

## **SUPPLEMENTAL MATERIALS**

Online Supplement for manuscript entitled: **Low natriuretic peptide levels and outcomes in patients with heart failure and preserved ejection fraction.**

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**Supplementary Table 1. Study design of I-Preserve, PARAGON-HF, DELIVER, and EMPEROR-Preserved trials.**

	<b>I- Preserve</b>	<b>PARAGON-HF</b>	<b>DELIVER</b>
<b>Number of patients</b>	4128	4796	6263
<b>Enrollment period</b>	2002-2005	2014-2016	2018-2020
<b>Intervention (target)</b>	Irbesartan 300 mg OD	Sacubitril/valsartan (LCZ696) 200 mg twice a day	Dapagliflozin 10mg once daily
<b>Control</b>	Placebo	Valsartan 160mg twice a day	Placebo
<b>Follow-up period</b>	Mean 49.5 months	Median 35 months	Median 2.3 years
<b>Key inclusion criteria</b>			
Age, years	≥ 60	≥ 50	≥ 40
NYHA class	II–IV	II–IV	II–IV
LVEF	≥45%	≥45%	>40%
	HF hospitalization within the last 6 months	NT-proBNP >300 pg/mL if not AF or >900 pg/mL if AF	NT-proBNP >300 pg/mL if not AF or >600 pg/mL if AF
	or	or	Medical history of typical symptoms/signs of heart failure ≥6weeks before enrolment with at least intermittent need for diuretic treatment (requiring recurrent intermittent dosing).
	NYHA III-IV and corroborative evidence of HF by at least 1 of the following findings	NT-proBNP >200 pg/mL if not AF or >600 pg/mL if AF, if HF hospitalization within 9 months	
	1) Chest x-ray evidence of pulmonary congestion	Symptom of HF requiring treatment with diuretic for 30 days	Structural heart disease evidenced by at least one of the following echocardiogram, and/or cardiac magnetic resonance
	2) ECG evidence of moderate or severe LVH (at least one of the following): SV1+RV5 or RV6 >3.5 mV, or RaVL >1.1 mV, or RaVL +SV3 >2.8 mV in men or 2.0 mV in women	Structural heart disease evidenced by at least one of the following echocardiography findings.	1) LA enlargement with at least one of the following: LA width (diameter) ≥3.8 cm, or LA length ≥5.0 cm, or LA area ≥20 cm <sup>2</sup> , or LA volume ≥55 mL, or LA volume index ≥29 mL/m <sup>2</sup> .
	3) Left bundle branch block on ECG	1) LA enlargement defined by at least one of the following: LA width (diameter) ≥3.8 cm, or LA length ≥5.0 cm, or LA area ≥20 cm <sup>2</sup> , or LA volume ≥55 ml, or LA volume index ≥29 ml/m <sup>2</sup>	2) LVH with septal thickness or posterior wall thickness ≥1.1 cm.
	4) Echocardiographic evidence of any one of the following: LVH (posterior wall+intraventricular septal thickness)/2 ≥1.3 cm, or posterior wall thickness ≥1.2 cm, or LA enlargement in the absence of AF (women ≥42 mm, men ≥46 mm)	2) LVH defined by septal thickness or posterior wall thickness ≥1.1 cm	Patients may be ambulatory, or hospitalized; patients must be off intravenous heart failure therapy.
<b>Body mass index exclusion criteria</b>	None	Body mass index >40 kg/m <sup>2</sup>	Body mass index >50 kg/m <sup>2</sup>
<b>Renal exclusion criteria</b>	Serum creatinine ≥ 2.5 mg/dL	eGFR <30 ml/min/1.73m <sup>2</sup>	eGFR <25 ml/min/1.73m <sup>2</sup>
<b>Primary outcome</b>	Death from any cause or cardiovascular hospitalization	Death from cardiovascular causes and total HF hospitalizations (first and recurrent)	Death from cardiovascular death or worsening HF event (hospitalization for HF or urgent HF visit)

AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; HF, heart failure; ECG, electrocardiography; I-Preserve, Irbesartan in Heart Failure with Preserved Ejection Fraction; LA, left atrium; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NTproBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; and PARAGON-HF, Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction.

**Supplementary Table 2. Patients characteristics according to NT-proBNP categories among those assigned to irbesartan versus placebo.**

	NT-proBNP <125 pg/mL		NT-proBNP ≥125 pg/mL	
	Irbesartan N=391	Placebo N=417	Irbesartan N=1,332	Placebo N=1,340
Age — years	68.5±6.1	68.7±6.1	72.5±6.8	72.7±7.0
Age group — no. (%)				
-70 years	235 (60.1%)	248 (59.5%)	471 (35.4%)	468 (34.9%)
>70 years	156 (39.9%)	169 (40.5%)	861 (64.6%)	872 (65.1%)
Region — no. (%)				
North America	17 (4.3%)	25 (6.0%)	122 (9.2%)	119 (8.9%)
Latin and Central America	82 (21.0%)	94 (22.5%)	228 (17.1%)	218 (16.3%)
Western Europe	120 (30.7%)	119 (28.5%)	482 (36.2%)	486 (36.3%)
Central and Eastern Europe (including Russia)	164 (41.9%)	175 (42.0%)	471 (35.4%)	482 (36.0%)
Asia-Pacific, and other	8 (2.0%)	4 (1.0%)	29 (2.2%)	35 (2.6%)
Male sex — no. (%)	135 (34.5%)	157 (37.6%)	566 (42.5%)	527 (39.3%)
Race — no. (%)				
White	368 (94.1%)	390 (93.5%)	1,248 (93.7%)	1,257 (93.8%)
Black	6 (1.5%)	9 (2.2%)	23 (1.7%)	24 (1.8%)
Asian	3 (0.8%)	1 (0.2%)	14 (1.1%)	14 (1.0%)
Others	14 (3.6%)	17 (4.1%)	47 (3.5%)	45 (3.4%)
Systolic blood pressure — mmHg	138±13	136±14	136±15	136±15
Diastolic blood pressure — mmHg	80±8	81±8	79±9	78±9
Heart rate — beats/min	71±9	71±9	72±11	71±11
In patients without AF in ECG — beats/min	71±9	71±9	70±10	70±10
In patients with AF in ECG — beats/min	71±6	77±6	77±12	75±11
Body-mass index — kg/m <sup>2</sup> *	30.3±5.1	30.5±4.8	29.5±5.3	29.2±5.2
Weight category — no. (%)				
Underweight	0 (0.0%)	1 (0.2%)	6 (0.5%)	9 (0.7%)
Normal	43 (11.0%)	40 (9.6%)	226 (17.0%)	261 (19.6%)
Overweight	165 (42.2%)	168 (40.3%)	566 (42.7%)	562 (42.2%)
Obese	183 (46.8%)	208 (49.9%)	529 (39.9%)	501 (37.6%)
Current smoker — no. (%)	64 (16.4%)	81 (19.4%)	244 (18.3%)	234 (17.5%)
<b>HF characteristics</b>				
Left ventricular hypertrophy or left atrial enlargement in echocardiography as inclusion criteria — no. (%)	338 (86.4%)	365 (87.5%)	1,166 (87.5%)	1,140 (85.1%)
NYHA functional class — no. (%)				
II	68 (17.4%)	71 (17.0%)	274 (20.6%)	298 (22.3%)
III	311 (79.5%)	342 (82.0%)	1,024 (76.9%)	1,001 (74.8%)
IV	12 (3.1%)	4 (1.0%)	34 (2.6%)	40 (3.0%)
Time from diagnosis of HF — no. (%)				
=<1 year	178 (45.6%)	185 (44.4%)	623 (46.8%)	664 (49.6%)
1-5 years	148 (37.9%)	185 (44.4%)	488 (36.7%)	467 (34.9%)
=> 5years	64 (16.4%)	47 (11.3%)	219 (16.5%)	208 (15.5%)
Hospitalization for HF within previous 6 months	135 (34.5%)	126 (30.2%)	608 (45.6%)	639 (47.7%)
Cause of HF — no. (%)				
Ischemic	73 (18.7%)	68 (16.3%)	386 (29.0%)	358 (26.7%)
Hypertension	289 (73.9%)	320 (76.7%)	808 (60.7%)	800 (59.7%)
Valvular heart disease	1 (0.3%)	0 (0.0%)	17 (1.3%)	25 (1.9%)
Others	28 (7.2%)	29 (7.0%)	121 (9.1%)	157 (11.7%)
LVEF — %	61.4±8.1	61.1±8.8	58.8±9.5	59.1±9.0
<b>MLHFQ</b>				
Total MLHFQ score	44.5 (30.0-62.0)	42.0 (29.0-55.0)	42.0 (27.0-59.0)	43.0 (29.0-60.0)

Physical dimension	23.0 (16.0-29.0)	22.0 (14.0-28.0)	22.0 (15.0-29.0)	23.0 (15.0-29.0)
Emotional dimension	9.0 (5.0-14.0)	7.0 (3.0-12.0)	8.0 (3.0-13.0)	8.0 (4.0-13.0)
<b>Markers of congestion — no. (%)</b>				
Pulmonary congestion in chest X ray	124 (32.3%)	130 (32.2%)	556 (43.3%)	546 (42.3%)
Peripheral edema				
None	175 (44.8%)	192 (46.0%)	612 (46.0%)	585 (43.7%)
Trace	133 (34.0%)	134 (32.1%)	385 (29.0%)	430 (32.1%)
1+ to 2+	78 (19.9%)	86 (20.6%)	306 (23.0%)	292 (21.8%)
3+ to 4+	5 (1.3%)	5 (1.2%)	26 (2.0%)	33 (2.5%)
Third heart sound	24 (6.1%)	29 (7.0%)	107 (8.1%)	124 (9.3%)
Elevated jugular venous pressure	19 (4.9%)	21 (5.0%)	126 (9.5%)	130 (9.7%)
Rales				
Clear	274 (70.1%)	310 (74.3%)	915 (68.8%)	923 (68.9%)
Wheezing only	7 (1.8%)	15 (3.6%)	21 (1.6%)	27 (2.0%)
Basilar rales	99 (25.3%)	83 (19.9%)	349 (26.3%)	347 (25.9%)
Diffuse rales	11 (2.8%)	9 (2.2%)	44 (3.3%)	43 (3.2%)
Liver enlargement	62 (15.9%)	82 (19.8%)	247 (18.6%)	257 (19.2%)
<b>Comorbidities — no. (%)</b>				
AF	39 (10.0%)	30 (7.2%)	452 (33.9%)	487 (36.3%)
Myocardial infarction	51 (13.0%)	48 (11.5%)	375 (28.2%)	365 (27.2%)
Angina pectoris	158 (40.4%)	165 (39.6%)	621 (46.6%)	599 (44.7%)
PCI or CABG	29 (7.4%)	31 (7.4%)	209 (15.7%)	190 (14.2%)
Hypertension	358 (91.6%)	379 (90.9%)	1,175 (88.2%)	1,172 (87.5%)
Diabetes	101 (25.8%)	97 (23.3%)	377 (28.3%)	388 (29.0%)
Stroke or transient ischemic attack	34 (8.7%)	25 (6.0%)	134 (10.1%)	141 (10.5%)
Chronic obstructive pulmonary disease or asthma	24 (6.1%)	33 (7.9%)	137 (10.3%)	123 (9.2%)
<b>ECG findings</b>				
AF or atrial flutter — no. (%)	9 (2.3%)	7 (1.7%)	287 (21.5%)	294 (21.9%)
QRS duration — msec	84 (80-100)	86 (80-100)	90 (80-104)	90 (80-104)
Left bundle brunch block — %	23 (6.0%)	22 (5.3%)	112 (9.0%)	108 (8.7%)
Right bundle brunch block — %	19 (5.0%)	31 (7.5%)	97 (7.8%)	96 (7.8%)
Left ventricular hypertrophy in ECG — %	108 (28.3%)	114 (27.6%)	399 (32.2%)	405 (32.7%)
<b>Laboratory data</b>				
N-terminal pro-B-type natriuretic peptide — pg/ml	65 (42-97)	70 (45-96)	541 (263-1238)	522 (255-1217)
In patients without AF in ECG	66 (42-97)	70 (44-96)	414 (229-899)	386 (218-897)
In patients with AF in ECG	59 (44-84)	64 (45-105)	1337 (820-2143)	1281 (799-1967)
eGFR — ml/min/1.73 m <sup>2</sup>	82±21	82±22	70±22	70±22
eGFR <60 ml/min/1.73 m <sup>2</sup> — no. (%)	60 (15.4%)	68 (16.4%)	478 (36.2%)	460 (34.5%)
Serum Creatinine — μmol/l	77±21	79±32	92±29	91±30
Blood urea nitrogen — mmol/l	6.7±2.1	6.5±2.1	7.9±3.5	7.9±3.7
Albumin — g/dl	4.2±1.3	4.2±1.3	4.6±1.7	4.6±1.9
Serum sodium — mmol/l	139±3	140±3	140±3	139±3
Haemoglobin — g/l	142±17	143±18	138±19	137±20
Anemia — no. (%)	25 (6.5%)	22 (5.3%)	192 (14.7%)	198 (15.1%)
<b>Drugs and interventions — no. (%)</b>				
ACE inhibitor	90 (23.0%)	88 (21.1%)	365 (27.4%)	353 (26.3%)
Beta blocker	200 (51.2%)	218 (52.3%)	826 (62.0%)	809 (60.4%)
Spirolactone	47 (12.0%)	49 (11.8%)	211 (15.8%)	224 (16.7%)
Diuretic	294 (75.2%)	322 (77.2%)	1,117 (83.9%)	1,137 (84.9%)
Loop diuretic	148 (37.9%)	141 (33.8%)	745 (55.9%)	774 (57.8%)
Calcium-channel blocker	182 (46.5%)	191 (45.8%)	526 (39.5%)	508 (37.9%)

Nitrate	85 (21.7%)	81 (19.4%)	369 (27.7%)	387 (28.9%)
Digoxin	20 (5.1%)	14 (3.4%)	218 (16.4%)	221 (16.5%)
Antiarrhythmic agent	21 (5.4%)	21 (5.0%)	131 (9.8%)	125 (9.3%)
Anticoagulant agent	19 (4.9%)	20 (4.8%)	281 (21.1%)	309 (23.1%)
In patients with AF in ECG	2 (22.2%)	4 (57.1%)	175 (61.0%)	192 (65.3%)
In patients with AF history	11 (28.2%)	9 (30.0%)	236 (52.2%)	267 (54.8%)
Implantable cardioverter-defibrillator	0 (0.0%)	1 (0.2%)	3 (0.2%)	5 (0.4%)
Pacemaker	9 (2.3%)	4 (1.0%)	92 (6.9%)	101 (7.5%)

Data are presented as mean±standard deviation or median (interquartile range).

\* Underweight, body mass index <18.5 kg/m<sup>2</sup>; Normal, body mass index 18.5-25.0 kg/m<sup>2</sup>; Overweight, body mass index 25.0-30.0 kg/m<sup>2</sup>; and Obese, body mass index ≥ 30 kg/m<sup>2</sup>.

Heart rate is missing in 3 cases; body mass index in 12 cases; current smoker and NYHA functional class in 1 case; time from diagnosis of HF in 4 cases; LVEF in 3 cases; MLHFQ score in 791 patients; pulmonary congestion in 118 cases; peripheral edema, third heart sound, elevated jugular venous pressure, and rales in 3 cases; liver enlargement in 10 cases; QRS duration in 211 cases; left bundle brunch block and left ventricular hypertrophy in ECG in 206 cases; right bundle brunch block in 210 cases; left ventricular hypertrophy in 206 cases; eGFR and serum creatinine in 23 cases; blood urea nitrogen, albumin, serum sodium in 24 cases; and hemoglobin in 65 cases.

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; CABG, coronary artery bypass graft; ECG, electrocardiography; eGFR; estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

**Supplementary Table 3. Patient characteristics according to NT-proBNP categories among those with age < 70 years versus ≥ 70 years.**

	Age < 70 years		Age ≥ 70 years	
	NT-proBNP <125 pg/ml N=483	NT-proBNP ≥125 pg/ml N=939	NT-proBNP <125 pg/ml N=325	NT-proBNP ≥125 pg/ml N=1,733
Age — years	64.4±2.9	65.2±2.8	74.8±4.0	76.6±4.8
Region — no. (%)				
North America	26 (5.4%)	65 (6.9%)	16 (4.9%)	176 (10.2%)
Latin and Central America	96 (19.9%)	133 (14.2%)	80 (24.6%)	313 (18.1%)
Western Europe	127 (26.3%)	253 (26.9%)	112 (34.5%)	715 (41.3%)
Central and Eastern Europe (including Russia)	228 (47.2%)	462 (49.2%)	111 (34.2%)	491 (28.3%)
Asia-Pacific, and other	6 (1.2%)	26 (2.8%)	6 (1.8%)	38 (2.2%)
Male sex — no. (%)	187 (38.7%)	436 (46.4%)	105 (32.3%)	657 (37.9%)
Race — no. (%)				
White	455 (94.2%)	873 (93.0%)	303 (93.2%)	1,632 (94.2%)
Black	8 (1.7%)	18 (1.9%)	7 (2.2%)	29 (1.7%)
Asian	4 (0.8%)	18 (1.9%)	0 (0.0%)	10 (0.6%)
Others	16 (3.3%)	30 (3.2%)	15 (4.6%)	62 (3.6%)
Systolic blood pressure — mmHg	137±13	136±15	137±15	136±15
Diastolic blood pressure — mmHg	81±8	80±9	79±9	78±9
Heart rate — beats/min	71±9	71±10	71±9	72±11
In patients without AF on ECG — beats/min	71±9	69±10	71±9	71±10
In patients with AF on ECG — beats/min	70±5	76±11	78±6	76±12
Body-mass index — kg/m <sup>2</sup>	30.9±5.0	30.1±5.3	29.6±4.9	28.9±5.1
Weight category — no. (%) *				
Underweight	0 (0.0%)	4 (0.4%)	1 (0.3%)	11 (0.6%)
Normal	39 (8.1%)	130 (13.9%)	44 (13.5%)	357 (20.7%)
Overweight	188 (38.9%)	385 (41.1%)	145 (44.6%)	743 (43.1%)
Obese	256 (53.0%)	418 (44.6%)	135 (41.5%)	612 (35.5%)
Current smoker — no. (%)	84 (17.4%)	187 (19.9%)	61 (18.8%)	291 (16.8%)
<b>HF characteristics</b>				
Left ventricular hypertrophy or left atrial enlargement on echocardiography as inclusion criteria — no. (%)	420 (87.0%)	809 (86.2%)	283 (87.1%)	1,497 (86.4%)
NYHA functional class — no. (%)				
II	90 (18.6%)	206 (22.0%)	49 (15.1%)	366 (21.1%)
III	384 (79.5%)	715 (76.2%)	269 (82.8%)	1,310 (75.6%)
IV	9 (1.9%)	17 (1.8%)	7 (2.2%)	57 (3.3%)
Time from diagnosis of HF — years	428 (119-1169)	423 (88-1269)	408 (115-1256)	383 (90-1265)
Hospitalization for HF in prior 6 months	158 (32.7%)	431 (45.9%)	103 (31.7%)	816 (47.1%)
Cause of HF — no. (%)				
Ischemic	69 (14.3%)	282 (30.0%)	72 (22.2%)	462 (26.7%)
Hypertension	388 (80.3%)	556 (59.2%)	221 (68.0%)	1,052 (60.7%)
Valvular heart disease	1 (0.2%)	14 (1.5%)	0 (0.0%)	28 (1.6%)
Others	25 (5.2%)	87 (9.3%)	32 (9.8%)	191 (11.0%)
LVEF — %	61.1±8.3	58.5±9.2	61.6±8.7	59.2±9.3
<b>MLHFQ</b>				
Total MLHFQ score	43 (29-57)	43 (29-60)	43 (31-60)	43 (27-59)
Physical dimension	22 (15-28)	22 (15-28)	23 (15-28)	23 (15-29)
Emotional dimension	7 (4-13)	8 (3-13)	8 (3-13)	8 (3-13)
<b>Markers of congestion — no. (%)</b>				
Pulmonary congestion in chest X ray	144 (30.6%)	325 (35.6%)	110 (34.6%)	777 (46.8%)
Peripheral edema				
None	216 (44.7%)	404 (43.1%)	151 (46.5%)	793 (45.8%)
Trace	172 (35.6%)	315 (33.6%)	95 (29.2%)	500 (28.9%)
1+ to 2+	90 (18.6%)	200 (21.3%)	74 (22.8%)	398 (23.0%)
3+ to 4+	5 (1.0%)	19 (2.0%)	5 (1.5%)	40 (2.3%)
Third heart sound	33 (6.8%)	74 (7.9%)	20 (6.2%)	157 (9.1%)
Elevated jugular venous pressure	20 (4.1%)	60 (6.4%)	20 (6.2%)	196 (11.3%)
Rales				
Clear	358 (74.1%)	659 (70.3%)	226 (69.5%)	1,179 (68.1%)
Wheezing only	14 (2.9%)	14 (1.5%)	8 (2.5%)	34 (2.0%)
Basilar rales	104 (21.5%)	241 (25.7%)	78 (24.0%)	455 (26.3%)

Diffuse rales	7 (1.4%)	24 (2.6%)	13 (4.0%)	63 (3.6%)
Liver enlargement	85 (17.6%)	202 (21.6%)	59 (18.2%)	302 (17.5%)
<b>Comorbidities — no. (%)</b>				
AF	34 (7.0%)	265 (28.2%)	35 (10.8%)	674 (38.9%)
Myocardial infarction	51 (10.6%)	283 (30.1%)	48 (14.8%)	457 (26.4%)
Angina pectoris	196 (40.6%)	455 (48.5%)	127 (39.1%)	765 (44.1%)
PCI or CABG	29 (6.0%)	138 (14.7%)	31 (9.5%)	261 (15.1%)
Hypertension	446 (92.3%)	842 (89.7%)	291 (89.5%)	1,505 (86.8%)
Diabetes	116 (24.0%)	288 (30.7%)	82 (25.2%)	477 (27.5%)
Stroke or transient ischemic attack	26 (5.4%)	88 (9.4%)	33 (10.2%)	187 (10.8%)
Chronic obstructive pulmonary disease or asthma	33 (6.8%)	79 (8.4%)	24 (7.4%)	181 (10.4%)
<b>ECG findings</b>				
AF or atrial flutter — no. (%)	8 (1.7%)	170 (18.1%)	8 (2.5%)	411 (23.7%)
QRS duration — msec	84 (80-100)	88 (80-100)	86 (80-100)	90 (80-108)
Left bundle branch block — %	25 (5.2%)	64 (7.0%)	20 (6.3%)	156 (10.0%)
Right bundle branch block — %	25 (5.2%)	59 (6.5%)	25 (7.9%)	134 (8.6%)
Left ventricular hypertrophy on ECG — %	137 (28.7%)	322 (35.3%)	85 (26.8%)	482 (30.8%)
<b>Laboratory data</b>				
N-terminal pro-B-type natriuretic peptide — pg/ml	63 (40-93)	431 (214-981)	75 (48-101)	601 (296-1373)
In patients without AF on ECG	63 (39-93)	339 (196-682)	75 (49-101)	444 (246-1003)
In patients with AF on ECG	68 (60-100)	1163 (733-1766)	46 (40-92)	1386 (836-2138)
eGFR — ml/min/1.73 m <sup>2</sup>	85±21	76±22	78±22	66±21
eGFR <60 ml/min/1.73 m <sup>2</sup> — no. (%)	57 (11.9%)	243 (26.1%)	71 (22.0%)	695 (40.3%)
Serum Creatinine — μmol/l	77±29	87±27	80±25	94±30
Blood urea nitrogen — mmol/l	6.4±1.8	7.1±2.9	7.0±2.5	8.4±3.8
Albumin — g/dl	4.2±1.3	4.5±1.6	4.2±1.3	4.7±1.9
Serum sodium — mmol/l	140±3	140±3	140±3	139±3
Hemoglobin — g/l	143±16	140±20	141±19	137±19
Anemia — no. (%)	25 (5.3%)	111 (12.1%)	22 (6.9%)	279 (16.4%)
<b>Drugs and interventions — no. (%)</b>				
ACE inhibitor	118 (24.4%)	264 (28.1%)	60 (18.5%)	454 (26.2%)
Beta-blocker	281 (58.2%)	652 (69.4%)	137 (42.2%)	983 (56.7%)
Spirolactone	50 (10.4%)	148 (15.8%)	46 (14.2%)	287 (16.6%)
Diuretic	369 (76.4%)	795 (84.7%)	247 (76.0%)	1,459 (84.2%)
Loop diuretic	162 (33.5%)	485 (51.7%)	127 (39.1%)	1,034 (59.7%)
Calcium-channel blocker	217 (44.9%)	394 (42.0%)	156 (48.0%)	640 (36.9%)
Nitrate	86 (17.8%)	229 (24.4%)	80 (24.6%)	527 (30.4%)
Digoxin	18 (3.7%)	140 (14.9%)	16 (4.9%)	299 (17.3%)
Antiarrhythmic agent	17 (3.5%)	68 (7.2%)	25 (7.7%)	188 (10.8%)
Anticoagulant agent	23 (4.8%)	154 (16.4%)	16 (4.9%)	436 (25.2%)
In patients with AF on ECG	2 (25.0%)	100 (58.8%)	4 (50.0%)	267 (65.0%)
In patients with AF history	10 (29.4%)	133 (50.2%)	10 (28.6%)	370 (54.9%)
Implantable cardioverter–defibrillator	0 (0.0%)	2 (0.2%)	1 (0.3%)	6 (0.3%)
Pacemaker	5 (1.0%)	27 (2.9%)	8 (2.5%)	166 (9.6%)

Data are presented as mean±standard deviation or median (interquartile range).

Heart rate is missing in 3 cases; body mass index in 12 cases; current smoker and NYHA functional class in 1 case; time from diagnosis of HF in 4 cases; LVEF in 3 cases; MLHFQ score in 791 patients; pulmonary congestion in 118 cases; peripheral edema, third heart sound, elevated jugular venous pressure, and rales in 3 cases; liver enlargement in 10 cases; QRS duration in 211 cases; left bundle branch block and left ventricular hypertrophy on ECG in 206 cases; right bundle branch block in 210 cases; eGFR and serum creatinine in 23 cases; blood urea nitrogen, albumin, serum sodium in 24 cases; and hemoglobin in 65 cases.

\* Underweight, body mass index <18.5 kg/m<sup>2</sup>; Normal, body mass index 18.5-25.0 kg/m<sup>2</sup>; Overweight, body mass index 25.0-30.0 kg/m<sup>2</sup>; and Obese, body mass index ≥ 30 kg/m<sup>2</sup>.

Abbreviations are the same in Supplementary Table 2.



**Supplementary Table 4. Patient characteristics according to NT-proBNP categories in patients with LVEF  $\geq$ 50%.**

	<b>Overall</b>	<b>NT-proBNP &lt;125</b>	<b>NT-proBNP <math>\geq</math>125</b>	<b>P-value</b>
	<b>N=3,062</b>	<b>pg/ml</b>	<b>pg/ml</b>	
		<b>N=768</b>	<b>N=2,294</b>	
Age — years	71.7 $\pm$ 6.9	68.6 $\pm$ 6.1	72.8 $\pm$ 6.9	<0.001
Age group — no. (%)				<0.001
< 70 years	1,244 (40.6%)	462 (60.2%)	782 (34.1%)	
$\geq$ 70 years	1,818 (59.4%)	306 (39.8%)	1,512 (65.9%)	
Region — no. (%)				<0.001
North America	262 (8.6%)	42 (5.5%)	220 (9.6%)	
Latin and Central America	549 (17.9%)	166 (21.6%)	383 (16.7%)	
Western Europe	1,069 (34.9%)	229 (29.8%)	840 (36.6%)	
Central and Eastern Europe (including Russia)	1,113 (36.3%)	320 (41.7%)	793 (34.6%)	
Asia-Pacific, and other	69 (2.3%)	11 (1.4%)	58 (2.5%)	
Male sex — no. (%)	1,164 (38.0%)	277 (36.1%)	887 (38.7%)	0.20
Race — no. (%)				0.52
White	2,868 (93.7%)	722 (94.0%)	2,146 (93.5%)	
Black	58 (1.9%)	14 (1.8%)	44 (1.9%)	
Asian	25 (0.8%)	3 (0.4%)	22 (1.0%)	
Others	111 (3.6%)	29 (3.8%)	82 (3.6%)	
Systolic blood pressure — mmHg	137 $\pm$ 15	137 $\pm$ 14	136 $\pm$ 15	0.28
Diastolic blood pressure — mmHg	79 $\pm$ 9	81 $\pm$ 8	78 $\pm$ 9	<0.001
Heart rate — beats/min	71 $\pm$ 10	71 $\pm$ 9	71 $\pm$ 11	0.77
In patients without AF on ECG — beats/min	70 $\pm$ 10	71 $\pm$ 9	70 $\pm$ 10	0.003
In patients with AF on ECG — beats/min	76 $\pm$ 11	74 $\pm$ 7	76 $\pm$ 11	0.47
Body-mass index — kg/m <sup>2</sup>	29.7 $\pm$ 5.2	30.4 $\pm$ 5.0	29.5 $\pm$ 5.2	<0.001
Weight category — no. (%) *				<0.001
Underweight	14 (0.5%)	1 (0.1%)	13 (0.6%)	
Normal	475 (15.6%)	79 (10.3%)	396 (17.3%)	
Overweight	1,270 (41.6%)	312 (40.6%)	958 (41.9%)	
Obese	1,293 (42.4%)	376 (49.0%)	917 (40.1%)	
Current smoker — no. (%)	535 (17.5%)	139 (18.1%)	396 (17.3%)	0.60
<b>HF characteristics</b>	<b>0.0<math>\pm</math>0.0</b>	<b>0.0<math>\pm</math>0.0</b>	<b>0.0<math>\pm</math>0.0</b>	
Left ventricular hypertrophy or left atrial enlargement on echocardiography as inclusion criteria — no. (%)	2,654 (86.7%)	669 (87.1%)	1,985 (86.5%)	0.68
NYHA functional class — no. (%)				0.021
II	618 (20.2%)	131 (17.1%)	487 (21.2%)	
III	2,368 (77.4%)	622 (81.0%)	1,746 (76.1%)	
IV	75 (2.5%)	15 (2.0%)	60 (2.6%)	
Time from diagnosis of HF — days	403 (93-1235)	418 (119-1208)	384 (88-1250)	0.34
Hospitalization for HF in prior 6 months	1,286 (42.0%)	241 (31.4%)	1,045 (45.6%)	<0.001
Cause of HF — no. (%)				<0.001
Ischemic	711 (23.2%)	132 (17.2%)	579 (25.2%)	
Hypertension	2,024 (66.1%)	582 (75.8%)	1,442 (62.9%)	
Valvular heart disease	36 (1.2%)	1 (0.1%)	35 (1.5%)	
Others	291 (9.5%)	53 (6.9%)	238 (10.4%)	
LVEF — %	61.2 $\pm$ 8.4	62.0 $\pm$ 8.0	61.0 $\pm$ 8.4	0.003
<b>MLHFQ</b>				
Total MLHFQ score	43 (29-59)	43 (29-58)	43 (28-59)	0.86
Physical dimension	23 (15-29)	22 (15-28)	23 (15-29)	0.48
Emotional dimension	8 (3-13)	8 (4-13)	8 (3-13)	0.82
<b>Markers of congestion — no. (%)</b>				
Pulmonary congestion in chest X ray	1,162 (39.3%)	238 (31.8%)	924 (41.9%)	<0.001
Peripheral edema				0.11
None	1,368 (44.7%)	346 (45.1%)	1,022 (44.6%)	
Trace	948 (31.0%)	254 (33.1%)	694 (30.3%)	
1+ to 2+	682 (22.3%)	159 (20.7%)	523 (22.8%)	
3+ to 4+	61 (2.0%)	9 (1.2%)	52 (2.3%)	
Third heart sound	233 (7.6%)	49 (6.4%)	184 (8.0%)	0.14
Elevated jugular venous pressure	243 (7.9%)	37 (4.8%)	206 (9.0%)	<0.001
Rales				0.031

Clear	2,168 (70.9%)	563 (73.3%)	1,605 (70.1%)	
Wheezing only	61 (2.0%)	22 (2.9%)	39 (1.7%)	
Basilar rales	744 (24.3%)	164 (21.4%)	580 (25.3%)	
Diffuse rales	86 (2.8%)	19 (2.5%)	67 (2.9%)	
Liver enlargement	553 (18.1%)	135 (17.6%)	418 (18.3%)	0.68
<b>Comorbidities — no. (%)</b>				
AF	864 (28.2%)	65 (8.5%)	799 (34.8%)	<0.001
Myocardial infarction	670 (21.9%)	93 (12.1%)	577 (25.2%)	<0.001
Angina pectoris	1,328 (43.4%)	306 (39.8%)	1,022 (44.6%)	0.023
PCI or CABG	396 (12.9%)	56 (7.3%)	340 (14.8%)	<0.001
Hypertension	2,740 (89.5%)	702 (91.4%)	2,038 (88.8%)	0.045
Diabetes	855 (27.9%)	189 (24.6%)	666 (29.0%)	0.018
Stroke or transient ischemic attack	291 (9.5%)	54 (7.0%)	237 (10.3%)	0.007
Chronic obstructive pulmonary disease or asthma	278 (9.1%)	53 (6.9%)	225 (9.8%)	0.015
<b>ECG findings</b>				
AF or atrial flutter — no. (%)	496 (16.2%)	15 (2.0%)	481 (21.0%)	<0.001
QRS duration — msec	90 (80-100)	85 (80-100)	90 (80-102)	<0.001
Left bundle branch block — %	204 (7.1%)	41 (5.4%)	163 (7.7%)	0.038
Right bundle branch block — %	218 (7.6%)	48 (6.4%)	170 (8.0%)	0.14
Left ventricular hypertrophy on ECG — %	891 (30.9%)	210 (27.8%)	681 (32.1%)	0.029
<b>Laboratory data</b>				
N-terminal pro-B-type natriuretic peptide — pg/ml	308 (124-879)	69 (43-96)	493 (244-1150)	<0.001
In patients without AF on ECG	235 (106-549)	69 (43-96)	371 (214-806)	<0.001
In patients with AF on ECG	1257 (754-1921)	60 (44-95)	1306 (816-1943)	<0.001
eGFR — ml/min/1.73 m <sup>2</sup>	73±22	82±22	70±22	<0.001
eGFR <60 ml/min/1.73 m <sup>2</sup> — no. (%)	930 (30.5%)	119 (15.6%)	811 (35.6%)	<0.001
Serum Creatinine — μmol/l	88±29	78±27	91±29	<0.001
Blood urea nitrogen — mmol/l	7.6±3.3	6.6±2.1	7.9±3.6	<0.001
Albumin — g/dl	4.5±1.7	4.2±1.3	4.6±1.8	<0.001
Serum sodium — mmol/l	140±3	140±3	140±3	0.63
Hemoglobin — g/l	139±19	143±17	137±20	<0.001
Anemia — no. (%)	381 (12.7%)	45 (6.0%)	336 (14.9%)	<0.001
<b>Drugs and interventions — no. (%)</b>				
ACE inhibitor	765 (25.0%)	171 (22.3%)	594 (25.9%)	0.044
Beta-blocker	1,798 (58.7%)	394 (51.3%)	1,404 (61.2%)	<0.001
Spirolactone	437 (14.3%)	88 (11.5%)	349 (15.2%)	0.010
Diuretic	2,496 (81.5%)	582 (75.8%)	1,914 (83.4%)	<0.001
Loop diuretic	1,543 (50.4%)	271 (35.3%)	1,272 (55.4%)	<0.001
Calcium-channel blocker	1,292 (42.2%)	361 (47.0%)	931 (40.6%)	0.002
Nitrate	782 (25.5%)	159 (20.7%)	623 (27.2%)	<0.001
Digoxin	373 (12.2%)	31 (4.0%)	342 (14.9%)	<0.001
Antiarrhythmic agent	256 (8.4%)	39 (5.1%)	217 (9.5%)	<0.001
Anticoagulant agent	556 (18.2%)	36 (4.7%)	520 (22.7%)	<0.001
In patients with AF on ECG	326 (65.7%)	5 (33.3%)	321 (66.7%)	0.007
In patients with AF history	462 (53.5%)	18 (27.7%)	444 (55.6%)	<0.001
Implantable cardioverter-defibrillator	8 (0.3%)	0 (0.0%)	8 (0.3%)	0.21
Pacemaker	182 (5.9%)	12 (1.6%)	170 (7.4%)	<0.001

Data are presented as mean±standard deviation or median (interquartile range).

\* Underweight, body mass index <18.5 kg/m<sup>2</sup>; Normal, body mass index 18.5-25.0 kg/m<sup>2</sup>; Overweight, body mass index 25.0-30.0 kg/m<sup>2</sup>; and Obese, body mass index ≥ 30 kg/m<sup>2</sup>.

Heart rate is missing in 3 cases; body mass index in 10 cases; current smoker and NYHA functional class in 1 case; time from diagnosis of HF in 4 cases; LVEF in 3 cases; MLHFQ score in 690 patients; pulmonary congestion in 108 cases; peripheral edema, third heart sound, elevated jugular venous pressure, and rales in 3 cases; liver enlargement in 10 cases; QRS duration in 186 cases; left bundle branch block and left ventricular hypertrophy on ECG in 182 cases; right bundle branch block in 185 cases; eGFR and serum creatinine in 17 cases; blood urea nitrogen, albumin, serum sodium in 18 cases; and hemoglobin in 57 cases.

Abbreviations are the same in Supplementary Table 2.

**Supplementary Table 5. Outcomes according to NT-proBNP categories in patients with LVEF  $\geq$ 50%.**

	<b>Overall N=3,062</b>	<b>NT-proBNP &lt;125 pg/ml N=768</b>	<b>NT-proBNP <math>\geq</math>125 pg/ml N=2,294</b>
<b>Cardiovascular death or HF hospitalization</b>			
No. of events (%)	728 (23.8)	59 (7.7)	669 (29.2)
Event rate per 100 person-years (95% CI)	6.3 (5.9-6.8)	1.8 (1.4-2.3)	8.1 (7.5-8.7)
Model 1: Hazard ratio (95% CI)*	-	0.23 (0.17-0.29)‡	Reference
Model 2: Hazard ratio (95% CI)†	-	0.36 (0.27-0.47)‡	Reference
<b>Cardiovascular death</b>			
No. of events (%)	405 (13.2)	37 (4.8)	368 (16.0)
Event rate per 100 person-years (95% CI)	3.2 (2.9-3.6)	1.1 (0.8-1.5)	4.0 (3.6-4.5)
Model 1: Hazard ratio (95% CI)*	-	0.27 (0.19-0.38)‡	Reference
Model 2: Hazard ratio (95% CI)†	-	0.44 (0.31-0.62)‡	Reference
<b>HF hospitalization</b>			
No. of events (%)	456 (14.9)	31 (4.0)	425 (18.5)
Event rate per 100 person-years (95% CI)	4.0 (3.6-4.3)	0.9 (0.7-1.3)	5.1 (4.7-5.7)
Model 1: Hazard ratio (95% CI)*	-	0.19 (0.13-0.27)‡	Reference
Model 2: Hazard ratio (95% CI)†	-	0.32 (0.22-0.47)‡	Reference
<b>All-cause death</b>			
No. of events (%)	590 (19.3)	58 (7.6)	532 (23.2)
Event rate per 100 person-years (95% CI)	4.7 (4.4-5.1)	1.7 (1.3-2.2)	5.8 (5.3-6.3)
Model 1: Hazard ratio (95% CI)*	-	0.29 (0.22-0.39)‡	Reference
Model 2: Hazard ratio (95% CI)†	-	0.48 (0.36-0.64)‡	Reference

\* Models were adjusted for treatment assignment.

† Models were adjusted for treatment assignment, age, sex, region, systolic blood pressure, heart rate, body mass index, New York Heart Association functional class, hospitalization for HF within previous 6 months, left ventricular ejection fraction, history of myocardial infarction, history of hypertension, history of diabetes, atrial fibrillation or atrial flutter in electrocardiography, and estimated glomerular filtration rate.

‡ All p-values were <0.001.

CI, confidence interval; HF, heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide.

**Supplementary Table 6. Characteristics of patients with an NT-proBNP >300 pg/mL if not AF or >600 pg/mL if AF in I-Preserve and those in PARAGON-HF and DELIVER.**

	<b>I-Preserve N=1,789</b>	<b>PARAGON-HF N=4,796</b>	<b>DELIVER N=5,398</b>	<b>p-value</b>
Age — yr	73.4±6.9	72.7±8.4	72.2±9.3	<0.001
Age group — no. (%)				<0.001
-70 yr	547 (30.6%)	1,613 (33.6%)	1,910 (35.4%)	
≥70 yr	1,242 (69.4%)	3,183 (66.4%)	3,488 (64.6%)	
Male sex — no. (%)	771 (43.1%)	2,317 (48.3%)	2,895 (53.6%)	<0.001
Race — no. (%)				<0.001
White	1,683 (94.1%)	3,907 (81.5%)	3,828 (70.9%)	
Black	33 (1.8%)	102 (2.1%)	146 (2.7%)	
Asian	13 (0.7%)	607 (12.7%)	1,090 (20.2%)	
Others	60 (3.4%)	180 (3.8%)	334 (6.2%)	
Systolic blood pressure — mmHg	136±16	131±15	129±15	<0.001
Diastolic blood pressure — mmHg	78±9	74±11	74±10	<0.001
Heart rate — beats/min	72±11	70±12	71±12	<0.001
Body-mass index — kg/m <sup>2</sup>	28.9±5.1	30.2±5.0	30.0±6.2	<0.001
Weight category — no. (%) *				<0.001
Underweight	12 (0.7%)	14 (0.3%)	48 (0.9%)	
Normal	362 (20.3%)	742 (15.5%)	1,127 (20.9%)	
Overweight	771 (43.3%)	1,681 (35.1%)	1,747 (32.4%)	
Obese	635 (35.7%)	2,357 (49.2%)	2,470 (45.8%)	
<b>HF characteristics</b>				
NYHA functional class III or IV — no. (%)	1,385 (77.5%)	951 (19.8%)	1,289 (23.9%)	<0.001
Time from diagnosis of HF — no. (%)				<0.001
- 6 Months	680 (38.0%)	1,348 (28.1%)	1,040 (19.3%)	
>6 - 12 Months	207 (11.6%)	621 (13.0%)	724 (13.4%)	
>1 - 2 Years	209 (11.7%)	684 (14.3%)	872 (16.2%)	
>2 - 5 Years	415 (23.2%)	984 (20.5%)	1,325 (24.6%)	
>5 Years	277 (15.5%)	1,152 (24.1%)	1,433 (26.6%)	
Previous hospitalization for HF †	935 (52.3%)	2,306 (48.1%)	2,131 (39.5%)	<0.001
Left ventricular ejection fraction — %	58.3±9.4	57.5±7.9	56.1±7.9	<0.001
<b>Comorbidities — no. (%)</b>				
Atrial fibrillation	754 (42.1%)	2,562 (53.5%)	3,175 (58.8%)	<0.001
Myocardial infarction	532 (29.7%)	1,083 (22.6%)	1,288 (23.9%)	<0.001
Hypertension	1,547 (86.5%)	4,584 (95.6%)	4,827 (89.4%)	<0.001
Diabetes	523 (29.2%)	2,062 (43.0%)	2,405 (44.6%)	<0.001
Stroke	198 (11.1%)	508 (10.6%)	523 (9.7%)	0.15
Chronic obstructive pulmonary disease	191 (10.7%)	670 (14.0%)	603 (11.2%)	<0.001
<b>ECG findings</b>				
AF — no. (%)	489 (27.3%)	1,550 (32.4%)	2,370 (43.9%)	<0.001
<b>Laboratory data ‡</b>				
N-terminal pro-B-type natriuretic peptide — pg/ml	942 (518-1687)	911 (464-1613)	990 (617-1690)	<0.001
In patients without AF on ECG	704 (443-1351)	599 (380-1055)	690 (454-1199)	<0.001
In patients with AF on ECG	1473 (1030-2256)	1587 (1168-2275)	1373 (949-2149)	<0.001
eGFR — ml/min/1.73 m <sup>2</sup>	67±21	64±20	61±19	<0.001
eGFR <60 ml/min/1.73 m <sup>2</sup> — no. (%)	714 (40.2%)	2,203 (46.1%)	2,695 (49.9%)	<0.001
Serum Creatinine — μmol/l	96±31	95±27	102±31	<0.001
<b>Drugs and interventions — no. (%) §</b>				
ACE inhibitor	519 (29.0%)	1,951 (40.7%)	1,929 (35.7%)	<0.001
ARB	-	2,207 (46.0%)	2,018 (37.4%)	<0.001
Beta-blocker	1,105 (61.8%)	3,821 (79.7%)	4,437 (82.2%)	<0.001
Mineralocorticoid antagonist	324 (18.1%)	1,239 (25.8%)	2,154 (39.9%)	<0.001
Diuretic	1,544 (86.3%)	4,585 (95.6%)	5,277 (97.8%)	<0.001

Data are presented as mean±standard deviation or median (interquartile range).

In DELIVER, patients with LVEF ≥ 45 % were shown.

\* Underweight, body mass index <18.5 kg/m<sup>2</sup>; Normal, body mass index 18.5-25.0 kg/m<sup>2</sup>; Overweight, body mass index 25.0-30.0 kg/m<sup>2</sup>; and Obese, body mass index ≥ 30 kg/m<sup>2</sup>.

† Within previous 6 months

‡ At screening in PARAGON-HF

§ ACE inhibitor and ARB are at screening in PARAGON-HF, and the others are at randomization.

Abbreviations are the same in Supplementary Table 2.

**Supplementary Table 7. Echocardiographic findings of patients with an NT-proBNP >300 pg/mL if not AF or >600 pg/mL if AF in I-Preserve and those in PARAGON-HF.**

	<b>I-Preserve N=320</b>	<b>PARAGON-HF N=1,097</b>	<b>p-value</b>
LV end diastolic diameter (cm)	5.0±0.6	4.6±0.6	<0.001
LV end-diastolic volume (ml), (ml/m <sup>2</sup> )	102±42, 54±20	102±38, 53±17	0.67*
LV end systolic diameter (cm)	3.3±0.7	3.3±0.7	0.26
LV end-systolic volume (ml), (ml/m <sup>2</sup> )	40±22, 21±11	43±23, 22±11	0.10*
Interventricular septum thickness (cm)	1.00±0.17	1.10±0.24	<0.001
LV wall posterior wall thickness (cm)	0.91±0.14	0.96±0.20	0.18
Mass (g), (g/height <sup>2.7</sup> )	176±51, 46±14	169±57, 43±13	0.014*
Relative wall thickness	0.38±0.08	0.43±0.12	<0.001
Mass/LV end-diastolic volume (g/ml)	1.92±0.76	1.80±0.71	0.025
LV ejection fraction (%)	62±10	59±9	<0.001
Fractional shortening (%)	33±10	29±9	<0.001
Stroke volume (ml)	62±25	59±20	0.071
MV peak e wave velocity (cm/s)	85±33	90±28	0.011
MV peak a wave velocity (cm/s)	77±31	74±26	0.13
E/A	1.26±1.01	1.33±0.73	0.33
Lateral e' (cm/s)	9.8±4.1	7.9±2.5	<0.001
Septal e' (cm/s)	7.5±3.3	5.8±1.8	<0.001
E/e' lateral	10.3±5.6	12.6±5.7	<0.001
Left MV deceleration time (msec)	204±76	171±41	<0.001
LA area (cm <sup>2</sup> ), (cm <sup>2</sup> /m <sup>2</sup> )	25±6, 14±4	23±6, 12±3	<0.001*
RV systolic pressure (mmHg)	40±14	39±11	0.74

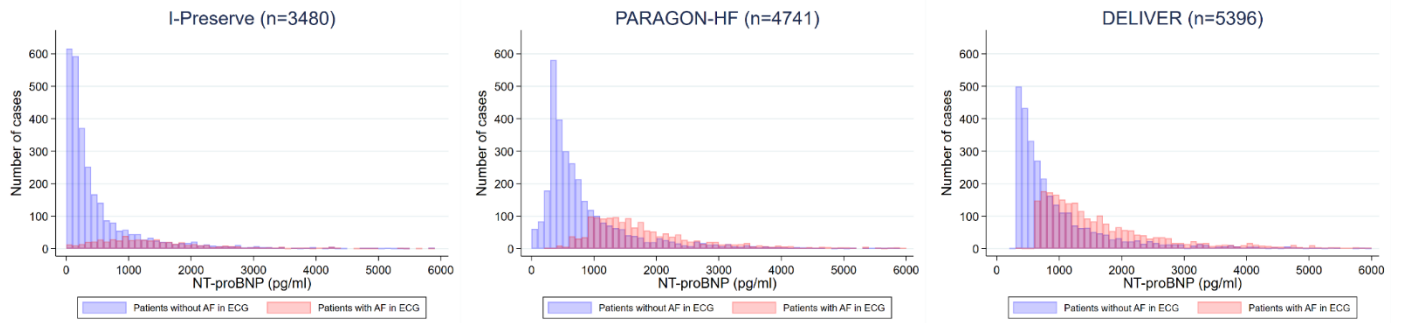
Data are presented as mean±SD.

\* Differences in LV end-diastolic volume index, LV end-systolic volume index, Mass index, and LA index.

† Right ventricular systolic pressure was estimated using peak tricuspid regurgitant velocity (V) as  $4(V^2)+10$  mm Hg.

AF, atrial fibrillation; I-Preserve, Irbesartan in Heart Failure with Preserved Ejection Fraction; LA, left atrial; LV, left ventricular; MV, mitral valve, MA, mitral annulus; NT-proBNP, N-terminal pro B-type natriuretic peptide; PARAGON-HF, Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction; RV, right ventricular.

## Supplementary Figure 1. Distribution of NT-proBNP for patients with and without atrial fibrillation.



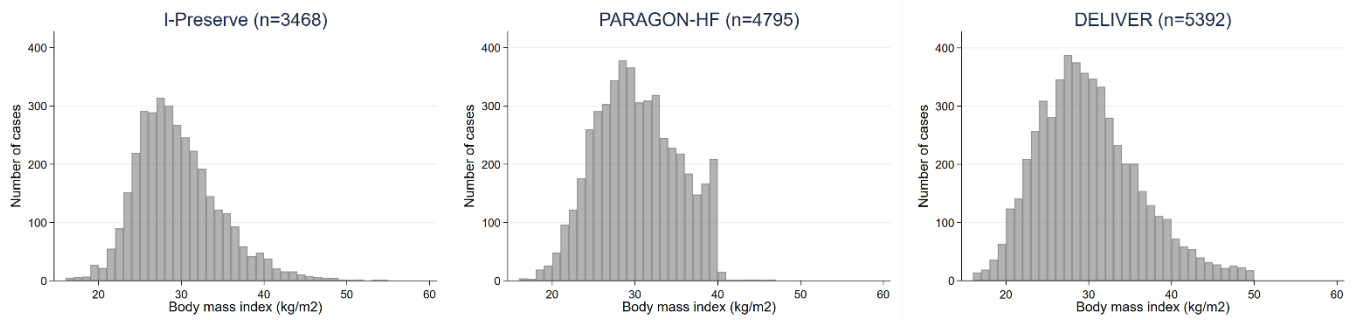
Atrial fibrillation includes atrial flutter.

In PARAGON-HF, NT-proBNP was missing in 39 patients and the ECG rhythm was missing in 16 patients.

In DELIVER, only patients with left ventricular ejection fraction  $\geq 45\%$  (n=5398) were included; NT-proBNP was missing in 1 patient and the ECG rhythm was missing in 1 patient.

DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; ECG, electrocardiography; I-Preserve, Irbesartan in Heart Failure with Preserved Ejection Fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; PARAGON-HF, Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction.

## Supplementary Figure 2. Distribution of body mass index.



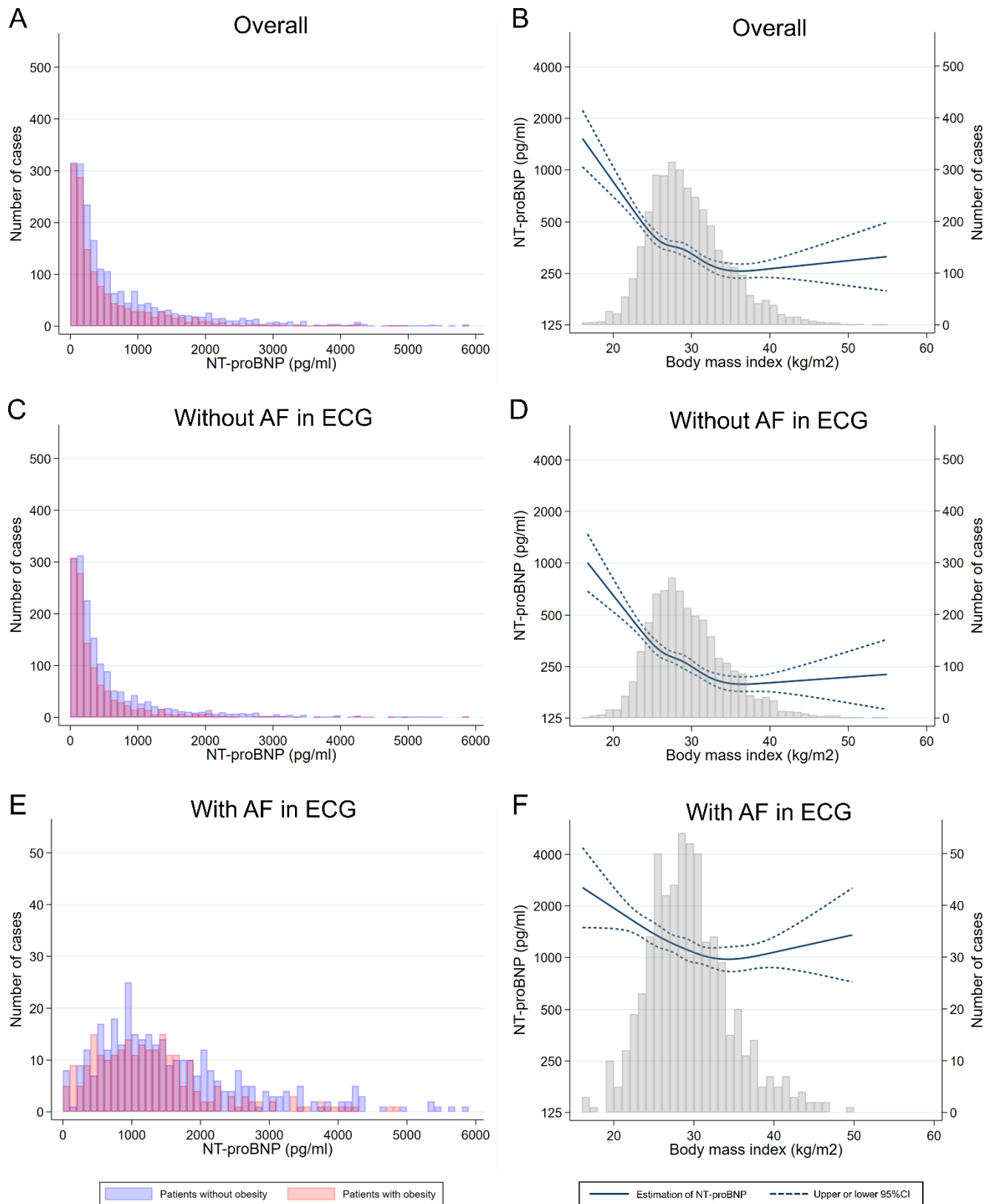
In I-Preserve, body mass index was missing in 12 patients.

In PARAGON-HF, body mass index was missing in 1 patient.

In DELIVER patients with left ventricular ejection fraction  $\geq 45\%$ , body mass index was missing in 6 patients.

DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; I-Preserve, Irbesartan in Heart Failure with Preserved Ejection Fraction; PARAGON-HF, Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction.

**Supplementary Figure 3. Relationship between NT-proBNP and obesity or body mass index.**



Panel (A) shows the distribution of NT-proBNP for patients with and without obesity for the overall population in I-Preserve, (C) for those without AF on ECG, and (E) for those with AF on ECG. Panel (B) shows the association between body mass index and NT-proBNP level for the overall population in I-Preserve, (D) for those without AF on ECG, and (F) for those with AF on ECG. Body mass index was missing in 12 patients.

Obesity was defined as a body mass index of 30 kg/m<sup>2</sup> or higher.

AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiography; I-Preserve, Irbesartan in Heart Failure with Preserved Ejection Fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide.