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Effects of Spironolactone and Chlorthalidone on Cardiovascular Structure and Function in Chronic Kidney Disease; A Randomized, Open-Label Trial

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Abstract

Background and objectives: In a randomized double blind, placebo controlled trial, treatment with spironolactone in early-stage chronic kidney disease, reduced left ventricular mass and arterial stiffness compared to placebo. It is not known if these effects were due to blood pressure reduction or specific vascular and myocardial effects of spironolactone.

Design, setting, participants and measurements: A prospective, randomized, open-label, blinded endpoint (PROBE) study conducted in four UK centers (Birmingham, Cambridge, Edinburgh & London) comparing spironolactone 25mg to chlorthalidone 25mg once daily for 40 weeks in 154 subjects with non-diabetic stage 2 and 3 chronic kidney disease (eGFR 30-89ml/min/1.73m^2). The primary endpoint was change in left ventricle mass on cardiac magnetic resonance. Subjects were on treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and had controlled blood pressure.

Results: There was no significant difference in left ventricular mass regression; at week 40 the adjusted mean difference for spironolactone compared to chlorthalidone was -3.8g (95% CI -8.1g, 0.5g), p=0.08. Office and 24-hour ambulatory blood pressures fell in response to both drugs with no significant differences between treatment. Arterial stiffness parameters were also not significantly different between groups. Hyperkalemia (defined ≥5.4mmol/L) occurred more frequently with spironolactone (12 vs. 2 subjects) but there were no cases of severe hyperkalemia (defined ≥6.5mmol/L). A decline in eGFR >30% occurred more frequently with chlorthalidone (8 vs. 2 subjects).

Conclusion: Spironolactone was not superior to chlorthalidone in reducing left ventricular mass, blood pressure or arterial stiffness in non-diabetic CKD.

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Introduction

~~Stage 1-3~~ ~~C~~ehronic kidney disease (CKD) stage 1-3 affects more than 10% of the population of developed countries (1). The risk of cardiovascular disease is increased, with a graded inverse relationship to estimated glomerular filtration rate (eGFR) and far exceeds the risk of kidney failure (2). Part of this risk is due to accelerated atheroma, but traditional cardiovascular risk models designed to predict death perform poorly in CKD (3) and non-atherosclerotic changes including left ventricular fibrosis and hypertrophy and arteriosclerosis are important (4). Pathophysiological mechanisms underlying these processes are likely to include activation of the renin-angiotensin system, systemic inflammation and altered bone mineral metabolism.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are widely used in CKD to control blood pressure (BP) and reduce proteinuria but often fail to suppress the elevated levels of aldosterone which occur in CKD as a result of both aldosterone escape and breakthrough (5). In addition to hypertension, experimental studies have shown that aldosterone exerts numerous adverse cardiovascular effects including endothelial dysfunction, and pro-hypertrophic, inflammatory and fibrotic effects on the myocardium and arterial walls, particularly in the presence of sodium overload as occurs in CKD (6). In a randomized double blind, placebo controlled trial, the addition of spironolactone to ACE inhibitors or ARBs reduced left ventricular mass and arterial stiffness and improved left ventricular diastolic function with a satisfactory safety profile but it was unclear whether these beneficial effects were due to unique actions of spironolactone or BP reduction (7). This follow-up trial examined the effects of spironolactone compared with an active antihypertensive control drug, chlorthalidone in order to achieve equal BP control. Our hypothesis was that spironolactone would cause greater reduction in left ventricular mass and arterial stiffness as a result of its inhibition of the multiple adverse effects of aldosterone.

Materials and Methods

Study Design and Treatment Regimens

A multi-center, prospective randomized open-label, blinded endpoint (PROBE) trial recruiting subjects with stage 2 and 3 CKD at four UK centers (Birmingham, Cambridge, Edinburgh & London) between June 2014-December 2016 (8). Participants were individually ~~randomised~~ randomized into the trial in a 1:1 ratio to either Spironolactone 25mg once daily or Chlorthalidone 25mg once daily for 40 weeks. Randomization was provided by a computer-generated programme at the Birmingham Clinical Trials Unit (BCTU), using a minimization algorithm to ensure balance between the arms with regard to the following important clinical variables: systolic BP (<130 mmHg, ≥130 mmHg), age (<55 years, ≥55 years) and gender (Male, Female). Follow up was completed by November 2017. Adherence to the Declaration of Helsinki, Ethical (West Midlands National Research Ethics Service September 2013 (13/WM/0304), Medicines and Healthcare products Regulatory Agency (Clinical Trials Authorization No. 21761/0295/001-0001), US National Institutes of Health database (NCT02502981) approvals were obtained.

Participants

The rationale and detailed trial design have been reported in full (8). In brief, subjects were eligible for inclusion if they were aged ≥18 years, had stable CKD stage 2 or 3 (eGFR 30-89ml/min/1.73m^2), were taking an ACE inhibitor or ARB with controlled BP using standard UK guideline blood pressure target values <130/80mmHg in 2015. Local investigators were encouraged not to change concomitant anti-hypertensive medication after study entry unless for a strong clinical indication. Aggregate blood pressure data by treatment arm were reviewed regularly by an independent Blood Pressure Monitoring Committee (BPMC). The committee was able to mandate changes in randomized treatment to ensure blood pressure in both arms was similar. Exclusion criteria included diabetes mellitus, left ventricular systolic

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dysfunction (ejection fraction <50%) or severe valvular disease, atrial fibrillation, recent acute myocardial infarction or other adverse cardiovascular event and documented previous hyperkalemia or serum potassium at screening of >5.0mmol/L (8).

Outcome Measures

Investigations were performed at baseline (< 6 weeks prior to initiating study medication) and at 40 weeks post-randomizsation, with a further 'run-out' study at 6 weeks after trial drugs ended (46 weeks). The primary endpoint was change in left ventricle mass at week 40; secondary endpoints have been reported (8) but included changes in aortic pulse wave velocity (aPWV), office and ambulatory BPs, and safety parameters (hyperkalemia, decline in kidney function of > 30% (requiring discontinuation of trial drugs). Analyses of cardiac MRI (NCE) and cfPWV (research nurses) data were performed by clinicians blinded to treatment allocation and clinical data.

Cardiac Magnetic Resonance Imaging: Studies were performed on 1.5-T (Avanto / Aera; Siemens, and Discovery™; GE) or 3T (Verio, Siemens) scanners. Left ventricular dimensions, function, and mass were assessed in accordance with validated methodology as previously described (9). Data were analysed in a Core Lab (Birmingham) using CVi 42® software (Circle Vascular Imaging, Canada).

Blood Pressure and Arterial Function: Office BP were recorded at each face-to-face clinical review using a semi-automated device. Three readings were performed in the seated position after 5 minutes of rest. The mean of the last 2 readings were used for analysis (8). Resting BP, 24-hour ambulatory BP monitoring (Mobil-O-Graph; IEM GmbH, Stolberg, Germany),

applanation tonometry (SphygmoCor, AtCor Medical, Sydney) and pulse wave velocity were assessed as previously described (10,11).

Biochemical and safety monitoring: Routine hematological and biochemical parameters were recorded at weeks 1, 2, 4, 8, 24, 40 and 46 after randomization. Modification to the doses of both treatments was made according to protocols (**Table 1**).

Study Outcomes & Statistical Analysis

The initial design of the study used a co-primary endpoint of change in left ventricular mass and change in cfPWV to replicate the original CRIB II methodology (7). This required a sample size of 350 subjects. However, recruitment was significantly slower than anticipated, and following discussion with the funder and the Trial Steering Committee, the trial design was revised with a single primary endpoint of change in left ventricular mass. This decision was made blinded to all data and reflected the superior prognostic value of LV mass and technical precision to ensure the study was appropriately powered with a reduced sample size (8). Using a standard deviation of change in left ventricle mass of 13g (data from CRIB 2) (7), to detect a minimum relevant difference in left ventricular mass of 7g (12), 63 patients per arm were required to provide 85% power with 2-sided alpha=0.05. After allowing for 15% drop-out, the total sample was 150 patients. The difference of 7g was chosen as the minimum clinically important difference because this value is at the limits of precision of measurement of left ventricular mass by cardiac magnetic resonance (13). Analyses were conducted as stated in our statistical analysis plan (**Supplementary Appendix: Statistical analyses**). In brief, estimates of differences between the groups for the primary and secondary endpoints are presented with 95% confidence intervals (95% CI) and p values from two-sided tests at the 5% significance level. All analyses were based on the intention to

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treat principle and used a model-based analysis with the minimization variables (age, systolic BP and gender) and baseline values (where available; e.g. left ventricular mass) included in the model as covariates. The chlorthalidone arm was the reference category. Continuous endpoints were analysed using a linear regression model to estimate an adjusted mean difference between groups at week 40. For PWV, systolic and diastolic office BP which were collected over multiple time-points, a secondary analysis using mixed effects linear regression models were performed. Categorical endpoints were analysed using a log-binomial regression model to estimate an adjusted relative risk. Sensitivity and exploratory analyses were performed; this included a per-protocol analysis and an analysis where missing data for the primary outcome were imputed using multiple imputation with chained equations. Fifty imputations were generated and imputed results were combined using Rubin's rule. Analyses were undertaken using Stata v15 and SAS v9.3.

Results

Study Subjects

A total of 154 patients were randomized to either spironolactone (n= 77) or chlorthalidone (n = 77). Subjects were well matched at baseline (**Table 2)**. Following randomization, a total of 16 subjects did not complete the study; 8 subjects in the spironolactone group (side effects n=3, medication concern n=2, follow up frequency n=2 and lost to follow up n=1) and 8 in the chlorthalidone group (side effects n=3, follow up frequency n=2, pregnant n=1, new medical finding unrelated to study n=1, randomization error n=1) **(Figure 1)**. Fifty patients randomized to spironolactone remained on full dose medication and 12 changed to half-dose; in the chlorthalidone group 52 patients were on full dose medication, and 4 on half-dose. Adherence to treatment (defined as >70% medication taken by pill count) was 81% for spironolactone and 73% for chlorthalidone.

Primary endpoint

The effects of both drugs on left ventricular mass are shown in **Table 3** and **Figure 2**. Both spironolactone and chlorthalidone reduced left ventricular mass at week 40 (estimated marginal mean -8.3g (95% CI -11.3, -5.3) vs. -4.5g (95% CI -7.5, -1.5) respectively), however there was no significant difference between treatments (adjusted mean difference -3.8g (95% CI: -8.1, 0.5), p=0.08). Sensitivity analyses using multiple imputation based on the 136 patients who had cardiac magnetic resonance studies at baseline (adjusted mean difference -3.8g (95% CI -8.2, 0.6) p=0.089) and a per-protocol analysis of subjects that received full doses of trial medications throughout the study (adjusted mean difference -3.1g (95% CI -8.2, 2.1) p=0.2) gave similar results. There was also no difference in left ventricular mass index (adjusted mean difference $-1.5g/m^2$ (95% CI -3.8, 0.7) p=0.2).

Secondary Outcomes: Blood Pressure

Both drugs reduced office and 24-hour ambulatory BPs over the treatment period with no significant differences between treatment groups; no changes in treatment were advised by the BP Monitoring Committee (**Table 3 and Figure 3**). For office systolic BP at week 40, the estimated marginal means for spironolactone and chlorthalidone were -11mmHg (95% CI -14, -8) vs -8mmHg (95% CI -12, -5) respectively, adjusted mean difference -3mmHg (95% CI -7, 2), p=0.3. For office diastolic BP at week 40, the estimated marginal means were -6mmHg (95% CI -8, -4) vs -3 mmHg (95% CI -5, -1) respectively, adjusted mean difference -2mmHg (95% CI: -5, 0) p=0.097. Repeated measures analysis also revealed no significant differences between the treatment arms. Mean 24-hour ambulatory BPs also fell with each drug and were not significantly different between treatments at week 40; adjusted mean difference 2mmHg (95% CI -2, 6, p=0.3) for systolic peripheral BP and 1mmHg (95% CI -1, 4) p=0.3 for diastolic peripheral BP (**Table 3**).

Other Secondary Outcome Measures

There was no significant difference between treatment arms in aPWV, AIx@75, left ventricular volumes, ejection fraction, UACR and NT pro-BNP (**Table 3**).

Blood pressure reduction and changes in left ventricular mass

This exploratory analysis suggested a possible graded relationship between changes in left ventricular mass from baseline versus changes in 24-hour ambulatory systolic BP (**Figure 4**).

Adverse Events and Side Effects

In accordance with the protocol, medication was reduced to half dose in 12 subjects in the spironolactone arm due to moderate hyperkalemia (6), decline in eGFR (4), hyponatremia (1)

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and symptomatic hypotension (1). In the chlorthalidone group medication was reduced to half dose in 4 subjects due to a decline in eGFR (2), symptomatic hypotension (1) and malaise (1). Permanent discontinuation of the study drug was required in 11 subjects taking spironolactone; patient reported side effects (8), decline in eGFR (1), decline in eGFR and moderate hyperkalemia (1), hyponatremia (1) and 19 subjects taking chlorthalidone; patient reported side effects (10), decline in eGFR (8), hyponatremia (1).

Hyperkalemia occurred in 12 subjects on spironolactone compared with 2 on chlorthalidone; mild hyperkalemia occurred in 10 on spironolactone and 2 on chlorthalidone; moderate hyperkalemia occurred in 1 subject on spironolactone (information missing for one participant). There were no episodes of severe hyperkalemia. Over 70% of the episodes of hyperkalemia occurred within 4 weeks of starting medication. The mean change in serum potassium at week 40 was $+0.2 \pm 0.5$mmol/L with spironolactone and -0.3 ± 0.4mmol/L with chlorthalidone, adjusted mean difference 0.5mmol/L (95% CI: 0.3, 0.6), p<0.001. A severe decline in kidney function (> 30% fall in eGFR) requiring discontinuation from trial therapy occurred in 2 subjects on spironolactone and 8 on chlorthalidone. There were no significant differences between the treatment arms for eGFR at week 40, adjusted mean difference 2ml/min/1.73m^2 (95% CI 1.1, 4.3), p=0.3. There were no cases of symptomatic hypotension requiring discontinuation of treatment in either treatment arm.

Discussion

In subjects with early-stage, non-diabetic CKD, left ventricular mass and BP were both reduced with spironolactone and chlorthalidone, with no statistically significant difference between groups at the end of the 40 week treatment period. There were also no statistically significant differences between spironolactone and chlorthalidone on measures of left ventricular geometry or function, arterial stiffness, UACR or NT pro-BNP. The hypothesis that spironolactone would be superior to chlorthalidone in reducing left ventricular mass due to its non-hemodynamic, mineralocorticoid antagonist specific mediated anti-hypertrophic and inflammatory effects was not confirmed despite the use of modern cardiac magnetic resonance imaging techniques capable of measuring left ventricular mass to an accuracy of less than 10g. Both treatments were well tolerated with a low incidence of major adverse effects.

In experimental work, spironolactone effectively inhibits multiple deleterious actions of aldosterone including vascular, myocardial, endothelial, pro-inflammatory, fibrotic and hypertrophic effects (6,14). It is also highly effective in reducing mortality and hospitalization for populations with heart failure due to reduced ejection fraction (<35%) and after acute myocardial infarction (15-16). In CRIB 2, spironolactone reduced left ventricular mass over 40 weeks by a mean of 14g in patients with CKD stage 2-3 compared to no change with inactive placebo.[7] Similar reductions in left ventricular mass with spironolactone were also reported in the 4E study in which the use of eplerenone and enalapril produced additive reductions in left ventricular mass in hypertensive subjects with left ventricular hypertrophy (17). These effects were similar to those of the present study. Our new finding however, that chlorthalidone, which activates rather than inhibits the renin angiotensin system, also reduces left ventricular mass to an extent not different to spironolactone, suggests that these actions are a result of BP reduction rather than other effects of mineralocorticoid antagonism. This

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conclusion is strengthened by the association between the changes in systolic pressure and left ventricular mass. The study illustrates the importance of comparing the effects of mineralocorticoid receptor blockers with active BP lowering control drugs, a design feature yet to be used in important trials of new non-steroidal mineralocorticoid receptor blockers (18).

Change in left ventricular mass was chosen as the primary outcome for this study because of the adverse prognostic importance of left ventricular hypertrophy in hypertension and CKD irrespective of BP (19-22), the non-dichotomous graded relationship between left ventricular mass and prognosis in essential hypertension (23) and the positive prognostic value of a reduction in left ventricular mass in essential hypertension, independent of baseline left ventricular mass and degree of BP reduction (24,25). In the Framingham study, left ventricular mass was second only to age in its ability to predict cardiovascular morbidity and mortality (19). While a meta-analysis has questioned the validity of using left ventricular mass as a surrogate for total mortality in CKD, many of the studies used the less accurate technique of echocardiography for measurement of left ventricular mass and few were large enough or of adequate duration to ascertain relevant changes (26). In a 5 year study in kidney failure, subjects classified as 'responders' each 1g reduction in left ventricular mass was associated with a 1% fall in cardiovascular mortality (27). There are no similar studies in early-stage CKD despite its much higher prevalence and presence of abnormalities of left ventricular mass, myocardial fibrosis and cardiac function (28-30). Our study shows that left ventricular mass in early-stage CKD is responsive to BP reduction irrespective of the mode of action of drug therapy, even when starting BP is controlled at Kidney Disease Improving Global Outcomes target and left ventricular mass is not in a range categorised as hypertrophy (31).

The possible relationship between BP reduction and fall in left ventricular mass provides support for a primarily BP mediated mode of action. The findings extend those of Simpson et al. who showed that in a group of subjects with left ventricular hypertrophy, left ventricular mass was reduced by BP lowering even when starting BP was in the normotensive range (32).

The BP lowering effects of both spironolactone and chlorthalidone on top of baseline treatment with an ACE inhibitor or ARB in this group of patients with CKD are of importance in their own right. Neither agent is in common use in CKD; spironolactone because of concerns about effects on serum potassium and kidney function and chlorthalidone principally because of concerns about efficacy of thiazide-like drugs in CKD. Our data suggest that both agents are similarly effective in lowering BP and well tolerated in subjects with CKD. The appropriate target for BP in patients with CKD remains uncertain. Evidence for positive effects of lowering BP on the progression of kidney disease remains inconclusive while the effects on cardiovascular endpoints in CKD are probably similar to those shown in the general population (33). Sub-group analysis of SPRINT trial subjects with CKD at baseline showed no effect modification by CKD status with a substantial reduction in the composite cardiovascular outcome of cardiovascular mortality and deaths (34). In a meta-analysis of the effects of intensive BP lowering on mortality in over 15,000 patients with predominantly later (stage 3-5) stage CKD, intensive treatments with a mean reduction in systolic BP of 16mmHg reduced all-cause mortality by 14% compared to control groups on standard therapy (35). Our finding, that intensive BP reduction reduces left ventricular mass in subjects with CKD, provides a plausible pathophysiological mechanism for this result.

With respect to safety and tolerability, although the number of events was small, hyperkalemia was more common with spironolactone, while clinically significant reductions in kidney function were more common with chlorthalidone. The effect of chlorthalidone on

office systolic BP in this study was similar to that observed in subjects with CKD treated with chlorthalidone in the ALLHAT study in whom systolic BP was reduced by approximately 11 mmHg over a 6-year treatment period (36). Several recent meta-analyses of the effects of mineralocorticoid receptor blockers in stage 3-4 CKD have shown similar reductions in BP to those seen in this study with spironolactone (37-39). In addition, these studies suggest possible beneficial effects on kidney function with consistent reductions in proteinuria though there were small excess risks of hyperkalemia (38-40). Thus, although spironolactone has not shown specific effects on the endpoints of our study, it remains an effective treatment option for patients with early-stage CKD that reduces BP, left ventricular mass and proteinuria and appears safe providing the starting potassium is not elevated and potassium is monitored during the weeks following its introduction. Problems with hyperkalemia in CKD may be circumvented by co-prescription of potassium binding agents (41).

There are limitations to our study. Recruitment was slower and more challenging than anticipated. This required us to change to a single primary endpoint of left ventricular mass to ensure the study was adequately powered to detect a clinically significant outcome. The 119 subjects who completed paired cardiac magnetic resonance studies provided 83% power to detect a 7g difference in LV mass with an alpha of 0.05. As some patients of our patients had dose reductions, the study might be regarded as under-powered. We were concerned about our ability to detect small changes in left ventricular mass, even with the use of cardiac magnetic resonance and it is reassuring that recently published data have confirmed the precision of cardiac magnetic resonance in the measurement of left ventricular mass (12). While the study was not powered to detect changes in left ventricular mass smaller than 7g, changes of this magnitude are of doubtful clinical significance and below the limits of accuracy of the measurement technique. We acknowledge that our results do not definitively exclude the possibility that spironolactone is superior to chlortalidone in the reduction of LV

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mass at an equal blood pressure; a larger study would be required to provide conclusive data. Patients with diabetes and previous serum potassium >5mmol/L were excluded on safety grounds, meaning that the low rates of hyperkalemia observed with spironolactone may not be generalisable to all subjects with early-stage CKD. We acknowledge that discontinuation of treatment and half dose treatment in both arms could have contributed to missing the treatment effect although a per-protocol analysis of all patients with no change to treatment schedule gave similar results for the primary analyses.

Conclusion

In patients with stable non-diabetic CKD stage 2 and 3 with controlled BP, on treatment with ACE inhibitors or ARBs, we found no evidence that spironolactone was superior to chlorthalidone in its effects on left ventricular mass. While previous experimental studies have shown spironolactone to mediate a wide variety of potentially beneficial anti-proliferative and anti-fibrotic effects on cardiac and vascular tissues, we could not demonstrate evidence for such pleiotropic effects over and above BP reduction. Both treatments effectively reduced BP to levels below present CKD guideline target recommendations and had a low level of adverse effects. While the specific class of anti-hypertensive may not be critical, intensively reducing systolic BP to further reduce left ventricular mass in CKD may be associated with long term prognostic benefit and requires further investigation.

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Data Sharing Statement: i) Individual de-identified participant data (clinical data acquired in the trial) and ii) related study documents (study protocol, statistical analysis plan) will be available for Researchers requesting data the Birmingham Clinical Trials Unit.

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Table 1. Treatment Modification for Potassium, eGFR and Sodium levels

Result	Action
Potassium (mmol/L)	
Subjects on chlorthalidone	
>3.5	No action
3.0-3.5	Remeasure serum potassium in 2 weeks. Dietary advice
<3.0	Stop drug
Subjects on spironolactone	
5.5-5.9	Reduce to alternate days
6.0-6.5	Stop for 1 week and recommence on alternate day if potassium <5mmol/L on repeat check
>6.5	Stop trial drug
eGFR reduction (%)	
<25	No action
25-30	Stop trial drug and restart after one week on alternate days
>30	Stop trial drug
Sodium (mmol/L)	
>135	No action
135-130	Re-measure serum sodium in 2 weeks
<125	Stop trial drug

Table 2. Baseline Patient Clinical Characteristics

	Spironolactone (n=77)	Chlorthalidone (n=77)
Age (yrs.)	57 (14)	56 (15)
Male, n (%)	53 (69)	53 (69)
BMI	29.5 (5.0)	27.6 (3.8)
Smoking		
Never smoked	37 (48)	37 (48)
Ex-Smoker	35 (46)	29 (38)
Current smoker	5 (6)	11 (14)
Office systolic BP (mmHg)	134 (14)	135 (14)
Office diastolic BP (mmHg)	80 (10)	81 (9)
Heart rate (bpm)	72 (14)	71 (12)
Serum creatinine (mg/dl)	1.45 (0.46)	1.32 (0.35)
eGFR (ml/min/1.73m^2)	52 (16)	57 (15)
Hemoglobin (g/dL	13.6 (1.3)	14.6 (1.6)
Cholesterol (mg/dL)	191.4 (37.9)	183.7 (40.4)
Serum potassium (~~mmol~~meq/l)	4.4 (0.4)	4.5 (0.3)
Number of patients on treatment with:		
ACE inhibitors	42 (55)	43 (56)
Angiotensin-receptor blockers	35 (45)	34 (44)
Beta-blockers	13 (17)	13 (17)
Calcium-channel blockers	33 (43)	23 (30)
Alpha blockers	13 (17)	6 (8)
Statins	31 (40)	35 (45)
Etiology of kidney disease: n (%)		
Known pathology	60 (78)	59 (77)
Primary glomerulonephritis	29 (38)	20 (26)
Interstitial nephropathies	5 (6)	10 (13)
Hereditary nephropathy	15 (19)	16 (21)
Kidney vascular disease	2 (3)	4 (5)
Hypertensive nephropathy	4 (5)	3 (4)
Secondary glomerulonephritis	0	3 (4)
Other multi system disease	2 (3)	2 (3)
Other	3 (4)	1 (1)
Cardiovascular history: n (%)		
Previous myocardial infarction	1 (1)	4 (5)
Previous hypertension	67 (87)	64 (83)
Previous stroke	1 (1)	1 (1)

Values are mean ± standard deviation for continuous data. Categorical data is number (percentage).

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ACE; angiotensin converting enzyme; BMI; Body mass index; diastolic BP; diastolic blood pressure; eGFR estimated glomerular filtration rate, systolic BP; Systolic blood pressure.

Table 3. Treatment Effects on Outcome Measures.

	Spironolactone		Chlorthalidone		Adjusted effect difference (95% CI)	P value
	Week 0	Week 40	Week 0	Week 40		
Primary outcome variable						
Left ventricular mass (g)	131 (28)	124 (24)	124 (33)	122 (37)	-3.8 (-8.1, 0.5)	0.08
Change in LV mass	-	-9 (11)	-	-4 (12)		
Left ventricular mass index (g/m^2)	66 (12)	62 (11)	64 (14)	63 (15)	-1.5 (-3.8, 0.7)	0.2
Change in LV mass index	-	-4 (6)	-	-2 (7)		
Secondary outcome variables						
cfPWV (ms)	7.4 (1.8)	7.3 (1.9)	7.6 (2.2)	7.50 (2.0)	0.04 (-0.4, 0.5)	0.9
Change in cfPWV	-	0.02 (1.3)	-	-0.16 (1.5)		
Serum potassium	4.4 (0.4)	4.6 (0.4)	4.5 (0.3)	4.2 (0.4)	0.45 (0.32, 0.58)	<0.01
Change in serum potassium	-	0.2 (0.5)	-	-0.3 (0.4)		
Office systolic BP (mmHg)	134 (11)	124 (15)	136 (14)	127 (14)	-3 (-7, 2)	0.3
Change in systolic BP	-	-10 (15)	-	-9 (16)		
Office diastolic BP (mmHg)	82 (8)	76 (11)	81 (10)	78 (8)	-2 (-5, 0)	0.1
Change in diastolic BP	-	-6 (9)	-	-3 (10)		
Left ventricular function (strain %)	-15.9 (2.1)	-15.8 (2.5)	-15.6 (2.7)	-15.4 (2.5)	0.05 (-0.9-1.0)	0.9
Change in strain	-	-0.1 (2.3)	-	-0.2 (2.6)		
eGFR	52 (16)	50 (17)	57 (15)	53 (17)	2 (-1, 4)	0.3
Change in eGFR	-	-2 (8)	-	-5 (8)		
Exploratory outcomes						
aPWV (m/s)	7.2 (1.8)	7.4 (1.9)	7.5 (2.2)	7.6 (1.9)	0.03 (-0.4, 0.4)	0.9
AIx @75 (%)	23.3 (11.3)	24.0 (11.2)	25.8 (10.8)	23.5 (11.6)	1.9 (-0.8, 4.7)	0.2
24h Central systolic BP (mmHg) †	116 (9)	111 (11)	117 (13)	110 (12)	2 (-2, 6)	0.3
24h Central diastolic BP (mmHg) †	80 (8)	77 (9)	81 (10)	76 (9)	1 (-1, 4)	0.3

24h Peripheral systolic BP (mmHg)†	127 (11)	122 (13)	128 (13)	121 (14)	2 (-2, 6)	0.3
24h Peripheral diastolic BP (mmHg)†	79 (8)	75 (9)	80 (9)	75 (8)	1 (-1, 4)	0.3
UACR (mg/mmol)*	6 [1-39]	5 [2-18]	5 [2-49]	2 [1-17]	2 (1, 3)*	0.05
Left ventricular EF (%)	74 (6)	74 (7)	73 (6)	72 (7)	0 (-2, 2)	0.7
NTpro BNP (ng/L)*	74 [41-161]	78 [38-171]	114 [39-189]	66 [31-162]	1.1 (0.9, 1.4)*	0.2

Values are mean (standard deviation) for parametric data otherwise median and [interquartile range]. Significance $p<0.05$; chlorthalidone is the reference group.

*Data were logged prior to analysis then exponentiated so the adjusted effect size for these outcomes is the ratio of geometric means.

†Blood pressure values given are derived from 24hr ambulatory blood pressure monitoring.

cfPWV; carotid-femoral pulse wave analysis, UACR; urinary albumin creatinine ratio. aPWV; Aortic pulse wave velocity adjusted mean systolic supine blood pressure. AIx@75; Augmentation index corrected for a heart rate of 75 beats per minute. Diastolic BP; Diastolic blood pressure. left ventricular EDV; Left ventricular end diastolic volume; left ventricular ESV; Left ventricular end systolic volume; LVEF; left ventricular ejection fraction; NT pro BNP; N-terminal pro b-type natriuretic peptide. Systolic BP; Systolic blood pressure

Figure Legends

Figure 1. CONSORT diagram; Eligibility, Randomization and Follow-up

*Side effects leading to patient withdrawal of Spironolactone; Inflammed gums, symptomatic hyponatremia and worsening of polymyalgia rheumatica and back and leg pain. Side effects leading to patient withdrawal of Chlorthalidone; Dizziness and headache, too many unwanted side effects from being on irbesartan necessary for the trial, patient concern about kidney function.

Figure 2. Change in Left Ventricular Mass and Left Ventricular Mass Index in Patients

Treated with Spironolactone and Chlorthalidone.

On intention to treat analysis there was no significant difference in either drug for change in left ventricular mass (p=0.080) or left ventricular mass indexed to BSA (p=0.185) using a linear regression model adjusted for minimization variables and baseline left ventricular mass.

Figure 3. Changes in Office Systolic and Diastolic Blood Pressure over follow up

Change in blood pressures associated with spironolactone (red) and ~~chorthalidone~~chlorthalidone (blue) from initiation to end of treatment at week 40 followed by re-assessment 4 weeks after cessation of the trial drug. Data are mean and 95% CI

Figure 4. Change in Left Ventricular Mass and Change in 24 hour Ambulatory Systolic

Blood Pressure After 40 Weeks of Treatment with Spironolactone or Chlorthalidone.

Supplemental material:

Table of Contents: Supplementary Appendix; Statistical Analysis

> **Commented [CJASN10]:** Please note that supplementary material is not systematically proof-read during the editing process. Accurate and legible supplementary materials are the responsibility of the authors, and will not undergo further revision or formatting prior to publication.