannot ascertain whether all of the patients herein included have 'true' rHT (despite using a cutoff of office BP >140/90 mmHg). In consequence, throughout the manuscript whenever rHT is referred to, it should be considered as prHT.

Blood pressure was measured in the seated position after at least 5 minutes of rest with a calibrated automatic sphygmomanometer and in the presence of the study physician and/or nurse at

each study site, taking the average of 3 consecutive measurements with a between-measurement interval of at least 1 minute.

Statistical Analysis

Patients` baseline characteristics were derived in the prHT versus no-prHT groups, and continuous variables are presented as mean±standard deviation (SD), and categorical variables are presented as number (n) and proportion (%). Effects on blood pressure (SBP, DBP) were evaluated using a mixed effect model repeat measurement (MMRM) model, which included subject as a random effect, baseline glycated hemoglobin (HbA1c) and baseline of the endpoint (SBP or DBP) as linear covariates and their interaction with visit in addition to baseline estimated glomerular filtration rate (eGFR) category, geographic region, baseline body mass index (BMI) category. Treatment, resistant hypertension at baseline and visit were also entered as fixed effects as well as all 2- and 3-way interactions thereof. Additionally, the model included a fixed categorical effect for 'time of randomization' to account for each patient's theoretical ability to 'reach' certain weeks in this study arising from the study design. A similar MMRM model was applied for the evaluation of effects on weight and HbA1c. We furthermore explored the proportion of patients that achieved SBP <130 mmHg during the trial. We then evaluated the treatment effects (pooled empagliflozin arms versus placebo) on time to first 3P-MACE, CV death, hospitalization for HF, the composite of CV death or HF hospitalization, incident/worsening nephropathy, and all-cause death, in those with and without prHT by Cox regression models. The Cox model included the interaction of presence of prHT at baseline by treatment to evaluate the treatment effect in patients with and without prHT at baseline separately. The model further included covariate terms for age, gender, BMI, HbA1c, eGFR, region, resistant hypertension at baseline, and treatment. All analyses are post hoc and not adjusted for multiplicity. All statistical analyses were performed using SAS Software, Version 9.4.

RESULTS

Baseline Characteristics

Overall, 1579 (22.5%) patients had prHT (as defined in the methods section); these patients had longer diabetes duration (>10 y: 63% versus 55%) and more concomitant diseases, including HF (17% versus 8%), retinopathy (27% versus 21%) and macroalbuminuria (15% versus 10%), as well as lower mean eGFR (68 mL/min/1.73 m^2 ± 21 (SD) versus 76 mL/min/1.73 m^2 ± 21 (SD)). The mean baseline SBP/DBP±SD was 142±18/78±11 mmHg in prHT versus 133±16/76±10 mmHg in no-prHT, and patients with prHT used more antihypertensive treatments, including mineralocorticoid receptor antagonists ([MRAs] Table 1). More patients with prHT added antihypertensive medications including beta blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers during the trial, compared to those with no-prHT. Fewer patients added concomitant medications in the empagliflozin versus placebo arms in both prHT and no-prHT groups. Addition of MRAs was balanced between treatments in patients with prHT (Table 2).

Blood Pressure Control

Systolic and diastolic BP were consistently reduced by empagliflozin in patients with prHT or no-prHT. Overall, the treatment effect of empagliflozin on SBP was consistent in patients with and without prHT throughout the trial (Figure 1). The mean difference (95% CI) of SBP change from baseline to week 12 with empagliflozin versus placebo was -4.5 (-5.9 to -3.1) mmHg in prHT versus -3.7 (-4.5 to -2.9) mmHg in no-prHT; a difference that was sustained during the follow-up (Figure 1). These changes were generally comparable between empagliflozin doses (Supplemental Figure 1). The differences in change in DBP from baseline to week 12 for empagliflozin versus placebo were smaller as compared to SBP in patients with and without prHT: -1.7 (-2.5 to -0.9) mmHg in prHT versus -1.2 (1.7 to -0.8) mmHg in no-prHT; a difference that was also sustained during the follow-up (Supplemental Figure 2).

The proportion of patients with prHT that achieved SBP <130 mmHg was higher with empagliflozin (versus placebo) throughout the follow-up (e.g., 38% versus 26% at week 12; Figure 2, Supplemental Figure 3 and Supplemental Table 1. Similarly, more patients without prHT treated with empagliflozin achieved SBP <130 mmHg compared with placebo (Figure 2, Supplemental Table 1**)**.

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Outcome Events

In both placebo- and empagliflozin-treated patients, patients with prHT were generally at increased risk for all outcomes compared to patients with no-prHT – with the only exception of all-cause mortality in the placebo group which only showed a weak trend in this respect (HR 1.13, 95% CI, 0.82–1.56) for prHT versus no prHT). For example, in placebo-treated patients, the hazard ratio for 3P-MACE was 1.31 (95% CI, 1.01–1.71) (Table 3).

Treatment Effects on Outcomes and HbA1c

Empagliflozin (versus placebo) consistently reduced the risk for all outcomes regardless of baseline prHT status (*P* value for interaction >0.1 for all outcomes; Figure 3). HbA1c levels and weight were reduced by empagliflozin treatment in patients with and without prHT (Supplemental Figures 4 and 5).

Adverse Events

For most AEs, incidence rates in patients with prHT were higher compared to patients with no-prHT irrespective of treatment (Supplemental Table 2). Empagliflozin-treated prHT patients experienced numerically fewer serious adverse events compared with placebo-treated prHT patients (45.7% versus 52.1%). Furthermore, rates of hyperkalemia were lower with empagliflozin than placebo, irrespective of prHT status, whereas incidence rates of genital infection were increased with empagliflozin in both subgroups.

DISCUSSION

In this analysis, treatment with empagliflozin resulted in early reductions in SBP in patients with T2D with and without prHT (-4.5 mmHg compared with placebo in patients with prHT at week 12) with sustained BP reduction throughout the follow-up. A higher proportion of empagliflozin-treated patients achieved a SBP <130 mmHg compared with those receiving placebo. Independent of treatment arm, patients with prHT had higher incidence of major CV (including HF) events compared to those with no-prHT after multivariable adjustment for risk factors including age and eGFR . Treatment with empagliflozin reduced major CV events irrespective of the patients` prHT status.

Treatment with empagliflozin has consistently been shown to reduce BP in patients with T2D, thereby improving the BP control in this population.[11-13] Reductions in major CV events and death with empagliflozin are likely explained by a multitude of mechanisms, including osmotic diuresis following increased urinary glucose excretion, improved glycemic control, weight loss, reduced arterial stiffness, and, importantly, a reduction in plasma volume.[14-16] Although a mediation analysis identified changes in markers of plasma volume as the most important mediators of the reduction of CV death in empagliflozin treated patients and showed that SBP and DBP had only neglible mediating effects,[16] it is well established that BP control is important to improve outcomes in patients with T2D and CVD.

In the EMPA-REG OUTCOME trial, patients with prHT represented 22% of the study population, supporting the high prevalence of rHT in patients with diabetes also reported in population-based cohorts.[17] Patients with rHT have high CV risk, which poses additional difficulties in the BP control, where a low BP target (SBP <130 mmHg) is desirable.[18] The Action to Control Cardiovascular Risk in Diabetes blood pressure trial (ACCORD-BP)[19] tested the effect of a target SBP <120 mmHg on major adverse cardiac effects among high-risk persons with type 2 diabetes (n=4733). Although this trial did not show a reduction in the primary composite outcome of MI, stroke or CV death, a reduction in stroke rate, a prespecified secondary outcome, was observed.[19] Subsequent large meta-analyses strongly support intensive BP-lowering strategies over standard regimens for CV protection in persons with diabetes, with benefits seen even at SBP values <120 mmHg.[20, 21] The Systolic Blood Pressure Intervention Trial (SPRINT), also supports a target of <120 mmHg among patients at high risk for CV events but without diabetes[22]. In order to achieve an adequate BP control in rHT patients, multiple drugs and drug-combinations are often used. In rHT patients participating in the PATHWAY-2 trial[23], spironolactone started at 25 mg daily, and up-titrated to 50 mg, reduced home SBP at 12 weeks by a mean of -8.7 (-9.7 to -7.7) mmHg, compared with placebo, and was more effective than alternative fourth-line drugs (bisoprolol or doxazosin) by a mean SBP margin of -4.3 (-5.1 to -3.4) mmHg. In the present study, treatment with empagliflozin resulted in a -4.5 (-5.9 to -3.1) mmHg greater reduction in SBP at week 12 compared with placebo in patients with prHT, suggesting that empagliflozin may have additional BP-lowering benefit on top of

standard of care[24]. The differences in trial design and populations preclude comparisons of BP effects between spironolactone and empagliflozin (e.g., PATHWAY-2 was a "cross-over" trial, enrolling only patients with resistant hypertension and where only 14% of the patients had T2D). Interestingly, in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, that enrolled patients with heart failure and preserved ejection fraction, of which 32% had diabetes, spironolactone reduced SBP by -6.1 (-8.9 to -3.3) mmHg at 16 weeks in those with prHT.[25] Together these results suggest that there may exist a potential interest in associating these drugs (spironolactone and empagliflozin) for the treatment of rHT in patients with T2D. These drugs showed morbidity and mortality reductions across different populations, and patients treated with empagliflozin had lower rates of hyperkalemia during the follow-up, which may be of particular interest when used concomitantly with an MRA. Analogously, another emerging treatment option is potassium binding. For example, the AMBER study (patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease) showed that patiromer enabled more patients to continue treatment with spironolactone with less hyperkalaemia[26] The findings reported in the present study are also concordant with those of the EMPA-REG BP trial where, compared with placebo, empagliflozin reduced ambulatory SBP by 3.4 (-4.8 to -2.1) mmHg and 4.2 (-5.5 to -2.8) mmHg in the 10 mg and 25 mg formulations, respectively in patients with T2D and hypertension.[12] The BP-lowering effect of empagliflozin was retained in patients who were receiving one or multiple antihypertensive medications.[13] The BP-lowering properties of empagliflozin, may likely be extended to a class effect, as dapagliflozin also reduced office BP in patients receiving background antihypertensive treatment,[27] and canagliflozin also reduced BP, especially in patients with baseline SBP >140 mmHg.[28]

Clinical and Research Implications

These findings may have major clinical and research implications as empagliflozin could be a therapeutic option for BP control in patients with hypertension and T2D, providing survival and renal protection benefits beyond its BP-lowering effects. As patients treated with empagliflozin had lower rates of hyperkalemia in our analysis as well as in previous analyses from EMPA-REG OUTCOME,[29]

future studies may evaluate the benefit of empagliflozin in reducing hyperkalemia risk in rHT patients treated with MRAs.

Limitations

Our analysis has some limitations. First, since it is post-hoc and non-prespecified, and the trial was not powered for subgroup analyses, the results must be regarded as hypothesis generating. Although blood pressure measurement was standardized, this was not a dedicated blood pressure trial, blood pressure was measured in the presence of the study personnel and sphygmomanometers might have been different between study sites; therefore, the precision of the values reported may be reduced. However, this imprecision was not systematic and may even reinforce the robustness of our findings (i.e., with variability similar to a 'real-world' setting). Finally, the American Heart Association (AHA) uses an inclusive definition of rHT: "rHT is defined as blood pressure (BP) that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, 1 of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose amounts".[9] The presence of 'true' rHT is difficult to ascertain in non-HT studies, due to the difficulty in confirming adherence to therapy and performing 24-hour ambulatory blood pressure measurements: such assessments were not performed within the framework of a cardiovascular outcome trial. Furthermore, doses of anti-hypertensive treatments were not captured.

CONCLUSIONS

Empagliflozin induced a clinically relevant reduction in SBP and consistently improved all outcomes regardless of the prHT status. Acknowledging that this is a post-hoc analysis, the consistent findings suggest that due to the optimal dual effect of BP control and CV event reduction, empagliflozin should be considered a therapeutic option for patients with hypertension and T2D.

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432

433

Figure Legends

Figure 1. Change from baseline in systolic blood pressure over time in patients a) with presumed resistant hypertension and b) no presumed resistant hypertension at baseline including all data up until individual trial termination: mixed effect repeated measurement model results.

*MMRM model on the overall population including subject as random effect and, among others, treatment, visit, and presumed resistant hypertension at baseline as well as their corresponding 2- and 3-way interactions as fixed effects (for details on other fixed effects and linear covariates, see "statistical analysis" section).

Figure 2. Proportion of patients a) with presumed resistant hypertension and b) without presumed resistant hypertension who achieved systolic blood pressure <130 mmHg during the trial in empagliflozin and placebo groups.

Figure 3. Treatment effects of empagliflozin versus placebo on outcomes in patients with or without presumed resistant hypertension.

*Based on a Cox regression model with terms for age sex, baseline BMI category, baseline HbA1c category, baseline eGFR category, geographical region, treatment, presumed resistant hypertension and treatment by presumed resistant hypertension interaction.

†excludes fatal stroke

Figure 1

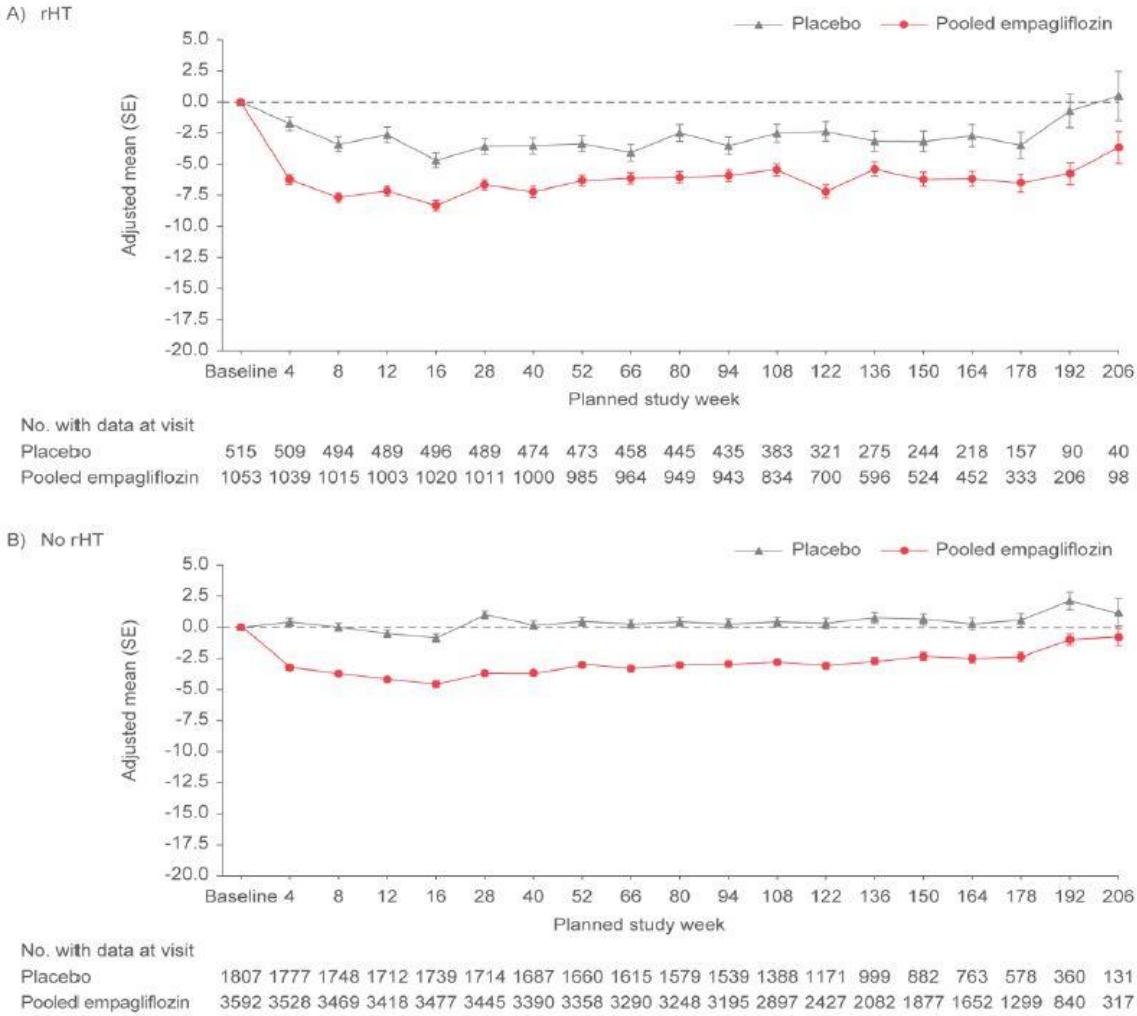

A) rHT
Placebo
Pooled empagliflozin
Adjusted mean (SE)
5.0
2.5
0.0
-2.5
-5.0
-7.5
-10.0
-12.5
-15.0
-17.5
-20.0
Baseline 4 8 12 16 28 40 52 66 80 94 108 122 136 150 164 178 192 206
Planned study week
No. with data at visit
Placebo 515 509 494 489 496 489 474 473 458 445 435 383 321 275 244 218 157 90 40
Pooled empagliflozin 1053 1039 1015 1003 1020 1011 1000 985 964 949 943 834 700 596 524 452 333 206 98
B) No rHT
Placebo
Pooled empagliflozin
Adjusted mean (SE)
5.0
2.5
0.0
-2.5
-5.0
-7.5
-10.0
-12.5
-15.0
-17.5
-20.0
Baseline 4 8 12 16 28 40 52 66 80 94 108 122 136 150 164 178 192 206
Planned study week
No. with data at visit
Placebo 1807 1777 1748 1712 1739 1714 1687 1660 1615 1579 1539 1388 1171 999 882 763 578 360 131
Pooled empagliflozin 3592 3528 3469 3418 3477 3445 3390 3358 3290 3248 3195 2897 2427 2082 1877 1652 1299 840 317

Figure 2

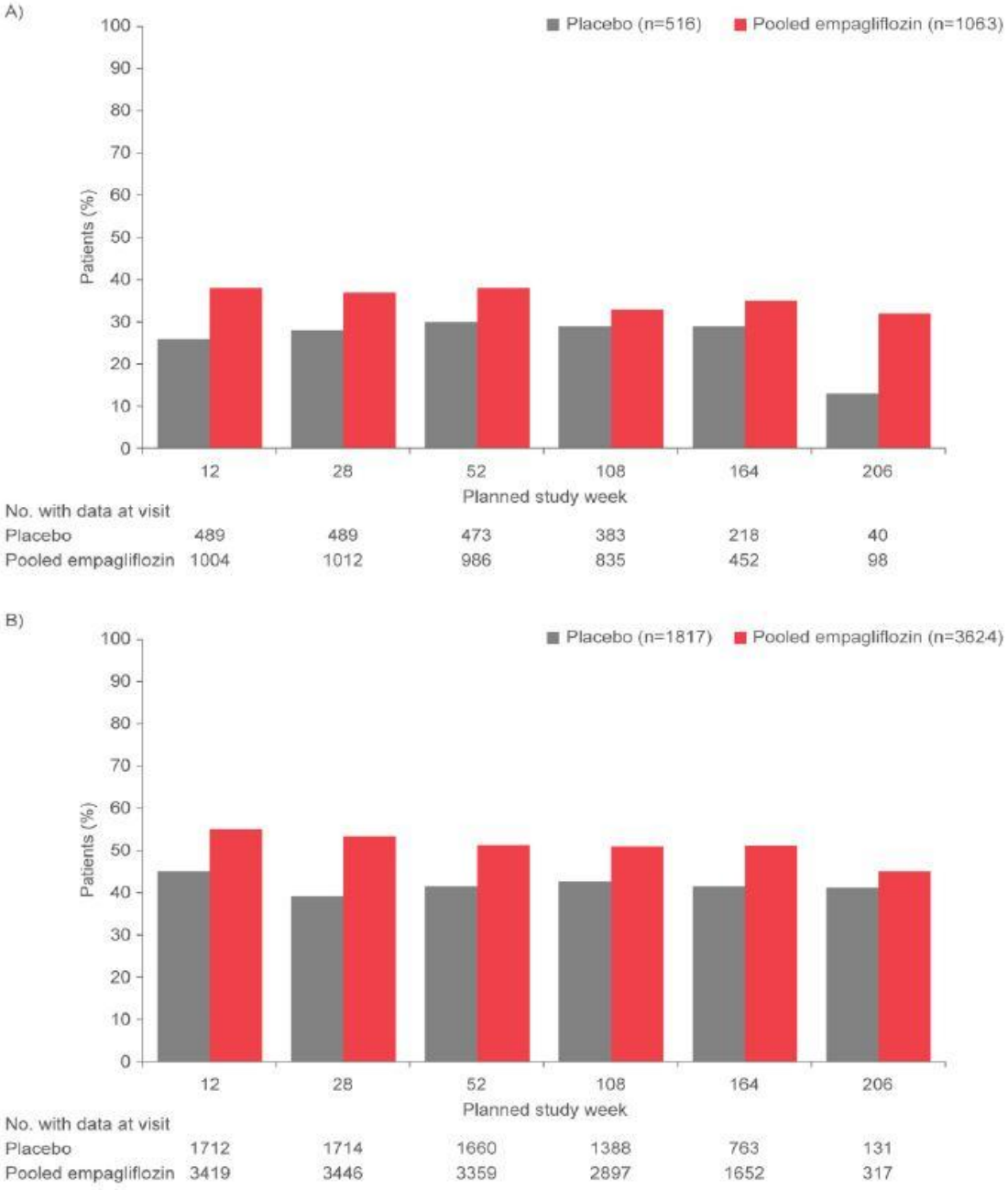

A)
Placebo (n=516)
Pooled empagliflozin (n=1063)
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
12
28
52
108
164
206
Planned study week
No. with data at visit
Placebo 489 489 473 383 218 40
Pooled empagliflozin 1004 1012 986 835 452 98
B)
Placebo (n=1817)
Pooled empagliflozin (n=3624)
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
12
28
52
108
164
206
Planned study week
No. with data at visit
Placebo 1712 1714 1660 1388 763 131
Pooled empagliflozin 3419 3446 3359 2897 1652 317

Figure 3

Baseline rHT	Placebo n/N	Placebo %	Placebo Rate/ 1000 PY	Pooled empagliflozin n/N	Pooled empagliflozin %	Pooled empagliflozin Rate/ 1000 PY	HR (95% CI)	Treatment Subgroup Interaction*
CV death								
All patients	137/2333	5.9	20.2	172/4687	3.7	12.4	0.62 (0.49, 0.77)	
rHT=no	93/1817	5.1	17.5	117/3624	3.2	10.9	0.63 (0.48, 0.82)	*p*=0.8471
rHT=yes	44/516	8.5	29.8	55/1063	5.2	17.8	0.60 (0.40, 0.89)	
HHF								
All patients	95/2333	4.1	14.5	126/4687	2.7	9.4	0.65 (0.50, 0.85)	
rHT=no	64/1817	3.5	12.4	73/3624	2.0	7.0	0.58 (0.41, 0.81)	*p*=0.2947
rHT=yes	31/516	6.0	22.0	53/1063	5.0	17.7	0.78 (0.50, 1.21)	
CV death or HHF†								
All patients	198/2333	8.5	30.1	265/4687	5.7	19.7	0.66 (0.55, 0.79)	
rHT=no	130/1817	7.2	25.2	168/3624	4.6	16.0	0.65 (0.51, 0.81)	*p*=0.9471
rHT=yes	68/516	13.2	48.4	97/1063	9.1	32.5	0.65 (0.48, 0.89)	
3P-MACE								
All patients	282/2333	12.1	43.9	490/4687	10.5	37.4	0.86 (0.74, 0.99)	
rHT=no	202/1817	11.1	40.0	334/3624	9.2	32.7	0.82 (0.69, 0.98)	*p*=0.4469
rHT=yes	80/516	15.5	57.9	156/1063	14.7	54.0	0.93 (0.71, 1.22)	
All-cause death								
All patients	194/2333	8.3	28.6	269/4687	5.7	19.4	0.68 (0.57, 0.82)	
rHT=no	143/1817	7.9	26.9	189/3624	5.2	17.6	0.66 (0.53, 0.82)	*p*=0.5516
rHT=yes	51/516	9.9	34.6	80/1063	7.5	25.9	0.75 (0.53, 1.06)	
Incident/progression of nephropathy								
All patients	388/2061	18.8	76.0	525/4124	12.7	47.8	0.61 (0.53, 0.70)	
rHT=no	276/1619	17.0	67.7	356/3229	11.0	40.9	0.59 (0.50, 0.69)	*p*=0.5611
rHT=yes	112/442	25.3	109.2	169/895	18.9	73.6	0.64 (0.51, 0.82)	

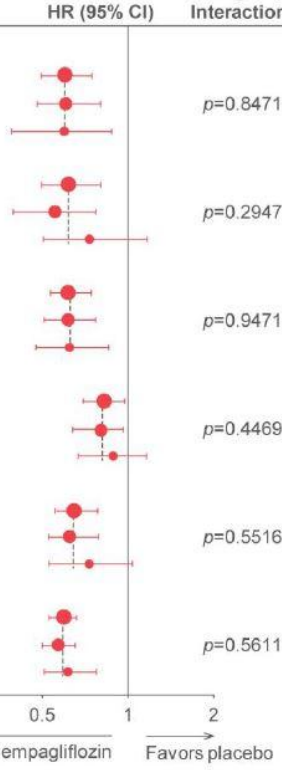


Table 1. Baseline Characteristics and Baseline Medication use by presumed Resistant Hypertension status

Characteristic	**No Resistant Hypertension N=5441**	**Resistant Hypertension N=1579**
Female sex	1543 (28.4)	461 (29.2)
Age, years	62.7±8.7	64.8±8.3
Body mass index, kg/m^2	30.2±5.2	32.2±5.1
Time since T2D diagnosis, years		
≤1	143 (2.6)	37 (2.3)
>1-5	906 (16.7)	177 (11.2)
>5-10	1382 (25.4)	364 (23.1)
>10	3010 (55.3)	1001 (63.4)
LDL-C, mg/dL	86.5±36.3	82.4±33.7
eGFR, mL/min/1.73 m²	75.8±21.4	68.1±20.5
<60	1239 (22.8)	580 (36.7)
Previous stroke, n (%)	1256 (23.1)	381 (24.1)
CAD*, n (%)	4065 (74.7)	1243 (78.7)
Heart failure, n (%)	433 (8.0)	273 (17.3)
HbA1c, %	8.1±0.9	8.1±0.8
SBP, mm Hg	133.4±16.1	142.4±18.2
DBP, mm Hg	76.4±9.6	77.6±10.7
Retinopathy, n (%)	1127 (20.7)	419 (26.5)
Urine albumin−to−creatinine ratio, mg/g, median (Q1, Q3)	16.8 (6.2, 62.8)	25.2 (7.1, 116.7)
Micro albuminuria†	1514 (27.8)	499 (31.6)
Macro albuminuria†	532 (9.8)	237 (15.0)
Left ventricular hypertrophy‡	101 (2.2)	39 (2.9)
Uric acid (mg/dL)	5.8±1.6	6.6±1.8
Baseline medication use		
Antihypertensive drugs	5088 (93.5)	1579 (100.0)
Beta blockers	3197 (58.8)	1357 (85.9)
Diuretics	1456 (26.8)	1579 (100.0)
ACE inhibitors/angiotensin receptor blockers	4140 (76.1)	1526(96.6)
Mineralocorticoid receptor antagonists	170 (3.1)	271 (17.2)
Statins	4097 (75.3)	1306 (82.7)
Anti-platelets	4645 (85.4)	1377 (87.2)
Metformin	4057 (74.6)	1136 (71.9)
Insulin	2447 (45.0)	940 (59.5)

All data are n (%) or mean±SE unless otherwise noted. "Resistant hypertension" was a post-hoc presumptive diagnosis. ACE indicates angiotensin converting enzyme; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.
*Coronary artery disease defined as any of the components of history of myocardial infarction, coronary artery bypass graft, multivessel coronary artery disease, single vessel coronary artery disease. †defined as microalbuminuria UACR 30 to ≤300 mg/g; macroalbuminuria UACR >300 mg/g. ‡defined on ECG as RV5/V6 + SV1/V2 >3.5 mV or RaVL ≥1.3 mV plus ≥1 of the following: left atrial abnormality, left axis deviation, and ST- and/or T-wave changes consistent with LVH.

Table 2. Anti-Coagulants, Lipid-Lowering, Antihypertensive and Antihypertensive Drugs Introduced Post-Baseline by presumed Resistant Hypertension status

	No Resistant Hypertension N=5441		**Resistant Hypertension N=1579**	
	Placebo n=1817	**All Empagliflozin n=3624**	**Placebo n=516**	**All Empagliflozin n=1063**
Anti-hypertensive	882 (48.5)	1550 (42.8)	308 (59.7)	538 (50.6)
Beta blockers	362 (19.9)	627 (17.3)	119 (23.1)	231 (21.7)
Diuretics	426 (23.4)	608 (16.8)	182 (35.3)	291 (27.4)
Mineralocorticoid receptor antagonists	89 (4.9)	86 (2.4)	47 (9.1)	91 (8.6)
ACE inhibitors/angiotensin receptor blockers	533 (29.3)	922 (25.4)	169 (32.8)	302 (28.4)
Statins	446 (24.5)	896 (24.7)	155 (30.0)	249 (23.4)
Anti-platelets	395 (21.7)	732 (20.2)	123 (23.8)	243 (22.9)

All data are n (%). “Resistant hypertension” was a post-hoc presumptive diagnosis. ACE indicates angiotensin-converting enzyme.

Table 3. Association of Outcomes with presumed Resistant Hypertension at Baseline

	Placebo			**Empagliflozin**		
	No resistant hypertension N=1817	**Resistant hypertension N=516**		**No Resistant Hypertension N=3624**	**Resistant Hypertension N=1063**	
	No of Patients With Events (%)	**No of Patients With Events (%)**	**HR* (95% Confidence Interval) Resistant Hypertension vs No Resistant Hypertension**	**No of Patients With Events (%)**	**No of Patients With Events (%)**	**HR* (95% Confidence Interval) Resistant Hypertension vs No Resistant Hypertension**
CV death	93 (5.1)	44 (8.5)	1.50 (1.04–2.16)	117 (3.2)	55 (5.2)	1.43 (1.03–1.98)
HHF	64 (3.5)	31 (6.0)	1.50 (0.97–2.32)	73 (2.0)	53 (5.0)	2.02 (1.41–2.91)
CV death or HHF†	130 (7.2)	68 (13.2)	1.68 (1.25–2.26)	168 (4.6)	97 (9.1)	1.70 (1.32–2.19)
3P-MACE	202 (11.1)	80 (15.5)	1.31 (1.01–1.71)	334 (9.2)	156 (14.7)	1.49 (1.23–1.81)
All-cause mortality	143 (7.9)	51 (9.9)	1.13 (0.82–1.56)	189 (5.2)	80 (7.5)	1.28 (0.98–1.67)
Incident/worsening nephropathy	276 (17.0)	112 (25.3)	1.55 (1.24–1.93)	356 (11.0)	169 (18.9)	1.68 (1.40–2.03)

*HR by multivariable Cox regression with the following variables: age, sex, region, HbA1c (category), BMI (category), eGFR (category), treatment, rHT, and treatment by resistant hypertension interaction. “Resistant hypertension” was a post-hoc presumptive diagnosis. †excluding fatal stroke.

	No resistant hypertension		Resistant hypertension	
n/N (%)	**Placebo n=1817**	**Empagliflozin n=3624**	**Placebo n=516**	**Empagliflozin n=1063**
Week 12	770/1712 (45.0)	1869/3419 (54.7)	129/489 (26.4)	379/1004 (37.7)
Week 28	672/1714 (39.2)	1842/3446 (53.5)	139/489 (28.4)	371/1012 (36.7)
Week 52	688/1660 (41.4)	1724/3359 (51.3)	142/473 (30.0)	371/986 (37.6)
Week 108	590/1388 (42.5)	1480/2897 (51.1)	110/383 (28.7)	271/835 (32.5)
Week 164	319/763 (41.8)	846/1652 (51.2)	64/218 (29.4)	156/452 (34.5)
Week 206	54/131 (41.2)	143/317 (45.1)	5/40 (12.5)	31/98 (31.6)

Supplemental Table 1. Number of patients with systolic blood pressure <130 mm Hg over time by presumed resistant hypertension at baseline, including all data up until individual trial termination.

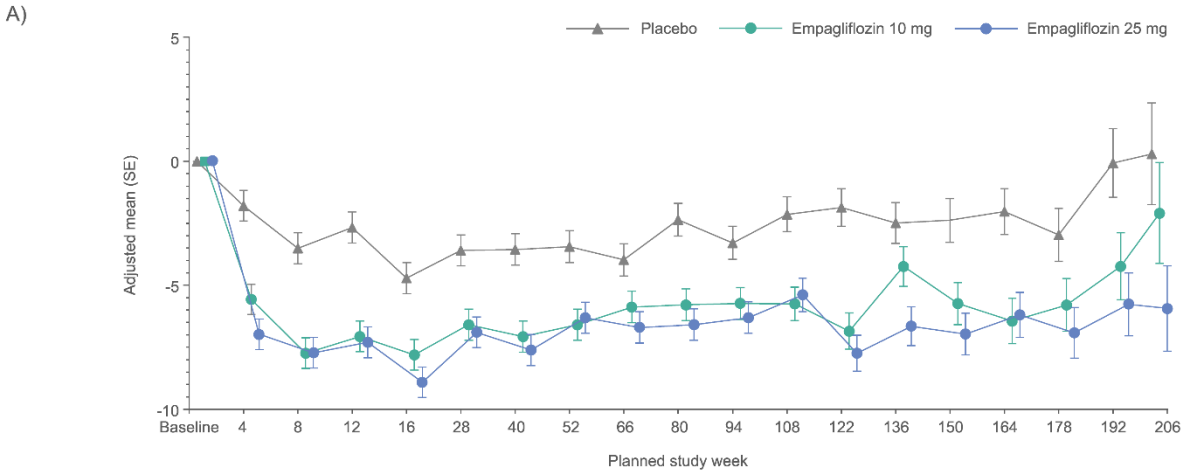
	Placebo				Empagliflozin			
	Without rHT (n=1817)		**With rHT (n=516)**		**Without rHT (n=3624)**		**With rHT (n=1063)**	
	N (%)	**Incidence rate/100 patient-years**	**N (%)**	**Incidence rate/100 patient-years**	**N (%)**	**Incidence rate/100 patient-years**	**N (%)**	**Incidence rate/100 patient-years**
Any AE	1654 (91.0)	165.34	485 (94.0)	246.44	3249 (89.7)	143.03	981 (92.3)	174.90
SAE	719 (39.6)	20.36	269 (52.1)	30.20	1303 (36.0)	17.30	486 (45.7)	24.42
Severe hypoglycemic episode requiring assistance	26 (1.4)	-	10 (1.9)	-	43 (1.2)	-	20 (1.9)	-
Genital infection	27 (1.5)	0.60	15 (2.9)	1.20	240 (6.6)	2.67	61 (5.7)	2.38
Volume depletion	82 (4.5)	1.86	33 (6.4)	2.70	162 (4.5)	1.77	77 (7.2)	3.01
Acute kidney injury	29 (1.6)	0.64	8 (1.6)	0.64	25 (0.7)	0.27	20 (1.9)	0.76
Hyperkalemia*	59 (3.2)	1.33	19 (3.7)	1.53	72 (2.0)	0.77	21 (2.0)	0.80

Supplemental Table 2. Frequency of key relevant adverse events by presumed resistant hypertension at baseline.

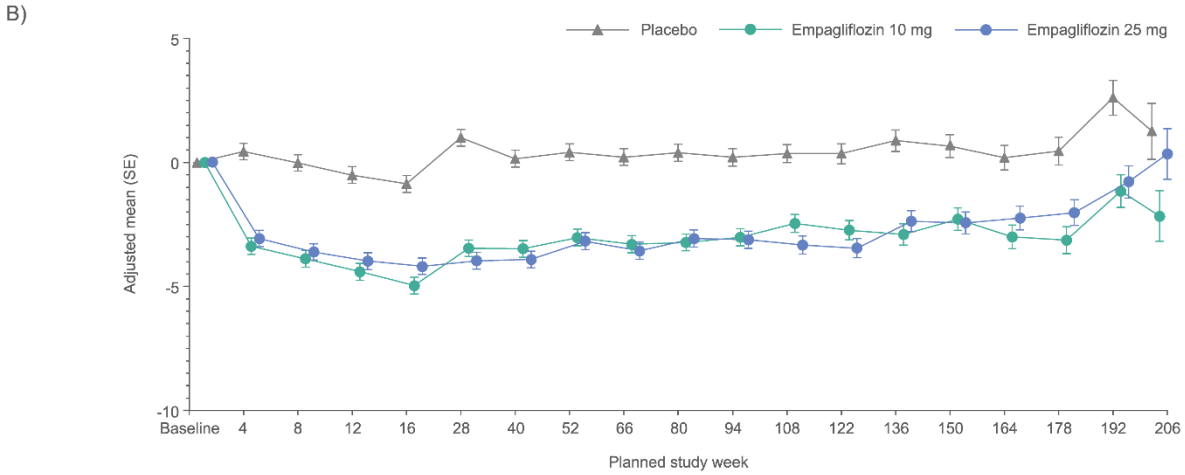
AE indicates adverse event; rHT, resistant hypertension; SAE, serious adverse event.

*Hyperkalemia defined by the MedDRA terms hyperkalemia and blood potassium increase.

Supplemental Figure 1. Change from baseline in systolic blood pressure over time up until individual trial termination in patients a) with presumed resistant hypertension and b) without presumed resistant hypertension: mixed effect repeated measurement model results in individual dose groups.



No. with data at visit	Baseline	4	8	12	16	28	40	52	66	80	94	108	122	136	150	164	178	192	206
Placebo	515	509	494	489	496	489	474	473	458	445	435	383	321	275	244	218	157	90	40
Empagliflozin 10 mg	527	522	510	509	509	504	497	491	479	468	468	411	349	292	258	222	160	96	40
Empagliflozin 25 mg	526	517	505	494	511	507	503	494	485	481	475	423	351	304	266	230	173	110	58

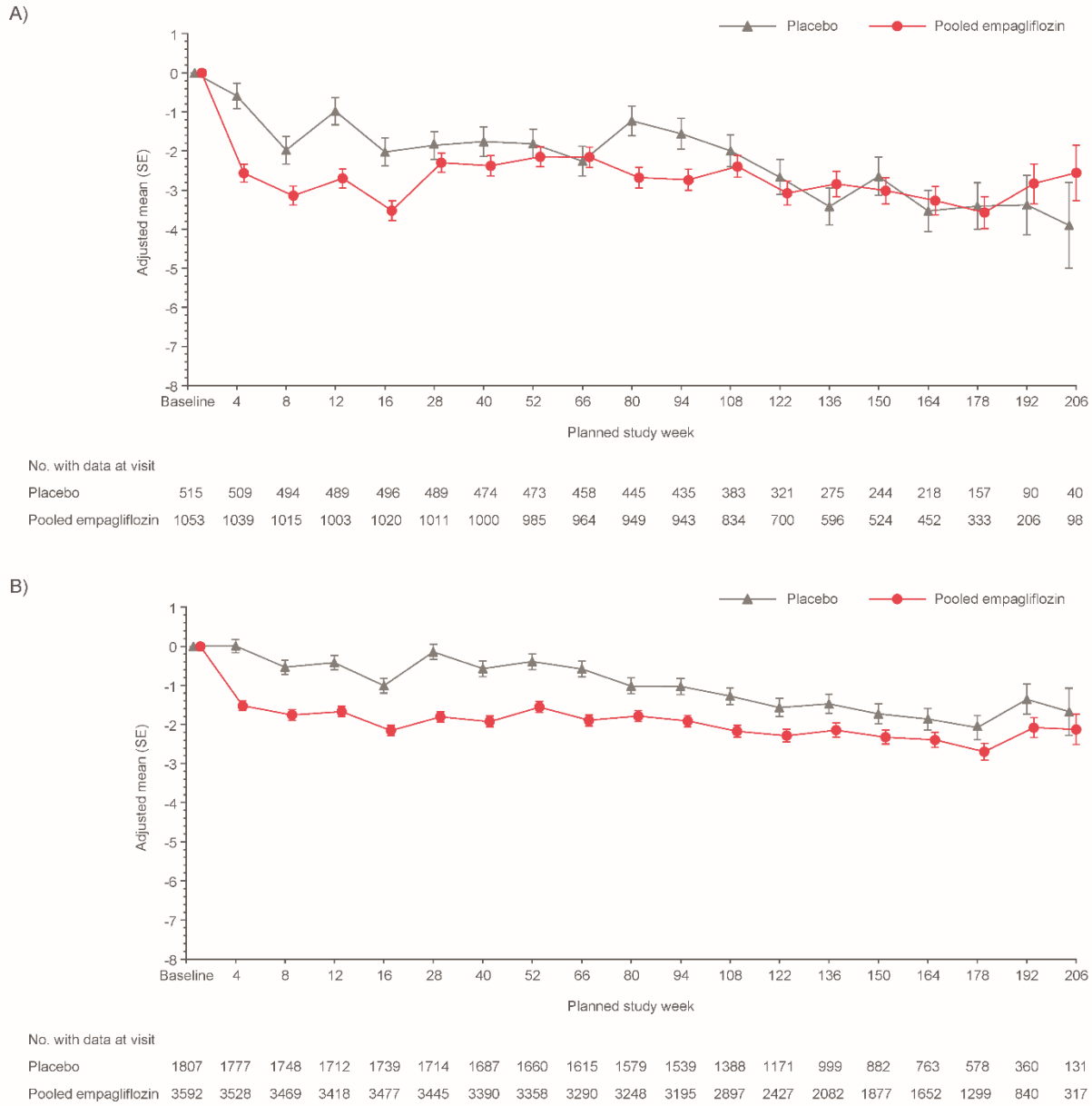


No. with data at visit	Baseline	4	8	12	16	28	40	52	66	80	94	108	122	136	150	164	178	192	206
Placebo	1807	1777	1748	1712	1739	1714	1687	1660	1615	1579	1539	1388	1171	999	882	763	578	360	131
Empagliflozin 10 mg	1795	1758	1727	1715	1741	1731	1696	1683	1646	1627	1604	1442	1207	1035	931	812	630	422	159
Empagliflozin 25 mg	1797	1770	1742	1703	1736	1714	1694	1675	1644	1621	1591	1455	1220	1047	946	840	669	418	158

MMRM model on the overall population including subject as random effect and, among others, treatment, visit, and presumed resistant hypertension at baseline as well as their corresponding 2- and

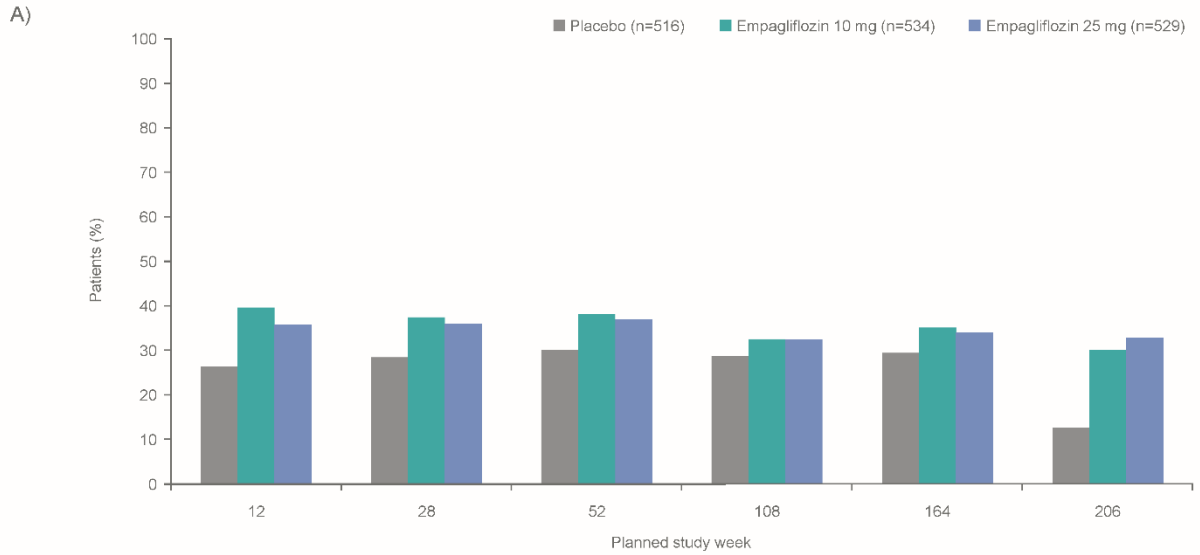
3-way interactions as fixed effects (for details on other fixed effects and linear covariates, see "statistical analysis" section).

Supplemental Figure 2. Change from baseline in diastolic blood pressure over time up until individual trial termination in patients a) with presumed resistant hypertension and b) without presumed resistant hypertension: mixed effect model repeated measurement model results.

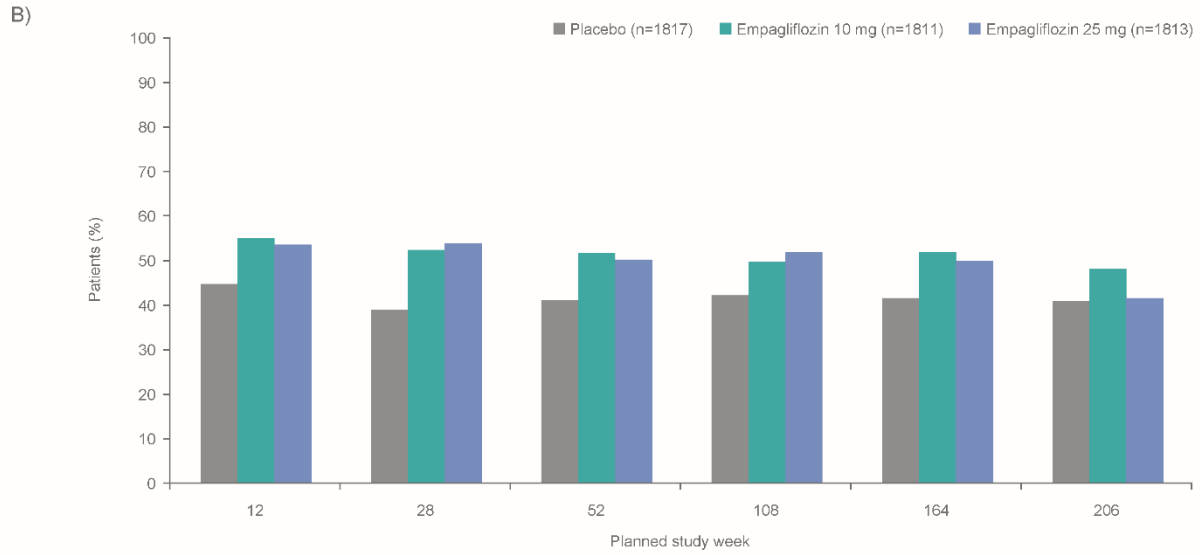


MMRM model on the overall population including subject as random effect and, among others, treatment, visit, and presumed resistant hypertension at baseline as well as their corresponding 2- and 3-way interactions as fixed effects (for details on other fixed effects and linear covariates, see "statistical analysis" section).

Supplemental Figure 3. Proportion of patients a) with presumed resistant hypertension and b) without presumed resistant hypertension who achieved systolic blood pressure <130 mm Hg during the trial in the placebo group and the two separate empagliflozin doses.

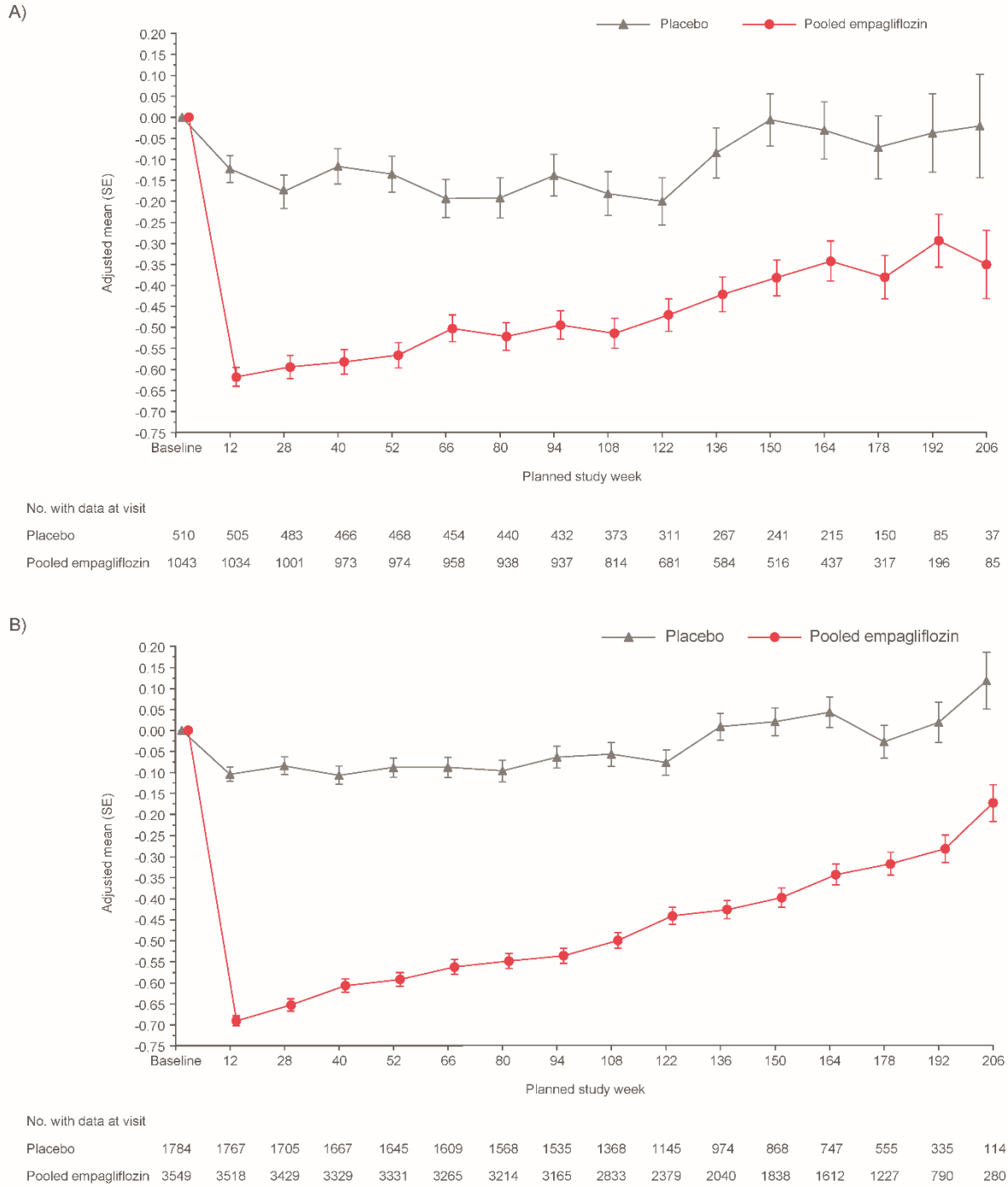


No. with data at visit						
Placebo	489	489	473	383	218	40
Empagliflozin 10 mg	510	505	492	412	222	40
Empagliflozin 25 mg	494	507	494	423	230	58



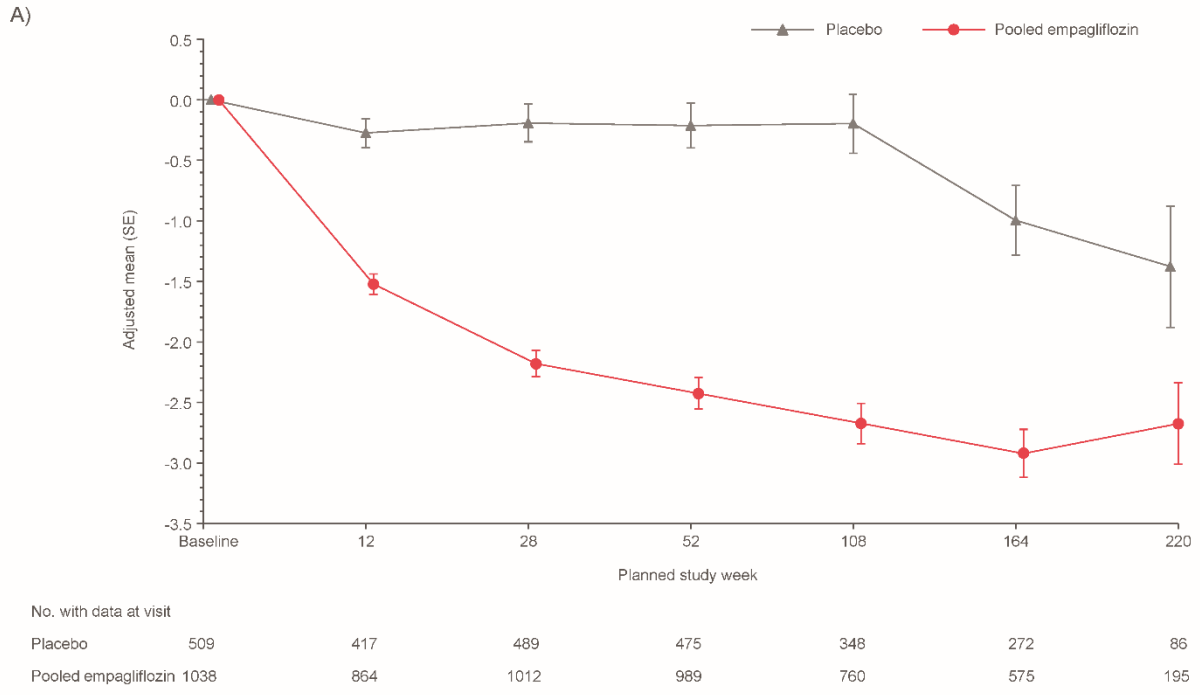
No. with data at visit						
Placebo	1712	1714	1660	1388	763	131
Empagliflozin 10 mg	1715	1731	1683	1442	812	159
Empagliflozin 25 mg	1704	1715	1676	1455	840	158

Supplemental Figure 4. Change in HbA1c levels (%) from baseline over time in patients a) with presumed resistant hypertension and b) without presumed resistant hypertension: mixed effect repeated measurement model results.

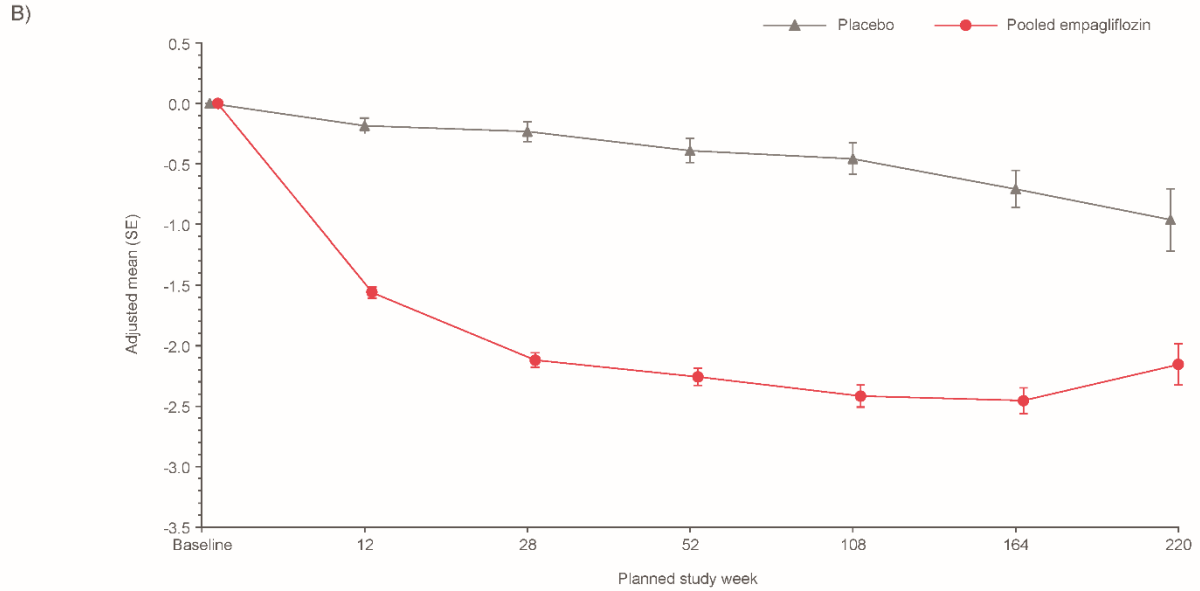


MMRM model on the overall population including subject as random effect and, among others, treatment, visit, and presumed resistant hypertension at baseline as well as their corresponding 2- and 3-way interactions as fixed effects (for details on other fixed effects and linear covariates, see "statistical analysis" section).

Supplemental Figure 5. Change in body weight (Kg) from baseline in patients a) with presumed resistant hypertension and b) without presumed resistant hypertension: mixed effect repeated measurement model results.



No. with data at visit							
Placebo	509	417	489	475	348	272	86
Pooled empagliflozin	1038	864	1012	989	760	575	195



No. with data at visit							
Placebo	1776	1498	1726	1663	1250	967	339
Pooled empagliflozin	3535	2920	3452	3363	2591	2058	777

MMRM model on the overall population including subject as random effect and, among others, treatment, visit, and presumed resistant hypertension at baseline as well as their corresponding 2- and 3-way interactions as fixed effects (for details on other fixed effects and linear covariates, see "statistical analysis" section).