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Effect of Spironolactone on Left Ventricular Mass and Aortic Stiffness in Early-Stage Chronic Kidney Disease

A Randomized Controlled Trial

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Objectives We sought to determine whether the addition of spironolactone to angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) improves left ventricular mass and arterial stiffness in early-stage chronic kidney disease (CKD).

Background Chronic kidney disease is associated with a high risk of cardiovascular disease and a high prevalence of left ventricular hypertrophy and arterial stiffness that confer an adverse prognosis. It is believed that these abnormalities are in part a result of activation of the renin-angiotensin-aldosterone system.

Methods After an active run-in phase with spironolactone 25 mg once daily, 112 patients with stage 2 and 3 CKD with good blood pressure control (mean daytime ambulatory blood pressure <130/85 mm Hg) on established treatment with ACE inhibitors or ARBs were randomized to continue spironolactone or to receive a matching placebo. Left ventricular mass (cardiac magnetic resonance) and arterial stiffness (pulse wave velocity/analysis, aortic distensibility) were measured before run in and after 40 weeks of treatment.

Results Compared with placebo, the use of spironolactone resulted in significant improvements in left ventricular mass (-14 ± 13 g vs. $+3 \pm 11$ g, $p < 0.01$), pulse wave velocity (-0.8 ± 1.0 m/s vs. -0.1 ± 0.9 m/s, $p < 0.01$), augmentation index ($-5.2 \pm 6.1\%$ vs. $-1.4 \pm 5.9\%$, $p < 0.05$), and aortic distensibility ($0.69 \pm 0.86 \times 10^{-3}$ mm Hg vs. $0.04 \pm 1.04 \times 10^{-3}$ mm Hg, $p < 0.01$).

Conclusions The use of spironolactone reduces left ventricular mass and improves arterial stiffness in early-stage CKD. These effects suggest that aldosterone exerts adverse cardiovascular effects in CKD and that spironolactone is worthy of further study as a treatment that could reduce adverse cardiovascular events. (Is Spironolactone Safe and Effective in the Treatment of Cardiovascular Disease in Mild Chronic Renal Failure; NCT00291720) (J Am Coll Cardiol 2009;54:505–12) © 2009 by the American College of Cardiology Foundation

Chronic kidney disease (CKD) is a major public health problem affecting >10% of adults in developed countries and conferring a high risk of cardiovascular disease (1). The major health risk for patients with CKD is not progression to end-stage renal disease but an increased risk of death from nonrenal, predominantly cardiovascular disease (2). Cardiovascular risk in patients with CKD increases in a graded inverse relationship with glomerular filtration rate (GFR), but even in patients with early-stage CKD cardiovascular risk is increased approximately 4-fold. We have recently shown major abnormalities of cardiovascular structure and function in this group of patients (3). Despite these findings, there is little available evidence on which to base treatment; most trials (4) of therapy directed at reducing cardiovascular risk have systematically excluded patients with CKD.

See page 513

The importance of the renin-angiotensin-aldosterone system as a driver of progressive renal and cardiovascular disease in patients with CKD is increasingly apparent (5,6). Both angiotensin II and aldosterone exert numerous adverse cardiovascular effects, including the development of left ventricular hypertrophy (LVH) and increased arterial stiffness (7). Although angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are effective in reducing the progression of renal and vascular damage in patients with CKD, they do not result in

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
Aug = aortic augmentation pressure
Aug Ix = augmentation index
Aug Ix 75 = augmentation index corrected for a heart rate of 75 beats/min
CKD = chronic kidney disease
CMR = cardiovascular magnetic resonance
EDV = end-diastolic volume
eGFR = estimated glomerular filtration rate
GFR = glomerular filtration rate
hsCRP = high-sensitivity C-reactive protein
LV = left ventricle/ventricular
LVH = left ventricular hypertrophy
PAC = plasma aldosterone concentration
PWA = pulse-wave analysis
PWV = pulse-wave velocity
RV = right ventricle/ventricular

complete suppression of aldosterone production, a stimulus to ventricular hypertrophy, fibrosis, and vascular inflammation (8). We hypothesized that in patients with early-stage CKD, continuing aldosterone production is an important cause of LVH and increased arterial stiffness (9,10), which are powerful risk factors for cardiovascular disease in the general population (11,12) and are highly prevalent and prognostically important in CKD (13,14). The CRIB (Chronic Renal Impairment in Birmingham) 2 trial has therefore examined the effect of the addition of the aldosterone antagonist spironolactone to ACE inhibitors or ARBs on these prognostic markers in a group of patients with early (stage 2 and 3) CKD.

Methods

Study design and treatment regimen. The study was a single-center, prospective, double-blind, placebo-controlled, randomized interventional trial that comprised a 4-week open-label run-in phase of 25 mg of spironolactone once daily, after which patients were randomized to continue a further 36 weeks of treatment with 25 mg of spironolactone or to receive placebo.

Setting and participants. Patients were recruited from renal clinics at a University teaching hospital in the United Kingdom from 2005 to 2007. Inclusion criteria were as follows: age 18 to 80 years, stage 2 (GFR 60 to 89 ml/min/1.73 m^2 and evidence of kidney damage for ≥3 months) or stage 3 (GFR 30 to 59 ml/min/1.73 m^2) CKD (15), treatment with an ACE inhibitor and/or ARB for at least 6 months, and controlled blood pressure (mean daytime blood pressure on ambulatory monitoring <130/85 mm Hg). Estimated glomerular filtration rate (eGFR) was measured by the 4-variable Modification of Diet in Renal Disease formula with serum creatinine recalibrated to be traceable to an isotope-derived mass spectroscopy method (16). Exclusion criteria were as follows: a history or other evidence of angina, myocardial infarction, heart failure, cerebral or peripheral vascular disease, diabetes mellitus, previous hyperkalemia, valvular heart disease, atrial fibrillation, renovascular disease, and anemia (hemoglobin <12 g/dl). The protocol was approved by South Birmingham Local Research Ethics Committee, and all patients supplied written informed consent.

Patients were assessed at baseline (before the run-in phase) and at the end of the study (week 40) with a clinical history and examination, 24-h ambulatory blood pressure monitoring, cardiovascular magnetic resonance (CMR) imaging, and measurement of pulse-wave velocity (PWV) and pulse-wave analysis (PWA). Venous blood samples were also collected after 30 min of supine rest for routine hematology and biochemistry, lipid profiles, and measurement of plasma renin, aldosterone, and angiotensin II. Urine samples were obtained for measurement of albumin-creatinine ratio. Biochemical and safety monitoring was performed at weeks 0, 1, 2, 4, 8, 16, 28, and 40. Patients were withdrawn if they developed serious hyperkalemia, defined as a single serum potassium concentration >6.5 or >6.0 mmol/l on urgent repeat sampling. Patients with potassium levels between 5.5 and 5.9 mmol/l received spironolactone 25 mg on alternate days, and repeat blood samples were taken 1 week later. An independent data and safety monitoring board monitored the progress of all aspects of the study.

Blood pressure, PWA, and PWV. All subjects underwent 24-h ambulatory blood pressure monitoring (Meditech ABPM-04, PMS Instruments, Maidenhead, United Kingdom) at baseline and at week 40. Office brachial blood pressure also was recorded with the subject lying supine after 10, 20, and 30 min in the nondominant arm and a validated oscillometric sphygmomanometer (Dinamap Procare, GE Healthcare, Hatfield, United Kingdom). Augmentation pressure (Aug) and index (Aug Ix) were assessed noninvasively by the use of radial artery waveforms obtained with a high-fidelity micromanometer (SPC-301, Millar Instruments, Houston, Texas). The corresponding central waveform was generated by the use of a validated transfer function (SphygmoCor, AtCor Medical, Sydney, Australia) (17,18). The Aug Ix was corrected for a heart rate of 75 beats/min (Aug Ix 75) (18). Aortic PWV was measured by use of the same device by sequentially recording electrocardiogram-gated carotid and femoral artery waveforms as described previously (19). All measurements were made in triplicate and mean values used in analysis.

Cardiovascular magnetic resonance imaging. Cardiovascular magnetic resonance imaging was performed on a 1.5-T scanner (Sonata Symphony, Siemens, Erlangen, Germany). Serial contiguous short axis cines were piloted from the vertical long axis and horizontal long axis of the right ventricle and left ventricle (electrocardiogram [ECG] gated, steady-state free precession imaging [True-FISP]; temporal resolution 40 to 50 ms, repetition time 3.2 ms, echo time 1.6 ms, flip angle 60°, slice thickness 7 mm) in accordance with previously validated methodologies (20). Analysis was performed off-line (Argus Software, Siemens) by a single blinded observer (N.E.) for the assessment of ventricular volumes (end-diastole, end-systole, stroke volume), ejection fraction, and left ventricular (LV) mass (20). Aortic distensibility was assessed in the ascending aorta at the level of the pulmonary artery and calculated by use of standard formulas (21).

Outcomes and follow-up. The study coprimary end points were change in LV mass and arterial stiffness measured by

PWV. Secondary end points were aortic distensibility, Aug AIx, blood pressure, and albuminuria.

Statistical analysis. We calculated that a sample size of 90 patients assigned equally to the 2 treatment groups would provide 95% power to detect a change in LV mass of 10 g (SD 12 g) on CMR and 80% power to detect a change in PWV of 0.6 m/s (SD 1.0 m/s) with an alpha error of 0.05 in each case (22). Data are expressed as mean ± SD (unless stated) and were log-transformed as necessary. Treatment groups were compared by the use of *t* tests or chi-square tests (at baseline) and repeated measures analysis of variance (for changes over time). Adjustments for changes in mean arterial pressure for parameters of arterial stiffness were based on linear regressions. Trend was assessed by the use of the Jonckheere-Terpstra test. Independent predictors of changes in LV mass and arterial stiffness were determined with the use of multivariate regression models. Intraobserver reproducibility was assessed by the use of intraclass correlation coefficients (23).

Results

Of 2,196 consecutive patients with nondiabetic CKD attending nephrology outpatient clinics, 1,911 were not immediately eligible for recruitment (46% were not on an ACE inhibitor or ARB, 29% had renovascular disease or uncontrolled hypertension, 15% had previous cardiovascular events, 2% had atrial fibrillation, and 8% other). Of the 285 patients who met the inclusion criteria, 170 patients declined to participate; therefore, 115 patients were enrolled. Three patients did not complete the run-in phase as described in the following text. One hundred twelve patients were randomized to receive spironolactone (n = 56) or placebo (n = 56). There were no significant clinical differences between groups (Table 1). The cause of renal disease was made by renal biopsy in 70% and by imaging in 23% of cases. A history of hypertension was documented in 72% of cases. Left ventricular hypertrophy on ECG voltage criteria was present in 1 patient. Mean values for LV ejection fraction, volume, and mass were within normal limits (20).

Table 1 Patient Characteristics at Baseline

	Placebo (n = 56)	Spironolactone (n = 56)
Age (yrs)	53 ± 12	54 ± 12
Male, n (%)	33 (59)	32 (57)
Office SBP (mm Hg)	130 ± 19	130 ± 16
Office DBP (mm Hg)	77 ± 10	77 ± 10
Serum creatinine (mg/dl)	1.4 ± 0.38	1.5 ± 0.39
eGFR (ml/min/1.73 m^2)	53 ± 11	49 ± 12
Heart rate (beats/min)	65 ± 11	66 ± 12
Hemoglobin (g/dl)	13.5 ± 1.6	13.5 ± 1.3
Cholesterol (mg/dl)	181.5 ± 42.5	189.2 ± 42.5
Serum potassium (mmol/l)	4.3 ± 0.3	4.4 ± 0.8
Number of patients on treatment with		
ACE inhibitors	39	38
Angiotensin-receptor blockers	19	19
Beta-blockers	8	15
Calcium-channel blockers	17	13
Statins	17	27
Diuretics	13	18

Values are mean ± SD unless otherwise indicated. There were no significant differences in baseline characteristics.

ACE = angiotensin-converting enzyme; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure.

Follow-up. No patients died. Two patients did not complete the follow-up period; 1 patient withdrew consent for further participation, and 1 patient had a relapse of Wegener granulomatosis causing acute renal failure. Two patients were hospitalized during their participation for unrelated medical conditions.

Treatment effects. HEMODYNAMIC, RENAL, AND ENDOCRINE EFFECTS. Compared with placebo, the use of spironolactone resulted in a significant decrease in office systolic blood pressure (−11 ± 12 mm Hg vs. −5 ± 14 mm Hg, $p < 0.05$) and pulse pressure (−5 ± 9 mm Hg vs. −1 ± 9 mm Hg, $p < 0.05$). Central systolic blood pressure (−12 ± 12 mm Hg vs. −4 ± 14 mm Hg, $p < 0.01$), central mean arterial pressure (−8 ± 9 mm Hg vs. −4 ± 10 mm Hg, $p < 0.05$), and central pulse pressure (−5 ± 9 mm Hg vs. −1 ± 8 mm Hg, $p < 0.01$) also were reduced. Twenty-four-hour ambulatory systolic blood pressure and pulse pressure also decreased significantly in the spironolactone group (Table 2). Office, central, and ambulatory diastolic pressures were not different between treatment groups (Table 2).

Compared with placebo, the use of spironolactone was not associated with a significant decrease in eGFR (spironolactone −3 ± 7 ml/min/1.73 m^2 vs. placebo −1 ± 5 ml/min/1.73 m^2, p = NS). Treatment with spironolactone reduced albuminuria by −21 ± 99 mg/mmol compared with −8 ± 37 mg/mmol with placebo, $p < 0.05$ (Table 2). Changes in plasma aldosterone, plasma renin, plasma angiotensin II, and high-sensitivity C-reactive protein concentrations are shown in Table 2.

CHANGES IN LV MASS, VOLUMES, AND FUNCTION. Compared with placebo, treatment with spironolactone resulted in significant reductions in LV mass and LV mass index (Table 2, Fig. 1). The prevalence of LVH decreased by 50% with spironolactone but was unchanged with placebo (Table 2). Baseline LV mass was not a predictor of LV mass regression on multivariable analysis. The reduction in LV mass index on spironolactone for those subjects with LVH at baseline was −8 ± 8 g compared with −6 ± 5 g for those with a normal baseline LV mass (p = NS). Spironolactone did not affect LV volumes or ejection fraction.

CHANGES IN PWV, AORTIC DISTENSIBILITY, AND AUG IX. Compared with placebo, the use of spironolactone resulted in a significant decrease in PWV (Table 3, Fig. 2A), central aortic pressure augmentation, Aug Ix, and Aug Ix 75 (Table

Table 2 Changes in Blood Pressure, Laboratory, and CMR Variables

	Placebo		Spironolactone	
	Week 0	Week 40	Week 0	Week 40
24-h SBP (mm Hg)	125 ± 10	124 ± 11	124 ± 11	119 ± 11*
24-h DBP (mm Hg)	77 ± 8	76 ± 7	76 ± 8	73 ± 8
Office SBP (mm Hg)	130 ± 19	125 ± 17	130 ± 16	119 ± 13†
Office DBP (mm Hg)	77 ± 10	73 ± 9	77 ± 10	71 ± 10
Central SBP (mm Hg)	120 ± 18	116 ± 16	121 ± 15	110 ± 13*
Central DBP (mm Hg)	78 ± 10	74 ± 9	78 ± 10	72 ± 10
ACR (mg/mmol)‡	8.2 ± 48.4	9.5 ± 34.9	17.8 ± 48.6	5.4 ± 34.9†
Renin (μU/ml)‡	87.0 ± 103.5	74.5 ± 108.8	71.0 ± 110.0	130.0 ± 188.0*
Angiotensin II (pg/ml)‡	8.0 ± 16.5	7.8 ± 13.7	8.0 ± 16.7	14.2 ± 41.0*
PAC (pg/ml)‡	67.0 ± 49.3	43.5 ± 51.8	60.0 ± 38.0	130.0 ± 117.3*
hsCRP (mg/dl)‡	1.08 ± 3.85	1.38 ± 2.06	2.22 ± 3.49	2.33 ± 3.64
LVEF (%)	72 ± 8	72 ± 7	69 ± 8	72 ± 9
LV mass (g)	110 ± 26	113 ± 28	119 ± 34	105 ± 30*
LV mass index (g/m^2)	59.2 ± 11.3	58.9 ± 12.0	60.7 ± 13.5	53.8 ±12.5*
LV hypertrophy (%)	8	8	11	5
LVEDV/BSA (ml/m^2)	54 ± 11	55 ± 12	56 ± 13	53 ± 11
LVSV/BSA (ml/m^2)	39 ± 8	39 ± 8	38 ± 7	38 ± 8
RVEDV/BSA (ml/m^2)	64 ± 12	66 ± 14	66 ± 12	64 ± 12
RVEF (%)	61 ± 6	59 ± 6	59 ± 7	59 ± 6

*$p < 0.01$; †$p < 0.05$. Normally distributed values are presented as mean ± SD; the remainder ‡were log transformed before comparison and are presented as median and interquartile range. To compare changes in the 2 groups, we used repeated measures analysis of variance with the time point (week 0, week 40) as the within-subjects factor and the group (spironolactone and placebo) as the between-subjects factor and tested the significance of the interaction between the 2.

ACR = albumin/creatinine ratio; BSA = body surface area; central DBP/SBP = central aortic blood pressure derived using a validated transfer function (SphygmoCor, AtCor Medical) recorded at hospital assessment; hsCRP = high-sensitivity C-reactive protein; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LV mass index = left ventricular mass/body surface area; office DBP/SBP = brachial blood pressure recorded at hospital assessment; PAC = plasma aldosterone concentration; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; other abbreviations as in Table 1.

3, Fig. 2B). Consistent with these changes, aortic distensibility increased with the use of spironolactone compared with placebo (Table 3, Fig. 2C). All of the changes in arterial stiffness remained significant after adjustment for the reduction in mean blood pressure that occurred with treatment (Table 3).

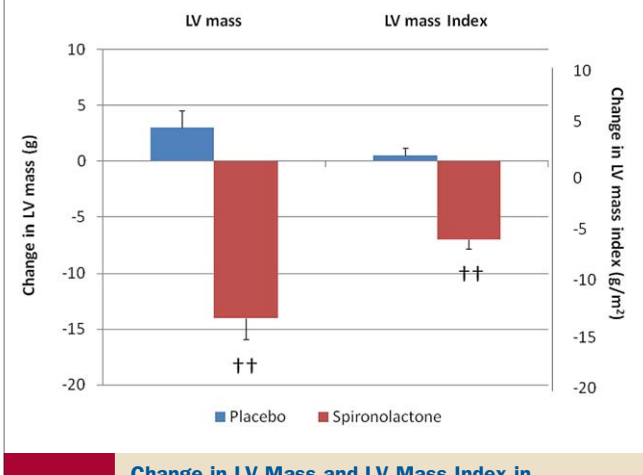

Figure 1 Change in LV Mass and LV Mass Index in Patients Treated With Spironolactone and Placebo

Data are mean ± SEM. ††$p < 0.01$ treatment by time interaction, repeated measures analysis of variance. LV = left ventricular.

EFFECT OF CHANGES IN BLOOD PRESSURE ON LV MASS AND PWV. The possible effects of the reduction in blood pressure caused by spironolactone on the changes in LV mass and PWV were examined by determining the association of these changes with the changes in systolic pressure by the use of multivariate regression models (Table 4). Independent variables known to influence LV mass and arterial stiffness were entered into the models. Only the change in central aortic systolic blood pressure was a significant independent predictor of change in LV mass. The difference in the strength of the association between the reduction in central aortic and ambulatory 24-h systolic pressures and change in LV mass is illustrated in Figure 3. When we added treatment with spironolactone to the model, the systolic blood pressure changes were rendered insignificant.

In a model with PWV as the dependent variable, the change in central systolic blood pressure ($r^2 = 0.28$, $p < 0.01$) and office systolic blood pressure ($r^2 = 0.28$, $p < 0.01$) were independent predictors and remained significant after the addition of treatment with spironolactone to the models ($r^2 = 0.33$ $p < 0.01$ and $r^2 = 0.36$, $p < 0.01$, respectively).

Adverse effects. During the open-label run-in phase, 1 patient with serious hyperkalemia (potassium 6.5 mmol/l) was withdrawn, 1 patient with hypotension and acute deterioration in renal function (eGFR decreased from 31 to 24 ml/min/1.73 m^2) was withdrawn, and 1 patient withdrew consent. During the open-label run-in phase, 6 (5%) pa-

Table 3 Arterial Stiffness Values (Absolute and Corrected for Changes in MAP Over Time by Linear Regression)

	Placebo		Spironolactone	
	Week 0	Week 40	Week 0	Week 40
PWV (m/s)	8.3 ± 1.7	8.1 ± 1.9	8.3 ± 1.6	7.5 ± 1.4*
Adjusted PWV		8.3 ± 1.9		7.9 ± 1.5*
Aortic distensibility ($\times 10^{-3}$ mm Hg)	2.3 ± 1.6	2.4 ± 1.6	2.6 ± 1.6	3.4 ± 1.9*
Adjusted aortic distensibility ($\times 10^{-3}$ mm Hg)		2.4 ± 1.6		3.4 ± 1.8*
Augmentation (mm Hg)	12.9 ± 8.8	12.4 ± 8.4	13.5 ± 5.9	10.2 ±5.2 *
Adjusted augmentation (mm Hg)		13.2 ± 8.1		11.7 ± 5.3*
Aug Ix (%)	28.3 ± 10.8	27.9 ± 10.1	30.8 ± 10.8	26.2 ± 9.5†
Adjusted Aug Ix		28.2 ± 10.2		26.7 ± 9.7†
Aug Ix 75 (%)	25.1 ± 10.9	23.4 ± 10.1	25.6 ± 9.6	20.6 ± 9.2†
Adjusted Aug Ix 75		22.4 ± 10.5		19.3 ± 9.3*

Values are mean ± SD. Adjusted results are corrected for change in mean arterial pressure from week 0 to 40. Adjustments were based on coefficients obtained from linear regressions by the use of baseline data for both groups combined. *$p < 0.01$; †$p < 0.05$ treatment by time interaction, repeated-measures analysis of variance.

Aug Ix = augmentation index; Aug Ix 75 = augmentation index corrected for heart rate of 75 beats/min; MAP = mean arterial pressure; PWV = pulse-wave velocity.

tients had potassium levels between 5.5 and 5.9 mmol/l and were switched to spironolactone on alternate days as per protocol. On blinded treatment between weeks 4 and 40, 4 patients had potassium levels between 5.5 and 5.9 mmol/l that required a dose reduction to alternate day treatment. Two of these 4 patients were found to have been on placebo after the unblinding. After randomization, no patients were withdrawn because of hyperkalemia, and there were no reported side effects, including gynecomastia. At week 40, serum potassium was slightly greater in the spironolactone group than in the placebo group (4.6 ± 0.6 mmol/l vs. 4.4 ± 0.4 mmol/l, $p < 0.05$).

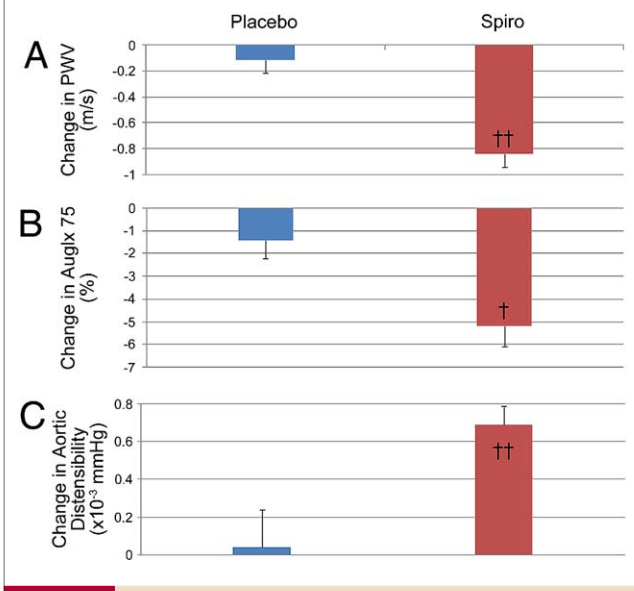

Figure 2 Changes in PWV, Aug Ix 75, and Aortic Distensibility

(A) Pulse-wave velocity (PWV), **(B)** augmentation index corrected for heart rate of 75 beats/min (Aug Ix 75), and **(C)** aortic distensibility on cardiovascular magnetic resonance in patients treated with spironolactone (Spiro) and placebo. Data are mean ± SEM. †$p < 0.05$; ††$p < 0.01$ treatment by time interaction, repeated measures analysis of variance.

Reproducibility of measurements. There was good intraobserver agreement for the primary end points: LV mass: $r = 0.97$ (112 ± 22 g vs. 115 ± 22 g, $p < 0.001$), PWV: $r = 0.92$ (7.2 ± 1.6 m/s vs. 7.2 ± 1.3 m/s, $p < 0.001$).

Discussion

This randomized trial has demonstrated that important structural and functional cardiovascular abnormalities

Table 4 Multivariate Regression Models for the Prediction of Change in Left Ventricular Mass

	No Treatment Effect Included in Model	Treatment Effect Included in Model
Model 1, r^2	0.16	0.38
Change in BP		
p value	<0.05	0.15
Beta + SE	0.109 + 0.05	0.065 + 0.044
Treatment group		
p value		<0.01
Beta + SE		−6.717 + 1.203
Model 2, r^2	0.15	0.38
Change in BP		
p value	0.08	0.19
Beta + SE	0.1 + 0.051	0.059 + 0.045
Treatment group		
p value		<0.01
Beta + SE		−6.778 + 1.202
Model 3, r^2	0.13	0.37
Change in BP		
p value	0.21	0.72
Beta + SE	0.109 + 0.086	0.027 + 0.076
Treatment group		
p value		<0.01
Beta + SE		−6.973 + 1.212

Model 1: age, sex, glomerular filtration rate (GFR), angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blockers, calcium-channel blocker, beta-blocker, statins, change in central aortic systolic blood pressure (BP) ± treatment group. Model 2: age, sex, GFR, ACE inhibitor, angiotensin-receptor blockers, calcium-channel blocker, beta-blocker, statins, change in office peripheral systolic BP ± treatment group. Model 3: age, sex, GFR, ACE inhibitor, angiotensin-receptor blockers, calcium-channel blocker, beta-blocker, statins, change in 24-h ambulatory systolic BP ± treatment group.

Beta = unstandardized beta coefficient; SE = standard error.

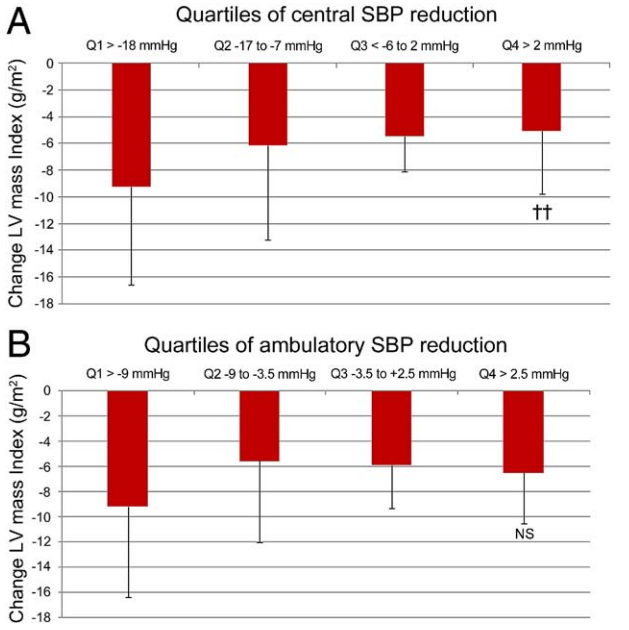

Figure 3 **Changes in LV Mass Index**

Shown are changes in left ventricular (LV) mass index associated with **(A)** quartiles of central systolic blood pressure reduction and **(B)** quartiles of ambulatory systolic blood pressure (SBP) reduction in patients randomized to spironolactone. Data are mean ± SD. ††$p < 0.01$ trend between quartiles.

present in early stage CKD (3,24,25) can be improved by mineralocorticoid receptor blockade. The addition of spironolactone to established treatment with ACE inhibitors or ARBs resulted in reduction in LV mass and improved arterial stiffness along with reduced blood pressure and albuminuria. These effects occurred despite excellent blood pressure control and a low prevalence of LVH at baseline. These findings provide further support for the importance of aldosterone as a major cause of the development of ventricular hypertrophy and vascular and ventricular stiffness in patients with early stage CKD. They also suggest that aldosterone antagonism should be further evaluated in larger trials as a possible powerful therapeutic option in the treatment of this high-risk group of patients. Such trials would of course have to examine carefully the safety of such treatment, most importantly the frequency of hyperkalemia. This study was not large enough or of sufficient duration to provide reliable data on this outcome, but the incidence was surprisingly low, which may have been due to the active run-in phase and the exclusion of patients with diabetic and renovascular CKD.

Although CKD is a major risk factor for atheromatous coronary artery disease, it is now evident from epidemiological studies that heart failure and arrhythmias, arising as the result of LVH and fibrosis, are the most common causes of cardiovascular morbidity and mortality (2,26). Increased arterial stiffness is a major factor in the development of LVH, fibrosis, and ventricular dysfunction in patients with CKD, diabetes, and systolic hypertension (27–29). Thus, our finding that spironolactone can improve these fundamental pathophysiological abnormalities is of importance and suggests that treatment commenced early in CKD may reduce the later burden of adverse cardiovascular events.

Furthermore, there is increasing evidence that aldosterone causes progressive renal injury in CKD; therefore, the use of aldosterone antagonists has the potential to slow the progression of renal disease (6). This prevention of further decline in renal function may have secondary benefits in the development of cardiovascular disease in CKD because the magnitude of risk is related to GFR. To date, beneficial effects of aldosterone antagonists on cardiovascular events and mortality have been observed in patients with heart failure, hypertension, and hyperaldosteronism but not in patients with CKD (30–33). The use of aldosterone antagonists in CKD has been restricted as the result of concerns about adverse effects on serum potassium and renal function. Reported studies have been small without cardiovascular end points but have consistently shown reductions in proteinuria and slowing of progression to end-stage kidney disease (34).

Reductions in LVH and arterial stiffness are associated with prognostic benefit in hypertension and CKD (35,36). In the LIFE (Losartan Intervention For Endpoint) study (35), which examined hypertensive patients with LV hypertrophy, a reduction in LV mass index during 12 months of 11% was associated with a 15% reduction in relative risk of cardiovascular events. In patients with end-stage CKD, a 10% reduction in LV mass achieved by multiple interventions was associated with a hazard ratio of 0.72 for cardiovascular death (36). We have shown a similar reduction in LV mass by using spironolactone despite a "normal" mean LV mass on entry.

Our results are also similar to those of the 4E study (37), in which the use of eplerenone and enalapril produced additive reductions in LV mass measured by CMR in subjects with LVH due to hypertension. Arterial stiffness is a strong prognostic marker in end-stage CKD, hypertension, and the general population; therefore, the vascular influence of spironolactone may be beneficial independently of changes in blood pressure or LV mass (38–40).

An important question raised by this study is the degree to which the reductions in LV mass and arterial stiffness (which remained significant after mathematical correction for the mean arterial pressure at which they were measured) were due to the effect of lowering systolic blood pressure relative to the direct effects of mineralocorticoid receptor blockade. Our use of an inactive placebo rather than a control antihypertensive agent means that we cannot provide a definitive answer to this question. The significant relationships between change in LV mass and PWV and the reduction in central aortic systolic blood pressure suggest that this be at least part of the mechanism of action of spironolactone. The blood pressure effects were much weaker than the treatment effect, so it is plausible that blockade of cardiac and vascular mineralo-

corticoid receptors reduced adverse effects of aldosterone such as inflammation, fibrosis, and hypertrophy (41).

It is also possible that ACE-2 activity may have increased under the influence of spironolactone, leading to an increase in angiotensin (1–7), which has vasodilatory, antifibrotic, and hypertrophic effects (42). Indeed, it is possible that the reduction in systolic pressure that occurred with spironolactone was a result rather than a cause of reduced arterial stiffness. In support of this theory is the finding that eplerenone treatment resulted in a reduction in the collagen/elastin ratio and in vitro arterial stiffness of resistance arteries in hypertensive patients (43). The lack of effect of spironolactone on C-reactive protein provides no support for an anti-inflammatory effect but does not exclude local effects on vascular inflammation. The significant associations between central aortic but not ambulatory blood pressure changes and the improvements in LV mass and PWV are consistent with recent work showing that central but not peripheral pressures are determinants of clinical outcome (12).

This study does not address whether maximizing doses of ACE inhibitors or ARBs would be as effective as adding 25 mg daily of spironolactone to standard therapy, but all patients were on doses of ACE inhibitors and ARBs that achieved blood pressure control for at least 6 months before recruitment. The dose of 25 mg of spironolactone was chosen because this low dose is efficacious and safe in heart failure (when GFR is often reduced) (32) and because tolerability was demonstrated in several small studies in CKD (34). We used peripheral blood pressure for the calculation of aortic distensibility. We acknowledge that central aortic blood pressure (measured by applanation tonometry) is the pressure "seen" by the LV and aorta, but because of the constraints of magnetic resonance technology, were not able to acquire this value at the time of imaging.

Conclusions

In patients with early-stage CKD, the use of spironolactone resulted in improvements in important prognostic markers of cardiovascular disease; most of these effects were statistically independent of the change in blood pressure. These data provide strong support for the further evaluation of spironolactone in patients with CKD in trials with clinical outcomes.

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Key Words: chronic kidney disease ■ arterial stiffness ■ left ventricular mass ■ renin-angiotensin-aldosterone system ■ spironolactone.