Spironolactone effect on circulating procollagen type I carboxy-terminal propeptide: pooled analysis of three randomized trials

Short communication

João Pedro Ferreira[1,2]; John G. Cleland[3]; Nicolas Girerd[2]; Patrick Rossignol[2]; Pierpaolo Pellicori[3]; Franco Cosmi[4]; Beatrice Mariottoni[4]; Arantxa González[5]; Javier Diez[5]; Scott D. Solomon[6]; Brian Claggett[6]; Marc A. Pfeffer[6]; Bertram Pitt[7]; Johannes Petutschnigg[8]; Burkert Pieske[8]; Frank Edelmann[8]; Faiez Zannad[2]

[1] Cardiovascular R&D Centre – UnIC@RISE, Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine of the University of Porto, Porto, Portugal & Internal Medicine Departament, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal.

[2] Université de Lorraine, Inserm, Centre d'Investigation Clinique Plurithématique 1433, U1116, CHRU de Nancy, F-CRIN INI-CRCT, Nancy, France.

[3] School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow.

[4] Department of Cardiology, Cortona Hospital, Arezzo, Italy.

[5] Program of Cardiovascular Diseases, CIMA. Universidad de Navarra and IdiSNA, Pamplona, Spain & CIBERCV, Carlos III Institute of Health, Madrid, Spain.

[6] Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA.

[7] Division of Cardiology, University of Michigan, Ann Arbor, MI, USA.

[8] Department of Internal Medicine and Cardiology, Campus Virchow Klinikum, Charité University Medicine Berlin, Berlin, Germany & German Centre for Cardiovascular Research (DZHK), Partner Site Berlin, Berlin, Germany.

Contact to:

Prof. João Pedro Ferreira

UnIC@RISE, Department of Physiology and Cardiothoracic Surgery, Faculty of Medicine of the University of Porto.

Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal.

Telef.: +351 22 551 36 00

Mail.: jpferreira@med.up.pt or jp7ferreira@hotmail.com

Abstract

Background: Spironolactone might improve the prognosis of patients with heart failure with preserved left ventricular ejection fraction (HFpEF), but the mechanisms by which it acts are uncertain. Serum concentrations of procollagen type I carboxy-terminal propeptide (PICP) reflect the synthesis of type I collagen and correlate well with histologically proven cardiac fibrosis.

Aims: To investigate the effect of spironolactone on serum PICP concentration in patients with stage B and C HFpEF across three trials (HOMAGE, ALDO-DHF, and TOPCAT) for which measurements of serum PICP were available.

Methods: Random-effects meta-analysis.

Results: A total of 1038 patients with PICP measurements available both at baseline and 9-12 months were included in this analysis: 488 (47.0%) from HOMAGE, 386 (37.2%) from ALDO-DHF, and 164 (15.8%) from TOPCAT. The median (percentile$_{25-75}$) serum PICP was 98 (76-128) ng/mL. Compared to placebo or usual care, administration of spironolactone for 9 to 12 months reduced serum PICP by -7.4 ng/mL, 95%CI -13.9 to -0.9, P-value =0.02. The effect was moderately heterogeneous (I^2 =64%) with the most pronounced effect seen in TOPCAT where PICP was reduced by -27.0 ng/mL, followed by HOMAGE where PICP was reduced by -8.1 ng/mL, and was least marked in ALDO-DHF where PICP changed by -2.9 ng/mL. The association between spironolactone and serum PICP was not mediated substantially by blood pressure.

Conclusions: Spironolactone reduced serum concentrations of PICP in patients with HFpEF with different severity and stages of disease. These findings are consistent with spironolactone having an anti-fibrotic effect.

Key-words: spironolactone; fibrosis; anti-fibrotic therapy; HFpEF.

Background

There is evidence that spironolactone might improve the prognosis of patients with heart failure with preserved left ventricular ejection fraction (HFpEF),[1-4] but the mechanisms by which it acts are uncertain.

Serum concentrations of procollagen type I carboxy-terminal propeptide (PICP) reflect the synthesis of type I collagen and correlate well with histologically proven cardiac fibrosis, thus serving as a minimally-invasive marker of fibrotic activity.[5-7] In the HOMAGE (heart 'OMics' in AGEing) trial, serum concentration of PICP was associated with left ventricular hypertrophy, left atrial enlargement, and left ventricular stiffness.[8] In patients at risk of developing HF enrolled in HOMAGE, spironolactone reduced serum PICP and improved cardiac structure and function, suggesting that spironolactone might have anti-fibrotic effects.[9]

We now explore the effects of spironolactone on serum PICP in three trials to determine whether the effect is observed consistently in different patient populations.

Aims

To investigate the effect of spironolactone on serum PICP concentration in patients with stage B and C HFpEF across three trials for which measurements of serum PICP were available at both baseline (before randomized treatment) and after 9 to 12 months of therapy.

Methods

Included studies

HOMAGE was a multicentre, prospective, randomized, open-label, blinded endpoint (PROBE) trial comparing the effect of spironolactone (25 to 50 mg/day) vs. usual care (without spironolactone or other MRA) on serum markers of collagen metabolism as well as cardiac structure and function in patients with stage B HF and a LVEF ≥45% (ClinicalTrials.gov Identifier: NCT02556450).[10,11] PICP measurements were performed at baseline and 9 months.

ALDO-DHF was a multicentre, prospective, randomized, double-blind, placebo-controlled trial comparing the effect of spironolactone (25 mg/day) to placebo in patients with mildly symptomatic HF (stage B/C) and a LVEF ≥50% and evidence of diastolic dysfunction, although many had a normal plasma NT-proBNP, unlike HOMAGE trial participants.[4] PICP measurements were performed at baseline and 12 months.

TOPCAT was a multicentre, prospective, randomized, double-blind, placebo-controlled trial comparing the effect of spironolactone (15 to 45 mg/day) vs. placebo in 3445 patients with symptomatic HF (stage C) and a LVEF ≥45%.[1] A subset of patients from TOPCAT-Americas had PICP measured at baseline and 12 months.[2,12]

Ethics approval was obtained for all trials. Informed consent was obtained from all participants participating in the respective trials.

PICP measurements

Serum PICP was measured by enzyme immunoassay (METRA; Quidel Corporation®) blinded to treatment allocation.

Statistical analysis

A meta-analysis using random-effects models was conducted.[13] Baseline clinical characteristics of patients were summarised with medians and 25th to 75th

percentiles for continuous variables, plus frequencies and percentages for categorical variables. Treatment effect estimates were assessed by analysis of covariance (ANCOVA) with PICP change as dependent variable plus treatment and the baseline PICP value as independent variables. A β coefficient and respective 95% confidence interval (95% CI) was obtained from the linear regression model, representing PICP changes with spironolactone. As PICP change was slightly "right skewed" (*Supplementary Figure 1*), we also performed the analysis with log transformed PICP and presented as relative change (%) from baseline. A treatment-by-trial interaction term was tested in the regression model.[14] Statistical analyses were performed using STATA®, version 17 (Stata Corp, College Station, TX, USA).

Results

Patient's characteristics

A total of 1038 patients with PICP measurements available both at baseline and 9-12 months (i.e., paired) were included in this analysis: 488 (47.0%) from HOMAGE, 386 (37.2%) from ALDO-DHF, and 164 (15.8%) from TOPCAT. The overall population included 38% women, 32% with diabetes mellitus, 86% with a history of hypertension and 55% with coronary artery disease. The median eGFR was 72 ml/min/1.73m^2. The median (percentile$_{25\text{-}75}$) serum PICP was 98 (76-128) ng/mL, with lowest values in HOMAGE (median 81 ng/mL) and highest values in TOPCAT (median 139 ng/mL). *Supplementary Table 1*.

Patients without available paired PICP (n =1678) were mostly from TOPCAT (n =1603). *Supplementary Table 2*.

Spironolactone effect on PICP levels

Compared to placebo or usual care, administration of spironolactone for 9 to 12 months reduced serum PICP by -7.4 ng/mL, 95%CI -13.9 to -0.9, P-value =0.02. The effect was moderately heterogeneous (I^2 =64%) with the most pronounced effect seen in TOPCAT where PICP was reduced by -27.0 ng/mL, 95%CI -48.3 to -5.7, followed by HOMAGE where PICP was reduced by -8.1 ng/mL, 95%CI -11.9 to -4.3, and was least marked in ALDO-DHF where PICP changed by -2.9 ng/mL, 95%CI -8.3 to 2.4. *Figure 1*. Log transformed relative changes provided similar results with an overall PICP reduction of 8%, 95%CI 14% to 2%, with a 16% reduction in TOPCAT, 9% in HOMAGE, and 3% in ALDO-DHF. *Supplementary Figure 2*.

Association of PICP changes with echocardiographic and clinical variables

Changes in PICP from baseline to 9-12 months were associated with corresponding changes in systolic blood pressure (β =0.15 per 1 mmHg of SBP, 95% 0.02-0.28, P-value =0.023) and diastolic blood pressure (β =0.29 per 1 mmHg of DBP, 95% 0.04-0.53, P-value =0.020). However, the association between spironolactone and serum PICP was not mediated substantially by blood pressure reduction: proportion of mediated effect =8.5%, P-value =0.13 for SBP and 6.7%, P-value =0.089 for DBP. Associations between change in PICP and changes in serum potassium and echocardiographic measurements were not statistically significant. *Supplementary Table 3*. The presence of coronary artery disease did not influence the effect of spironolactone on PICP change (interactionP =0.44).

Conclusions

This analysis shows that spironolactone reduces serum concentrations of PICP in patients across a broad spectrum of patients at risk of or with HFpEF. The effect was

most pronounced in patients with more severe symptoms enrolled in TOPCAT but was also observed in patients with few symptoms (stage B) patients, such as those enrolled in HOMAGE. Although patients in ALDO-DHF had impaired exercise capacity; markers of cardiac dysfunction, such as plasma NT-pro BNP and left atrial dilation, were less markedly disturbed compared to those enrolled in HOMAGE (and TOPCAT). These findings lend support to the concept that spironolactone has anti-fibrotic effects. However, the heterogeneity observed in treatment effects across studies, suggests that the anti-fibrotic effects of spironolactone may be influenced by the degree of neurohormonal activation across HFpEF phenotypes; still, this hypothesis requires further investigation.[15] Although spironolactone reduced blood pressure, this did not appear to mediate the reduction in serum PICP, suggesting that the effect of spironolactone on PICP might be a direct cellular effect.[7]

This work has some limitations. This is a non-prespecified, post-hoc analysis of randomized trials. There will have been differences among trials in sample storage conditions, in assays and in duration of follow-up. HOMAGE was an open-label trial, whereas ALDO-DHF and TOPCAT were placebo-controlled; however, for all trials, PICP was measured blind to treatment allocation.

In conclusion, spironolactone reduced serum concentrations of PICP in patients with HFpEF with different severity and stages of disease. These findings are consistent with spironolactone having an anti-fibrotic effect.

Funding

This work was supported by the European Commission HOMAGE project (grant 305507) and by the Instituto de Salud Carlos III (CB16/11/00483 & PI18/01469).

Disclosures

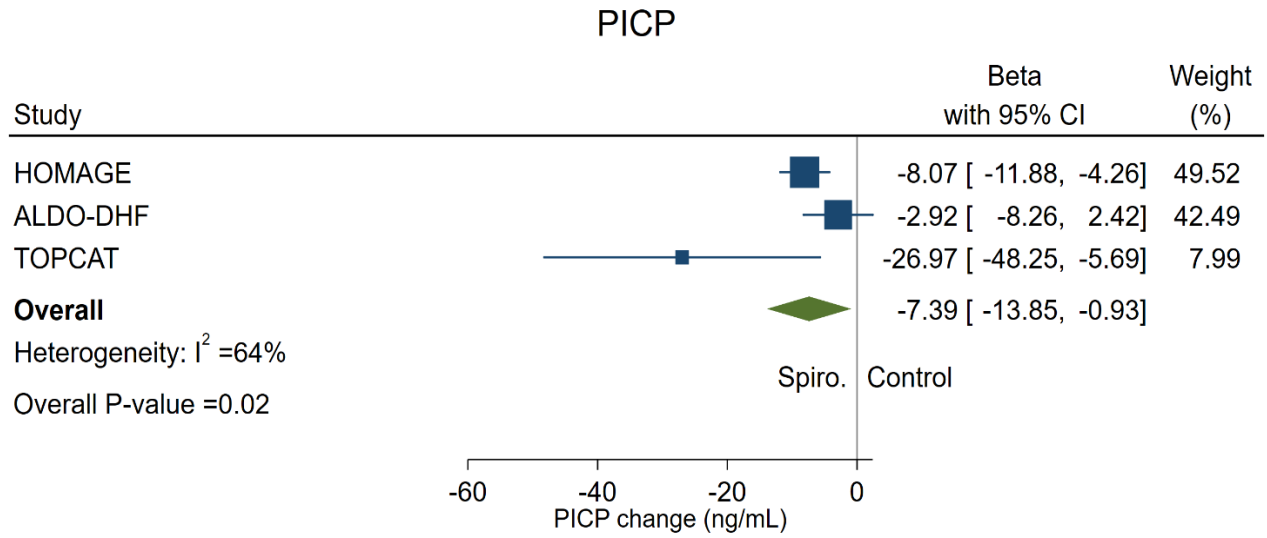
The authors have nothing to disclose in relation to this work.

References

1. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383-1392. doi: 10.1056/NEJMoa1313731
2. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. *Circulation*. 2015;131:34-42. doi: 10.1161/circulationaha.114.013255
3. Cleland JGF, Ferreira JP, Mariottoni B, Pellicori P, Cuthbert J, Verdonschot JAJ, Petutschnigg J, Ahmed FZ, Cosmi F, Brunner La Rocca HP, et al. The effect of spironolactone on cardiovascular function and markers of fibrosis in people at increased risk of developing heart failure: the heart 'OMics' in AGEing (HOMAGE) randomized clinical trial. *Eur Heart J*. 2020. doi: 10.1093/eurheartj/ehaa758
4. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Loffler M, et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *Jama*. 2013;309:781-791. doi: 10.1001/jama.2013.905
5. Querejeta R, Lopez B, Gonzalez A, Sanchez E, Larman M, Martinez Ubago JL, Diez J. Increased collagen type I synthesis in patients with heart failure of hypertensive origin: relation to myocardial fibrosis. *Circulation*. 2004;110:1263-1268. doi: 10.1161/01.cir.0000140973.60992.9a
6. Lopez B, Gonzalez A, Ravassa S, Beaumont J, Moreno MU, San Jose G, Querejeta R, Diez J. Circulating Biomarkers of Myocardial Fibrosis: The Need for a Reappraisal. *J Am Coll Cardiol*. 2015;65:2449-2456. doi: 10.1016/j.jacc.2015.04.026
7. López B, Ravassa S, Moreno MU, José GS, Beaumont J, González A, Díez J. Diffuse myocardial fibrosis: mechanisms, diagnosis and therapeutic approaches. *Nat Rev Cardiol*. 2021;18:479-498. doi: 10.1038/s41569-020-00504-1
8. Kobayashi M, Girerd N, Ferreira JP, Kevin D, Huttin O, González A, Bozec E, Clark AL, Cosmi F, Cuthbert J, et al. The association between markers of type I collagen synthesis and echocardiographic response to spironolactone in patients at risk of heart failure: findings from the HOMAGE trial. *Eur J Heart Fail*. 2022. doi: 10.1002/ejhf.2579
9. Ferreira JP, Verdonschot J, Wang P, Pizard A, Collier T, Ahmed FZ, Brunner-La-Rocca HP, Clark AL, Cosmi F, Cuthbert J, et al. Proteomic and Mechanistic Analysis of Spironolactone in Patients at Risk for HF. *JACC Heart Fail*. 2021. doi: 10.1016/j.jchf.2020.11.010
10. Cleland JGF, Ferreira JP, Mariottoni B, Pellicori P, Cuthbert J, Verdonschot JAJ, Petutschnigg J, Ahmed FZ, Cosmi F, Brunner La Rocca HP, et al. The effect of spironolactone on cardiovascular function and markers of fibrosis in people at increased risk of developing heart failure: the heart 'OMics' in AGEing (HOMAGE) randomized clinical trial. *Eur Heart J*. 2021;42:684-696. doi: 10.1093/eurheartj/ehaa758

11. Pellicori P, Ferreira JP, Mariottoni B, Brunner-La Rocca HP, Ahmed FZ, Verdonschot J, Collier T, Cuthbert JJ, Petutschnigg J, Mujaj B, et al. Effects of spironolactone on serum markers of fibrosis in people at high risk of developing heart failure: rationale, design and baseline characteristics of a proof-of-concept, randomised, precision-medicine, prevention trial. The Heart OMics in AGing (HOMAGE) trial. *Eur J Heart Fail*. 2020;22:1711-1723. doi: 10.1002/ejhf.1716
12. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Deswal A, Anand IS, Fleg JL, Pitt B, Pfeffer MA, Solomon SD. Prognostic Importance of Changes in Cardiac Structure and Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. *Circ Heart Fail*. 2015;8:1052-1058. doi: 10.1161/circheartfailure.115.002249
13. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *Eur Heart J*. 2014;35:3336-3345. doi: 10.1093/eurheartj/ehu424
14. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *Bmj*. 2010;340:c221. doi: 10.1136/bmj.c221
15. Vergaro G, Aimo A, Prontera C, Ghionzoli N, Arzilli C, Zyw L, Taddei C, Gabutti A, Poletti R, Giannoni A, et al. Sympathetic and renin-angiotensin-aldosterone system activation in heart failure with preserved, mid-range and reduced ejection fraction. *Int J Cardiol*. 2019;296:91-97. doi: 10.1016/j.ijcard.2019.08.040

Figure 1. Effect of spironolactone on PICP changes



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

Caption: Spironolactone reduced serum PICP from baseline to 9-12 months by -7.4 (-13.9 to -0.9) ng/mL, P =0.02. Moderate heterogeneity of effect (I^2 =64%, heterogeneity P-value =0.001) was found between studies with a modest effect in ALDO-DHF and a marked but unprecise effect in TOPCAT.

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/m2	29 (24, 35)	31 (26, 37)	27 (22, 33)	33 (27, 42)
LVMi, g/m2	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/m2	29 (24, 35)	29 (22, 36)	0.17
LVMi, g/m2	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.

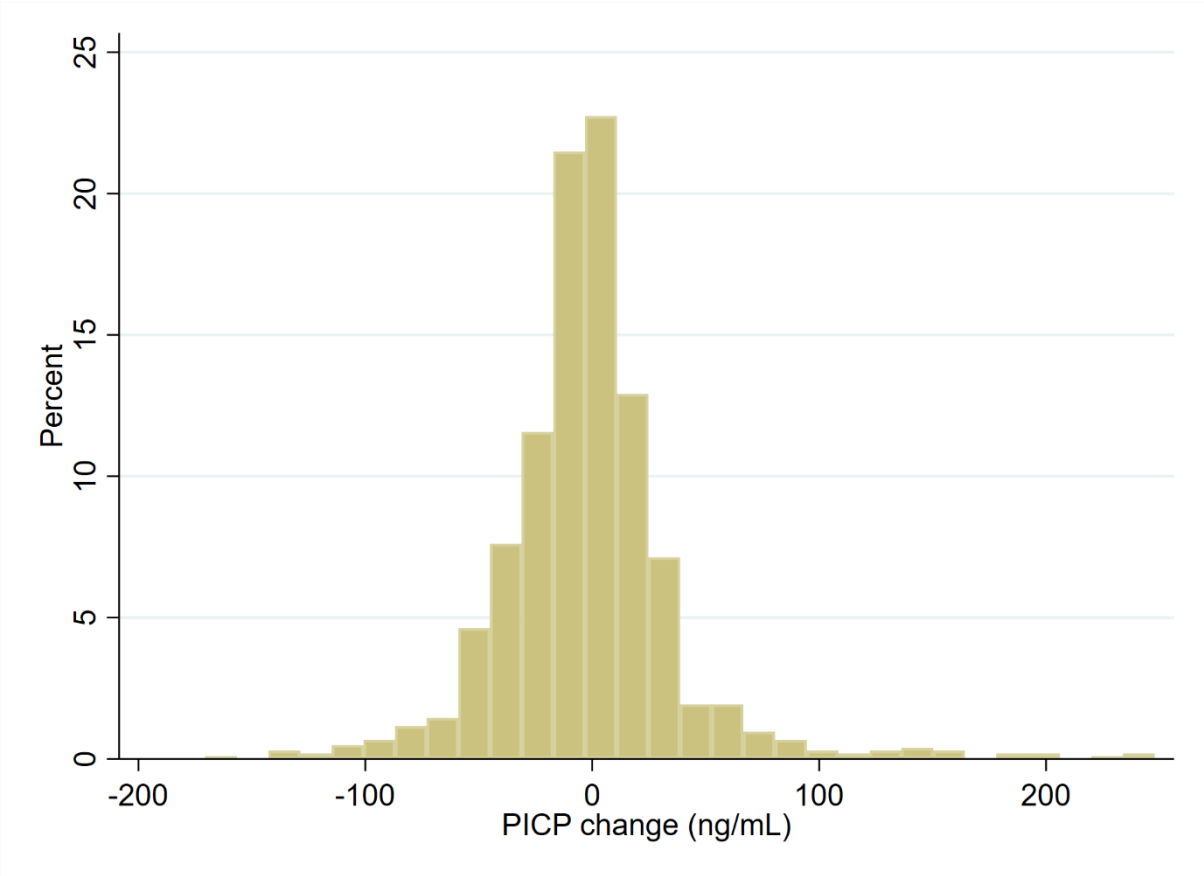
Supplementary Table 3. Association of PICP changes with corresponding changes in echocardiographic and clinical parameters

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/m2)	0.27 (-0.10 to 0.65)	0.16
LVMi (per 1 g/m2)	-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.

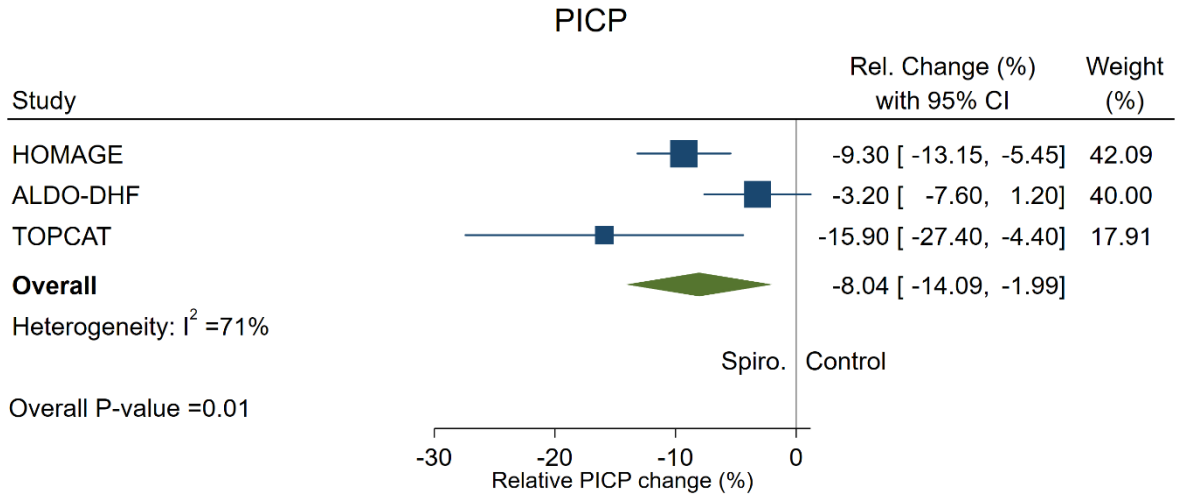
Caption: Only changes in blood pressure were associated with PICP changes within the same time-frame; however, the effect of spironolactone on PICP was not mediated by the changes in blood pressure: proportion of mediated effect =8.5%, P =0.13 for SBP and 6.7%, P =0.089 for DBP.

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.