A Randomised Multicentre Open Label Blinded End Point Trial to Compare the Effects of Spironolactone to Chlortalidone on Left Ventricular Mass in Stage 2 and Stage 3 Chronic Kidney Disease

FINAL REPORT

Version 1.0

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Report Prepared by: Samir Mehta

Reviewed by: Natalie Ives

Sponsor:	University of Birmingham
Chief Investigator:	Professor Jonathan Townend
Coordinating Unit:	Birmingham Clinical Trials Unit
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1. Screening information

Table 1: Screening Information

Total screened	Total (N=9325)
Total ineligible/ not approached	**9171**
Reason for ineligibility/not approached:	
Diabetes	2257
Patient on diuretic	171
Contraindicated medication	625
Past medical history, including recent pertinent hospital admissions	1918
Atrial fibrillation	264
Patient not on ACEi or ARB	591
Patient on both ACEi and ARB	22
Patients age and social circumstances	283
Blood pressure out of range	370
Taking part in another study	57
Not interested in trial	295
Insufficient information supplied	162
eGFR out of range (marginal)	57
Unknown	2099
Total randomised	**154**

2. Recruitment

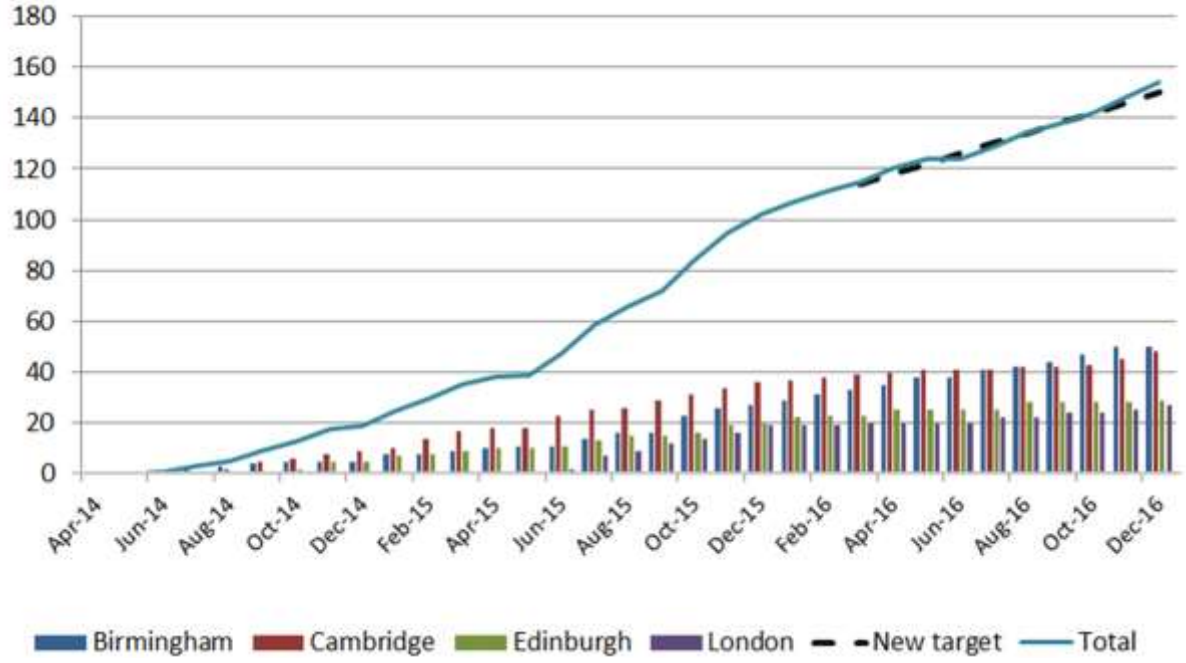
The trial opened for recruitment on the 3rd June 2014 and the first patient was randomised on the 26th June 2014 and the last patient was randomised on the 21st December 2016. A total of 154 patients were randomised into the SPIRO-CKD trial with 4 centres recruiting patients into the trial.

The table and figure below gives the breakdown of recruitment by centre and the overall recruitment graph.

Table 2: Recruitment by centre

Centre	Year			Total
	2014	*2015*	*2016*	
Queen Elizabeth Hospital, Birmingham	5	22	23	**50**
Addenbrookes Hospital, Cambridge	9	27	12	**48**
Western General Hospital, Edinburgh	5	15	9	**29**
Royal Free Hospital, London	0	19	8	**27**
Total	**19**	**83**	**52**	**154**

Figure 1: Recruitment Graph



3. Baseline data and Form return rates

Table 3: Baseline characteristics

Baseline Data	Spironolactone (N=77)	Chlortalidone (N=77)	Total (N=154)
Demographic data			
Age category [£]			
<55 years	35 (45.5%)	35 (45.5%)	70 (45.5%)
≥55 years	42 (54.5%)	42 (54.5%)	84 (54.5%)
Age (years)			
Mean [SD]	56.5 [13.8]	56.3 [15.1]	56.4 [14.4]
Min ; Max	28 - 89	20 - 86	20 - 89
Gender [£]			
Female	24 (31.2%)	24 (31.2%)	48 (31.2%)
Male	53 (68.8%)	53 (68.8%)	106 (68.8%)
Height (Metres)			
Mean [SD]	1.7 [0.1]	1.7 [0.1]	1.7 [0.1]
Min ; Max	1.5 - 1.9	1.5 - 1.8	1.5 - 1.9
Weight (Kilograms)			
Mean [SD]	85.5 [15.7]	80.1 [13.7]	82.8 [14.9]
Min ; Max	54 - 152	53 - 115	53 - 152
BMI			
Mean [SD]	29.5 [5.0]	27.6 [3.8]	28.5 [4.5]
Min ; Max	20.1 - 45.9	21.1 - 36.2	20.1 - 45.9
Smoking Status			
Never Smoker	37 (48.1%)	37 (48.1%)	74 (48.1%)
Ex-Smoker	35 (45.5%)	29 (37.7%)	64 (41.6%)
Current Smoker	5 (6.5%)	11 (14.3%)	16 (10.4%)
Office Blood Pressure			
Systolic Blood pressure category [£]			
<130 mmHg	32 (41.6%)	32 (41.6%)	64 (41.6%)
≥130 mmHg	45 (58.4%)	45 (58.4%)	90 (58.4%)
Systolic Blood pressure (mmHg) [$]			
N	75	75	150
Mean [SD]	133.9 [13.8]	135.3 [14.4]	134.6 [14.1]
Min ; Max	100 - 171	108.5 - 173.5	100 - 173.5
Diastolic Blood pressure (mmHg)			
N	75	75	150
Mean [SD]	80.3 [10.3]	80.5 [9.3]	80.4 [9.8]
Min ; Max	54.5 - 105	62 - 107.5	54.5 - 107.5
Pulse Rate (BPM)			
N	75	75	150
Mean [SD]	71.8 [13.6]	70.8 [12.4]	71.3 [13]
Min ; Max	50 - 106	42 - 103	42 - 106
Laboratory assessments			
Creatinine (umol/L)			
N	75	75	150
Mean [SD]	128.4 [40.5]	117.2 [31.2]	122.8 [36.5]
Min ; Max	53 - 238	64 - 189	53 - 238
eGFR (4v-MDRD) (mL/min/1.73m^2) [2) &]			
N	75	75	150
Mean [SD]	52.2 [16.1]	56.9 [15.3]	54.6 [15.8]
Min ; Max	23 - 90	30 - 90	23 - 90

Baseline Data		Spironolactone (N=77)	Chlortalidone (N=77)	Total (N=154)
Potassium (mmol/L)				
	N	75	73	148
	Mean [SD]	4.4 [0.4]	4.5 [0.3]	4.5 [0.4]
	Min ; Max	3.3 - 5.6	3.8 - 5.3	3.3 - 5.6
Medical History				
Chronic Kidney Disease (CKD)				
Is the cause of CKD known?	No	17 (22.1%)	18 (23.4%)	35 (22.7%)
	Yes	60 (77.9%)	59 (76.6%)	119 (77.3%)
Cause of CKD:				
Primary glomerulonephritis		29	20	49
Interstitial nephropathies		5	10	15
Hereditary Nephropathy		15	16	31
Renal vascular disease		2	4	6
Hypertensive nephropathy		4	3	7
Secondary Glomerulonephritis		0	3	3
Other multisystem disease		2	2	4
Other†		3	1	4
Cardiovascular System				
Patient with previous myocardial Infarction (MI)				
	No	76 (98.7%)	73 (94.8%)	149 (96.7%)
	Yes	1 (1.3%)	4 (5.2%)	5 (3.3%)
Patients with a history of hypertension				
	No	10 (13.0%)	13 (16.9%)	23 (14.9%)
	Yes	67 (87.0%)	64 (83.1%)	131 (85.1%)
Patients with a history of hypercholesterolemia				
	No	47 (61.0%)	43 (55.8%)	90 (58.4%)
	Yes	30 (39.0%)	34 (44.2%)	64 (41.6%)
Patients previously had a CVA or TIA				
	No	76 (98.7%)	76 (98.7%)	152 (98.7%)
	Yes	1 (1.3%)	1 (1.3%)	2 (1.3%)
Respiratory System				
Patients with Asthma				
	No	69 (89.6%)	66 (85.7%)	135 (87.7%)
	Yes	8 (10.4%)	11 (14.3%)	19 (12.3%)
Patients with COPD				
	No	76 (98.7%)	76 (98.7%)	152 (98.7%)
	Yes	1 (1.3%)	1 (1.3%)	2 (1.3%)
Gastrointestinal System				
Patients with liver disease				
	No	74 (96.1%)	76 (98.7%)	150 (97.4%)
	Yes	3 (3.9%)	1 (1.3%)	4 (2.6%)
Malignancy				
Patients with a previous malignancy				
	No	72 (93.5%)	71 (92.2%)	143 (92.9%)
	Yes	5 (6.5%)	6 (7.8%)	11 (7.1%)
Antihypertensive medications				
ACE inhibitor				
	No	35 (45.5%)	36 (46.8%)	71 (46.1%)
	Yes	40 (51.9%)	41 (53.2%)	81 (52.6%)
	Missing	2 (2.6%)	0 (0%)	2 (1.3%)
ARB				
	No	42 (54.5%)	45 (58.4%)	87 (56.5%)
	Yes	33 (42.9%)	32 (41.6%)	65 (42.2%)
	Missing	2 (2.6%)	0 (0%)	2 (1.3%)

Baseline Data		Spironolactone (N=77)	Chlortalidone (N=77)	Total (N=154)
CCB				
	No	42 (54.5%)	54 (70.1%)	96 (62.3%)
	Yes	33 (42.9%)	23 (29.9%)	56 (36.4%)
	Missing	2 (2.6%)	0 (0%)	2 (1.3%)
Alpha blocker				
	No	62 (80.5%)	71 (92.2%)	133 (86.4%)
	Yes	13 (16.9%)	6 (7.8%)	19 (12.3%)
	Missing	2 (2.6%)	0 (0%)	2 (1.3%)
Beta blocker				
	No	62 (80.5%)	64 (83.1%)	126 (81.8%)
	Yes	13 (16.9%)	13 (16.9%)	26 (16.9%)
	Missing	2 (2.6%)	0 (0%)	2 (1.3%)

*all values are numbers and percentages unless specified

£=Minimisation variable

$-systolic blood pressure summary is from blood pressure collected on the baseline CRF (rather than the randomisation systolic blood pressure which is what the minimisation variable is based on)

&-eGFR value presented in table is from data collected on the baseline CRF. Eligibility was based on eGFR at screening. The eGFR min;max values at screening were (30-88) so all patients met this eligibility criteria.

† Other causes of CKD included

Spironolactone group

Born with a single left kidney - ureteric reimplantation as a child; Multiple renal cysts; Congenitally dysplastic left kidney

Chlortalidone group

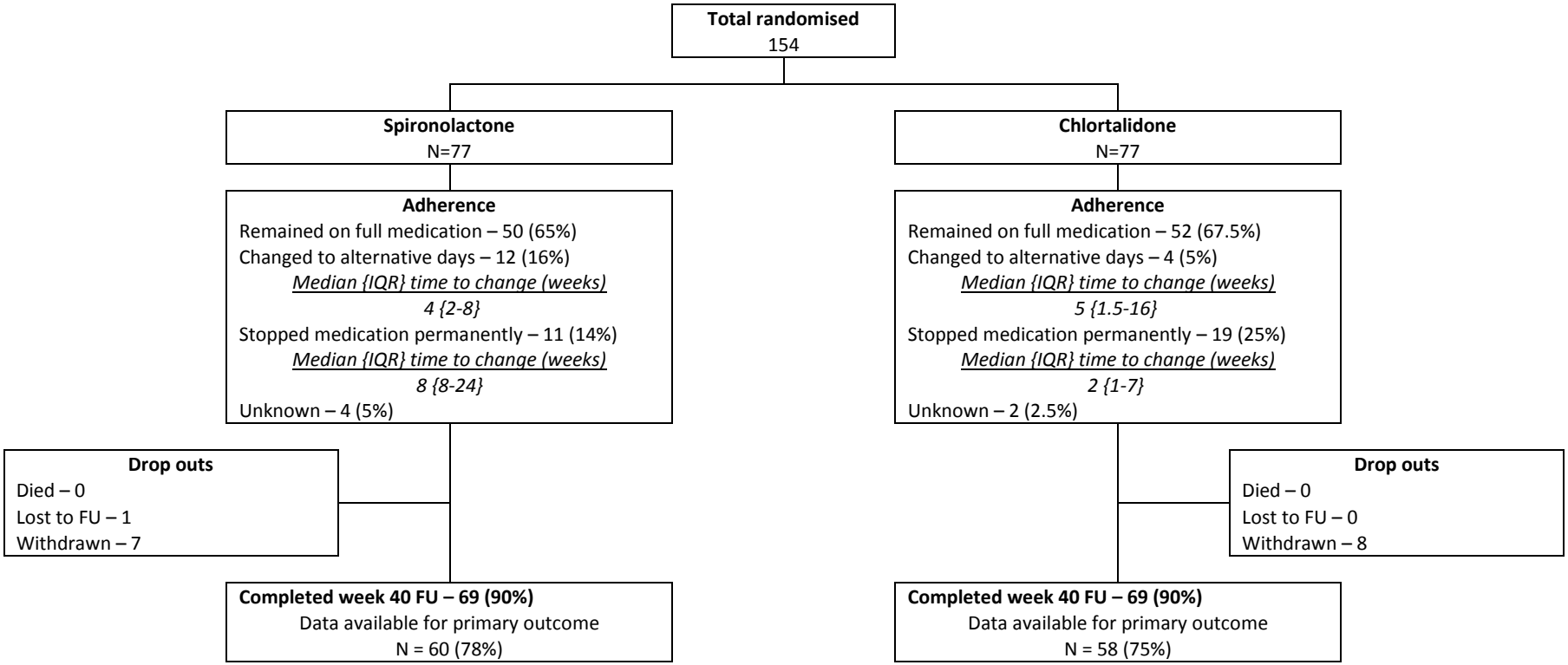
Cycstic kidney disease

Table 4: Form return rates

Form	Time (weeks)	Expected	Returned	Percent Returned
Baseline	0	153	150	98%
Follow Up	1	153	147	96%
	2	153	145	95%
	4	153	145	95%
	8	149	146	98%
	24	145	142	98%
	40	142	138	97%
	46	140	133	95%
CMR	0	153	140	92%
	40	142	123	87%
Sphygmocor	0	153	150	98%
	4	153	145	95%
	24	145	142	98%
	40	142	138	97%
	46	140	132	94%
Ambulatory BP	0	153	148	97%
	40	142	137	96%

4. Consort diagram

Figure 2: Consort diagram



Reason for drop-out
Withdrawn consent - concerns regarding medication **x 2**
Withdrawn consent - side effects **x3**
Withdrawn consent - started new job
Withdrawn consent - too much follow-up
Lost to follow up

Reason for drop-out
Ineligible and randomised in error
Withdrawn consent - side effects **x 3**
Withdrawn consent - too much follow-up
Withdrawn consent - patient became pregnant
Withdrawn consent - no longer wants to take part in study
Withdrawn consent - medical finding unrelated to the study

5. Treatment adherence

Adherence to treatment is summarised by treatment group in terms of patients that:

1) Had no change to treatment schedule, i.e. remained on "Full-dose"
2) Had treatment schedule altered to alternative days, i.e. "Half-dose"
3) Had stopped treatment completely, i.e. "Off-medication"

The median time to treatment schedule alteration and reason for change is also summarised by treatment group.

We also describe adherence to treatment in terms of the percentage of medication taken (i.e. compliance to medication). This was computed for each patient as the (expected dose minus actual dose taken) divided by the expected dose. Patients were required to take 1 dose a day for 40 weeks and so for patients that remained on full dose for the duration of the trial, their expected dose was 280 doses. For patients that had their medication dose altered from full-dose to half-dose (as allowed per the protocol), their expected dose was adjusted from the time (weeks) when this change was made to reflect the change to half-dose. For any patients that went off medication completely, compliance was calculated up to the time point they stopped taking the trial medication. A patient is deemed compliant if they took at least 70% of their trial medication.

Table 5: Treatment adherence by dosage and treatment group

Dose regime	Adherence	Spironolactone N=77	Chlortalidone N=77
Full dose throughout[1]	>=70% of medication taken	50	52
	<70% of medication taken	0	0
	Undetermined*	4	2
Changed to half dose[2]	>=70% of medication taken	12	4
	<70% of medication taken	0	0
	Undetermined*	0	0
Off medication[3]	>=70% of medication taken prior to coming off	11	17
	<70% of medication taken prior to coming off	0	2
	Undetermined*	0	0

**some patients had no follow-up visits and so compliance for these patients was not able to be determined*
1-Full dose: No change to treatment schedule
2-Half dose: Treatment schedule changed to alternative days as allowed per the protocol
Median {IQR} time to change (weeks) - Spironolactone: 4 {2-8}; Chlortalidone: 5 {1.5-16}
3-Off medication: Stopped trial treatment completely
Median {IQR} time to change (weeks) - Spironolactone: 8 {8-24}; Chlortalidone: 2 {1-7}

Table 6: Reasons for dose alteration by treatment group

Reason for dose alteration	Spironolactone		Chlortalidone		Total	
	Half dose (N=12)	Off meds (N=11)	Half dose (N=4)	Off meds (N=19)	Half dose (N=16)	Off meds (N=30)
Drop in eGFR	4	1	2	8	6	9
High potassium	6	0	0	0	6	0
Drop in eGFR and high potassium	0	1	0	0	0	1
Low sodium	1	1	0	1	1	2
Symptomatic hypotension	1	0	1	0	2	0
Adverse event	0	8	1	10	1	18

6. Primary outcome

The primary outcome is change between baseline and 40 weeks in LV mass measured by cardiac magnetic resonance imaging.

A linear regression model was fitted with LV mass at week 40 as the outcome variable, and treatment group (with Chlortalidone as the reference category), baseline LV mass and all the minimisation variables (age, systolic blood pressure and gender) included as covariates in the model.

LV mass indexed to body surface area was also analysed separately as a sensitivity analysis using the same analysis methods as described above for LV mass.

As an additional sensitivity analysis, LV mass data was also analysed accounting for any missing data at week 40 using multiple imputation methods to impute missing data (Table 8).

Table 7: Primary outcome data summary and results

Primary outcome	Time point	Statistic	Spironolactone	Chlortalidone	Linear regression model	
					Adjusted Mean Difference[1] (95% CI)	P-value
LV mass (g)	**Baseline**	N Mean [SD] Min - Max	68 130.6 [27.7] 84 - 208	68 123.9 [33.1] 74 - 279		
	Week 40	N Mean [SD] Min - Max	60 124 [24.3] 75 - 183	59 122.2 [37.3] 69 - 290	-3.830 (-8.128, 0.467)	0.080
Sensitivity analysis						
LV mass indexed to Body Surface Area (g/m^2)	**Baseline**	N Mean [SD] Min - Max	68 65.6 [11.9] 43.8 - 91.4	68 64.1 [13.9] 37.9 - 121.3		
	Week 40	N Mean [SD] Min - Max	60 62.2 [11.4] 40.8 - 91.5	59 63.1 [14.9] 41.8 - 126.6	-1.527 (-3.794, 0.740)	0.185

1-Adjusted for baseline LV mass and all minimisation variables

Lower values indicate better scores, so a negative difference favours spironolactone group

Table 8: Primary outcome sensitivity analysis using multiple imputation

Primary outcome after multiple imputation	Linear regression model	
LV mass (g)	**Adjusted Mean Difference[1] (95% CI)**	**P-value**
	-3.778 (-8.146, 0.591)	0.089

Analysis based on 136/154 patients. Patients with missing scans at both baseline and 40 weeks were not included in the imputation.

1-Adjusted for baseline LV mass and all minimisation variables

Lower values indicate better scores, so a negative difference favours spironolactone group

7. Secondary outcomes

7.1. Change in arterial stiffness between baseline and 40 weeks.

The main analysis for this outcome was conducted using a linear regression model with PWV at week 40 as the outcome variable, and treatment group (with Chlortalidone as the reference category), baseline PWV and all the minimisation variables included as covariates in the model.

A secondary analysis was also conducted using a mixed effects repeated measures model with the outcome being the repeated measure for PWV, and treatment group (with Chlortalidone as the reference category), baseline PWV, all the minimisation variables and a time variable included as covariates in the model. The time variable was considered as a continuous data variable in the repeated measures model. An unstructured covariance data structure was used in the model. A treatment by time interaction term was also included in the initial model to check for its significance, if the treatment by time p-value was not significant, then a model excluding the treatment by time interaction term was fitted.

Table 9: Arterial stiffness PWV data summary and results

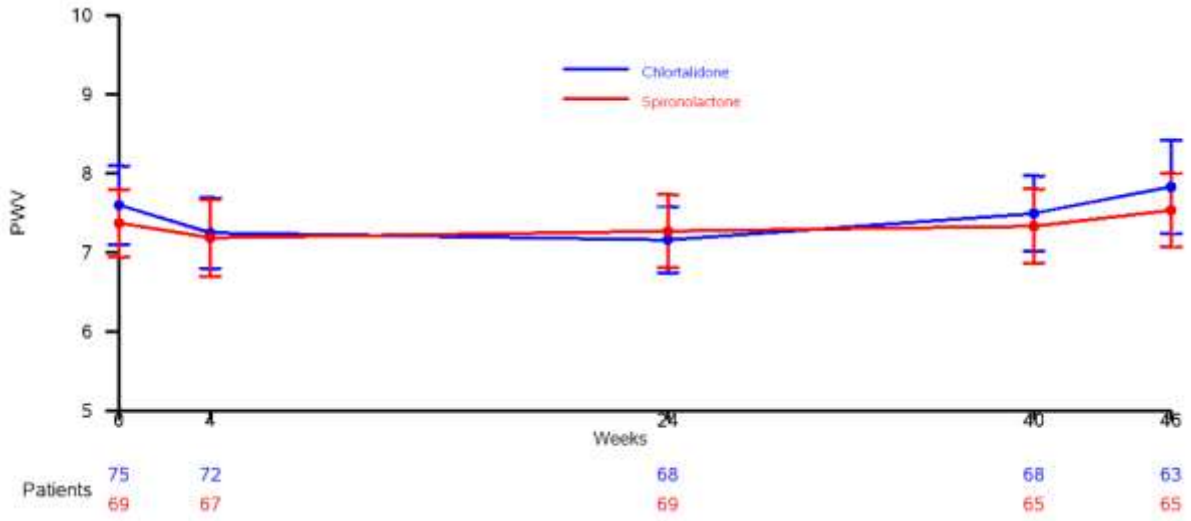
Arterial stiffness	Time point	Statistic	Spironolactone	Chlortalidone	Linear regression model		Repeated measures model (includes data up to week 40)		
					Adjusted Mean Difference[1] (95% CI)	P-value	Adjusted Mean Difference[2] (95% CI)	P-value	Treatment by Time P-value
PWV (m/s)	**Baseline**	N Mean [SD] Min – Max	69 7.37 [1.78] 2.10 - 11.80	75 7.60 [2.17] 3.15 - 16.15			0.132 (-0.193, 0.457)	0.422	0.728
	Week 4	N Mean [SD] Min – Max	67 7.19 [2.00] 4.20 - 15.85	72 7.25 [1.90] 3.85 - 14.30					
	Week 24	N Mean [SD] Min – Max	69 7.27 [1.92] 3.95 - 14.85	68 7.16 [1.73] 2.85 - 12.10					
	Week 40	N Mean [SD] Min – Max	65 7.34 [1.90] 4.05 - 11.80	68 7.50 [1.97] 4.35 - 15.05	0.038 (-0.384, 0.459)	0.860			

1-Adjusted for baseline pulse wave velocity and all minimisation variables

2-Adjusted for baseline pulse wave velocity, all minimisation variables and time. Mean difference taken from model without treatment by time interaction term.

Lower values indicate better scores, so a negative difference favours spironolactone group

Figure 3: Longitudinal plot of PWV overtime by treatment



As a sensitivity analysis, PWV data was also analysed after adjusting for mean systolic supine blood pressure and age. There are 2 readings for systolic supine blood pressure at each time-point, and so the mean of the 2 readings was calculated for each time-point. A linear regression model was fitted with PWV as the outcome variable, and age and mean systolic supine blood pressure at each time-point included as covariates in the model. The residuals for each patient was then calculated and the regression equation was used to predict what the PWV would be for each patient based on their age and their mean systolic supine blood pressure over all time-points. This predicted PWV value was then added to each of the residuals calculated to give the adjusted PWV values (i.e. adjusted for age and mean systolic supine blood pressure from all time points). The final analysis was then conducted using a linear regression model with the outcome being the calculated PWV at week 40 (adjusted for mean supine blood pressure and age), and treatment group (Chlortalidone as the reference category), baseline PWV and all other minimisation variables included as covariates in the model.

Table 10: Arterial stiffness PWV data sensitivity analysis

Arterial stiffness sensitivity analysis	**Linear regression model**	
PWV (m/s)	**Adjusted Mean Difference[1] (95% CI)**	**P-value**
	0.029 (-0.376, 0.434)	0.888

1-Adjusted for baseline pulse wave velocity and all minimisation variables

Lower values indicate better scores, so a negative difference favours spironolactone group

7.2. Incidence of Hyperkalaemia

A binomial model with a log-link was fitted with the outcome being a binary yes/no where yes=number of patients that reported at least one incident of hyperkalaemia. Treatment group (with Chlortalidone as the reference category), and all the minimisation variables were included as covariates in the model.

Note: 15 patients were excluded from this analysis (7 in Spironolactone group and 8 in Chlortalidone group) because these patients withdrew, were lost to follow up or died prior to incidence of hyperkalaemia and did not complete the 40 weeks of trial follow up. Hence for this reason they could not be assumed to be in the "no" category and were therefore excluded from the analysis.

Table 11: Hyperkalaemia

Hyperkalaemia	Spironolactone (N=70)	Chlortalidone (N=69)	Total (N=139)	Log-Binomial model	
				Adjusted Relative Risk[1] (95% CI)	P-value
No	58 (83%)	67 (97%)	125 (90%)	5.467 (1.351, 22.127)	0.017
Yes	12 (17%)	2 (3%)	14 (10%)		

1-Relative risk adjusted for all minimisation variables
Higher values indicate worse outcome for spironolactone group and so relative risk<1 favours spironolactone.

A Poisson regression model was also fitted with the outcome being the total number of cases of hyperkalaemia per patient. Treatment group (with Chlortalidone as the reference category), and all the minimisation variables were included as covariates in the model.

Table 12: Hyperkalaemia

Hyperkalaemia	Statistic	Spironolactone (N=70)	Chlortalidone (N=69)	Total (N=139)	Poisson model	
					Adjusted IRR[1] (95% CI)	P-value
Incidence of hyperkalaemia	N (%) of patients with:				10.200 (2.383, 43.656)	0.002
	0 incidence of hyperkalaemia	58	67	125		
	1 incidence of hyperkalaemia	7	2	9		
	2 incidences of hyperkalaemia	2	0	2		
	3 incidences of hyperkalaemia	2	0	2		
	4 incidences of hyperkalaemia	1	0	1		

1-Incidence Rate Ratio from Poisson model adjusted for all minimisation variables
Higher values indicate worse outcome for spironolactone group

7.3. Changes in blood pressure

Office blood pressure

Systolic and diastolic office blood pressure was collected at baseline and at each follow-up visit. The analysis for office blood pressure was conducted separately for both systolic and diastolic blood pressure.

The main analysis for this outcome was conducted using a linear regression model with blood pressure at week 40 as the outcome variable, and treatment group (with Chlortalidone as the reference category), baseline blood pressure and all the minimisation variables included as covariates in the model.

A secondary analysis was also conducted using a mixed effects repeated measures model with the outcome being the repeated measure for blood pressure, and treatment group (with Chlortalidone as the reference category), baseline blood pressure, all the minimisation variables and a time variable included as covariates in the model. The time variable was considered as a continuous data variable in the repeated measures model. An unstructured covariance data structure was used in the model. A treatment by time interaction term was also included in the initial model to check for its significance, if the treatment by time p-value was not significant, then a model excluding the treatment by time term was fitted.

Ambulatory blood pressure

Various types of readings for blood pressure data were collected as part of the ambulatory blood pressure data collection. For the main analysis, only the mean 24 hour peripheral and mean 24 central blood pressure data were analysed. Ambulatory blood pressure data was collected at week 40 and at baseline for both systolic and diastolic blood pressure.

All together 4 separate analyses of ambulatory blood pressure data were conducted:

- Mean 24 hour peripheral systolic BP
- Mean 24 hour peripheral diastolic BP
- Mean 24 hour central systolic BP
- Mean 24 hour central diastolic BP

The analyses for ambulatory blood pressure were conducted using a linear regression model with blood pressure at week 40 as the outcome variable, and treatment group (with Chlortalidone as the reference category), baseline blood pressure and all the minimisation variables included as covariates in the model.

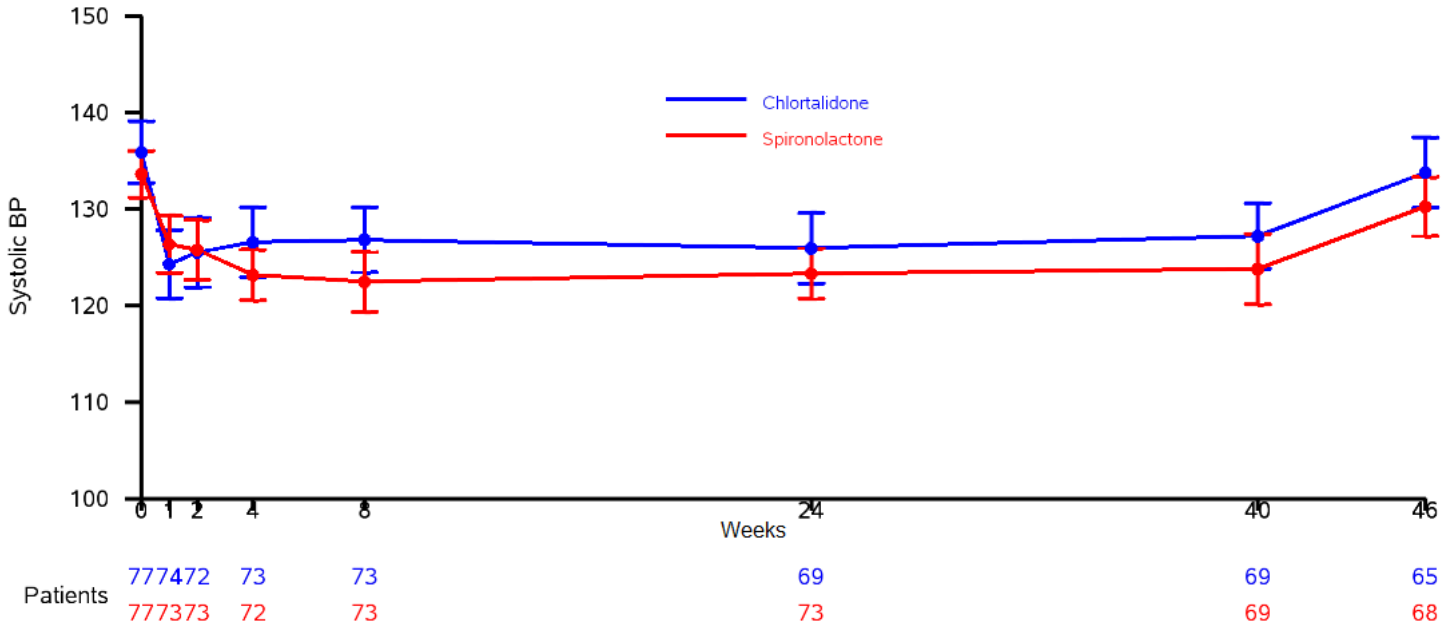
Table 13: Office blood pressure data summary and analysis

Office BP	Time point	Statistic	Spironolactone	Chlortalidone	Linear regression model		Repeated measures model (includes data up to week 40)		
					Adjusted Mean Difference[1] (95% CI)	P-value	Adjusted Mean Difference[2] (95% CI)	P-value	Treatment by Time P-value
Systolic BP (mmHg)	Baseline	N Mean [SD]	77 133.6 [10.7]	77 135.9 [14.2]			0.020 (-2.761, 2.802)	0.989	0.367
	Week 1	N Mean [SD]	73 126.4 [12.7]	74 124.3 [15.3]					
	Week 2	N Mean [SD]	73 125.8 [13.3]	72 125.5 [15.4]					
	Week 4	N Mean [SD]	72 123.2 [11.2]	73 126.6 [15.6]					
	Week 8	N Mean [SD]	73 122.5 [13.4]	73 126.8 [14.5]					
	Week 24	N Mean [SD]	73 123.3 [11.2]	69 126.0 [15.2]					
	Week 40	N Mean [SD]	69 123.8 [15.3]	69 127.2 [14.2]	-2.540 (-7.209, 2.129)	0.284			
Diastolic BP (mmHg)	Baseline	N Mean [SD]	77 81.7 [8.1]	77 81.2 [9.6]			-0.724 (-2.437, 0.990)	0.405	0.198
	Week 1	N Mean [SD]	73 77.1 [8.9]	74 76.2 [9.2]					
	Week 2	N Mean [SD]	73 76.5 [10.3]	72 76.8 [10.1]					
	Week 4	N Mean [SD]	72 75.8 [10.4]	73 76.4 [8.6]					
	Week 8	N Mean [SD]	73 75.9 [10.4]	73 77.1 [8.3]					
	Week 24	N Mean [SD]	73 75.3 [8.0]	69 75.7 [8.8]					
	Week 40	N Mean [SD]	69 75.8 [11.1]	69 77.6 [8.2]	-2.398 (-5.239, 0.442)	0.097			

1-Adjusted for baseline blood pressure and all minimisation variables

2-Adjusted for baseline blood pressure, all minimisation variables and time. Mean difference taken from model without treatment by time interaction term.

Figure 4: Longitudinal plot of office systolic blood pressure overtime by treatment



The treatment effect from the repeated measures analysis for systolic blood pressure was 0.02 mmHg. This means that on average the systolic blood pressure was 0.02 mmHg higher in the spironolactone group. This result appears to be inconsistent with the data presented in figure 4. The above analyses were undertaken in the analysis package SAS. We first re-ran the analyses in another analysis package Stata to check the result. Stata would not fit the model with an unstructured covariance data structure stating that the identity covariance data structure was a better fit. We therefore undertook various sensitivity analyses to assess the robustness of the results, which are shown below.

Table 14: Sensitivity analyses for office systolic blood pressure

	Unstructured (SAS)				Identity (Stata)			
Repeated Measures Model	**Mean difference**	**95% CI**		**P-value**	**Mean difference**	**95% CI**		**P-value**
Including all minimisation variables as covariates in the model	**0.020**	**-2.761**	**2.802**	**0.989**	-0.304	-3.099	2.491	0.831
Including all minimisation variables as covariates in the model, excluding data points at weeks 1 and 2	-1.953	-5.021	1.115	0.210				
No adjustment for covariates in the model	-1.249	-4.816	2.317	0.490				
Including **only** systolic blood pressure as a covariate in the model	0.038	-2.726	2.801	0.979				
Including age and gender as covariates in the model (excluding systolic blood pressure)	-1.243	-4.771	2.286	0.488				
Repeated with adjustment for all minimisation variables but using baseline systolic BP	-0.554	-3.439	2.332	0.705				

Note: Minimisation variables were age, gender and systolic blood pressure (at randomisation)

Observations from the data in Table 13 and Figure 4:

- The blood pressure in the chlortalidone group reduces more steeply from baseline to week 1 (than the blood pressure in the spironolactone group), and then the blood pressure increases slightly out to week 4 before remaining reasonably constant out to week 40. Whilst there is also an initial decrease in blood pressure in the spironolactone group between baseline and week 1, the blood pressure then continues to decrease out to week 4, before remaining reasonably constant out to week 40. If you remove the week 1 and 2 blood pressure data (where there is the most variability before the blood pressure stabilises) from the analysis, the blood pressure is 1.953 mgHg lower in the spironolactone group which is more consistent with the plot.

- There is greater variability in the baseline blood pressure in the chlortalidone group (SD=14.2) compared with the spironolactone group (SD=10.7). The relationship between the baseline blood pressure and the subsequent blood pressure measurements may therefore be less clear in the chlortalidone group than it is in the spironolactone group.

To summarise,

- All models rule out any important effect on blood pressure. The mean differences range from -1.95 to +0.02 mmHg, and the mean differences are all consistent and contained within the 95% confidence intervals for each model.

Figure 5: Longitudinal plot of office diastolic blood pressure overtime by treatment

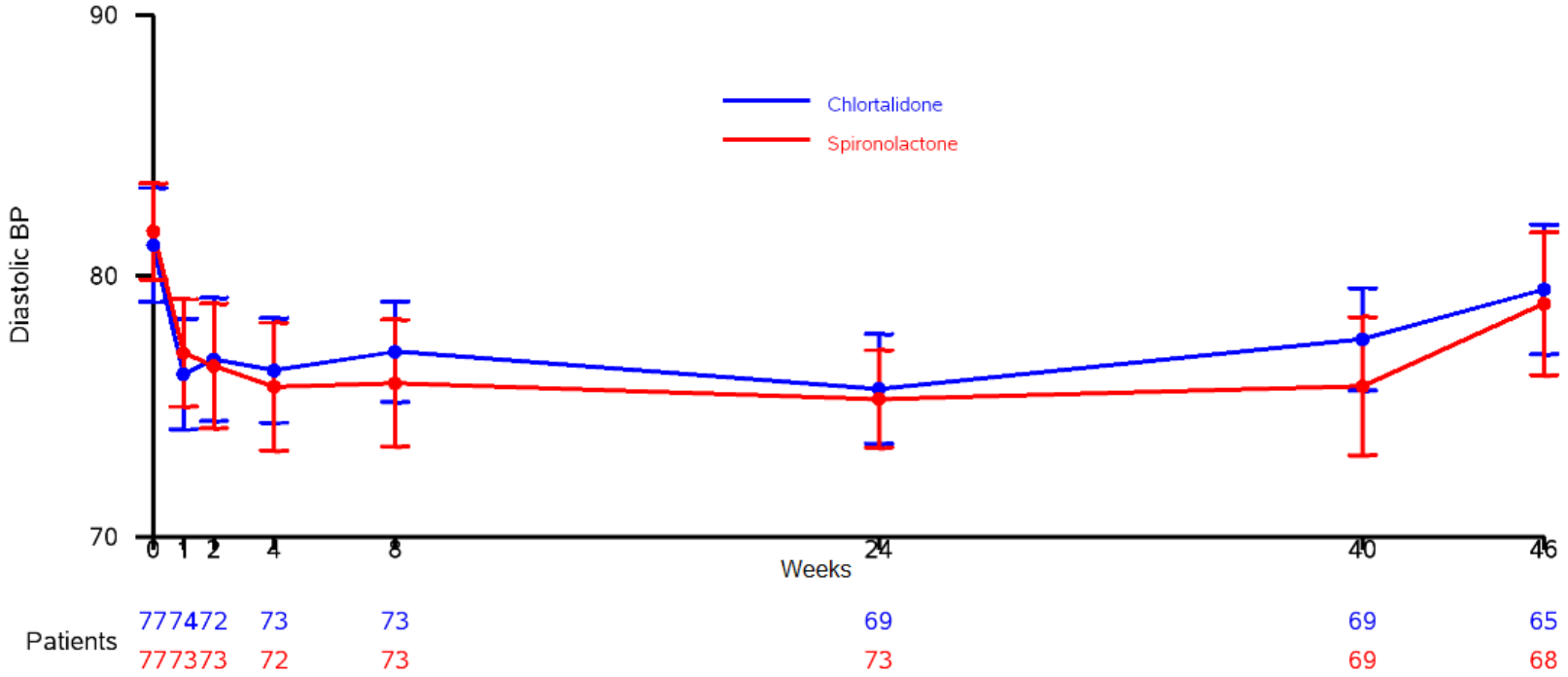


Table 15: Ambulatory blood pressure data summary and analysis

Ambulatory BP	Time point	Statistic	Spironolactone	Chlortalidone	Linear regression model	
					Adjusted Mean Difference[1] (95% CI)	P-value
Mean 24 hour peripheral systolic BP	**Baseline**	N Mean [SD]	69 126.5 [11.1]	70 127.6 [13.4]		
	Week 40	N Mean [SD]	62 121.8 [12.5]	64 121.4 [14]	2.035 (-1.667, 5.738)	0.279
Mean 24 hour peripheral diastolic BP	**Baseline**	N Mean [SD]	69 78.8 [8.4]	70 79.5 [9.3]		
	Week 40	N Mean [SD]	62 75.4 [9]	64 74.6 [7.9]	1.286 (-0.951, ,3.523)	0.257
Mean 24 hour central systolic BP	**Baseline**	N Mean [SD]	67 115.6 [9]	68 117.4 [12.6]		
	Week 40	N Mean [SD]	58 111.3 [10.6]	64 110.4 [11.5]	1.974 (-1.503, 5.452)	0.263
Mean 24 hour central diastolic BP	**Baseline**	N Mean [SD]	67 80 [8.1]	68 81 [9.7]		
	Week 40	N Mean [SD]	58 76.9 [9.2]	64 75.6 [8.6]	1.187 (-1.237, 3.612)	0.334

1-Adjusted for baseline blood pressure and all minimisation variables

7.4. Changes in urinary albumin:creatine (UACR) ratio

Albumin:Creatinine ratio (UACR) was collected at baseline, week 4 and week 40. The analysis was conducted using a linear regression model with UACR at week 40 as the outcome variable, and treatment group (with Chlortalidone as the reference category), baseline UACR and all the minimisation variables included as covariates in the model.

Table 16: UACR ratio data summary and analysis

Secondary outcome	Time point	Statistic	Spironolactone	Chlortalidone	Linear regression model	
					Adjusted Mean Difference[1] (95% CI)	P-value
UACR (mg/mmol)	Baseline	N Mean [SD] Median {IQR} Min – Max	75 24.2 [38.1] 5.5 {1.2-38.6} 0 - 148.9	75 40.7 [92.2] 5 {1.5-49} 0 - 658.2		
	Week 4	N Mean [SD] Median {IQR} Min – Max	72 17.1 [26.5] 5.3 {1.3-20.5} 0 - 114	73 26.1 [62.7] 1.7 {.6-21.2} 0 - 382.2		
	Week 40	N Mean [SD] Median {IQR} Min – Max	69 17.1 [27.6] 4.8 {1.8-18} 0 - 133	69 28.3 [76.5] 2.1 {.6-16.6} 0 - 508.5	1.504 (-10.396, 13.404)	0.803

1-Adjusted for baseline UACR and all minimisation variables

Lower values indicate better scores for spironolactone group, so a negative difference favours spironolactone.

The analysis above for the UACR was based on the actual untransformed data. The UACR data was skewed and not normally distributed. Since the data was not normally distributed, we also conducted analyses on actual untransformed data using the non-parametric Mann Whitney U-Test (Table 17) and also on log-transformed data to meet the distributional assumptions for the regression model (Table 18) For the log transformation as a correction factor, a value of 0.05 was used for all instances where a value of "0" was recorded for UACR.

Table 17: Mann Whitney U test for UACR at week 40

Secondary outcome	Time point	Statistic	Spironolactone	Chlortalidone	Mann Whitney Test P-value
UACR (mg/mmol)	**Baseline**	N Mean [SD] Median {IQR} Min – Max	75 24.2 [38.1] 5.5 {1.2-38.6} 0 - 148.9	75 40.7 [92.2] 5.0 {1.5-49} 0 - 658.2	
	Week 40	N Mean [SD] Median {IQR} Min – Max	69 17.1 [27.6] 4.8 {1.8-18} 0 - 133	69 28.3 [76.5] 2.1 {0.6-16.6} 0 - 508.5	0.195

Lower values indicate better scores for spironolactone group

Table 18: Log transformed UACR data summary and analysis at week 40

Secondary outcome	Time point	Statistic	Spironolactone	Chlortalidone	log-mean[1] (95% CI)	P-value
Log-UACR (mg/mmol)	**Baseline**	N Mean [SD] Median {IQR} Min – Max	75 1.6 [2.3] 1.7 {0.2-3.7} -3 - 5	75 1.9 [2.1] 1.6 {0.4-3.9} -3 - 6.5		
	Week 40	N Mean [SD] Median {IQR} Min – Max	69 1.5 [2] 1.6 {0.6-2.9} -3 - 4.9	69 1.1 [2.2] 0.7 {-0.5-2.8} -3 - 6.2	0.510 (0.008, 1.011)	0.046

1-Adjusted for baseline UACR and all minimisation variables

Lower values indicate better scores, so a negative difference favours spironolactone group

7.5. Decline in renal function (requiring discontinuation from trial therapy)

A binomial model with a log-link was fitted with the outcome being a binary yes/no where yes=number of patients in each treatment group with any incidence of a decline in renal function that required permanent discontinuation from trial treatment. Treatment group (with Chlortalidone as the reference category), and all the minimisation variables were included as covariates in the model.

Note: 15 patients were excluded from this analysis (8 in Spironolactone group and 7 in Chlortalidone group) because these patients withdrew, were lost to follow up or died prior to having an event for decline in renal function that required permanently stopping of trial medication and did not complete the 40 weeks of trial follow up. Hence for this reason they could not be assumed to be in the "no" category and were therefore excluded from the analysis.

Table 19: Decline in renal function requiring permanent discontinuation of trial medication

Decline in renal function requiring permanent discontinuation of medication	Spironolactone (N=69)	Chlortalidone (N=70)	Total (N=139)	Log-Binomial model	
				Adjusted Relative Risk[1] (95% CI)	P-value
No	67 (97%)	62 (89%)	129 (93%)	0.246 (0.054, 1.118)	0.069
Yes	2 (3%)	8 (11%)	10 (7%)		

1-Adjusted for all minimisation variables

Higher values indicate worse outcome for spironolactone group. RR < 1 favours spironolactone group

7.6. Symptomatic hypotension (requiring discontinuation from trial therapy)

This outcome was to be analysed using a binomial model with a log-link with the outcome being a binary yes/no where yes=number of patients in each treatment group with any incidence of symptomatic hypotension that required permanent discontinuation from trial treatment. Treatment group (with Chlortalidone as the reference category), and all the minimisation variables were to be included as covariates in the model.

However, only 2 patients (one in each group) required a medication change from full dose to half dose due to symptomatic hypotension, and no patients permanently stopped their medication due to symptomatic hypotension. So no formal model fitting could be undertaken.

Note: 16 patients were excluded from this analysis (8 in Spironolactone group and 8 in Chlortalidone group) because these patients withdrew, were lost to follow up or died prior to having an event of symptomatic hypotension that required permanently stopping of trial medication and did not complete the 40 weeks of trial follow up. Hence for this reason they could not be assumed to be in the "no" category and were therefore excluded from the analysis.

Table 20: Symptomatic hypotension requiring permanent discontinuation of trial medication

Symptomatic hypotension requiring permanent discontinuation of medication	Spironolactone (N=69)	Chlortalidone (N=69)	Total (N=154)	Log-Binomial model	
				Adjusted Relative Risk[1] (95% CI)	P-value
No	69 (100%)	69 (100%)	138 (100%)	N/A	-
Yes	0 (0%)	0 (0%)	0 (0%)		

1-Adjusted for all minimisation variables

Higher values indicate worse outcome for spironolactone group. RR < 1 favours spironolactone group

7.7. Incidence of side effects (requiring discontinuation from trial therapy)

A binomial model with a log-link was fitted with the outcome being a binary yes/no where yes=number of patients in each treatment group with any incidence of any side effects that required permanent discontinuation from trial treatment. Treatment group (with Chlortalidone as the reference category), and all the minimisation variables were included as covariates in the model.

Note: 13 patients were excluded from this analysis (6 in Spironolactone group and 7 in Chlortalidone group) because these patients withdrew, were lost to follow up or died prior to having any side-effects that required permanently stopping of trial medication and did not complete the 40 weeks of trial follow up. Hence for this reason they could not be assumed to be in the "no" category and were therefore excluded from the analysis.

Table 21: Incidence of any side effects requiring permanent discontinuation of trial medication

Incidence of any side effects requiring permanent discontinuation of medication	Spironolactone (N=71)	Chlortalidone (N=70)	Total (N=154)	Log-Poisson model*	
				Adjusted Relative Risk[1] (95% CI)	P-value
No	60 (85%)	51 (73%)	111 (79%)	0.556 (0.292, 1.058)	0.074
Yes	11 (15%)	19 (27%)	30 (21%)		

* Based on Poisson model with robust standard errors as binomial model did not converge

1-Adjusted for all minimisation variables

Higher values indicate worse outcome for spironolactone group. RR < 1 favours spironolactone group

7.8. Changes in left ventricular volumes and systolic function

This data was collected from the CMR scan at baseline and week 40 as LV end volume for systolic and diastolic. A separate analysis was conducted for LV end-systolic volume and LV end-diastolic volume.

A linear regression model was fitted with LV end-systolic/diastolic volume at week 40 as the outcome variable, and treatment group (with Chlortalidone as the reference category), baseline LV end-systolic/diastolic volume and all the minimisation variables included as covariates in the model.

LV end-systolic/diastolic volume indexed to body surface area was also analysed separately as a sensitivity analysis using the same analysis methods as described above for LV end-systolic/diastolic volume.

Table 22: LV end-systolic volume data summary and analysis

LV end volume	Time point	Statistic	Spironolactone	Chlortalidone	Linear regression model	
					Adjusted Mean Difference[1] (95% CI)	P-value
LV end-systolic volume						
LV end-systolic volume (mL)	**Baseline**	N Mean [SD] Min - Max	68 30.6 [11.3] 13 - 63	68 32 [13.1] 13 - 79		
	Week 40	N Mean [SD] Min - Max	60 30.8 [12.1] 6 - 64	59 30.7 [12.6] 12 - 66	1.073 (-1.408, 3.554)	0.393
Sensitivity analysis **LV end-systolic volume indexed to Body Surface Area (mL/m^2)**	**Baseline**	N Mean [SD] Min - Max	68 15.4 [5.5] 6.9 - 34.1	68 16.6 [6.3] 6.6 - 37.3		
	Week 40	N Mean [SD] Min - Max	60 15.5 [6.1] 3.2 - 35.2	59 15.9 [6.0] 6.2 - 34.4	0.472 (-0.807, 1.751)	0.466
LV end-diastolic volume						
LV end-diastolic volume (mL)	**Baseline**	N Mean [SD] Min - Max	68 116 [26.1] 74 - 197	68 114.1 [27.4] 65 - 191		
	Week 40	N Mean [SD] Min - Max	60 114.2 [26.7] 55 - 189	59 108.2 [26.5] 63 - 179	4.205 (-1.526, 9.936)	0.149
Sensitivity analysis **LV end-diastolic volume indexed to Body Surface Area (mL/m^2)**	**Baseline**	N Mean [SD] Min - Max	68 58.4 [12.3] 37.1 - 101.1	68 59.3 [12.7] 32.5 - 95.7		
	Week 40	N Mean [SD] Min - Max	60 57.4 [13.4] 27.2 - 103.8	59 56.3 [12.3] 35 - 92.4	1.813 (-1.006, 4.632)	0.205

1-Adjusted for all minimisation variables and baseline score

Lower values indicate better scores, so negative difference favours spironolactone group

7.9. Changes in plasma NT-pro-BNP

Plasma NT-pro-BNP data was collected at baseline, week 24 and week 40. The analysis was conducted using a linear regression model with NT-pro-BNP at week 40 as the outcome variable, and treatment group (with Chlortalidone as the reference category), baseline NT-pro-BNP and all the minimisation variables included as covariates in the model. The analysis of the week 24 data is shown in section 7.10.

Table 23: Plasma NT-pro-BNP data summary and analysis

NT-pro-BNP	Time point	Statistic	Spironolactone	Chlortalidone	Linear regression model	
					Adjusted Mean Difference[1] (95% CI)	P-value
NT-pro-BNP (pg/mL)	Baseline	N Mean [SD] Median {IQR} Min - Max	70 130.4 [136.1] 74 {41-161} 7 - 653	70 184.5 [341.7] 113.5 {39-189} 5 - 2670		
	Week 40	N Mean [SD] Median {IQR} Min - Max	63 117.5 [107.4] 78 {38-171} 7 - 437	56 153.3 [323.5] 65.5 {31-162} 8 - 2330	-12.938 (-73.100, 47.225)	0.671

1-Adjusted for baseline NT-pro-BNP and all minimisation variables

Lower values indicate better scores, so a negative difference favours spironolactone group

The analysis above for the NT-pro-BNP was based on the actual untransformed data. The NT-pro-BNP data was skewed and not normally distributed. Since the data was not normally distributed, we also conducted analyses on actual untransformed data using the non-parametric Mann Whitney U-Test (Table 24) and also on log-transformed data to meet the distributional assumptions for the regression model (Table 25).

Table 24: Mann Whitney U test for NT-pro-BNP at week 40

Secondary outcome	Time point	Statistic	Spironolactone	Chlortalidone	Mann Whitney Test P-value
NT-pro-BNP (pg/mL)	**Baseline**	N Mean [SD] Median {IQR} Min – Max	70 130.4 [136.1] 74 {41-161} 7 - 653	70 184.5 [341.7] 113.5 {39-189} 5 - 2670	
	Week 40	N Mean [SD] Median {IQR} Min – Max	63 117.5 [107.4] 78 {38-171} 7 - 437	56 153.3 [323.5] 65.5 {31-162} 8 - 2330	0.476

Lower values indicate better scores

Table 25: Log transformed NT-pro-BNP data summary and analysis at week 40

Secondary outcome	Time point	Statistic	Spironolactone	Chlortalidone	Log-mean[1] (95% CI)	P-value
NT-pro-BNP (pg/mL)	**Baseline**	N Mean [SD] Median {IQR} Min – Max	70 4.4 [1] 4.3 {3.7-5.1} 1.9 - 6.5	70 4.5 [1.2] 4.7 {3.7-5.2} 1.6 - 7.9		
	Week 40	N Mean [SD] Median {IQR} Min – Max	63 4.4 [0.9] 4.4 {3.6-5.1} 1.9 - 6.1	56 4.3 [1.1] 4.2 {3.4-5.1} 2.1 - 7.8	0.135 (-0.071, 0.341)	0. 198

1-Adjusted for baseline NT-pro-BNP and all minimisation variables

Lower values indicate better scores, so a negative difference favours spironolactone group

7.10. Changes NT-pro-BNP, PWV, Augmentation index and aortic blood pressure at 24 weeks

The analyses for each outcome below were conducted using a linear regression model with the data at week 24 as the outcome variable, and treatment group (with Chlortalidone as the reference category), the baseline value and all the minimisation variables included as covariates in the model.

Table 26: PWV, Augmentation index and Central aortic blood pressure data summary and analysis

	Time point	Statistic	Spironolactone	Chlortalidone	Linear regression model	
					Adjusted Mean Difference[1] (95% CI)	P-value
NT-pro-BNP						
NT-pro-BNP (pg/mL)	**Baseline**	N Mean [SD] Min - Max	70 130.4 [136.1] 7 - 653	70 184.5 [341.7] 5 - 2670		
	Week 24	N Mean [SD] Min - Max	65 98.5 [97.8] 10 - 503	64 137.6 [161.8] 7 - 625	-20.908 (-59.960, 18.143)	0.291
Pulse Wave Velocity (PWV)						
PWV (m/s)	**Baseline**	N Mean [SD] Min - Max	69 7.4 [1.8] 2.1 - 11.8	75 7.6 [2.2] 3.2 - 16.2		
	Week 24	N Mean [SD] Min - Max	69 7.3 [1.9] 4 - 14.9	68 7.2 [1.7] 2.9 - 12.1	0.276 (-0.134, 0.685)	0.185
Augmentation Index AIx						
Augmentation Index AIx (%)	**Baseline**	N Mean [SD] Min - Max	74 23.3 [11.3] -2.5 - 54	76 25.8 [10.8] 2 - 55		
	Week 24	N Mean [SD] Min - Max	72 21.8 [12.2] -1 - 54.5	68 24.1 [12.5] -7.5 - 55.5	-0.314 (-3.222, 2.594)	0.831
Central aortic blood pressure						
Central aortic systolic BP (mmHg)	**Baseline**	N Mean [SD] Min - Max	74 120.8 [13.6] 91 - 160.5	76 122.1 [16.4] 94.5 - 174.5		
	Week 24	N Mean [SD] Min - Max	72 113.4 [11.1] 89.5 - 151.5	69 115 [15.8] 85 - 162	-0.109 (-3.865, 3.648)	0.954
Central aortic diastolic BP (mmHg)	**Baseline**	N Mean [SD] Min - Max	74 78.8 [10.5] 54 - 102	76 79 [9.1] 60.5 - 109		
	Week 24	N Mean [SD] Min - Max	72 75.3 [8.8] 43 - 97	69 74.7 [9.2] 56 - 104.5	1.124 (-1.554, 3.802)	0.408

1-Adjusted for baseline value and all minimisation variables

The analysis above for the NT-pro-BNP was based on the actual untransformed data. The NT-pro-BNP data was skewed and not normally distributed. Since the data was not normally distributed, we also conducted analyses on actual untransformed data using the non-parametric Mann Whitney U-Test (Table 27) and also on log-transformed data to meet the distributional assumptions for regression model (Table 28).

Table 27: Mann Whitney U test for NT-pro-BNP at week 24

Secondary outcome	Time point	Statistic	Spironolactone	Chlortalidone	Mann Whitney Test P-value
NT-pro-BNP (pg/mL)	**Baseline**	N Mean [SD] Median {IQR} Min – Max	70 130.4 [136.1] 74 {41-161} 7 - 653	70 184.5 [341.7] 113.5 {39-189} 5 - 2670	
	Week 24	N Mean [SD] Median {IQR} Min – Max	65 98.5 [97.8] 66 {37-117} 10 - 503	64 137.6 [161.8] 65 {32.5-185} 7 - 625	0.696

Lower values indicate better scores

Table 28: Log transformed NT-pro-BNP data summary and analysis at week 24

Secondary outcome	Time point	Statistic	Spironolactone	Chlortalidone	Log-mean[1] (95% CI)	P-value
NT-pro-BNP (pg/mL)	**Baseline**	N Mean [SD] Median {IQR} Min – Max	70 4.4 [1] 4.3 {3.7-5.1} 1.9 - 6.5	70 4.5 [1.2] 4.7 {3.7-5.2} 1.6 - 7.9		
	Week 24	N Mean [SD] Median {IQR} Min – Max	65 4.2 [.9] 4.2 {3.6-4.8} 2.3 - 6.2	64 4.3 [1.1] 4.2 {3.5-5.2} 1.9 - 6.4	0.054 (-0.147, 0.255)	0.594

1-Adjusted for baseline NT-pro-BNP and all minimisation variables

Lower values indicate better scores, so a negative difference favours spironolactone group

8. Adverse events

Note: 6 patients (4 in Spironolactone group and 2 in Chlortalidone group) did not have any follow-up and so for this reason they are not included in the denominator for this analysis as it was only at the follow up visit where the adverse events can be obtained.

Table 29: Adverse events data summary

Adverse Event	Spironolactone		Chlortalidone		Total	
	N (%) of pts (N=73)	*N of Events*	*N (%) of pts (N=75)*	*N of Events*	*N (%) of pts (N=148)*	*N of Events*
Anorexia	2 (2.7%)	2	0 (0%)	0	2 (1.4%)	2
Breast tenderness/enlargement	4 (5.5%)	4	0 (0%)	0	4 (2.7%)	4
Constipation	1 (1.4%)	1	4 (5.3%)	4	5 (3.4%)	5
Diarrhoea	8 (11.0%)	10	5 (6.7%)	5	13 (8.8%)	15
Dizziness	13 (17.8%)	21	22 (29.3%)	32	35 (23.6%)	53
Drowsiness	4 (5.5%)	7	5 (6.7%)	5	9 (6.1%)	12
GI Cramping	1 (1.4%)	1	4 (5.3%)	4	5 (3.4%)	5
Gastric irritation	6 (8.2%)	6	5 (6.7%)	5	11 (7.4%)	11
Gynecomastia	3 (4.1%)	6	0 (0%)	0	3 (2.0%)	6
Headache	11 (15.1%)	14	9 (12.0%)	13	20 (13.5%)	27
Hyperkalaemia	3 (4.1%)	5	0 (0%)	0	3 (2.0%)	5
Hypersensitivity reactions	2 (2.7%)	3	0 (0%)	0	2 (1.4%)	3
Hypokalaemia	0 (0%)	0	1 (1.3%)	1	1 (0.7%)	1
Muscle spasms	8 (11.0%)	8	6 (8.0%)	7	14 (9.5%)	15
Nausea	7 (9.6%)	7	5 (6.7%)	5	12 (8.1%)	12
Paraesthesia	3 (4.1%)	5	3 (4.0%)	4	6 (4.1%)	9
Rashes	10 (13.7%)	13	3 (4.0%)	5	13 (8.8%)	18
Restlessness	1 (1.4%)	1	2 (2.7%)	4	3 (2.0%)	5
Sexual dysfunction	1 (1.4%)	2	1 (1.3%)	1	2 (1.4%)	3
Symptomatic hypotension	7 (9.6%)	12	9 (12.0%)	12	16 (10.8%)	24
Vertigo	1 (1.4%)	1	1 (1.3%)	1	2 (1.4%)	2
Vomiting	3 (4.1%)	3	1 (1.3%)	1	4 (2.7%)	4
Weakness	7 (9.6%)	7	5 (6.7%)	5	12 (8.1%)	12
Total	**-**	**139**	**-**	**114**	**-**	**253**
N of pts with at least one AE	**60 (82%)**		**65 (87%)**		**125 (84%)**	
Chi^2 test for difference in number of patients with at least one AE between treatment groups P-value = 0.453						

* The adverse events (AE's) listed above are those that were captured as expected AE's on the case report form. Patients also experienced other AE's which were recorded as free text on the case report form and in the database. The most common of these AE's were 1) Dry mouth, 2) Change in urinary frequency, 3) Hyponatraemia, 4) Musculoskeletal pain, 5) Itching or pruritus, and 6) Gout.

9. Serious adverse events

There were 9 serious adverse events (SAEs) reported in 5 patients randomised to spironolactone and 6 SAEs reported in 6 patients randomised to chlortalidone.

Table 30: Serious adverse events data summary

SAE's	Spironolactone (N=77)	Chlortalidone (N=77)	Total (N=154)	Chi^2 Test P-value
Patients with at least one SAE:				
No	72 (93.5%)	71 (92.2%)	143 (92.9%)	0.754
Yes	5 (6.5%)	6 (7.8%)	11 (7.1%)	
No of patients with:				
1 SAE	2	6	8	
2 SAE's	2	0	2	-
3 SAE's	1	0	1	-
Total number of SAE's	**9**	**6**	**15**	-

Table 31: List of all SAE's by treatment group

Spironolactone – Total 9 SAE's from 5 patients

Patient	SAE No	Start date	SAE description	Causality	Action taken	Outcome
1031	1	18/05/2015	Kidney pain	Probably unrelated to treatment		Recovered
1042	1	20/11/2015	Elective reconstruction of right ankle due to osteoarthritis	Probably unrelated to treatment	None	Recovered
1042	2	28/11/2015	Whilst sitting brushing her teeth she collapsed with loss of consciousness which has resulted in a fractured left ankle which was confirmed on 30-Nov-2015. In the emergency room she was found to have a prolonged QTC on ECG, possibly due to hypotension	Possibly related to treatment	Treatment stopped	Recovered
1055	1	17/11/2015	Perforated diverticulum. Was given 5 day course of IV Tazpsin 4.5mg TID from 18-Nove-2015-22-Nov-2015. Discharged on 22-Nov-2015	Probably unrelated to treatment	Treatment delayed	Recovered
1055	2	22/12/2015	Admitted to hospital with a four day history of upper and lower abdominal pain, diarrhoea, nausea and vomiting, Imaging revealed duodenitis.	Probably unrelated to treatment	Treatment delayed	Recovered
1055	3	02/02/2016	Subject tripped and fell onto left side and was admitted into AE and thoracic surgery with a rib fracture and small pneumothorax on left side	Probably unrelated to treatment	None	Recovered
1115	1	25/05/2016	Chest pain (sharp, not on exertion) 5 days post angiogram; increase in troponin T level	Probably unrelated to treatment	None	Recovered
1129	1	23/08/2016	Shortness of breath, muscle cramps, anaemia and tiredness	Probably unrelated to treatment	None	Recovered
1129	2	30/08/2016	Admitted due to shortness of breath.	Probably unrelated to treatment	Treatment stopped	Recovered

Chlortalidone – Total 6 SAE's from 6 patients

Patient	SAE No	Start date	SAE description	Causality	Action taken	Outcome
1024	1	08/06/2015	Patient was admitted at royal orthopaedic hospital for and elective (R) knee replacement	Probably unrelated to treatment	None	Recovered
1046	1	30/06/2015	Viral gastroenteritis increase in creatinine and fall in eGFR	Probably unrelated to treatment	Treatment delayed	Recovered
1053	1	23/06/2016	Presented with chest pain typical of angina - new onset. Angiography performed 24-Jun-2016 (report attached). Discharge expected 24 June 2016	Probably unrelated to treatment	None	Recovered
1123	1	28/10/2016	Patient notified Cecilio Andujar that she is pregnant. She stopped trial medication as soon as she found out. Patient had been advised regarding suitable contraception and avoiding pregnancy during trial and for 6 weeks following the last dose of trial treatment. This had also been advised and discussed with other clinicians involved with her care.	Probably unrelated to treatment	Treatment stopped	Recovered
1132	1	02/09/2016	Developed a rash on chest. Advised to stop study drug over weekend and re-assess. Exacerbation of rash and admitted to hospital with this plus acute kidney injury. Rash improving with high dose oral steroids (Prednisolone 60mg). Acute kidney injury also improving. Likely hypersensitivity reaction to sulponamide	Probably related to treatment	Treatment stopped	Recovered
1139	1	12/07/2017	Admitted for cholecystitis for 10 days. Losartan and Chlortalidone temporarily paused for hypotension.	Probably unrelated to treatment	Treatment delayed	Recovered

10. Exploratory analysis

Three exploratory outcomes were specified in the Statistical Analysis Plan: mortality, cardiovascular events and ejection fraction.

10.1. Mortality

No deaths were observed during the study.

10.2. Cardiovascular Events

The analysis for cardiovascular events will be conducted later once the events have been reviewed.

10.3. Ejection Fraction

Ejection fraction is a percentage score computed using the following formulae:
[(LV end-diastolic volume – LV end-systolic volume) / LV end-diastolic volume)] x 100

The table below summarises the ejection fraction at each time point and also provides the results from the linear regression model for the week 40 value adjusting for all minimisation variables and baseline value.

Table 32: Ejection fraction data summary and results

Ejection fraction	Time point	Statistic	Spironolactone	Chlortalidone	Linear regression model	
					Adjusted Mean Difference[1] (95% CI)	P-value
Ejection fraction (%)	Baseline	N Mean [SD] Min - Max	68 74.0 [6.0] 58.5 - 85.6	68 72.6 [6.0] 54.6 - 82.8		
	Week 40	N Mean [SD] Min - Max	60 73.5 [6.9] 58.1 - 89.8	59 72.3 [7.0] 54.0 - 87.2	0.301 (-1.450, 2.052)	0.734

1-Adjusted for baseline ejection fraction and all minimisation variables