

Supplementary Material Online

Biomarker-based phenotyping of myocardial fibrosis identifies patients with heart failure with preserved ejection fraction resistant to the beneficial effects of spironolactone: results from the Aldo-DHF trial.

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Figure S1. Participants flow diagram. *Values above the range determined by the respective standard curves were excluded. Patients with undetectable values were included in the study by setting the levels of biomarkers to the limit of sensitivity as specified by the corresponding commercial kits

Figure S2. (A) Serum carboxy-terminal propeptide of procollagen type I (PICP) and (B) carboxy-terminal telopeptide of collagen type I to matrix metalloproteinase-1 ratio (CITP:MMP-1) levels (log) according to assigned study treatment. (C) Direct correlations between absolute changes in serum PICP levels (log) and absolute changes in the peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity (E:e') ratio after 12 months of treatment. (D) Direct correlations between absolute changes in serum PICP levels (log) and absolute changes in serum amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels (log) after 12 months of treatment. Data in panels A and B are expressed as mean values and 95% confidence interval at baseline and at 12 months, in patients treated with placebo (○) or with spironolactone (●). Medians (interquartile range) for values at baseline and at 12 months are shown below graphs in panels A and B.

*P<0.01 spironolactone at 12 month vs baseline.

Figure S3. Serum amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels (log) according to study treatment in patients with low (A), medium (B) and high (C) serum carboxy-terminal telopeptide of collagen type-I to matrix metalloproteinase-1 ratio levels as classified by tertiles. Data are expressed as mean values and 95% confidence interval at baseline and at 12 months in patients treated with placebo (○) or with spironolactone (●).

Median (interquartile range) for values at baseline and at 12 months are shown below each graph. *P<0.01 spironolactone at 12 month vs baseline.

Table S1. Correlations of CITP:MMP-1 ratio and PICP at baseline

Variable	Correlation coefficient (<i>P</i> -value)					
	Log CITP:MMP-1			Log PICP		
	Bivariate*	Partial [†]	Partial [‡]	Bivariate*	Partial [†]	Partial [‡]
E/e' ratio	-0.106 (0.038)	-0.091 (0.076)	-0.098 (0.060)	0.001 (0.98)	-0.021 (0.69)	0.017 (0.74)
E-wave velocity	-0.048 (0.35)	-0.040 (0.44)	-0.014 (0.79)	0.116 (0.023) [§]	0.119 (0.020) [§]	0.089 (0.089)
Left atrial volume index	-0.052 (0.31)	-0.048 (0.36)	-0.047 (0.37)	0.129 (0.012) [§]	0.159 (0.002) [§]	0.108 (0.039)
Log NT-proBNP	-0.057 (0.27)	-0.036 (0.48)	-0.007 (0.90)	0.127 (0.013) [§]	0.170 (0.001) [§]	0.170 (0.001) [§]
Maximum exercise duration	0.113 (0.028)	0.100 (0.052)	0.085 (0.102)	0.026 (0.62)	0.016 (0.76)	0.039 (0.46)
V _E /VCO ₂ slope	-0.094 (0.07)	-0.085 (0.10)	-0.078 (0.14)	-0.057 (0.27)	-0.038 (0.46)	-0.061 (0.24)
Borg score	0.133 (0.010) [§]	0.132 (0.010) [§]	0.130 (0.013) [§]	-0.041 (0.43)	-0.047 (0.36)	-0.049 (0.35)

CITP means carboxy-terminal telopeptide of collagen type-I; MMP-1, matrix metalloproteinase-1; PICP, carboxy-terminal propeptide of procollagen type-I; E, peak early transmitral ventricular filling velocity; e', early diastolic tissue Doppler velocity; V_E, expired volume per unit time; VCO₂, volume of expired carbon dioxide.

*Pearson's correlation coefficient without adjustment for covariables.

[†]Partial correlation coefficient, controlling for age and sex.

[‡]Partial correlation coefficient, controlling for age and sex, atrial fibrillation, mean arterial pressure, estimated glomerular filtration rate, hemoglobin, and log NT-proBNP (except when analyzed as variable)

[§]Significant after Benjamini-Hochberg multiple test correction

Table S2. Demographic, clinical and biochemical characteristics at baseline in patients classified according to PICP tertiles

	1st tertile (n=127)	2nd tertile (n=127)	3rd tertile (n=127)	P for trend
PICP, ng/mL	<98.7	98.7-128	>128	
<u>Demographics</u>				
Age, years	67.7 ± 7.7	66.9 ± 7.4	66.5 ± 7.8	0.21
Male gender, n (%)	58 (45.7)	69 (54.3)	55 (43.3)	0.71
<u>Medical History, n (%)</u>				
Hospitalized within 12 months	49 (38.6)	45 (35.4)	49 (38.6)	0.99
Coronary artery disease	51 (40.2)	56 (44.1)	45 (35.4)	0.44
History of myocardial infarction	19 (15.0)	31 (24.4)	13 (10.2)	0.31
Atrial fibrillation	19 (15.0)	19 (15.0)	25 (19.7)	0.31
Hypertension	116 (91.3)	120 (94.5)	113 (89.0)	0.50
Hyperlipidaemia	76 (59.8)	85 (66.9)	64 (50.4)	0.13
Diabetes mellitus	22 (17.3)	21 (16.5)	19 (15.0)	0.61
Cerebrovascular diseases	9 (7.1)	14 (11.0)	17 (13.4)	0.10
Peripheral arterial occlusive disease	4 (3.1)	6 (4.7)	5 (3.9)	0.75
COPD	5 (3.9)	2 (1.6)	6 (4.7)	0.73
<u>Physical examination</u>				
BMI, kg/m ²	28.9 ± 3.8	29.2 ± 3.4	29.0 ± 3.5	0.81
SBP, mmHg	135 ± 18.7	139 ± 19.2	134 ± 16.5	0.71
DBP, mmHg	78.5 ± 11.7	82.0 ± 10.5	77.5 ± 10.1	0.44
MAP, mmHg	97.2 ± 12.4	101 ± 11.8	96.2 ± 10.7	0.50
HR, beats/min	66.7 ± 12.0	66.7 ± 11.5	66.8 ± 11.2	0.97
<u>Signs and symptoms, n(%)</u>				
NYHA class				
II	107 (84.3)	108 (85.0)	111 (87.4)	0.48
III	20 (15.7)	19 (15.0)	16 (12.6)	
Peripheral edema	50 (39.4)	50 (39.4)	54 (42.5)	
Paroxysmal nocturnal dyspnoea	21 (16.5)	29 (22.8)	16 (12.6)	0.41
Nocturnal cough	20 (15.7)	20 (15.7)	20 (15.7)	1.00
<u>Laboratory measures</u>				
Hemoglobin, g/dL	13.8 ± 1.2	13.9 ± 1.2	13.6 ± 1.2	0.29
Sodium, mmol/L	139 ± 3.3	140 ± 2.7	141 ± 2.7	<0.001
Potassium, mmol/L	4.2 ± 0.4	4.1 ± 0.4	4.2 ± 0.4	0.89
eGFR, mL/min/1.73 m ²	74.5 ± 20.3	77.7 ± 17.8	74.9 ± 19.3	0.88
<u>Baseline medications, n (%)</u>				
ACE inhibitor or ARB	98 (77.2)	99 (78.0)	95 (74.8)	0.66
Beta-blocker	88 (69.3)	96 (75.6)	91 (71.7)	0.68
Diuretics	64 (50.4)	69 (54.3)	69 (54.3)	0.53
Calcium channel blocker	23 (18.1)	42 (33.1)	30 (23.6)	0.31
Lipid-lowering drug	67 (52.8)	76 (59.8)	65 (51.2)	0.80
Spirolactone	64 (50.4)	64 (50.4)	67 (52.8)	0.71

PICP means carboxy-terminal propeptide of procollagen type-I; COPD, chronic obstructive pulmonary disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme; ARB, angiotensin II type 1 receptor blockers. Values are expressed as mean ± SD and categorical variables as numbers and percentages.

Table S3. Echocardiography, exercise testing, biomarkers and quality of life at baseline in patients classified according to PICP tertiles

	1 st tertile (n=127)	2 nd tertile (n=127)	3 rd tertile (n=127)	P for trend
PICP, ng/mL	<98.7	98.7-128	>128	
<u>Echocardiography</u>				
LVEF, %	68.2 ± 7.9	67.0 ± 7.8	67.9 ± 7.9	0.81
LVEDD, mm	46.5 ± 6.8	46.8 ± 6.2	46.3 ± 6.0	0.80
LVESD, mm	25.5 ± 6.9	25.4 ± 6.6	24.7 ± 6.0	0.31
LVMI, g/m ²	109 ± 27.7	111 ± 30.5	106 ± 26.9	0.35
RWT	0.50 ± 0.09	0.50 ± 0.09	0.50 ± 0.08	0.79
Left atrial volume index, mL/m ²	27.0 ± 7.5	27.6 ± 7.5	30.3 ± 9.8	0.002
E-wave velocity, cm/s	71.2 ± 15.6	71.0 ± 16.7	76.0 ± 20.1	0.016
Medial e' wave velocity, cm/s	6.9 ± 1.4	7.0 ± 1.5	7.3 ± 1.7	0.06
E/e' ratio	12.8 ± 3.4	12.4 ± 3.7	12.9 ± 3.8	0.85
E:A ratio	0.89 ± 0.28	0.88 ± 0.32	0.93 ± 0.36	0.36
IVRT, ms	88.6 ± 25.1	88.2 ± 23.6	84.5 ± 26.7	0.20
DT, ms	249 ± 61.2	241 ± 62.4	241 ± 66.0	0.35
<u>Biomarkers, median (IQR)</u>				
NT-proBNP, ng/L	130 (72.1-279)	169 (79.6-284)	192 (92.6-522)	0.001
CITP:MMP-1 ratio	3.58 (1.88-6.21)	4.00 (1.90-7.33)	4.04 (1.76-6.09)	0.69
<u>Cardiopulmonary exercise testing</u>				
Maximum exercise duration, s	539 ± 180	537 ± 169	540 ± 181	0.95
Peak VO ₂ , mL/min/kg	16.3 ± 3.7	16.2 ± 3.4	16.3 ± 3.4	0.88
ATVO ₂ , mL/min/kg	11.7 ± 3.8	11.3 ± 3.3	11.5 ± 2.6	0.62
V _E /VCO ₂ slope	30.0 ± 4.1	30.5 ± 4.7	29.6 ± 3.9	0.46
Borg scale	5.3 ± 1.8	5.2 ± 1.9	5.1 ± 1.7	0.35
<u>Six-minute walk test</u>				
Walk distance, m	524 ± 84.9	537 ± 73.3	546 ± 75.1	0.08
<u>Health-related quality of life scores</u>				
SF-36 physical function score	61.1 ± 22.9	65.8 ± 21.5	61.4 ± 22.0	0.89
PHQ-Sum	6.2 ± 4.2	5.0 ± 4.1	5.8 ± 4.2	0.52

PICP means carboxy-terminal propeptide of procollagen type-I; LVEF, left ventricular (LV) ejection fraction; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; LVMI, LV mass index; RWT, relative wall thickness; E, peak early transmitral ventricular filling velocity; e', early diastolic tissue Doppler velocity; A, peak atrial transmitral ventricular filling velocity; IVRT, isovolumetric relaxation time; DT, deceleration time; NT-proBNP, amino-terminal pro-brain natriuretic peptide; CITP, carboxy-terminal telopeptide of collagen type-I; MMP-1, matrix metalloproteinase-1; VO₂, oxygen consumption; ATVO₂, oxygen consumption at anaerobic threshold; V_E, expired volume per unit time; VCO₂, volume of expired carbon dioxide; SF-36, short form 36; PHQ-Sum, Patient Health Questionnaire sum score. Higher values indicate better performance for LVEF, medial e' wave velocity, duration of exercise, peak VO₂, ATVO₂, Borg scale, walk distance and SF-36 physical function score. Lower values indicate better performance for left atrial volume index, E/e' (medial) velocity ratio, VE/VCO₂ slope and PHQ-Sum. Values are expressed as mean ± SD, median and interquartile range (IQR) and categorical variables as numbers and percentages.

Table S4. Spironolactone versus placebo differences in patients after 12 months of treatment

	Placebo (n=180) ^a	Spironolactone (n=190) ^a	Spironolactone-Placebo ^b	
			Difference (95% CI)	P value
<u>Primary endpoints</u>				
E/e' (medial) velocity ratio	13.7 (13.3-14.1)	12.1 (11.7-12.5)	-1.56 (-2.14 to -0.97)	<0.0001
Peak VO ₂ , mL/min/kg	16.6 (16.1-17.1)	16.6 (16.1-17.2)	0.01 (-0.71 to 0.72)	0.98
<u>Six-minute walk test</u>				
Walk distance, m	533 (524-542)	516 (507-525)	-16.7 (-29.6 to -3.88)	0.011
<u>Other clinical variables</u>				
NYHA class, n (%)				
I	8 (4.4)	8 (4.2)		
II	159 (88.3)	164 (86.3)	1.11 (0.58 to 2.09) ^c	0.76
III	13 (7.2)	18 (9.5)		
Peripheral edema, n (%)	76 (42.2)	76 (40.0)	0.67 (0.40 to 1.12) ^c	0.13
SBP, mm Hg	137 (135-139)	129 (127-131)	-8.50 (-11.5 to -5.49)	<0.0001
DBP, mm Hg	80.5 (79.2-81.8)	77.0 (75.8-78.3)	-3.46 (-5.27 to -1.66)	0.0001
HR, beats/min	66.7 (65.3-68.0)	67.8 (66.5-69.1)	1.15 (-0.70 to 3.01)	0.22
Sodium, mmol/L	140 (140-141)	139 (139-140)	-0.94 (-1.46 to -0.43)	0.0004
Potassium, mmol/L	4.15 (4.10-4.20)	4.39 (4.34-4.44)	0.24 (0.17 to 0.32)	<0.0001
Hemoglobin, g/dL	13.8 (13.7-14.0)	13.5 (13.4-13.7)	-0.30 (-0.48 to -0.12)	0.001
eGFR, mL/min/1.73 m ²	74.9 (73.5-76.4)	69.8 (68.4-71.2)	-5.08 (-7.12 to -3.05)	<0.0001
<u>Other echocardiographic variables</u>				
E-wave velocity, cm/s	76.3 (74.4-78.2)	72.2 (70.4-74.1)	-4.07 (-6.73 to -1.41)	0.003
Medial e' wave velocity, cm/s	7.01 (6.83-7.19)	7.37 (7.20-7.54)	0.36 (0.12 to 0.61)	0.004
E/A velocity ratio	0.96 (0.92-0.99)	0.91 (0.88-0.95)	-0.04 (-0.10 to 0.01)	0.10
IVRT, ms	88.0 (84.4-91.7)	85.6 (82.0-89.2)	-2.46 (-7.59 to 2.67)	0.35
DT, ms	238 (229-247)	242 (233-250)	3.93 (-8.42 to 16.3)	0.53
LVEF, %	65.8 (64.7-66.9)	67.5 (66.4-68.7)	1.76 (0.17 to 3.34)	0.031
LVMI, g/m ²	106 (103-110)	100 (96.9-103)	-6.19 (-10.9 to -1.52)	0.009
Left atrial volume index, mL/m ²	27.8 (26.9-28.6)	27.4 (26.6-28.2)	-0.33 (-1.48 to 0.82)	0.58
LVEDD, mm	46.2 (45.5-47.1)	44.8 (44.0-45.6)	-1.50 (-2.64 to -0.35)	0.010
LVESD, mm	26.2 (25.4-27.1)	25.5 (24.7-26.3)	-0.72 (-1.90 to 0.46)	0.23
<u>Biomarkers, median (IQR)</u>				
NT-proBNP, ng/L	164 (81.7-338)	156 (80.5-312)	0.85 (0.74 to 0.98) ^d	0.027
PICP, ng/mL	108 (88.1-129)	104 (81.4-129)	0.95 (0.91 to 0.99) ^d	0.050
CITP:MMP-1 ratio	3.92 (1.74-6.95)	3.75 (1.63-6.21)	0.96 (0.84 to 1.09) ^d	0.53
<u>Cardiopulmonary exercise testing</u>				
Maximum exercise duration, s	533 (518-548)	539 (524-554)	5.69 (-15.6 to 27.0)	0.60
ATVO ₂ , mL/min/kg	12.1 (11.6-12.5)	11.7 (11.2-12.2)	-0.38 (-1.06 to 0.31)	0.28
V _E /VCO ₂ slope	31.1 (30.6-31.6)	32.0 (31.5-32.5)	0.93 (0.17 to 1.68)	0.016
Borg scale	4.55 (4.27-4.83)	4.62 (4.34-4.90)	0.07 (-0.33 to 0.46)	0.73
<u>Health-related quality of life scores</u>				
SF-36 physical function score	64.0 (61.7-66.4)	65.2 (62.8-67.6)	1.14 (-2.25 to 4.54) ^d	0.51
PHQ-Sum	5.66 (5.21-6.11)	5.53 (5.07-5.98)	-0.13 (-0.78 to 0.51) ^d	0.68

E means peak early transmitral ventricular filling velocity; e', early diastolic tissue Doppler velocity; VO₂, oxygen consumption; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate; A, peak atrial transmitral ventricular filling velocity; IVRT, isovolumetric relaxation time; DT, deceleration time; LVEF, left ventricular (LV) ejection fraction; LVMI, LV mass index; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; NT-proBNP, amino-terminal pro-brain natriuretic peptide; PICP, carboxy-terminal propeptide of procollagen type-I; CITP, carboxy-terminal telopeptide of collagen type-I; MMP-1, matrix metalloproteinase-1; ATVO₂, oxygen consumption at anaerobic threshold; V_E, expired volume per unit time; VCO₂, volume of expired carbon dioxide; SF-36, short form 36; PHQ-Sum, Patient Health Questionnaire sum score; IQR, interquartile range. Higher values indicate better performance for LVEF, medial e' wave velocity, duration of exercise, peak VO₂, ATVO₂, Borg scale, walk distance and SF-36 physical function score. Lower values indicate better performance for left atrial volume index, E/e' (medial) velocity ratio, VE/VCO₂ slope and PHQ-Sum.

^aData are expressed as groupwise mean (95%CI) unless otherwise indicated. ^bBetween-group differences are from analysis of covariance, adjusting for baseline. ^cOdds ratio (95% CI). ^dGeometric mean ratio (95% CI).

Table S5. Demographic, clinical and biochemical characteristics at baseline in patients classified according to CITP:MMP-1 ratio tertiles and treatment

	1st tertile			2nd tertile			3rd tertile		
	Placebo (n=59)	Spironolactone (n=68)	<i>P</i>	Placebo (n=66)	Spironolactone (n=61)	<i>P</i>	Placebo (n=61)	Spironolactone (n=66)	<i>P</i>
CITP:MMP-1 ratio	<2.50			2.50-5.49			>5.49		
<u>Demographics</u>									
Age, years	68.4 ± 7.5	67.6 ± 7.5	0.52	66.7 ± 7.5	67.6 ± 8.1	0.55	65.8 ± 7.8	66.4 ± 7.4	0.62
Male gender, n (%)	26 (44.1)	35 (51.5)	0.41	35 (53.0)	26 (42.6)	0.24	29 (47.5)	31 (47.0)	0.95
<u>Medical History, n (%)</u>									
Hospitalized within 12 months	23 (39.0)	25 (36.8)	0.80	26 (39.4)	22 (36.1)	0.70	20 (32.8)	27 (40.9)	0.34
Coronary artery disease	28 (47.5)	31 (45.6)	0.83	25 (37.9)	25 (41.0)	0.72	17 (27.9)	26 (39.4)	0.17
History of myocardial infarction	14 (23.7)	15 (22.1)	0.82	6 (9.1)	10 (16.4)	0.22	7 (11.5)	11 (16.7)	0.40
Atrial fibrillation	14 (23.7)	11 (16.2)	0.29	12 (18.2)	8 (13.1)	0.43	9 (14.8)	9 (13.6)	0.86
Hypertension	56 (94.9)	62 (91.2)	0.41	60 (90.9)	59 (96.7)	0.18	53 (86.9)	59 (89.4)	0.66
Hyperlipidaemia	35 (59.3)	37 (54.4)	0.58	43 (65.2)	34 (55.7)	0.28	40 (65.6)	36 (54.5)	0.21
Diabetes mellitus	8 (13.6)	14 (20.6)	0.30	14 (21.2)	6 (9.8)	0.08	9 (14.8)	11 (16.7)	0.77
Cerebrovascular diseases	7 (11.9)	9 (13.2)	0.82	7 (10.6)	7 (11.5)	0.88	5 (8.2)	5 (7.6)	0.90
Peripheral arterial occlusive disease	1 (1.7)	1 (1.5)	0.72	5 (7.6)	4 (6.6)	0.82	3 (4.9)	1 (1.5)	0.28
COPD	1 (1.7)	3 (4.4)	0.37	1 (1.5)	4 (6.6)	0.16	1 (1.6)	3 (4.5)	0.35
<u>Physical examination</u>									
BMI, kg/m ²	28.5 ± 3.5	28.7 ± 3.9	0.78	29.3 ± 3.6	29.7 ± 3.2	0.56	29.4 ± 3.4	28.5 ± 3.6	0.13
SBP, mmHg	132 ± 21.0	134 ± 17.2	0.75	137 ± 18.7	139 ± 17.5	0.60	138 ± 15.4	134 ± 19.1	0.22
DBP, mmHg	75.1 ± 11.7	77.4 ± 9.2	0.23	81.2 ± 12.3	79.6 ± 10.6	0.45	82.0 ± 10.4	80.5 ± 10.5	0.43
MAP, mmHg	94.2 ± 12.9	96.1 ± 10.2	0.37	99.8 ± 12.4	99.4 ± 11.5	0.83	101 ± 10.5	98.7 ± 12.5	0.34
HR, beats/min	65.7 ± 9.6	65.7 ± 10.6	0.99	65.6 ± 12.4	68.5 ± 12.6	0.19	66.9 ± 13.3	68.0 ± 10.6	0.63
<u>Signs and symptoms, n (%)</u>									
NYHA class									
II	52 (88.1)	59 (86.8)	0.82	57 (86.4)	47 (77.0)	0.17	54 (88.5)	57 (86.4)	0.71
III	7 (11.9)	9 (13.2)		9 (13.6)	14 (23.0)		7 (11.5)	9 (13.6)	
Peripheral edema	26 (44.1)	26 (38.2)	0.51	25 (37.9)	27 (44.3)	0.47	27 (44.3)	23 (34.8)	0.28
Paroxysmal nocturnal dyspnoea	8 (13.6)	9 (13.2)	0.96	10 (15.2)	13 (21.3)	0.37	13 (21.3)	13 (19.7)	0.82
Nocturnal cough	12 (20.3)	10 (14.7)	0.40	10 (15.2)	9 (14.8)	0.95	9 (14.8)	10 (15.2)	0.63
<u>Laboratory measures</u>									
Hemoglobin, g/dL	13.6 ± 1.2	13.7 ± 1.3	0.54	13.9 ± 1.1	13.8 ± 1.2	0.82	14.0 ± 1.3	13.8 ± 1.1	0.54
Sodium, mmol/L	140 ± 2.8	140 ± 3.5	0.97	141 ± 2.0	140 ± 3.2	0.39	140 ± 3.1	141 ± 2.8	0.29
Potassium, mmol/L	4.2 ± 0.4	4.2 ± 0.4	0.69	4.2 ± 0.4	4.2 ± 0.3	0.96	4.1 ± 0.4	4.2 ± 0.4	0.11

eGFR, mL/min/1.73 m ²	71.6 ± 22.3	74.6 ± 18.4	0.42	75.7 ± 16.8	76.8 ± 18.2	0.69	80.7 ± 19.6	75.0 ± 19.2	0.10
<u>Baseline medications, n (%)</u>									
ACE inhibitor or ARB	49 (83.1)	58 (85.3)	0.73	49 (74.2)	48 (78.7)	0.56	42 (68.9)	46 (69.7)	0.92
Beta-blocker	47 (79.7)	48 (70.6)	0.24	49 (74.2)	42 (68.9)	0.50	43 (70.5)	46 (69.7)	0.92
Diuretics	30 (50.8)	41 (60.3)	0.29	35 (53.0)	35 (57.4)	0.62	32 (52.5)	29 (43.9)	0.34
Calcium channel blocker	14 (23.7)	12 (17.6)	0.40	20 (30.3)	17 (27.9)	0.76	18 (29.5)	14 (21.2)	0.28
Lipid-lowering drug	33 (55.9)	38 (55.9)	0.99	36 (54.5)	33 (54.1)	0.96	37 (60.7)	31 (47.0)	0.12

CITP means carboxy-terminal telopeptide of collagen type-I; MMP-1, matrix metalloproteinase-1; COPD, chronic obstructive pulmonary disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme; ARB, angiotensin II type 1 receptor blockers . Values are expressed as mean ± SD and categorical variables as numbers and percentages.

Table S6. Echocardiography, biomarkers, exercise testing and quality of life at baseline in patients categorized according to CITP:MMP-1 ratio tertiles and treatment

	1st tertile			2nd tertile			3rd tertile		
	Placebo (n=59)	Spirolactone (n=68)	<i>P</i>	Placebo (n=66)	Spirolactone (n=61)	<i>P</i>	Placebo (n=61)	Spirolactone (n=66)	<i>P</i>
CITP:MMP-1 ratio	<2.50			2.50-5.49			>5.49		
<u>Echocardiography</u>									
LVEF, %	69.1 ± 8.7	66.9 ± 7.7	0.14	65.9 ± 6.6	67.2 ± 7.5	0.31	69.3 ± 7.4	68.0 ± 9.0	0.36
LVEDD, mm	46.6 ± 6.2	46.0 ± 7.2	0.63	46.7 ± 5.4	46.7 ± 6.1	0.99	47.7 ± 6.9	45.8 ± 6.0	0.12
LVESD, mm	25.6 ± 7.0	25.2 ± 5.3	0.75	25.7 ± 7.2	25.0 ± 6.1	0.58	25.3 ± 6.5	24.4 ± 6.9	0.48
LVMI, g/m ²	111 ± 31.6	110 ± 34.4	0.98	105 ± 22.3	110 ± 26.6	0.31	113 ± 27.6	104 ± 26.5	0.08
RWT	0.50 ± 0.08	0.52 ± 0.10	0.15	0.49 ± 0.08	0.50 ± 0.08	0.77	0.50 ± 0.09	0.51 ± 0.09	0.61
Left atrial volume index, mL/m ²	28.5 ± 8.3	29.6 ± 7.6	0.45	27.2 ± 7.1	27.4 ± 9.4	0.70	28.3 ± 7.9	27.9 ± 10.9	0.78
E-wave velocity, cm/s	73.6 ± 17.9	72.8 ± 15.2	0.78	73.4 ± 17.4	73.7 ± 16.6	0.93	71.2 ± 19.5	71.7 ± 19.7	0.71
Medial e' wave velocity, cm/s	6.8 ± 1.3	6.9 ± 1.4	0.68	7.1 ± 1.9	7.2 ± 1.5	0.92	7.0 ± 1.5	7.3 ± 1.6	0.27
E/e' ratio	13.1 ± 3.9	13.1 ± 3.4	0.83	12.2 ± 3.3	13.0 ± 4.0	0.23	12.5 ± 3.7	12.2 ± 3.5	0.61
E:A ratio	0.90 ± 0.33	0.90 ± 0.34	0.73	0.90 ± 0.28	0.85 ± 0.24	0.24	0.91 ± 0.36	0.95 ± 0.36	0.23
IVRT, ms	88.5 ± 26.8	91.3 ± 26.2	0.56	83.7 ± 22.3	88.7 ± 26.9	0.27	87.5 ± 25.0	83.2 ± 23.6	0.33
DT, ms	243 ± 67.5	251 ± 61.3	0.48	256 ± 75.6	239 ± 58.6	0.50	243 ± 54.8	229 ± 57.3	0.17
<u>Biomarkers, median (IQR)</u>									
NT-proBNP, ng/L	180 (97.6-276)	192 (112-339)	0.39	130 (70.8-285)	154 (60.6-269)	0.88	148 (82.5-343)	189 (86.4-334)	0.52
PICP, ng/mL	110 (88.5-134)	112 (89.4-140)	0.62	111 (91.0-136)	107 (94.4-136)	0.63	116 (93.5-138)	110 (90.6-138)	0.73
CITP:MMP-1 ratio	1.18 (0.77-1.90)	1.35 (0.69-1.87)	0.84	3.80 (3.09-4.46)	4.14 (3.48-4.46)	0.07	9.43 (6.77-12.9)	8.44 (6.18-10.7)	0.11
<u>Cardiopulmonary exercise testing</u>									
Maximum exercise duration, s	520 ± 152	523 ± 180	0.93	542 ± 178	512 ± 172	0.34	575 ± 187	558 ± 182	0.59
Peak VO ₂ , mL/min/kg	16.3 ± 3.7	16.3 ± 3.5	0.94	16.1 ± 3.5	15.9 ± 3.4	0.76	16.3 ± 3.1	16.8 ± 3.8	0.45
ATVO ₂ , mL/min/kg	11.0 ± 3.1	11.9 ± 3.2	0.23	11.4 ± 3.1	11.6 ± 3.2	0.99	11.0 ± 2.7	12.1 ± 3.9	0.07
V _E /VCO ₂ slope	31.5 ± 5.2	30.2 ± 3.7	0.38	29.7 ± 4.1	29.5 ± 4.1	0.61	29.6 ± 4.0	29.7 ± 4.1	0.82
Borg scale	4.8 ± 1.7	4.9 ± 1.9	0.91	5.3 ± 1.8	5.1 ± 1.8	0.50	5.7 ± 2.0	5.3 ± 1.6	0.15
<u>Six-minute walk test</u>									
Walk distance, m	534 ± 78.0	530 ± 80.0	0.76	537 ± 75.8	535 ± 63.3	0.83	540 ± 81.8	538 ± 89.9	0.92
<u>Health-related quality of life scores</u>									
SF-36 physical function score	64.1 ± 22.0	60.4 ± 20.3	0.34	60.6 ± 24.0	62.1 ± 23.2	0.74	66.3 ± 22.0	63.1 ± 22.1	0.44
PHQ-Sum	5.7 ± 4.1	5.8 ± 4.3	0.94	5.2 ± 4.6	5.8 ± 4.1	0.30	6.1 ± 4.5	5.5 ± 3.7	0.59

CITP means carboxy-terminal telopeptide of collagen type-I; MMP-1, matrix metalloproteinase-1; LVEF, left ventricular (LV) ejection fraction; LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; LVMI, LV mass index; RWT, relative wall thickness; E, peak early transmitral ventricular filling velocity; e', early diastolic tissue Doppler velocity; A, peak atrial transmitral ventricular filling velocity; IVRT,

isovolumetric relaxation time; DT, deceleration time; NT-proBNP, amino-terminal pro-brain natriuretic peptide; PICP, carboxy-terminal propeptide of procollagen type-I; VO_2 , oxygen consumption; ATVO_2 , oxygen consumption at anaerobic threshold; V_E , expired volume per unit time; VCO_2 , volume of expired carbon dioxide; SF-36, short form 36; PHQ-Sum, Patient Health Questionnaire sum score. Higher values indicate better performance for LVEF, medial e' wave velocity, duration of exercise, peak VO_2 , ATVO_2 , Borg scale, walk distance and SF-36 physical function score. Lower values indicate better performance for left atrial volume index, E/e' (medial) velocity ratio, VE/VCO_2 slope and PHQ-Sumb. Values are expressed as mean \pm SD, median and interquartile range (IQR) and categorical variables as numbers and percentages.

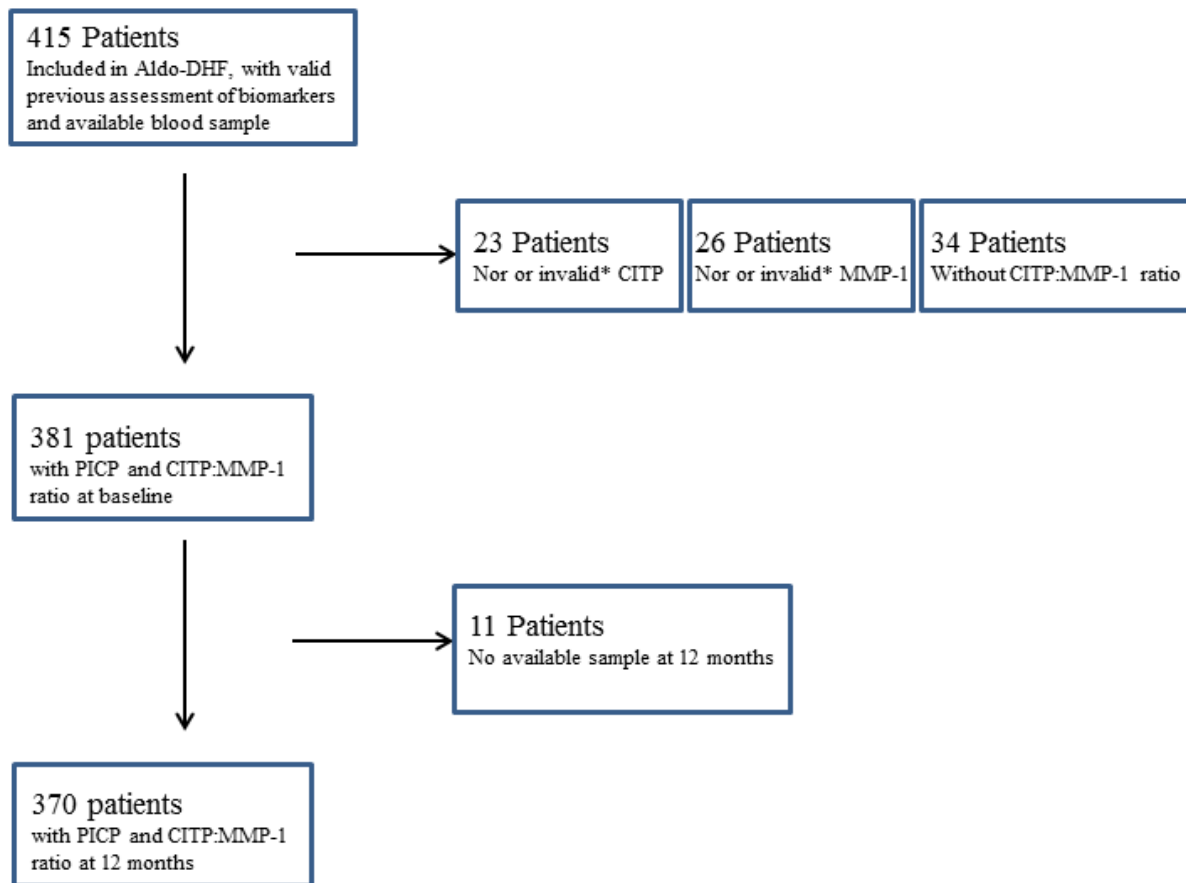
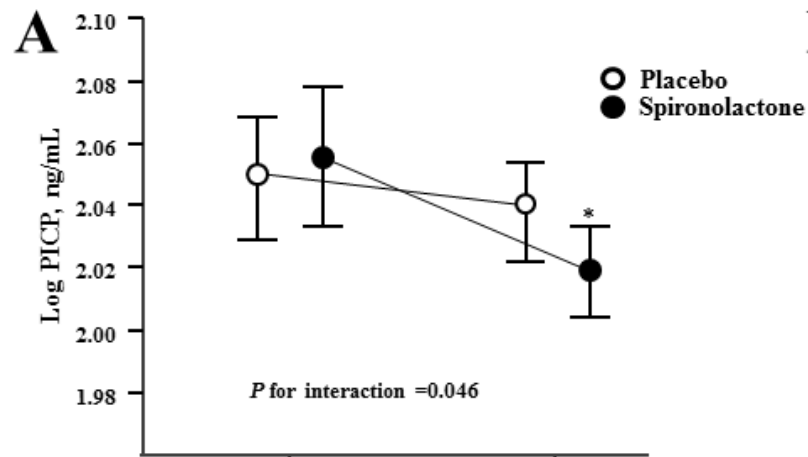
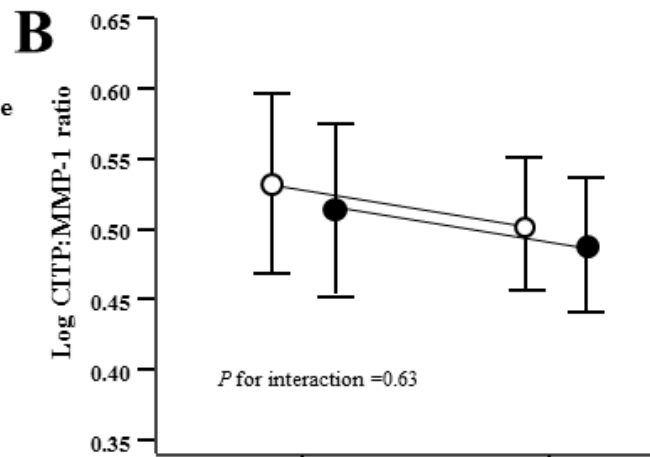


Fig. S1



	Baseline	12 months
Placebo		
N° of patients	186	180
Median (IQR), ng/ml	111 (91.8-135)	108 (88.1-129)
Spironolactone		
N° of patients	195	190
Median (IQR), ng/ml	111 (92.1-137)	104 (81.4-129)



	Baseline	12 months
N° of patients	186	180
Median (IQR)	3.81 (1.94-6.76)	3.92 (1.74-6.95)
N° of patients	195	190
Median (IQR)	4.10 (1.75-6.25)	3.75 (1.63-6.21)

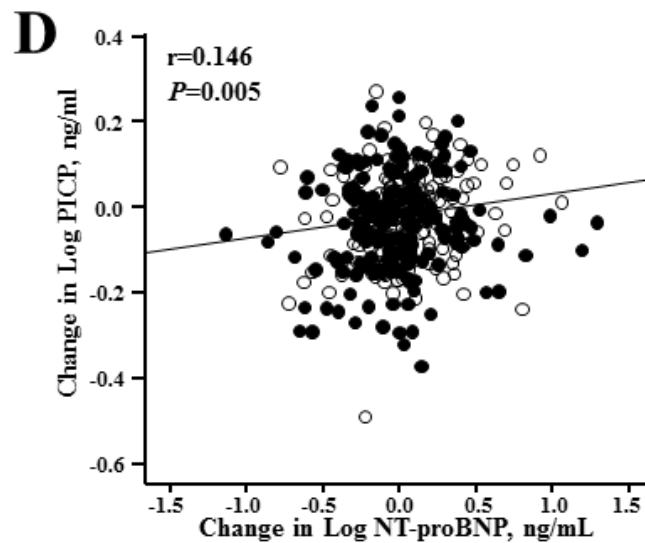
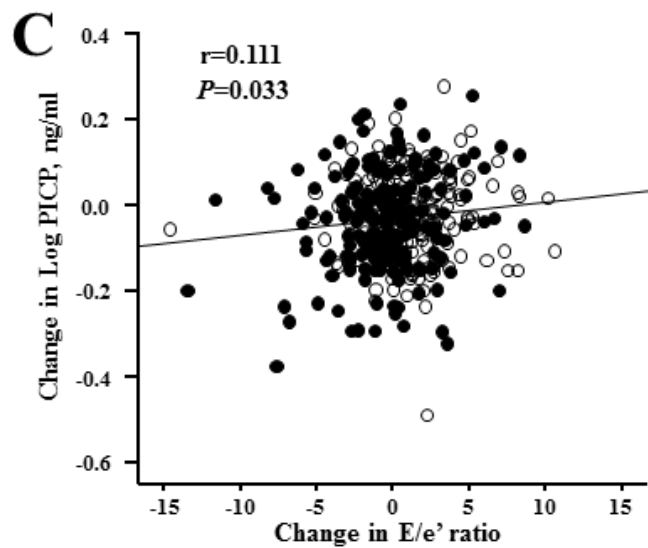


Fig. S2

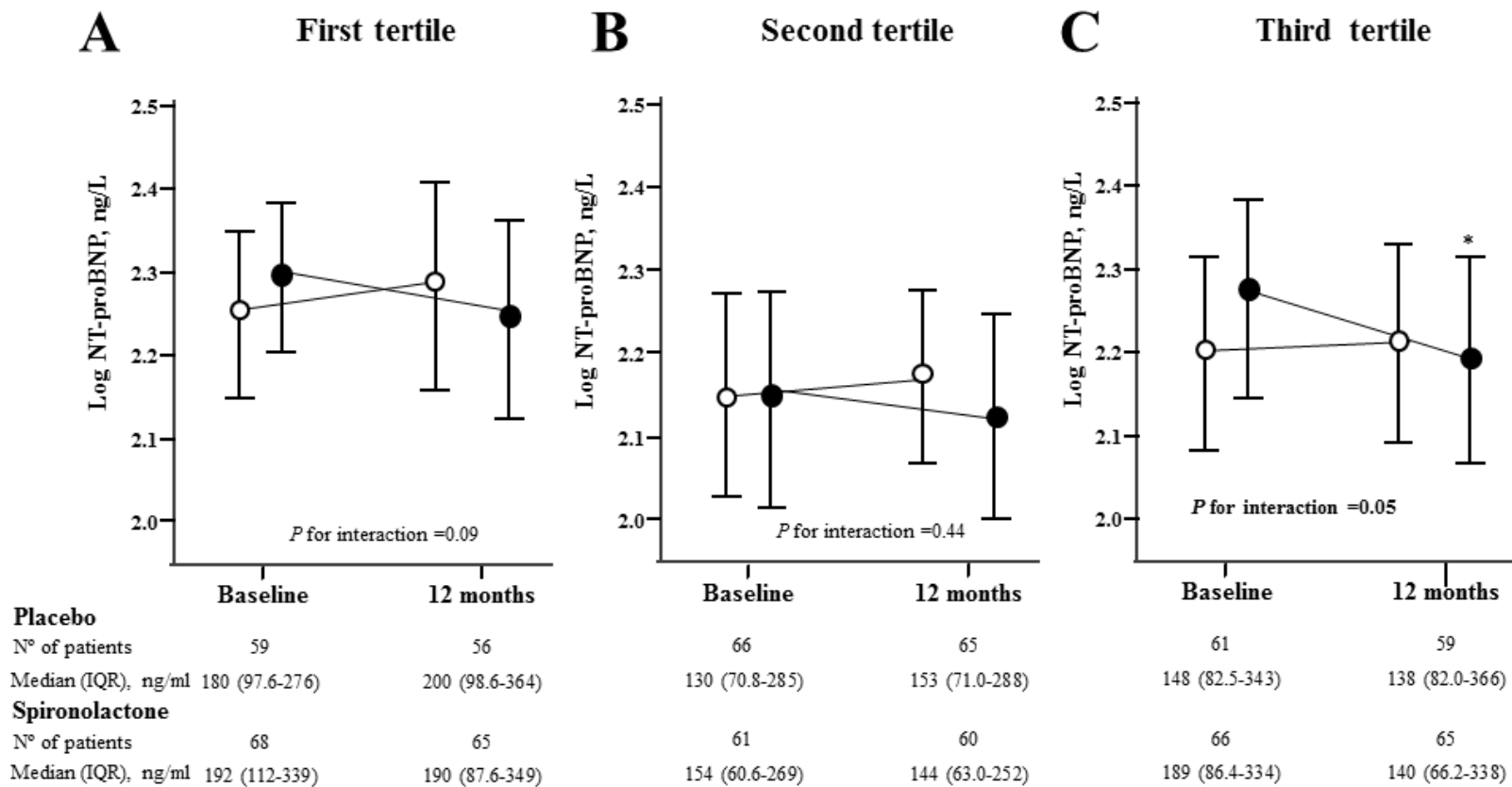


Fig. S3