

## **Effect of dapagliflozin in DAPA-HF according to background glucose-lowering therapy**

### **SUPPLEMENT**

**Supplemental Table 1: Baseline Characteristics by glucose-lowering therapy use at randomization in patients with diabetes**

	No glucose lowering therapy n=543	Glucose lowering therapy n=1,596	p-value
Age – yr	66.8±10.7	66.4±9.6	0.50
Sex - no (%)			0.24
Female	131 (24.1)	346 (21.7)	
Male	412 (75.9)	1,250 (78.3)	
Race – no. (%)†			0.66
White	370 (68.1)	1,119 (70.1)	
Asian	135 (24.9)	356 (22.3)	
Black	31 ( 5.7)	97 ( 6.1)	
Other	7 ( 1.3)	24 ( 1.5)	
Region – no. (%)			<0.001
Asia/Pacific	132 (24.3)	347 (21.7)	
Europe	270 (49.7)	681 (42.7)	
North America	75 (13.8)	260 (16.3)	
South America	66 (12.2)	308 (19.3)	
NYHA functional classification – no. (%)			0.002
II	316 (58.2)	1,046 (65.5)	
III	217 (40.0)	538 (33.7)	
IV	10 ( 1.8)	12 ( 0.8)	
Heart rate – beats/min	71.7±11.0	72.5±11.5	0.14
Systolic Blood Pressure – mmHg	121.4±15.7	124.0±16.8	0.002
Left ventricular ejection fraction – %	30.9±6.9	31.3±6.6	0.16
Median NT-proBNP (IQR) – pg/ml	1584.8 (930.6-3049.3)	1444.6 (887.3-2763.3)	0.057
Median KCCQ-TSS (IQR)	75.0 (55.2-90.6)	75.0 (56.2-91.7)	0.63
HbA1c – %	6.9±1.2	7.5±1.6	<0.001
HbA1c – mmol/mol	52.3±12.8	59.0±17.6	<0.001
Median time from diagnosis of diabetes to randomization (years)	0.5 (0.0-5.0)	8.6 (3.9-15.0)	<0.001
Body-mass index§	28.4±5.7	29.6±6.1	<0.001
Principal cause of heart failure – no. (%)			0.29
Ischaemic	323 (59.5)	1,010 (63.3)	
Non-ischaemic	178 (32.8)	476 (29.8)	
Unknown	42 ( 7.7)	110 ( 6.9)	
Medical history – no. (%)			
Hospitalization for heart failure	263 (48.4)	786 (49.2)	0.74
Atrial fibrillation	224 (41.3)	572 (35.8)	0.024
Estimated GFR – ml/min/1.73 m <sup>2</sup> of body-surface area	64.3±19.6	63.0±19.3	0.18
Estimated GFR rate < 60 ml/min/1.73 m <sup>2</sup> – no. (%)	238 (43.8)	744 (46.6)	0.26
Device therapy – no (%)			
Implantable cardioverter-defibrillator‡	140 (25.8)	437 (27.4)	0.47
Cardiac-resynchronization therapy*	32 ( 5.9)	119 ( 7.5)	0.22
Heart failure medication at randomization visit – no (%)			
Diuretic	476 (87.7)	1,408 (88.2)	0.73
ACE-inhibitor	297 (54.7)	875 (54.8)	0.96
ARB	152 (28.0)	463 (29.0)	0.65

Sacubitril-valsartan	66 (12.2)	163 (10.2)	0.21
Beta-blocker	518 (95.4)	1,549 (97.1)	0.064
Mineralocorticoid receptor antagonist	398 (73.3)	1,131 (70.9)	0.28
Digitalis	116 (21.4)	313 (19.6)	0.38
Glucose lowering medication — no.(%)			
Metformin	0 ( 0.0)	1,020 (63.9)	-
Sulfonylurea	0 ( 0.0)	440 (27.6)	-
DPP-4 inhibitor	0 ( 0.0)	310 (19.4)	-
Insulin	0 ( 0.0)	540 (33.8)	-
GLP-1 receptor agonist	0 ( 0.0)	21 ( 1.3)	-
Alpha glucosidase inhibitors	0 ( 0.0)	91 ( 5.7)	-
Thiazolidinediones	0 ( 0.0)	12 ( 0.8)	-
Other medications**	0 ( 0.0)	31 ( 1.9)	-

ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, DPP-4 dipeptidyl peptidase 4, GFR glomerular filtration rate, GLP-1 glucagon-like peptide 1, IQR interquartile range, LVEF left ventricular ejection fraction, MRA mineralocorticoid receptor antagonist, N-terminal pro-B-type natriuretic peptide and NYHA New York Heart Association. KCCQ-TSS Kansas City Cardiomyopathy Questionnaire total symptom score - range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. A score of 75 or above is considered to reflect satisfactory health status.

† Race was reported by the investigators

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Either implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator.

\*Cardiac-resynchronisation therapy with or without a defibrillator.

\*\*Other medications were: glinides (n=28[1.8%]); aldose reductase inhibitors (n=2[0.1%]); and SGLT2-inhibitors (n=2[0.1%]).

**Supplemental Table 2: Baseline Characteristics by class of glucose-lowering therapy at randomization in patients with diabetes**

	<b>All patients n=2,139</b>	<b>Biguanide n=1,020</b>	<b>Sulfonylurea n=440</b>	<b>DPP-IV inhibitor n=310</b>	<b>Insulin n=540</b>
Age – yr	66.5±9.9	65.9±9.6	66.3±9.8	68.5±9.4	66.1±8.9
Sex - no (%)					
Female	477 (22.3)	230 (22.5)	96 (21.8)	58 (18.7)	128 (23.7)
Male	1,662 (77.7)	790 (77.5)	344 (78.2)	252 (81.3)	412 (76.3)
Race – no. (%)†					
White	1,489 (69.6)	745 (73.0)	304 (69.1)	151 (48.7)	404 (74.8)
Asian	491 (23.0)	192 (18.8)	106 (24.1)	144 (46.5)	87 (16.1)
Black or African American	128 (6.0)	64 (6.3)	26 ( 5.9)	13 (4.2)	41 (7.6)
Other	31 (1.4)	19 (1.9)	4 ( 0.9)	2 (0.6)	8 (1.5)
Region – no. (%)					
Asia/Pacific	479 (22.4)	186 (18.2)	103 (23.4)	143 (46.1)	82 (15.2)
Europe	951 (44.5)	445 (43.6)	201 (45.7)	93 (30.0)	228 (42.2)
North America	335 (15.7)	153 (15.0)	71 (16.1)	48 (15.5)	123 (22.8)
South America	374 (17.5)	236 (23.1)	65 (14.8)	26 (8.4)	107 (19.8)
NYHA functional classification – no. (%)					
II	1,362 (63.7)	684 (67.1)	274 (62.3)	239 (77.1)	335 (62.0)
III	755 (35.3)	331 (32.5)	164 (37.3)	69 (22.3)	198 (36.7)
IV	22 (1.0)	5 (0.5)	2 ( 0.5)	2 (0.6)	7 (1.3)
Heart rate – beats/min	72.3±11.3	73.0±11.7	74.3±11.6	72.6±11.1	71.6±11.4
Systolic Blood Pressure – mmHg	123.3±16.5	124.0±17.0	125.3±16.9	123.6±17.8	124.3±17.1
Left ventricular ejection fraction – %	31.2±6.7	31.4±6.5	31.1±6.7	31.4±6.7	31.6±6.4
Median NT-proBNP (IQR) – pg/ml	1484 (894-2818)	1432 (867-2617)	1504.7 (887.5-2741.2)	1348 (876-2337)	1481 (891-2876)
Median KCCQ-TSS (IQR)	75.0 (56.3-91.7)	75.0 (57.3-91.7)	77.1 (57.3- 91.7)	83.3 (64.6-97.9)	69.8 (50.0-87.5)
HbA1c – %	7.4±1.5	7.5±1.7	7.8±1.7	7.3±1.3	8.2±1.6
HbA1c – mmol/mol	57.3±16.8	58.2±18.2	61.6±18.9	56.5±14.5	66.7±17.9
Median time from diagnosis of diabetes to randomization (years)	6.6 (1.7-12.8)	7.7 (3.4-14.0)	8.3 (4.4-15.1)	9.9 (4.9-16.4)	12.9 (7.7-18.3)

Body-mass index§	29.3±6.0	29.7±6.0	29.3±5.9	28.2±6.3	30.7±6.4
Principal cause of heart failure – no. (%)					
Ischemic	1,333 (62.3)	617 (60.5)	281 (63.9)	189 (61.0)	369 (68.3)
Non-ischemic	654 (30.6)	323 (31.7)	128 (29.1)	101 (32.6)	135 (25.0)
Unknown	152 (7.1)	80 (7.8)	31 ( 7.0)	20 (6.5)	36 (6.7)
Medical history – no. (%)					
Hospitalization for heart failure	1,049 (49.0)	486 (47.6)	206 (46.8)	151 (48.7)	274 (50.7)
Atrial fibrillation	796 (37.2)	358 (35.1)	142 (32.3)	108 (34.8)	185 (34.3)
Estimated GFR – ml/min/1.73 m <sup>2</sup> of body-surface area	63.4±19.4	66.3±19.0	63.5±19.5	59.1±17.9	59.0±19.6
Estimated GFR rate < 60 ml/min/1.73 m <sup>2</sup> – no. (%)	982 (45.9)	402 (39.4)	198 (45.0)	164 (52.9)	304 (56.3)
Device therapy – no (%)					
Implantable cardioverter-defibrillator‡	577 (27.0)	259 (25.4)	103 (23.4)	74 (23.9)	173 (32.0)
Cardiac-resynchronization therapy*	151 (7.1)	70 (6.9)	24 ( 5.5)	26 (8.4)	52 (9.6)
Heart failure medication at randomization visit – no (%)					
Diuretic	1,884 (88.1)	889 (87.2)	398 (90.5)	264 (85.2)	500 (92.6)
ACE-inhibitor	1,172 (54.8)	571 (56.0)	229 (52.0)	134 (43.2)	302 (55.9)
ARB	615 (28.8)	304 (29.8)	136 (30.9)	111 (35.8)	142 (26.3)
Sacubitril-valsartan	229 (10.7)	100 (9.8)	42 ( 9.5)	41 (13.2)	60 (11.1)
Beta-blocker	2,067 (96.6)	986 (96.7)	427 (97.0)	295 (95.2)	527 (97.6)
Mineralocorticoid receptor antagonist	1,529 (71.5)	743 (72.8)	311 (70.7)	194 (62.6)	368 (68.1)
Digitalis	429 (20.1)	209 (20.5)	93 (21.1)	45 (14.5)	106 (19.6)
Glucose lowering medication — no.(%)					
Metformin	1,020 (47.7)	1,020 (100.0)	269 (61.1)	173 (55.8)	223 (41.3)
Sulfonylurea	440 (20.6)	269 (26.4)	440 (100.0)	82 (26.5)	62 (11.5)
DPP-4 inhibitor	310 (14.5)	173 (17.0)	82 (18.6)	310 (100.0)	75 (13.9)
Insulin	540 (25.2)	223 (21.9)	6 ( 1.4)	75 (24.2)	540 (100.0)
GLP-1 receptor agonist	21 (1.0)	9 (0.9)	62 (14.1)	1 (0.3)	11 (2.0)
Alpha glucosidase inhibitors	91 (4.3)	40 (3.9)	1 ( 0.2)	19 (6.1)	23 (4.3)
Thiazolidinediones	12 (0.6)	9 (0.9)	23 ( 5.2)	5 (1.6)	1 (0.2)
Other medications**	31 (1.4)	10 (1.0)	3 ( 0.7)	9 (2.9)	10 (1.9)

ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, DPP-4 dipeptidyl peptidase 4, GFR glomerular filtration rate, GLP-1 glucagon-like peptide 1, IQR interquartile range, LVEF left ventricular ejection fraction, MRA mineralocorticoid receptor antagonist, N-terminal pro-B-type natriuretic peptide and NYHA New York Heart Association. KCCQ-TSS Kansas City Cardiomyopathy Questionnaire total symptom score - range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. A score of 75 or above is considered to reflect satisfactory health status.

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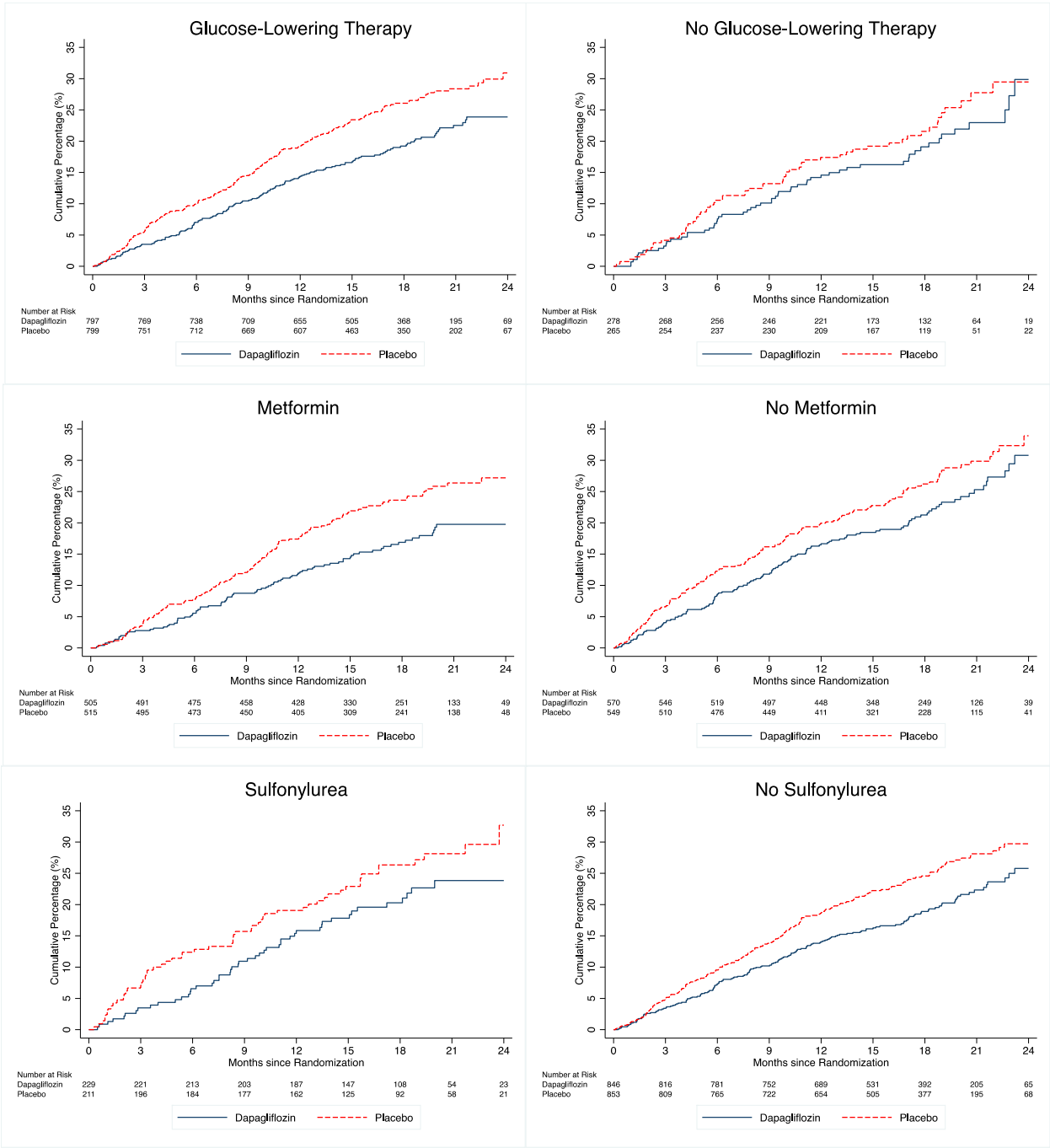
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

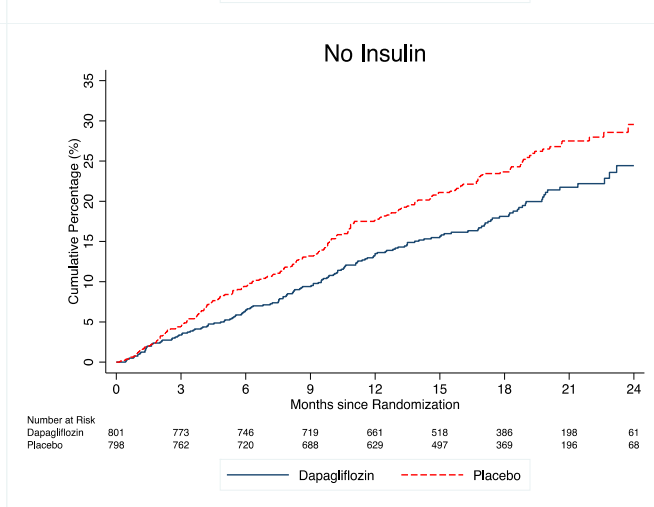
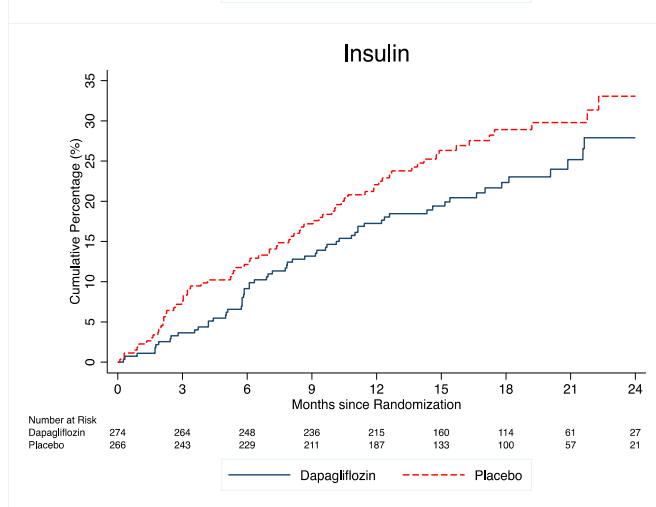
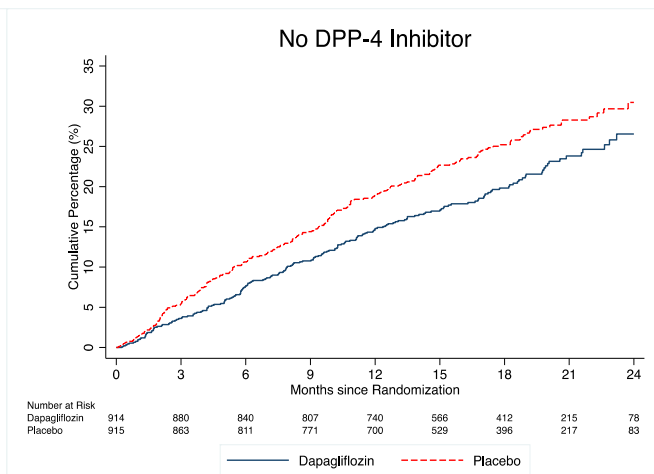
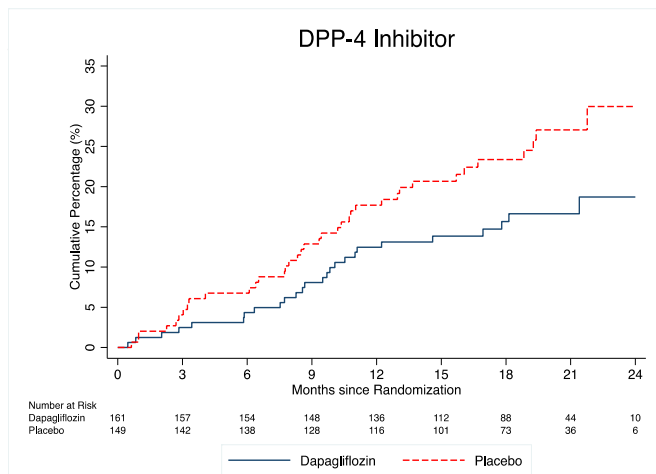
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\*Cardiac-resynchronisation therapy with or without a defibrillator.

\*\*Other medications were: glinides (n=28[1.8%]); aldose reductase inhibitors (n=2[0.1%]); and SGLT2-inhibitors (n=2[0.1%])

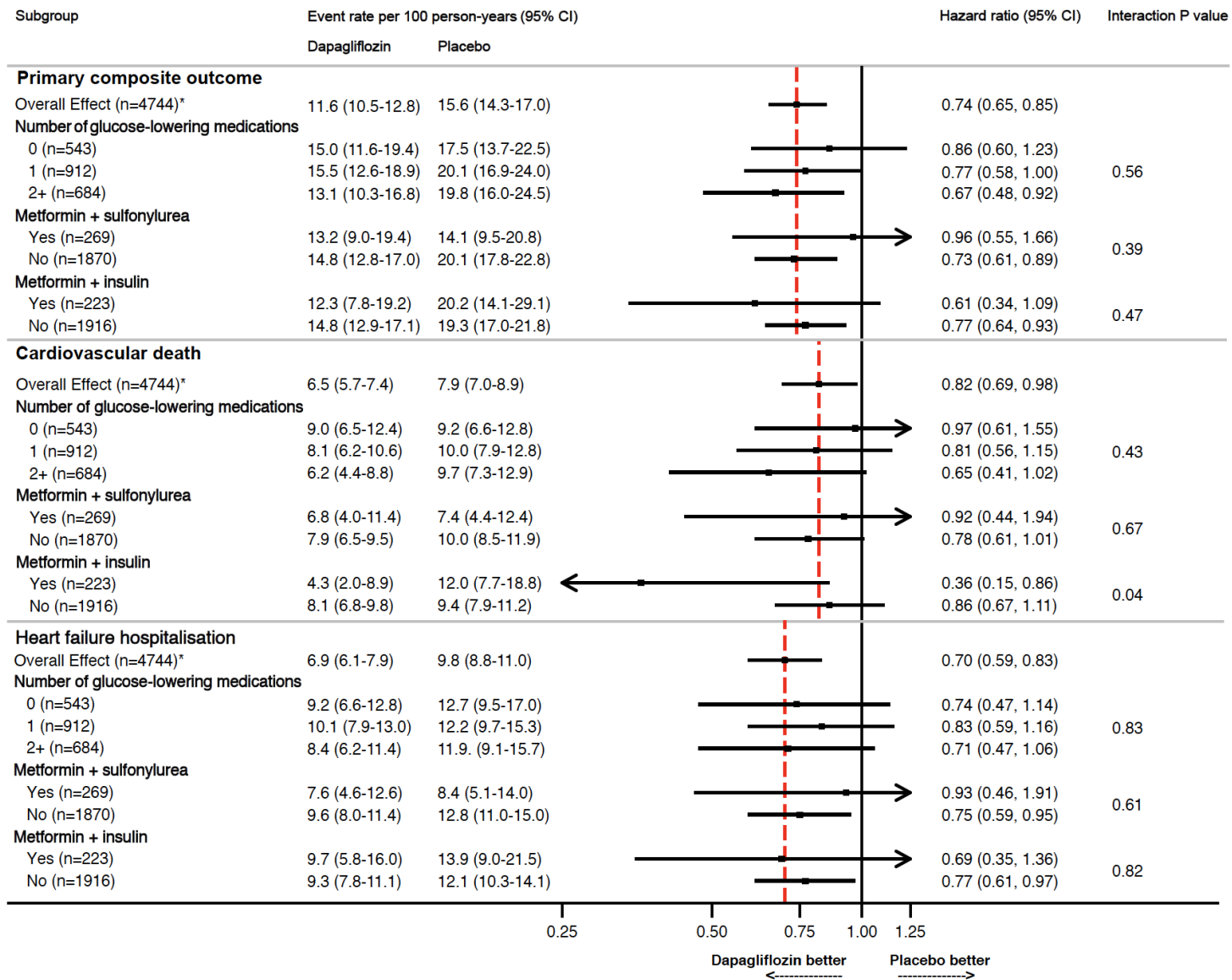
**Supplemental Figure 1: Cumulative incidence of cardiovascular death or worsening heart failure event by background glucose-lowering therapy use in patients with diabetes**





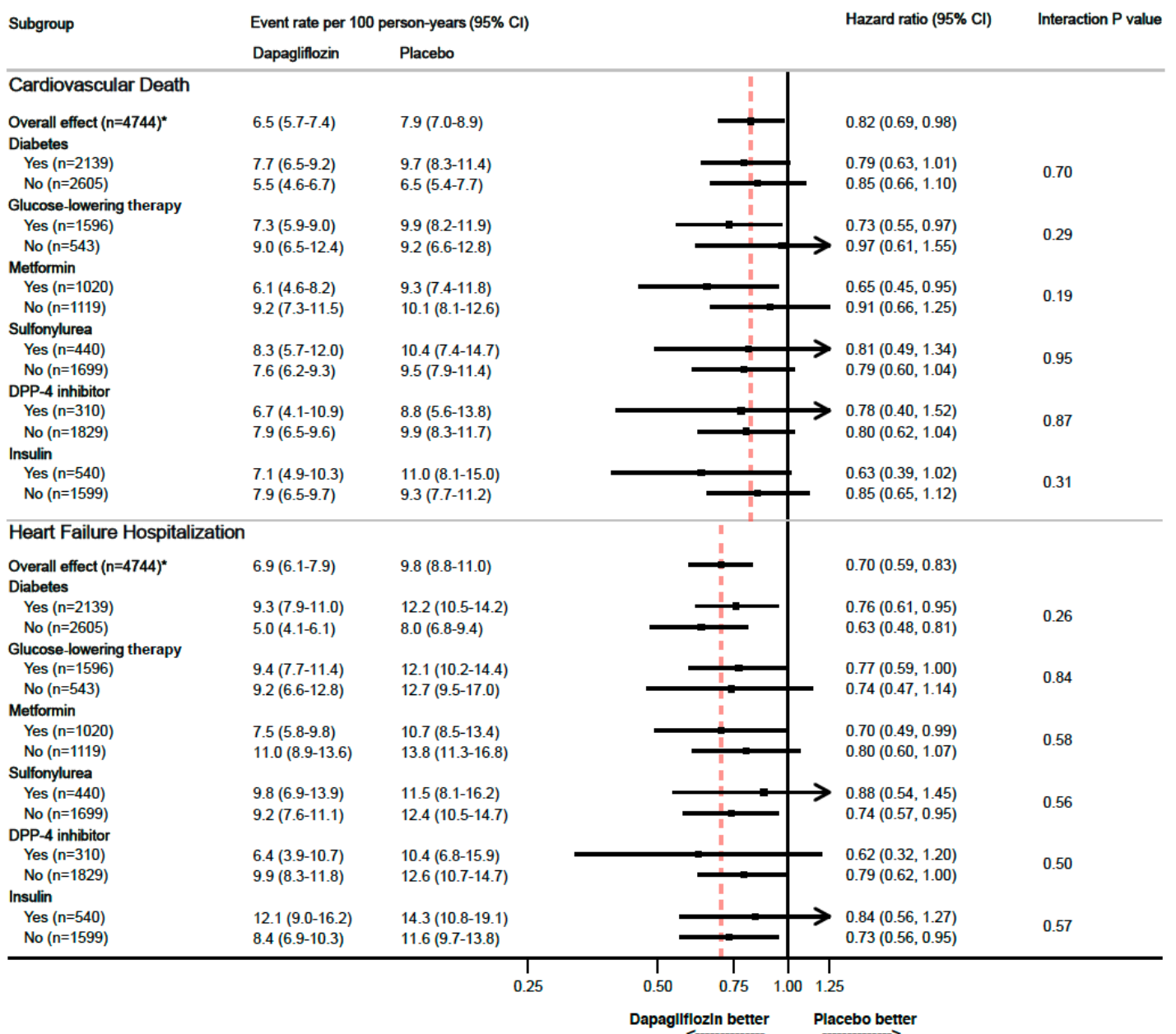


**Supplemental Figure 2: Effect of dapagliflozin compared to placebo on the risk of outcomes by combinations of background glucose-lowering therapy in patients with diabetes**



\*Overall effect calculated in all randomized patients (n=4744)

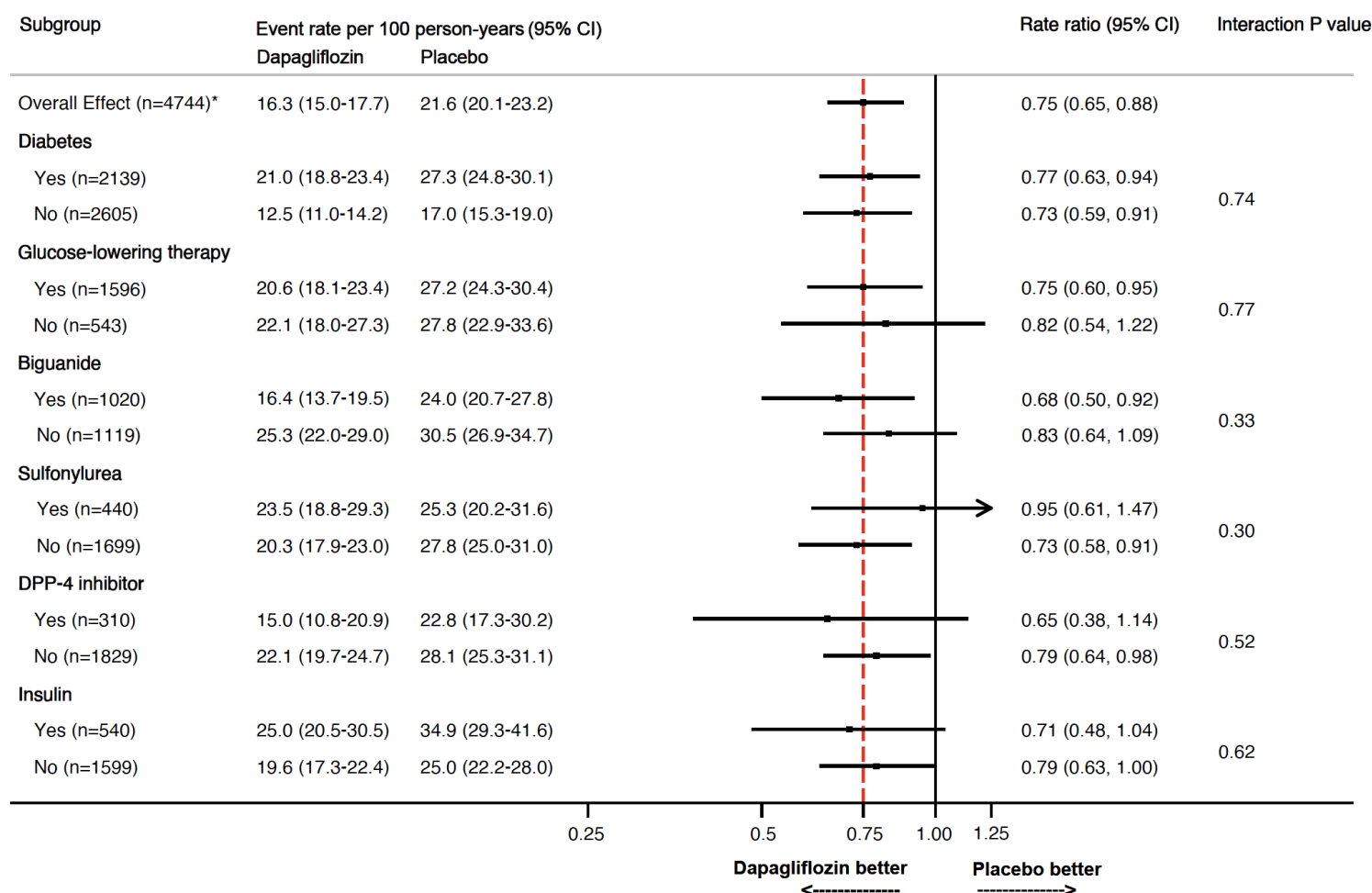
**Supplemental Figure 3: Effect of dapagliflozin compared to placebo on the risk of cardiovascular death and heart failure hospitalization by background glucose-lowering therapy in patients with diabetes**



\*Overall effect calculated in all randomized patients (n=4744)

DPP-4 = dipeptidyl peptidase-4; CI = confidence interval.

**Supplemental Figure 4: Effect of dapagliflozin compared to placebo on the risk of first and recurrent HF hospitalizations and cardiovascular death by background glucose-lowering therapy in patients with diabetes**

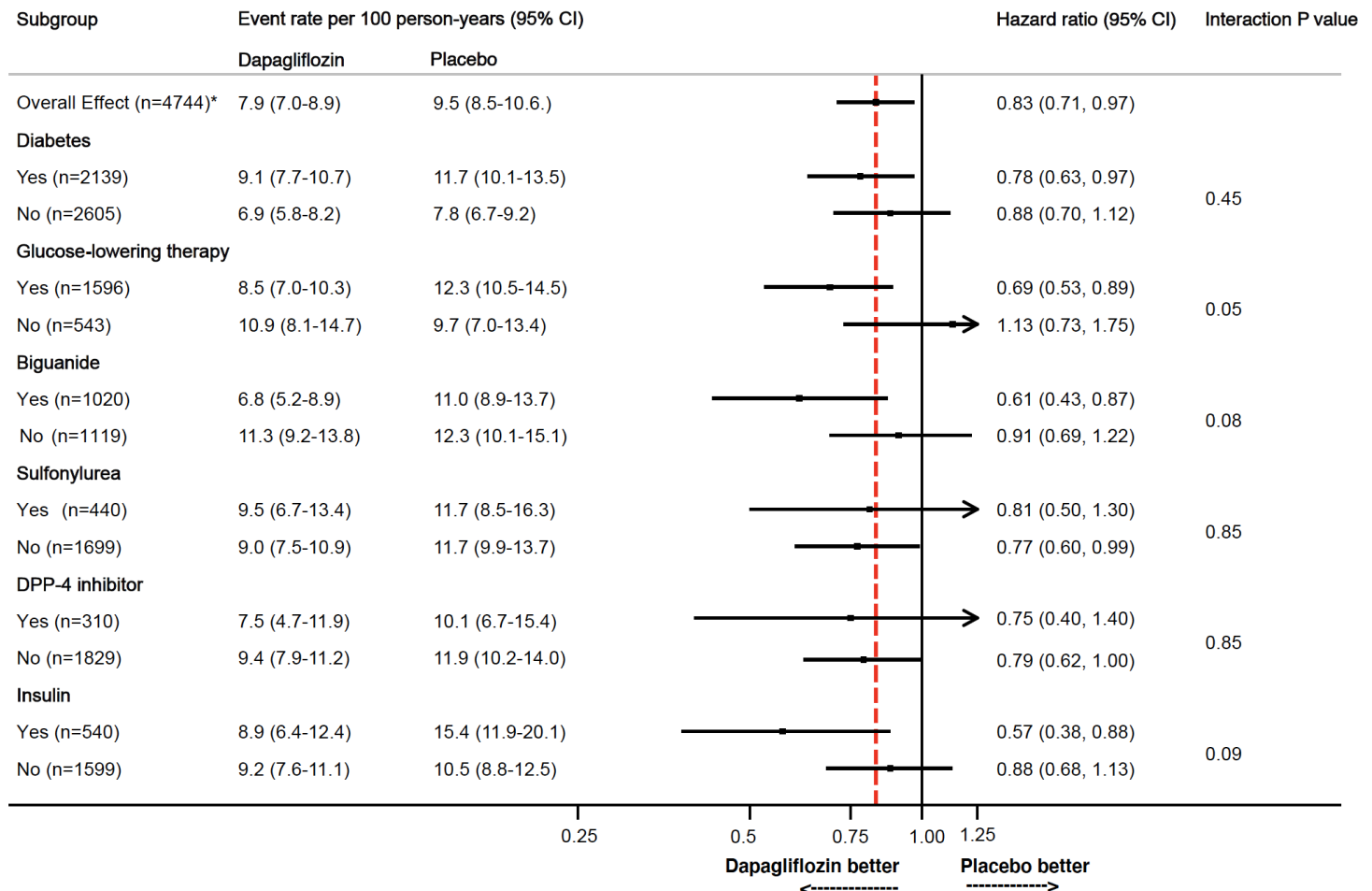


\*Overall effect calculated in all randomized patients (n=4744)

The treatment effect estimate is displayed as a rate ratio which was calculated using a semiparametric proportional-rates model to calculate total (including recurrent) events (as described by Lin DY et al. in *Semiparametric regression for the mean and rate functions of recurrent events. J R Stat Soc Series B Stat Methodol* 2000; 62: 711-30)

DPP-4 = dipeptidyl peptidase-4; CI = confidence interval.

**Supplemental Figure 5: Effect of dapagliflozin compared to placebo on the risk of death from any cause by background glucose-lowering therapy in patients with diabetes**



\*Overall effect calculated in all randomized patients (n=4744)

DPP-4 = dipeptidyl peptidase-4; CI = confidence interval.