

Supplemental Material

Supplementary Table 1. Patient's characteristics in pooled data and individual studies

Characteristic	Pooled	HOMAGE	ALDO-DHF	TOPCAT
N.	1038	488 (47.0%)	386 (37.2%)	164 (15.8%)
PICP, ng/mL	98 (76, 128)	81 (66, 97)	111 (91, 137)	139 (109, 167)
Age, years	71 (66, 77)	73 (69, 78)	68 (62, 73)	73 (66, 79)
Women	393 (37.9%)	120 (24.6%)	201 (52.1%)	72 (43.9%)
BMI, kg/m ²	29 (26, 32)	28 (25, 32)	29 (27, 32)	33 (28, 38)
Hypertension	892 (85.9%)	381 (78.1%)	354 (91.7%)	157 (95.7%)
Diabetes mellitus	336 (32.4%)	195 (40.0%)	66 (17.1%)	75 (45.7%)
CAD	574 (55.3%)	354 (72.5%)	152 (39.4%)	68 (41.5%)
Heart rate, bpm	64 (57, 71)	61 (55, 67)	65 (59, 73)	68 (60, 75)
SBP, mmHg	136 (124, 148)	140 (127, 155)	134 (124, 147)	126 (118, 136)
DBP, mmHg	77 (70, 85)	78 (71, 85)	80 (71, 87)	70 (62, 78)
Potassium, mmol/L	4.2 (4.0, 4.5)	4.3 (4.1, 4.6)	4.2 (3.9, 4.4)	4.1 (3.9, 4.4)
eGFR, ml/min/1.73m ²	72 (60, 84)	72 (62, 84)	74 (61, 86)	64 (49, 77)
Hb, g/dL	13.8 (12.9, 14.7)	14.0 (13.1, 14.9)	13.8 (13.0, 14.6)	13.0 (12.0, 14.2)
NT-pro BNP, pg/mL	187 (109, 329)	210 (134, 342)	158 (84, 302)	NA
BNP, pg/mL	-	NA	NA	524 (242, 1111)
LAVi, ml/m ²	29 (24, 35)	31 (26, 37)	27 (22, 33)	33 (27, 42)
LVMi, g/m ²	100 (85, 118)	95 (81, 113)	107 (91, 126)	99 (86, 117)
IVS diastole, mm	12 (10, 13)	11 (10, 12)	12 (11, 13)	12 (11, 13)
E/e'	11 (9, 13)	9 (8, 11)	12 (10, 14)	10 (7, 13)
LVEF, %	64 (60, 69)	63 (58, 67)	67 (62, 73)	60 (57, 64)
Spiro. allocation	525 (50.6%)	245 (50.2%)	198 (51.3%)	82 (50.0%)

Legend: PICP, procollagen type I carboxy-terminal propeptide; BMI, body mass index; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (CKD-EPI-creatinine); Hb, hemoglobin; NT-pro BNP, N-terminal pro brain natriuretic peptide; BNP, brain natriuretic peptide; LAVi, left atrial volume index; LVMi, left ventricular mass index; IVS, interventricular septum; LVEF, left ventricular ejection fraction.

Supplementary Table 2. Comparison of patients with versus without determined PICP

Factor	With PICP	Without PICP	P-value
N.	1038	1678	
HOMAGE	488 (47.0%)	39 (2.3%)	<0.001
ALDO-DHF	386 (37.2%)	36 (2.1%)	
TOPCAT	164 (15.8%)	1603 (95.5%)	
Age, years	71 (66, 77)	72 (64, 79)	0.10
Women	393 (37.9%)	845 (50.4%)	<0.001
BMI, kg/m ²	29 (26, 32)	33 (28, 38)	<0.001
Hypertension	892 (85.9%)	1496 (89.3%)	0.010
Diabetes mellitus	336 (32.4%)	739 (44.1%)	<0.001
CAD	574 (55.3%)	537 (32.0%)	<0.001
Heart rate, bpm	64 (57, 71)	68 (60, 76)	<0.001
SBP, mmHg	136 (124, 148)	130 (118, 139)	<0.001
DBP, mmHg	77 (70, 85)	71 (62, 80)	<0.001
Potassium, mmol/L	4.2 (4.0, 4.5)	4.2 (3.9, 4.5)	0.059
eGFR, ml/min/1.73m ²	72 (60, 84)	61 (50, 77)	<0.001
Hb, g/dL	13.8 (12.9, 14.7)	12.8 (11.7, 14.0)	<0.001
NT-pro BNP, pg/mL	187 (109, 329)	207 (127, 408)	0.33
BNP, pg/mL	524 (242, 1111)	391 (185, 794)	0.011
LAVi, ml/m ²	29 (24, 35)	29 (22, 36)	0.17
LVMi, g/m ²	100 (85, 118)	108 (88, 126)	<0.001
IVS diastole, mm	12 (10, 13)	12 (11, 13)	<0.001
E/e'	11 (9, 13)	11 (8, 15)	0.001
LVEF, %	64 (60, 69)	61 (56, 65)	<0.001
Spiro. allocation	525 (50.6%)	839 (50.0%)	0.77

Legend: PICP, procollagen type I carboxy-terminal propeptide; BMI, body mass index; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (CKD-EPI-creatinine); Hb, hemoglobin; NT-pro BNP, N-terminal pro brain natriuretic peptide; BNP, brain natriuretic peptide; LAVi, left atrial volume index; LVMi, left ventricular mass index; IVS, interventricular septum; LVEF, left ventricular ejection fraction.

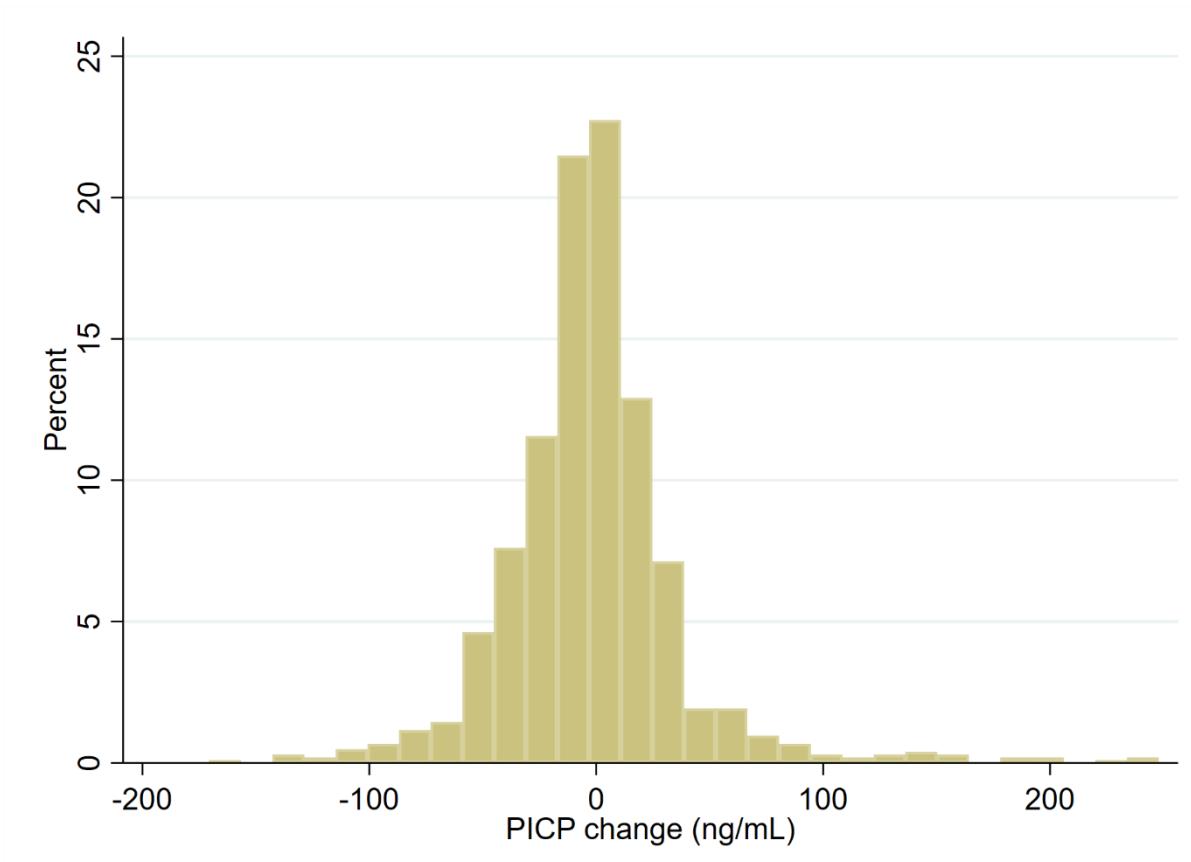
Supplementary Table 3. Association of PICP changes with corresponding changes in echocardiographic and clinical parameters

Parameter change	PICP change (ng/mL) Beta coef. (95%CI)	P-value
SBP (per 1 mmHg)	0.15 (0.02 to 0.28)	0.023
DBP (per 1 mmHg)	0.29 (0.04 to 0.53)	0.020
Potassium (per 1 mmol/L)	-0.36 (-5.95 to 5.23)	0.90
eGFR (per 1 ml/min)	-0.10 (-0.30 to 0.09)	0.31
LAVi (per 1 ml/m ²)	0.27 (-0.10 to 0.65)	0.16
LVMi (per 1 g/m ²)	-0.04 (-0.14 to 0.07)	0.49
IVS (per 1 mm)	-1.13 (-2.89 to 0.63)	0.21
E/e' (per 1 unit)	0.60 (-0.13 to 1.34)	0.11
LVEF (per 1 %)	-0.07 (-0.39 to 0.25)	0.67

Legend: PICP, procollagen type I carboxy-terminal propeptide; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (CKD-EPI-creatinine); LAVi, left atrial volume index; LVMi, left ventricular mass index; IVS, interventricular septum; LVEF, left ventricular ejection fraction.

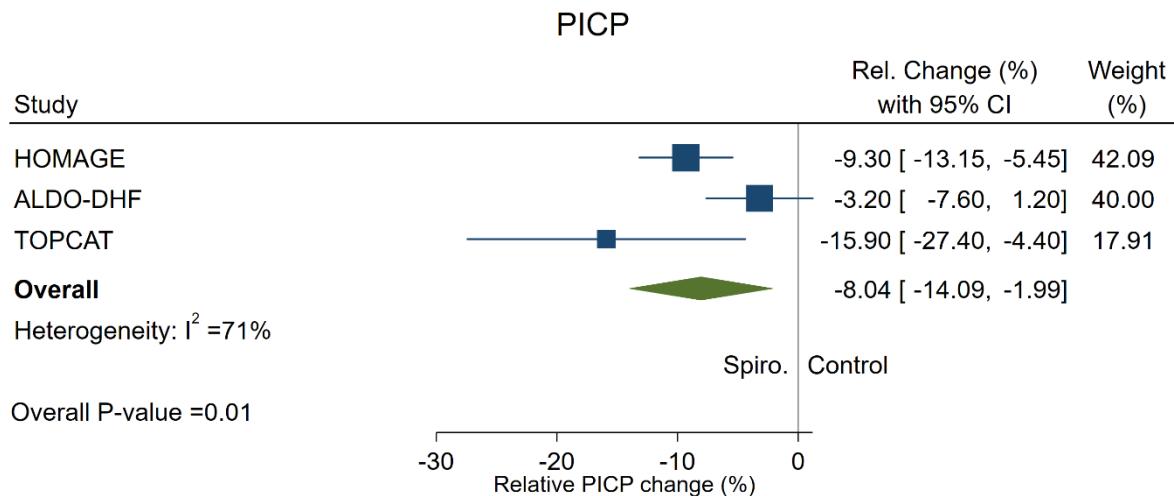
Caption: Only changes in blood pressure were associated with PICP changes within the same time-frame; however, the effect of spironolactone on PICP was not mediated by the changes in blood pressure: proportion of mediated effect =8.5%, P =0.13 for SBP and 6.7%, P =0.089 for DBP.

Supplementary Figure 1. PICP change distribution



Legend: PICP, procollagen type I carboxy-terminal propeptide.

Supplementary Figure 2. Effect of spironolactone on log transformed relative PICP changes



Legend: PICP, procollagen type I carboxy-terminal propeptide.

Caption: Spironolactone reduced serum PICP from baseline to 9-12 months by -8 (-14 to -2) %, $P = 0.01$. Moderate heterogeneity of effect ($I^2 = 71\%$, heterogeneity P -value = 0.02) was found between studies with a modest effect in ALDO-DHF and a marked but unprecise effect in TOPCAT.