Supplementary material

Książczyk M, Lelonek M. The efficacy and safety of predischarge initiation of angiotensin receptor/neprilysin inhibitor in patients with severe left ventricle dysfunction hospitalized for acute decompensated heart failure – single center experience.

Table S1. Comparison of baseline characteristics of participants between groups, depending on left ventricular ejection fraction value

	LVEF <25% (***n*** **= 20)**	**LVEF ≥25%** (***n*** **= 22)**	***P*-value**
Age – mean (SD)	59.65 (13.07)	63.05 (9.29)	0.34
Sex – *n* (%)			0.69
male	16 (80)	19 (86.4)	
female	4 (20)	3 (13.6)	
BMI, kg/m^2 – mean (SD)	27.8 (5.45)	29.37 (4.52)	0.32
NYHA class – *n* (%)			1.00
II	0 (0)	1 (4.8)	
III	18 (94.7)	19 (90.5)	
IV	1 (5.3)	1 (4.8)	
6-MWT – mean (SD)	371.2 (46.61)	327.57 (57.90)	0.18
Haemodynamic parameters			
SBP, mmHg – mean (SD)	117.79 (10.10)	123.7 (11.83)	0.10
DBP, mmHg – median (Q1–Q3)	75 (70–77)	71 (70–76.25)	0.99
Ischaemic HF – *n* (%)	13 (65)	13 (59.1)	0.94
HHF within 1 year – *n* (%)	12 (60)	5 (22.7)	**0.03**
Number of prior HHF – median (Q1–Q3)	1 (1–2)	2 (2–3)	0.14
History of HF – *n* (%)			0.62
<5 years	11 (55)	14 (63.6)	
5–10 years	4 (20)	2 (9.1)	
>10 years	5 (25)	6 (27.3)	

Concomitant diseases – *n* (%)			
AH	15 (75)	19 (86.4)	0.45
T2DM	9 (45)	12 (54.5)	0.76
AF	8 (40)	7 (31.8)	0.82
CABG/PCI	15 (75)	14 (63.6)	0.51
history of VT/VF	6 (30)	2 (9.1)	0.12
ICD	11 (55)	5 (22.7)	0.06
CRT	4 (20)	3 (13.6)	0.69
hypercholesterolaemia	17 (85)	16 (72.7)	0.46
CKD	6 (30)	7 (31.8)	1.00
COPD	2 (10)	2 (9.1)	1.00
ACEI/ARB pharmacotherapy – *n* (%)			
ACEI	16 (80)	16 (72.7)	0.72
ARB	3 (15)	5 (22.7)	0.70
ACEI/ARB naïve	1 (5)	1 (4.5)	1.00
Other HF pharmacotherapy – *n* (%)			
beta-blocker	19 (95)	20 (90.9)	1.00
MRA	6 (30)	2 (9.1)	0.12
loop diuretic	18 (90)	17 (77.3)	0.41
ivabradine	12 (60)	13 (59.1)	1.00
digoxin	2 (10)	0 (0)	0.22
MAGGIC – Heart Failure Risk Calc.			
total score, points – mean (SD)	25.79 (5.04)	22.3 (5.01)	**0.04**
1-year mortality, % – median (Q1–Q3)	16 (11.65–23.75)	11.1 (9.75–17.9)	**0.049**
3-year mortality, % – median (Q1–Q3)	36.9 (28.05–50.65)	26.9 (23.75–42.7)	0.06
Laboratory parameters			
NT-proBNP, pg/ml – median (Q1–Q3)	2019.5 (928.25–4778.5)	972.1 (701.42–2030.25)	**0.03**
hs-cTnT, µg/l – median (Q1–Q3)	22 (15.75–74)	19 (12–33)	0.52
haemoglobin, g/dl – mean (SD)	14.11 (1.45)	14.06 (1.94)	0.92
RDW, % – mean (SD)	15.51 (1.89)	15.04 (2.05)	0.51

sodium, mmol/l – mean (SD)	139.24 (3.02)	138.55 (2.54)	0.45
potassium, mmol/l – mean (SD)	4.48 (0.32)	4.44 (0.34)	0.70
creatinine, µmol/l – median (Q1–Q3)	86 (76–114.5)	95 (81–110)	0.85
eGFR, ml/min/1.73m^2 – mean (SD)	73.03 (26.75)	73.04 (22.41)	0.99
fasting glucose, mmol/l – median (Q1–Q3)	6.14 (5.18–6.63)	6.26 (5.38–7.89)	0.48
TC, mmol/l – mean (SD)	3.69 (0.97)	4.1 (1.28)	0.33
LDL-C, mmol/l – median (Q1–Q3)	1.99 (1.31–2.49)	1.75 (1.4–2.8)	0.82
HDL-C, mmol/l – mean (SD)	1.11 (0.26)	1.12 (0.38)	0.94
TG, mmol/l – median (Q1–Q3)	1.12 (0.85–1.56)	1.07 (0.93–1.98)	0.58
bilirubin, mg/dl – median (Q1–Q3)	19.25 (12.02–23.72)	12.05 (9.45–17.35)	0.11
ALT, U/l – median (Q1–Q3)	19 (15–29.65)	19.6 (17–23.3)	0.80
AST, U/l – median (Q1–Q3)	25 (19–30.5)	24 (19–30.4)	0.71
Electrocardiogram			
AF – *n* (%)	4 (20)	5 (22.7)	1.00
QRS, ms – median (Q1–Q3)	115 (110–140)	110 (100–120)	0.32
Echocardiographic parameters			
LVEDD, mm – mean (SD)	70.53 (9.88)	61.59 (9.2)	**0.005**
LVEDV, ml – mean (SD)	247.43 (71.74)	196.45 (61.36)	0.07
LVESV, ml – mean (SD)	201.15 (58.34)	136.45 (41.27)	**0.005**
LVEF, % – mean (SD)	20.1 (2.87)	31.1 (4.05)	**<0.001**
FMR grade – median (Q1–Q3)	2 (1–3)	1 (1–3)	0.29
RVD prox, mm – mean (SD)	34.32 (5.51)	33.71 (6.21)	0.75
TAPSE, mm – mean (SD)	15.16 (4.26)	18.76 (4.44)	**0.01**
TRV, m/s – mean (SD)	2.79 (0.45)	2.8 (0.68)	0.95
SPAP, mmHg – median (Q1–Q3)	46 (43–54)	45 (33.75–56.75)	0.74

Data are presented as the number of subjects (*n*) in percentage and mean (SD) or median (Q1–Q3), depending on their distribution.

Abbreviations: 6-MWT, 6-minute walking test; ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; AH, arterial hypertension; ARB, angiotensin receptor blocker; ALT, alanine transaminase; AST, asparagine transaminase; BMI, body mass index; CABG, coronary artery by-pass grafting; CKD, chronic kidney

disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FMR, functional mitral regurgitation; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HHF, hospitalization for heart failure; hs-cTnT, high sensitive cardiac troponin T; LDL-C, low-density lipoprotein cholesterol; LVEDV, left ventricle end-diastolic volume; LVEDD, left ventricle end-diastolic diameter; LVESV, left ventricle end-systolic volume; LVEF, left ventricle ejection fraction; MAGGIC, Meta-analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RDW, red cell distribution width; RVD prox, proximal right ventricle diameter; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; T2DM, type-2 diabetes mellitus; TAPSE, tricuspid annular plane systolic excursion; TC, total cholesterol; TG, triglycerides; TRV, tricuspid regurgitation velocity; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table S2. Comparison of baseline characteristics of participants between groups, depending on N-terminal B-type natriuretic peptide value

	NT-proBNP >1000 pg/ml (*n* = 23)	**NT-proBNP ≤1000 pg/ml (*n* = 19)**	***P*-value**
Age – mean (SD)	61.78 (12.98)	61 (9.02)	0.69
Sex – *n* (%)			0.11
male	17 (73.9)	18 (94.7)	
female	6 (26.1)	1 (5.3)	
BMI, kg/m^2 – mean (SD)	27.79 (5.49)	29.54 (4.32)	0.26
NYHA class – *n* (%)			1.00
II	1 (4.8)	0 (0)	
III	19 (90.5)	18 (94.7)	
IV	1 (4.8)	1 (5.3)	
6-MWT – mean (SD)	315 (75.61)	361.12 (40.59)	0.32
Haemodynamic parameters			
SBP, mmHg – mean (SD)	115.81 (8.07)	126.67 (11.85)	**0.003**
DBP, mmHg – mean (SD)	70.81 (5.32)	77.44 (8.03)	**0.006**
Ischaemic HF – *n* (%)	13 (56.5)	13 (68.4)	0.64
HHF within 1 year – *n* (%)	13 (56.5)	4 (21.1)	**0.03**
Number of prior HHF – median (Q1–Q3)	2 (1–2)	1 (1–1.25)	0.20
History of HF – *n* (%)			0.83
<5 years	13 (56.5)	12 (63.2)	
5–10 years	3 (13)	3 (15.8)	
>10 years	7 (30.4)	4 (21.1)	
Concomitant diseases – *n* (%)			
AH	17 (73.9)	17 (89.5)	0.26
T2DM	12 (52.2)	9 (47.4)	1.00
AF	10 (43.5)	5 (26.3)	0.34

CABG/PCI	15 (65.2)	14 (73.7)	0.74
history of VT/VF	5 (21.7)	3 (15.8)	0.71
ICD	9 (39.1)	7 (36.8)	1.00
CRT	5 (21.7)	2 (10.5)	0.43
hypercholesterolaemia	16 (69.6)	17 (89.5)	0.15
CKD	9 (39.1)	4 (21.1)	0.32
COPD	4 (17.4)	0 (0)	0.11
ACEI/ARB pharmacotherapy – *n* (%)			
ACEI	15 (65.2)	17 (89.5)	0.08
ARB	6 (26.1)	2 (10.5)	0.26
ACEI/ARB naïve	2 (8.7)	0 (0)	0.49
Other HF pharmacotherapy – *n* (%)			
beta-blocker	21 (91.3)	18 (94.7)	1.00
MRA	3 (13)	5 (26.3)	0.43
loop diuretic	19 (82.6)	16 (84.2)	1.00
ivabradine	12 (52.2)	13 (68.4)	0.45
digoxin	2 (8.7)	0 (0)	0.49
MAGGIC – Heart Failure Risk Calc.			
total score, points – mean (SD)	25.65 (5.28)	22.26 (4.77)	**0.04**
1-year mortality, % – median (Q1–Q3)	15.45 (11.1–24.8)	11.1 (9.75–17.3)	**0.048**
3-year mortality, % – median (Q1–Q3)	35.65 (26.9–52.3)	26.9 (23.7–41.2)	0.06
Laboratory parameters			
NT-proBNP, pg/ml – median (Q1–Q3)	3125.0 (1947.0–4777.0)	691.0 (461.5–914.0)	**<0.001**
hs-cTnT, µg/l – median (Q1–Q3)	20 (12–38)	21 (16–33)	0.81
haemoglobin, g/dl – median (Q1–Q3)	13.8 (12.9–15.35)	14.1 (13.7–14.6)	0.98
RDW, % – mean (SD)	15.4 (1.8)	15.02 (2.25)	0.62
sodium, mmol/l – mean (SD)	138.68 (2.8)	139.11 (2.8)	0.63
potassium, mmol/l – mean (SD)	4.45 (0.33)	4.48 (0.33)	0.78
creatinine, µmol/l – median (Q1–Q3)	93 (76–124)	86 (82–107)	0.94
eGFR, ml/min/1.73m^2 – mean (SD)	69.35 (25.3)	77.11 (22.99)	0.32

fasting glucose, mmol/l – mean (SD)	5.94 (1.03)	7.36 (2.36)	0.08
TC, mmol/l – median (Q1–Q3)	3.4 (2.95–4.67)	4.59 (3.41–5.06)	0.19
LDL-C, mmol/l – median (Q1–Q3)	1.87 (1.28–2.46)	2.34 (1.57–2.82)	0.28
HDL-C, mmol/l – mean (SD)	1.15 (0.37)	1.07 (0.24)	0.49
TG, mmol/l – median (Q1–Q3)	0.99 (0.85–1.4)	1.78 (1.08–2.23)	**0.02**
bilirubin, mg/dl – median (Q1–Q3)	17.2 (10.72–23.72)	12.5 (9.45–17.35)	0.23
ALT, U/l – median (Q1–Q3)	19.6 (16–31)	19 (15–22.65)	0.24
AST, U/l – mean (SD)	27.76 (9.27)	22.81 (6.74)	0.06
Electrocardiogram			
AF – *n* (%)	8 (34.8)	1 (5.3)	**0.03**
QRS, ms – median (Q1–Q3)	120 (105–140)	110 (110–120)	0.64
Echocardiographic parameters			
LVEDD, mm – mean (SD)	68 (9.62)	63.11 (10.95)	0.14
LVEDV, ml – mean (SD)	234.75 (65.02)	207.67 (81.33)	0.41
LVESV, ml – median (Q1–Q3)	190 (151–218)	124 (113–158)	0.12
LVEF, % – mean (SD)	23.74 (6.05)	28.63 (6.08)	**0.01**
FMR grade – median (Q1–Q3)	2 (1–3)	1 (1–2)	0.12
RVD prox, mm – mean (SD)	35.68 (5.46)	31.94 (5.71)	**0.04**
TAPSE, mm – mean (SD)	15.05 (3.87)	19.5 (4.46)	**0.002**
TRV, m/s – mean (SD)	2.84 (0.57)	2.58 (0.38)	0.30
SPAP, mmHg – mean (SD)	49.18 (11.2)	35.25 (9.07)	**0.04**

Data are presented as the number of subjects (*n*) in percentage and mean (SD) or median (Q1–Q3), depending on their distribution.

Abbreviations: see Table S1.

Table S3. Angiotensin receptor/neprilysin inhibitor dose achieved or drug discontinuation, dose reduction, monitored events and study endpoints in participants at month 6 and 12 of follow-up, depending on left ventricular ejection fraction value

	6-month follow-up			**12-month follow-up**		
	LVEF <25% (*n* = 20)	**LVEF ≥25% (*n* = 22)**	***P*-value**	**LVEF <25% (*n* = 20)**	**LVEF ≥25% (*n* = 22)**	***P*-value**
Dose achieved as percent of target dose or drug discontinuation[a] – *n* (%)			0.40			0.47
100%	15 (78.9)	18 (85.7)		13 (68.4)	16 (80)	
50%	4 (21.1)	2 (9.5)		5 (26.3)	2 (10)	
<50%	0 (0)	0 (0)		0 (0)	0 (0)	
drug discontinuation	0 (0)	1 (4.8)		1 (5.3)	2 (10)	
Dose reduction[b] – *n* (%)						
hypotension				4 (21.1)	2 (10)	0.41
eGFR				0 (0)	2 (10)	0.49
Monitored events[c] – *n* (%)						
AKI	1 (4.3)	1 (5.3)	1.00	0 (0)	1 (5.6)	1.00
HHF	5 (21.7)	1 (5.3)	0.20	5 (25)	3 (13.6)	0.26
HTx	0 (0)	0 (0)	–	2 (10)	0 (0)	0.22

death	1 (4.3)	1 (5.3)	1.00	1 (5)	3 (13.6)	0.61
Study endpoints[d] – *n* (%)						
primary endpoint	–	–	–	5 (25)	5 (22.7)	1.00
secondary endpoint	4 (21.1)	3 (14.3)	0.69	6 (31.6)	4 (20)	0.48

Data are presented as the number of subjects (*n*) in percentage.

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HTx, heart transplantation; LVEF, left ventricle ejection fraction.

Definition of variables and data sources:

[a] Dose achieved as percent of target dose or drug discontinuation:

100% defined as 97/103 mg of sacubitril/valsartan administered bis in die or

50% defined as 49/51 mg of sacubitril/valsartan administered bis in die or

<50% defined as 24/26 mg of sacubitril/valsartan administered bis in die or

drug discontinuation – drug discontinuation during the study.

[b] Dose reduction – any permanent dose reduction or temporary dose reduction with possible further increase in dose during the study due to:

hypotension defined as SBP <90 mmHg or SBP 90–100 mmHg if symptomatic and/or

eGFR decrease <30 ml/min/1.73 m^2.

[c] Monitored events:

AKI defined as increase in serum creatinine by 26.5 µmol/l or more within 48 hours or increase in serum creatinine to 1.5 times or more baseline within the prior 7 days or urine volume less than 0.5 ml/kg/hour for at least 6 hours (Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120:c179-84. doi: 10.1159/000339789).

HHF defined as admission for ≥24 hours with a primary diagnosis of heart failure, with ≥1 symptom and ≥2 physical examination, laboratory, or invasive findings of heart failure, and receives a heart failure-specific treatment (Abraham W, Psotka M, Fiuzat M, et al. Standardized Definitions for Evaluation of Heart Failure Therapies: Scientific Expert Panel From the Heart Failure Collaboratory and Academic Research Consortium. J Am Coll Cardiol HF. 2020;8:961–972. doi: 10.1016/j.jchf.2020.10.002).

[d] Study endpoints

primary endpoint defined as composite of HHF or death at month 12,

secondary endpoint defined as composite of ≤50% of target dose or drug discontinuation at month 6 or 12.

Table S4. Angiotensin receptor/neprilysin inhibitor dose achieved or drug discontinuation, dose reduction, monitored events and study endpoints in participants at month 6 and 12 of follow-up, depending on N-terminal B-type natriuretic peptide value

	6-month follow-up			**12-month follow-up**		
	NT-proBNP >1000 pg/ml (*n* = 23)	**NT-proBNP ≤1000 pg/ml (*n* = 19)**	***P*-value**	**NT-proBNP >1000 pg/ml (*n* = 23)**	**NT-proBNP ≤1000 pg/ml (*n* = 19)**	***P*-value**
Dose achieved as percent of target dose or drug discontinuation[a] – *n* (%)			0.20			**0.04**
100%	17 (77.3)	16 (88.9)		15 (71.4)	14 (77.8)	
50%	5 (22.7)	1 (5.6)		6 (26)	1 (5.6)	
<50%	0 (0)	0 (0)		0 (0)	0 (0)	
drug discontinuation	0 (0)	1 (5.6)		0 (0)	3 (16.7)	
Dose reduction[b] – *n* (%)						
hypotension				6 (28.6)	0 (0)	**0.02**
eGFR				0 (0)	2 (11.1)	0.61
Monitored events[c] – *n* (%)						
AKI	1 (4.3)	1 (5.3)	1.00	0 (0)	1 (5.6)	0.46
HHF	5 (21.7)	1 (5.3)	0.20	6 (26.1)	2 (10.5)	0.26
HTx	0 (0)	0 (0)	–	2 (8.7)	0 (0)	0.49

death	1 (4.3)	1 (5.3)	1.00	2 (8.7)	2 (10.5)	1.00
Study endpoints[d] – *n* (%)						
primary endpoint	–	–	–	7 (30.4)	3 (15.8)	0.30
secondary endpoint	5 (22.7)	2 (11.1)	0.43	6 (28.6)	4 (22.2)	0.73

Data are presented as the number of subjects (*n*) in percentage.

Abbreviations: AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HTx, heart transplantation; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

Definition of variables and data sources: see Table S3.

Table S5. Comparison of baseline characteristics of participants between predischarge initiation group in TRANSITION study and study population

	Predischarge initiation group in TRANSITION study (*n* = 495)	**Study population (*n* = 42)**	***P*-value**
Age – mean (SD)	66.7	61.43 (11.2)	**0.004**
Male sex – *n* (%)	371 (74.9)	35 (83.3)	0.23
BMI, kg/m^2 – median (Q1–Q3)	27.9 (17.6–58.8)	28.7 (25.0–31.5)	–
NYHA class – *n* (%)			**<0.001**
II	320 (64.6)	1 (2.5)	
III	166 (33.5)	37 (92.5)	
IV	7 (1.4)	2 (5)	
Haemodynamic parameters			
SBP, mmHg – mean (SD)	124 (13.8)	121 (11.3)	0.09
Ischaemic HF – *n* (%)	218 (44.0)	26 (61.9)	**0.03**
HHF within 1 year – *n* (%)	236 (47.7)	17 (40.5)	0.37
Concomitant diseases – *n* (%)			
AH	372 (75.2)	34 (81)	0.40
T2DM	226 (45.7)	21 (50)	0.59
AF	243 (49.1)	15 (35.7)	0.10
ICD	73 (14.7)	16 (38.1)	**<0.001**
CRT	38 (7.7)	7 (16.7)	**0.04**
ACEI/ARB pharmacotherapy – *n* (%)			
ACEI	250 (50.5)	32 (76.2)	**0.001**
ARB	123 (24.8)	8 (19.0)	0.40
ACEI/ARB naïve	122 (24.6)	2 (4.8)	**0.003**
Other HF pharmacotherapy – *n* (%)			
beta-blocker	213 (43.0)	39 (92.9)	**<0.001**

MRA	169 (34.1)	35 (83.3)	**<0.001**
loop diuretic	238 (48.1)	25 (59.5)	0.15
digoxin	63 (12.7)	2 (4.8)	0.13
Laboratory parameters			
NT-proBNP. pg/ml – median (Q1–Q3)	1902 (945–3847)	1444 (733–3197)	–
hs-cTnT, ng/l – median (Q1–Q3)	29 (18–45)	21(13–37)	–
eGFR, ml/min/1.73m^2 – mean (SD)	61.6 (20.5)	73.03 (24.24)	**0.005**
Echocardiographic parameters			
LVEF, % – mean (SD)	28.6 (7.5)	25.95 (6.5)	**0.02**

Data are presented as the number of subjects (*n*) in percentage and mean (SD) or median (Q1–Q3), depending on their distribution.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; AH, arterial hypertension; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; hs-cTnT, high sensitive cardiac troponin T; ICD, implantable cardioverter-defibrillator; LVEF, left ventricle ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; T2DM, type-2 diabetes mellitus; TRANSITION, Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event.