

# SUPPLEMENTAL MATERIAL

## **Efficacy and Safety of Dapagliflozin in Heart Failure with Reduced Ejection Fraction According to N-Terminal Pro-B-Type Natriuretic Peptide: Insights from the DAPA-HF trial**

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**Supplemental Table I. Baseline characteristics associated with NT-proBNP level above median at baseline**

	Odds ratio (95% CI)
Age (per 10-year increase)	1.13 (1.04-1.22)
Sex	
Male	Reference
Female	1.07 (0.92-1.26)
Race	
White	Reference
Asian	0.73 (0.30-1.80)
Black	1.43 (1.02-1.99)
Other	0.97 (0.56-1.68)
Geographic region	
North America	Reference
South America	1.52 (1.20-1.92)
Europe	1.35 (1.10-1.67)
Asia/Pacific	1.47 (0.60-3.61)
Systolic blood pressure (per 10 mmHg increase)	0.97 (0.93-1.01)
Heart rate (per 10 bpm increase)	1.21 (1.14-1.29)
BMI (per 5-unit increase)	0.75 (0.70-0.80)
Glycated hemoglobin (per 1% increase)	0.99 (0.93-1.05)
eGFR (per 10-unit increase)	0.82 (0.78-0.85)
Main cause of HF	
Ischemic	Reference
Non-ischemic	1.06 (0.88-1.28)
Unknown	0.90 (0.69-1.17)
LVEF (per 5% increase)	0.79 (0.75-0.83)
NYHA class	
II	Reference
III/IV	1.26 (1.09-1.46)
KCCQ-TSS (per 5-point increase)	0.94 (0.93-0.96)
Hypertension	0.99 (0.84-1.17)
Type 2 diabetes (medical history)	1.14 (0.96-1.34)
Atrial fibrillation (history of)	1.84 (1.60-2.12)
Hospitalization for HF	1.03 (0.91-1.17)
Previous MI	0.85 (0.71-1.00)

*BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; MI, myocardial infarction; NYHA, New York Heart Association.*

**Supplemental Table II. Time to first event according to NT-proBNP quartiles**

	<857 pg/mL N=1,187	857-1,437 pg/mL N=1,185	1,438-2,650 pg/mL N=1,185	>2,650 pg/mL N=1,185
<b>Worsening HF event or cardiovascular death</b>				
N (%)	89 (7.5)	166 (14.0)	225 (19.0)	408 (34.4)
Event rate per 100 person-years (95% CI)	5.2 (4.2-6.4)	9.9 (8.5-11.6)	13.8 (12.1-15.7)	28.3 (25.7-31.2)
HR (95% CI)*	Reference	1.90 (1.47-2.46)	2.63 (2.06-3.37)	5.30 (4.21-6.67)
HR (95% CI)†	Reference	1.82 (1.40-2.36)	2.47 (1.92-3.18)	4.38 (3.43-5.58)
HR (95% CI)‡	Reference	1.82 (1.40-2.35)	2.48 (1.93-3.18)	4.39 (3.44-5.60)
<b>HF hospitalization or cardiovascular death</b>				
N (%)	85 (7.2)	165 (13.9)	223 (18.8)	404 (34.1)
Event rate per 100 person-years (95% CI)	4.9 (4.0-6.1)	9.9 (8.5-11.5)	13.6 (12.0-15.5)	27.9 (25.3-30.8)
HR (95% CI)*	Reference	1.98 (1.52-2.57)	2.74 (2.13-3.51)	5.48 (4.33-6.92)
HR (95% CI)†	Reference	1.89 (1.45-2.47)	2.57 (1.99-3.32)	4.51 (3.52-5.77)
HR (95% CI)‡	Reference	1.89 (1.45-2.46)	2.57 (1.99-3.32)	4.51 (3.52-5.77)
<b>HF hospitalization</b>				
N (%)	46 (3.9)	94 (7.9)	158 (13.3)	251 (21.2)
Event rate per 100 person-years (95% CI)	2.7 (2.0-3.6)	5.6 (4.6-6.9)	9.7 (8.3-11.3)	17.3 (15.3-19.6)
HR (95% CI)*	Reference	2.09 (1.47-2.97)	3.58 (2.58-4.98)	6.20 (4.52-8.49)
HR (95% CI)†	Reference	1.94 (1.36-2.77)	3.23 (2.31-4.52)	4.86 (3.49-6.77)
HR (95% CI)‡	Reference	1.93 (1.35-2.76)	3.22 (2.30-4.50)	4.88 (3.51-6.80)
<b>HF hospitalization or urgent HF visit</b>				
N (%)	50 (4.2)	95 (8.0)	160 (13.5)	258 (21.8)
Event rate per 100 person-years (95% CI)	2.9 (2.2-3.8)	5.7 (4.6-6.9)	9.8 (8.4-11.4)	17.9 (15.9-20.2)
HR (95% CI)*	Reference	1.94 (1.38-2.73)	3.33 (2.43-4.58)	5.88 (4.34-7.97)
HR (95% CI)†	Reference	1.80 (1.28-2.55)	3.00 (2.17-4.16)	4.63 (3.36-6.38)
HR (95% CI)‡	Reference	1.80 (1.27-2.54)	3.00 (2.16-4.15)	4.67 (3.39-6.43)
<b>Cardiovascular death</b>				
N (%)	46 (3.9)	94 (7.9)	102 (8.6)	258 (21.8)
Event rate per 100 person-years (95% CI)	2.6 (2.0-3.5)	5.4 (4.4-6.6)	5.9 (4.8-7.1)	16.1 (14.3-18.2)
HR (95% CI)*	Reference	2.03 (1.42-2.88)	2.20 (1.55-3.11)	6.05 (4.42-8.28)
HR (95% CI)†	Reference	1.95 (1.37-2.79)	2.09 (1.47-2.98)	4.92 (3.53-6.86)
HR (95% CI)‡	Reference	1.96 (1.37-2.80)	2.08 (1.46-2.97)	4.85 (3.48-6.77)
<b>All-cause death</b>				
N (%)	58 (4.9)	117 (9.9)	126 (10.6)	304 (25.7)
Event rate per 100 person-years (95% CI)	3.3 (2.6-4.3)	6.7 (5.6-8.0)	7.2 (6.1-8.6)	19.0 (17.0-21.3)
HR (95% CI)*	Reference	2.00 (1.46-2.74)	2.15 (1.58-2.94)	5.67 (4.28-7.51)
HR (95% CI)†	Reference	1.94 (1.41-2.66)	2.06 (1.50-2.83)	4.82 (3.58-6.50)
HR (95% CI)‡	Reference	1.95 (1.42-2.68)	2.05 (1.49-2.82)	4.77 (3.54-6.44)
<b>Total number of hospitalizations for heart failure or cardiovascular death</b>				
N	107	233	325	644
RR (95% CI)*	Reference	2.17 (1.63-2.89)	3.03 (2.31-3.97)	6.36 (4.93-8.20)
RR (95% CI)†	Reference	2.03 (1.51-2.72)	2.74 (2.08-3.61)	4.97 (3.81-6.48)
RR (95% CI)‡	Reference	2.03 (1.52-2.71)	2.73 (2.07-3.59)	4.99 (3.83-6.50)

\*Adjusted for a history of HF hospitalization (apart from all cause death), randomized treatment and stratified by diabetes status

†Adjusted for a history of HF hospitalization, randomized treatment, age, sex, heart rate, systolic blood pressure, body mass index, HF etiology, left ventricular ejection fraction, NYHA functional class, atrial fibrillation and estimated glomerular filtration rate, and stratified by diabetes status.

‡Adjusted for a history of HF hospitalization, randomized treatment, age, sex, heart rate, systolic blood pressure, body mass index, HF etiology, left ventricular ejection fraction, NYHA functional class, atrial fibrillation, estimated glomerular filtration rate, and medical therapy (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor neprilysin inhibitor, beta-blocker, mineralocorticoid receptor antagonist, diuretic, digoxin, oral anticoagulant, antiplatelet, statin, and cardiac resynchronization therapy), and stratified by diabetes status.

**Supplemental Table III. Change in NT-proBNP from baseline to 8 months**

	Main model		Additional adjustment for change in eGFR		Additional adjustment for baseline eGFR and change in eGFR	
	Mean treatment difference at 8 months (95% CI)	Ratio: Dapagliflozin/placebo at 8 months (95% CI)	Mean treatment difference at 8 months (95% CI)	Ratio: Dapagliflozin/placebo at 8 months (95% CI)	Mean treatment difference at 8 months (95% CI)	Ratio: Dapagliflozin/placebo at 8 months (95% CI)
All patients (N=4,222)	-303 (-457, -150)	0.92 (0.88 – 0.96)	-302 (-449, -155)	0.92 (0.88 – 0.96)	-305 (-451, -159)	0.92 (0.88 – 0.96)
NT-proBNP quartile 1 (N= 1,100)	-82 (-170, 7)	0.94 (0.86 – 1.02)	-53 (-131, 25)	0.95 (0.88 – 1.04)	-51 (-129, 27)	0.96 (0.88 – 1.04)
NT-proBNP quartile 2 (N=1,086)	-232 (-357, -107)	0.94 (0.87 – 1.01)	-246 (-371, -121)	0.93 (0.86 – 1.00)	-251 (-375, -126)	0.92 (0.86 – 1.00)
NT-proBNP quartile 3 (N=1,064)	-536 (-836, -237)	0.85 (0.78 – 0.92)	-543 (-842, -244)	0.85 (0.78 – 0.92)	-563 (-862, -265)	0.84 (0.77 – 0.91)
NT-proBNP quartile 4 (N=972)	-395 (-945, 154)	0.96 (0.86 – 1.07)	-361 (-879, 157)	0.94 (0.85 – 1.05)	-318 (-831, 196)	0.96 (0.86 – 1.07)

*Of the 4,742 patients with an available baseline NT-proBNP measurement, 4,222 patients had NT-proBNP measured at 8 months (225 missing NT-proBNP due to death, 295 missing for reasons other than death). The proportions of patients with missing NT-proBNP at 8 months for reasons other than death were similar in the dapagliflozin and placebo groups at 8 months (6.0% vs 7.1%, respectively).*

*CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.*

## **Reference 51**

51. Zelniker TA, Morrow DA, Mosenson O, Goodrich EL, Jarolim P, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding J et al. Relationship between baseline cardiac biomarkers and cardiovascular death or hospitalization for heart failure with and without sodium-glucose co-transporter 2 inhibitor therapy in DECLARE-TIMI 58. *Eur J Heart Fail.* 2020.