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RESEARCH ARTICLE

Spironolactone effect on cardiac structure and function of patients with heart failure and preserved ejection fraction: a pooled analysis of three randomized trials

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Aims Spironolactone is currently used in a large proportion of patients with heart failure and preserved ejection fraction (HFpEF), yet its effect on cardiac structure and function in a large population has not been well established. The aim of this study was to evaluate the impact of spironolactone on key echocardiographic parameters in HFpEF.

Methods and results An individual-patient-data meta-analysis of three randomized trials (HOMAGE, Aldo-DHF, and TOPCAT) was performed comparing spironolactone (9–12 month exposure) to placebo (or control) for the changes in left atrial volume index (LAVi), left ventricular mass index (LVMi), interventricular septum (IVS) thickness, E/e′ ratio, and left ventricular ejection fraction (LVEF) among patients with stage B (HOMAGE) or C (Aldo-DHF and TOPCAT) HFpEF. Analysis of covariance was used to test the effect of spironolactone on echocardiographic changes. A total of 984 patients were included in this analysis: 452 (45.9%) from HOMAGE, 398 (40.4%) from Aldo-DHF, and 134 (13.6%) from TOPCAT. The pooled-cohort patient's median age was 71 (66–77) years and 39% were women. Median LAVi was 29 (24–35) ml/m^2, LVMi 100 (84–118) g/m^2, IVS thickness 12 (10–13) mm, E/e′ ratio 11 (9–13), and LVEF 64 (59–69)%. Spironolactone reduced LAVi by −1.1 (−2.0 to −0.1) ml/m^2 ($p = 0.03$); LVMi by −3.6 (−6.4 to −0.8) g/m^2 ($p = 0.01$); IVS thickness by −0.2 (−0.3 to −0.1) mm ($p = 0.01$); E/e′ ratio by −1.3 (−2.4 to −0.2) ($p = 0.02$); and increased LVEF by 1.7 (0.8–2.6)% ($p < 0.01$). No treatment-by-study heterogeneity was found except for E/e′ ratio with a larger effect in Aldo-DHF and TOPCAT (interaction $p < 0.01$).

Conclusions Spironolactone improved cardiac structure and function of patients with HFpEF.

Keywords Spironolactone • HFpEF • Echocardiography • Cardiac structure and function • Treatment effect

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Introduction

Spironolactone reduced heart failure (HF) hospitalizations and cardiovascular mortality in patients with HF and a preserved ejection fraction (HFpEF) enrolled in TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist), at least in those with a left ventricular ejection fraction (LVEF) up to 55–60%.[1–3] The smaller trials HOMAGE (Heart 'OMics' in AGEing) and Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) provided additional mechanistic insight on the effects of spironolactone to improve cardiac function and reduce fibrosis.[4–6]

Echocardiographic sub-studies were performed in TOPCAT, Aldo-DHF, and HOMAGE, but each of these individual studies might have been underpowered to assess the effect of spironolactone on key measures of cardiac structure and function.[4,5,7]

A pooled analysis of these trials would allow more power to study the effect of spironolactone on key echocardiographic parameters. Thus, in this individual-patient-data (IPD) meta-analysis of three randomized trials (HOMAGE, Aldo-DHF, and TOPCAT) comparing spironolactone to placebo or control, we assessed the effect of spironolactone treatment (9–12 month exposure) on the changes of echocardiographic parameters (left atrial volume index [LAVi], left ventricular mass index [LVMi], interventricular septum [IVS] thickness, E/e′ ratio, and LVEF) among patients with stage B (HOMAGE) or C (Aldo-DHF and TOPCAT) HFpEF.

Methods

Included studies

HOMAGE was a multicentre, prospective, randomized, open-label, blinded endpoint trial comparing the effect of spironolactone (25–50 mg/day) versus usual care (without spironolactone or other mineralocorticoid receptor antagonists [MRAs]) 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).[5,8] In short, patients aged 60 years or older with established coronary artery disease or at least two risk factors for cardiovascular disease (of type 2 diabetes mellitus, hypertension, microalbuminuria, or an abnormal electrocardiogram) as well as elevated natriuretic peptides were included. An echocardiogram was performed at baseline and last visit (9 months).

Aldo-DHF was a multicentre, prospective, randomized, double-blind, placebo-controlled trial comparing the effect of spironolactone (25 mg/day) versus placebo in patients with symptomatic HF and a LVEF ≥50% and evidence of diastolic dysfunction. The co-primary outcome measure was the change in E/e′ ratio from baseline to 12 months (the other co-primary outcome was peak oxygen consumption) (EudraCT Number: 2006-002605-31). An echocardiogram was performed at baseline and last visit (12 months).[4]

TOPCAT was a multicentre, prospective, randomized, double-blind, placebo-controlled trial comparing the effect of spironolactone (15–45 mg/day) versus placebo in 3445 patients with symptomatic HF and a LVEF ≥45%. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF (ClinicalTrials.gov Identifier: NCT00094302).[1] We selected the subset of patients from the Americas due to important regional differences found in the trial.[9] A subset of patients from TOPCAT-Americas performed an echocardiographic substudy at baseline and 12 months.[7]

Informed consent was obtained from all patients participating in the respective trials. Ethics approval was obtained for all trials and each participating centre.

Echocardiographic measurements

Our primary hypothesis was that spironolactone would reduce LAVi. In all three studies, echocardiograms were performed by dedicate staff experienced in echocardiographic imaging at a core laboratory in each individual study. To homogenize the echocardiographic methods, we used the same technique of cardiac structure and function assessment across studies. Specifically, LAVi was determined using the biplane Simpson's method at end-systole from the frame preceding mitral valve opening (i.e. LAVi minimum) and adjusted for body surface area. LVMi was calculated according to the American Society of Echocardiography (ASE) recommended formula for estimation of left ventricular mass (from left ventricular linear dimensions) and indexed to body surface area.[10] IVS thickness was determined at end-diastole from the apical 4-chamber view. Peak early diastolic tissue velocity (e′) was measured from the septal and lateral aspects of the mitral annulus. Mitral inflow velocity was assessed by pulsed-wave Doppler from the apical 4-chamber view, by positioning the sample volume at the tip of the mitral leaflets. The deceleration time of the E wave was measured as the interval from the peak E wave to its extrapolation to the baseline. E/e′ ratio was calculated as lateral E wave divided by e′. LVEF was determined by manually tracing the left ventricular endocardial borders at end-diastole and end-systole in the apical 4- and 2-chamber views and left ventricular volumes derived according to the biplane Simpson's method.

Left atrial volume index change was determined in 331 patients in HOMAGE, 385 patients in Aldo-DHF, and 102 patients in TOPCAT (LAVi pooled total $n = 818$). LVMi change was determined in 415 patients in HOMAGE, 388 patients in Aldo-DHF, and 124 patients in TOPCAT (LVMi pooled total $n = 927$). IVS thickness change was determined in 419 patients in HOMAGE, 397 patients in Aldo-DHF, and 129 patients in TOPCAT (IVS thickness pooled total $n = 945$). E/e′ ratio change was determined in 402 patients in HOMAGE, 396 patients in Aldo-DHF, and 92 patients in TOPCAT (E/e′ ratio pooled total $n = 890$). LVEF change was determined in 256 patients in HOMAGE, 398 patients in Aldo-DHF, and 134 patients in TOPCAT (LVEF pooled total $n = 788$).

Statistical analysis

A meta-analysis using random-effects models was conducted.[11] Baseline clinical characteristics of patients were summarized by study (and randomized treatment) with medians and 25th–75th percentiles for continuous variables, plus frequencies and percentages for categorical variables. Treatment effect estimates were assessed by analysis of covariance (ANCOVA) with the change in each echocardiographic parameter of interest as dependent variable plus treatment and the baseline value of the studied echocardiographic parameter as independent variables. A β coefficient and respective 95% confidence interval (CI) was obtained from the linear regression model, representing the changes in the echocardiographic parameter of interest with assignment to spironolactone. An ordered treatment-by-study interaction term ('interaction p-trend') was tested in the regression model.[12]

Statistical analyses were performed using STATA®, version 17 (Stata Corp, College Station, TX, USA).

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Table 1 Patient's characteristics

Characteristics	Pooled	HOMAGE	Aldo-DHF	TOPCAT
Patients, *n* (%)	984	452 (45.9)	398 (40.4)	134 (13.6)
Age, years	70.8 (65.7–76.5)	72.7 (68.3–78.1)	68.0 (62.0, 73.0)	71.5 (64.0, 78.0)
Women, *n* (%)	386 (39.2)	112 (24.8)	210 (52.8)	64 (47.8)
BMI, kg/m^2	29.0 (26.1–32.2)	28.1 (25.4–31.6)	29.0 (26.5–31.5)	33.0 (28.8–38.5)
Hypertension, *n* (%)	838 (85.2)	351 (77.7)	364 (91.5)	123 (91.8)
Diabetes mellitus, *n* (%)	314 (31.9)	184 (40.7)	66 (16.6)	64 (47.8)
CAD, *n* (%)	523 (53.2)	331 (73.2)	153 (38.4)	39 (29.1)
Heart rate, bpm	64 (57–71)	61 (54–67)	65 (59–73)	67 (60–76)
Atrial fibrillation, *n* (%)	44 (1.6)	0	0	44 (32.8)
SBP, mmHg	136 (124–149)	140 (128–156)	134 (124–147)	124 (112–134)
DBP, mmHg	78.0 (70–85)	78 (71–85)	80 (71–87)	70 (61–80)
Potassium, mmol/L	4.3 (4.0–4.5)	4.3 (4.1–4.6)	4.2 (3.9–4.4)	4.2 (3.9–4.5)
Creatinine, mg/dl	0.9 (0.8–1.1)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	1.1 (0.9–1.4)
eGFR, ml/min/1.73 m^2	71.5 (59.8–84.0)	72.6 (61.6–84.1)	73.4 (61.0–85.6)	61.6 (50.7–74.3)
Haemoglobin, g/dl	13.8 (12.8–14.7)	14.0 (13.1–14.9)	13.8 (13.0–14.7)	12.6 (11.6–13.4)
NT-proBNP, pg/ml	186 (107–332)	210 (135–356)	158 (85–302)	NA
BNP, pg/ml	533 (276–967)	NA	NA	533 (276–967)
LAVi, ml/m^2	28.9 (24.2–35.2)	31.1 (26.2–36.5)	26.6 (22.3–32.6)	30.8 (25.0–40.2)
LVMi, g/m^2	100.3 (83.9–118.3)	94.7 (80.7–112.3)	106.4 (91.0–125.7)	100.9 (80.4–123.4)
IVS, mm	11.6 (10.2–13.1)	11.0 (9.8–12.3)	12.0 (11.0–13.0)	11.6 (10.5–13.0)
E/e′	10.7 (8.6–13.1)	9.3 (7.5–11.5)	11.9 (10.3–14.0)	10.5 (7.8–14.5)
LVEF, %	64.0 (59.4–69.0)	62.9 (58.3–66.7)	67.0 (62.0–73.0)	60.5 (56.6–65.7)
Spironolactone allocation, *n* (%)	495 (50.3)	224 (49.6)	203 (51.0)	68 (50.7)

Values are given as median (25th–75th percentile), unless otherwise indicated.
BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IVS, interventricular septum thickness (end-diastolic); LAVi, left atrial volume(index); LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; NA, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

Results

Patient's characteristics

A total of 984 patients had the required echocardiographic parameters and were included in this analysis: 452 (45.9%) from HOMAGE, 398 (40.5%) from Aldo-DHF, and 134 (13.6%) from TOPCAT. The pooled-cohort median age of the patients was 71 (66–77) years, HOMAGE and TOPCAT patients had similar median age around 72 years, while Aldo-DHF patients were younger with a median age of 68 years. In the pooled cohort, 39% of the patients were women, HOMAGE had fewer women (25%) than Aldo-DHF and TOPCAT that included roughly 50% women. Comorbidities such as diabetes (32%), hypertension (85%) and coronary artery disease (53%) were highly prevalent, atrial fibrillation was present in 1.6% of the patients, all from TOPCAT. The median systolic blood pressure was 136 mmHg, median potassium was 4.3 mmol/L, and the median estimated glomerular filtration rate was 72 ml/min/1.73 m^2. The median LAVi was 29 (24–35) ml/m^2, LAVi was larger in HOMAGE and TOPCAT (31 ml/m^2) than in Aldo-DHF (27 ml/m^2); median LVMi was 100 (84–118) g/m^2, LVMi was higher in Aldo-DHF (106 g/m^2) than in TOPCAT (101 g/m^2) and HOMAGE (95 g/m^2); median IVS thickness was 12 (10–13) mm, and was similar across studies; median E/e′ ratio was 11 (9–13), and was higher in Aldo-DHF (12) than in TOPCAT (11) and HOMAGE (9); median LVEF was 64 (59–69)%, and was higher in Aldo-DHF (67%) than in HOMAGE (63%) and TOPCAT (61%) (*Table 1*). Randomization to spironolactone was balanced with around 50% of the patients randomized to active treatment and the other half to placebo (in Aldo-DHF and TOPCAT) or usual care (in HOMAGE) without significant differences in patient characteristics between treatment groups (online supplementary *Table S1*). The comparison of patients with and without an echocardiogram performed is presented in online supplementary *Table S2*, showing no major differences between groups.

Spironolactone effect on cardiac structure and function

Compared to placebo or usual care, spironolactone reduced LAVi by −1.1 (−2.0 to −0.1) ml/m^2 (p = 0.03), without significant heterogeneity between trials (interaction p = 0.23); reduced LVMi by −3.6 (−6.4 to −0.8) g/m^2 (p = 0.01, interaction p = 0.28); reduced IVS thickness by −0.2 (−0.3 to −0.1) mm (p = 0.01, interaction p = 0.74); reduced E/e′ ratio by −1.3 (−2.4 to −0.2) (p = 0.02), with a gradient effect from HOMAGE (smallest) to TOPCAT (largest) (interaction $p < 0.01$); and increased LVEF by 1.7 (0.8–2.6)% ($p < 0.01$, interaction p = 0.67) (*Figure 1*. The mean values of paired echocardiographic measures at baseline and 9–12 months, and respective changes with treatment are described in online supplementary *Table S3*.

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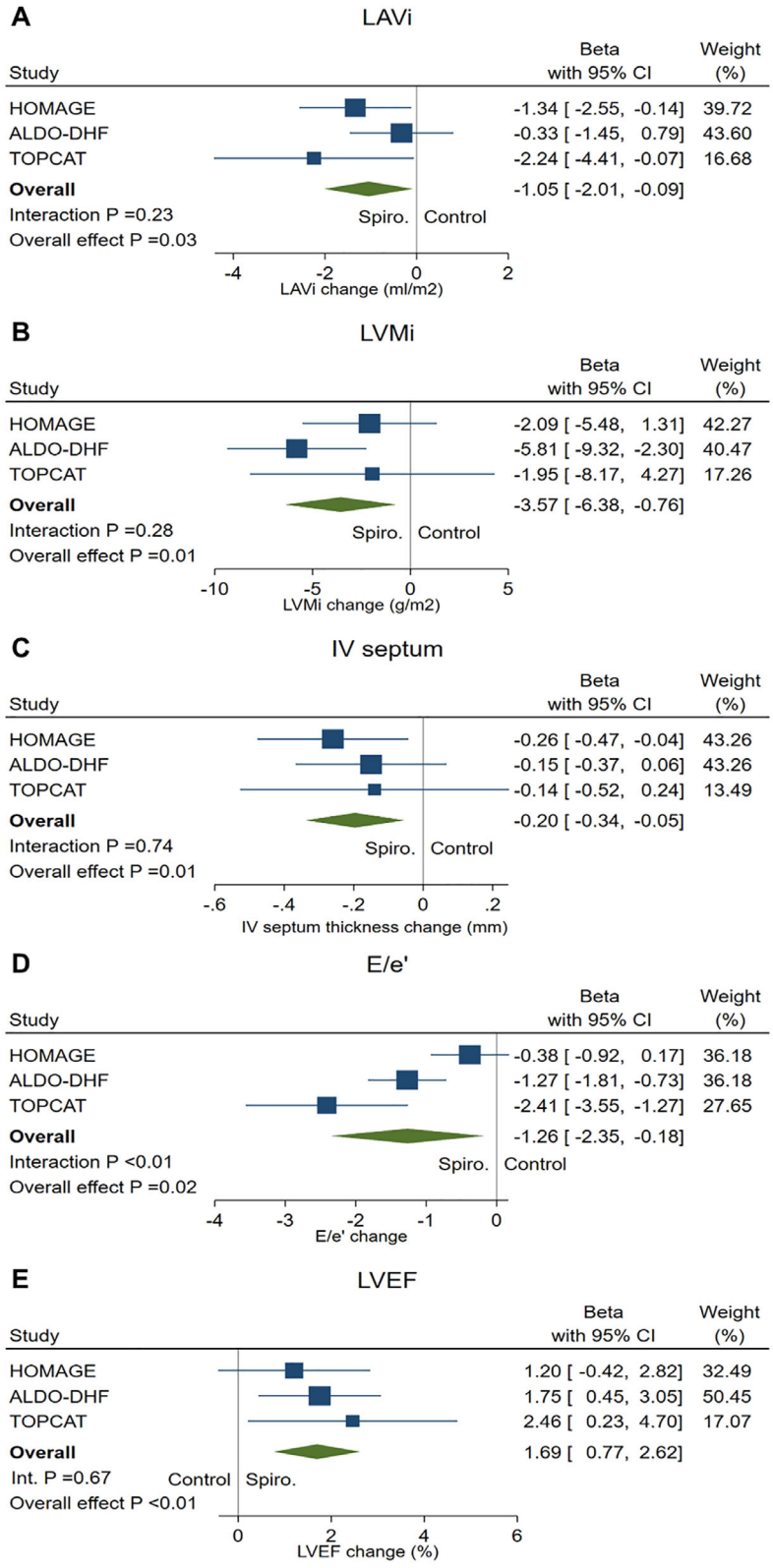

Figure 1 Effect of spironolactone on cardiac structure and function. CI, confidence interval; LAVi, left atrial volume index; LVMi, left ventricular mass index; IVS, interventricular septum thickness (end-diastolic); LVEF, left ventricular ejection fraction.

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Subgroup analyses according to age, sex, diabetes, coronary artery disease and hypertension status are displayed in online supplementary *Table S4*, without significant treatment-by-subgroup interactions.

Discussion

This individual-patient-data meta-analysis of HOMAGE, Aldo-DHF and TOPCAT showed that spironolactone (compared to placebo or usual care) reduced LAVi, LVMi, IVS thickness, E/e′ ratio, and increased LVEF. These findings, in a large population including patients with stage B and C HFpEF, support the use of spironolactone to improve the cardiac structure and function of patients with HFpEF.

The effect of spironolactone to reduce LAVi, LVMi and IVS thickness, and to increase LVEF was relatively homogeneous across trials; however, the effect of spironolactone on E/e′ ratio exhibited some heterogeneity, with a more pronounced effect in Aldo-DHF and TOPCAT than in HOMAGE. These differences in E/e′ ratio reduction with spironolactone treatment are likely related to the baseline value of E/e′ ratio in each trial. Due to differences in the studied population and inclusion criteria, baseline E/e′ ratio was lower in HOMAGE than in TOPCAT and Aldo-DHF; thus, the margin to reduce E/e′ was lower in HOMAGE. Similarly, LAVi reduction was less pronounced in Aldo-DHF (although without statistical heterogeneity) than in HOMAGE and TOPCAT, probably because baseline LAVi was also lower in Aldo-DHF than in HOMAGE and TOPCAT; thus, providing lower margin for reduction with spironolactone in Aldo-DHF. In any case, the effect of spironolactone was overall consistent and directionally similar across trials.

Left atrial enlargement has been associated with an increased risk of cardiovascular events and mortality across several populations with different degrees of cardiovascular risk.[13–16] The risk of worsening HF, atrial fibrillation and stroke increases several fold in HFpEF patients with enlarged left atria compared to patients with normal atria.[17] Importantly, a reduction in left atrial volume has been associated with improvement in clinical outcomes.[18,19] The clinical impact of left atrial volume reduction with MRAs is important as it may be associated with reductions in the incidence of worsening HF and new onset of atrial fibrillation, as demonstrated with eplerenone in patients with HF with reduced LVEF and finerenone in patients with type 2 diabetes and chronic kidney disease.[20,21]

Increased left ventricular mass and left ventricular hypertrophy (herein assessed by LVMi and IVS thickness) are strongly associated with an increased risk for the development of overt HF and a poor prognosis in patients with cardiovascular risk factors, such as those with hypertension.[22,23] Left ventricular hypertrophy is common in patients with HFpEF and is associated with a poor prognosis in this population as well.[24,25] The reduction of LVMi and IVS thickness with spironolactone adds to the favourable effects of this agent in improving cardiac remodelling. Along with spironolactone (and other MRAs), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, thiazide-type diuretics and sodium–glucose cotransporter 2 inhibitors also demonstrated to reduce left ventricular mass and IVS thickness in people at risk of HF development.[26–32]

Despite its modest correlation with invasively-determined left ventricular filling pressures, E/e′ ratio is used as a non-invasive measure of diastolic dysfunction and left ventricular filling pressures.[33–35] The present meta-analysis confirms findings from other studies, suggesting that spironolactone may decrease E/e′.[4,36] However, such effect was more pronounced in patients with higher baseline E/e′ ratio who had higher margin for E/e′ reduction.

Echocardiographic assessment of LVEF is used to phenotype and select therapies for patients with HF.[37,38] Furthermore, LVEF has strong prognostic implications.[39] Spironolactone improves LVEF in patients with HF with reduced LVEF.[40,41] Patients with mildly reduced and preserved ejection fraction have higher LVEF and therefore a lower margin for LVEF improvement with treatment. Still, in our study, spironolactone increased LVEF by 1.7%, adding to the favourable cardiac remodelling effects of this agent in HFpEF.

Limitations

Some limitations should be acknowledged in this study. This is a non-pre-specified post-hoc analysis of randomized trials and some differences in echocardiographic measurements and reporting might have occurred; still, the effect of spironolactone was beneficial in improving cardiac structure and function across studies. The studied populations had some differences in age, comorbidities, HF symptoms, follow-up time, and echocardiographic parameters. Such differences may have contributed to some of the treatment effect heterogeneity observed between trials. Still, the heterogeneity was only statistically significant for E/e′ ratio. HOMAGE was an open-label study, whereas Aldo-DHF and TOPCAT were placebo-controlled; still, the echocardiographic assessment was blinded to treatment in HOMAGE.

Conclusions

Spironolactone (compared to placebo or control) reduced LAVi, LVMi, IVS thickness, E/e′ ratio, and increased LVEF in patients with stage B and C HFpEF. These findings provide mechanistic support for the use of spironolactone in HFpEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Conflict of interest: none declared.

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