

SUPPLEMENTARY DATA

Supplementary Table 1. Patient demographics and baseline characteristics (treated patients).

	Placebo (n=188)	Empagliflozin 10 mg (n=186)	Empagliflozin 25 mg (n=189)	Total (n=563)
Gender, n (%)				
Male	75 (40)	97 (52)	84 (44)	256 (45)
Female	113 (60)	89 (48)	105 (56)	307 (55)
Age (years)	55.3 ± 10.1	56.7 ± 8.7	58.0 ± 9.4	56.7 ± 9.5
Race, n (%)				
White	174 (93)	175 (94)	182 (96)	531 (94)
Black/African-American	8 (4)	7 (4)	4 (2)	19 (3)
Other	6 (3)	4 (2)	3 (2)	13 (2)
Time since diagnosis of type 2 diabetes, n (%)				
≤1 year	1 (1)	0	0	1 (<1)
>1 to 5 years	17 (9)	22 (12)	11 (6)	50 (9)
>5 to 10 years	40 (21)	44 (24)	38 (20)	122 (22)
>10 years	130 (69)	120 (65)	140 (74)	390 (69)
Body weight (kg)	95.5 ± 17.5	96.7 ± 17.9	95.9 ± 17.3	96.0 ± 17.5
Body mass index (kg/m ²)	34.7 ± 4.3	34.7 ± 3.8	35.0 ± 4.0	34.8 ± 4.1
HbA _{1c} (%)	8.33 ± 0.72	8.39 ± 0.74	8.29 ± 0.72	8.34 ± 0.73
HbA _{1c} (mmol/mol)	68 ± 7.9	68 ± 8.1	67 ± 7.9	68 ± 8.0
Fasting plasma glucose (mmol/L)	8.41 ± 2.54	8.83 ± 2.66	8.34 ± 2.70	8.52 ± 2.64
Systolic blood pressure (mmHg)	132.6 ± 15.8	134.2 ± 16.4	132.9 ± 14.2	133.3 ± 15.5
Diastolic blood pressure (mmHg)	78.2 ± 8.8	79.5 ± 8.5	78.7 ± 8.5	78.8 ± 8.6
eGFR (mL/min/1.73 m ² [MDRD equation])	83.4 ± 15.4	84.1 ± 17.8	84.4 ± 16.6	84.0 ± 16.6
Antidiabetes background medication, n (%)				
Metformin and insulin	135 (72)	128 (69)	137 (72)	400 (71)
Insulin only	53 (28)	58 (31)	52 (28)	163 (29)
Insulin dose (IU/day)	93.1 ± 48.6	89.9 ± 38.0	92.9 ± 45.8	92.0 ± 44.3
Insulin dose (IU/kg)	1.0 ± 0.4	0.9 ± 0.4	1.0 ± 0.4	1.0 ± 0.4
Basal (IU/day)	52.7 ± 31.6	49.3 ± 23.2	50.8 ± 25.0	–
Basal (IU/kg)	0.6 ± 0.3	0.5 ± 0.2	0.5 ± 0.3	–
Prandial (IU/day)	39.6 ± 29.1	40.0 ± 28.6	41.2 ± 34.9	–
Prandial (IU/kg)	0.4 ± 0.3	0.4 ± 0.3	0.4 ± 0.3	–
Number of prandial shots	2.6 ± 0.7	2.7 ± 0.6	2.6 ± 0.8	–
Number of prandial shots per day, n (%)				
0	2 (1)	0	4 (2)	6 (1)

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1	12 (6)	12 (6)	12 (6)	36 (6)
2	44 (23)	34 (18)	37 (20)	115 (20)
3	120 (64)	133 (72)	128 (68)	381 (68)
≥4	8 (4)	3 (2)	6 (3)	17 (3)
Metformin dose (mg/day)	2023 ± 586	1977 ± 527	2077 ± 511	2027 ± 542
≥1500 mg, <i>n</i> (%*)	121 (90)	118 (92)	131 (96)	370 (93)
<1500 mg, <i>n</i> (%*)	14 (10)	10 (8)	6 (4)	30 (8)

Data are mean ± SD unless otherwise indicated. *Percentage of patients receiving metformin. MDRD, Modification of Diet in Renal Disease. IU, international units.

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Supplementary Table 2. Summary of changes in blood pressure.

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
SBP at baseline (mmHg)	132.6 ± 1.2	134.2 ± 1.2	132.9 ± 1.0
SBP at week 18 (mmHg)	131.7 ± 1.1	130.2 ± 1.1	130.3 ± 1.0
Change from baseline in SBP (mmHg)	-1.2 ± 0.8	-3.6 ± 0.8	-2.9 ± 0.8
Difference vs. placebo (95% confidence interval); <i>P</i> value		-2.4 ± 1.2 (-4.7, -0.2); 0.037	-1.7 ± 1.1 (-3.9, 0.6); 0.141
SBP at week 52 (mmHg)	130.1 ± 1.3	130.8 ± 1.2	129.0 ± 1.3
Change from baseline in SBP (mmHg)	-2.9 ± 1.0	-3.4 ± 1.0	-3.8 ± 1.0
Difference vs. placebo (95% confidence interval); <i>P</i> value		-0.6 ± 1.4 (-3.4, 2.3); 0.700	-0.9 ± 1.4 (-3.7, 1.9); 0.531
DBP at baseline (mmHg)	78.2 ± 0.6	79.5 ± 0.6	78.7 ± 0.6
DBP at week 18 (mmHg)	78.2 ± 0.5	78.0 ± 0.7	77.8 ± 0.6
Change from baseline in DBP (mmHg)	-0.3 ± 0.5	-1.2 ± 0.5	-1.0 ± 0.5
Difference vs. placebo (95% confidence interval); <i>P</i> value		-1.0 ± 0.7 (-2.4, 0.4); 0.179	-0.7 ± 0.7 (-2.1, 0.7); 0.310
DBP at week 52 (mmHg)	78.0 ± 0.7	77.9 ± 0.8	76.6 ± 0.8
Change from baseline in DBP (mmHg)	-0.5 ± 0.6	-1.2 ± 0.6	-2.5 ± 0.6
Difference vs. placebo (95% confidence interval); <i>P</i> value		-0.7 ± 0.9 (-2.4, 1.1); 0.464	-1.9 ± 0.9 (-3.7, -0.1); 0.035

Data are mean ± SE except for change from baseline values and difference vs. placebo, which are adjusted mean ± SE. SBP and DBP at week 18: ANCOVA in FAS using LOCF. SBP and DBP at week 52: ANCOVA in PPS-completers-52 using LOCF. PPS-completers-52: patients in the FAS who were on treatment up to day 357 and did not have important protocol violations.

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Supplementary Table 3. Laboratory measurements.

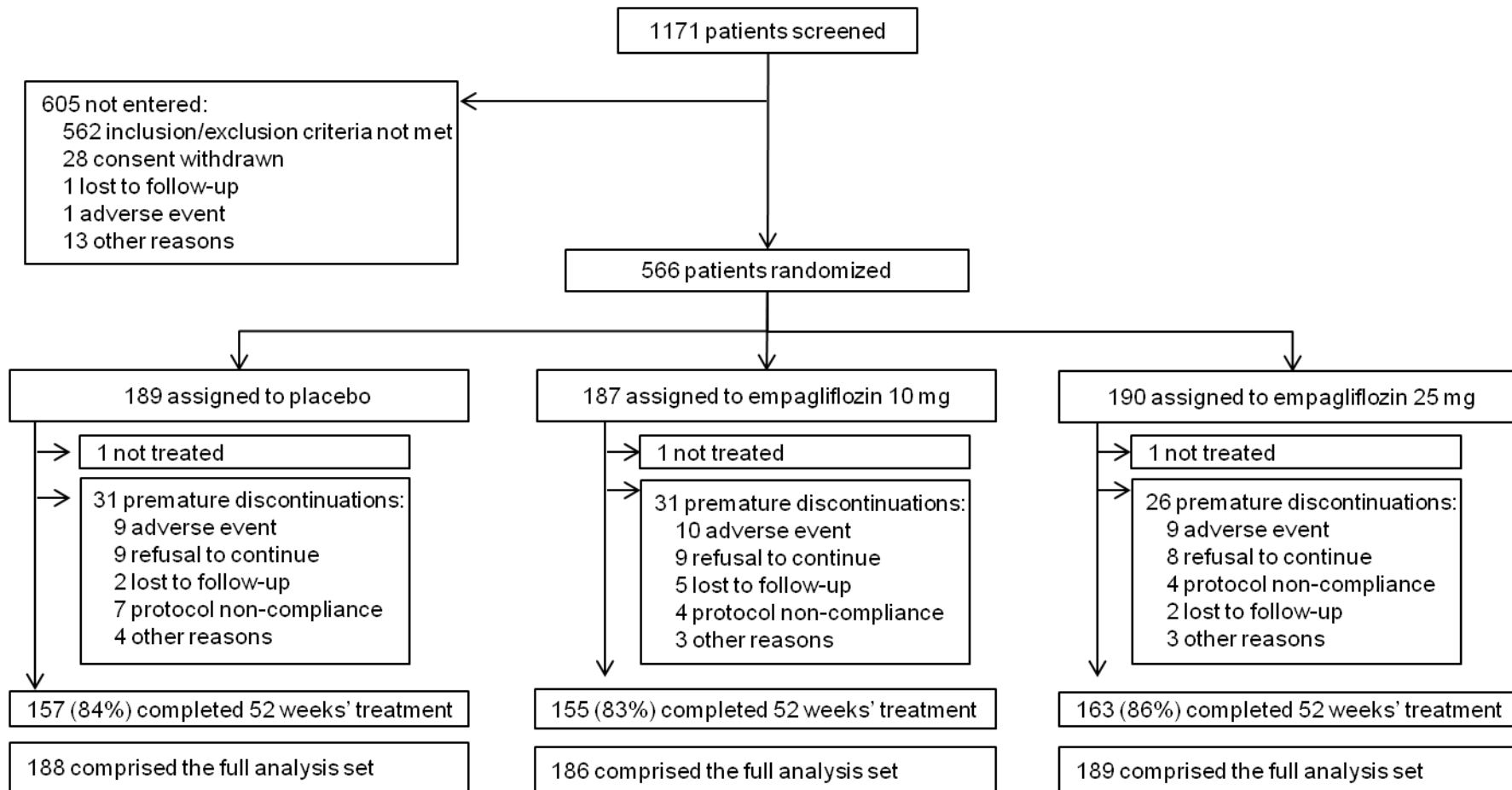
	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
Hematocrit (%) [*]	42.6 ± 5.8	0.7 ± 4.1	41.8 ± 5.3	4.8 ± 4.1	43.1 ± 5.4	4.4 ± 4.1
Follow-up [†]	41.4 ± 4.4	0.7 ± 2.9	41.4 ± 4.1	2.0 ± 2.8	41.9 ± 3.8	1.7 ± 2.7
Uric acid (μmol/L) [*]	326 ± 121	12 ± 81	326 ± 127	-23 ± 95	331 ± 123	-42 ± 92
eGFR (mL/min/1.73m ² [MDRD])	83.4 ± 5.4	-2.0 ± 11.4	84.1 ± 17.8	-1.6 ± 11.5	84.4 ± 16.6	-1.6 ± 11.3
Follow-up [†]	82.4 ± 5.0	-0.9 ± 11.5	83.9 ± 17.6	2.4 ± 13.0	83.8 ± 15.8	0.9 ± 11.8
Electrolytes (mmol/L) [*]						
Sodium	141 ± 2	1 ± 2	141 ± 2	1 ± 2	141 ± 2	1 ± 2
Potassium	4.2 ± 0.3	0.1 ± 0.3	4.2 ± 0.3	0.0 ± 0.4	4.2 ± 0.3	0.0 ± 0.3
Calcium	9.8 ± 0.4	-0.1 ± 0.4	9.8 ± 0.4	-0.1 ± 0.4	9.8 ± 0.4	-0.1 ± 0.3
Magnesium	1.8 ± 0.2	-0.0 ± 0.1	1.8 ± 0.2	0.1 ± 0.1	1.8 ± 0.2	0.1 ± 0.2
Phosphate	3.7 ± 0.3	0.0 ± 0.3	3.7 ± 0.3	0.1 ± 0.3	3.7 ± 0.3	0.1 ± 0.3
Total cholesterol (mmol/L) [‡]	4.79 ± 0.09	0.10 ± 0.06	4.70 ± 0.09	0.05 ± 0.06	4.78 ± 0.09	0.06 ± 0.06
Difference vs. placebo				-0.05 ± 0.08		-0.04 ± 0.08
<i>P</i> value				0.523		0.642
Follow-up [†]	4.79 ± 0.10	0.02 ± 0.09	4.71 ± 0.11	0.07 ± 0.08	4.78 ± 0.09	0.14 ± 0.07
HDL-cholesterol (mmol/L) [‡]	1.17 ± 0.02	-0.02 ± 0.01	1.19 ± 0.02	0.01 ± 0.01	1.20 ± 0.02	0.01 ± 0.01
Difference vs. placebo				0.03 ± 0.02		0.03 ± 0.02
<i>P</i> value				0.088		0.085
Follow-up [†]	1.17 ± 0.02	-0.03 ± 0.02	1.20 ± 0.03	0.00 ± 0.01	1.20 ± 0.03	0.03 ± 0.02
LDL-cholesterol (mmol/L) [‡]	2.73 ± 0.08	0.12 ± 0.05	2.68 ± 0.08	-0.06 ± 0.05	2.71 ± 0.07	0.06 ± 0.05
Difference vs. placebo				-0.18 ± 0.07		-0.06 ± 0.07
<i>P</i> value				0.012		0.391
Follow-up [†]	2.73 ± 0.08	0.05 ± 0.07	2.67 ± 0.09	-0.02 ± 0.07	2.70 ± 0.08	0.12 ± 0.06
Triglycerides (mmol/L) [‡]	2.02 ± 0.14	0.01 ± 0.10	1.94 ± 0.10	0.20 ± 0.10	1.92 ± 0.08	-0.03 ± 0.10
Difference vs. placebo				0.19 ± 0.14		-0.04 ± 0.14
<i>P</i> value				0.191		0.793
Follow-up [†]	2.03 ± 0.16	0.03 ± 0.10	1.93 ± 0.11	0.13 ± 0.09	1.90 ± 0.09	0.01 ± 0.08

Data are mean ± SD in treated set, unless otherwise indicated. Changes from baseline are last value on treatment unless otherwise stated.

^{*}Normalized to standard reference range. [†]Patients in FAS with data available 3-6 weeks after last dose of study medication based on observed results. [‡]Baseline data are mean ± SE, change from baseline data are adjusted mean ± SE based on ANCOVA using LOCF including values on rescue medication; data are week 52 except for follow-up.

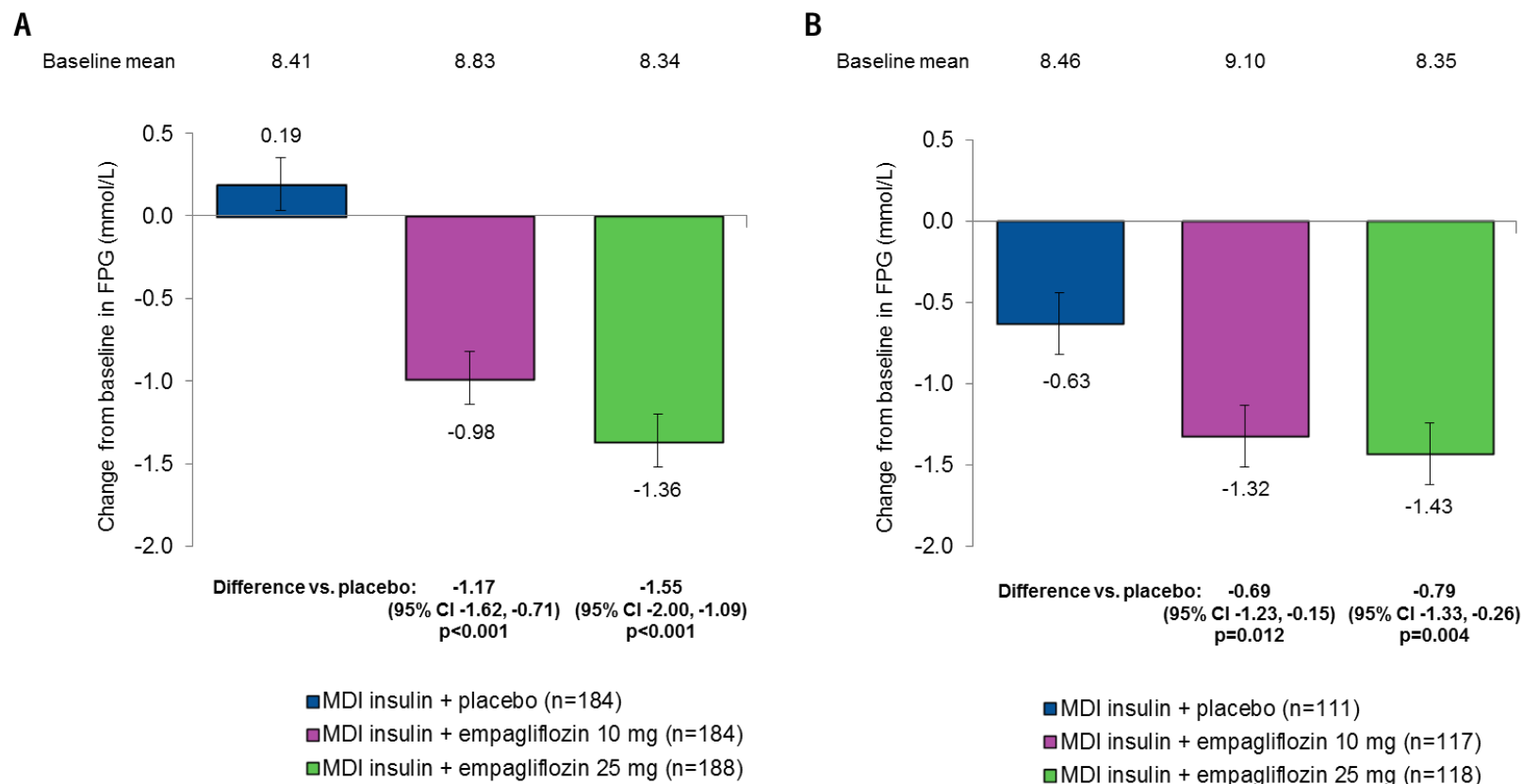
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Supplementary Figure 1. Study flow.



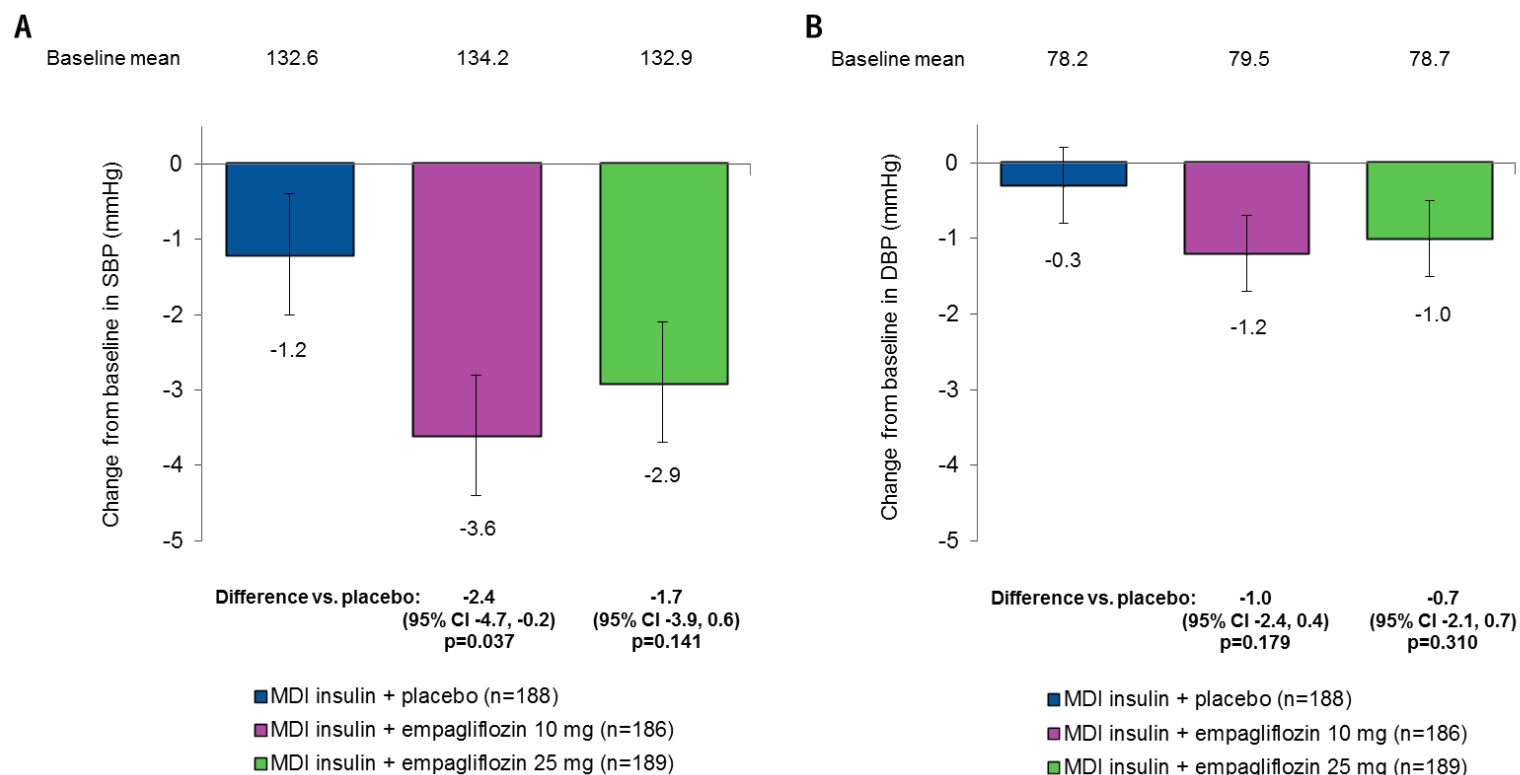
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Supplementary Figure 2. Effect of empagliflozin on FPG. (A) Change from baseline in FPG at week 18 (ANCOVA, full analysis set [FAS], last observation carried forward [LOCF] imputation at week 18; (B) change from baseline in FPG at week 52 (ANCOVA, PPS-completers-52, LOCF). Data are mean±SE at baseline and adjusted mean±SE on treatment. PPS-completers-52 set: patients who were on treatment up to day 357 and did not have important protocol violations. Blue bars = MDI insulin + placebo; purple bars = MDI insulin + empagliflozin 10 mg; green bars = MDI insulin + empagliflozin 25 mg.



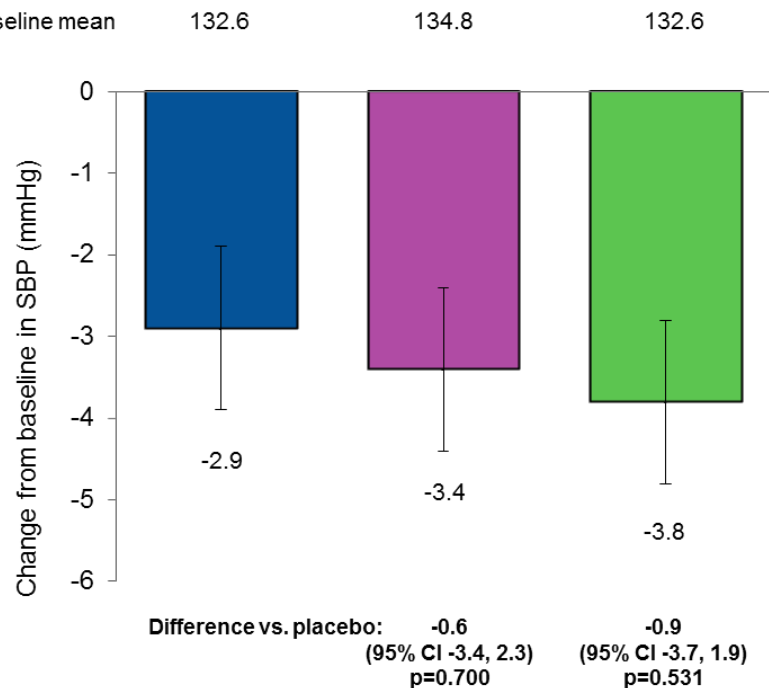
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Supplementary Figure 3. Effect of empagliflozin on blood pressure. (A) Change from baseline in SBP at week 18 (ANCOVA, full analysis set [FAS], last observation carried forward [LOCF]); (B) change from baseline in DBP at week 18 (ANCOVA, FAS, LOCF); (C) change from baseline in SBP at week 52 (ANCOVA, PPS-completers-52, LOCF); (D) change from baseline in DBP at week 52 (ANCOVA, PPS-completers-52, LOCF). Data are mean±SE at baseline and adjusted mean±SE on treatment. PPS-completers-52 set: patients who were on treatment up to day 357 and did not have important protocol violations. Blue bars = MDI insulin + placebo; purple bars = MDI insulin + empagliflozin 10 mg; green bars = MDI insulin + empagliflozin 25 mg.



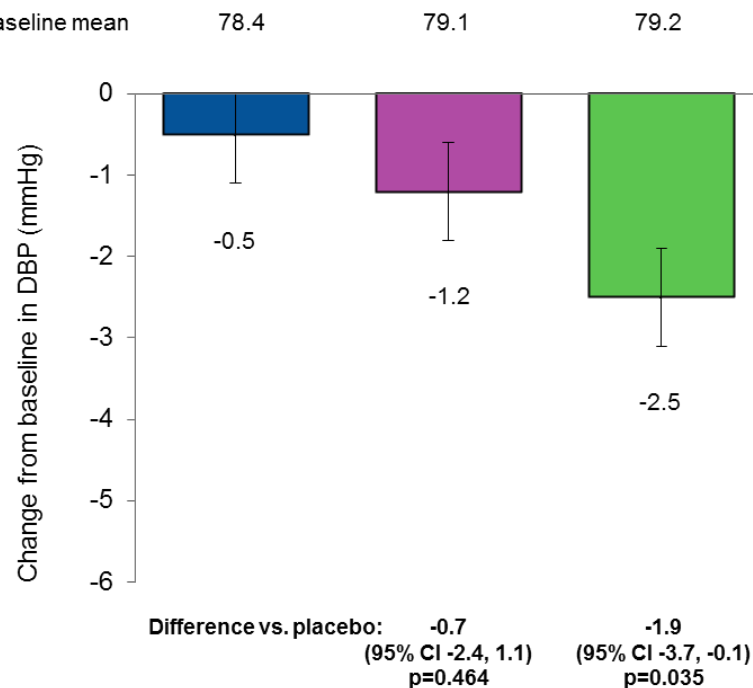
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C



- MDI insulin + placebo (n=115)
- MDI insulin + empagliflozin 10 mg (n=119)
- MDI insulin + empagliflozin 25 mg (n=118)

D



- MDI insulin + placebo (n=115)
- MDI insulin + empagliflozin 10 mg (n=119)
- MDI insulin + empagliflozin 25 mg (n=118)