Supplemental Material:

Supplementary Appendix: Statistical analyses

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All primary analyses (primary and secondary outcomes including safety outcomes) were by intention-to-treat (ITT). Participants were analysed in the intervention group to which they were randomised, and participants included whether or not they received the allocated intervention. Differences between the intervention groups were estimated using regression models with the minimisation variables (age, systolic BP, sex) and baseline values (where available) included in the model as covariates. Age and systolic blood pressure were included as continuous variables. The chlorthalidone arm was the reference category. Intervention effects are presented with 95% confidence intervals (95% CI) and p values from two-sided tests at the 5% significance level.

Continuous outcomes (e.g. LV mass, pulse wave velocity (PWV), blood pressure) were analysed using a linear regression model to estimate an adjusted mean difference between intervention groups at week 40. PWV, systolic and diastolic office BP were collected over multiple time-points, therefore a secondary analysis using mixed effects repeated measures models was performed. In these analyses, the outcome was the repeated measure, for example, PWV with intervention group, baseline PWV, all the minimisation variables and a time variable included in the model as covariates. The time variable was included as a continuous data variable in the repeated measures model. An unstructured covariance data structure was used. A treatment by time interaction term was included in the initial models to check for its significance. The interaction terms were not significant in all models, and so models were fitted without the interaction term.

Binary outcomes (e.g. hyperkalaemia) were analysed as a categorical binary outcome using a log-binomial model. The outcome for the model was binary (yes/no), with yes being patients in each intervention group with any incidence of hyperkalaemia. Results are presented as an adjusted relative risk and 95% confidence interval.

Randomisation

Participants were individually randomised into the trial in a 1:1 ratio to either Spironolactone or Chlortalidone. Randomisation was provided by a computer generated programme at the Birmingham Clinical Trials Unit (BCTU), using a minimisation algorithm to ensure balance between the arms with regard to the following important clinical variables: systolic blood pressure (<130 mmHg, ≥130 mmHg), age (<55 years, ≥55 years) and sex (Male, Female).

Participants were randomised into the trial via a secure 24 hour internet based randomisation service or by a telephone call to the BCTU. Telephone randomisations were available Monday-Friday, 09:00-17:00. For the secure internet randomisation, each site and each randomiser were provided with a unique log-in username and password in order to access the online system.

Once answers to all questions and data items on the Randomisation Form had been provided, the participant could be randomised, and the treatment allocation and a unique trial number was given. A confirmatory email was sent to the randomising investigator, the local Principle

Investigator and the named research nurse. The hospital pharmacy also received notification of the randomisation by email

Sensitivity Analyses

Two sensitivity analyses were planned for the primary outcome: a per-protocol analysis and an analysis to assess the impact of missing data on the primary outcome. The per-protocol population consisted of those participants who remained on full dose for the duration of the trial; this analysis included 45 spironolactone and 42 chlortalidone participants who remained on full dose and had primary outcome data available. The analysis to assess the impact of missing data used multiple imputation. Missing data was imputed using multiple imputation with chained equations. Covariates included to aid imputation were all of the minimisation variables (i.e. age, gender, systolic BP) and baseline LV mass. The "MI" command and the "regress" option in Stata 15 was used since the primary outcome is a continuous data item. Fifty imputations were generated for any missing data for the primary outcome (i.e. LV mass at week 40) and all minimisation variables (age, systolic blood pressure, gender), intervention group and baseline LV mass included in multiple imputation procedure. The imputed results were combined using Rubin's rule.

All analyses were undertaken using Stata version 15 and SAS version 9.3.

Data Monitoring Committee (DMC)

Interim analyses of major outcome measures and safety data were conducted and provided in strict confidence to the independent DMC. It was agreed that any decision to stop the trial early would be based on a balance of efficacy and safety.

The DMC reviewed the accumulating data and assessed whether, in their view, any of the randomised comparisons in the trial provided both: a) proof beyond reasonable doubt that for all, or for some, types of participant one particular intervention was definitely indicated or definitely contra-indicated in terms of a net difference of a major endpoint, and b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results.

Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, the DMC therefore adopted the guideline of observing a difference of at least $p<0.001$ (similar to a Haybittle-Peto stopping boundary) in an interim analysis of a major endpoint as possible justification for halting, or modifying, the study prematurely. This approach gives the practical advantage that the exact number of interim analyses is of little importance, so no fixed schedule was needed or proposed, and no adjustment for multiple testing (to control the overall type I error rate) is required.