

**SUPPLEMENTAL MATERIAL**

Initial decline (“dip”) in estimated glomerular filtration rate following initiation of dapagliflozin in patients with heart failure and reduced ejection fraction: Insights from DAPA-HF.

Tables S1-S4

Figures S1-S4

**Supplementary Table 1: Change in eGFR at 14 days by baseline eGFR**

	eGFR $\geq 75$		eGFR $< 75 - \geq 60$		eGFR $< 60 - \geq 45$		eGFR $< 45$	
	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin
<b>Overall mean change</b>								
Mean change in eGFR (95%CI) - ml/min/1.73m <sup>2</sup>	-2.3 (-3.0,-1.5)	-5.0 (-5.7,-4.3)	-0.9 (-1.7,-0.1)	-4.6 (-5.4,-3.8)	-0.2 (-0.9,0.5)	-3.7 (-4.4,-3.0)	-0.5 (-1.3,0.3)	-2.9 (-3.7,-2.1)
Between treatment difference (95% CI)	-2.7 (-3.8, -1.7)		-3.7 (-4.8,-2.5)		-3.5 (-4.5,-2.5)		-2.4 (-3.5,-1.3)	
<b>Overall percentage change</b>								
Mean change in eGFR (95% CI) - %	-2.6 (-3.4,-1.7)	-5.7 (-6.5,-4.8)	-1.4 (-2.6,-0.2)	-6.9 (-8.1,-5.7)	-0.5 (-1.8, 0.9)	-7.2 (-8.6,-5.8)	-1.2 (-3.4, 0.9)	-7.5 (-9.6,-5.4)
Between treatment difference (95% CI)	-3.1 (-4.3,-1.9)		-5.5 (-7.2,-3.8)		-6.7 (-8.7,-4.8)		-6.3 (-9.3,-3.3)	
<b><math>\geq 5</math>ml/min decrease in eGFR</b>								
Number with decrease (%)	227/725 (31.3)	357/767 (46.5)	212/648 (32.7)	320/601 (53.2)	143/586 (24.4)	280/591 (47.4)	77/350 (22.0)	127/350 (36.3)

OR for decrease with dapagliflozin over placebo (95%CI)	1.9 (1.6-2.4)		2.3 (1.9-3.0)		2.8 (2.2-3.6)		2.0 (1.5-2.8)	
<b>≥ 10 ml/min decrease in eGFR</b>								
Number with decrease (%)	124/725 (17.1)	213/767 (27.8)	92/648 (14.2)	160/601 (26.6)	46/586 (7.9)	119/591 (20.1)	19/350 (5.4)	31/350 (8.9)
OR for decrease with dapagliflozin over placebo (95%CI)	1.9 (1.5-2.4)		2.2 (1.7-2.9)		3.0 (2.1-4.3)		1.7 (0.9-3.1)	

CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; WRF, worsening renal function

**Supplementary Table 2a.** Baseline characteristics according to extent of initial eGFR decline (“dip”) – all patients.

	<b>No decline</b>	<b>Up to 10% decline</b>	<b>&gt;10% decline</b>	<b>p-value (trend)</b>
	<b>N=1,797</b>	<b>N=1,455</b>	<b>N=1,366</b>	
Age	65.5±11.1	66.2±10.9	67.6±10.5	<0.001
Sex				0.03
Female	408 (22.7)	305 (21.0)	360 (26.4)	
Male	1,389 (77.3)	1,150 (79.0)	1,006 (73.6)	
Race				0.002
Asian	424 (23.6)	365 (25.1)	291 (21.3)	
Black	77 ( 4.3)	66 ( 4.5)	78 ( 5.7)	
Other	13 ( 0.7)	28 ( 1.9)	27 ( 2.0)	
White	1,283 (71.4)	996 (68.5)	970 (71.0)	
Region				<0.001
Asia/Pacific	419 (23.3)	359 (24.7)	284 (20.8)	
Europe	865 (48.1)	641 (44.1)	592 (43.3)	
North America	224 (12.5)	230 (15.8)	204 (14.9)	
South America	289 (16.1)	225 (15.5)	286 (20.9)	
NYHA class				0.91
II	1,210 (67.3)	1,015 (69.8)	913 (66.8)	
III	571 (31.8)	429 (29.5)	438 (32.1)	
IV	16 ( 0.9)	11 ( 0.8)	15 ( 1.1)	
KCCQ-TSS	78.1 (60.4-91.7)	79.2 (60.4-92.7)	76.0 (56.2-91.7)	0.15
Pulse (bpm)	71.8±11.8	71.1±11.4	71.5±11.9	0.25
Systolic BP (mmHg)	121.3±15.6	122.0±16.6	122.7±16.9	0.06
LVEF (%)	31.1±6.8	30.9±6.9	31.3±6.6	0.54
Main etiology of HF				0.23
Ischemic	1,038 (57.8)	793 (54.5)	766 (56.1)	
Non-ischemic	617 (34.3)	551 (37.9)	481 (35.2)	
Unknown	142 ( 7.9)	111 ( 7.6)	119 ( 8.7)	
Prior HF hospitalization	868 (48.3)	666 (45.8)	663 (48.5)	0.99
Time from diagnosis of HF				0.027
0 - 3 months	58 ( 3.2)	51 ( 3.5)	35 ( 2.6)	
>3 - 6 months	171 ( 9.5)	107 ( 7.4)	106 ( 7.8)	
>6 - 12 months	227 (12.6)	167 (11.5)	148 (10.8)	
>1 - 2 years	277 (15.4)	195 (13.4)	198 (14.5)	
>2 - 5 years	415 (23.1)	325 (22.3)	325 (23.8)	
>5 years	649 (36.1)	610 (41.9)	554 (40.6)	
Time from last HF hospitalization				0.89
0 - 3 months	139 (16.0)	119 (17.9)	98 (14.8)	

>3 - 6 months	161 (18.5)	118 (17.7)	120 (18.1)	
>6 - 12 months	212 (24.4)	142 (21.3)	158 (23.8)	
>1 - 2 years	129 (14.9)	106 (15.9)	107 (16.1)	
>2 - 5 years	130 (15.0)	99 (14.9)	97 (14.6)	
>5 years	97 (11.2)	82 (12.3)	83 (12.5)	
NT-proBNP (pg/ml)	1376.1 (829.3-2485.1)	1431.4 (841.7-2620.6)	1520.7 (897.0-2752.8)	0.01
eGFR (mL/min/1.73 m <sup>2</sup> )	65.8±19.2	68.4±20.6	63.0±18.0	0.001
Baseline HbA1c (%)	6.5±1.4	6.4±1.3	6.6±1.4	0.08
Body Mass Index (kg/m <sup>2</sup> )	28.1±5.9	27.9±5.7	28.5±6.2	0.15
Hypertension	1,322 (73.6)	1,058 (72.7)	1,054 (77.2)	0.03
Prior MI	800 (44.5)	654 (44.9)	578 (42.3)	0.24
Atrial fibrillation	694 (38.6)	546 (37.5)	535 (39.2)	0.81
History of TIIDM	738 (41.1)	584 (40.1)	607 (44.4)	0.08
TIIDM by history / HbA1c	785 (43.7)	623 (42.8)	668 (48.9)	0.01
Device therapy				
ICD	451 (25.1)	386 (26.5)	376 (27.5)	0.12
CRT	137 ( 7.6)	94 ( 6.5)	115 ( 8.4)	0.48
Heart failure medication				
ACEI or ARB	1,519 (84.5)	1,206 (82.9)	1,121 (82.1)	0.06
ARNI	172 ( 9.6)	152 (10.4)	167 (12.2)	0.02
ACEI/ARB/ARNI	1,686 (93.8)	1,352 (92.9)	1,283 (93.9)	0.98
Beta blocker	1,718 (95.6)	1,408 (96.8)	1,313 (96.1)	0.39
MRA	1,289 (71.7)	1,020 (70.1)	967 (70.8)	0.52
Digoxin	351 (19.5)	260 (17.9)	248 (18.2)	0.29
Diuretic	1,529 (85.1)	1,184 (81.4)	1,190 (87.1)	0.21

**Supplementary Table 2b.** Baseline characteristics according to extent of initial eGFR decline (“dip”) in placebo and dapagliflozin groups separately.

	PLACEBO			DAPAGLIFLOZIN		
	No decline N=1,091	Up to 10% decline N=734	>10% decline N=484	No decline N=706	Up to 10% decline N=721	>10% decline N=882
Age	65.7±11.2	67.0±10.5	67.3±10.2	65.2±10.8	65.3±11.2	67.8±10.7
Sex						
Female	229 (21.0)	157 (21.4)	139 (28.7)	179 (25.4)	148 (20.5)	221 (25.1)
Male	862 (79.0)	577 (78.6)	345 (71.3)	527 (74.6)	573 (79.5)	661 (74.9)
Race						
Asian	251 (23.0)	192 (26.2)	110 (22.7)	173 (24.5)	173 (24.0)	181 (20.5)
Black	40 (3.7)	34 (4.6)	28 (5.8)	37 (5.2)	32 (4.4)	50 (5.7)
Other	9 (0.8)	11 (1.5)	11 (2.3)	4 (0.6)	17 (2.4)	16 (1.8)
White	791 (72.5)	497 (67.7)	335 (69.2)	492 (69.7)	499 (69.2)	635 (72.0)
Region						
Asia/Pacific	248 (22.7)	189 (25.7)	106 (21.9)	171 (24.2)	170 (23.6)	178 (20.2)
Europe	525 (48.1)	306 (41.7)	195 (40.3)	340 (48.2)	335 (46.5)	397 (45.0)
North America	138 (12.6)	124 (16.9)	69 (14.3)	86 (12.2)	106 (14.7)	135 (15.3)
South America	180 (16.5)	115 (15.7)	114 (23.6)	109 (15.4)	110 (15.3)	172 (19.5)
NYHA class at enrolment						
II	727 (66.6)	511 (69.6)	327 (67.6)	483 (68.4)	504 (69.9)	586 (66.4)
III	353 (32.4)	219 (29.8)	149 (30.8)	218 (30.9)	210 (29.1)	289 (32.8)
IV	11 (1.0)	4 (0.5)	8 (1.7)	5 (0.7)	7 (1.0)	7 (0.8)
KCCQ-TSS	79.2 (61.5-93.8)	79.2 (62.5-93.8)	75.0 (55.2-89.1)	78.1 (58.3-90.6)	79.2 (60.4-91.7)	77.1 (56.2-93.8)
Pulse (bpm)	71.4±11.8	71.4±11.3	72.0±12.4	72.3±11.8	70.8±11.5	71.1±11.6
Systolic BP (mmHg)	121.4±15.6	122.2±17.0	121.2±17.0	121.1±15.6	121.7±16.3	123.5±16.8
LVEF (%)	30.9±6.9	30.9±6.9	30.7±6.8	31.2±6.7	30.9±6.8	31.6±6.6
Main etiology of HF						
Ischemic	639 (58.6)	408 (55.6)	271 (56.0)	399 (56.5)	385 (53.4)	495 (56.1)
Non-ischemic	366 (33.5)	269 (36.6)	178 (36.8)	251 (35.6)	282 (39.1)	303 (34.4)
Unknown	86 (7.9)	57 (7.8)	35 (7.2)	56 (7.9)	54 (7.5)	84 (9.5)
Prior HF hospitalization	530 (48.6)	333 (45.4)	231 (47.7)	338 (47.9)	333 (46.2)	432 (49.0)
Time from diagnosis of HF						
0 - 3 months	34 (3.1)	18 (2.5)	13 (2.7)	24 (3.4)	33 (4.6)	22 (2.5)
>3 - 6 months	106 (9.7)	61 (8.3)	43 (8.9)	65 (9.2)	46 (6.4)	63 (7.1)
>6 - 12 months	144 (13.2)	83 (11.3)	54 (11.2)	83 (11.8)	84 (11.7)	94 (10.7)

>1 - 2 years	174 (15.9)	98 (13.4)	84 (17.4)	103 (14.6)	97 (13.5)	114 (12.9)
>2 - 5 years	229 (21.0)	171 (23.3)	113 (23.3)	186 (26.3)	154 (21.4)	212 (24.0)
>5 years	404 (37.0)	303 (41.3)	177 (36.6)	245 (34.7)	307 (42.6)	377 (42.7)
Time from last HF hosp.						
0 - 3 months	75 (14.2)	54 (16.2)	31 (13.4)	64 (18.9)	65 (19.5)	67 (15.5)
>3 - 6 months	100 (18.9)	65 (19.5)	49 (21.2)	61 (18.0)	53 (15.9)	71 (16.4)
>6 - 12 months	138 (26.0)	70 (21.0)	60 (26.0)	74 (21.9)	72 (21.6)	98 (22.7)
>1 - 2 years	80 (15.1)	49 (14.7)	36 (15.6)	49 (14.5)	57 (17.1)	71 (16.4)
>2 - 5 years	78 (14.7)	54 (16.2)	30 (13.0)	52 (15.4)	45 (13.5)	67 (15.5)
>5 years	59 (11.1)	41 (12.3)	25 (10.8)	38 (11.2)	41 (12.3)	58 (13.4)
NT-proBNP (pg/ml)	1360.2 (808.4-2430.1)	1480.5 (866.1-2620.6)	1587.1 (922.5-3045.1)	1389.8 (856.0-2614.5)	1385.1 (815.7-2603.1)	1485.0 (891.6-2606.9)
eGFR (mL/min/1.73 m <sup>2</sup> )	65.4±19.1	67.3±20.2	63.7±18.1	66.6±19.3	69.5±20.9	62.6±17.9
Baseline HbA1c (%)	6.5±1.3	6.4±1.2	6.6±1.6	6.5±1.4	6.4±1.3	6.6±1.3
Body Mass Index (kg/m <sup>2</sup> )	28.3±6.0	27.7±5.6	28.3±6.2	27.8±5.7	28.2±5.8	28.6±6.2
Hypertension	810 (74.2)	538 (73.3)	364 (75.2)	512 (72.5)	520 (72.1)	690 (78.2)
Prior MI	494 (45.3)	338 (46.0)	198 (40.9)	306 (43.3)	316 (43.8)	380 (43.1)
AF	430 (39.4)	273 (37.2)	176 (36.4)	264 (37.4)	273 (37.9)	359 (40.7)
History of TIIDM	461 (42.3)	304 (41.4)	194 (40.1)	277 (39.2)	280 (38.8)	413 (46.8)
TIIDM by history / HbA1c	489 (44.8)	323 (44.0)	216 (44.6)	296 (41.9)	300 (41.6)	452 (51.2)
Device therapy						
ICD	272 (24.9)	191 (26.0)	140 (28.9)	179 (25.4)	195 (27.0)	236 (26.8)
CRT	72 ( 6.6)	49 ( 6.7)	37 ( 7.6)	65 ( 9.2)	45 ( 6.2)	78 ( 8.8)
HF medications						
ACEI or ARB	921 (84.4)	592 (80.7)	385 (79.5)	598 (84.7)	614 (85.2)	736 (83.4)
ARNI	105 ( 9.6)	81 (11.0)	66 (13.6)	67 ( 9.5)	71 ( 9.8)	101 (11.5)
ACEI/ARB/ARNI	1,023 (93.8)	672 (91.6)	451 (93.2)	663 (93.9)	680 (94.3)	832 (94.3)
Beta blocker	1,049 (96.2)	709 (96.6)	460 (95.0)	669 (94.8)	699 (96.9)	853 (96.7)
MRA	785 (72.0)	495 (67.4)	350 (72.3)	504 (71.4)	525 (72.8)	617 (70.0)
Digoxin	218 (20.0)	122 (16.6)	88 (18.2)	133 (18.8)	138 (19.1)	160 (18.1)
Diuretic	926 (84.9)	601 (81.9)	426 (88.0)	603 (85.4)	583 (80.9)	764 (86.6)

Data are presented as means±SD or medians (IQR) for continuous measures, and n (%) for categorical measures.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BP, blood pressure; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire-total symptom

score; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; T2DM, type 2 diabetes mellitus



**Supplementary Table 3.** Systolic blood pressure change at 14 days in subgroups of left ventricular ejection fraction

	LVEF <30%		LVEF ≥30%	
	Placebo	Dapagliflozin	Placebo	Dapagliflozin
Mean change in SBP at 14 days (± SD)	-0.1 ± 12.0	-2.6 ± 11.7	-0.1 ± 12.0	-3.5 ± 12.8
Between treatment group difference	-1.6 (-2.5, -0.7)		-3.2 (-4.1, -2.3)	

Interaction p value (dichotomized LVEF and randomized treatment) = 0.02

LVEF, left ventricular ejection fraction; SBP, systolic blood pressure

**Supplementary Table 4A.** Number of patients permanently discontinuing treatment with renin-angiotensin-aldosterone-system antagonist (RAASi) during study follow up according to initial (14 day) change in eGFR.

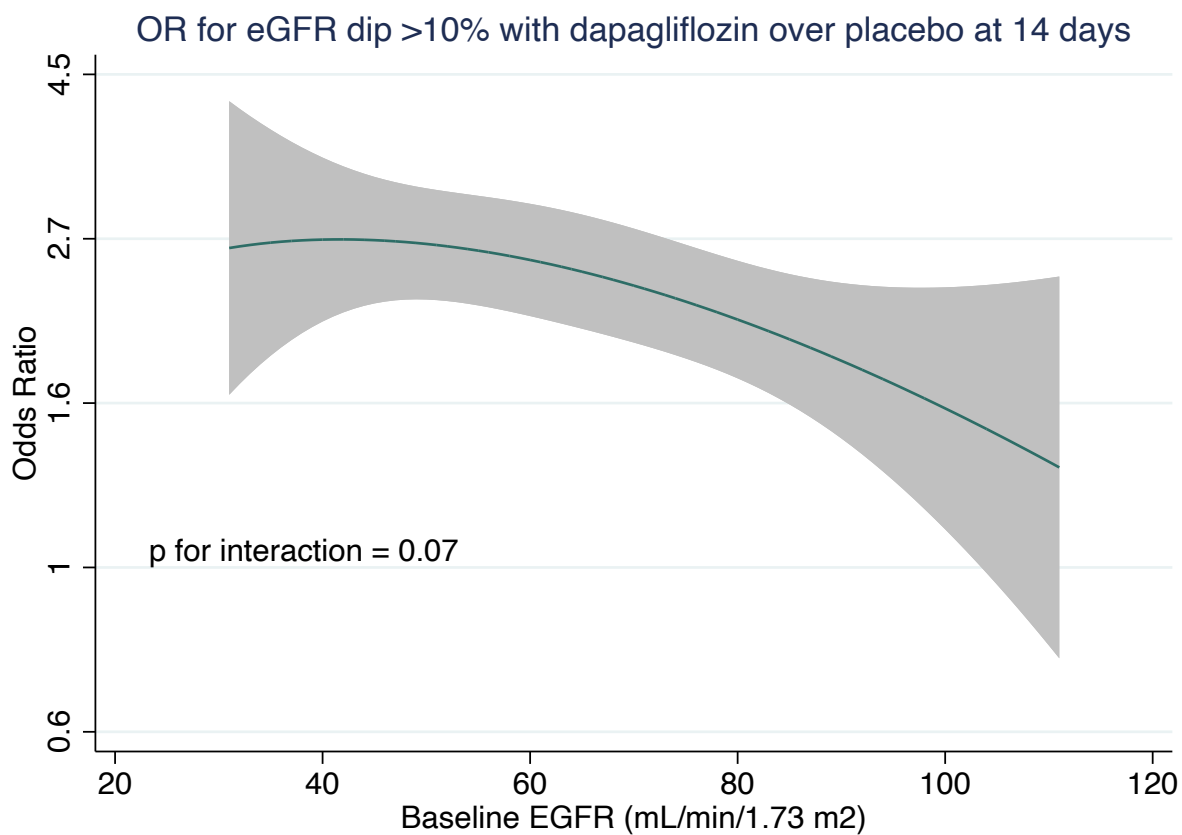
	No decline in eGFR N stopped / N total	Up to 10% decline in eGFR N stopped / N total	>10% decline in eGFR N stopped / N total	Any decline in eGFR N stopped / N total
Placebo (n = 2309)	25/1091 (2.3%)	32/734 (4.4%)	19/484 (3.9%)	51/1218 (4.2%)
Dapagliflozin (n = 2309)	21/706 (3.0%)	17/721 (2.4%)	29/882 (3.3%)	46/1603 (2.9%)
Difference between treatment groups*	P = 0.37	P = 0.03	P = 0.54	P = 0.06

\* Difference between randomized treatment groups within each eGFR change category compared using a chi-square test

**Supplementary Table 4B.** Number of patients with stops in treatment with RAASi in each treatment arm, followed by the number of patients who restarted

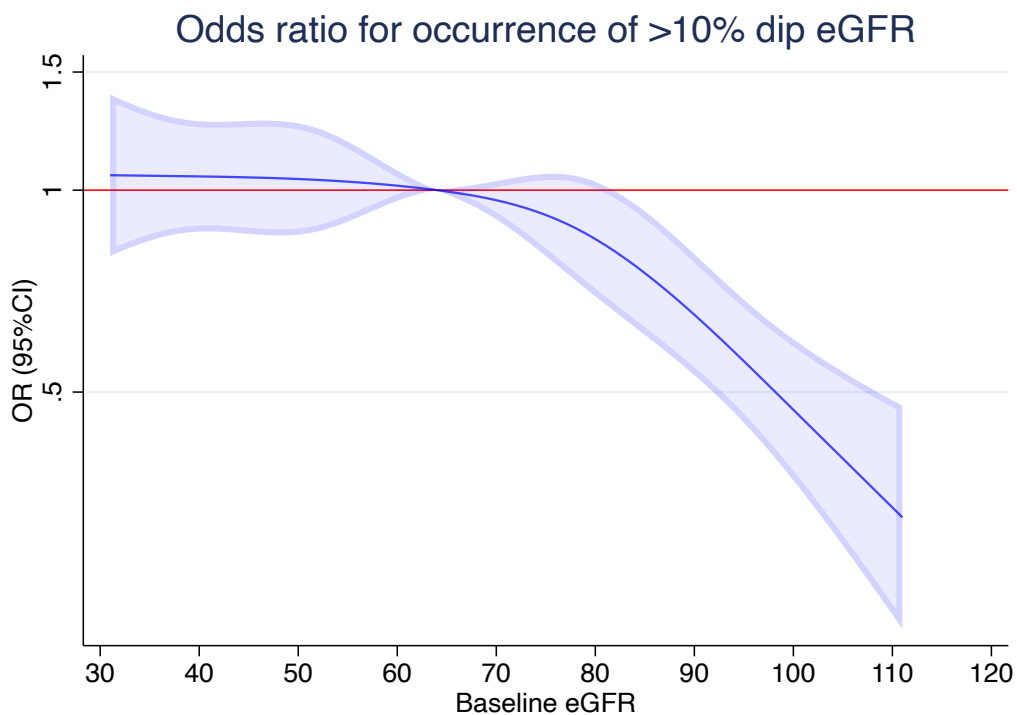
	1 <sup>st</sup> stop	Restarted	2 <sup>nd</sup> stop	Restarted	3 <sup>rd</sup> stop	Restarted	4 <sup>th</sup> stop	Restarted	5 <sup>th</sup> stop	Restarted
Placebo	177	100 (56%)	30	16 (53%)	5	2 (40%)	1	0	0	0
Dapagliflozin	182	109 (60%)	29	18 (62%)	8	5 (63%)	3	1 (33%)	1	0

**Supplementary Figure 1:** Odds ratio for a >10% decline in eGFR with dapagliflozin compared with placebo between baseline and day 14 according to baseline eGFR



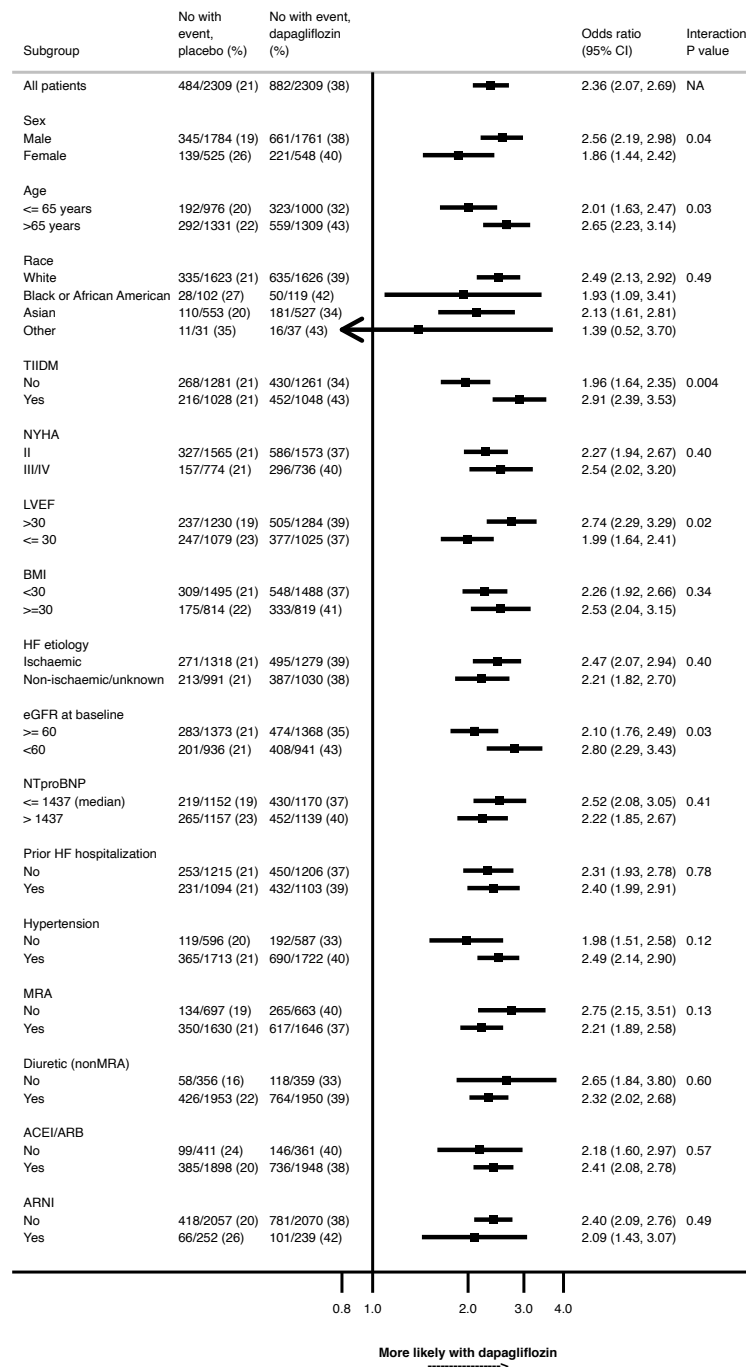
Fractional polynomial plot for odds ratio for occurrence of >10% decline in eGFR for dapagliflozin compared with placebo across the range of baseline eGFR

**Supplementary Figure 2:** Odds ratio for a >10% decline in eGFR between baseline and day 14 according to baseline eGFR in all patients



Odds ratio for occurrence of eGFR dip across baseline eGFR modelled using a restricted cubic spline including patients in both randomized treatment groups (unadjusted)

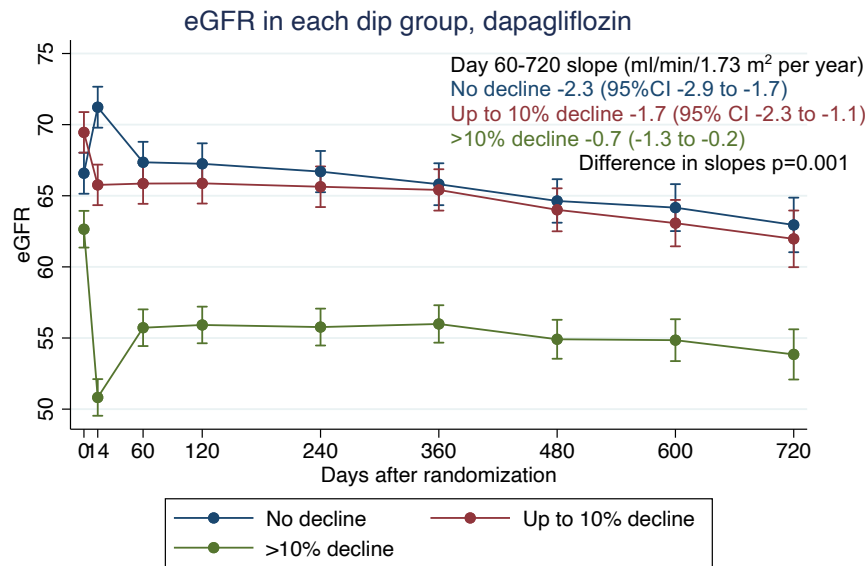
**Supplementary Figure 3.** Odds ratio for an early decline (“dip”) of >10% vs ≤10% decline/no change/improvement in eGFR for patients on dapagliflozin compared with placebo.



ACEI, angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; ARNI, Angiotensin receptor-neprilysin inhibitors; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; TIIDM, type 2 diabetes

**Supplementary Figure 4.** Chronic eGFR slope (day 60 to 720) according to initial change in eGFR (no decline, up to 10% decline and >10% decline) in the dapagliflozin [A] and placebo [B] groups.

**A**



**B**

