

## Supplemental Online Content

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### **eAppendix**

**eTable 1.** Baseline characteristics by all cause death among HFimpEF and LVEF consistently > 40%

**eTable 2.** Baseline characteristics by treatment group in those with HFimpEF

**eTable 3.** Baseline characteristics of HFimpEF by LVEF <50 or ≥50%

This supplemental material has been provided by the authors to give readers additional information about their work.

## **eAppendix**

### **Definition of Sudden Cardiac Death (excerpted from the Clinical Endpoint Committee Charter)**

Sudden Cardiac Death refers to a death that occurs unexpectedly and not within 30 days of an acute MI.

Sudden cardiac death includes the following scenarios:

- a. Death witnessed and occurring without new or worsening symptoms
- b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
- c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
- d. Death after unsuccessful resuscitation from cardiac arrest (e.g., implantable cardioverter defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest)
- e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
- f. Unwitnessed death in a subject seen alive and clinically stable  $\leq$  24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

**eTable 1. Baseline characteristics by all cause death among HFimpEF and LVEF consistently > 40%**

	HFimpEF alive n=961	HFimpEF death n=190		LVEF consistently >40% alive n=4279	LVEF consistently >40% death n=833	
Age	70 [64 , 77 ]	74 [66 , 81 ]	p<0.001	72 [66 , 78 ]	75 [68 , 81 ]	p<0.001
<u>Age Group</u>			p<0.001			p<0.001
<= 65	300 (31.2%)	42 (22.1%)		1015 (23.7%)	147 (17.6%)	
> 75	287 (29.9%)	87 (45.8%)		1576 (36.8%)	397 (47.7%)	
>65 - 75	374 (38.9%)	61 (32.1%)		1688 (39.4%)	289 (34.7%)	
Men	641 (66.7%)	133 (70.0%)	p=0.38	2232 (52.2%)	510 (61.2%)	p<0.001
<u>Race</u>			p=0.29			p<0.001
White	635 (66.1%)	139 (73.2%)		3026 (70.7%)	639 (76.7%)	
Asian	254 (26.4%)	36 (18.9%)		885 (20.7%)	99 (11.9%)	
Black Or African American	29 (3.0 %)	7 (3.7 %)		104 (2.4 %)	19 (2.3 %)	
American Indian Or Alaska Native	18 (1.9 %)	3 (1.6 %)		140 (3.3 %)	28 (3.4 %)	
Other	25 (2.6 %)	5 (2.6 %)		124 (2.9 %)	48 (5.8 %)	
<u>Geographic Region</u>			p=0.040			p<0.001
Europe and Saudi Arabia	398 (41.4%)	84 (44.2%)		2074 (48.5%)	449 (53.9%)	
Asia	252 (26.2%)	32 (16.8%)		848 (19.8%)	94 (11.3%)	
Latin America	162 (16.9%)	36 (18.9%)		795 (18.6%)	188 (22.6%)	
North America	149 (15.5%)	38 (20.0%)		562 (13.1%)	102 (12.2%)	
History: Atrial Fib/Flutter	483 (50.3%)	110 (57.9%)	p=0.05	2460 (57.5%)	499 (59.9%)	p=0.20
History of stroke	77 (8.0 %)	19 (10.0%)	p=0.37	386 (9.0 %)	115 (13.8%)	p<0.001
History: Dyslipidaemia	641 (66.7%)	127 (66.8%)	p=0.97	2688 (62.8%)	534 (64.1%)	p=0.48
History: Type 2 Diabetes Mellitus	435 (45.3%)	94 (49.5%)	p=0.29	1871 (43.7%)	406 (48.7%)	p=0.008
History: Chronic Obstructive Pulmonary Disease	116 (12.1%)	34 (17.9%)	p=0.030	428 (10.0%)	114 (13.7%)	p=0.002
History: Non-Coronary Revascularization	19 (2.0 %)	6 (3.2 %)	p=0.31	86 (2.0 %)	29 (3.5 %)	p=0.009
History: Sleep Apnoea	79 (8.2 %)	17 (8.9 %)	p=0.74	325 (7.6 %)	64 (7.7 %)	p=0.93
History: Myocardial Infarction	339 (35.3%)	61 (32.1%)	p=0.40	993 (23.2%)	246 (29.5%)	p<0.001
History: Hypertension	807 (84.0%)	172 (90.5%)	p=0.021	3822 (89.3%)	752 (90.3%)	p=0.41
Prior HF Hospitalization Flag	453 (47.1%)	107 (56.3%)	p=0.021	1578 (36.9%)	401 (48.1%)	p<0.001
Any Coronary Artery Disease	570 (59.3%)	110 (57.9%)	p=0.72	2076 (48.5%)	462 (55.5%)	p<0.001
Any Atherosclerotic Cardiovascular Disease	612 (63.7%)	120 (63.2%)	p=0.89	2327 (54.4%)	539 (64.7%)	p<0.001
<u>Smoking Status</u>			p=0.43			p=0.041
Current	102 (10.6%)	16 (8.4 %)		302 (7.1 %)	64 (7.7 %)	
Former	423 (44.0%)	79 (41.6%)		1444 (33.7%)	315 (37.8%)	
Never	436 (45.4%)	95 (50.0%)		2533 (59.2%)	454 (54.5%)	
Baseline Body Mass Index	28.5 [25.0 , 33.0 ]	29.3 [24.2 , 32.9 ]	p=0.58	29.3 [25.7 , 33.7 ]	29.1 [25.1 , 33.1 ]	p=0.09
<u>Body Mass Index Group (kg/m2)</u>			p=0.002			p=0.55
<18.5 (Underweight)	3 (0.3 %)	5 (2.6 %)		36 (0.8 %)	10 (1.2 %)	
18.5-24.9 (Normal weight)	233 (24.3%)	51 (26.8%)		871 (20.4%)	188 (22.6%)	
25.0-29.9 (Overweight)	327 (34.1%)	47 (24.7%)		1421 (33.2%)	278 (33.4%)	

30.0-34.9 (Class I obesity)	228 (23.8%)	56 (29.5%)		1091 (25.5%)	199 (23.9%)	
35.0-39.9 (Class II obesity)	115 (12.0%)	20 (10.5%)		558 (13.1%)	105 (12.6%)	
>=40 (Class III obesity)	54 (5.6%)	11 (5.8%)		298 (7.0%)	52 (6.2%)	
<u>Time from Diagnosis of HF to Baseline</u>			p=0.05			p=0.001
0 - 3 Months	48 (5.0%)	13 (6.8%)		443 (10.4%)	64 (7.7%)	
>3 - 6 Months	66 (6.9%)	4 (2.1%)		442 (10.3%)	80 (9.6%)	
>6 - 12 Months	94 (9.8%)	20 (10.5%)		628 (14.7%)	100 (12.0%)	
>1 - 2 Years	132 (13.7%)	17 (8.9%)		714 (16.7%)	132 (15.9%)	
>2 - 5 Years	288 (30.0%)	62 (32.6%)		1015 (23.7%)	204 (24.5%)	
>5 Years	333 (34.7%)	74 (38.9%)		1033 (24.2%)	252 (30.3%)	
<u>NYHA Class at Baseline</u>			p<0.001			p<0.001
II	787 (81.9%)	131 (68.9%)		1 (0.0%)	0 (0.0%)	
III	171 (17.8%)	58 (30.5%)		3243 (75.8%)	552 (66.3%)	
IV	3 (0.3%)	1 (0.5%)		1026 (24.0%)	276 (33.1%)	
Baseline LVEF(%)	49 [44 , 56 ]	47 [43 , 55 ]	p=0.15	55 [48 , 60 ]	54 [47 , 60 ]	p=0.001
<u>LVEF Group</u>			p=0.08			p=0.004
<= 40	1 (0.1%)	0 (0.0%)		3 (0.1%)	0 (0.0%)	
>=41-49	507 (52.8%)	116 (61.1%)		1204 (28.1%)	285 (34.2%)	
50-59	288 (30.0%)	40 (21.1%)		1629 (38.1%)	299 (35.9%)	
>= 60	165 (17.2%)	34 (17.9%)		1443 (33.7%)	249 (29.9%)	
Baseline NT-proBNP (ng/L)	953 [597 , 1528 ]	1554 [908 , 2875 ]	p<0.001	955 [606 , 1647 ]	1332 [765 , 2708 ]	p<0.001
NT-proBNP in AFF (ECG)	1307 [967 , 2030 ]	2048 [1286 , 3375 ]	p<0.001	1346 [936 , 2082 ]	1796 [1117 , 3187 ]	p<0.001
NT-proBNP when no AFF (ECG)	704 [477 , 1190 ]	1140 [641 , 2362 ]	p<0.001	675 [450 , 1162 ]	1022 [540 , 2144 ]	p<0.001
Baseline ECG Atrial Fibrillation/Flutter	344 (35.8%)	80 (42.1%)	p=0.10	1851 (43.3%)	369 (44.3%)	p=0.59
Baseline Systolic Blood Pressure (mmHg)	128 [115 , 139 ]	128 [115 , 138 ]	p=0.84	128 [118 , 138 ]	128 [117 , 138 ]	p=0.030
Baseline Diastolic Blood Pressure (mmHg)	73 [66 , 80 ]	72 [64 , 80 ]	p=0.18	75 [68 , 81 ]	73 [66 , 80 ]	p=0.015
Baseline HbA1c (%)	6.2 [5.7 , 7.0 ]	6.3 [5.8 , 7.4 ]	p=0.14	6.1 [5.7 , 6.9 ]	6.2 [5.7 , 7.2 ]	p=0.06
Baseline Pulse (beats/min)	69 [62 , 78 ]	71 [64 , 78 ]	p=0.17	70 [63 , 78 ]	71 [64 , 78 ]	p=0.35
Baseline Creatinine (umol/L)	97 [81 , 117 ]	110 [92 , 135 ]	p<0.001	95 [79 , 116 ]	104 [84 , 133 ]	p<0.001
Baseline eGFR (mL/min/1.73m2)	62 [49 , 77 ]	55 [40 , 67 ]	p<0.001	61 [47 , 76 ]	54 [41 , 69 ]	p<0.001
eGFR >=60	534 (55.6%)	73 (38.4%)	p<0.001	2237 (52.3%)	348 (41.8%)	p<0.001
Loop diuretics	724 (75.3%)	159 (83.7%)	p=0.013	3229 (75.5%)	699 (83.9%)	p<0.001
Ace inhibitor (ACEi)	376 (39.1%)	82 (43.2%)	p=0.30	1507 (35.2%)	330 (39.6%)	p=0.016
Angiotensin receptor blocker (ARB)	286 (29.8%)	51 (26.8%)	p=0.42	1665 (38.9%)	270 (32.4%)	p<0.001
Neprilysin inhibitor/ARB (ARNI)	125 (13.0%)	27 (14.2%)	p=0.65	126 (2.9%)	23 (2.8%)	p=0.77
Beta Blocker	834 (86.8%)	157 (82.6%)	p=0.13	3513 (82.1%)	673 (80.8%)	p=0.37

Mineralocorticoid receptor antagonist (MRA)	493 (51.3%)	87 (45.8%)	p=0.17	1720 (40.2%)	367 (44.1%)	p=0.038
Pacemaker	89 (9.3%)	30 (15.8%)	p=0.007	438 (10.2%)	105 (12.6%)	p=0.042
ICD	48 (5.0%)	11 (5.8%)	p=0.65	46 (1.1%)	8 (1.0%)	p=0.77

**eTable 2. Baseline characteristics by treatment group in those with HFimpEF**

Characteristic	Treatment Groups		P-value
	Dapagliflozin	Placebo	
Age	69.9 ± 10.3	70.3 ± 9.8	p=0.58
Male sex	387 (67.7%)	387 (66.8%)	p=0.77
<u>Race</u>			p=0.10
White	382 (66.8%)	392 (67.7%)	
Asian	140 (24.5%)	150 (25.9%)	
Black Or African American	16 (2.8 %)	20 (3.5 %)	
American Indian Or Alaska Native	12 (2.1 %)	9 (1.6 %)	
Other	22 (3.8 %)	8 (1.4 %)	
<u>Geographic Region</u>			p=0.64
Europe and Saudi Arabia	236 (41.3%)	246 (42.5%)	
Asia	136 (23.8%)	148 (25.6%)	
Latin America	106 (18.5%)	92 (15.9%)	
North America	94 (16.4%)	93 (16.1%)	
History of Atrial Fibrillation or Flutter	279 (48.8%)	314 (54.2%)	p=0.06
Type 2 Diabetes Mellitus	285 (49.8%)	244 (42.1%)	p=0.009
History of Myocardial Infarction	197 (34.4%)	203 (35.1%)	p=0.83
History of HF Hospitalization	270 (47.2%)	290 (50.1%)	p=0.33
Any Coronary Artery Disease	338 (59.1%)	338 (58.4%)	p=0.81
Any Atherosclerotic Cardiovascular Disease	367 (64.2%)	362 (62.5%)	p=0.56
Current smoker	49 (8.6 %)	69 (11.9%)	P = 0.17
Baseline Body Mass Index	29.7 ± 6.2	29.2 ± 5.7	p=0.16
<u>Time from Diagnosis of HF to Baseline</u>			p=0.62
0 - 3 Months	31 (5.4 %)	30 (5.2 %)	
>3 - 6 Months	36 (6.3 %)	34 (5.9 %)	
>6 - 12 Months	63 (11.0%)	51 (8.8 %)	
>1 - 2 Years	80 (14.0%)	69 (11.9%)	
>2 - 5 Years	168 (29.4%)	182 (31.4%)	
>5 Years	194 (33.9%)	213 (36.8%)	
<u>NYHA Class at Baseline</u>			p=0.89
I			
II	453 (79.2%)	465 (80.3%)	
III	117 (20.5%)	112 (19.3%)	
IV	2 (0.3 %)	2 (0.3 %)	
Baseline LVEF(%)	50.3 ± 7.9	50.8 ± 8.7	p=0.29
<u>LVEF Group</u>			p=0.47
≤ 40	1 (0.2 %)	0 (0.0 %)	

	>=41-49	313 (54.7%)	310 (53.5%)	
	50-59	167 (29.2%)	161 (27.8%)	
	>= 60	91 (15.9%)	108 (18.7%)	
	Baseline NT-proBNP (ng/L)	1010 [627 , 1812 ]	1007 [614 , 1688 ]	p=0.40
	Baseline ECG Atrial Fibrillation/Flutter	1512 [986 , 2580 ]	1307 [990 , 2087 ]	p=0.15
	Baseline Systolic Blood Pressure (mmHg)	127.3 ± 16.8	127.2 ± 16.5	p=0.87
	Baseline eGFR (mL/min/1.73m <sup>2</sup> )	61.9 ± 19.0	61.8 ± 19.3	p=0.90
<u>Medications</u>				
	Loop diuretics	446 (78.0%)	437 (75.6%)	p=0.34
	Ace inhibitor (ACEi)	224 (39.2%)	234 (40.5%)	p=0.65
	Angiotensin receptor blocker (ARB)	166 (29.0%)	171 (29.6%)	p=0.83
	Neprilysin inhibitor/ARB (ARNI)	73 (12.8%)	79 (13.7%)	p=0.65
	Beta Blocker	486 (85.0%)	505 (87.4%)	p=0.24
	Mineralocorticoid receptor antagonist (MRA)	290 (50.7%)	290 (50.2%)	p=0.86
	ICD	36 (6.3 %)	23 (4.0 %)	p=0.07
	ACE Inhibitor, ARB, ARNI and Beta-Blocker	399 (69.8%)	427 (73.9%)	p=0.12
	ACE Inhibitor, ARB, ARNI, Beta-Blocker and MRI	208 (36.4%)	217 (37.5%)	p=0.68

**eTable 3. Baseline characteristics of HFimpEF by LVEF <50 or ≥50%**

	Improved EF with baseline LVEF < 50 n=624	Improved EF baseline LVEF ≥ 50 n=527	
Age	69 [63 , 76 ]	72 [66 , 79 ]	p<0.001
<u>Age Group</u>			p<0.001
≤ 65	217 (34.8%)	125 (23.7%)	
> 75	167 (26.8%)	207 (39.3%)	
>65 - 75	240 (38.5%)	195 (37.0%)	
Men	468 (75.0%)	306 (58.1%)	p<0.001
<u>Race</u>			p=0.06
White	423 (67.8%)	351 (66.6%)	
Asian	166 (26.6%)	124 (23.5%)	
Black Or African American	12 (1.9%)	24 (4.6%)	
American Indian Or Alaska Native	9 (1.4%)	12 (2.3%)	
Other	14 (2.2%)	16 (3.0%)	
<u>Geographic Region</u>			p<0.001
Europe and Saudi Arabia	303 (48.6%)	179 (34.0%)	
Asia	162 (26.0%)	122 (23.1%)	
Latin America	88 (14.1%)	110 (20.9%)	
North America	71 (11.4%)	116 (22.0%)	
History: Atrial Fib/Flutter	279 (44.7%)	314 (59.6%)	p<0.001
History of stroke	49 (7.9%)	47 (8.9%)	p=0.51
History: Dyslipidaemia	397 (63.6%)	371 (70.4%)	p=0.015
History: Type 2 Diabetes Mellitus	276 (44.2%)	253 (48.0%)	p=0.20
History: Chronic Obstructive Pulmonary Disease	89 (14.3%)	61 (11.6%)	p=0.18
History: Non-Coronary Revascularization	20 (3.2%)	5 (1.0%)	p=0.009
History: Sleep Apnoea	45 (7.2%)	51 (9.7%)	p=0.13
History: Myocardial Infarction	258 (41.3%)	142 (26.9%)	p<0.001
History: Hypertension	507 (81.2%)	472 (89.6%)	p<0.001
Prior HF Hospitalization Flag	321 (51.4%)	239 (45.4%)	p=0.039
Any Coronary Artery Disease	414 (66.3%)	266 (50.5%)	p<0.001
Any Atherosclerotic Cardiovascular Disease	431 (69.1%)	301 (57.1%)	p<0.001
<u>Smoking Status</u>			p=0.002
Current	75 (12.0%)	43 (8.2%)	
Former	289 (46.3%)	213 (40.4%)	
Never	260 (41.7%)	271 (51.4%)	
Baseline Body Mass Index	28.1 [24.7 , 32.4 ]	29.1 [25.3 , 33.8 ]	p=0.008
<u>Body Mass Index Group (kg/m<sup>2</sup>)</u>			p=0.049
<18.5 (Underweight)	4 (0.6%)	4 (0.8%)	
18.5-24.9 (Normal weight)	170 (27.2%)	114 (21.7%)	
25.0-29.9 (Overweight)	206 (33.0%)	168 (31.9%)	
30.0-34.9 (Class I obesity)	153 (24.5%)	131 (24.9%)	
35.0-39.9 (Class II obesity)	65 (10.4%)	70 (13.3%)	
≥40 (Class III obesity)	26 (4.2%)	39 (7.4%)	



<u>Time from Diagnosis of HF to Baseline</u>			p=0.028
0 - 3 Months	24 (3.8%)	37 (7.0%)	
>3 - 6 Months	32 (5.1%)	38 (7.2%)	
>6 - 12 Months	62 (9.9%)	52 (9.9%)	
>1 - 2 Years	73 (11.7%)	76 (14.4%)	
>2 - 5 Years	206 (33.0%)	144 (27.3%)	
>5 Years	227 (36.4%)	180 (34.2%)	
 <u>NYHA Class at Baseline</u>			p=0.14
II	491 (78.7%)	427 (81.0%)	
III	129 (20.7%)	100 (19.0%)	
IV	4 (0.6%)	0 (0.0%)	
Baseline LVEF(%)	45 [42 , 46 ]	56 [53 , 62 ]	p<0.001
<u>LVEF Group</u>			p<0.001
<= 40	1 (0.2%)	0 (0.0%)	
>=41-49	623 (99.8%)	0 (0.0%)	
50-59	0 (0.0%)	328 (62.2%)	
>= 60	0 (0.0%)	199 (37.8%)	
Baseline NT-proBNP (ng/L)	1026 [623 , 1943 ]	981 [623 , 1573 ]	p=0.07
NT-proBNP in AFF (ECG)	1539 [1015 , 2642 ]	1323 [962 , 2002 ]	p=0.011
NT-proBNP when no AFF (ECG)	807 [503 , 1509 ]	678 [460 , 1130 ]	p<0.001
Baseline ECG Atrial Fibrillation/Flutter	189 (30.3%)	235 (44.6%)	p<0.001
Baseline Systolic Blood Pressure (mmHg)	126 [114 , 138 ]	128 [118 , 141 ]	p<0.001
Baseline Diastolic Blood Pressure (mmHg)	72 [66 , 80 ]	74 [66 , 80 ]	p=0.85
Baseline Pulse (beats/min)	70 [62 , 78 ]	69 [62 , 78 ]	p=0.79
Baseline HbA1c (%)	6.1 [5.7 , 6.9 ]	6.2 [5.8 , 7.1 ]	p=0.046
Baseline Creatinine (umol/L)	99 [85 , 119 ]	99 [81 , 119 ]	p=0.35
Baseline eGFR (mL/min/1.73m2)	63 [49 , 77 ]	59 [45 , 74 ]	p=0.015
eGFR >=60	345 (55.3%)	262 (49.7%)	p=0.06
Loop diuretics	479 (76.8%)	404 (76.7%)	p=0.97
Ace inhibitor (ACEi)	267 (42.8%)	191 (36.2%)	p=0.024
Angiotensin receptor blocker (ARB)	157 (25.2%)	180 (34.2%)	p<0.001
Nepriylsin inhibitor/ARB (ARNI)	108 (17.3%)	44 (8.3%)	p<0.001
Beta Blocker	551 (88.3%)	440 (83.5%)	p=0.019
Mineralocorticoid receptor antagonist (MRA)	360 (57.7%)	220 (41.7%)	p<0.001
Pacemaker	65 (10.4%)	54 (10.2%)	p=0.92
ICD	46 (7.4%)	13 (2.5%)	p<0.001

