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Benefits of aldosterone receptor antagonism in chronic kidney disease: the BARACK-D RCT

F D Richard Hobbs, Richard McManus, Clare Taylor, Nicholas Jones, Joy Rahman, Jane Wolstenholme, Louise Jones, Jennifer Hirst, Sam Mort and Ly-Mee Yu on behalf of the BARACK-D Investigators

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Extended Research Article

Benefits of aldosterone receptor antagonism in chronic kidney disease: the BARACK-D RCT

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Abstract

Background: Chronic kidney disease affects around 10% of the global population and is associated with significant risk of progression to end-stage renal disease and vascular events. Aldosterone receptor antagonists such as spironolactone have shown prognostic benefits in patients with heart failure, but effects on patients with chronic kidney disease are uncertain.

Objectives: To determine the effect of low-dose spironolactone on mortality and cardiovascular outcomes in people with chronic kidney disease stage 3b.

Design: Prospective randomised open blinded end-point trial.

Settings: Three hundred and twenty-nine general practitioner practices throughout the United Kingdom.

Participants: Patients meeting the criteria for chronic kidney disease stage 3b (estimated glomerular filtration rate 30–44 ml/minute/1.73 m^2) according to National Institute for Health and Care Excellence guidelines were recruited. Due to the higher than anticipated measurement error/fluctuations, the eligible range was extended to 30–50 ml/minute/1.73 m^2 following the initial recruitment period.

Intervention: Participants were randomised 1 : 1 to receive either spironolactone 25 mg once daily in addition to standard care, or standard care only.

Outcome measures: Primary outcome was the first occurring of all-cause mortality, first hospitalisation for heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, failed sudden death), stroke, heart failure, transient ischaemic attack or peripheral arterial disease, or first occurrence of any condition not listed at baseline. Secondary outcome measures included changes in blood pressure, renal function, B-type natriuretic peptide, incidence of hyperkalaemia and treatment costs and benefits.

Results: One thousand four hundred and thirty-four participants were randomised of the 3022 planned. We found no evidence of differences between the intervention and control groups in terms of effectiveness with the primary combined vascular end points, nor with the secondary clinical outcomes, including progression in renal decline. These results were similar for the total treatment periods or a 3-year follow-up period as originally planned. More adverse events were experienced and more participants discontinued treatment in the intervention group. Two-thirds of participants randomised to spironolactone stopped treatment within six months because they met pre-specified safety stop criteria. The addition of low-dose spironolactone was estimated to have a cost per quality-adjusted life-year gained value above the National Institute for Health and Care Excellence's threshold of £30,000.

Limitations: Main limitations were difficulties in recruiting eligible participants resulting in an underpowered trial with poor ethnic diversity taking twice as long as planned to complete. We have explored the data in secondary analyses that indicate that, despite these difficulties, the findings were reliable.

Conclusions: The benefits of aldosterone receptor antagonism in chronic kidney disease trial found no evidence to support adding low-dose spironolactone (25 mg daily) in patients with chronic kidney disease stage 3b: there were no changes to cardiovascular events during the trial follow-up, either for the combined primary or individual components. There was also no evidence of benefit observed in rates of renal function decline over the trial, but much higher initial creatinine rise and estimated glomerular filtration rate decline, and to a higher percentage rate, in the intervention arm in the first few weeks of spironolactone treatment, which resulted in a high proportion of participants discontinuing spironolactone treatment at an early stage. These higher rates of negative renal change reduced in scale over the study but did not equalise between arms. The addition of 25 mg of spironolactone therefore provided no reno- or cardio-protection and was associated with an increase in adverse events.

Future work: These findings might not be applicable to different mineralocorticoid receptor antagonists.

Study registration: Current Controlled Trials ISRCTN44522369.

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List of supplementary material

Report Supplementary Material 1 Statistical analysis plan

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/PYFT6977).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ACR	albumin-creatinine ratio
AE	adverse event
AR	adverse reaction
ARA	aldosterone receptor antagonist
ARB	angiotensin II receptor blockers
BNP	B-type natriuretic peptide
BP	blood pressure
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVD	cardiovascular disease
DM	diabetes mellitus
DMEC	Data Monitoring and Ethics Committee
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ESRF	end-stage renal failure
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
EQ-VAS	EuroQoL visual analogue scale
GP	general practitioner
HbA1c	glycated haemoglobin
HRA	Health Research Authority
IB	investigators brochure
ICECAP-A	ICEpop CAPability measure for Adults
ICER	incremental cost-effectiveness ratio
IMP	investigational medicinal product
KDQoL-SF	Kidney Disease Quality of Life – Short Form
LDL	low-density lipoprotein
LV	left ventricular
LVH	left ventricular hypertrophy
MDRD	modification of diet in renal disease
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
NICE	National Institute for Health and Care Excellence
OBP	Office blood pressure
PI	principal investigator
PROBE	prospective randomised open blinded endpoint
PWV	pulse wave velocity
QALY	quality-adjusted life-year
QoL	quality of life
RAAS	renin–angiotensin–aldosterone system
RALES	Randomized Aldactone Evaluation Study
REC	Research Ethics Committee
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
TIA	transient ischaemic attack
VAS	visual analogue scale

Plain language summary

What was the problem?

Chronic kidney disease describes a long-term reduction in kidney function due to any cause. Chronic kidney disease is divided into five stages of severity, with stage 5 being the most severe. These stages are determined by a kidney function blood test called the estimated glomerular filtration rate and/or the amount of protein in the urine.

Chronic kidney disease affects around 10% of people in the United Kingdom and is more common with increasing age and in people with other illnesses, such as hypertension, diabetes, obesity and underlying primary kidney disease. People with chronic kidney disease are at an increased risk of developing cardiovascular disease (heart disease and stroke), including heart failure and sudden cardiac death. However, conventional treatments for cardiovascular disease have had disappointing results in people with chronic kidney disease. There are also limited treatment options to prevent further decline in kidney function.

Established drugs called aldosterone receptor antagonists reduce deaths in patients with heart disease and showed promise in small-scale studies. There is also evidence that these drugs may reduce kidney damage attributed to circulating aldosterone.

What did we do?

In this study, we compared the effect of a low-dose aldosterone receptor antagonist, spironolactone, in people with moderate to severe chronic kidney disease compared to any other routine care to find out if this changed how long people survived, and if they were protected from cardiovascular disease or kidney damage.

What did we find?

We found no evidence that the addition of low-dose spironolactone improved cardiovascular or renal outcomes over three years and longer of treatment compared to the standard standard of care.

Scientific summary

Background

Chronic kidney disease (CKD) is a major cause of increased mortality and morbidity through increased vascular events and progression to end-stage renal failure (ESRF). These increased events result in CKD having high cost to healthcare systems, with the dialysis required in ESRF benchmarked as at the maximum acceptable cost-effectiveness threshold for an intervention by most healthcare systems. However, the most important component of CKD in terms of mortality and morbidity is cardiovascular disease (CVD).

While the cardiovascular risk of end-stage CKD is extreme, in public health terms the burden resides in early-stage (CKD stages 1–3) disease, which is more prevalent, affecting around 40% of those over 70 years. When added to conventional risk factors, renal markers substantially improve risk stratification and CKD is therefore an important and under-recognised risk factor for CVD in the general population. Although the risks of myocardial infarction and other manifestations of coronary artery disease are increased in CKD, the pattern of CVD is atypical, with a much greater incidence of heart failure and sudden cardiac death than in the general CVD population.

Few therapies have proved effective in modifying the increased CVD risk or the rate of renal decline in CKD. There are accumulating data that aldosterone receptor antagonists (ARAs) may offer cardio-protection and delay renal impairment in patients with the cardiovascular (CV) phenotype in CKD. The use of ARA in CKD has therefore been increasingly advocated and even termed the 'renal aspirin'. Prior to the initiation of benefits of aldosterone receptor antagonism in chronic kidney disease (BARACK-D), no large study of ARAs with renal or CVD outcomes was underway. This trial evaluates the benefits of an ARA, spironolactone, in patients with stage 3b CKD.

Objectives

The primary objective was to determine the effect of aldosterone receptor antagonism with spironolactone on mortality and cardiovascular outcomes in people with CKD stage 3b. Secondary objectives included determining the effect on renal function and blood pressure control, cost-effectiveness and the safety of this treatment approach.

End points

Primary end point

The primary outcome was the time from randomisation to the first occurring of all-cause mortality, hospitalisation for heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, failed sudden death), stroke, heart failure, transient ischaemic attack or peripheral arterial disease, or first onset of any of these conditions in the primary care record if not listed at baseline.

Secondary end points

Secondary outcome measures included

- Individual components of the primary outcome, including all-cause mortality, heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, failed sudden death), stroke, heart failure peripheral artery disease or transient ischaemic attack.
- Measures of cardiovascular haemodynamics, including changes in blood pressure and prevalence of hypotension.
- The effect on left ventricular (LV) function, determined by changes in B-type natriuretic peptide.
- A decline in renal function, measured by changes in estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio.

- Safety measures, including incidence of hyperkalaemia.
- Cost-effectiveness, including changes in health status measured on EuroQol-5 Dimensions, five-level version.

Study design and methodology

The BARACK-D was a prospective, randomised, open, blinded endpoint (PROBE) trial. 1985 eligible patients, from a minimum of 120 practices, with previously recorded blood test results suggesting CKD stage 3b, were invited to take part in the study and randomised to either spironolactone 25 mg once daily in addition to standard care or standard care alone. Blood pressure in both groups was titrated (monitored and adjusted accordingly) by the clinicians against NICE guideline standards and checks of electrolytes undertaken.

Study recruitment was initially much slower than planned because of excessive delays to negotiating appropriate service support costs, and initial concern by practices to engage with the study on the grounds that they would need to subsidise their time. Also, there was refusal to fund the (minimal) excess treatment costs from some clinical commissioning groups (CCGs). While various measures were put in place and recruitment did improve, in March 2018 the decision was taken with the Health Technology Assessment to close the study to recruitment as of July 2018, and to follow up those enrolled for 3 years (as per protocol) then close the trial.

In addition to these delays, the number of patients recruited per practice recruitment was lower than expected. Mail-out numbers were less than anticipated, and the response rate to those mail-outs was also low.

Results

One thousand four hundred and thirty-four participants were randomised of the 3022 we planned. One thousand three hundred and seventy-two (96%) were included in the analysis. Of the participants, 113/677 (16.7%) in the spironolactone arm and 111/695 (16.0%) in the standard care arm had a primary combined vascular event. We found no evidence of differences between the intervention and control groups in terms of effectiveness with the primary outcome [hazard ratio 1.05, 95% confidence interval (0.81 to 1.37); $p = 0.70$], nor with the secondary clinical outcomes, including progression in renal decline. These findings were consistent whether analysing the total treatment periods or a 3-year follow-up period as was originally planned. Adverse events were experienced more often, and participants were more likely to discontinue treatment in the intervention group. Two-thirds of participants randomised to spironolactone discontinued taking treatment within six months, with the most frequenst reasons being a decrease in the estimated glomerular filtration rate that met pre-specified stop criteria ($n = 239$, 35.4%), treatment side-effects ($n = 128$, 18.9%) and hyperkalaemia ($n = 54$, 8.0%). The addition of low-dose spironolactone was unlikely to be cost-effective

Conclusions

The BARACK-D trial found no evidence of benefit with the addition of low-dose spironolactone at 25 mg daily in patients with CKD 3b on the high rates of cardiovascular events seen in the trial follow-up, either for the combined primary or for individual components. There was also no benefit observed in rates of renal function decline over the trial with much higher initial creatinine rise and eGFR decline, and to a higher percentage rate, in the first few weeks of spironolactone treatment. These higher rates of negative renal change reduced in scale over the study but did not equalise between arms. The addition of 25 mg of spironolactone therefore provided no reno- or cardio-protection but was associated with more adverse events.

Trial registration

Current Controlled Trials ISRCTN44522369.

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This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 12/01/52) and is published in full in *Health Technology Assessment*; Vol. 29, No. 5. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction

Background

Chronic kidney disease (CKD) is a major cause of increased mortality and morbidity through increased vascular events and progression to end-stage renal failure (ESRF).[1] These high event rates lead to high healthcare system costs, with the dialysis required in ESRF benchmarked as the maximum acceptable cost-effectiveness threshold for an intervention by most healthcare systems. However, the most important sequela of CKD in terms of mortality and morbidity is cardiovascular disease (CVD).[2–6]

While cardiovascular risk in end-stage CKD is extreme, the main public health burden of CKD resides in early-stage (CKD stages 1–3) disease, which is more prevalent, affecting around 40% of those over 70 years. Added to conventional risk factors, renal markers substantially improve risk stratification and CKD is therefore an important and under-recognised risk factor for CVD in the general population.[7,8] However, the pattern of CVD is atypical in CKD with a much greater incidence of heart failure and sudden cardiac death than in the general CVD population.[9–11] Few therapies have proved effective in modifying the increased CVD risk or the rate of renal decline in CKD, although the angiotensin receptor antagonist spironolactone has been postulated as the potential 'renal aspirin'.[12]

Chronic kidney disease is increasingly common and is the 12th leading cause of death globally.[13] Estimates of prevalence vary widely depending on the approach used and the geographic region,[14,15] but global prevalence is around 9%, with highest prevalence in regions with the lowest social deprivation.[13] It is associated with an age-related decline in renal function that is accelerated in those with hypertension, diabetes mellitus (DM), obesity and primary renal disorders.[16] CKD is defined and categorised into five stages using estimated glomerular filtration rate (eGFR) and/or evidence of renal damage (imaging or proteinuria).[17]

A diagnosis of CKD is made if there is a sustained reduction in renal function (usually measured by an eGFR below 60 ml/minute/1.73 m^2), or evidence of renal damage [such as a raised albumin-creatinine ratio (ACR) above 3 mg/mmol], or both for more than 3 months duration. Population studies have primarily used the four-variable modification of diet in renal disease (MDRD) formula to determine eGFR.[18] In patients aged 65 or over, up to 35% have an eGFR of < 60 ml/minute/1.73 m^2.[19]

Diagnosis of chronic kidney disease

The historic standard equation for estimating GFR was the MDRD formula.[18] However, this formula results in an underestimation bias for higher levels of renal function. The more recent Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[20] has been validated in general populations (excluding very elderly persons),[21–23] as well as in different ethnic groups with appropriate equation modification (as per MDRD)[24,25] and has shown greater accuracy. The MDRD equation has some utility in cardiac risk prediction[26,27] but CKD-EPI based CKD staging improves risk prediction.[28–30] This may influence policy as countries switch to CKD-EPI for GFR reporting.[31–33] Evidence for the optimal GFR estimation method in primary care populations has been systematically summarised and CKD-EPI has been shown to exhibit less bias than MDRD compared to GFR measured using isotope methods.[22]

Chronic kidney disease, renal decline and cardiovascular disease

Chronic kidney disease is a major cause of increased mortality,[5] and morbidity through increased vascular events, progression to ESRF,[34–36] and higher rates of CVD.[5,37] These result in CKD having a high cost to healthcare systems, with the dialysis required in ESRF benchmarked as at the maximum acceptable cost-effectiveness threshold for an intervention by most healthcare systems. However, the most important aspect of CKD in terms of mortality and morbidity is its close association with CVD.[2,37] After adjustment for age, sex and other risk factors, there is an inverse relationship between eGFR and all-cause mortality, cardiovascular mortality, coronary heart disease, stroke, heart failure or any hospitalisations,[2,37] and a direct relationship between urinary ACR and all cardiovascular outcomes.[16,37] This elevated risk of CVD in those with a mild decline in kidney function suggests that there is a need to focus greater attention in global health policy decision-making to address the potential increasing burden on healthcare systems from

those living with earlier stages of CKD. When added to conventional risk factors, renal markers substantially improve cardiovascular risk stratification and CKD is therefore an important risk factor for CVD in the general population.[8]

Although the risks of myocardial infarction (MI) and other manifestations of coronary artery disease are increased in CKD, the pattern of CVD is atypical, with a much greater incidence of heart failure and sudden cardiac death than in the general CVD population.[10,37] Traditional risk factors such as hypertension and diabetes do not fully account for the burden of CVD in CKD.[38] Left ventricular hypertrophy (LVH) and arterial wall calcification are powerful independent risk factors for mortality in patients with CKD.[39,40]

LVH describes an increase in mass of the left ventricle, through either thickening of the cardiac muscle, enlargement of the chamber, or both. It is highly prevalent in CKD,[41] and increases as kidney function decreases. Reported prevalence is over 30% in those whose GFR ≥ 60 ml/minute/1.73 m^2, around 50% in stage 3 CKD (eGFR 30–59) and in 75% in patients with eGFR < 30 ml/minute/1.73 m^2. Importantly, the increase in left ventricular (LV) mass is a strong independent predictor of mortality in CKD[39] (as in non-CKD states) and regression of LVH is associated with improved cardiac outcome. LVH is often accompanied by evidence of fibrosis, an excessive accumulation of connective tissue leading to organ dysfunction,[42–44] which is also a strong predictor of mortality in CKD.[43]

Large arteries buffer changes in blood pressure (BP) from fluctuations in cardiac output, but as arteries become more rigid, they are less able to accommodate changes in the volume of blood pumped from the left ventricle. This arterial wall thickening, stiffening and calcification (atherosclerosis)[40] therefore leads to increased systolic and pulse pressure, and the resultant increase in afterload is a major cause of LVH and its progression over time.[45] Meta-analysis evidence reports the prevalence of coronary artery calcification in CKD to be around 60% in pre-dialysis patients and 65% in those on haemodialysis.[46] Coronary artery calcification is a strong predictor of cardiovascular and all-cause mortality in people with mild to moderate CKD.[47] Medial artery calcification, which causes vascular stiffening and decreased compliance of the vessel,[48] is more prevalent in patients with CKD[49] than intimal calcification which is associated with atherosclerosis. Prospective studies have demonstrated that measures of increased aortic stiffness, such as high aortic pulse wave velocity (PWV), and augmentation of central aortic pressure by early wave reflections (AIx), are strong independent predictors of all-cause and cardiovascular mortality in patients on dialysis.[40,45] Lowering aortic PWV, mainly by use of an angiotensin-converting enzyme inhibitor (ACEI), is associated with an improved survival in dialysis patients.[50] In the latter study, the reduction in aortic PWV was associated with a parallel reduction in mean arterial and pulse pressure in survivors. In contrast, in those dying from cardiovascular events neither pulse pressure nor aortic PWV were significantly modified by ACE inhibition, although mean arterial pressure (the usual measure in clinical practice) was lowered to the same extent as in survivors. All these data suggest that arterial stiffness is not merely a marker of arterial damage but a potentially reversible factor contributing to mortality.

Therefore, although patients with CKD also suffer typical patterns of CVD (coronary and peripheral artery atherosclerosis), the excess rates of cardiovascular events in CKD may relate more to vascular wall and ventricular changes than to atherosclerosis. The causes of atherosclerosis and LVH in CKD are complex but it is likely that as renal function declines, the onset of sodium overload combined with hypertension, chronic anaemia, oxidative stress and activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system all contribute to this development of atherosclerosis, myocardial hypertrophy and fibrosis.[51] Furthermore, many of these factors cause vascular endothelial dysfunction which, as well as leading to atherosclerotic disease, is a major functional component of arterial stiffening.[52] It is the early development of arterial stiffening, causing loss of arterial compliance, increased afterload and exposure of end organs to high phasic pressures, which is thought to be a key factor in the causation of LVH and small vessel damage in the brain and kidney.[53,54]

Chronic kidney disease and management options

In light of this vascular pathophysiology, it is unsurprising that traditional cardiovascular risk factors are less predictive of outcomes in CKD than in the general population,[55] and much less predictive than eGFR and protein excretion,[37,55] even after controlling for variables, such as BP.[37] Furthermore, interventions to reduce the increased cardiovascular risk in CKD have proved disappointing, with only limited evidence for traditional therapies in terms of cardiovascular outcomes. For example, the Study of Heart and Renal Protection trial[56] aimed to assess the safety and efficacy of reducing low-density lipoprotien (LDL) cholesterol in more than 9000 patients with CKD with a low-dose

of a statin (simvastatin 20 mg daily). The trial showed that lowering of LDL cholesterol safely reduced the risk of major atherosclerotic events in patients with CKD. However, the reduction in non-fatal MI or coronary death was not significant.

There are also limited therapeutic options for the prevention of further renal functional decline. When the benefits of aldosterone receptor antagonism in chronic kidney disease (BARACK-D) trial was initiated, the only interventions shown to reduce or prevent renal function decline for most patients with CKD were avoidance of renal damage [e.g. treating infections and avoiding non-steroidal anti-inflammatory drugs (NSAIDs) in at-risk people], and effective treatment of risk factors, namely hypertension and DM. In addition, drugs acting on the renin-angiotensin-aldosterone system (RAAS) offer modest additional benefits to BP lowering alone in patients with diabetic nephropathy with proteinuria.[57,58]

In light of this, better treatment options are needed, especially given the increasing burden of the disease. Desirable clinical outcomes for any new therapies would be the effective and safe reduction of cardiovascular events and premature death and/or delay in progression of renal decline. The most important target CKD population for such preventive interventions are those with CKD stage 3b (eGFR 30–44 ml/minute/1.73 m^2), since this has high prevalence at 3% of adults, represents progressive renal disease, and is associated with a 12-fold increase in CVD, compared to those with eGFR above 60 ml/minute/1.73 m^2. In contrast, relative cardiovascular risk is twofold in CKD stage 3a (eGFR 45–59), though the prevalence is nearer 15%.[5]

There are some promising newer treatments, which offer renal and cardiovascular protective effects. In 2019, a systematic review and meta-analysis of randomised trials found that sodium-glucose cotransporter 2 inhibitor (SGLT-2) treatment in people with type 2 diabetes and CKD resulted in improvements in kidney function, including eGFR, and reduced the risk of major adverse cardiovascular events by 19% and heart failure by 39%.[59] However, there were only modest reductions in other cardiac outcomes or all-cause mortality.[59] In 2020, a meta-analysis of four trials in patients with CKD regardless of diabetic status, similarly found that SGLT-2s reduced risk of heart failure, but also MI and composite kidney outcomes.[60] These studies have resulted in new indications for SGLT-2s in cardio- and reno-protection in CKD. However, renal monitoring is needed since renal function initially declines markedly on SGLT-2 initiation, although then plateaus and may then reduce further renal functional decline.[61]

Other important new candidates for potential cardio-protection in CKD are drugs that act on the aldosterone pathway of RAAS.

The role of aldosterone in cardiovascular disease and as potential therapeutic target in renal disease progression

Blockade of RAAS with ACEIs and angiotensin II receptor blockers (ARBs) has shown mortality benefit[62–64] and lower risk of hospitalisation[65] in patients with chronic heart failure and a reduced LV ejection fraction (EF) and in those with, or at high risk of, coronary artery disease. The benefits are attributed to the attenuation of cardiac remodelling which is regulated by angiotensin II.[66]

Aldosterone is a mineralocorticoid hormone that regulates electrolyte balance and BP, but overexpression can result in cardiac and vascular damage.[67] There is increasing evidence that local mineralocorticoid receptor (MR) activation by aldosterone leads to endothelial dysfunction, inflammation, oxidative stress and fibrosis in the heart vasoconstriction and cardiac remodelling.[68] Plasma aldosterone levels have been shown to be independently associated with CVD and all-cause mortality in patients undergoing coronary angioplasty.[69] MR activation has been widely evaluated at cardiac level and been shown to be involved in the transition to hypertension, heart failure, MI and induce myocardial fibrosis by promoting inflammation.[70]

Treatment with mineralocorticoid receptor antagonists (MRAs) reduces LVH dilation and progression to heart failure. This class of drugs was previously commonly known as aldosterone receptor blockers or antagonists (hence the acronym BARACK-D) but MRA is now the accepted terminology, hence its use in this paper. aldosterone receptor antagonist (ARA) and MRA however are interchangeable. MRAs that are currently used include spironolactone, eplerenone[71] and finerenone.[72] In humans, there are reliable and large studies that show that targeting aldosterone improves outcomes in established CVD. Spironolactone was the first MRA, which was produced as a diuretic drug.[73]

In 1999, a landmark study, Randomized Aldactone Evaluation Study (RALES) demonstrated that beyond its diuretic benefits, spironolactone reduced the risk of mortality by 30%, as well as cardiovascular mortality and hospitalisation in patients with severe heart failure (LV EF ≤ 35% and New York Heart Association score of III or IV).[74] It is non-cardiac specific and steroidal in nature, meaning it can have undesirable side effects including hyperkalaemia and gynaecomastia.[72,74]

Eplerenone is a second-generation MRA and is more cardio-selective. It has greater selectivity for the MR than spironolactone and fewer side effects but requires higher doses to achieve the same effect.[71] Two major studies demonstrated its mortality benefits in heart failure patients. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) and Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) showed that treatment reduced mortality by 15% in people with severe heart failure[75] and 22% in people with mild heart failure symptoms,[76] as well as cardiovascular mortality and hospitalisations in both studies.

More recently, finerenone, a novel potent selective and non-steroidal MRA with stronger MR potential compared with eplerenone and spironolactone, has been developed.[72] The Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure (FINEARTS-HF) compared finerenone to eplerenone and found that it resulted in similar reductions in N-terminal pro b-type natriuretic peptide markers and a composite end point of mortality or hospitalisation as eplerenone in patients with heart failure with reduced EF.[77]

Further, treatment with MRAs in addition to ACEIs prevents adverse LV remodelling after MI and effectively reduces LVH in drug resistant hypertension.[78] This indicates that an anti-fibrotic effect of MRA therapy may also be important. After MI, MRA inhibited aldosterone and cardiac collagen synthesis and fibrosis by blocking mineralocorticoid receptors (MRs).[78] Furthermore, myocardial collagen turnover is significantly reduced by spironolactone, and this reduction is related to the mortality benefit.[74]

ACE inhibitors and ARBs appear superior to other BP lowering drugs in slowing the progression of CKD, though the effect may be marginal.[62] These agents are therefore widely recommended in international guidelines as 'reno-protection' for CKD patients, especially those with proteinuria or DM. They are also recommended in people with proteinuric CKD, irrespective of BP. However, after an initial drop in plasma aldosterone levels following ACEI treatment, there tends to be a rise to baseline levels.[79]

Renal specialists have avoided the use of MRAs because of a perceived risk of azotaemia and hyperkalaemia, though similar restrictions were applied to ACEIs until outcome data were reported. There are, however, accumulating data on their combined treatment with ACEIs to improve renal function in patients with CKD[80] and that they can improve measures of kidney function in populations with CKD.[72,81,82]

The role of mineralocorticoid receptor antagonists in chronic kidney disease

Beyond their effect on kidney function, there have been several recent trials providing accumulating evidence that MRAs may offer cardio-protection and delay renal impairment in patients with CKD. Early data on the efficacy of ARA on cardiovascular outcomes for people with early-stage CKD were published from the CRIB II trial in 2010.[83] This double-blind trial including 112 patients with stage 2 and 3 CKD with good BP control treated with ACEIs or ARBs showed that the addition of spironolactone improved myocardial abnormalities and reduced LV mass and arterial stiffness compared to placebo. Because it was unclear whether these beneficial effects were due to the actions of spironolactone or BP reduction, a second trial randomised 154 participants to either spironolactone or the diuretic, chlorthalidone.[84] It found no significant differences in LV mass reduction or BP control between the two drugs. Their finding, that chlorthalidone and spironolactone reduce LV mass by a similar amount, suggests that BP control is contributing to LV mass reduction. The study illustrates the importance of comparing the effects of MRAs with active BP-lowering control drugs.

Studies of MRAs in people with CKD looking at clinical outcomes have produced mixed results. An analysis of health insurance data from over 14,000 people with CKD stage 3 and 4 in Taiwan found that spironolactone use was associated with a 34% lower incidence of end-stage kidney disease compared with non-use.[85] The study also

found that there was no impact on cardiovascular events or mortality, but there was a substantially higher incidence of hospitalisation associated with hyperkalaemia in those taking spironolactone. Among a second cohort of 27,000 pre-dialysis patients with stage 5 CKD in Taiwan's National Health Insurance data set, spironolactone treatment was associated with higher risks of all-cause mortality and hospitalisation for heart failure compared to non-users.[86]

A small randomised trial in 48 participants who received eplenerone or placebo found that MRA treatment had renal protective effects independent of BP[87] in terms of higher eGFR in the eplenerone-treated group.

A recent trial recruited patients with CKD and type 2 diabetes receiving finerenone and found they had a 18% lower risk of composite kidney outcomes and a 14% lower risk of a composite cardiovascular outcomes event than those who received placebo.[88] Later trials found that finerenone reduced the risk of hospitalisation due to heart failure by 29%, composite cardiovascular outcomes by 13% and the risk of CKD progression in patients with CKD and type 2 diabetes.[89,90,91] These results suggest that in patients with CKD and type 2 diabetes, finerenone may be an effective treatment for kidney disease and offer some cardiovascular protection, though the finereone trials excluded patients with non-albuminuric CKD meaning that the use of MRA remains uncertain among people with moderate stage, non-albuminuric CKD who do not have diabetes.

Given the burden of disease in CKD, alternative treatment options to provide protection from vascular events or delay progression are needed. ARA/MRA therapy might therefore be an effective candidate for improved cardiovascular outcomes, through the prevention of aldosterone-mediated vascular endothelial dysfunction as well as widespread cardiovascular inflammation, fibrosis and hypertrophy. Spironolactone is well recognised as an effective antihypertensive agent for patients with hypertension, even when this is resistant to other drugs.

Rationale for trial

CKD is common and increasing in prevalence. CVD is a major cause of morbidity and death in CKD, though of a different phenotype to the general CVD population. Currently, few therapies have proved effective in modifying the increased CVD risk or the rate of renal decline in CKD. There are accumulating data that MRAs may offer cardio-protection and delay renal impairment in patients with the cardiovascular phenotype in CKD. The use of ARA/MRA in CKD has therefore been increasingly advocated and even termed the 'renal aspirin'.[12] Recent trials have been relatively small and have evaluated surrogate end points.[84] Furthermore, the majority of ARA trials have been based in secondary care, yet the majority of patients with early CKD are managed in primary care.[92,93] Studies of finereone have recruited patients with albuminuric CKD who also have diabetes.[90] These patients have different demographics to secondary care populations, being older, have different comorbidities and usually have non-proteinuric kidney disease.[94,95] In 2016, a feasibility trial of spironolactone treatment on arterial stiffness in early-stage CKD in UK primary care was terminated due to low recruitment.[96] It remains uncertain whether the steroidal MRA, spironolactone, offers the same treatment benefits as the non-steroidal MRA finerenone. To date, no large study of spironolactone use in primary care populations has been undertaken to evaluate the effect on mortality or renal and CVD outcomes.

Research objectives

The primary objective was to determine the effect of low-dose spironolactone on mortality and cardiovascular outcomes (onset or progression of CVD) in patients with stage 3b CKD.

Secondary objectives were to determine the effect of spironolactone in patients on measures of: cardiovascular haemodynamics; LV function; decline in renal function; treatment costs and benefits; and to determine the safety of spironolactone in patients with stage 3b CKD.

Chapter 2 Methods

The detailed methods for the BARACK-D trial have been previously published and are summarised here.[97] Some text in this chapter has been reproduced from the study protocol.[97] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The text below includes minor additions and formatting changes to the original text.

Trial design

Benefits of aldosterone receptor antagonism in chronic kidney disease was a prospective randomised open blinded endpoint (PROBE) trial where neither the patients, general practitioners (GPs), physicians nor statisticians are blinded to the trial treatment. However, the primary end points were assessed by an independent end-point committee who were blinded to the treatment arm. The end-point committee was recruited in early 2014 at the start of the trial and was made up of three independent members: Paul Aveyard, Professor of Behavioural Medicine, Bernard Prendergast, Consultant Cardiologist and Chris O'Callaghan, Professor of Medicine and Nephrologist. Chris O'Callaghan volunteered to act as independent chair of the end-point committee moving forward. All members agreed to the committee Terms of Reference for adjudicating. The document laid out the preferred mechanism for the committee to perform their function. Case information was distributed to members via secure e-mail. Two out of the three reviewers [selected at random by the Clinical Trial Unit (CTU) trial team] were sent information independently and assessed the end points remotely. Members adjudicated each end point without reference to others on a 'yes/no/maybe' basis. If there was discordance between the two reviews, the information was sent to a third reviewer for assessment. The outcome was based on the agreement of two out of three of the reviewers. Each reviewer returned the end point forms endorsed with their signature and the date.

Eligible patients, from a minimum of 120 collaborating primary care practices, recruited by six NIHR School for Primary Care Research departments, with previously recorded blood tests results suggesting CKD stage 3b were invited to take part in the study and randomised between (1) ARA spironolactone 25 mg once daily (OD) on top of standard care, and (2) standard care alone. BP in both groups was titrated (monitored and adjusted accordingly) by the physicians against National Institute for Health and Care Excellence (NICE) guideline standards and routine checks of electrolytes undertaken. Primary end point was the time to change in cardiovascular events (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, resuscitated sudden death), stroke, transient ischaemic attack (TIA), peripheral arterial disease (PAD) or heart failure, either new onset or hospitalisation for CVD, or death (regardless of cause). See *Appendix 1* for the trial flow chart.

An internal pilot was conducted which, in addition to testing study procedures and documentation, enabled us to test our assumptions regarding:

1. practice uptake of the invitation to participate
2. rates of eligible CKD patients in practice populations on existing disease registers
3. the response rates to patient invitations
4. the rates of consent at baseline visits.

These early recruitment data were used to determine whether any changes were needed to the overall recruitment strategy in the other centres, for example whether numbers of practice sites need to be supplemented.

Amendments to the protocol

Substantial amendments to the protocol since conception were approved by the funder, the sponsor, the Research Ethics Committee (REC), the Health Research Authority (HRA) and the Medicines and Healthcare products Regulatory

Agency (MHRA), and were significant for patient safety, as well as to help to increase recruitment and provide clarification to sites. They included the following:

- Removal of a gift voucher and addition of travel expenses at the request of the REC.
- Addition of 'Lay Title' at the request of the REC.
- To correct the trial phase within the synopsis and clarify the primary end point; to update the blood sample detail within the schedule; to update the home BP measurement section following further expert clinical input; to correct the Study Treatment Compliance monitoring detail; to update and clarify the statistics section; to update the concomitant medications schedule; to make minor changes throughout the protocol to correct typos and provide clarification.
- To report change of funder from NIHR School for Primary Care Research to NIHR HTA.
- To add two questionnaires to measure patients' overall quality of life (QoL), ICEpop CAPability measure for Adults (ICECAP-A) and QoL VAS, however these were subsequently removed.
- To alter the search strategy and eGFR inclusion criterion to improve patient identification; to introduce an additional screening visit to improve patient identification; improved patient invitation strategy; and to provide minor clarifications throughout the protocol given feedback from sites.
- To alter the inclusion criterion eGFR range to 30–50 ml/minute/1.73 m^2 to encompass larger than anticipated measurement error/fluctuations following initial recruitment; to change the sample size to reflect alteration to eGFR range; to update the causality assessment definitions in the Safety Reporting section; to make minor clarifications throughout.
- To add a patient-facing poster.
- To remove the planned secondary outcomes of BP variability and more intensive phenotyping (given the recruitment difficulties).
- To revise the statistical section to reflect extension of recruitment phase; to clarify long-term follow-up; to do minor clarifications throughout the protocol.
- To add GP and reminder letters.
- Addition of sites throughout England including addition of a Clinical Research Network (CRN), and addition of Northern Ireland and Wales.
- Change in principal investiogators (PIs) in in collaborating centres/practices.
- Clarification of process at Derby.
- Added PAD back into the list of composite vascular end points of the primary outcome.

There have been 24 amendments in all, some of which have been combined in the above list for ease of writing, that is changes in Principal Investigators (PI), addition of sites and addition of Northern Ireland and Wales.

Transparency statement from the trialists

The investigators applied a late amendment of the protocol (version 8) prior to study data lock and analysis to add PAD back into the synopsis and outcomes tables. PAD had been accidentally omitted in the tables in Protocol version 3 when the outcomes were amended to include independent adjudication of events and new onset events. PAD remained elsewhere in the protocol as documented below. This error was not detected until the adjudication panel met in late 2021. By correcting this earlier error in the synopsis table, the amendment regularised the trial documentation which correctly included PAD in the individual components of the combined primary end point in all other sections of the protocol, such as background, prior studies and the powering of the trial, plus being individually listed in the trial end-point form from the start, and the detailed statistical analysis plan (SAP). This late amendment therefore brings the protocol in line with the study as commissioned by the funders (NIHR HTA Programme). The sponsor is satisfied that at the point of this amendment the investigators remained blind to allocation and the numbers of primary end points by type.

Ethics and other approvals

Approvals for the study were received from the sponsor, Thames Valley REC Ref: 13/SC/0114 on 9 April 2013, and the MHRA, research and development and the HRA.

Sponsorship

The sponsor was The University of Oxford Clinical Trials and Research Governance, which later became known as Research Governance, Ethics and Assurance (RGEA).

Objectives

Primary objective

The primary objective was to determine the effect of aldosterone receptor antagonism on mortality and cardiovascular outcomes (onset or progression of CVD) in patients with stage 3b CKD.

A primary long-term objective of interest was to determine the effect of aldosterone receptor antagonism (even short-term use) on long-term mortality and cardiovascular outcomes in patients with stage 3b CKD.

Secondary objectives

The secondary objectives were as follows:

- To determine the effect of adding an aldosterone receptor antagonism in patients on the individual components of the composite primary outcome.
- To determine the effect of adding an aldosterone receptor antagonism in patients on measures of renal function.
- To determine the effect of adding an aldosterone receptor antagonism in patients on healthcare cost evaluation.
- To determine the effect of adding an aldosterone receptor antagonism in patients on safety.

See *Appendix 2* for a full summary of the study objectives and outcome measures.

Target population

Patients who had been diagnosed with CKD stage 3b (eGFR 30–44 ml/minute/1.73 m^2 but widened to 30–50 ml/minute/1.73 m^2 following initial recruitment to encompass larger than anticipated measurement error/fluctuations) based on their recent blood tests were identified by their GPs or physicians. Patients declining to participate were asked for consent to review their records for comparative data.

Inclusion criteria

Participants must have fulfilled either the *Search 1* or *Search 2* criteria specified below:

Search 1

- Evidence of stage 3b CKD using the MDRD equation. This included patients on the CKD register undergoing annual monitoring who had two or more recent blood samples in the 30–50 ml/minute/1.73 m^2 range in the preceding 24 months, with a minimum of 6 weeks between tests.
- Where only one test had been performed in the preceding 24 months and was in the 3b range, the patient was invited to attend the baseline at least 6 weeks from the initial test, and the eGFR result from this was taken as the second confirmatory test. Physicians were reminded that standard care suggests a second confirmatory test.

Search 2

- Patients with eGFR results in the preceding 24 months with a reading of 25–29 ml/minute/1.73 m^2.
- Participant was willing and able to give informed consent for participation in the study.
- Male or female, aged 18 years or above.
- Able (in the recruiting physician's opinion) and willing to comply with all study requirements.
- Willing to allow his or her GP and consultant, if appropriate, to be notified of participation in this study.

- Willing to provide contact details to the research team (encompassing recruitment centre and practice staff), for use at any time should the need arise, on trial related matters.
- If the participant was female of childbearing potential, they were willing to ensure effective contraception during the trial period.

Exclusion criteria

The participant was not able to enter the study if any of the following applied:

- Female participants who were pregnant, lactating or planning pregnancy during the study.
- Type 1 DM.
- Terminal disease or felt otherwise unsuitable by their physician.
- Chronic heart failure clinical diagnosis or known left ventricular systolic dysfunction (LVSD) with EF < 40%.
- Recent MI (within 6 months).
- Active cancer with less than 1 year life expectancy or in palliative care.
- Alcohol or drug abuse.
- Suspected or known current hazardous or harmful drinking, as defined by an alcohol intake of > 42 units every week.
- Suspected or known current substance misuse.
- Most recent potassium result > 55.5 mmol/L, where not thought to be spurious, or previous raised potassium needing a reduced dose of ACEI/ARB or intolerance to spironolactone.
- eGFR > 60 ml/minute/1.73 m^2 in the last 6 months and no identifiable reason for a temporary reduction in eGFR.
- Serum potassium at baseline over 5 mmol/L.
- Documented Addisonian crisis and/or on fludrocortisone.
- Documented symptomatic hypotension or baseline systolic BP under 100 mmHg.
- Recent acute kidney injury or admission for renal failure.
- ACR> 70 mg/mmol.
- Prescription of medications with known harmful interactions with spironolactone as documented in the British National Formulary including tacrolimus, lithium and cyclosporine.
- Any other significant disease or disorder which, in the opinion of the recruiting physician, may either put the participants at risk because of participation in the study, or may influence the results of the study, or the participant's ability to participate in the study.

Settings and locations

Six NIHR School for Primary Care Research departments recruited approximately 300 GP practices across England, Wales and Northern Ireland. Just over 200 of these practices recruited 1434 patients. All participating practices and regional PIs are named in the acknowledgements section below.

Recruitment procedure

Baseline assessments

Potentially eligible patients were invited to attend a baseline clinic at a trial practice where the trial was explained. Informed consent was obtained and baseline assessments were performed.

Following consent, all patients had the following information taken and investigations performed at the initial visit:

- Age.
- Gender.
- Self-assigned ethnicity.
- Residential postcode.

- Clinical history.
- Past medical history.
- Current medication.
- Smoking status.
- Physical examination.
- Weight.
- Height.
- Waist circumference (using validated method).
- Office blood pressure (OBP) measurement using a British and Irish Hypertension Society validated automated device after 5 minutes rest.
- Venepuncture for routine haematology and biochemistry including renal function [including eGFR calculated using MDRD and CKD-EPI formulae, hepatic and bone profiles, full blood count, fasting blood sugar, glycated haemoglobin (HbA1c), lipids, and, where local labs allow, B-type natriuretic peptide (BNP)]. Tests were performed by a suitably qualified member of the Research Team (e.g. GP or research/practice nurse).
- 12-lead electrocardiograph – where practice equipment availability allowed.
- QoL questionnaires [EuroQol-5 Dimensions, five-level version (EQ-5D-5L) and Kidney Disease Quality of Life – Short Form (KDQoL-SF) questionnaire].
- Issued diary card to monitor side effects of trial medication.
- Pregnancy tests were performed on women of childbearing potential, if deemed necessary, at the discretion of the physician.

Following the baseline visit, the same mechanisms were utilised as with all laboratory analyses returned to the GP practice/specialist renal group under routine care. Blood results (normally returned within one working day) were reviewed as soon as practically possible and no later than 72 hours after receipt, reports were signed by the recruiting physician, or delegate (e.g. the patient's own GP), and the results were recorded in the case report form including assessment of whether they were normal, abnormal but not clinically significant, or abnormal and clinically significant. In the latter case, the eligibility of the participants was reviewed. The patient's GP was contacted to confirm eligibility if the following applied:

- BP ≥ 180/110 mmHg.
- ACR ≥ 70 mg/mmol: referred to GP to consider referral to nephrology specialist if patients had not been reviewed by nephrologist in the past 5 years since the diagnosis.
- ACR = 30–69 mg/mmol and BP ≥ 140/90 mmHg and NOT on either ACEI or ARB: referred to GP to consider for ACE inhibitor/ARB. Patients were re-invited to participate in BARACK-D study after they had been on ACEI/ARB for at least 6 weeks.
- ACR = 30–69 mg/mmol with haematuria: referred to GP for review.
- Once eligibility was confirmed, the physician randomised the patient (by accessing Sortition, the online randomisation software described below, to obtain the randomisation code), arranged and issued the spironolactone prescription to patients randomised to the intervention group. An appointment was made for the patient to return for the next visit after taking spironolactone for 7 days for those in the intervention arm or 7 days following randomisation for those assigned to the routine care arm.

Subsequent assessments and follow-up

Subsequent assessments continued for both treatment arms for a further 36 months with follow-up visits at weeks 1, 2, 4, 12, 26, and then every 13 weeks until the end of their participation at 156 weeks. Windows either side of the visits were 2 days for V1 and V2, 4 days at V3 and V4, 7 days for V5 and 2 weeks thereafter (all calculated from date of randomisation). Patients were also flagged with ONS for long-term follow-up of mortality, with initial assessment at 5 years. Measurements at each follow-up visit varied according to the schedule but consisted of a combination of:

- OBP measurement, using a validated automated device.
- Venepuncture for creatinine and electrolyte levels.
- eGFR (MDRD and CKD-EPI estimations).
- Monitoring for side effects.

- Additional blood samples for fasting blood sugar and HbA1c, BNP (where local labs allowed), lipids, full blood count and samples for future analysis.
- QoL questionnaires.
- Issue of drug monitoring diary card.
- Urinalysis using ACR.
- Home BP measurement recorded on diary card.

Patients were also supplied with a validated home BP monitoring machine, along with an additional diary card and an instruction sheet, for 1 week every 6 months to document their self-assessed BPs. They were asked to take two readings twice daily, that is two each morning and two each evening over the week. The readings for the first 2 days were discarded and the mean of the remaining readings taken as the home BP level.

Physicians were strongly encouraged to manage BP according to NICE CKD guidelines[98] as follows: CKD and ACR < 70 mg/mmol: systolic BP target of < 140 mmHg (target range 120–139 mmHg) and diastolic BP target < 90 mmHg. Choice of antihypertensive agents: ACEIs/ARBs if not already prescribed were offered to people with hypertension and ACR ≥ 30 mg/mmol. The remainder (people with CKD and hypertension and ACR < 30 mg/mmol) were offered a choice of antihypertensive treatment according to the NICE guidance on hypertension (NICE clinical guideline CG127 or its update) to prevent or ameliorate progression of CKD.

Intervention

Spironolactone 25 mg OD was selected as the trial MRA, to be used in the 'standard care + spironolactone' arm, since it has a large evidence base for effective treatment in hypertension and heart failure. There are considerable data from these trials on the drug's renal safety in high-risk cardiovascular populations. Spironolactone is also the most cost-effective MRA being available as a generic prescription. The modest cost of the prescription to the National Health Service (NHS) was treated as an excess treatment cost but this was not anticipated as likely to cause local barriers to recruitment.

End-point measures

A full outline of the trial procedures and time points can be found in *Appendix 3*. These are summarised as follows:

Primary end point

The primary end point is the time from randomisation until the first occurring of: death, hospitalisation for heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, failed sudden death), stroke, heart failure, TIA, PAD, or first onset of any condition listed above not present at baseline. The primary end point was adjudicated by an independent end-points committee blinded to the treatment arm.

The primary long-term end point is the annual rates of death, hospitalisation for heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, resuscitated sudden death), stroke, TIA, PAD, or heart failure, or first onset of any condition listed above not present at baseline.

Secondary end points

- Change in BP annually and at final visit.
- Changes in BNP.
- Change in ACR.
- Change in eGFR.
- Difference in health status on EQ-ED-5L, KDQoL and NHS resource use.
- Rates of hypotension.
- Rates of adverse events (AEs).
- Rates of hyperkalaemia.

Sample size

The estimated cardiovascular (CV) event rate (defined by hospitalisation for coronary heart disease, heart failure, ischaemic stroke and PAD) and total mortality rate in patients with CKD 3b (eGFR 30–44 ml/minute/1.73 m^2) was 11.29 and 4.76 per 100 person-years, respectively, which gave a combined event rate of 16.05 per 100 person-years.[2] In those with eGFR in the range 45–50 ml/minute/1.73 m^2, the event rate was conservatively estimated to be 0.667 times as high (10.7 events per 100 person-years)[36] and assumed half the participants would fall in this range giving an overall event rate of 13.4 events per 100 person-years. To detect a 20% relative risk reduction in death or cardiovascular events within 3 years in the intervention group as compared with the control group [i.e. hazard ratio (HR) = 0.8] with an anticipated treatment withdrawal rate of 13% (which gives a diluted estimated treatment effect = 0.84) and a two-sided significance of 0.05, 1511 participants per group (3022 in total) were required at 80% power and assuming 10% attrition rate.

We decided to power the trial conservatively on a 20% risk reduction since this proposed treatment effect is around half the risk reduction observed in the ARA mild heart failure trial (EMPHASIS). The estimated HR in the EMPHASIS eplerenone versus placebo mild heart failure trial (only mildly symptomatic patients were included) was 0.63 [95% confidence interval (CI) 0.54 to 0.74; $p < 0.001$] for the composite end point of death from CV causes or hospitalisation for heart failure at the median follow-up of 21 months. The conservative upper CI for the treatment effect was 26% reduction. The placebo CV event rate in the EMPHASIS trial was similar to observational data on CV events in CKD 3b patients.[2]

Randomisation and blinding in the analysis stage

Randomisation was carried out using Sortition, a validated randomisation system within the University of Oxford's Primary Care Clinical Trial Unit (PCCTU), with block randomisation with randomly varying block size. Randomisation was stratified by practice, ensuring a balance of the two arms within each practice. Patients were randomised to either treatment with spironolactone 25 mg OD prescribed on top of routine care, or to continue with routine care alone.

Benefits of aldosterone receptor antagonism in chronic kidney disease was a PROBE trial where neither the patients, GPs or physicians were blinded to treatment, but the primary end points were assessed by an independent end-point committee who were blinded to the treatment arm. The statisticians were blinded to treatment allocation when carrying out the statistical analysis.

Data cleaning

The CTU data management team carried out day-to-day cleaning of the data. In addition, statistical data checking by means of distribution analysis and range estimates to ensure values and dates were valid were also performed by the statisticians. Data points identified as out of range were flagged and these were sent to the Data Manager to be checked. These were performed before the final data lock.

Definition of population for analysis

The primary analysis was carried out on all eligible randomised participants, assuming non-informative censoring for those that withdrew or were lost to follow-up. Based on the intention-to-treat (ITT) principle, participants who withdrew from treatment (e.g. for safety reasons) but consented to continue follow-up were still included in the analysis population. Participants who withdrew or were lost to follow-up were censored at the date of withdrawal or date of last follow-up respectively. All participants were analysed in the groups to which they were allocated, regardless of treatment compliance.

The safety population included all participants who took at least one tablet of the study medication. However, those participants that had taken at least one tablet of study medication prior to being found to be ineligible following randomisation are not included in the safety analysis.

Deviation from statistical analysis plan

The analysis followed the strategies in the SAP as closely as possible, and all deviations from the SAP are described and justified below.

One participant who died during the study period did not have a date of death recorded on the end-point form. Attempts to obtain this information were made and a note was received from the site that said the patient had died and the grace period to access their records had passed meaning it was no longer possible to obtain a date of death. In the analysis for this participant the date of final visit was used as their date of death, instead of censoring them.

It was pre-specified in the SAP that all models in the primary and secondary analyses would be adjusted for GP practice as a random effect. Participants were randomised from 214 GP practices across the UK, all the practices recruited a small number of participants and several only recruited one or two participants to the trial. Due to the large number of practices, many of the statistical models could not run with the adjustment for GP practice as a random effect. It was therefore decided to not adjust any of the analyses for GP practice, and due to the large number of recruiting GP practices, this information is also not presented in the baseline characteristics table.

It was originally planned in the SAP that the primary analysis would be conducted using a mixed-effect Cox-proportional hazards model adjusting for randomised treatment allocation as a fixed effect, and GP practice as a random effect. As described above, it was decided not to adjust for GP practice, as such the primary analysis was conducted using a Cox-proportional hazards model adjusted for randomised treatment allocation as a covariate only.

It was planned that the change in natriuretic peptide (NP) outcome would be analysed as part of the secondary outcomes, as specified in both the protocol and version 1.0 of the SAP. However, this outcome was accidentally removed from the SAP when it was updated to version 2.0. NP outcomes were therefore analysed as detailed in version 1.0 of the SAP.

It is stated in the SAP that the analysis of the secondary outcomes would include the outcome at all measured assessment time points to aid with the estimation of the treatment effects in the presence of missing data. NP was meant to be measured at all assessment time points, but participants did not have their BNP measurements at week 1 (visit 1), week 2 (visit 2), week 4 (visit 3) or week 65 (visit 8) follow-up; only one participant had a BNP measurement at week 12 (visit 4), week 91 (visit 10) and week 130 (visit 13); only two participants had a BNP measurement at week 78 (visit 9), week 117 (visit 12) and week 143 (visit 14) follow-up; and only three participants had a BNP measurement at week 39 (visit 6). As such, the analysis for BNP excludes these assessment time points and only the data from month 6 (visit 5), year 1 (visit 7), year 2 (visit 11) and year 3 (visit 15) follow-up are included as outcome measures.

The SAP specified that the secondary analysis for ACR at 3 years follow-up would be conducted using a linear mixed-effects model adjusted for randomised treatment allocation, baseline ACR, assessment time point, baseline factors that predict missingness of ACR at 3 years, and an interaction between randomised treatment allocation and time point as fixed effects, and GP practice as a random effect. As described above, GP practice was not included as a random effect, as such ACR at 3 years was analysed using a linear regression model adjusting for the fixed effects covariates only.

It is stated in the SAP that the safety population will include all participants who took at least one tablet of the study medication. Although this was the case, it was pre-specified in the SAP that the question 'Please confirm you are taking the spironolactone as prescribed' on the diary card records at the first post-randomisation visit *was to be used* to determine if a participant had taken at least one tablet of the study medication. If the participant had indicated that they were not taking the medication on the diary card records, the study discontinuation form *was to be used* to determine whether they took at least one dose. However, it was not possible to determine from the discontinuation form if the participant had taken at least one dose of the study medication, as this information was not collected on the discontinuation form. Instead, participants were included in the safety population if they had answered 'yes' to the above question at any of the follow-up assessments during the study, as opposed to the information being obtained from the discontinuation form.

The SAP stated that summary statistics and descriptions of AEs that led to withdrawals would be presented. However, the AE reporting form did not collect data on the event leading to withdrawal from the study, or which event was responsible for the withdrawal (in cases of withdrawal due to safety concerns). As such, these data have not been reported. These analyses were carried out before the unblinding of results to the trial management team.

Statistical methods

Primary analysis

The primary objective was to determine the effect of low-dose spironolactone on mortality and cardiovascular outcomes (onset or progression of CVD) in patients with stage 3b CKD. This was assessed by the primary end point of time from randomisation until the first occurring of death or hospitalisation for heart disease (arrhythmia, atrial fibrillation, sudden death, resuscitated sudden death), stroke, TIA, PAD or heart failure, or first onset of any condition listed above not present at baseline. The primary end point was adjudicated by an independent end-points committee that was blinded to treatment arm.

The events of interest to the primary end point were hospitalisation for heart disease, onset of CVD, and all-cause mortality. The primary end point was computed using the date of the earliest event minus the date of randomisation. The participants who did not experience an event were censored at the date of last follow-up or at the date of withdrawal from the study (whichever is later). The primary analysis population was based on the ITT principle, that is according to the groups that they were randomly allocated to, regardless of deviation from protocol. Participants who withdrew from treatment but consented to further follow-up were censored at the date of last follow-up rather than the date of withdrawal from treatment.

The time to first occurrence of a primary end-point event was analysed by a Cox-proportional hazards model adjusted for randomised treatment allocation. The HRs between the randomised groups with a 95% CI and the associated *p*-value were obtained from the model.

Chapter 3 Results

Representativeness of study sample and patient throughput

A Consolidated Standards of Reporting Trials flow diagram of the participants throughout the study period at the time points relevant to the statistical analysis can be found in *Figure 1*.

One thousand nine hundred and eighty-five people who responded to an invite from their GP surgery to participate in the study were screened and assessed for eligibility of whom 551 (27.8%) were excluded from the trial due to not meeting the inclusion criteria. A total of 1434 participants were recruited and randomised: 710 (49.5%) were allocated to spironolactone (25 mg OD) + standard care and 724 (50.5%) were allocated to standard care only. Of those who were allocated to the treatment arm, 95% (677/710) received the allocated treatment. It was found that 62 participants were ineligible after randomisation and were subsequently excluded from the analysis. All randomised and eligible participants were included in the primary analysis population.

Recruitment

The first participant was recruited on 6 December 2013 and the final participant was recruited on 31 August 2018. A total of 1434 people were recruited and randomised to the trial. The trial failed to recruit to the planned target of 3022, mainly due to fewer eligible patients on practice lists than expected, poor patient response rates to the invitations to participate, and difficulties in engaging the additional practices therefore needed to participate in the trial. On the advice of the Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC), the trial continued to its planned end point aiming to collect as much evidence as possible.

The trial was not stopped early. Follow-up continued until all active participants reached the end of follow-up as per protocol.

Baseline characteristics of participants

Table 1 provides the baseline characteristics of the eligible participants included in the analysis by randomised group, as well as overall.

Numbers analysed

The frequency and percentage of the number of participants completing follow-up assessments, withdrawing and lost to follow-up are presented in *Table 2* by randomised arm and overall. Six hundred and seventy-seven and 695 eligible participants randomised to the treatment and standard care arms, respectively, were included in the primary outcome analysis. Safety analysis included all participants who had actually received the treatment (n = 677) versus the total in standard care (n = 757) with the addition of 33 subjects allocated to spironolactone who did not take any medication. The number and percentage of the availability of the primary and secondary end-point data are presented in *Table 3* by randomised arm and overall. Missing baseline data were imputed using mean imputation if the proportion of missing data was small (< 10%), and multiple imputation using predictive mean matching was used if there were substantial missing data at baseline. A comparison between the two randomised arms is presented in *Table 4* with those who completed follow-up and those who withdrew, discontinued or were lost to follow-up during the trial. A breakdown of the participants who completed follow-up and those who were withdrawn, discontinued or were lost to follow-up is presented in *Table 5*. Results are presented in relation to randomised arm and baseline covariates, as well as a test of statistical significance for association between baseline characteristics association and withdrawal from the study. Individual logistic regression analyses were performed for each baseline covariate to obtain the p-value for the

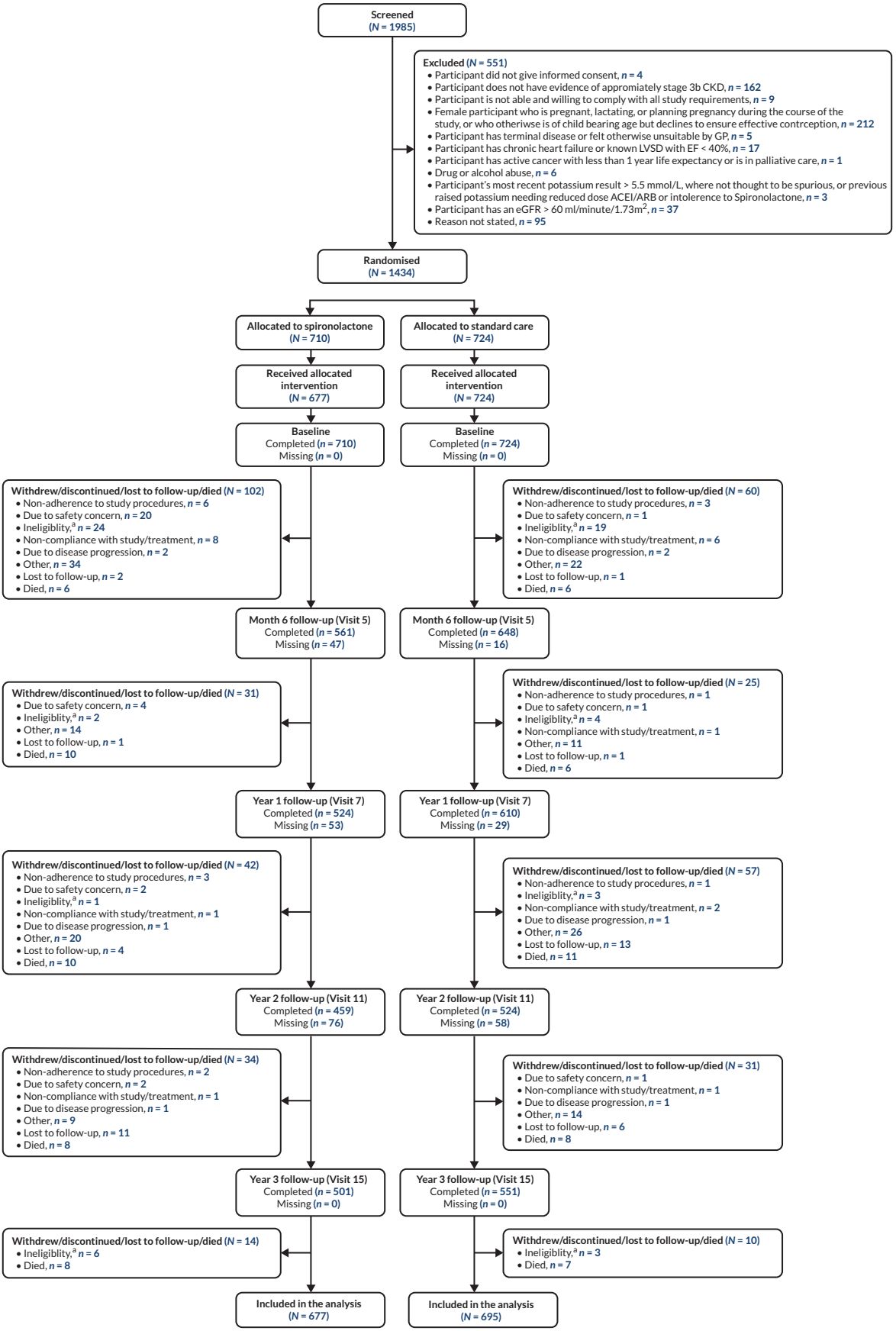


FIGURE 1 Consolidated Standards of Reporting Trials flow diagram. a, Participants found to be ineligible after randomisation, excluded from the analysis population. LVSD, left ventricular systolic dysfunction.

TABLE 1 Baseline characteristics

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	Overall (*N* = 1372)
Age (years), mean (SD) (*N*)	75.1 (8.0) (676)	74.5 (8.3) (695)	74.8 (8.12) (1371)
Age groups (EudraCT guidelines), n/N (%)			
18–64 years	55/676 (8.1)	64/695 (9.2)	119/1371 (8.7)
65–84 years	567/676 (83.9)	584/695 (84.0)	1151/1371 (84.0)
85 years and older	54/676 (8.0)	47/695 (6.8)	101/1371 (7.4)
Additional age groups, n/N (%)			
18–54 years	9/676 (1.3)	18/695 (2.6)	27/1371 (2.0)
55–64 years	46/676 (6.8)	46/695 (6.6)	92/1371 (6.7)
65–74 years	264/676 (39.1)	267/695 (38.4)	531/1371 (38.7)
75–84 years	303/676 (44.8)	317/695 (45.6)	620/1371 (45.2)
85 years and older	54/676 (8.0)	47/695 (6.8)	101/1371 (7.4)
Sex, n/N (%)			
Male	306/676 (45.3)	318/695 (45.8)	624/1371 (45.5)
Female	370/676 (54.7)	377/695 (54.2)	747/1371 (54.5)
Ethnicity, n/N (%)			
White	652/673 (96.9)	668/693 (96.4)	1320/1366 (96.6)
Mixed/multiple ethnic groups	2/673 (0.3)	4/693 (0.6)	6/1366 (0.4)
Asian/Asian British	8/673 (1.2)	8/693 (1.2)	16/1366 (1.2)
Black/African/Caribbean/Black British	8/673 (1.2)	11/693 (1.6)	19/1366 (1.4)
Other ethnic group	3/673 (0.4)	2/693 (0.3)	5/1366 (0.4)
Past medical history, n/N (%)			
Hypertension	508/676 (75.1)	544/695 (78.3)	1052/1371 (76.7)
Diabetes	165/676 (24.4)	168/695 (24.2)	333/1371 (24.3)
Impaired fasting glucose and/or glucose tolerance[a]	47/509 (9.2)	57/524 (10.9)	104/1033 (10.1)
Ischaemic heart disease	121/676 (17.9)	118/694 (17.0)	239/1370 (17.4)
Heart failure	14/676 (2.1)	17/694 (2.4)	31/1370 (2.3)
Atrial fibrillation	77/676 (11.4)	90/694 (13.0)	167/1370 (12.2)
Cerebrovascular disease	60/676 (8.9)	77/694 (11.1)	137/1370 (10.0)
Peripheral vascular disease	27/674 (4.0)	30/694 (4.3)	57/1368 (4.2)
Renal disease	103/675 (15.3)	115/694 (16.6)	218/1369 (15.9)
Childhood urinary tract infection	12/669 (1.8)	22/693 (3.2)	34/1362 (2.5)
Adulthood urinary tract infection	211/673 (31.4)	223/694 (32.1)	434/1367 (31.7)
Thyroid disease	105/675 (15.6)	110/693 (15.9)	215/1368 (15.7)
Anaemia	104/674 (15.4)	96/695 (13.8)	200/1369 (14.6)

continued

TABLE 1 Baseline characteristics (*continued*)

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	Overall (*N* = 1372)
Osteopenia	27/673 (4.0)	31/693 (4.5)	58/1366 (4.2)
Osteoporosis	45/671 (6.7)	41/693 (5.9)	86/1364 (6.3)
Indices of multiple deprivation (IMD) quintile, n/N (%)			
1 (Most deprived)	68/664 (10.2)	74/683 (10.8)	142/1347 (10.5)
2	95/664 (14.3)	95/683 (13.9)	190/1347 (14.1)
3	122/664 (18.4)	148/683 (21.7)	270/1347 (20.0)
4	189/664 (28.5)	178/683 (26.1)	367/1347 (27.2)
5 (Least deprived)	190/664 (28.6)	188/683 (27.5)	378/1347 (28.1)
Current medication, n/N (%)			
Beta-blockers	181/677 (26.7)	181/695 (26.0)	362/1372 (26.4)
ACEIs	272/677 (40.2)	277/695 (39.9)	549/1372 (40.0)
ARBs	248/677 (36.6)	254/695 (36.5)	502/1372 (36.6)
Statins	409/677 (60.4)	418/695 (60.1)	827/1372 (60.3)
Antihypertensives	484/677 (71.5)	523/695 (75.3)	1007/1372 (73.4)
Smoking status, n/N (%)			
Never smoker	305/674 (45.3)	337/693 (48.6)	642/1367 (47.0)
Current smoker	25/674 (3.7)	32/693 (4.6)	57/1367 (4.2)
Former smoker	344/674 (51.0)	324/693 (46.8)	668/1367 (48.9)
Weight (kg), mean (SD) (*n*)	82.0 (15.6) (675)	81.6 (16.2) (695)	81.8 (15.9) (1370)
Height (cm), mean (SD) (*n*)	165.8 (9.6) (676)	166.2 (9.7) (695)	166.0 (9.6) (1371)
Waist circumference (cm), mean (SD) (*n*)	100.7 (13.0) [673]	100.5 (13.2) (687)	100.6 (13.1) (1360)
Hip circumference (cm), mean (SD) (*n*)	109.3 (11.3) (672)	108.8 (11.8) (686)	109.0 (11.6) (1358)
OBP measurement (mmHg), mean (SD) (n)			
Systolic BP left arm	138.2 (18.2) (669)	136.8 (18.0) (689)	137.5 (18.1) (1358)
Systolic BP right arm	139.0 (18.2) (673)	137.8 (18.4) (693)	138.4 (18.3) (1366)
Diastolic BP left arm	77.4 (11.1) (669)	76.1 (11.3) (689)	76.7 (11.2) (1358)
Diastolic BP right arm	77.3 (10.8) (673)	76.3 (11.4) (693)	76.8 (11.1) (1366)
Laboratory and ECG test results			
Renal profile, n/N (%)			
Normal	79/673 (11.7)	77/693 (11.1)	156/1366 (11.4)
Abnormal (not clinically significant)	531/673 (78.9)	537/693 (77.5)	1068/1366 (78.2)
Abnormal (clinically significant)	63/673 (9.4)	79/693 (11.4)	142/1366 (10.4)
Liver function tests, n/N (%)			
Normal	568/674 (84.3)	563/695 (81.0)	1131/1369 (82.6)
Abnormal (not clinically significant)	100/674 (14.8)	131/695 (18.8)	231/1369 (16.9)
Abnormal (clinically significant)	6/674 (0.9)	1/695 (0.1)	7/1369 (0.5)

TABLE 1 Baseline characteristics (*continued*)

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	Overall (*N* = 1372)
Bone profile, n/N (%)			
Normal	595/668 (89.1)	589/688 (85.6)	1184/1356 (87.3)
Abnormal (not clinically significant)	70/668 (10.5)	98/688 (14.2)	168/1356 (12.4)
Abnormal (clinically significant)	3/668 (0.4)	1/688 (0.1)	4/1356 (0.3)
Lipids, n/N (%)			
Normal	458/669 (68.5)	459/683 (67.2)	917/1352 (67.8)
Abnormal (not clinically significant)	194/669 (29.0)	208/683 (30.5)	402/1352 (29.7)
Abnormal (clinically significant)	17/669 (2.5)	16/683 (2.3)	33/1352 (2.4)
Full blood count, n/N (%)			
Normal	385/672 (57.3)	383/688 (55.7)	768/1360 (56.5)
Abnormal (not clinically significant)	271/672 (40.3)	289/688 (42.0)	560/1360 (41.2)
Abnormal (clinically significant)	16/672 (2.4)	16/688 (2.3)	32/1360 (2.4)
HbA1c, n/N (%)			
Normal	456/665 (68.6)	501/688 (72.8)	957/1353 (70.7)
Abnormal (not clinically significant)	171/665 (25.7)	149/688 (21.7)	320/1353 (23.7)
Abnormal (clinically significant)	38/665 (5.7)	38/688 (5.5)	76/1353 (5.6)
Fasting blood sugar, n/N (%)			
Normal	479/622 (77.0)	513/643 (79.8)	992/1265 (78.4)
Abnormal (not clinically significant)	116/622 (18.6)	113/643 (17.6)	229/1265 (18.1)
Abnormal (clinically significant)	27/622 (4.3)	17/643 (2.6)	44/1265 (3.5)
BNP, n/N (%)			
Normal	439/598 (73.4)	460/608 (75.7)	899/1206 (74.5)
Abnormal (not clinically significant)	119/598 (19.9)	111/608 (18.3)	230/1206 (19.1)
Abnormal (clinically significant)	40/598 (6.7)	37/608 (6.1)	77/1206 (6.4)
ECG, n/N (%)			
Normal	431/618 (69.7)	458/622 (73.6)	889/1240 (71.7)
Abnormal (not clinically significant)	161/618 (26.1)	139/622 (22.3)	300/1240 (24.2)
Abnormal (clinically significant)	26/618 (4.2)	25/622 (4.0)	51/1240 (4.1)
ACR (mg/mmol), median (IQR) (*n*)	1.5 (0.7–4.4) (633)	1.5 (0.6–4.2) (637)	1.5 (0.6–4.3) (1270)
eGFR (ml/minute/1.73 m^2), mean (SD) (*n*)	43.9 (6.9) (676)	43.1 (6.8) (695)	43.5 (6.9) (1371)
Potassium (mmol/L), mean (SD) (*n*)	4.4 (0.4) (677)	4.5 (0.4) (695)	4.5 (0.4) (1372)
Creatinine (µmol/L), mean (SD) (*n*)	122.8 (23.3) (677)	125.2 (25.0) (695)	124.0 (24.2) (1372)

ECG, electrocardiogram; EudraCT, European Union Drug Regulating Authorities Clinical Trials; IQR, interquartile range; SD, standard deviation.
a Only includes those without diabetes.

Note
Percentages have been computed with the number of participants with the response available as the denominator.

TABLE 2 Completion of follow-up assessments, withdrawals and loss to follow-up

	Spironolactone	Standard care	Overall
Screened	–	–	1985
Excluded (not randomised)	–	–	551
Randomised	710	724	1434
Study visit available, n/N (%)			
Baseline	710/710 (100.0)	724/724 (100.0)	1434/1434 (100.0)
Visit 1 – Week 1 follow-up	675/682 (99.0)	698/706 (98.9)	1373/1388 (98.9)
Visit 2 – Week 2 follow-up	655/672 (97.5)	688/702 (98.0)	1343/1374 (97.7)
Visit 3 – Week 4 follow-up	645/662 (97.4)	689/694 (99.3)	1334/1356 (98.4)
Visit 4 – Week 12 follow-up	606/636 (95.3)	679/685 (99.1)	1285/1321 (97.3)
Visit 5 – Month 6 follow-up	561/608 (92.3)	648/664 (97.6)	1209/1272 (95.0)
Visit 6 – Week 39 follow-up	538/592 (90.9)	620/651 (95.2)	1158/1243 (93.2)
Visit 7 – Year 1 follow-up	524/577 (90.8)	610/639 (95.5)	1134/1216 (93.3)
Visit 8 – Week 65 follow-up	498/564 (88.3)	582/623 (93.4)	1080/1187 (91.0)
Visit 9 – Week 78 follow-up	488/555 (87.9)	561/604 (92.9)	1049/1159 (90.5)
Visit 10 – Week 91 follow-up	459/542 (84.7)	530/590 (89.8)	989/1132 (87.4)
Visit 11 – Year 2 follow-up	459/535 (85.8)	524/582 (90.0)	983/1117 (88.0)
Visit 12 – Week 117 follow-up	442/528 (83.7)	513/579 (88.6)	955/1107 (86.3)
Visit 13 – Week 130 follow-up	429/515 (83.3)	500/570 (87.7)	929/1085 (85.6)
Visit 14 – Week 143 follow-up	414/505 (82.0)	486/561 (86.6)	900/1066 (84.4)
Visit 15 – Year 3 follow-up	501/501 (100.0)	551/551 (100.0)	1052/1052 (100.0)
Withdrew/discontinued/lost to follow-up after randomisation/died, n/N (%)			
Non-adherence to study procedures	11/215 (5.1)	5/176 (2.8)	16/391 (4.1)
Due to safety concerns	28/215 (13.0)	3/176 (1.7)	31/391 (7.9)
Ineligibility found after randomisation[a]	33/215 (15.3)	29/176 (16.5)	62/391 (15.9)
Non-compliance with study/treatment	10/215 (4.7)	10/176 (5.7)	20/391 (5.1)
Due to disease progression	4/215 (1.9)	4/176 (2.3)	8/391 (2.0)
Other reason	77/215 (35.8)	73/176 (41.5)	150/391 (38.4)
Lost to follow-up	18/215 (8.4)	21/176 (11.9)	39/391 (10.0)
Died[b]	34/215 (15.8)	31/176 (17.6)	65/391 (16.6)
End-point form available, *n/N* (%)	123/710 (17.3)	122/724 (16.9)	245/1434 (17.1)
Included in analysis population, *n/N* (%)[c]	677/710 (95.4)	695/724 (96.0)	1372/1434 (95.7)
Safety analysis population, *n*[d]	677	757	1434

a Excluded from analysis population.
b Not including participants who died after their 3-year follow-up visit.
c Numbers of participants randomised minus those found to be ineligible after randomisation.
d Numbers of participants randomised who took at least one dose of allocated treatment vs. those not receiving any medication (including 33 subjects allocated to intervention who did not take any medication).

TABLE 2 Completion of follow-up assessments, withdrawals and loss to follow-up (*continued*)

Notes
Percentages for the study visit available have been computed with the number of participants remaining in the study at each time point, and the percentages for the withdrew/discontinued/lost to follow-up/died has been computed with the number of participants that either withdrew, discontinued, were lost to follow-up or died after randomisation. This does not include participants who discontinued treatment but agreed to continue in the trial follow-up.
The end-point form was only available for participants who experienced a hospitalisation, CV event or death during the study. The number of participants with an end-point form available was more than the number of participants experiencing the primary end point due to several participants' events being clinically judged as not being a primary end point. All randomised participants except those who were found to be ineligible after randomisation and withdrawn from the study are included in the analysis population. Participants that did not have an end-point form available are included in the analysis population and are treated as not experiencing the primary end point.

TABLE 3 Availability of outcome data at each time point

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	Overall (*N* = 1372)
Primary end point			
Primary end point, *n*/*N* (%)	677 (100.0)	695 (100.0)	1372 (100.0)
Primary end-point components, n/N (%)			
Hospitalisation	677 (100.0)	695 (100.0)	1372 (100.0)
CVD	677 (100.0)	695 (100.0)	1372 (100.0)
Death	677 (100.0)	695 (100.0)	1372 (100.0)
Secondary end points			
Office measurements of systolic BP, n/N (%)			
Baseline[a]	676 (99.9)	695 (100.0)	1371 (99.9)
6 months	553 (81.7)	636 (91.5)	1189 (86.7)
1 year	518 (76.5)	603 (86.8)	1121 (81.7)
2 years	434 (64.1)	494 (71.1)	928 (67.6)
3 years	460 (67.9)	515 (74.1)	975 (71.1)
Rate of hypotension, *n*/*N* (%)	658 (97.2)	686 (98.7)	1344 (98.0)
NP (BNP)			
Baseline[a]	536 (79.2)	553 (79.6)	1089 (79.4)
6 months	451 (66.6)	512 (73.7)	963 (70.2)
1 year	425 (62.8)	475 (68.3)	900 (65.6)
2 years	352 (52.0)	396 (57.0)	748 (54.5)
3 years	363 (53.6)	413 (59.4)	776 (56.6)
ACR, n/N (%)			
Baseline[a]	633 (93.5)	637 (91.7)	1270 (92.6)
3 years	361 (53.3)	403 (58.0)	764 (55.7)
eGFR, n/N (%)			
Baseline[a]	676 (99.9)	695 (100.0)	1371 (99.9)
6 months	550 (81.2)	635 (91.4)	1185 (86.4)

continued

TABLE 3 Availability of outcome data at each time point (*continued*)

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	Overall (*N* = 1372)
1 year	515 (76.1)	599 (86.2)	1114 (81.2)
2 years	425 (62.8)	484 (69.6)	909 (66.3)
3 years	462 (68.2)	518 (74.5)	980 (71.4)
Safety end point			
Hyperkalaemia, *n*/*N* (%)	677 (100.0)	695 (100.0)	1372 (100.0)

a Numbers differ from baseline table as the numbers presented in this table are based on the raw data. Missing baseline data have been imputed for the baseline table.

TABLE 4 Association between randomised arm and withdrawing, discontinuing or being lost to follow-up

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	Odds ratio (95% CI)[a]	*p*-value[b]
Completion of follow-up, n/N (%)			1.37 (1.07 to 1.76)	0.013
Completed	495/677 (73.1)	548/695 (78.8)		
Withdrawn	182/677 (26.9)	147/695 (21.2)		

a Spironolactone vs. standard care. Logistic regression of the availability of the completion of follow-up modelled against randomised intervention arm.
b Level of significance = 0.05.

TABLE 5 Baseline covariates of those participants who were withdrawn, discontinued or were lost to follow-up, and the probability of each covariate predicting withdrawal

	Predicting withdrawal from the study (*p*-value)[a]	Spironolactone (*N* = 677)		Standard care (*N* = 695)	
		Completed (*N* = 495)	Withdrawn (*N* = 182)	Completed (*N* = 548)	Withdrawn (*N* = 147)
Age (years), mean (SD) (*N*)	0.001	74.5 (7.8) (495)	76.8 (8.2) (181)	74.3 (7.8) (548)	75.3 (9.8) (147)
Age groups (EudraCT guidelines), n/N (%)	< 0.001				
18–64 years		39/495 (7.9)	16/181 (8.8)	50/548 (9.1)	14/147 (9.5)
65–84 years		426/495 (86.1)	141/181 (77.9)	470/548 (85.8)	114/147 (77.6)
85 years and older		30/495 (6.1)	24/181 (13.3)	28/548 (5.1)	19/147 (12.9)
Additional age groups, n/N (%)	< 0.001				
18–54 years		7/495 (1.4)	2/181 (1.1)	13/548 (2.4)	5/147 (3.4)
55–64 years		32/495 (6.5)	14/181 (7.7)	37/548 (6.8)	9/147 (6.1)
65–74 years		207/495 (41.8)	57/181 (31.5)	211/548 (38.5)	56/147 (38.1)

TABLE 5 Baseline covariates of those participants who were withdrawn, discontinued or were lost to follow-up, and the probability of each covariate predicting withdrawal (*continued*)

	Predicting withdrawal from the study (*p*-value)[a]	Spironolactone (*N* = 677)		Standard care (*N* = 695)	
		Completed (*N* = 495)	Withdrawn (*N* = 182)	Completed (*N* = 548)	Withdrawn (*N* = 147)
75–84 years		219/495 (44.2)	84/181 (46.4)	259/548 (47.3)	58/147 (39.5)
85 years and older		30/495 (6.1)	24/181 (13.3)	28/548 (5.1)	19/147 (12.9)
Sex, n/N (%)	0.394				
Male		223/495 (45.1)	83/181 (45.9)	245/548 (44.7)	73/147 (49.7)
Female		272/495 (54.9)	98/181 (54.1)	303/548 (55.3)	74/147 (50.3)
Ethnicity, n/N (%)	0.125				
White		485/495 (98.0)	167/178 (93.8)	531/546 (97.3)	137/147 (93.2)
Mixed/multiple ethnic groups		2/495 (0.4)	0/178 (0.0)	1/546 (0.2)	3/147 (2.0)
Asian/Asian British		5/495 (1.0)	3/178 (1.7)	5/546 (0.9)	3/147 (2.0)
Black/African/Caribbean/ Black British		3/495 (0.6)	5/178 (2.8)	9/546 (1.6)	2/147 (1.4)
Other ethnic group		0/495 (0.0)	3/178 (1.7)	0/546 (0.0)	2/147 (1.4)
Indices of multiple deprivation (IMD) quintile, n/N (%)	0.002				
1 (Most deprived)		41/487 (8.4)	27/177 (15.3)	57/537 (10.6)	17/146 (11.6)
2		68/487 (14.0)	27/177 (15.3)	73/537 (13.6)	22/146 (15.1)
3		100/487 (20.5)	22/177 (12.4)	121/537 (22.5)	27/146 (18.5)
4		127/487 (26.1)	62/177 (35.0)	135/537 (25.1)	43/146 (29.5)
5 (Least deprived)		151/487 (31.0)	39/177 (22.0)	151/537 (28.1)	37/146 (25.3)
Past medical history, n/N (%)					
Hypertension	0.091	363/495 (73.3)	145/181 (80.1)	426/548 (77.7)	118/147 (80.3)
Diabetes	0.523	119/495 (24.0)	46/181 (25.4)	130/548 (23.7)	38/147 (25.9)
Impaired fasting glucose and/or glucose tolerance	0.216	37/375 (9.9)	10/134 (7.5)	48/419 (11.5)	9/105 (8.6)
Ischaemic heart disease	0.014	86/495 (17.4)	35/181 (19.3)	81/547 (14.8)	37/147 (25.2)
Heart failure	0.133	10/495 (2.0)	4/181 (2.2)	10/547 (1.8)	7/147 (4.8)
Atrial fibrillation	0.053	53/495 (10.7)	24/181 (13.3)	64/547 (11.7)	26/147 (17.7)
Cerebrovascular disease	0.051	40/495 (8.1)	20/181 (11.0)	55/548 (10.0)	22/146 (15.1)
Peripheral vascular disease	0.088	18/495 (3.6)	9/179 (5.0)	20/547 (3.7)	10/147 (6.8)
Renal disease	0.306	78/495 (15.8)	25/180 (13.9)	94/548 (17.2)	21/146 (14.4)

continued

TABLE 5 Baseline covariates of those participants who were withdrawn, discontinued or were lost to follow-up, and the probability of each covariate predicting withdrawal (*continued*)

	Predicting withdrawal from the study (*p*-value)[a]	Spironolactone (*N* = 677)		Standard care (*N* = 695)	
		Completed (*N* = 495)	Withdrawn (*N* = 182)	Completed (*N* = 548)	Withdrawn (*N* = 147)
Childhood urinary tract infection	0.402	9/493 (1.8)	3/176 (1.7)	19/546 (3.5)	3/147 (2.0)
Adulthood urinary tract infection	0.946	158/494 (32.0)	53/179 (29.6)	172/547 (31.4)	51/147 (34.7)
Thyroid disease	0.343	75/494 (15.2)	30/181 (16.6)	83/546 (15.2)	27/147 (18.4)
Anaemia	0.563	77/494 (15.6)	27/180 (15.0)	72/548 (13.1)	24/147 (16.3)
Osteopenia	0.960	19/494 (3.8)	8/179 (4.5)	25/546 (4.6)	6/147 (4.1)
Osteoporosis	0.512	33/493 (6.7)	12/178 (6.7)	30/546 (5.5)	11/147 (7.5)
Current medication, n/N (%)					
Beta-blockers	0.187	130/495 (26.3)	51/182 (28.0)	136/548 (24.8)	45/147 (30.6)
ACEIs	0.228	193/495 (39.0)	79/182 (43.4)	215/548 (39.2)	62/147 (42.2)
ARBs	0.731	176/495 (35.6)	72/182 (39.6)	203/548 (37.0)	51/147 (34.7)
Statins	0.827	304/495 (61.4)	105/182 (57.7)	323/548 (58.9)	95/147 (64.6)
Antihypertensives	0.132	351/495 (70.9)	133/182 (73.1)	404/548 (73.7)	119/147 (81.0)
Smoking status, n/N (%)	0.532				
Never smoker		221/493 (44.8)	84/181 (46.4)	272/548 (49.6)	65/145 (44.8)
Current smoker		16/493 (3.2)	9/181 (5.0)	24/548 (4.4)	8/145 (5.5)
Former smoker		256/493 (51.9)	88/181 (48.6)	252/548 (46.0)	72/145 (49.7)
Weight (kg), mean (SD) (*n*)	0.854	82.7 (15.4) (494)	80.1 (15.9) (181)	80.9 (15.4) (548)	84.1 (18.6) (147)
Height (m), mean (SD) (*n*)	0.690	165.9 (9.5) (495)	165.3 (9.8) (181)	166.1 (9.4) (548)	166.3 (10.7) (147)
Waist circumference, mean (SD) (*n*)	0.453	100.8 (12.7) (494)	100.3 (13.7) (179)	100.1 (13.0) (544)	102.1 (14.0) (143)
Hip circumference, mean (SD) (*n*)	0.547	109.5 (11.2) (493)	108.5 (11.6) (179)	108.4 (11.3) (543)	110.4 (13.5) (143)
OBP measurement (mmHg), mean (SD) (n)					
Systolic BP left arm	0.719	138.1 (18.1) (491)	138.5 (18.5) (178)	136.7 (18.2) (544)	136.9 (17.2) (145)
Systolic BP right arm	0.867	138.7 (18.1) (492)	139.8 (18.7) (181)	138.0 (18.6) (546)	137.0 (17.6) (147)
Diastolic BP left arm	0.986	77.4 (11.3) (491)	77.2 (10.7) (178)	76.1 (11.3) (544)	76.2 (11.5) (145)
Diastolic BP right arm	0.835	77.3 (10.6) (492)	77.3 (11.2) (181)	76.2 (11.5) (546)	76.3 (11.0) (147)
Laboratory and ECG test results					
Renal profile, n/N (%)	0.058				
Normal		59/494 (11.9)	20/179 (11.2)	58/546 (10.6)	19/147 (12.9)
Abnormal (not clinically significant)		395/494 (80.0)	136/179 (76.0)	431/546 (78.9)	106/147 (72.1)

TABLE 5 Baseline covariates of those participants who were withdrawn, discontinued or were lost to follow-up, and the probability of each covariate predicting withdrawal (*continued*)

	Predicting withdrawal from the study (*p*-value)[a]	Spironolactone (*N* = 677)		Standard care (*N* = 695)	
		Completed	Withdrawn	Completed	Withdrawn
		(*N* = 495)	(*N* = 182)	(*N* = 548)	(*N* = 147)
Abnormal (clinically significant)		40/494 (8.1)	23/179 (12.8)	57/546 (10.4)	22/147 (15.0)
Liver function tests, n/N (%)	0.157				
Normal		419/493 (85.0)	149/181 (82.3)	445/548 (81.2)	118/147 (80.3)
Abnormal (not clinically significant)		71/493 (14.4)	29/181 (16.0)	103/548 (18.8)	28/147 (19.0)
Abnormal (clinically significant)		3/493 (0.6)	3/181 (1.7)	0/548 (0.0)	1/147 (0.7)
Bone profile, n/N (%)	0.149				
Normal		444/489 (90.8)	151/179 (84.4)	467/544 (85.8)	122/144 (84.7)
Abnormal (not clinically significant)		44/489 (9.0)	26/179 (14.5)	76/544 (14.0)	22/144 (15.3)
Abnormal (clinically significant)		1/489 (0.2)	2/179 (1.1)	1/544 (0.2)	0/144 (0.0)
Lipids, n/N (%)	0.051				
Normal		342/488 (70.1)	116/181 (64.1)	360/540 (66.7)	99/143 (69.2)
Abnormal (not clinically significant)		135/488 (27.7)	59/181 (32.6)	172/540 (31.9)	36/143 (25.2)
Abnormal (clinically significant)		11/488 (2.3)	6/181 (3.3)	8/540 (1.5)	8/143 (5.6)
Full blood count, n/N (%)	0.072				
Normal		289/493 (58.6)	96/179 (53.6)	309/542 (57.0)	74/146 (50.7)
Abnormal (not clinically significant)		195/493 (39.6)	76/179 (42.5)	222/542 (41.0)	67/146 (45.9)
Abnormal (clinically significant)		9/493 (1.8)	7/179 (3.9)	11/542 (2.0)	5/146 (3.4)
HbA1c, n/N (%)	0.221				
Normal		342/490 (69.8)	114/175 (65.1)	391/544 (71.9)	110/144 (76.4)
Abnormal (not clinically significant)		125/490 (25.5)	46/175 (26.3)	124/544 (22.8)	25/144 (17.4)
Abnormal (clinically significant)		23/490 (4.7)	15/175 (8.6)	29/544 (5.3)	9/144 (6.3)
Fasting blood sugar, n/N (%)	0.005				
Normal		369/466 (79.2)	110/156 (70.5)	408/511 (79.8)	105/132 (79.5)
Abnormal (not clinically significant)		81/466 (17.4)	35/156 (22.4)	94/511 (18.4)	19/132 (14.4)

continued

TABLE 5 Baseline covariates of those participants who were withdrawn, discontinued or were lost to follow-up, and the probability of each covariate predicting withdrawal (*continued*)

	Predicting withdrawal from the study (*p*-value)[a]	Spironolactone (*N* = 677)		Standard care (*N* = 695)	
		Completed (*N* = 495)	Withdrawn (*N* = 182)	Completed (*N* = 548)	Withdrawn (*N* = 147)
Abnormal (clinically significant)		16/466 (3.4)	11/156 (7.1)	9/511 (1.8)	8/132 (6.1)
BNP, n/N (%)	0.011				
Normal		333/444 (75.0)	106/154 (68.8)	383/491 (78.0)	77/117 (65.8)
Abnormal (not clinically significant)		83/444 (18.7)	36/154 (23.4)	80/491 (16.3)	31/117 (26.5)
Abnormal (clinically significant)		28/444 (6.3)	12/154 (7.8)	28/491 (5.7)	9/117 (7.7)
Electrocardiogram, n/N (%)	0.013				
Normal		327/457 (71.6)	104/161 (64.6)	378/502 (75.3)	80/120 (66.7)
Abnormal (not clinically significant)		114/457 (24.9)	47/161 (29.2)	107/502 (21.3)	32/120 (26.7)
Abnormal (clinically significant)		16/457 (3.5)	10/161 (6.2)	17/502 (3.4)	8/120 (6.7)
ACR (mg/mmol), median (IQR) (*n*)	0.123	1.5 (0.6–4.3) (464)	1.6 (0.7–4.4) (169)	1.4 (0.6–3.7) (500)	1.9 (0.8–5.2) (137)
eGFR (ml/minute/1.73 m^2), mean (SD) (*n*)	0.012	44.4 (6.9) (494)	42.8 (6.8) (182)	43.3 (6.7) (548)	42.6 (7.1) (147)
Potassium (mmol/L), mean (SD) (*n*)	0.743	4.5 (0.4) (495)	4.4 (0.4) (182)	4.5 (0.4) (548)	4.5 (0.4) (147)
Creatinine (µmol/L), mean (SD) (*n*)	0.011	121.5 (23.1) (495)	126.2 (23.6) (182)	124.5 (24.9) (548)	127.9 (25.0) (147)

EudraCT, European Union Drug Regulating Authorities Clinical Trials; IQR, interquartile range; SD, standard deviation.
a Logistic regression of the completion of follow-up modelled against baseline characteristics. Level of significance = 0.05.

Note
Percentages have been computed with the number of participants with the response available as the denominator.

association with missingness. The missing at random (MAR) assumption was tested for each secondary outcome as far as possible by analysing each baseline covariate in a logistic regression to determine which, if any, were associated with missingness of the secondary outcome.

Primary analysis

The frequency and percentage of the proportion of participants that reached the primary end point, and the time at risk and the incidence rate are presented in *Table 6*. A Kaplan–Meier curve for the time to first occurrence of a primary end-point event is presented in *Figure 2* split by randomised arm. The individual components of the primary end point (hospitalisation, CVD and death) are also presented descriptively by frequency and percentages of the proportion of participants experiencing each event, and the time at risk and the incidence rate. Kaplan–Meier curves for each individual component of the primary end point are presented in *Appendix 4*, *Figures 13–15*. The individual components

were analysed by a Cox-proportional hazards model similar to the analysis for the main primary end point. The HRs between the randomised groups with a 95% CI and the associated *p*-values were obtained from the model and are presented in *Table 6*.

There were 113/677 (16.7%) participants in the spironolactone arm, and 111/695 (16.0%) participants in the standard care arm that experienced the primary end point of either death or hospitalisation for heart disease (arrhythmia, atrial fibrillation, sudden death, resuscitated sudden death), stroke, TIA, PAD or heart failure, or first onset of any condition listed above not present at baseline. A breakdown of these events is reported in *Table 7*. For the participants in the spironolactone arm the total time at risk of an event was 1653.9 years and the incidence rate per 100 years at risk was 6.83 (n = 661), and for the participants in the standard care arm the total time at risk of an event was 1769.8 years and the incidence rate per 100 years at risk was 6.27 (n = 687).

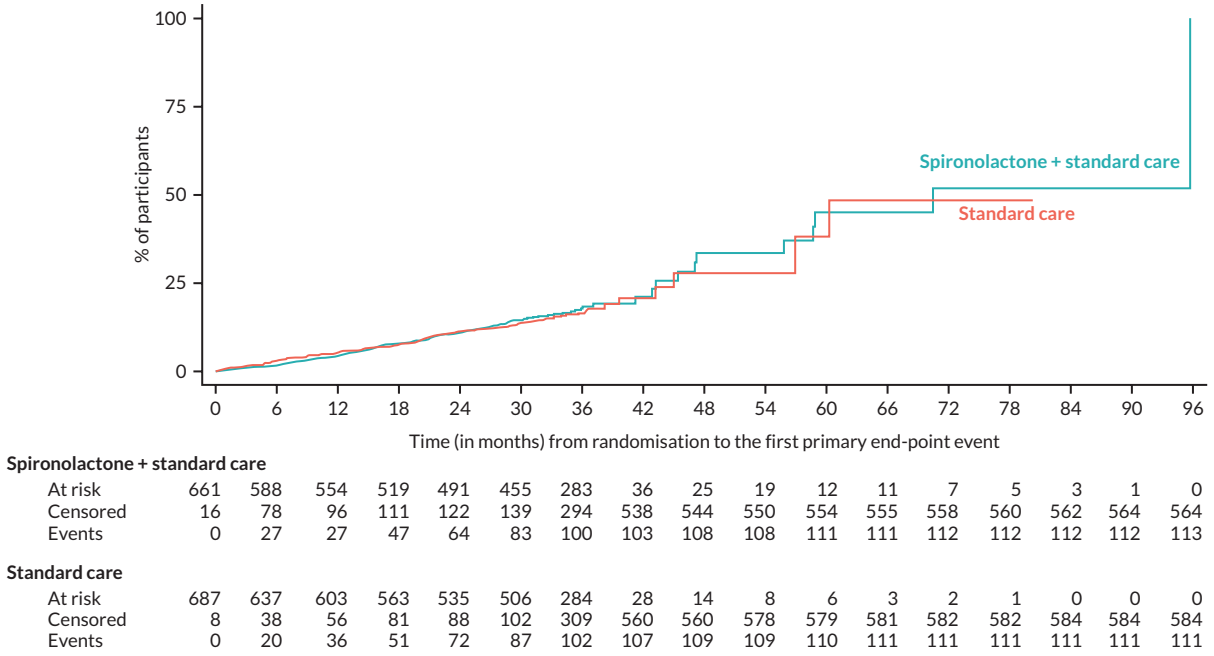
The Cox-proportional hazards model showed no evidence of a statistically significant difference between the two groups (p = 0.702). Results from the analysis showed a HR of 1.05 (95% CI 0.81 to 1.37), indicating that the participants in the spironolactone arm had an increased chance of experiencing the primary end point of 5% compared to those participants in the standard care (95% CI: a decrease of 19% to an increase of 37%), although this finding was non-significant.

The Cox-proportional hazards model also showed no evidence of a statistically significant difference between the two groups for the individual components of the primary end point, including hospitalisation [HR 0.99 (95% CI 0.64 to 1.53); p = 0.970], CVD [HR 1.14 (95% CI 0.80 to 1.61); p = 0.478] or death [HR 1.09 (95% CI 0.70 to 1.70); p = 0.699] (Table 6).

TABLE 6 Summary statistics and the HRs for the primary analysis

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	HR (95% CI)[a]	*p*-value[b]
Primary analysis				
Primary end point[c]				
Experienced, *n*/*N* (%)	113/677 (16.7)	111/695 (16.0)	–	–
Time at risk (years) (incidence rate per 100 years at risk)[d]	1653.9 (6.83) (661)	1769.8 (6.27) (687)	1.05 (0.81 to 1.37)	0.702
Primary end-point component: hospitalisation[c]				
Experienced, *n*/*N* (%)	39/677 (5.8)	42/695 (6.0)	–	–
Time at risk (years) (incidence rate per 100 years at risk)	1703.4 (2.29) (661)	1807.9 (2.32) (687)	0.99 (0.64 to 1.53)	0.970
Primary end-point component: CVD[c]				
Experienced, *n*/*N* (%)	66/677 (9.7)	61/695 (8.8)	–	–
Time at risk (years) (incidence rate per 100 years at risk)	1661.0 (3.97) (661)	1780.7 (3.43) (687)	1.14 (0.80 to 1.61)	0.478
Primary end-point component: death[c]				
Experienced, *n*/*N* (%)	42/677 (6.2)	38/695 (5.5)	–	–
Time at risk (years) (incidence rate per 100 years at risk)	1767.4 (2.38) (661)	1889.7 (2.01) (687)	1.09 (0.70 to 1.70)	0.699

a Spironolactone vs. standard care.
b Level of significance = 0.05.
c Cox-proportional hazards model adjusted for randomised arm.
d Primary end point.



Spironolactone + standard care																	
At risk	661	588	554	519	491	455	283	36	25	19	12	11	7	5	3	1	0
Censored	16	78	96	111	122	139	294	538	544	550	554	555	558	560	562	564	564
Events	0	27	27	47	64	83	100	103	108	108	111	111	112	112	112	112	113
Standard care																	
At risk	687	637	603	563	535	506	284	28	14	8	6	3	2	1	0	0	0
Censored	8	38	56	81	88	102	309	560	560	578	579	581	582	582	584	584	584
Events	0	20	36	51	72	87	102	107	109	109	110	111	111	111	111	111	111

FIGURE 2 Kaplan–Meier curve for the time (in months) from randomisation to the first primary end-point event.

TABLE 7 Summary statistics for the breakdown of the primary end point

	Spironolactone (*N* = 113)	Standard care (*N* = 111)
Primary end-point breakdown: first event		
Death, n (%)	*29 (25.7)*	*29 (26.1)*
Cardiovascular	3 (2.7)	5 (4.5)
Not cardiovascular	20 (17.7)	20 (18.0)
Not stated (missing)	6 (5.3)	4 (3.6)
CVD n (%)	*63 (55.8)*	*59 (53.2)*
Heart disease	35 (31.0)	37 (33.3)
ACS	10 (8.8)	8 (7.2)
CHD	11 (9.7)	9 (8.1)
MI	3 (2.7)	6 (5.4)
Arrhythmia	6 (5.3)	8 (7.2)
AF	5 (4.4)	6 (5.4)
Cardiac arrest	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)
Heart failure	5 (4.4)	3 (2.7)
Stroke	0 (0.0)	5 (4.5)
TIA	3 (2.7)	0 (0.0)

TABLE 7 Summary statistics for the breakdown of the primary endpoint (*continued*)

	Spironolactone (*N* = 113)	Standard care (*N* = 111)
PAD	20 (17.7)	14 (12.6)
Not stated (missing)	0 (0.0)	0 (0.0)
Hospitalisation n (%)	*21 (18.6)*	*23 (20.7)*
Heart disease	15 (13.3)	17 (15.3)
ACS	7 (6.2)	10 (9.0)
CHD	1 (0.9)	1 (0.9)
MI	6 (5.3)	4 (3.6)
Arrhythmia	0 (0.0)	1 (0.9)
AF	1 (0.9)	1 (0.9)
Cardiac arrest	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)
Heart failure	2 (1.8)	1 (0.9)
Stroke	2 (1.8)	0 (0.0)
TIA	1 (0.9)	1 (0.9)
PAD	1 (0.9)	2 (1.8)
Not stated (missing)	0 (0.0)	2 (1.8)

ACS, acute coronary syndrome; AF, atrial fibrillation; CHD, coronary heart disease.

Note
Percentages have been computed with the number of participants who experienced the primary end point as the denominator.

The proportional hazards assumptions were tested by plotting a log–log plot of survival and by plotting a Kaplan–Meier predicted survival plot for the primary end point and for the separate end point components (see *Appendix 5*, *Figures 16–19*). A formal test of the proportional hazards assumption on the basis of Schoenfeld residuals was conducted for the analysis of the primary end point and for the separate primary end-point components. The *p*-values from the proportional hazards assumption test were non-statistically significant, indicating that there is no evidence that the proportional hazards assumption has been violated (primary end point $p = 0.522$, hospitalisation $p = 0.135$, CVD $p = 0.389$, death $p = 0.816$).

Secondary analyses

Office measurements of systolic blood pressure

Office measurements of systolic BP were measured at baseline and all subsequent follow-up visits and are presented descriptively using means and standard deviations at baseline, 6 months, 1 year, 2 years and 3 years follow-up (Table 8). Office measurements of systolic BP were analysed by fitting a linear mixed-effects model to the data with the end-point measure at all available post-randomisation follow-up time points as the dependent variable. The model was adjusted for randomised treatment allocation, assessment time point, baseline office measurement of systolic BP, and an interaction between randomised treatment allocation and assessment time point to allow the treatment effect to be estimated at each time point as fixed effects; and a random intercept for each participant to account for the repeated measures on the same participant.

The mixed-effects model is valid under the MAR assumption, that is that the probability of a value being missing depends on variables included in the model. The MAR assumption was tested for office measurement of systolic BP at 3 years by analysing each baseline covariate using a logistic regression model to determine which (if any) are associated with missingness; the baseline factors found to be associated with missingness that were included in the model as additional fixed effects are age, indices of multiple deprivation quintile, peripheral vascular disease, full blood count, fasting blood sugar, electrocardiogram and eGFR.

The adjusted mean differences between the randomised groups with 95% CIs and associated *p*-values were obtained from the models using a linear contrast statement at 6 months, 1 year, 2 years and 3 years follow-up and are presented in *Table 8*.

The normality assumptions of the linear mixed-effects model were assessed by plotting a histogram of the office measurements of systolic BP at each time point split by randomised group, a histogram of the model residuals, an inverse normal plot of the standardised model residuals, and a scatter plot of the fitted values versus the model residuals, and these are presented in *Appendix 6*, *Figure 20*.

Rate of hypotension

Rate of hypotension was measured over the study period and is presented descriptively using frequency and percentages (Table 8). Rate of hypotension was analysed by a log-binomial regression model fitted to the data with the end point as a binary category (yes/no) as the dependent variable. The model was adjusted for randomised treatment allocation.

The MAR assumption was tested for rate of hypotension by analysing each baseline covariate using a logistic regression model to determine which (if any) are associated with missingness; no baseline factors were found to be associated with missingness.

The adjusted relative risks between the randomised groups with 95% CIs and associated *p*-values were obtained from the models and are presented in presented in *Table 8*.

Natriuretic peptide

Natriuretic peptide was measured at baseline and at all subsequent follow-up visits and is presented descriptively using means and standard deviations at baseline, 6 months, 1 year, 2 years and 3 years follow-up. The data for NP were highly skewed and the model residual plots from the mixed model indicated issues with the model fit; different transformations of the data were assessed and it was decided that the logarithmic transformation was the most appropriate to achieve normality of the data. NP was analysed using a linear mixed-effects model fitted to the data with the log of the end-point measure at all available post-randomisation follow-up time points as the dependent variable. The model was adjusted for randomised treatment allocation and assessment time point to allow the treatment effect to be estimated at each timepoint as fixed effects; and a random intercept for each participant to account for the repeated measure on the same participant.

The missing at random assumption was tested for NP at 3 years by analysing each baseline covariate using a logistic regression model to determine which (if any) were associated with missingness; the baseline factors found to be associated with missingness that were included in the model as additional covariates are age, thyroid disease, indices of multiple deprivation quintile, renal profile and electrocardiogram.

The estimates from the model were back transformed and the adjusted mean differences between the randomised groups with 95% confidence intervals and associated *p*-values were obtained from the model using a linear contrast statement at 6 months, 1 year, 2 years and 3 years follow-up, and they are presented in *Table 8*.

The normality assumptions of the linear mixed-effects model were assessed by plotting a histogram of the NP at each time point split by randomised group, a histogram of the model residuals, an inverse normal plot of the standardised model residuals, and a scatter plot of the fitted values versus the model residuals. Along with the logarithmic transformation of NP these are presented in *Appendix 6*, *Figures 21* and *22*.

TABLE 8 Summary statistics and the adjusted treatment differences for the secondary analyses

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	Adjusted treatment effect (95% CI)[a]	*p*-value[b]
Secondary analyses				
Office measurements of systolic BP (mmHg), mean (SD) (n)[c]				
Baseline	138.6 (17.66) (677)	137.3 (17.51) (695)	–	–
6 months	131.2 (16.03) (553)	134.1 (15.87) (636)	−3.32 (−5.05 to −1.59)	< 0.001
1 year	130.9 (15.86) (518)	133.4 (16.15) (603)	−2.66 (−4.43 to −0.90)	0.003
2 years	132.0 (17.21) (434)	133.5 (15.91) (494)	−1.33 (−3.22 to 0.56)	0.169
3 years	134.2 (16.46) (460)	134.8 (16.34) (515)	−1.69 (−3.55 to 0.16)	0.074
Rate of hypotension, n/N (%)[d]				
During the study	49/658 (7.4)	32/686 (4.7)	1.60 (1.04 to 2.46)	0.034
NP (pg/mL), mean (SD) (n)[c]				
Baseline	311.8 (505.01) (677)	323.8 (477.94) (695)	–	–
6 months	289.3 (819.26) (451)	308.6 (511.56) (512)	−1.30 (−1.63 to −1.03)	0.026
1 year	302.4 (513.36) (425)	358.2 (626.15) (475)	−1.28 (−1.61 to −1.01)	0.039
2 years	360.8 (604.48) (352)	367.3 (592.75) (396)	−1.09 (−1.39 to 1.17)	0.487
3 years	384.6 (568.18) (363)	451.6 (740.31) (413)	−1.20 (−1.53 to 1.06)	0.146
ACR, n/N (%) and mean (SD) (n)[e]				
Baseline	4.9 (8.43) (677)	5.3 (9.38) (695)	–	–
< 3	429/677 (63.4)	439/695 (63.2)	–	–
3–30	229/677 (33.8)	233/695 (33.5)	–	–
> 30	19/677 (2.8)	23/695 (3.3)	–	–
3 years	10.5 (36.07) (361)	8.2 (18.22) (403)	1.03 (−1.50 to 1.59)	0.897
< 3	212/361 (58.7)	253/403 (62.8)	–	–
3–30	123/361 (34.1)	116/403 (28.8)	–	–
> 30	26/361 (7.2)	34/403 (8.4)	–	–
eGFR (ml/minute/1.73 m2), mean (SD) (n)[c]				
Baseline	43.9 (6.90) (677)	43.1 (6.79) (695)	–	–
6 months	42.1 (8.01) (550)	43.2 (7.22) (635)	−1.68 (−2.41 to −0.94)	< 0.001
1 year	42.0 (8.13) (515)	43.7 (8.09) (599)	−2.33 (−3.08 to −1.58)	< 0.001
2 years	42.5 (8.79) (425)	43.0 (8.33) (484)	−0.89 (−1.69 to −0.09)	0.029
3 years	41.7 (9.18) (462)	42.0 (8.75) (518)	−1.14 (−1.92 to −0.37)	0.004

a Spironolactone vs. standard care.
b Level of significance = 0.05.
c Linear mixed-effects model adjusted for randomised arm, baseline measurement, assessment time point, an interaction between randomised arm and assessment time point, and baseline factors that predict missingness of the end point as fixed effect, and a random intercept for each participant.
d Log-binominal regression model adjusted for randomised arm, and baseline factors that predict missingness of the end point as covariates.
e Linear regression model adjusted for randomised arm, baseline measurement, and baseline factors that predict missingness of the end point as covariates.

Albumin-creatinine ratio

Albumin-creatinine ratio was measured at baseline and at 3 years follow-up and is presented descriptively using means and standard deviations. The data for ACR were highly skewed and the model residual plots from the mixed model indicated issues with the model fit, different transformations of the data were assessed and it was decided that the logarithmic transformation was the most appropriate to achieve normality of the data. ACR was analysed by a linear regression model fitted to the data with the log of the end-point measure at 3 years as the dependent variable. The model was adjusted for randomised treatment allocation and baseline log ACR.

The MAR assumption was tested for ACR at 3 years by analysing each baseline covariate using a logistic regression model to determine which (if any) are associated with missingness; the baseline factors found to be associated with missingness that were included in the model as additional covariates are age, indices of multiple deprivation quintile, ischaemic heart disease, thyroid disease, systolic BP right arm and electrocardiogram.

The estimates from the model were back transformed and the adjusted mean difference between the randomised groups with 95% CI and associated *p*-value were obtained from the model at 3 years follow-up, and they are presented in *Table 8*.

The normality assumptions of the linear mixed-effects model were assessed by plotting a histogram of the ACR at each time point split by randomised group, a histogram of the model residuals, an inverse normal plot of the standardised model residuals, and a scatter plot of the fitted values versus the model residuals; these are presented in *Appendix 6*, *Figure 23*, and also of the logarithmic transformation of the ACR presented in *Appendix 6*, *Figure 24*.

Estimated glomerular filtration rate

Estimated glomerular filtration rate was measured at baseline and all subsequent follow-up visits and is presented descriptively using means and standard deviations at baseline, 6 months, 1 year, 2 years and 3 years follow-up.
The eGFR was analysed by a linear mixed-effects model fitted to the data with eGFR at all available post-randomisation follow-up time points as the dependent variable. The model was adjusted for randomised treatment allocation, assessment time point, baseline eGFR, and an interaction between randomised treatment allocation and assessment time point to allow the treatment effect to be estimated at each time point as fixed effects; and a random intercept for each participant to account for the repeated measures on the same participant.

The mixed-effects model is valid under the MAR assumption, this assumption was tested for eGFR at 3 years by analysing each baseline covariate using a logistic regression model to determine which (if any) are associated with missingness; the baseline factors found to be associated with missingness that were included in the model as additional fixed effects were age, indices of multiple deprivation quintile, ischaemic heart disease, ACEIs, bone profile, full blood count, fasting blood sugars, BNP, electrocardiogram and eGFR.

The adjusted mean differences between the randomised groups with 95% CIs and associated *p*-values were obtained from the models using a linear contrast statement at 6 months, 1 year, 2 years and 3 years follow-up, and these are presented in *Table 8*.

The normality assumptions of the linear mixed-effects model were assessed by plotting a histogram of the eGFR at each time point split by randomised group, a histogram of the model residuals, an inverse normal plot of the standardised model residuals, and a scatter plot of the fitted values versus the model residuals, and these are presented in *Appendix 6*, *Figure 25*.

Secondary results interpretations

Participants in the spironolactone arm had a mean office measure of systolic BP of 138.6 mmHg (SD = 17.66) at baseline, 131.2 mmHg (SD = 16.03) at 6 months post randomisation, 130.9 mmHg (SD = 15.86) at 1 year post randomisation, 132.0 mmHg (SD = 17.21) at 2 years post randomisation, and 134.2 mmHg (SD = 16.46) at 3 years post randomisation (*Figure 3*). Participants in the standard care arm had a mean systolic BP of 137.3 mmHg

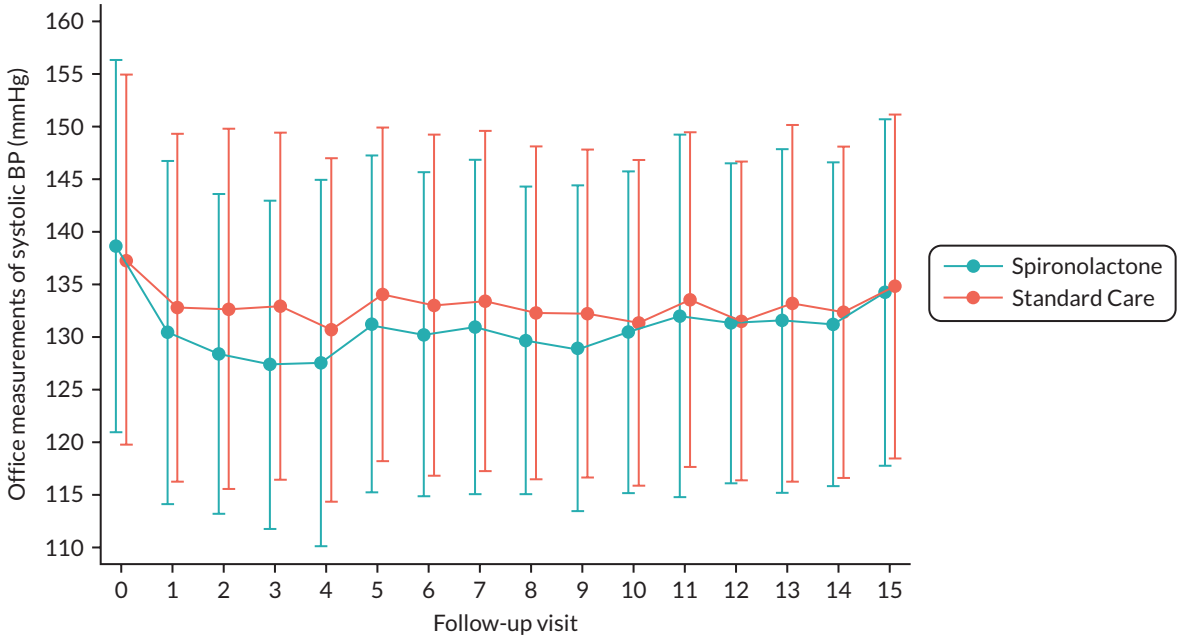


FIGURE 3 Mean office measurements of systolic BP with standard deviations at each follow-up visit time point by randomised group.

(SD = 17.51) at baseline, 134.1 mmHg (SD = 15.87) at 6 months post randomisation, 133.4 mmHg (SD = 16.15) at 1 year post randomisation, 133.5 mmHg (SD = 15.91) at 2 years post randomisation, and 134.8 mmHg (SD = 16.34) at 3 years post randomisation (*Figure 3*). There was a statistically significant mean difference between the two groups for office measurements of systolic BP at both 6 months and 1 year post randomisation [−3.32 (95% CI −5.05 to −1.59); $p < 0.001$, and −2.66 (95% CI −4.43 to −0.90); $p = 0.003$], indicating that the participants in the spironolactone arm had an initial reduction in their systolic BP by 3.32 mmHg compared to the participants in the standard care arm. However, this difference between the groups was not observed at 2 and 3 years post randomisation [−1.33 (95% CI −3.22 to 0.56]; $p = 0.169$, and −1.69 (95% CI −3.55 to 0.16); $p = 0.074$].

This pattern was also observed for NPs [6 months: −1.30 (95% CI: −1.63 to −1.03); $p = 0.026$, 1 year: −1.28 (95% CI −1.61 to −1.01); $p = 0.039$, 2 years: −1.09 (95% CI −1.39 to 1.17); $p = 0.487$, and 3 years: −1.20 (95% CI: −1.53 to 1.06); $p = 0.146$]. Participants in the spironolactone arm had an initial reduction in their NPs of 1.30 pg/mL compared to the participants in the standard care arm at both 6 months and 1 year post randomisation from baseline; however, this difference between the groups was not observed at 2 and 3 years post randomisation.

The mean eGFR in the spironolactone arm was 43.9 ml/minute/1.73 m^2 (SD = 6.90) at baseline, 42.1 ml/minute/1.73 m^2 (SD = 8.01) at 6 months post randomisation, 42.0 ml/minute/1.73 m^2 (SD = 8.13) at 1 year post randomisation, 42.5 ml/minute/1.73 m^2 (SD = 8.79) at 2 years post randomisation, and 41.7 ml/minute/1.73 m^2 (SD = 9.18) at 3 years post randomisation (*Figure 4*). In the standard care arm the mean eGFR was 43.1 ml/minute/1.73 m^2 (SD = 6.79) at baseline, 43.2 ml/minute/1.73 m^2 (SD = 7.22) at 6 months post randomisation, 43.7 ml/minute/1.73 m^2 (SD = 8.09) at 1 year post randomisation, 43.0 ml/minute/1.73 m^2 (SD = 8.33) at 2 years post randomisation, and 42.0 ml/minute/1.73 m^2 (SD = 8.75) at 3 years post randomisation (*Figure 4*). A statistically significant mean difference between the two groups for eGFR was observed at each post-randomisation follow-up visit [6 months: −1.68 (95% CI −2.41 to −0.94); $p < 0.001$, 1 year: −2.33 (95% CI −3.08 to −1.58); $p < 0.001$, 2 years: −0.89 (95% CI −1.69 to −0.09); $p = 0.029$, 3 years: −1.14 (95% CI −1.92 to -0.37); $p = 0.004$]. Participants in the spironolactone arm had an initial reduction in their eGFR of 1.68 ml/minute/1.73 m^2 at 6 months post randomisation compared to the participants in the standard care arm. By the end of the study at 3 years post randomisation, this reduction from baseline between the two groups had reduced to 1.14 ml/minute/1.73 m^2.

There were 49/658 (7.4%) participants in the spironolactone arm and 32/686 (4.7%) participants in the standard care arm that experienced hypotension during the study. A significant difference in the risk for rate of hypertension during

the trial was detected. The adjusted relative risk for hypertension for the spironolactone and standard care comparison was 1.60 (95% CI 1.04 to 2.46); $p = 0.034$, indicating that those participants in the spironolactone arm had a 60% increase in their risk of experiencing hypotension.

The mean ACR in the spironolactone arm was 4.9 (SD = 8.43) at baseline, and 10.5 (SD = 36.07) at 3 years post randomisation. In the standard care arm, the mean ACR was 5.3 (SD = 9.38) at baseline, and 8.2 (SD = 18.22) at 3 years post randomisation. No evidence of a statistically significant difference for the ACR at 3 years between the two randomised arms was detected. The adjusted mean difference was 1.03 (−1.50 to 1.59); $p = 0.897$.

Exploratory analyses

In addition to the secondary outcomes of ACR and eGFR, the number and percentage of participants with a ≥ 30% increase in creatinine from baseline, as well as the number and percentage of participants with a drop of ≥ 25% in eGFR from baseline, and ≥ 20% drop in eGFR from previously reported are also presented in *Table 9*. No formal statistical analysis was performed.

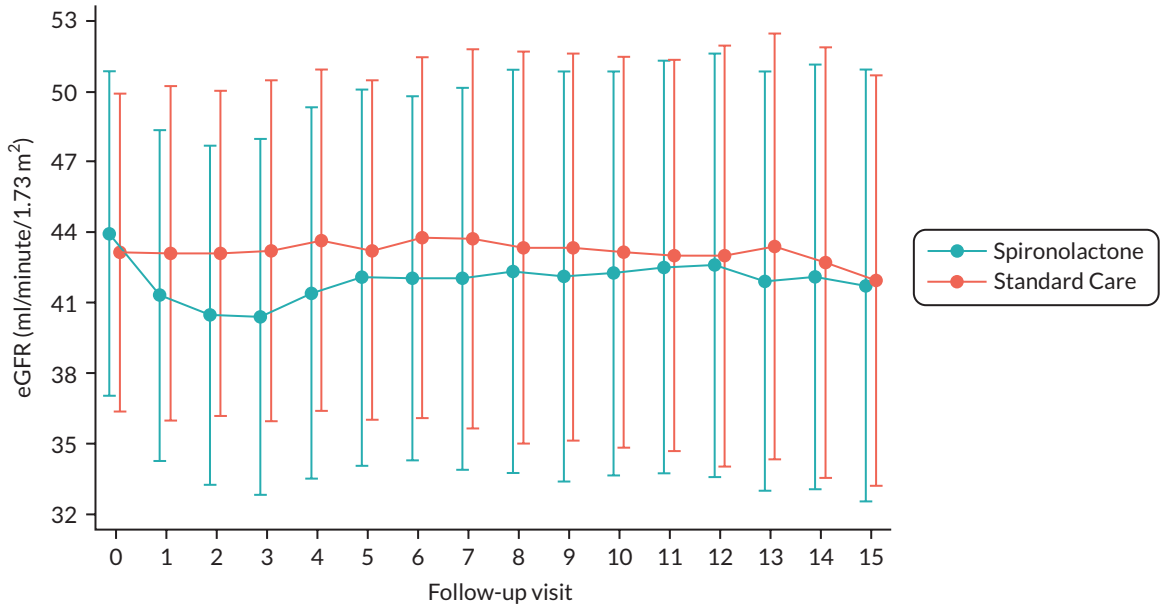


FIGURE 4 Mean eGFR with standard deviations at each follow-up visit time point by randomised group.

TABLE 9 Summary statistics for the exploratory analyses

	Spironolactone (*N* = 677)	Standard care (*N* = 695)
Exploratory analyses		
Increase in creatinine ≥ 30% from baseline, n/N (%)		
Visit 1 – Week 1 follow-up	12/648 (1.9)	4/671 (0.6)
Visit 2 – Week 2 follow-up	25/635 (3.9)	7/664 (1.1)
Visit 3 – Week 4 follow-up	40/631 (6.3)	5/671 (0.7)
Visit 4 – Week 12 follow-up	27/595 (4.5)	3/663 (0.5)
Visit 5 – Month 6 follow-up	13/551 (2.4)	8/635 (1.3)
Visit 6 – Week 39 follow-up	12/529 (2.3)	5/609 (0.8)
Visit 7 – Year 1 follow-up	19/515 (3.7)	12/599 (2.0)

TABLE 9 Summary statistics for the exploratory analyses (*continued*)

	Spironolactone (*N* = 677)	Standard care (*N* = 695)
Visit 8 – Week 65 follow-up	23/491 (4.7)	13/573 (2.3)
Visit 9 – Week 78 follow-up	20/480 (4.2)	11/551 (2.0)
Visit 10 – Week 91 follow-up	13/438 (3.0)	12/504 (2.4)
Visit 11 – Year 2 follow-up	7/425 (1.6)	10/484 (2.1)
Visit 12 – Week 117 follow-up	16/412 (3.9)	19/477 (4.0)
Visit 13 – Week 130 follow-up	25/406 (6.2)	13/463 (2.8)
Visit 14 – Week 143 follow-up	18/383 (4.7)	15/456 (3.3)
Visit 15 – Year 3 follow-up	34/459 (7.4)	21/517 (4.1)
Decrease in eGFR ≥ 25% from baseline, n/N (%)		
Visit 1 – Week 1 follow-up	23/647 (3.6)	4/669 (0.6)
Visit 2 – Week 2 follow-up	34/634 (5.4)	8/660 (1.2)
Visit 3 – Week 4 follow-up	45/630 (7.1)	7/669 (1.0)
Visit 4 – Week 12 follow-up	32/595 (5.4)	5/663 (0.8)
Visit 5 – Month 6 follow-up	21/550 (3.8)	10/635 (1.6)
Visit 6 – Week 39 follow-up	20/529 (3.8)	7/609 (1.1)
Visit 7 – Year 1 follow-up	31/515 (6.0)	15/599 (2.5)
Visit 8 – Week 65 follow-up	29/490 (5.9)	20/572 (3.5)
Visit 9 – Week 78 follow-up	29/480 (6.0)	16/550 (2.9)
Visit 10 – Week 91 follow-up	24/438 (5.5)	25/504 (5.0)
Visit 11 – Year 2 follow-up	21/425 (4.9)	16/484 (3.3)
Visit 12 – Week 117 follow-up	28/412 (6.8)	21/476 (4.4)
Visit 13 – Week 130 follow-up	33/406 (8.1)	19/463 (4.1)
Visit 14 – Week 143 follow-up	31/383 (8.1)	25/455 (5.5)
Visit 15 – Year 3 follow-up	46/462 (10.0)	36/518 (6.9)
Decrease in eGFR ≥ 20% from previous reported, n/N (%)		
Visit 1 – Week 1 follow-up	50/647 (7.7)	12/669 (1.8)
Visit 2 – Week 2 follow-up	35/634 (5.5)	13/660 (2.0)
Visit 3 – Week 4 follow-up	23/630 (3.7)	13/669 (1.9)
Visit 4 – Week 12 follow-up	18/595 (3.0)	9/663 (1.4)
Visit 5 – Month 6 follow-up	17/550 (3.1)	22/635 (3.5)
Visit 6 – Week 39 follow-up	17/529 (3.2)	12/609 (2.0)
Visit 7 – Year 1 follow-up	14/515 (2.7)	13/599 (2.2)
Visit 8 – Week 65 follow-up	19/490 (3.9)	21/572 (3.7)
Visit 9 – Week 78 follow-up	17/480 (3.5)	17/550 (3.1)
Visit 10 – Week 91 follow-up	10/438 (2.3)	19/504 (3.8)

continued

TABLE 9 Summary statistics for the exploratory analyses (*continued*)

	Spironolactone (*N* = 677)	Standard care (*N* = 695)
Visit 11 – Year 2 follow-up	11/425 (2.6)	15/484 (3.1)
Visit 12 – Week 117 follow-up	12/412 (2.9)	21/476 (4.4)
Visit 13 – Week 130 follow-up	19/406 (4.7)	13/463 (2.8)
Visit 14 – Week 143 follow-up	10/383 (2.6)	18/455 (4.0)
Visit 15 – Year 3 follow-up	16/462 (3.5)	22/518 (4.2)

Sensitivity analysis

One sensitivity analysis was pre-specified in the SAP to examine the robustness of the result of the primary end-point analysis. The Cox-proportional hazard model used in the primary analysis section was re-run with three pre-specified baseline prognostic factors included in the model as additional covariates. These prognostic factors are: type 2 diabetes at baseline, coronary artery disease at baseline, and diastolic and/or systolic BP at baseline below or above NICE target which is defined as: lower than 140/90 mmHg for people aged under 80 years, and lower than 150/90 mmHg for people aged 80 years or over. The HR between the randomised groups with a 95% CI and the associated *p*-value was obtained from the model and is presented in *Table 10*.

The proportional hazards assumptions were tested by plotting a log–log plot of survival and by plotting a Kaplan–Meier predicted survival plot for the sensitivity analysis. A formal test of the proportional hazards assumption on the basis of Schoenfeld residuals was conducted for the sensitivity analysis. The *p*-value from the PH-assumption test was non-statistically significant, indicating that there is no evidence that the proportional hazards assumption has been violated ($p = 0.130$).

Subgroup analyses

This trial was not designed to detect subgroup effects and thus lacks statistical power. All subgroup analyses should be considered exploratory in nature.

The Cox-proportional hazard model used in the primary analysis section was re-run with an indicator variable for the subgroups of interest as an additional covariate in the model. The HR between the randomised groups with a 95% CI and the associated *p*-values from the test of interaction were obtained from the model and are presented in *Table 11*. A forest plot of the results from the subgroup analyses is presented in *Figure 5*. The subgroups of interest are:

- Presence/absence of type 2 diabetes at baseline.
- Presence/absence of coronary artery disease at baseline.
- Systolic and/or diastolic BP below/above the NICE targets at baseline (defined as people aged under 80 years: lower than 140/90 mmHg, people aged over 80 years: lower than 150/90 mmHg).

The proportional hazards assumptions were tested by plotting a log–log plot of survival and by plotting a Kaplan–Meier predicted survival plot for each of the subgroup analyses separately. A formal test of the proportional hazards assumption on the basis of Schoenfeld residuals was conducted for the each of the subgroups. The *p*-values from the PH-assumption test were non-statistically significant, indicating that there is no evidence that the proportional hazards assumption has been violated (type 2 diabetes subgroup $p = 0.705$, coronary artery disease at baseline subgroup $p = 0.078$, BP below/above the NICE target at baseline subgroup $p = 0.816$).

TABLE 10 Summary statistics and the HR for the sensitivity analysis

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	HR (95% CI)[a]	*p*-value[b]
Sensitivity analysis				
Primary end point[c]				
Experienced, *n*/*N* (%)	113/677 (16.7)	111/695 (16.0)	–	–
Time at risk (years) (incidence rate per 100 years at risk)	1653.9 (6.83) (661)	1769.8 (6.27) (687)	1.03 (0.79 to 1.35)	0.805

a Spironolactone vs. standard care.
b Level of significance = 0.05.
c Cox-proportional hazards model adjusted for randomised arm, type 2 diabetes at baseline, coronary artery disease at baseline, and BP below or above NICE target at baseline.

TABLE 11 Summary statistics for the subgroup analyses and the HRs

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	HR (95% CI)[a]	Test of interaction[b]
Subgroup analyses				
Subgroup: type 2 diabetes at baseline[c]				0.979
Present				
Experienced primary end point, *n*/*N* (%)	31/165 (18.8)	31/168 (18.5)	–	
Time at risk (years) (incidence rate per 100 years at risk)	388.4 (7.98) [161]	411.8 (7.53) [164]	1.06 [0.64 to 1.74]	
Absent				
Experienced primary end point, *n*/*N* (%)	82/511 (16.0)	80/527 (15.2)	–	
Time at risk (years) (incidence rate per 100 years at risk)	1265.5 (6.48) [500]	1358.0 (5.89) [523]	1.05 [0.77 to 1.43]	
Subgroup: coronary artery disease at baseline[c]				0.567
Present				
Experienced primary end point, *n*/*N* (%)	29/121 (24.0)	29/118 (24.6)	–	
Time at risk (years) (incidence rate per 100 years at risk)	276.4 (10.49) [118]	259.2 (11.19) [114]	0.91 [0.54 to 1.52]	
Absent				
Experienced primary end point, *n*/*N* (%)	84/555 (15.1)	82/576 (14.2)	–	
Time at risk (years) (incidence rate per 100 years at risk)	1377.5 (6.10) [543]	1507.6 (5.44) [572]	1.08 [0.80 to 1.47]	
Subgroup: systolic and/or diastolic BP below/above the NICE target at baseline[c]				0.798
Below NICE target				
Experienced primary end point, *n*/*N* (%)	102/607 (16.8)	103/636 (16.2)	–	

continued

TABLE 11 Summary statistics for the subgroup analyses and the HRs (*continued*)

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	HR (95% CI)[a]	Test of interaction[b]
Time at risk (years) (incidence rate per 100 years at risk)	1484.8 (6.87) [592]	1612.4 (6.39) [628]	1.04 [0.79 to 1.37]	
Above NICE target				
Experienced primary end point, *n*/*N* (%)	11/70 (15.7)	8/59 (13.6)	–	
Time at risk (years) (incidence rate per 100 years at risk)	169.1 (6.51) [69]	157.3 (5.08) [59]	1.18 [0.47 to 3.00]	

a Spironolactone vs. standard care.
b Level of significance = 0.05.
c Cox-proportional hazards model adjusted for randomised arm, an indicator variable for the subgroup, and an interaction between randomised arm and the subgroup indicator variable as a fixed effect.

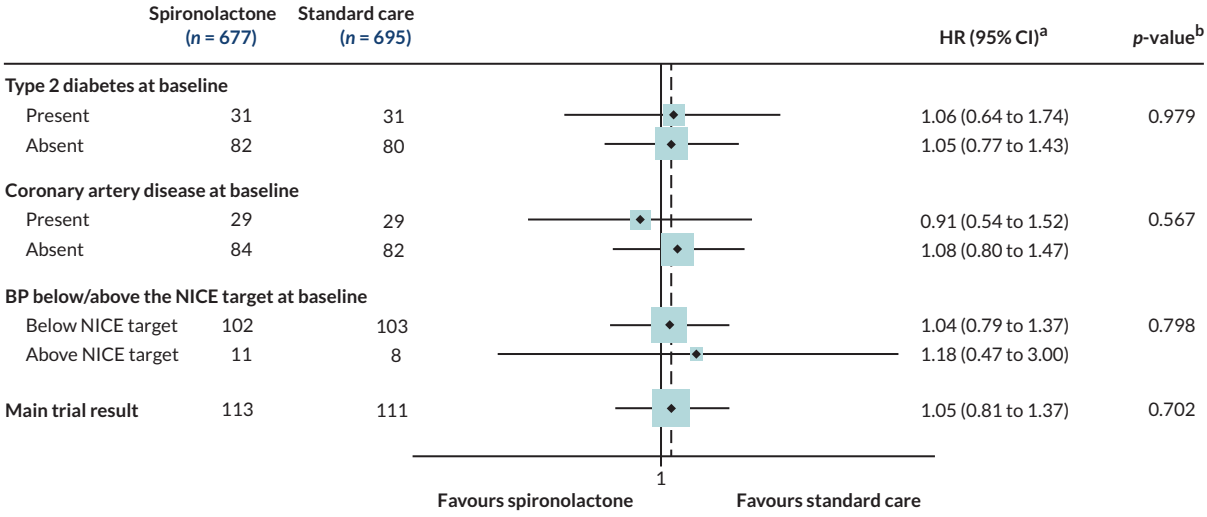


FIGURE 5 Forest plot of the results from the subgroup analyses. a, Spironolactone vs. standard care. Cox-proportional hazards model adjusted for randomised arm, an indicator variable for the subgroup, and an interaction between randomised arm and the subgroup indicator variable as a fixed effect; b, Level of significance = 0.05.

Safety analyses

All participants are included in the safety analyses and are analysed based on whether they took at least one dose of the study medication or not, instead of the arm they were randomised to. The definitions of safety events are based upon standard MHRA guidance.[99]

Adverse events

An AE has been defined as 'any untoward medical occurrence in a participant to whom a medicinal product (or study intervention) has been administered, including occurrences which are not necessarily caused by or related to that product'.[100] See *Appendix 7* for a list of AEs that are clinically evaluated to be related to the study drug that were reported during the trial.

Adverse reactions

An adverse reaction (AR) is defined as an untoward and unintended response in a participant to an investigational medicinal product (IMP) which is related to any dose administered to that participant.

The phrase 'response to any investigational medicinal product' means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, that is the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the trial medication qualify as ARs. Causality of all cases were judged by a medically qualified doctor.

Serious adverse events

A serious adverse event (SAE) is any untoward medical occurrence that:[100]

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Consists of a congenital anomaly or birth defect. (Pregnancy is not in itself a SAE. In the event that the participant or his/her partner becomes pregnant while taking part in a clinical trial or during a stage where the fetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long halflife), the pregnancy should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of 'serious'.)
- Other 'important medical events' may also be considered a SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

See *Appendix 8* for a full list of all SAEs reported during the trial.

Serious adverse reactions

An AE that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected unexpected serious adverse reactions

A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out:

- In the case of a product with a marketing authorisation, in the approved Summary of Product Characteristics for that product.
- In the case of any other IMP, in the approved investigator's brochure (IB) relating to the trial in question.

NOTE: To avoid confusion or misunderstanding of the difference between the terms 'serious' and 'severe', the following note of clarification is provided: 'Severe' is often used to describe the intensity of a specific event, which may be of relatively minor medical significance. 'Seriousness' is the regulatory definition supplied above.

Assessment of causality

The relationship of each AE to the trial medication was determined by a medically qualified doctor according to the following definitions:

- Unrelated – where an event is not considered to be related to the IMP.
- Possibly – although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- Probably – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP.

- Definitely – the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause.

All AEs (SAEs) labelled possibly, probably or definitely were considered as related to the IMP.

Safety analysis interpretation

In total, 455 participants randomised to spironolactone had their treatment discontinued because of safety concerns and two-thirds of patients randomised to spironolactone stopped treatment within six months. The most frequent reasons for this were a decrease in the eGFR that met the pre-specified stop criteria (n=239, 35.4%), treatment side-effects 128 (18.9%) and hyperkalaemia (n=54, 8.0%).

The participants randomised to treatment with spironolactone were more likely to experience an AE during the trial compared to people randomised to the standard care arm (562/677, 83% vs. 384/757, 50.7%, $p < 0.001$) and to experience hyperkalaemia of any severity (spironolactone 167/676, 24.7%, vs. standard care 95/708, 13.4%; $p < 0.001$) and it was likely that these events were related to the study drug (*Table 12*). Most cases of hyperkalaemia were mild in both arms but 12% of the raised K+ levels events that occurred were levels above 6 mmol/L and therefore required dose suspension or adjustment. However, the severity of these events and the proportion of SAEs were similar between the intervention and control groups (*Table 12*). MedDRA codes for safety events are listed in *Table 13*.

TABLE 12 Frequency and percentage of hyperkalaemia, AEs and SAEs

	Spironolactone (*N* = 677)[a]	Standard care (*N* = 757)[a]	*p*-value[b]
Safety analyses			
Hyperkalaemia, n/N (%)			
Experienced	167/676 (24.7)	95/708 (13.4)	< 0.001
Mild (5.5–5.9 mmol/l)	147/167 (88.0)	85/95 (89.5)	
Moderate (6.0–6.4 mmol/l)	16/167 (9.6)	10/95 (10.5)	
Severe (> 6.5 mmol/l)	4/167 (2.4)	0/95 (0.0)	
AEs, n/N (%)			
Experienced at least one	562/677 (83.0)	384/757 (50.7)	< 0.001
None	115/677 (17.0)	373/757 (49.3)	
1	259/677 (38.3)	192/757 (25.4)	
2	153/677 (22.6)	89/757 (11.8)	
3	69/677 (10.2)	52/757 (6.9)	
4	37/677 (5.5)	24/757 (3.2)	
≥ 5	44/677 (6.5)	27/757 (3.6)	
Severity of AEs, n/N (%)			
N	1179	789	0.017
Mild	778/1178 (66.0)	519/789 (65.8)	
Moderate	325/1178 (27.6)	194/789 (24.6)	
Severe	75/1178 (6.4)	76/789 (9.6)	
Plausible relationship of AE to study drug, n/N (%)			
N	1179	789	< 0.001
Unrelated	523/1178 (44.4)	786/789 (99.6)	
Possibly related	351/1178 (29.8)	2/789 (0.3)	

TABLE 12 Frequency and percentage of hyperkalaemia, AEs and SAEs (*continued*)

	Spironolactone (*N* = 677)[a]	Standard care (*N* = 757)[a]	*p*-value[b]
Probably related	229/1178 (19.4)	1/789 (0.1)	
Definitely related	75/1178 (6.4)	0/789 (0.0)	
SAEs, n/N (%)			
Experienced at least one	103/677 (15.2)	113/757 (14.9)	0.883
None	574/677 (84.8)	644/757 (85.1)	
1	68/677 (10.0)	84/757 (11.1)	
2	29/677 (4.3)	17/757 (2.2)	
≥ 3	6/677 (0.9)	12/757 (1.6)	

a Included all randomised participants who actually received treatment or standard care.
b Level of significance = 0.05. Fisher's exact test or Chi-squared test.

TABLE 13 Adverse events coded by MedDRA system organ class

System organ class Number of participants (%) number of events	Spironolactone (*N* = 677)	Standard care (*N* = 757)	Overall (*N* = 1434)
Blood and lymphatic system disorders	4 (0.6) 4	2 (0.3) 3	6 (0.4) 7
Cardiac disorders	28 (4.1) 35	36 (4.8) 47	64 (4.5) 82
Congenital, familial and genetic disorders	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Ear and labyrinth disorders	2 (0.3) 2	4 (0.5) 4	6 (0.4) 6
Endocrine disorders	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Eye disorders	9 (1.3) 9	6 (0.8) 7	15 (1.0) 16
Gastrointestinal disorders	79 (11.7) 124	35 (4.6) 72	114 (7.9) 196
General disorders and administration site conditions	63 (9.3) 76	33 (4.4) 37	96 (6.7) 113
Hepatobiliary disorders	3 (0.4) 3	2 (0.3) 5	5 (0.3) 8
Immune system disorders	0 (0.0) 0	2 (0.3) 3	2 (0.1) 3
Infections and infestations	63 (9.3) 74	58 (7.7) 75	121 (8.4) 149
Injury, poisoning and procedural complications	27 (4.0) 42	26 (3.4) 32	53 (3.7) 74
Investigations	392 (57.9) 570	259 (34.2) 384	651 (45.4) 954
Metabolism and nutrition disorders	47 (6.9) 58	21 (2.8) 23	68 (4.7) 81
Musculoskeletal and connective tissue disorders	60 (8.9) 80	24 (3.2) 34	84 (5.9) 114
Neoplasms: benign, malignant and unspecified (including cysts and polyps)	22 (3.2) 32	24 (3.2) 26	46 (3.2) 58
Nervous system disorders	79 (11.7) 106	38 (5.0) 47	117 (8.2) 153
Psychiatric disorders	10 (1.5) 12	2 (0.3) 2	12 (0.8) 14
Renal and urinary disorders	47 (6.9) 52	24 (3.2) 32	71 (5.0) 84

continued

TABLE 13 Adverse events coded by MedDRA system organ class (*continued*)

System organ class	Spironolactone	Standard care	Overall
Number of participants (%) number of events	(*N* = 677)	(*N* = 757)	(*N* = 1434)
Reproductive system and breast disorders	29 (4.3) 34	3 (0.4) 4	32 (2.2) 38
Respiratory, thoracic and mediastinal disorders	25 (3.7) 29	22 (2.9) 32	47 (3.3) 61
Skin and subcutaneous tissue disorders	15 (2.2) 17	5 (0.7) 5	20 (1.4) 22
Social circumstances	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Surgical and medical procedures	29 (4.3) 32	31 (4.1) 35	60 (4.2) 67
Vascular disorders	63 (9.3) 68	35 (4.6) 44	98 (6.8) 112
Missing	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1

Post hoc analysis not specified in the statistical analysis plan

Two additional analyses were conducted after the initial blinded results in this report were presented to the chief investigator and trial team. These were not described or detailed in the SAP, however they follow the broad principles laid down there. The suggestions for the following analysis were carefully considered, discussed and agreed upon between the trial statistician, a senior trial statistician and the chief investigator. The results from these analyses should be considered exploratory.

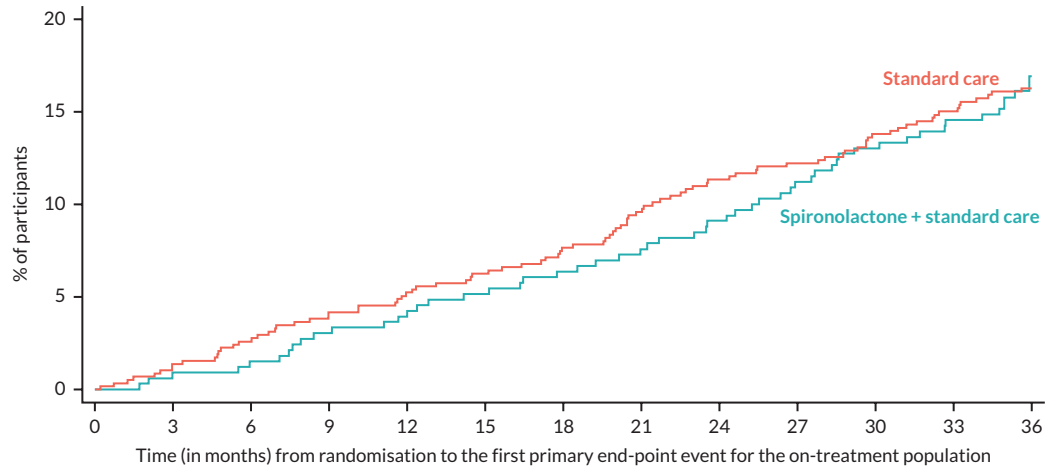
The first post hoc analysis is based on an a per-protocol principle and an on-treatment population (*Figure 6*). The on-treatment population is defined as all participants who either completed the 3 years follow-up, or died and did not withdraw from the study, or withdrew from the study but experienced the primary end point before withdrawing, and self-reported taking at least one dose of the IMP for the participants in the IMP arm.

Participants were followed up for 3 years as described in the protocol, however as part of the long-term follow-up analysis all medical notes were obtained, as several participants were recorded as experiencing their first primary end point more than 3 years after randomisation. In the primary analysis, the date of the first primary end point was used regardless of when it occurred, even if it occurred more than 3 years after randomisation. A per-protocol principle was applied to the post hoc analysis considering only the events that happened in the first 3 years after randomisation. Participants who experienced their first primary end point after 3 years from randomisation were classified as not experiencing an event and censored at the date 3 years from when they were randomised.

The second post hoc analysis was suggested by the funders, removing PAD from the definition of the primary end point, as it had been mis-specified in an earlier version of the protocol (*Figure 7*).

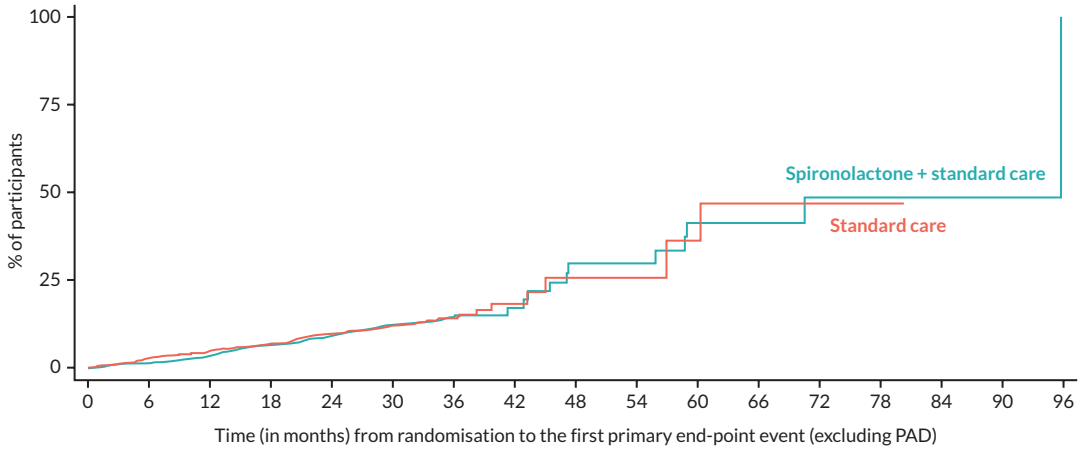
The HRs between the randomised groups with 95% CIs and the associated *p*-values were obtained from the model and are presented in *Table 14*. The proportional hazards assumptions were tested by plotting a log–log plot of survival and by plotting a Kaplan–Meier predicted survival plot for the post hoc analysis (see *Appendix 9*, *Figures 26* and *27*). A formal test of the proportional hazards assumption on the basis of Schoenfeld residuals was conducted for the post hoc analyses. The *p*-value from the PH-assumption test was non-statistically significant, indicating that there is no evidence that the proportional hazards assumption has been violated ($p = 0.114$ and $p = 0.513$).

Finally, to test whether the withdrawals due to non-eligibility judged after randomisation influenced the results, we also repeated the analysis with all the late ineligible subjects allocated to their original randomisation group. The results were very similar, with the primary analysis: $N = 1372$, HR = 1.05 (95% CI 0.81 to 1.37); $p = 0.702$; compared to post hoc analysis including all randomised subjects: $N = 1434$, HR = 1.03 (95% CI 0.79 to 1.34); $p = 0.819$.



Spironolactone + standard care													
At risk	331	327	325	320	316	313	309	305	300	293	387	381	176
Censored	0	1	1	1	1	1	1	1	1	1	1	2	100
Events	0	3	5	10	14	17	21	25	30	37	43	48	55
Standard care													
At risk	576	568	560	550	543	537	528	517	507	502	492	483	278
Censored	0	0	1	2	3	3	4	4	4	4	5	7	205
Events	0	8	15	24	30	36	44	55	65	70	79	86	93

FIGURE 6 Kaplan–Meier curve for the time (in months) from randomisation to the first primary end point for the post hoc analysis based on a per-protocol principle and an on-treatment population.



Spironolactone + standard care																	
At risk	661	590	559	527	501	468	295	37	26	20	12	11	7	5	3	1	0
Censored	16	79	97	112	123	140	300	556	562	568	573	574	577	579	581	583	583
Events	0	8	21	38	53	69	82	84	89	89	92	92	93	93	93	93	94
Standard care																	
At risk	687	638	606	568	543	516	289	28	14	8	6	3	2	1	0	0	0
Censored	8	39	57	82	90	104	318	575	587	593	594	596	597	598	599	599	599
Events	0	18	32	45	62	75	88	92	94	94	95	96	96	96	96	96	96

FIGURE 7 Kaplan–Meier curve for the time (in months) from randomisation to the first primary end point excluding peripheral arterial disease.

TABLE 14 Summary statistics and the HR for the post hoc analysis based on a per-protocol principle and an on-treatment population

	Spironolactone (*N* = 677)	Standard care (*N* = 695)	HR (95% CI)[a]	*p*-value[b]
Post hoc analysis				
Per-protocol principle and an on-treatment population: primary end point[c]				
Experienced, *n*/*N* (%)	55/331 (16.6)	93/576 (16.1)	–	–
Time at risk (years) (incidence rate per 100 years at risk)	919.0 (5.98) (331)	1575.1 (5.90) [576]	1.01 (0.72 to 1.41)	0.946
Excluding PAD: primary end point[c]				
Experienced, *n*/*N* (%)	94/677 (13.9)	96/695 (13.8)	–	–
Time at risk (years) (incidence rate per 100 years at risk)[b]	1679.5 (5.60) (661)	1786.5 (5.37) (687)	0.99 (0.75 to 1.33)	0.973

a Spironolactone vs. standard care.
b Level of significance = 0.05.
c Cox-proportional hazards model adjusted for randomised arm.

Chapter 4 Economic evaluation

Methods

Overview

The main objective of the health economic evaluation was to assess the comparative cost-effectiveness of treatment with ARA spironolactone (25 mg OD) prescribed in addition to standard care (henceforth 'spironolactone') versus standard care alone for patients with stage 3b CKD. To that end, a systematic comparison of the cost of resource inputs used by participants in the two groups of the trial and the health consequences associated with the interventions was conducted. The analysis adopted the NHS healthcare perspective.

The primary economic evaluation took the form of a cost-utility analysis (CUA), expressed in terms of incremental cost per quality-adjusted life-year (QALY) gained. The time horizon covered the period from randomisation to end of follow-up at 156 weeks (3 years) post randomisation. All costs and health outcomes were discounted at an annual rate of 3.5%.

Changes from the protocol

Due to patient burden in completing questionnaires, two outcome measures indicated in the published protocol[97,101] were not administered to patients, the ICECAP-A[102] and VAS QoL.[103] The frequency of administering the healthcare resource use diary cards was reduced from every 13 weeks throughout follow-up to every 13 weeks throughout the first year of follow-up and then annually.

Measuring and valuing resource use

Data were collected on NHS healthcare resource use, including all relevant hospital and GP consultations, medications, referrals, tests, equipment and any other relevant healthcare resources. The healthcare resource use data was sourced from patient and clinician-reported resource utilisation diaries. Patients were administered with the healthcare resource use diaries at the following time points: baseline, every 12 weeks until 52 weeks and then annually, and asked to complete them prospectively, covering the following periods: baseline to week 12; week 13–26; and subsequent 13-week periods until 52 weeks and then annually. Medication use was recorded at 26-week intervals from baseline to week 156. The resource use associated with the intervention of spironolactone and standard care was recorded over the trial period. In reporting, they are grouped into three time points: 'Year 1' – all resource use from baseline up to week 52; 'Year 2' – week 53–104; and 'Year 3' – week 105–156.

Resource use was valued by attaching unit costs derived from national compendia in accordance with the *NICE Health Technology Evaluations: The Manual* published in January 2022 by the NICE.[104] The key sources of unit costs were the 2019–20 *National Cost Collection for the NHS*,[105] the *British National Formulary*[106] and the *Unit Costs of Health and Social Care 2021* compendium published by the Personal Social Services Research Unit (PSSRU).[107] All costs were expressed in pounds (£) valued in 2021 prices. Where appropriate, costs were inflated to 2021 prices using the Hospital and Community Health Services Pay and Prices Inflation Index reported in the PSSRU 2021 compendium.[107]

The unit cost for each Healthcare Resource Group (HRG) code was sourced from the 2019 to 2020 *National Cost Collection for the NHS*.[105] Per diem costs for hospital inpatient admissions were calculated individually as a weighted average of the HRG codes of related procedures and/or clinical diagnoses. Community-based health services were valued by applying unit costs from the PSSRU 2021 compendium[107] to resource use volume. Costs of medications for individual participants were estimated based on their reported doses and frequencies. If the latter were not reported, either the daily dosage recommended by the *British National Formulary*[106] or the dosage of other trial participants taking the same medication were used.

Summary statistics were generated for resource use costs by time point and treatment group. Statistics generated using (1) all available data and (2) using patients with complete data over follow-up time points were presented separately. Between-group differences in resource use costs at each time point were compared using the two-sample

t-test. Statistical significance was assessed at the 5% significance level. The bootstrap 95% CIs, calculated from 1000 bootstrap replications, for the between-group differences in mean resource use and cost estimates were reported.

Measuring and valuing outcomes

The primary outcome for CUA was QALY gained in accordance with NICE guidelines.[104] A QALY combines length of life and preference-based health-related quality of life (HRQoL) into a single metric. The HRQoL of trial participants was measured by patient-reported EQ-5D-5L and EuroQoL visual analogue scale (EQ-VAS) collected at baseline and at weeks 26 (month 6), 52 (year 1), 104 (year 2) and 156 (year 3). The EQ-5D-5L defines HRQoL in terms of five dimensions: (1) mobility, (2) self-care, (3) usual activities, (4) pain or discomfort and (5) anxiety or depression.[108] Responses in each dimension are divided into five ordinal levels: (1) no problems, (2) slight problems, (3) moderate problems, (4) severe problems and (5) extreme problems.[108] The EQ-VAS (range 0–100) measures the patient's self-rated health on a vertical VAS, where the end points are labelled 'The best health you can imagine' (EQ-VAS = 100) and 'The worst health you can imagine' (EQ-VAS = 0).[108]

The dimension responses to the EQ-5D-5L were converted into health utility index scores (anchored on a scale with 0 = dead and 1 = full health or no problem on all dimensions) using the latest algorithm that maps the EQ-5D-5L descriptive system data on to the EQ-5D-3L valuation set.[109] The index scores were combined with within-trial survival data to estimate the QALYs, assuming linear interpolation between health utility measurements across assessment points. In sensitivity analysis, EQ-VAS rescaled from 0–100 to 0–1 range was used as an alternative to EQ-5D-3L index in weighting the length of life to calculate the QALY.

The KDQoL-SF, a self-report measure developed for CKD patients,[110] was used to capture disease-specific HRQoL of patients at baseline, month 6, and years 1–3. The measure contains 80 items, 43 of them kidney disease-specific, 36 generic health core, and 1 overall health rating. All items are scored on the 0–100 range with higher scores always reflecting better QoL. Certain item scores are averaged to obtain the dimension/scale scores.[110] Here, we report the scores for the following scales: kidney disease symptom (12 items averaged); effects of kidney disease (8 items); burden of kidney disease (4 items); kidney disease composite (average of kidney disease symptom, effects and burden); and physical and mental composites from generic health items.

The EQ-5D-5L index scores, dimension responses, EQ-VAS scores and KDQoL scale scores were summarised by time point and treatment group, distinguishing between statistics generated from all available cases and complete cases. Between-group differences in EQ-5D-5L index scores, EQ-VAS scores and KDQoL scale scores were assessed for statistical significance using the two-sample *t*-test and bootstrapping, in a similar way to the analyses of resource use costs.

Cost-effectiveness analysis methods

Missing data

Multiple imputation was conducted to impute missing data and avoid bias around using complete case analysis. Multiple imputation was carried out based on Rubin's rule.[111] Predicted mean matching (PMM) was carried out at the level of QALY and cost, using a chained rule.[112] PMM is a semi-parametric imputation approach; it is known that PMM performs better than linear regression based imputation approach despite the similarities in method. The missing data mechanism falls under one of the following categories: covariate-dependent missing completely at random (MCAR), MAR, MCAR or missing not at random.[113] In this study, the assumption of MAR was made, which is a common assumption in economic evaluation.[114] This assumption implies that the probability of missing data is independent of the missing data itself but may depend on other observed variables, allowing for more accurate imputations.[114] Withdrawals were included in the imputation process except for the cases that dropped out of the trial before baseline data collection. Imputation was performed using a chained rule from baseline to year 1, year 2 and year 3. Consequently, the imputation process in this study encompasses the entire duration of the study.

It is recommended to include potential predictors used in the analysis model for multiple imputation.[115] Including explanatory variables enables multiple imputation by chained equations (MICE). In chained equations, missing values for a certain variable are replaced by draws from the posterior distribution of the certain variable and imputation is conducted repeatedly using the values of other explanatory variables.[115]

In this study, the imputation model used baseline covariates (age, gender, ethnicity and treatment group). Consequently, the PMM method used these baseline covariates, health outcomes and cost components at the total cost and QALY (EQ-5D-5L index as HRQoL weight in base case and EQ-VAS in sensitivity analysis) for MICE at each time point. Twenty imputed data sets were generated with the five nearest neighbours (knn = 5).

Cost-effectiveness estimation

Seemingly unrelated regression (SUR) was used to examine the effect of the intervention, using both the complete case data set and multiple imputation data set. SUR allows for individual error terms to be correlated through the correlation parameter;[116] hence, this method is expected to adjust for correlation between costs and health outcomes in the parameter estimation.[117] Cost-effectiveness was estimated using a bootstrap method to capture the sampling uncertainty. Non-parametric bootstrapping generates multiple replications of the statistic of outcome measures and costs by drawing replications from the original data.[118,119] Currently, there is no clear consensus on which approach, bootstrapping imputed data sets or imputing bootstrapped samples, performs better. A recent simulation-based study[120] concluded that both approaches are appropriate to calculate randomisation-valid CIs when combining bootstrapping with multiple imputation. We bootstrapped from the imputed data sets. A total of 1000 bootstrap samples were generated and both incremental costs and incremental effectiveness were estimated with the bootstrap samples. For incremental costs and effectiveness, mean differences between the treatment groups were reported with 1000 times bootstrapped 95% CIs. Regression was conducted with estimates from each imputed data set based on Rubin's rule.[121] All analyses were implemented on STATA version 17 [Stata Statistical Software: Release 17 (program), 2019; StataCorp LP, College Station, TX, USA].

Presentation of cost-effectiveness results

The cost-effectiveness results are presented in terms of the incremental cost-effectiveness ratio (ICER) which is calculated as the difference between treatment groups in mean total costs divided by the difference in mean total QALYs. The bootstrap replicates generated by the non-parametric bootstrapping (as described above) were used to populate the cost-effectiveness scatterplots presented on the cost-effectiveness plane. Cost-effectiveness acceptability curves (CEACs) were plotted showing the probability that spironolactone is cost-effective relative to standard care (i.e. proportion of bootstrap replicates with positive incremental net benefit) across a range of cost-effectiveness thresholds.

Sensitivity analysis

In the sensitivity analysis, the QALY was calculated using EQ-VAS (rescaled from 0–100 to 0–1 scale) as the HRQoL measure weighting the length of life. Cost-effectiveness estimation was conducted for both complete case and multiple imputation data sets. The cost-effectiveness results were presented as described above.

Long-term cost-effectiveness modelling

The protocol allowed for modelling to estimate the longer-term cost-effectiveness of spironolactone versus standard care. However, this was based on the trial results demonstrating clinical effectiveness. Therefore, no long-term cost-effectiveness modelling was performed.

Health economics results

Data availability

Figure 8 shows the availability of resource use and EQ-5D-5L data for the health economic analysis by time point and treatment group. *Appendix 10*, *Tables 21* and *22* provide greater detail on the causes of unavailable resource use and EQ-5D-5L data respectively, distinguishing between attrition due to withdrawal and death between time points and missing/incomplete responses from participating patients. From baseline to year 1 for the spironolactone group, for example, there were 91 withdrawals and 16 deaths. Among the participants remaining at year 1, 476 provided sufficient resource use data for health economic analysis; the other 94 provided missing/incomplete responses (see *Appendix 10*, *Table 21*).

Outcome comparisons by treatment group

Appendix 10, *Table 23* presents the healthcare resource use frequencies by time point and treatment group, while *Appendix 10*, *Table 24* reports the unit costs used to calculate the resource use costs. The frequencies and unit costs were used to calculate the healthcare resource use costs. *Tables 15* and *16* below present these costs by time point and treatment group using all available cases and complete cases, respectively. There was no statistically significant between-group difference in total healthcare cost or in component healthcare cost types (primary care, secondary care and medication) for all time points.

Tables 17 and *18* present the EQ-5D-5L index scores by time point and treatment group using all available cases and complete cases, respectively. For both available and complete cases, there were statistically significant between-group differences in the mean index scores within the third year of follow-up, with higher mean scores for spironolactone versus standard care. No significant difference was observed for other time points. *Appendix 10*, *Tables 25* and *26* present the EQ-5D-5L dimension responses by time point and treatment group using available cases and complete cases, respectively.

Results of between-group comparisons for further outcomes are presented in *Appendix 10*: EQ-VAS from available and complete cases (see *Appendix 10*, *Tables 27* and *28*, respectively); and KDQoL scale scores from available and complete cases (see *Appendix 10*, *Tables 29* and *30*, respectively). Significantly higher mean EQ-VAS values were found for spironolactone at month 6 (mean difference = 2.6; $p = 0.041$) and year 3 (mean difference = 8.2; $p = 0.026$) time points from complete cases. No significant difference in mean EQ-VAS was found from available cases at any time point. Statistically significant differences were found for KDQoL burden of kidney disease scale from available cases at year 1 (spironolactone 91.0, standard care 93.2; $p = 0.017$) and KDQoL physical composite scale from complete cases at year 3 (spironolactone 42.9, standard care 39.6; $p = 0.008$). The former difference was in unexpected direction. No significant difference was found for other KDQoL scales at any time point from both available and complete cases.

Cost-effectiveness results

Table 19 summarises the cost-effectiveness analysis results with EQ-5D-5L index as the HRQoL weight used to calculate the QALY, using (1) complete case data set and (2) imputed data set. The ICER point estimates were £64,583 per QALY gained using the complete case data set and £38,379 per QALY gained using the imputed data set.

Figure 9 Cost-effectiveness plane for spironolactone versus standard care under complete case analysis using EQ-5D-5L weights for the QALY shows the scatterplot on the cost-effectiveness plane of the bootstrap replicates using the complete case data set. Most replicates are in the north-east quadrant with incremental cost and QALY. *Figure 10* shows the CEAC using complete cases for the probability of spironolactone being cost-effective versus standard care across a range of cost-effectiveness thresholds. At the cost-effectiveness threshold of £20,000 per QALY gained, there was 12.6% probability of spironolactone being cost-effective versus standard care, and 21.8% at the £30,000 per QALY gained threshold.

Figure 11 shows the scatterplot on the cost-effectiveness plane of the bootstrap replicates using the imputed data set. *Figure 12* shows the CEAC using the imputed data set for the probability of spironolactone being cost-effective versus standard care across a range of cost-effectiveness thresholds. At the cost-effectiveness threshold of £20,000 per QALY

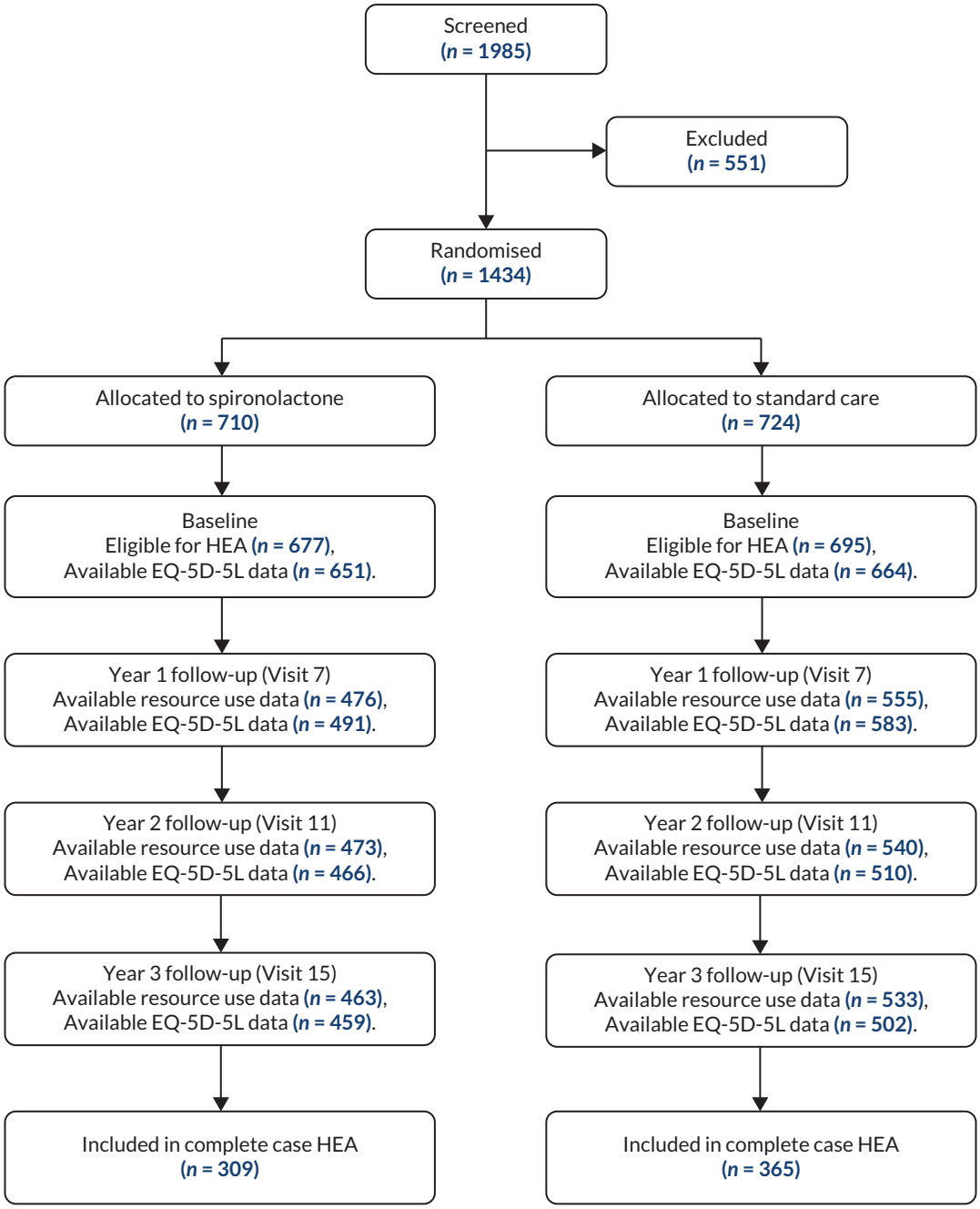


FIGURE 8 Availability of resource use and EQ-5D-5L data for health economic analysis by time point. HEA, health economic analysis.

gained, there was 21.3% probability of spironolactone being cost-effective versus standard care, and 36.4% at the £30,000 per QALY gained threshold.

Sensitivity analysis results

Table 20 summarises the cost-effectiveness analysis results with EQ-VAS score (rescaled to 0–1 range) as the HRQoL weight used to calculate the QALY, using (1) complete case data set and (2) imputed data set. The ICER point estimates were £78,169 per QALY gained using the complete case data set and £29,316 per QALY gained using the imputed data set.

Appendix 10, *Figure 28* shows the scatterplot on the cost-effectiveness plane of the bootstrap replicates using the complete case data set and EQ-VAS as weights used to calculate the QALY. *Appendix 10*, *Figure 29* shows the CEAC using the complete case data set for the probability of spironolactone being cost-effective versus standard care across

TABLE 15 Healthcare resource use costs from available cases by time point and treatment group

Time point	Cost type	Cost for spironolactone[a]	Cost for standard care[a]	Mean difference[a]	*p*-value	Bootstrap 95% CI
Year 1	Primary care[b]	229.3	238.6	−9.3	0.574	−39.8 to 23.4
	Secondary care[c]	450.0	476.1	−26.1	0.601	−125.0 to 61.1
	Medication cost	1216.2	1089.8	126.4	0.642	−362.6 to 677.3
	Total cost	1895.5	1804.5	91.0	0.746	−401.5 to 590.0
Year 2	Primary care[b]	159.8	143.5	16.3	0.652	−32.7 to 105.1
	Secondary care[c]	447.8	328.7	119.1	0.407	−71.6 to 495.7
	Medication cost	578.7	538.8	39.9	0.807	−263.8 to 431.5
	Total cost	1186.2	1010.9	175.3	0.479	−252.4 to 681.0
Year 3	Primary care[b]	123.2	123.5	−0.3	0.992	−44.0 to 59.8
	Secondary care[c]	250.3	286.0	−35.7	0.393	−127.7 to 38.6
	Medication cost	706.1	726.4	−20.3	0.922	−394.8 to 378.7
	Total cost	1079.6	1135.8	−56.2	0.796	−462.7 to 377.8
	Spironolactone	486.0	0.0	486.0	n/a	477.7 to 496.3

A&E, accident and emergency; HDU, high dependency unit; ITU, intensive therapy unit.
a All costs expressed in £ 2021 prices.
b This consists of family doctor (GP), practice nurse, home visit – family doctor (GP), home visit – practice nurse, dietitian, occupational therapist, counselling/psychological support.
c This consists of hospital outpatient department, hospital inpatient department, hospital A&E department, ITU and HDU.

TABLE 16 Healthcare resource use costs from complete cases by time point and treatment group

Time point	Cost type	Cost for spironolactone[a]	Cost for standard care[a]	Mean difference[a]	*p*-value	Bootstrap 95% CI
Year 1	Primary care[b]	319.3	287.2	32.0	0.164	−11.0 to 73.5
	Secondary care[c]	645.5	582.2	63.3	0.374	−80.1 to 197.1
	Medication cost	1128.8	1123.2	5.5	0.987	−640.0 to 638.3
	Total cost	2093.5	1992.6	100.9	0.775	−612.2 to 795.9
Year 2	Primary care[b]	184.9	194.8	−9.8	0.595	−44.3 to 27.9
	Secondary care[c]	467.7	436.2	31.4	0.594	−72.0 to 158.3
	Medication cost	706.7	593.3	113.3	0.616	−286.1 to 681.0
	Total cost	1359.3	1224.3	134.9	0.589	−288.7 to 627.9
Year 3	Primary care[b]	162.8	175.9	−13.1	0.588	−58.6 to 38.2
	Secondary care[c]	378.7	398.0	−19.3	0.746	−143.8 to 105.5
	Medication cost	1101.8	862.2	239.6	0.449	−364.1 to 857.2
	Total cost	1643.3	1436.2	207.1	0.530	−411.7 to 928.7
	Spironolactone	547.5	0.0	547.5	n/a	536.2 to 557.8

A&E, accident and emergency; HDU, high dependency unit; ITU, intensive therapy unit.
a All costs expressed in £ 2021 prices.
b This consists of family doctor (GP), practice nurse, home visit – family doctor (GP), home visit – practice nurse, dietitian, occupational therapist, counselling/psychological support.
c This consists of hospital outpatient department, hospital inpatient department, hospital A&E department, ITU and HDU.

TABLE 17 EuroQol-5 Dimensions, five-level version index scores from available cases by time point and treatment group

Time point	Spironolactone	Standard care	Mean difference	*p*-value	Bootstrap 95% CI
Baseline	0.768	0.760	0.007	0.502	−0.012 to 0.028
Month 6	0.773	0.757	0.016	0.198	−0.006 to 0.042
Year 1	0.756	0.743	0.013	0.333	−0.013 to 0.041
Year 2	0.762	0.744	0.017	0.217	−0.010 to 0.044
Year 3	0.751	0.719	0.032	0.037	0.001 to 0.060

TABLE 18 EuroQol-5 Dimensions, five-level version index scores from complete cases by time point and treatment group

Time point	Spironolactone	Standard care	Mean difference	*p*-value	Bootstrap 95% CI
Baseline	0.791	0.777	0.014	0.354	−0.015 to 0.044
Month 6	0.791	0.764	0.027	0.094	−0.005 to 0.057
Year 1	0.777	0.759	0.018	0.284	−0.014 to 0.047
Year 2	0.768	0.742	0.026	0.108	−0.004 to 0.060
Year 3	0.758	0.722	0.036	0.031	0.006 to 0.067

TABLE 19 Cost-effectiveness analysis results with EQ-5D-5L index weights within QALY

(1) Complete cases						
Spironolactone (*N* = 309)	**Standard care (*N* = 365)**	**Spironolactone (*N* = 309)**	**Standard care (*N* = 365)**	**Incremental cost (£)[a] of spironolactone (95% CI)**	**Incremental QALY[b] of spironolactone (95% CI)**	**ICER[a] (£ per QALY gained)**
Mean (SE) cost (£)[a]		**Mean (SE) QALY[b]**				
5767.4 (615.7)	4217.0 (566.5)	0.774 (0.010)	0.750 (0.009)	1550.4 (−118.8 to 3219.6)	0.024 (−0.004 to 0.052)	64,583
(2) Multiple imputed data						
Spironolactone (*N* = 677)	**Standard care (*N* = 695)**	**Spironolactone (*N* = 677)**	**Standard care (*N* = 695)**	**Incremental cost (£)[a] of spironolactone (95% CI)**	**Incremental QALY[b] of spironolactone (95% CI)**	**ICER[a] (£ per QALY gained)**
Mean (SE) cost (£)[a]		**Mean (SE) QALY[b]**				
5524.3 (465.7)	4526.5 (392.5)	0.776(0.011)	0.750 (0.012)	997.9 (58.1 to 1938.9)	0.026 (0.012 to 0.041)	38,379

SE, standard error.
a All costs expressed in £ 2021 prices.
b EQ-5D-5L index scores used as HRQoL to weight length of life.

a range of cost-effectiveness thresholds. At the cost-effectiveness threshold of £20,000 per QALY gained, there was 10.3% probability of spironolactone being cost-effective versus standard care, and 17.9% at the £30,000 per QALY gained threshold.

Appendix 10, *Figure 30* shows the scatterplot on the cost-effectiveness plane of the bootstrap replicates using complete and multiple imputed cases using EQ-VAS as weights within QALY. *Appendix 10*, *Figure 31* shows the CEAC using the imputed data set for the probability of spironolactone being cost-effective versus standard care across a range of cost-effectiveness thresholds. At the cost-effectiveness threshold of £20,000 per QALY gained, there was 29.7% probability of spironolactone being cost-effective versus standard care, and 52.7% at the £30,000 per QALY gained threshold.

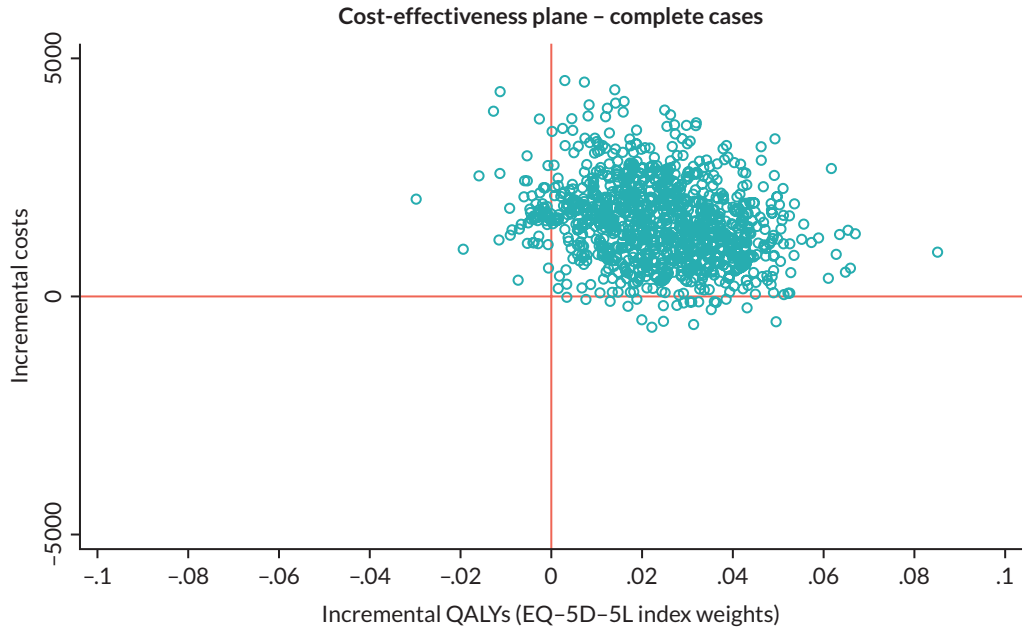


FIGURE 9 Cost-effectiveness plane for spironolactone vs. standard care under complete case analysis using EQ-5D-5L weights for the QALY.

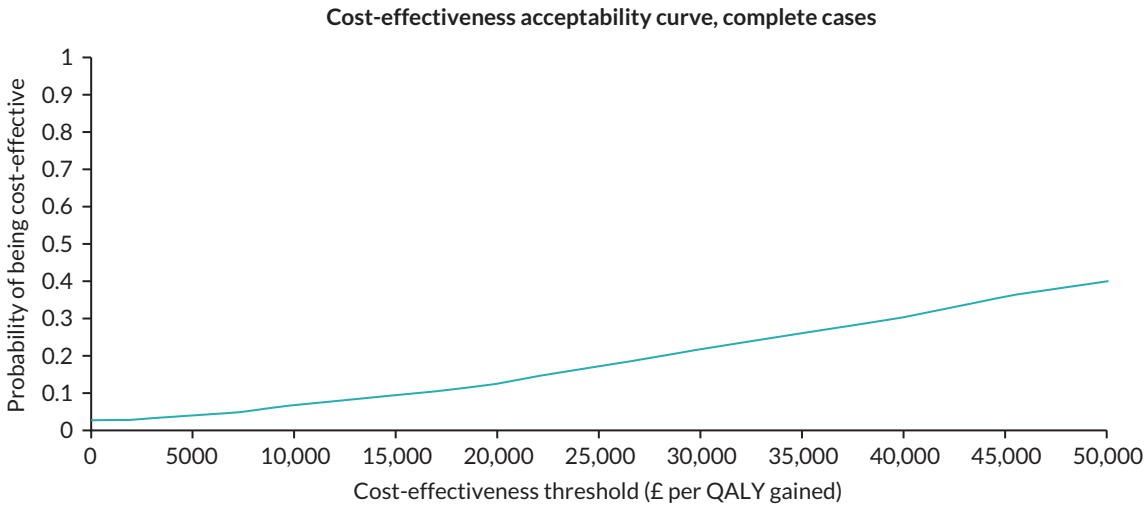


FIGURE 10 Cost-effectiveness acceptability curve for spironolactone vs. standard care under complete case analysis with EQ-5D-5L weights for the QALY.

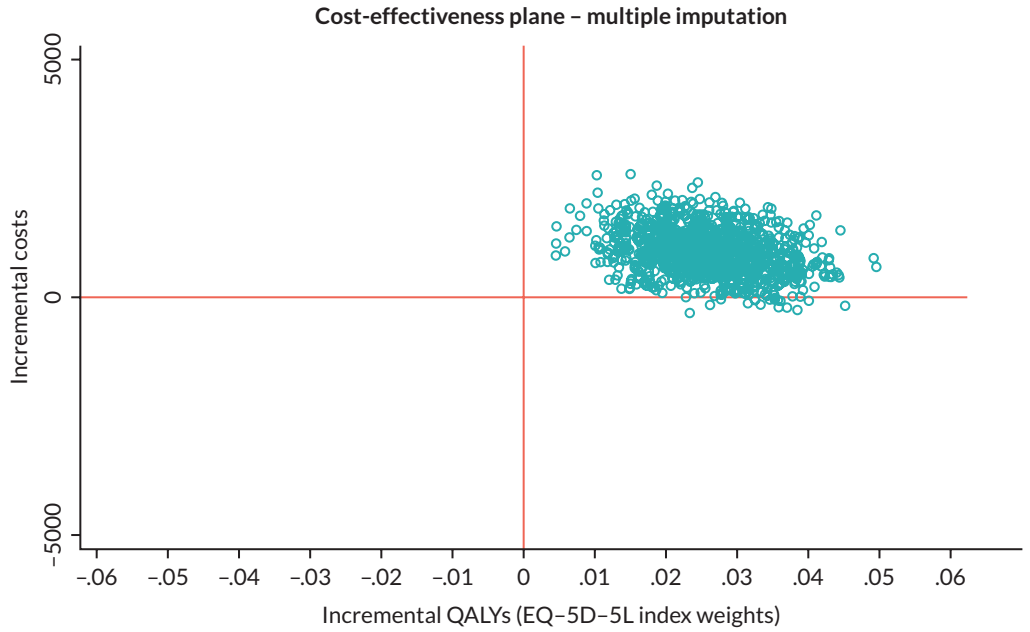


FIGURE 11 Cost-effectiveness plane for spironolactone vs. standard care with imputed resource use and QALY data and EQ-5D-5L weights for the QALY.

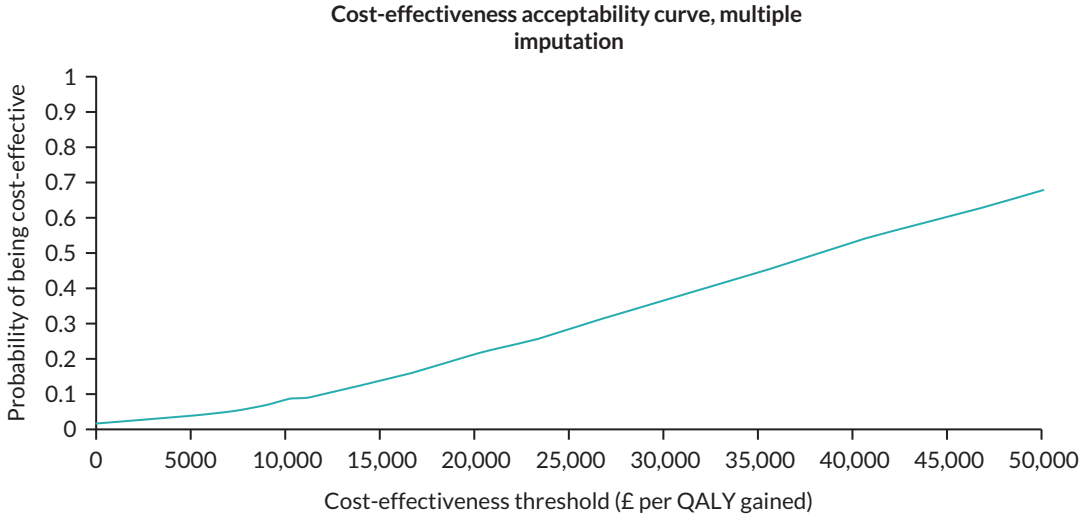


FIGURE 12 Cost-effectiveness acceptability curve for spironolactone vs. standard care with imputed resource use and QALY data and EQ-5D-5L weights for the QALY.

Discussion for economic evaluation

Health economic analysis showed higher costs and higher QoL in the spironolactone arm compared with the standard care arm over the 3-year follow-up, with incremental costs of £1550 (95% CI £−118.8 to £3219.6) and incremental QALY of 0.024 (95% CI −0.004 to 0.052). At a cost-effectiveness threshold of £30,000 per QALY gained, there was 21.8% chance of spironolactone being cost-effective versus standard care. The health economic evaluation indicates that the added treatment of spironolactone to standard care is likely to be not cost-effective when compared with standard care. This remained the case after multiple imputation was performed and in sensitivity analyses using EQ-VAS (rescaled to 0–1) as an alternative HRQoL weight to calculate the QALY. Only with the EQ-VAS weight and imputed data set did the probability of spironolactone being cost-effective versus standard care become marginally higher than 50% (52.7%). These cost-effectiveness results were consistent with the general lack of statistically significant between-group differences observed for healthcare cost, EQ-5D-5L index, EQ-VAS, and several kidney disease-specific scales generated by KDQoL-SF.

TABLE 20 Cost-effectiveness results under sensitivity analysis with EQ-VAS weights within QALY

(1) Complete cases						
Spironolactone (*N* = 309)	**Standard care (*N* = 365)**	**Spironolactone (*N* = 309)**	**Standard care (*N* = 365)**	**Incremental cost (£)[a] of spironolactone (95% CI)**	**Incremental QALY[b] of spironolactone (95% CI)**	**ICER[a] (£ per QALY gained)**
Mean (SE) cost (£)[a]		**Mean (SE) QALY[b]**				
5823.5 (628.0)	4241.1 (583.6)	0.778 (0.009)	0.758 (0.008)	1582.4 (−114.0 to 3278.7)	0.020 (−0.003 to 0.044)	78,169
(2) Multiply imputed cases in addition to complete cases						
Spironolactone (*N* = 677)	**Standard care (*N* = 695)**	**Spironolactone (*N* = 677)**	**Standard care (*N* = 695)**	**Incremental cost (£)[a] of spironolactone (95% CI)**	**Incremental QALY[b] of spironolactone (95% CI)**	**ICER[a] (£ per QALY gained)**
Mean (SE) cost (£)[a]		**Mean (SE) QALY[b]**				
5490.5 (431.5)	552.3 (406.7)	0.791 (0.009)	0.759 (0.008)	938.1 (2.1 to 1874.2)	0.032 (0.019 to 0.044)	29,316

SE, standard error.
a All costs expressed in £ 2021 prices.
b EQ-VAS scores used as HRQoL to weight length of life.

This health economic analysis has some limitations. First, there were high rates of missing responses for all health economic outcomes and particularly for healthcare resource use variables. Of 570 patients who participated in year 1 data collection, for example, 94 (16.5%) provided insufficient data to calculate their healthcare use. Second, there were several changes from the original protocol concerning the type and frequency of outcome measurement. It is possible that more frequent resource use data collection and the inclusion of outcome measures that capture broader aspects of social well-being (e.g. ICECAP-A[102]) may have identified significant between-group differences. That said, given the high missing response rates already mentioned, it is unlikely that higher-intensity data collection would have substantially improved the data quality. Finally, only a few baseline covariates (age, gender, ethnicity and treatment group) were used for multiple imputation of missing healthcare cost and QALY data. Given the non-trivial differences in the cost-effectiveness results between complete case and imputed data sets, further research should explore alternative imputation models.

Chapter 5 Study overall discussion

The BARACK-D trial screened 1985 potentially eligible patients with CKD 3b and randomised 1434 participants of the 3022 target number needed for the trial after up to 8 years of follow-up. A further 62 participants were found to be ineligible post randomisation, meaning 1372 eligible participants were included in the study analysis. The trial proved very difficult to recruit to by the regional centres with only the Oxford centre recruiting at a sustained rate. By the end of May 2017, the regional centres were closed after only 577 patients had been recruited, of which 352 had been recruited by Oxford, and all subsequent national recruitment and follow-up was managed by Oxford centrally.

Participants at baseline represented an older, white, multimorbid population. More than 90% were over 64 years (7.4% over 84), 97% were white, 54% were female, and 77% had hypertension, 24% had diabetes, 17% had ischaemic heart disease and 12% had atrial fibrillation.

There were high rates of withdrawal following randomisation, with 162 (11%) of participants withdrawing between the baseline and first follow-up visit, and there initially were more withdrawals in those randomised to spironolactone due to safety concerns. Two-thirds of participants randomised to spironolactone discontinued taking the treatment by six months follow-up, often because of a decline in kidney function that met pre-specified safety stop criteria. Participants withdrew from study follow-up in the spironolactone arm (27%) at a higher rate compared with the standard care arm (21%). The main baseline characteristics associated with higher rates with withdrawal were age, deprivation level, ischaemic heart disease, fasting blood sugar, BNP, electrocardiogram, eGFR and creatinine.

Pre-specified primary analyses

There were only minor non-significant differences between the study arms in the occurrence of the combined primary end point with similar rates of death, new onset CVD or hospital admission, individually as well as combined. The small differences observed between the individual components were also non-significant. The primary events also occurred at a fairly constant rate throughout the trial follow-up. These analyses were conducted using Cox-proportional hazards models and further tested by plotting a Kaplan–Meier predicted survival plot and testing the assumptions on the Schoenfeld residuals which confirmed that the lack of significant differences was robust.

The trial demonstrated the high cardiovascular risk associated with CKD stage 3b with over 16% of patients suffering the primary end point, including 6% who died. However, the incidence rate of vascular events per 100 years at risk was 6.54, which compares to the 16.05 rate reported in the analysis by Go *et al.* that was used to power the trial.[2]

Pre-specified secondary analyses

As expected, there was a modest difference in BP between the trial arms which was largest at 6 months follow-up with systolic BP being 3 mmHg lower in the spironolactone arm [131.2 vs. 134.1, −3.32 (95% CI −5.05 to −1.59); *p*-value < 0.001] At 1 year systolic BP was 3 mmHg lower [−2.66 (−4.43 to −0.9); 0.003], 1 mmHg at 2 years [−1.33 (−3.22 to 0.56); 0.169], and 3 years [−1.69 (−3.55 to 0.16); 0.074].

There were 60% more episodes of hypotension experienced in the spironolactone versus control arm [49 vs. 32, 1.6 (1.04 to 2.46); 0.034], a significant difference. Hypotension was stated as the reason for 11 withdrawals from treatment.

In terms of NP levels, participants who were allocated spironolactone recorded significantly lower levels than participants in control arm at 6 months [−1.30 mean (−1.63 to −1.03); 0.026] and at 1 year [−1.28 mean (−1.61 to −1.01); 0.039], but the lower mean levels observed at 2 and 3 years were non-significant, after adjustment for the highly skewed levels and missing values. The mean NP levels rose during follow-up in both arms of the study, exceeding the mean baseline levels in the control group by 12 months and in the spironolactone group by 2 years.

In terms of renal function, the mean eGFR at baseline was at the upper (less severe) end of the 3b CKD range at 44 ml/minute in the spironolactone arm and 43 ml/minute in the control arm. Modest decline in mean eGFR was observed in the spironolactone arm at 6 months to 42 ml/minute, which then remained stable at 1, 2 and 3 years. The mean eGFR in the control group was stable up to 2 years and then a small decline to 42 ml/minute at year 3. Though small differences, these slightly lower mean eGFRs in the spironolactone patients were significant at each follow-up time point. Importantly, 35.4% of patients randomised to spironolactone had the treatment discontinued because of a decline in kidney function.

For ACR levels (a measure of renal damage), these showed around two thirds of participants in both arms had acceptable levels of protein excretion at baseline (ACR < 3), with most of the remainder having an ACR of 3–30 and only 3% of participants with major proteinuria with (ACR > 30). At 3 years, the mean ACR levels had worsened in both arms from means of 4.9 to 10.5 and 5.3 to 8.2 in the spironolactone versus control arms, respectively. The difference in ACR between the two arms was non-significant.

We also performed exploratory analyses of patients who experienced eGFR drops of > 20% and > 25%, and creatinine increases of > 30% from baseline values at each time point of the follow-up. These were also part of the safety procedures. In terms of the > 30% creatinine increase, this was seen more frequently in the spironolactone group at every time point. This was especially evident within the first few weeks of randomisation, with 3–6 times the rates observed with spironolactone versus control (1.9% vs. 0.6% at 1 week, 3.9% vs. 1.1% at 2 weeks, 6.3% vs. 0.7% at 4 weeks, and 4.5% vs. 0.5% at 12 weeks) and persisted at approximately double the rate at each subsequent time point. In terms of the eGFR drops, a similar pattern was observed to the raised creatinine levels with around double the rates of an eGFR decline of > 25% at each time point throughout the trial but higher rates in the first 12 weeks with 3.6% versus 0.6% at 1 week, 5.4% versus 1.2% at 2 weeks, 7.1% versus 1% at 4 weeks and 5.4% versus 0.8% at 12 weeks. For eGFR decline > 20% 7.7% versus 1.8% at 1 week, 5.5% versus 2% at 2 weeks, 3.7% versus 1.9% at 4 weeks and 3% versus 1.4% at 12 weeks but the rates then became similar between trial arms until the final visit.

Given that the renal function declined over time, as would be expected with ageing, the proportions of the study population that met these pre-specified creatinine increases and eGFR reductions from their baseline level increased during the trial, with 7.4% in the spironolactone versus 4.1% in the control group experiencing a > 30% creatinine increase at 3 years follow-up. The equivalent rates for > 25% and > 20% eGFR declines were 10% versus 6.9% and 3.5% versus 4.2%, respectively.

Adverse events

As expected, patients in the spironolactone group experienced significantly more episodes of hyperkalaemia, with 24.7% overall versus 13.4% in the control group. Most of these were mild in both arms but 12% of the raised K+ levels events that occurred were levels above 6 mmol/l and therefore required dose suspension or adjustment and 54 (8%) participants had spironolactone discontinued on the basis of an elevated potassium.

The patients on spironolactone were also significantly more likely to experience an AE during the trial, to suffer more multiple AEs, and to have such events related to the spironolactone. However, the severity of these events and the proportion of SAEs were similar between the intervention and control groups.

Pre-specified sensitivity analyses

On the pre-specified sensitivity analysis, the baseline presence of DM, coronary artery disease, and BP that were either above or below the recommended NICE BP range by age were examined in relation to the combined primary end point. For these presumed prognostic factors, the presence or absence of any of the three factors did not influence the observed rates of the primary outcomes.

Though underpowered analyses, we also observed the effect of each of these three risk factors separately and again observed no effects on the primary outcome.

Additional post hoc sensitivity analyses

The slow rate of recruitment meant that the follow-up of earlier recruits was longer than planned, which would have increased the chance of competing risks influencing the primary outcomes of interest. We therefore performed a post hoc analysis restricted to events observed in 3 years of follow-up of participants, as originally planned. This did not alter the conclusion that low-dose spironolactone did not influence rates of death, new-onset CVD or hospitalisation in these patients with CKD stage 3b compared to standard care.

An additional post hoc analysis, performed because of the late reintroduction of PAD as part of the combined primary outcome, showed that the inclusion or exclusion of PAD did not change the results observed. Because of the number of withdrawals due to non-eligibility noted after randomisation, which was mainly due to eGFR and ACR baseline results outside of permitted ranges, we also performed a repeat main analysis where all patients, including the late ineligible ones, were allocated to their original randomisation group, with very similar results to the primary analysis.

Strengths and limitations of the trial

This is the largest randomised controlled trial of low-dose spironolactone in patients with CKD and provides a definitive answer to whether this treatment improves the high rates of vascular disease predicted in this CKD 3b population. The trial also benefited from a wide geographic recruitment across England, with good socioeconomic spread, and the selection of patients meeting the inclusion criteria from the registered practice populations of many practices. These characteristics mean the trial results should be representative of the English population with the important exception of those from ethnic minority groups who were under-represented.

A major strength of the trial was its pragmatic nature, conducted in primary care where the majority of patients with CKD 3b are identified and managed. Had the trial been positive, then this would have aided implementation of the findings. However, had this been the case, there would have been a safety signal in that the early worsening of renal function observed in the trial, which was anticipated, but nonetheless posed challenges to the recruiting practices who were sometimes late to respond to these changes where they met the protocol requirement to suspend or withdraw spironolactone. This necessitated the investigators to develop a central system for monitoring all blood results as soon as they were reported and provide follow-up prompts to the practices where necessary. Since all the bloods were routinely analysed as part of routine care with the initiation of an MRA, obtaining the necessary permissions and operationalising this central service rapidly in the early stages of the trial was challenging but successful. The trial complexity, especially over eligibility criteria that partly relied on baseline tests that were often delayed in results, also meant that some patients were determined as ineligible after randomisation and therefore withdrawn from the study and the analysis. The main reasons for these late ineligibles were ACR and eGFR results outside the permitted range for inclusion.

A limitation of the trial was the non-placebo-controlled nature, which would have added prohibitive cost. However, given the negative trial result this is unlikely to be a significant limitation. We also reduced the impact of lack of placebo by blinding the investigators to the study outcomes, which were independently adjudicated by a clinical panel of specialist and generalist clinicians not involved in the trial design or delivery.

The slow recruitment, another limitation, caused immense issues for the investigators, requiring a redesign of the recruitment strategy to a single national centre from local centres. This slow recruitment, as well as producing an underpowered study, also led to a much longer study than anticipated and this may also have influenced the trial result. However, we performed a post hoc analysis of the primary end point censored at 3 years of follow-up per patient which should have minimised the potential for competing risks to have influenced the trial outcome and revealed the same result. We therefore believe there is no benefit of spironolactone even for a short-term period.

The trial was ongoing during the COVID-19 pandemic, during which time patient follow-up became challenging. All face-to-face visits were temporarily suspended for safety reasons and to adhere to the government guidelines on social distancing. This impacted on the number of patients who missed at least one study visit, with over 15% not attending for study visit 14. Despite this, we were able to obtain complete information with respect to the primary outcome for all participants.

Equality and diversity inclusion

Another major limitation was lack of ethnic diversity amongst subjects in the trial. People of minority ethnic groups were included in the trial but remained under-represented with non-white groups comprising less than 4% of all participants. This was disappointing despite a recruitment strategy which targeted general practices across all areas of the UK. Since the trial began, the 'Equality, Diversity and Inclusion' (EDI) agenda in research has become much more central. Our more recent studies have additional EDI input to ensure that study participants reflect the UK population.

Comparison with other studies

The trial demonstrated the high cardiovascular risk associated with CKD stage 3b with over 16% of patients suffering the primary end point, including 6% who died. The incidence rate per 100 years at risk was 6.54, which compares to the combined event rate of 16.05 per 100 person-years reported by Go *et al.* used to power the trial .[2]

The results of BARACK-D differ from previous randomised trials of MRA, which demonstrated a reduction in risk of progression of CKD or future CVD among people with albuminuric CKD and type 2 diabetes treated with finerenone.[90] The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) study randomised 7437 patients with CKD, type 2 diabetes and moderate albuminuria to treatment with finerenone or placebo and focused on the effect of finerenone on cardiovascular outcomes.[89] Over a median follow-up of 3.4 years, finerenone was associated with a 13% relative reduction (HR 0.87, 95% CI 0.76 to 0.98; p = 0.03) in the risk of the primary composite outcome of death from cardiovascular cause, non-fatal MI, non-fatal stroke or hospitalisation for heart failure.[89] The The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study randomised 6734 patients with predominantly stage 3–4 CKD, significant albuminuria and type 2 diabetes to finerenone or placebo and focused upon renal outcomes with the primary outcome a composite of kidney failure, a sustained 40% reduction in eGFR from baseline, or death from renal cause.[91] Randomisation to finerenone was associated with a 14% reduction in the primary outcome (HR 0.86, 95% CI 0.75 to 0.99; p = 0.03).[91] The FIDELITY study pooled individual patient data from these two studies and confirmed these associations among the larger pool of trial participants.[90]

While these results do contrast with the findings of the study, there were important differences in the study populations. FIGARO and FIDELIO included people with type 2 diabetes only, and less than a quarter of our participants had type 2 diabetes. Our population was older (mean age 74.8 years vs. median age of 64.8 years in FIDELITY) and 54.5% were women, compared to just 31.3% of those in FIDELITY. Nearly double the proportion of patients in the study died (16.6%) compared to those in FIDELITY (9.0%), though our follow-up was longer.[90] The mean baseline eGFR in the study was significantly lower than FIDELITY (43.9 vs. 57.5 ml/minute/1.73 m^2) but 98.2% of those in FIDELITY had moderate to significant proteinuria, compared to a mean baseline urinary ACR of just 1.5 mg/mmol (IQR 0.6–4.3) in BARACK-D.[90] Renal outcome benefits were also seen in another non-steroidal MRA esaxerenone in the ESAX-DN trial in patients with type 2 diabetes mellitus and albuminuria.[126] Although it is also possible that this study failed to detect a treatment effect of spironolactone because of the comparatively small sample size, there is no suggestion of this from the data.

The only positive data on cardiovascular outcomes with spironolactone were seen in the RALES trial,[74] but this was in patients with severe heart failure rather than CKD, and similarly for eplerenone in the EPHESUS trial in patients with left ventricular systolic dysfunction[75] and EMPHASIS trial in patients with mild systolic heart failure,[76] but without CKD. BARACK-D is the only trial data for spironolactone in CKD patients. In terms of renal measure outcomes, there

are more limited data on spironolactone from meta-analyses of subsets of CKD patients recruited as part of trials in hypertension and heart failure.

The high proportion of patients who discontinued taking spironolactone within the first six months of treatment may in part explain our results and implies that the relatively poor tolerability of spironolactone may be a barrier to its widespread use in this population. It is possible the differences in effect are related to the different modes of action between finerenone or spironolactone. There are pharmacological differences between these MRAs, principally defined as whether the MRA is steroidal (spironolactone and eplerenone) or non-steroidal (newer MRAs such as finerenone). The latter were developed to reduce the adverse effects of older MRAs, such as gynaecomastia and reduce the risk of hyperkalaemia. However, these 'off-target' treatment benefits may also be associated with direct benefits on clinical outcomes.

Differences in results between BARACK-D and the finereone trials may also reflect differences in the study populations, BARACK-D recruited an older population with CKD 3b whose renal decline was probably more likely due to age decline renal impairment than to renal damage, such as associated with diabetes. It is possible that MRAs might modify the factors associated with renal damage, such as protein excretion, but not influence the loss of nephrons in age-related renal functional decline.There was also a higher proporiton of women in BARACK-D compared to previous studies

Finally, we only explored spironolactone in low dose and cannot provide data on higher doses of 50 mg or 100 mg. However, given the lack of any signal for 25 mg we would not recommend trials of higher doses, especially since these doses would confer more risk. Further, our data only relate to patients with CKD 3b and cannot be extrapolated to other stages. However, patients at this stage of CKD comprise the largest number of CKD patients who have the most potential for gain from reduced disease progression and improved vascular outcomes.

Because spironolactone is inexpensive and generic it has sometimes been used off-label in CKD as an alternative to newer non-steroidal MRAs, but on the basis of BARACK-D this would offer no treatment benefits to patients with CKD 3b and carry attendant risks of increased monitoring requirements and AEs.

Since the design of the current trial, other novel interventions than MRAs have been trialled in CKD. Recent large randomised controlled trials have explored the impact of SGLT-2 inhibitors on CKD progression and cardiovascular outcomes. The CREDENCE trial recruited 4401 participants with type 2 diabetes and albuminuric CKD and randomised to canagliflozin or placebo.[127] After a median follow-up of 2.62 years, the relative risk of a composite of end-stage kidney disease, a doubling of serum creatinine level or death from renal or cardiovascular causes was lowered by 34% (HR 0.66, 95% CI 0.53 to 0.81; $p < 0.001$).[127] The DAPA-CKD trial of dapagliflozin versus placebo recruited 4304 participants with and without type 2 diabetes.[128] Over a median of 2.4 years, there was a 39% risk reduction (HR 0.61, 95% CI 0.51 to 0.72; $p < 0.001$) in the primary outcome of 50% decline in eGFR, end-stage kidney disease or death from renal or cardiovascular causes.[128] Most recently, the EMPA-KIDNEY trial recruited 6609 participants with CKD with either an eGFR 20–44 ml/minute or an eGFR 45–89 ml/minute with urinary ACR > 200.[129] During a 2.0 year median follow-up, there was a 28% risk reduction (HR 0.72, 95% CI 0.64 to 0.82; $p < 0.001$) in the composite primary outcome of progression of kidney disease or death from cardiovascular causes.[129] The SGLT-2 inhibitor trial findings have informed updates in guideline recommendations and are likely to significantly change the management of patients with CKD in practice.

Future work

In terms of unanswered questions, the value of spironolactone in the renal damage CKD phenotype was not answered by BARACK-D and might be worthy of future research. In addition, the potential role for finerenone in non-diabetic age-related renal decline could be tested.

Conclusions

The BARACK-D trial found no evidence that the addition of low-dose spironolactone at 25 mg daily in patients with CKD 3b had any benefit on the high rates of cardiovascular events seen in the trial follow-up, either for the combined primary or individual components. There was also no benefit observed in rates of renal function decline over the trial, with much higher initial creatinine rise and eGFR decline, and to a higher percentage rate, in the first few weeks of spironolactone treatment. These higher rates of negative renal change reduced in scale over the study but did not equalise between arms. The addition of 25 mg of spironolactone therefore provided no reno- or cardio-protection and was associated with more AEs.

Patient and public involvement

As acknowledged above, Barry Clark was a member of the Trial Steering Committee and commented on the drafting of the protocol and the patient information sheets, informed consent forms and this report.

Additional information

CRediT contribution statement

Richard Hobbs (https://orcid.org/0000-0001-7976-7172): Conceptualisation (lead), Funding acquisition (lead), Methodology (share), Interpretation (lead), Writing – drafting (equal), Writing – editing (equal).

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Sam Mort (https://orcid.org/0000-0001-6332-4641): Analysis (share), Methodology (share), Writing – editing (share).

Ly-Mee Yu (https://orcid.org/0000-0003-0331-7364): Methodology (lead), Writing – editing (share).

John Townend: Conceptualisation (share), Funding acquisition (share), Methodology (share).

Charles Ferro: Conceptualisation (share), Funding acquisition (share), Methodology (share).

Peter Bower: Trial delivery (share), Resources (share).

Dan Lasserson: Trial delivery (share), Resources (share).

Gene Feder: Trial delivery (share), Resources (share).

Paul Little: Trial delivery (share), Resources (share).

Nadeem Qureshi: Trial delivery (share), Resources (share).

Rafael Perera-Salazar: Methodology (share).

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The BARACK-D Trial Team

Professor Richard Hobbs was Chief Investigator. Louise Jones, Ben Thompson, Joy Rahman and Charles Vicary were the Trial Managers at separate durations throughout the trial. Lysbeth Evans was Trial Co-ordinator and Elaine Egden was the Trial Administrator. Meena Patil was the Data Manager, and Ly-Mee Yu and Sam Mort were the trial statisticians.

Co-investigators

Co-investigators include John Townend, Charles Ferro, Peter Bower, Dan Lasserson, Gene Feder, Paul Little, Nadeem Qureshi, Rafael Perera-Salazar and Emma Ogburn.

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The BARACK-D team would further like to thank the PIs at the regional co-ordinating centres and their colleagues for recruiting and monitoring sites: **Oxford regional co-ordinating centre team:** Richard Hobbs (Chief Investigator), Dan Lasserson, Richard McManus, Rafael Perera, Andrew Farmer, David Timmins, Ben Thompson, Louise Jones, Joy Rahman, Charles Vicary.

Birmingham regional co-ordinating centre team: David Fitzmaurice (PI), John Townend, Charles Ferro, Gurdip Heer, Rachel Della, Helen Duffy, Fiona McRonald, Deborah Popoola, Kirandeep Jheeta.

Birmingham co-ordinating centre closed on 23 March 2016 with all patient follow-up appointments becoming the responsibility of the Oxford co-ordinating centre. At the time of closure, Birmingham co-ordinating centre had recruited 15 patients. Overall, 19 patients were recruited from the Birmingham region.

Bristol regional co-ordinating centre team: Gene Feder (PI), Susan Bryant.

Bristol co-ordinating centre closed on 31 May 2017. At the time of closure, the centre had recruited 238 patients. Patient recruitment and follow-up was continued by Oxford co-ordinating Centre. 340 patients were recruited from the Bristol region overall.

Derby regional co-ordinating centre team: Maarten Taal (PI), Yvonne Newey, Deborah Morgan.

Derby co-ordinating centre closed on 29 April 2016. At the time of closure, the centre had recruited 12 patients. Patient recruitment and follow-up was continued by Oxford co-ordinating centre. Overall, 12 patients were recruited from the Derby region.

Manchester regional co-ordinating centre team: Peter Bower (PI), Caroline Gardner, Victoria Lee, Thomas Blakeman.

Manchester co-ordinating centre closed on 31 May 2017. At the time of closure, the centre had recruited 104 patients. Patient recruitment and follow-up was continued by Oxford co-ordinating centre. 108 patients were recruited from the Manchester region overall.

Nottingham regional co-ordinating centre: Nadeem Qureshi (PI), Laura Cross-Bardell, Christina Brindley.

Nottingham co-ordinating centre closed in late 2015, with all patient follow-up appointments becoming the responsibility of the Oxford co-ordinating centre. At the time of closure, 27 patients had been recruited. 28 patients were recruited from the Nottingham region overall.

Southampton regional co-ordinating centre: Paul Little (PI), Jane Barnett, Karen Middleton.

Southampton co-ordinating centre closed on 31 May 2017. At the time of closure, the centre had recruited 181 patients. Patient recruitment and follow-up was continued by Oxford co-ordinating centre. Three hundred and seventy-one patients were recruited from the Southampton region overall.

The BARACK-D team would also like to thank all sites covered by those regions for recruiting and monitoring trial participants. They are (in order of co-ordinating centre):

Oxford regional co-ordinating centre sites: The Boathouse Surgery, Pangbourne; Aston Clinton Surgery, Westongrove; Broadshires Health Centre, Carterton; Ridgeway View Family Practice, Swindon; Eynsham Medical Group, Witney; Elm Tree Surgery, Shrivenham; Park Road Surgery, Camberley; Mann Cottage Surgery, Morton in Marsh; Yorkley Medical Centre, Gloucester; The Rycote Practice, Thame; The Chipping Surgery, Gloucester; Yorkleigh Surgery, Cheltenham; Hawthorn Medical Centre, Swindon; Chipping Campden Surgery, Gloucester; Cotswold Medical Practice, Bourton on the Water; Wymondham Medical Practice, Norfolk; Beccles Medical Centre, Suffolk; Eldene Surgery, Swindon; Kingsthorpe Medical Centre, Northants; The Peninsula Practice, Suffolk; The Chesterfield Drive Practice, Suffolk; Martlesham Heath Surgery, Suffolk; Wickham Market Medical Centre, Suffolk; Danetre Medical Practice, Northants; Humbleyard Practice, Norfolk; Rosedale Surgery, Suffolk; Andaman Surgery, Suffolk; Winyates Health Centre, Worcester; Hoveton and Wroxham Medical Centre, Norfolk; Thaxted Surgery, Essex; Harvey Group Practice, Herts; Fakenham Medical Practice, Norfolk; St Mary's Surgery, Cambridgeshire; The Nelson Medical Practice, East Norfolk; Crawley Road Medical Centre, Leyton; Prospect Medical Centre, Norfolk; Bridge Road Surgery, Suffolk; St Stephen's Gate Medical Practice, Norfolk; Sheringham Medical Practice, Norfolk; Bradford on Avon and Melksham Health Partnership, Wiltshire; South Oxford Health Centre, Oxford; Wokingham Medical Centre, Wokingham; Gladstone Surgery, Chesham, Bucks; Didcot Health Centre, Oxford; Wellington House Practice, Princes Risborough; Primrose Lane Surgery, Wolverhampton; Lakeside Medical Centre, Wolverhampton; Furlong Medical Centre, Tunstall; The Cloisters

Medical Practice, Lichfield; Tamar Medical Centre, Wolverhampton; Adderley Green Surgery, Stoke on Trent; Ashley Surgery, Shropshire; Park Medical Centre, Staffordshire; Broseley Medical Centre, Shropshire; The Leiston Surgery, Suffolk; Creffield Medical Centre, Colchester; Brockworth Surgery, Gloucester; Great Bentley Surgery, Colchester; Barrack Lane Medical Centre, Ipswich; Vauxhall Primary Health Care, Liverpool; Milman Road Health Centre, Reading; Mitcham Family Practice, Surrey; Gladstone Medical Centre, London; Royal Arsenal Medical Centre, London; Brigstock and South Norwood Partnership, Surrey; Streatham Common Practice, London; Preston Hill Surgery, Harrow; Gordon House Surgery, Ealing; Upper Norwood Group Practice, London; Manor Place Surgery, London; Fairview Medical Centre, London; Rushey Green Group Practice, London; Wallington Family Practice, Wallington; Premier Medical Centre, Wembly; Clapham Park Group Practice, London; The Alverton Practice, Cornwall; The Three Spires Medical Practice, Cornwall; Brannam Medical Centre, Barnstaple; Bideford Medical Centre, Devon; Whitefield Health Care, Nelson; Llanedeyrn Health Centre, Cardiff; Practice of Health, Barry; Llandaff North Medical Centre, Cardiff; St. Andrews Practice, Tonypandy; Ashgrove Surgery, Pontypridd; Clarence Medical Centre, Rhyl; Marches Medical Practice, Broughton; The Beech House Surgery, Denbigh; Oak Tree Surgery, Bridgend; Ely Bridge Surgery, Cardiff.

Birmingham regional co-ordinating centre sites: Coseley Medical Centre, Dudley; Balaji Surgery, Sparkbrook; Parkside Medical Practice, Walsall; Greenridge Surgery, Yardley Wood; Darlaston Health Centre, Walsall; Grange Hill Surgery, Kings Norton; Yardley Wood Health Centre, Yardley Wood; Bellevue Medical Centre, Highgate; Blackwood Health Centre, Sutton Coldfield.

Bristol regional co-ordinating centre sites: Westlake Surgery, Somerset; Helios Medical Centre, Bristol; Clevedon Riverside Group, Clevedon; Axbridge and Wedmore Medical Practice, Axbridge; Vine Surgery, Somerset; East Quay Medical Centre, Bridgewater, Somerset; Wrington Vale Medical Practice, Wrington; Yeo Vale Medical Practice, Bristol; Langport Surgery, Langport, Somerset; Backwell and Nailsea Medical Group, Bristol; Crown Medical Centre, Bristol; Sunnyside Surgery, Clevedon; The Cedars Surgery, Weston Super Mare; The Lennard Surgery, Bristol; Tawstock Medical Centre, Chard, Somerset; Glastonbury Surgery, Glastonbury; Long Ashton Surgery, Bristol; Bradgate Surgery, Bristol; Cranleigh Gardens Medical Centre, Bridgwater, Somerset; Vine Surgery, Somerset; West Walk Surgery, Bristol; Wells City Practice, Wells, Somerset; Fishponds Family Practice, Fishponds, Bristol; Westlake Surgery, Somerset; Chew Medical Practice, Bristol; The Pulteney Practice, Bath, Somerset; Rowden Medical Partnership, Chippenham, Wiltshire; Park Medical Partnership, Shepton Mallet; Oldfield Surgery, Bath, Somerset; Portishead Medical Group, Bristol; Pembroke Road Surgery, Bristol; Horfield Health Centre, Bristol; Fallodon Way Medical Centre, Bristol; Westbury on Trym Primary Care Centre, Bristol; Greenway Community Practice, Bristol; Monks Park Surgery, Bristol; Whiteladies Health Centre.

Derby regional co-ordinating centre sites: Royal Derby Hospital.

Manchester regional co-ordinating centre sites: Oakenhurst Medical Practice, Blackburn; Burnside Surgery, Bolton; The Gill Medical Centre, Manchester; Nantwich Health Centre, Nantwich; Queen Square Medical Practice, Lancaster; The Mount View Practice, Fleetwood; The Village Practice, Thornton Cleveleys; Windermere and Bowness Medical Practice, Windermere; Sandbach GPs, Cheshire; Kiltearn Medical Centre, Nantwich; Claughton Medical Centre, Birkenhead; Shifa Surgery, Blackburn; Garswood Surgery, Wigan; Cleveleys Group Practice, Thornton Cleveleys; Crescent Surgery, Thornton Cleveleys; Coastal Medical Group, Morecambe; Jubilee Medical Group, Longfield; Westbourne Medical Centre, Middlesbrough; Woodland Medical Practice, Lincoln; Branch End Surgery, Stocksfield; Belford Medical Practice, Northumberland; Willington Medical Group, Crook; The Sele Medical Practice, Hexham.

Nottingham regional co-ordinating centre sites: Tall Trees Surgery, Retford; Bentley Surgery, Doncaster; Bawtry and Blyth Medical, Doncaster; Ecclesfield Group Practice, Sheffield; The Scott Practice, Doncaster; Thurmaston Health Centre, Leicester; The Burns Practice, Doncaster.

Southampton regional co-ordinating centre sites: Highlands Practice, Fareham; Forest End Surgery, Waterlooville; Cowplain Family Practice, Waterlooville; Wareham Surgery, Dorset; Three Swans Surgery, Salisbury; Hathaway Medical Centre, Chippenham; Avenue Surgery, Warminster, Wiltshire; The Oaklands Practice, Yateley; Adcroft Surgery, Trowbridge; Nightingale Surgery, Romsey; Tolsey Surgery, Malmesbury; Homewell Curlew Practice, Havant; Market

Lavington Surgery, Wiltshire; Friars Gate Surgery, Winchester; Patford House Surgery, Palne; The Denmead Practice, Waterlooville; Adam Practice, Poole; Chawton Park Surgery, Basingstoke; Bermuda Practice, Basingstoke; Highcliffe Medical Centre, Dorset; Liphook and Liss Surgery, Hants; Stokewood Surgery, Hants; Towerhouse Medical Centre, Bristol; St. Helens Medical Centre, Isle of Wight; Swanage Medical Practice, Bournemouth; Rowlands Gill Medical Centre, Newcastle-Upon-Tyne; Westlands Medical Centre, Porchester; Yealm Medical Centre, Plymouth; Budleigh Salterton Medical Centre, Exeter; Mount Pleasant Health Centre, Exeter; Raleigh Surgery, Exmouth; The Bovey Tracey and Chudleigh Practice, Torquay; Rolle Medical Partnership, Exmouth; Brunel Medical Practice, Torquay; Teign Estury Medical Practice, Torquay; Barton Surgery, Dawlish; Richmond House Surgery, Teignmouth; Claremont Medical Practice, Exmouth; Sea Road Surgery, Bexhill; Hawkinge and Elham Valley Practice, Folkestone; Pulborough Medical Group, Redhill; Northbourne Medical Centre, Shoreham-By-Sea; Cathedral Medical Practice, Chichester; Cossington House Surgery, Canterbury; Beaconsfield Surgery, Hastings; Channel View Medical Group, Teignmouth.

Patient and public involvement

Barry Clark was a member of the Trial Steering Committee and commented on the drafting of the protocol and the patient information sheets, informed consent forms and this report.

Data-sharing statement

All data are securely stored under the Data Protection Act 2004 and adhere to the PCCTU data-sharing standard operating procedure in which data-sharing agreements have to be approved by both the Trial Management Group and the sponsor. All available data can be obtained by contacting the corresponding author.

Ethics statement

The Thames Valley Research Ethics Committee approved the study Ref: 13/SC/0114 on 9 April 2013.

Information governance statement

The BARACK-D trial was co-ordinated by the PCCTU. The PCCTU stores data on University of Oxford Medical Sciences Division Information Technology hosted servers.

Disclosure of interests

***Full disclosure of interests*:** Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/PYFT6977.

***Primary conflicts of interest*:** Richard Hobbs reports that he is the Director of the NIHR Applied Research Collaboration Oxford and Thames Valley, President of the IPCCS and Chair of the EPCCS. He has received part-funding from the NIHR ARC and the NIHR Oxford Medtech and In-Vitro Diagnostics Co-operative (MIC). He was a member of the HTA Clinical Evaluation and Trials Committee from October 2010 to November 2015.

Clare Taylor reports that she is a member of the Pumping Marvellous Foundation Clinical Advisory Board, a member of the British Society of Heart Failure Education and Training Committee and a member of the Dutch Heart Foundation Independent Scientific Advisory Board. She receives an NIHR appraisal award, funding for an academic clinical lectureship, and personal fees from Roche Diagnostics and the Royal College of General Practitioners.

Richard McManus reports grants during the conduct of the study from NIHR HTA, SPCR, Research Fellowship, PGfAR and ARC, and grants from Omron and Sensyne, all paid to his institution. He has been the Chair of the BP Monitoring Standing Committee since 2011 to the present.

Jane Wolstenholme reports grants during the conduct of the study from the NIHR HTA, i4i and PGfAR.

Nicholas Jones reports that he is Trustee of the two UK charities, Scoliosis Association UK and Cardiac Risk in the Young. He receives private consulting fees for Oxford Epidemiology and funds for a Wellcome Trust Doctoral Research Fellowship.

Jennifer Hirst reports that she was a member of the HTA General Committee from July 2017 to July 2018.

Ly-Mee Yu reports that she was a member of the HTA Efficient Study Designs from November 2015 to July 2016.

Publication

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References

1. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004;**164**:659–63. https://doi.org/10.1001/archinte.164.6.659
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-yuan. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**:1296–305. https://doi.org/10.1056/NEJMoa041031
3. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC study. *Kidney Int* 2003;**64**:610–5. https://doi.org/10.1046/j.1523-1755.2003.00109.x
4. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007;**298**:2038–47. https://doi.org/10.1001/jama.298.17.2038
5. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, *et al.*; Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;**375**:2073–81. https://doi.org/10.1016/s0140-6736(10)60674-5
6. Van Biesen W, De Bacquer D, Verbeke F, Delanghe J, Lameire N, Vanholder R. The glomerular filtration rate in an apparently healthy population and its relation with cardiovascular mortality during 10 years. *Eur Heart J* 2007;**28**:478–83. https://doi.org/10.1093/eurheartj/ehl455
7. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, *et al.* Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005;**352**:2049–60. https://doi.org/10.1056/NEJMoa043161
8. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, *et al.* Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006;**17**:2034–47. https://doi.org/10.1681/ASN.2005101085
9. Collins AJ, Li S, Gilbertson DT, Liu J, Chen S-C, Herzog CA. Chronic kidney disease and cardiovascular disease in the Medicare population. *Kidney Int Suppl* 2003:S24–31. https://doi.org/10.1046/j.1523-1755.64.s87.5.x
10. Foley RN, Curtis BM, Randell EW, Parfrey PS. Left ventricular hypertrophy in new hemodialysis patients without symptomatic cardiac disease. *Clin J Am Soc Nephrol* 2010;**5**:805–13. https://doi.org/10.2215/CJN.07761109
11. Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, Collins AJ. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005;**16**:489–95. https://doi.org/10.1681/ASN.2004030203
12. Bomback AS, Kshirsagar AV, Klemmer PJ. Renal aspirin: will all patients with chronic kidney disease one day take spironolactone? *Nat Clin Pract Nephrol* 2009;**5**:74–5.
13. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. *Lancet* 2020;**395**:709–33.
14. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FDR. Global prevalence of chronic kidney disease – a systematic review and meta-analysis. *PLOS ONE* 2016;**11**:e0158765. https://doi.org/10.1371/journal.pone.0158765
15. de Lusignan S, Tomson C, Harris K, van Vlymen J, Gallagher H. Creatinine fluctuation has a greater effect than the formula to estimate glomerular filtration rate on the prevalence of chronic kidney disease. *Nephron Clin Pract* 2011;**117**:c213–24. https://doi.org/10.1159/000320341

16. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, *et al.* Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**:339–52. https://doi.org/10.1016/s0140-6736(13)60595-4

17. KDIGO. Kidney disease: improving global outcomes (KDIGO). CKD work group 2012: clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;**Supplement 3**:1–150.

18. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**:461–70.

19. Hallan SI, Dahl K, Oien CM, Grootendorst DC, Aasberg A, Holmen J, Dekker FW. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. *BMJ* 2006;**333**:1047. https://doi.org/10.1136/bmj.39001.657755.BE

20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, *et al.*; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.

21. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis* 2010;**55**:622–7.

22. McFadden EC, Hirst JA, Verbakel JY, McLellan JH, Hobbs FDR, Stevens RJ, *et al.* Systematic review and metaanalysis comparing the bias and accuracy of the modification of diet in renal disease and chronic kidney disease epidemiology collaboration equations in community-based populations. *Clin Chem* 2018;**64**:475–85. https://doi.org/10.1373/clinchem.2017.276683

23. Stevens LA, Schmid CH, Greene T, Zhang YL, Beck GJ, Froissart M, *et al.* Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) study equations for estimating GFR levels above 60 mL/minute/1.73 m^2. *Am J Kidney Dis* 2010;**56**:486–95.

24. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD Epidemiology Collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. *Am J Kidney Dis* 2010;**56**:32–8. https://doi.org/10.1053/j.ajkd.2010.02.344

25. Soares AA, Eyff TF, Campani RB, Ritter L, Weinert LS, Camargo JL, Silveiro SP. Performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) study equations in healthy South Brazilians. *Am J Kidney Dis* 2010;**55**:1162–3. https://doi.org/10.1053/j.ajkd.2010.03.008

26. Hippisley-Cox J, Coupland C. Predicting the risk of chronic kidney disease in men and women in England and Wales: prospective derivation and external validation of the QKidney Scores. *BMC Fam Pract* 2010;**11**:49.

27. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. *Am Heart J* 2009;**158**:629–36. https://doi.org/10.1016/j.ahj.2009.06.031

28. Matsushita K, Selvin E, Bash LD, Astor BC, Coresh J. Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD study equation for estimated GFR: the atherosclerosis risk in communities (ARIC) study. *Am J Kidney Dis* 2010;**55**:648–59.

29. Stevens LA, Padala S, Levey AS. Advances in glomerular filtration rate-estimating equations. *Curr Opin Nephrol Hypertens* 2010;**19**:298–307.

30. Shafi T, Matsushita K, Selvin E, Sang Y, Astor BC, Inker LA, Coresh J. Comparing the association of GFR estimated by the CKD-EPI and MDRD study equations and mortality: the third national health and nutrition examination survey (NHANES III). *BMC Nephrol* 2012;**13**:42.

31. NICE. *Chronic Kidney Disease: Assessment and Management*, *NICE Guideline [NG203]*; 2021. URL: www.nice.org.uk/guidance/ng203/chapter/Recommendations (accessed 15 December 2021).

32. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. *JAMA* 2015;**313**:837–46. https://doi.org/10.1001/jama.2015.0602

33. Becker BN, Vassalotti JA. A software upgrade: CKD testing in 2010. *Am J Kidney Dis* 2010; **55**:8–10. https://doi.org/10.1053/j.ajkd.2009.11.005

34. Clase CM, Gao P, Tobe SW, McQueen MJ, Grosshennig A, Teo KK, *et al.*; ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in Angiotensin-Converting-Enzyme-Inhibitor Intolerant Subjects with Cardiovascular Disease). Estimated glomerular filtration rate and albuminuria as predictors of outcomes in patients with high cardiovascular risk: a cohort study. *Ann Intern Med* 2011;**154**:310–8. https://doi.org/10.7326/0003-4819-154-5-201103010-00005

35. Fox CS, Matsushita K, Woodward M, Bilo HJG, Chalmers J, Heerspink HJL, *et al.*; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;**380**:1662–73.

36. Mahmoodi BK, Matsushita K, Woodward M, Blankestijn PJ, Cirillo M, Ohkubo T, *et al.*; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. *Lancet* 2012;**380**:1649–61.

37. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, *et al.*; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* 2015;**3**:514–25.

38. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, *et al.*; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003;**108**:2154–69. https://doi.org/10.1161/01.Cir.0000095676.90936.80

39. Bansal N, Roy J, Chen HY, Deo R, Dobre M, Fischer MJ, *et al.*; CRIC Study Investigators. Evolution of echocardiographic measures of cardiac disease from CKD to ESRD and risk of all-cause mortality: findings from the CRIC study. *Am J Kidney Dis* 2018;**72**:390–9.

40. Kouis P, Kousios A, Kanari A, Kleopa D, Papatheodorou SI, Panayiotou AG. Association of non-invasive measures of subclinical atherosclerosis and arterial stiffness with mortality and major cardiovascular events in chronic kidney disease: systematic review and meta-analysis of cohort studies. *Clin Kidney J* 2020;**13**:842–54.

41. Böckmann I, Lischka J, Richter B, Deppe J, Rahn A, Fischer D-C, *et al.* FGF23-mediated activation of local RAAS promotes cardiac hypertrophy and fibrosis. *Int J Mol Sci* 2019;**20**:4634. https://doi.org/10.3390/ijms20184634

42. Gutiérrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, *et al.* Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation* 2009;**119**:2545–52.

43. Isakova T, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, Xie H, *et al.* Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011;**79**:1370–8.

44. Panizo S, Martínez-Arias L, Alonso-Montes C, Cannata P, Martín-Carro B, Fernández-Martín JL, *et al.* Fibrosis in chronic kidney disease: pathogenesis and consequences. *Int J Mol Sci* 2021;**22**:408. https://doi.org/10.3390/ijms22010408

45. Chue CD, Townend JN, Steeds RP, Ferro CJ. Arterial stiffness in chronic kidney disease: causes and consequences. *Heart* 2010;**96**:817–23. https://doi.org/10.1136/hrt.2009.184879

46. Wang XR, Zhang JJ, Xu XX, Wu Y-G. Prevalence of coronary artery calcification and its association with mortality, cardiovascular events in patients with chronic kidney disease: a systematic review and meta-analysis. *Ren Fail* 2019;**41**:244–56.

47. Chen J, Budoff MJ, Reilly MP, Yang W, Rosas SE, Rahman M, *et al.*; CRIC Investigators. Coronary artery calcification and risk of cardiovascular disease and death among patients with chronic kidney disease. *JAMA Cardiol* 2017;**2**:635–43.

48. Ho CY, Shanahan CM. Medial arterial calcification. *Arterioscler Thromb Vasc Biol* 2016;**36**:1475–82. https://doi.org/10.1161/ATVBAHA.116.306717

49. Goodman WG, London G, Amann K, Block GA, Giachelli C, Hruska KA, *et al.*; Vascular Calcification Work Group. Vascular calcification in chronic kidney disease. *Am J Kidney Dis* 2004;**43**:572–9. https://doi.org/10.1053/j.ajkd.2003.12.005

50. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001;**103**:987–92. https://doi.org/10.1161/01.cir.103.7.987

51. Duni A, Liakopoulos V, Rapsomanikis KP, Dounousi E. Chronic kidney disease and disproportionally increased cardiovascular damage: does oxidative stress explain the burden? *Oxid Med Cell Longev* 2017;**2017**:9036450. https://doi.org/10.1155/2017/9036450

52. Roumeliotis S, Mallamaci F, Zoccali C. Endothelial dysfunction in chronic kidney disease, from biology to clinical outcomes: a 2020 update. *J Clin Med* 2020;**9**:2359.

53. London GM. Arterial stiffness in chronic kidney disease and end-stage renal disease. *Blood Purif* 2018;**45**:154–8. https://doi.org/10.1159/000485146

54. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension* 2005;**46**:200–4. https://doi.org/10.1161/01.Hyp.0000168052.00426.65

55. Muntner P, He J, Astor BC, Folsom AR, Coresh J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. *J Am Soc Nephrol* 2005;**16**:529–38. https://doi.org/10.1681/asn.2004080656

56. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, *et al.*; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181–92. https://doi.org/10.1016/s0140-6736(11)60739-3

57. Hirst JA, Taylor KS, Stevens RJ, Blacklock CL, Roberts NW, Pugh CW, Farmer AJ. The impact of renin–angiotensin–aldosterone system inhibitors on Type 1 and Type 2 diabetic patients with and without early diabetic nephropathy. *Kidney Int* 2012;**81**:674–83. https://doi.org/10.1038/ki.2011.413

58. Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. *Cochrane Database Syst Rev* 2005:CD004136. https://doi.org/10.1002/14651858.CD004136.pub2

59. Toyama T, Neuen BL, Jun M, Ohkuma T, Neal B, Jardine MJ, *et al.* Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis. *Diabetes Obes Metab* 2019;**21**:1237–50. https://doi.org/10.1111/dom.13648

60. Salah HM, Al'Aref SJ, Khan MS, Al-Hawwas M, Vallurupalli S, Mehta JL, *et al.* Effect of sodium-glucose cotransporter 2 inhibitors on cardiovascular and kidney outcomes-systematic review and meta-analysis of randomized placebo-controlled trials. *Am Heart J* 2021;**232**:10–22. https://doi.org/10.1016/j.ahj.2020.10.064

61. Scheen AJ. Pharmacokinetics, pharmacodynamics and clinical use of SGLT2 inhibitors in patients with type 2 diabetes mellitus and chronic kidney disease. *Clin Pharmacokinet* 2015;**54**:691–708. https://doi.org/10.1007/s40262-015-0264-4

62. Casas JP, Chua WL, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, MacAllister RJ. Effect of inhibitors of the renin–angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005;**366**:2026–33. https://doi.org/10.1016/s0140-6736(05)67814-2

63. Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, Solomon SD; RALES Investigators. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol* 2012;**60**:2082–9. https://doi.org/10.1016/j.jacc.2012.07.048

64. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G; Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–53. https://doi.org/10.1056/nejm200001203420301

65. Kuno T, Ueyama H, Fujisaki T, Briasouli A, Takagi H, Briasoulis A. Meta-analysis evaluating the effects of renin–angiotensin–aldosterone system blockade on outcomes of heart failure with preserved ejection fraction. *Am J Cardiol* 2020;**125**:1187–93. https://doi.org/10.1016/j.amjcard.2020.01.009

66. Shearer F, Lang CC, Struthers AD. Renin–angiotensin–aldosterone system inhibitors in heart failure. *Clin Pharmacol Ther* 2013;**94**:459–67. https://doi.org/10.1038/clpt.2013.135

67. Funder JW. Minireview: aldosterone and mineralocorticoid receptors: past, present, and future. *Endocrinology* 2010;**151**:5098–102. https://doi.org/10.1210/en.2010-0465

68. Funder JW. Aldosterone and mineralocorticoid receptors in the cardiovascular system. *Prog Cardiovasc Dis* 2010;**52**:393–400. https://doi.org/10.1016/j.pcad.2009.12.003

69. Tomaschitz A, Pilz S, Ritz E, Meinitzer A, Boehm BO, März W. Plasma aldosterone levels are associated with increased cardiovascular mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *Eur Heart J* 2010;**31**:1237–47. https://doi.org/10.1093/eurheartj/ehq019

70. Kuster GM, Kotlyar E, Rude MK, Siwik DA, Liao R, Colucci WS, Sam F. Mineralocorticoid receptor inhibition ameliorates the transition to myocardial failure and decreases oxidative stress and inflammation in mice with chronic pressure overload. *Circulation* 2005;**111**:420–7. https://doi.org/10.1161/01.Cir.0000153800.09920.40

71. Buonafine M, Bonnard B, Jaisser F. Mineralocorticoid receptor and cardiovascular disease. *Am J Hypertens* 2018;**31**:1165–74. https://doi.org/10.1093/ajh/hpy120

72. Rico-Mesa JS, White A, Ahmadian-Tehrani A, Anderson AS. Mineralocorticoid receptor antagonists: a comprehensive review of finerenone. *Curr Cardiol Rep* 2020;**22**:140. https://doi.org/10.1007/s11886-020-01399-7

73. Capelli I, Gasperoni L, Ruggeri M, Donati G, Baraldi O, Sorrenti G, *et al.* New mineralocorticoid receptor antagonists: update on their use in chronic kidney disease and heart failure. *J Nephrol* 2020;**33**:37–48. https://doi.org/10.1007/s40620-019-00600-7

74. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–17. https://doi.org/10.1056/NEJM199909023411001

75. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, *et al.*; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–21. https://doi.org/10.1056/NEJMoa030207

76. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, *et al.*; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21. https://doi.org/10.1056/NEJMoa1009492

77. Filippatos G, Anker SD, Böhm M, Gheorghiade M, Køber L, Krum H, *et al.* A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J* 2016;**37**:2105–14.

78. Hayashi M, Tsutamoto T, Wada A, Tsutsui T, Ishii C, Ohno K, *et al.* Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. *Circulation* 2003;**107**:2559–65. https://doi.org/10.1161/01.Cir.0000068340.96506.0f

79. Struthers AD. The clinical implications of aldosterone escape in congestive heart failure. *Eur J Heart Fail* 2004;**6**:539–45. https://doi.org/10.1016/j.ejheart.2004.04.013

80. Chung EY, Ruospo M, Natale P, Bolignano D, Navaneethan SD, Palmer SC, Strippoli GF. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev* 2020;**10**:CD007004.

81. Baran W, Krzemińska J, Szlagor M, Wronka M, Młynarska E, Franczyk B, Rysz J. Mineralocorticoid receptor antagonists-use in chronic kidney disease. *Int J Mol Sci* 2021;**22**:9995.

82. Alexandrou ME, Papagianni A, Tsapas A, Loutradis C, Boutou A, Piperidou A, *et al.* Effects of mineralocorticoid receptor antagonists in proteinuric kidney disease: a systematic review and meta-analysis of randomized controlled trials. *J Hypertens* 2019;**37**:2307–24. https://doi.org/10.1097/hjh.0000000000002187

83. Edwards NC, Ferro CJ, Kirkwood H, Chue CD, Young AA, Stewart PM, *et al.* Effect of spironolactone on left ventricular systolic and diastolic function in patients with early stage chronic kidney disease. *Am J Cardiol* 2010;**106**:1505–11. https://doi.org/10.1016/j.amjcard.2010.07.018

84. Edwards NC, Price AM, Mehta S, Hiemstra TF, Kaur A, Greasley PJ, *et al.* Effects of spironolactone and chlorthalidone on cardiovascular structure and function in chronic kidney disease: a randomized, open-label trial. *Clin J Am Soc Nephrol* 2021;**16**:1491–501. https://doi.org/10.2215/cjn.01930221

85. Yang CT, Kor CT, Hsieh YP. Long-term effects of spironolactone on kidney function and hyperkalemia-associated hospitalization in patients with chronic kidney disease. *J Clin Med* 2018;**7**:459.

86. Tseng WC, Liu JS, Hung SC, Kuo K-L, Chen Y-H, Tarng D-C, Hsu C-C. Effect of spironolactone on the risks of mortality and hospitalization for heart failure in pre-dialysis advanced chronic kidney disease: a nationwide population-based study. *Int J Cardiol* 2017;**238**:72–8. https://doi.org/10.1016/j.ijcard.2017.03.080

87. Minakuchi H, Wakino S, Urai H, Kurokochi A, Hasegawa K, Kanda T, *et al.* The effect of aldosterone and aldosterone blockade on the progression of chronic kidney disease: a randomized placebo-controlled clinical trial. *Sci Rep* 2020;**10**:16626.

88. Bakris G, Yang YF, Pitt B. Mineralocorticoid receptor antagonists for hypertension management in advanced chronic kidney disease: BLOCK-CKD trial. *Hypertension* 2020;**76**:144–9. https://doi.org/10.1161/hypertensionaha.120.15199

89. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, *et al.* Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;**385**:2252–63. https://doi.org/10.1056/NEJMoa2110956

90. Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, *et al.*; FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J* 2022;**43**:474–84. https://doi.org/10.1093/eurheartj/ehab777

91. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, *et al.*; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;**383**:2219–29. https://doi.org/10.1056/NEJMoa2025845

92. Murphree DD, Thelen SM. Chronic kidney disease in primary care. *J Am Board Fam Med* 2010;**23**:542–50. https://doi.org/10.3122/jabfm.2010.04.090129

93. Richards N, Harris K, Whitfield M, O'Donoghue D, Lewis R, Mansell M, *et al.* Primary care-based disease management of chronic kidney disease (CKD), based on estimated glomerular filtration rate (eGFR) reporting, improves patient outcomes. *Nephrol Dial Transplant* 2008;**23**:549–55. https://doi.org/10.1093/ndt/gfm857

94. Glassock RJ, Rule AD. The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. *Kidney Int* 2012;**82**:270–7.

95. Glassock RJ, Winearls C. Ageing and the glomerular filtration rate: truths and consequences. *Trans Am Clin Climatol Assoc* 2009;**120**:419–28.

96. Ng KP, Jain P, Gill PS, Heer G, Townend JN, Freemantle N, *et al.* Results and lessons from the Spironolactone To Prevent Cardiovascular Events in Early Stage Chronic Kidney Disease (STOP-CKD) randomised controlled trial. *BMJ Open* 2016;**6**:e010519.

97. Hill NR, Lasserson D, Thompson B, Perera-Salazar R, Wolstenholme J, Bower P, *et al.* Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK D) trial – a multi-centre, prospective, randomised, open, blinded end-point, 36-month study of 2616 patients within primary care with stage 3b chronic kidney disease to compare the efficacy of spironolactone 25 mg once daily in addition to routine care on mortality and cardiovascular outcomes versus routine care alone: study protocol for a randomized controlled trial. *Trials* 2014;**15**:160. https://doi.org/10.1186/1745-6215-15-160

98. NICE. *National Institute for Health and Care Excellence: Chronic Kidney Disease in Adults: Assessment and Management CG182*; 2014. URL: www.nice.org.uk/guidance/cg182 (accessed 18 December 2023).

99. Medicines and Healthcare products Regulatory Agency. *Clinical Trials for Medicines: Manage Your Authorisation, Report Safety Issues: Gov.UK*; 2014. URL: www.gov.uk/guidance/clinical-trials-for-medicines-manage-your-authorisation-report-safety-issues (accessed 4 March 2024).

100. Slater R, Hartley C, Moultrie F, Adams E, Juszczak E, Rogers R, *et al.*; Poppi Trial Team. A blinded randomised placebo-controlled trial investigating the efficacy of morphine analgesia for procedural pain in infants: trial protocol. *Wellcome Open Res* 2016;**1**:7.

101. Hill NR, Lasserson D, Thompson B, Perera-Salazar R, Wolstenholme J, Bower P, *et al.* Correction: Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK D) trial – a multi-centre, prospective, randomised, open, blinded end-point, 36-month study of 2616 patients within primary care with stage 3b chronic kidney disease to compare the efficacy of spironolactone 25 mg once daily in addition to routine care on mortality and cardiovascular outcomes versus routine care alone: study protocol for a randomized controlled trial. *Trials* 2022;**23**:1–2.

102. Al-Janabi H, Flynn T N, Coast J. Development of a self-report measure of capability wellbeing for adults: the ICECAP-A. *Qual Life Res* 2012;**21**:167–76.

103. Participation and Quality of Life (PAR-QoL). *Visual Analogue Scale – Quality of Life (VAS QL)*; 2018. URL: http://parqol.com/visual-analogue-scale-quality-of-life-vas-ql/ (accessed 18 December 2023).

104. National Institute for Health and Care Excellence. *NICE Health Technology Evaluations: The Manual. Process and Methods (PMG36)*. National Institute for Health and Care Excellence; 2022.

105. NHS England. *National Cost Collection Data Publication*; 2021. URL: www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ (accessed 18 December 2023).

106. National Institute for Health and Care Excellence. *British National Formulary (BNF)*; 2022. URL: https://bnf.nice.org.uk/ (accessed 16 November 2022).

107. Jones K, Burns A. *Unit Costs of Health and Social Care 2021*. Kent, UK: Personal Social Services Research Unit; 2021.

108. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;**20**:1727–36.

109. Hernández Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English population study. In York UoSa, editor. *Policy Research Unit in Economic Evaluation of Health and Care Interventions*; 2020.

110. Hays RD, Kallich J, Mapes D, Coons SJ, Amin N, Carter WB, Kamberg C. *Kidney Disease Quality of Life Short Form (KDQOL-SF™), Version 1.3: A Manual for Use and Scoring*. Santa Monica, CA: Rand; 1997.

111. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons; 2004.

112. Van Buuren S, Groothuis-Oudshoorn CG. MICE: multivariate imputation by chained equations in R. *J Stat Softw* 2011;**45**:1–67.

113. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *PharmacoEcon* 2014;**32**:1157–70.

114. Mason AJ, Gomes M, Grieve R, Carpenter JR. A Bayesian framework for health economic evaluation in studies with missing data. *Health Econ* 2018;**27**:1670–83. https://doi.org/10.1002/hec.3793

115. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;**30**:377–99.

116. Gomes M, Ng ES-W, Grieve R, Nixon R, Carpenter J, Thompson SG. Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. *Med Decis Making* 2012;**32**:350–61.

117. Greene WH. *Econometric Analysis*. Pearson Education India; 2003.

118. Glick HA, Doshi JA, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials*. Oxford: Oxford University Press; 2014.

119. Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. CRC Press; 1994.

120. Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. *Stat Med* 2018;**37**:2252–66. https://doi.org/10.1002/sim.7654

121. Royston P. Multiple imputation of missing values. *Stata J* 2004;**4**:227–41. https://doi.org/10.1177/1536867X0400400301

122. Curtis LA, Burns A. *Unit Costs of Health and Social Care 2018*. PSSRU, UK; 2018.

123. Curtis L. *Unit Costs of Health and Social Care 2010*. Canterbury: PSSRU, University of Kent; 2010.

124. NHS England. *2019/20 National Cost Collection Data Publication*. 2021. URL: www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ (accessed 18 December 2023).

125. UK Renal Registry. *Acute Kidney Injury (AKI) in England – A Report on the Nationwide Collection of AKI Warning Test Scores From 2018*. Association UK; 2020.

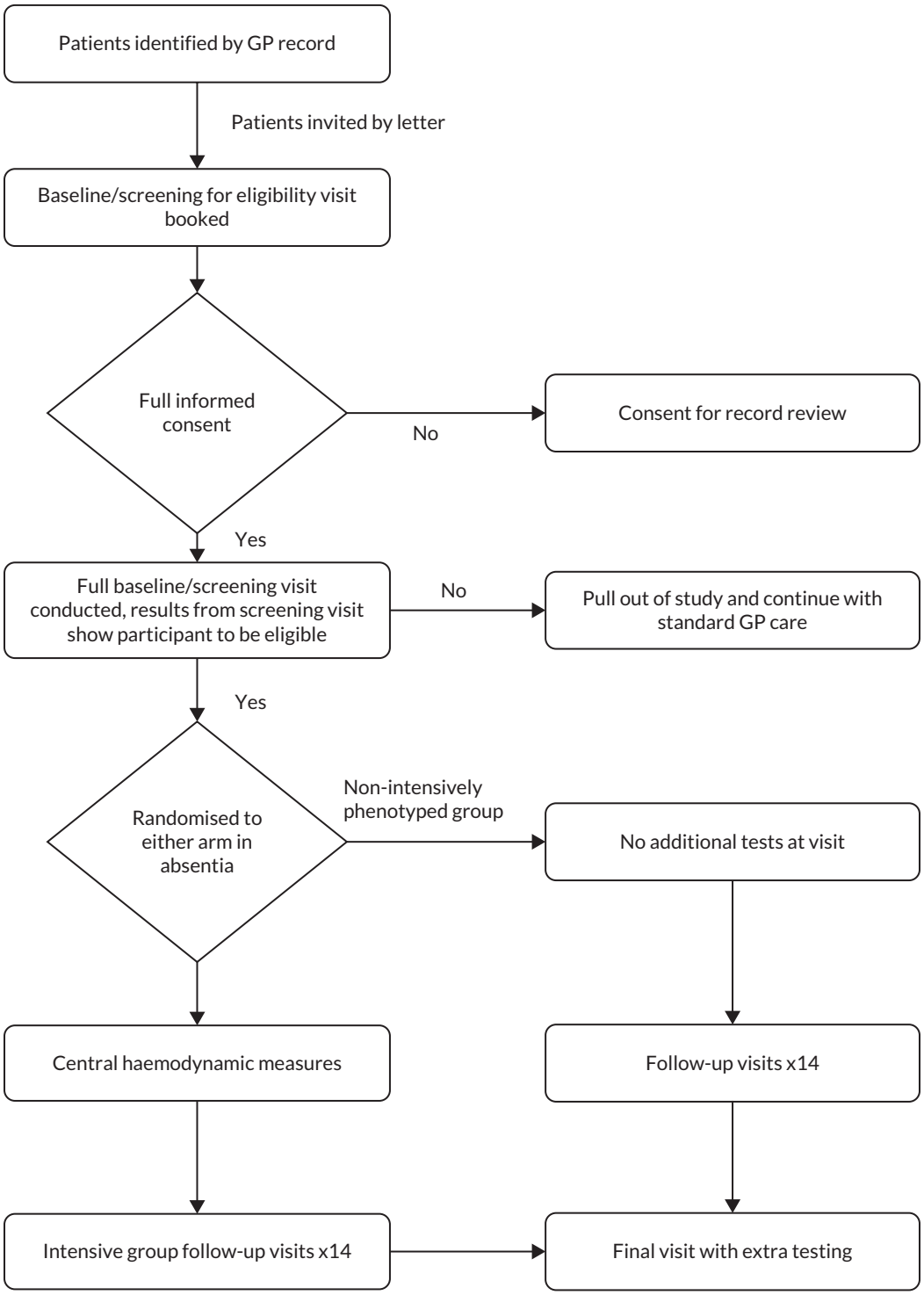
126. Ito S, Kashihara N, Shikata K, Nangaku M, Wada T, Okuda Y, Sawanobori T. Esaxerenone (CS-3150) in patients with type 2 diabetes and microalbuminuria (ESAX-DN): phase 3 randomized controlled clinical trial. *Clin J Am Soc Nephrol* 2020;**15**:1715–27. https://doi.org/10.2215/CJN.06870520

127. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, *et al.*; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–306. https://doi.org/10.1056/NEJMoa1811744

128. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, *et al.*; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–46. https://doi.org/10.1056/NEJMoa2024816

129. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, *et al.*; The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med* 2023;**388**:117–27. https://doi.org/10.1056/NEJMoa2204233

Appendix 1 Trial flow chart



Appendix 2 Objectives and outcome measures

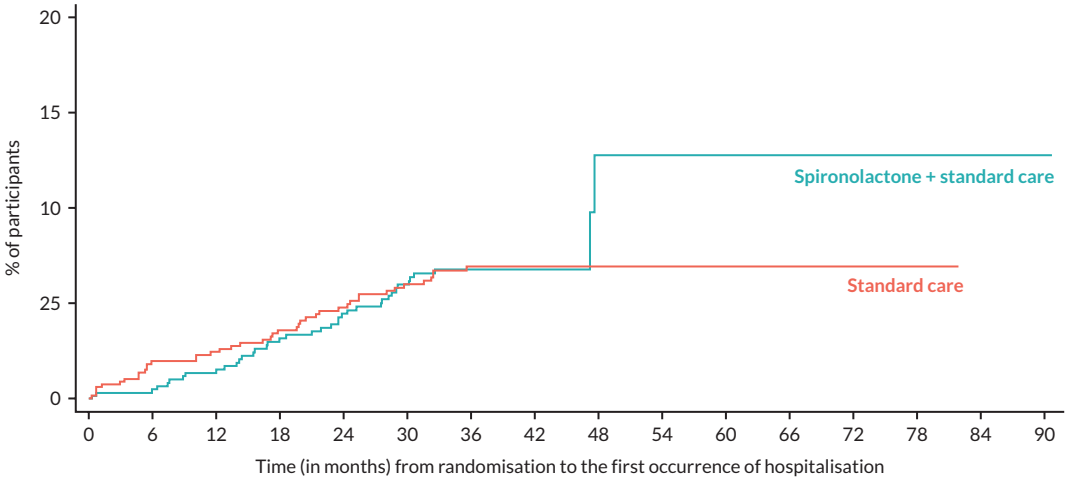
Objectives effect of aldosterone receptor	Outcome measures	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objective To determine the antagonism on mortality and cardiovascular outcomes (onset or progression of CVD) in patients with stage 3b CKD.	Time from randomisation until the first occurring of: • Death or • Hospitalisation for heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, resuscitated sudden death), stroke, TIA, PAD, or heart failure, or • First onset of any condition listed above not present at baseline. Primary end points were adjudicated by an independent end-points committee blinded to treatment arm.	Time from randomisation to first occurrence.
Primary Long-Term Objective To determine the effect of aldosterone receptor antagonism (event short-term use) on long-term mortality and cardiovascular outcomes in patients with stage 3b CKD.	Annual rates of: ◦ Death ◦ Hospitalisation for heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, resuscitated sudden death), stroke, TIA, PAN, or heart failure ◦ First onset of any condition listed above not present at baseline	Annual rates, collected via medical notes review.
Secondary Objectives		
To determine the effect of adding an aldosterone receptor antagonism in patients on 1–5 below:	Hospitalisation or new onset heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, resuscitated sudden death), stroke, TIA, PAN, or heart failure.	Total occurrences.
1. The individual components of the composite primary outcome		
2. Measures of cardiovascular haemodynamics	Change in blood pressure annually and at final visit.	Annually and at final visit.
3. Measures of renal function	◦ Changes in NP ◦ Change in ACR ◦ Changes in eGFR	Change from baseline, annually and to final visit for NP, ACR and eGFR.
4. Healthcare cost evaluation	Change in health status on EQ-5D-5L, KQoL, (ICECAP-A and QoL VAS – Oxford only) and NHS resource use (records).	Change from baseline, annually and to final visit.
5. Safety	◦ Rates of hypotension (< 100 mmHg systolic or > 20 mmHg systolic drop on standing) ◦ Rates of AEs ◦ Rates of hyperkalaemia	Total occurrences.

Appendix 3 Schedule of procedures

		Treatment and follow-up																
Week		B		1	2	4	12	26	39	52	65	78	91	104	117	130	143	156
Visit	S	V	0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Valid informed consent	Renal profile screening visits where applicable + Informed consent	X	Randomisation *in absentia* and prescription produced once blood results received															
Full demographic details		X																
Medical history		X																X
Clinical history		X																
Concomitant medications		X					X	X		X		X		X		X		X
Weight, height, waist/hip		X																X
Physical examination		X																
OBP measurement		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Home BP measurement							X			X		X		X		X		X
KDQoL-SF questionnaire		X						X		X				X				X
QoL EQ-5D-5L questionnaire		X						X		X				X				X
ICECAP-A questionnaire		X						X		X				X				X
QoL VAS		X						X		X				X				X
Diary card (medication monitoring)		X					X	X		X		X		X		X		X
Diary care (health economics)		X					X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine ACR		X																X
12 lead ECG		X																X
Blood tests for:																		
Full blood count		X																X
Renal profile		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver function test and bone profile		X						X		X				X				X
Lipids		X						X		X				X				X

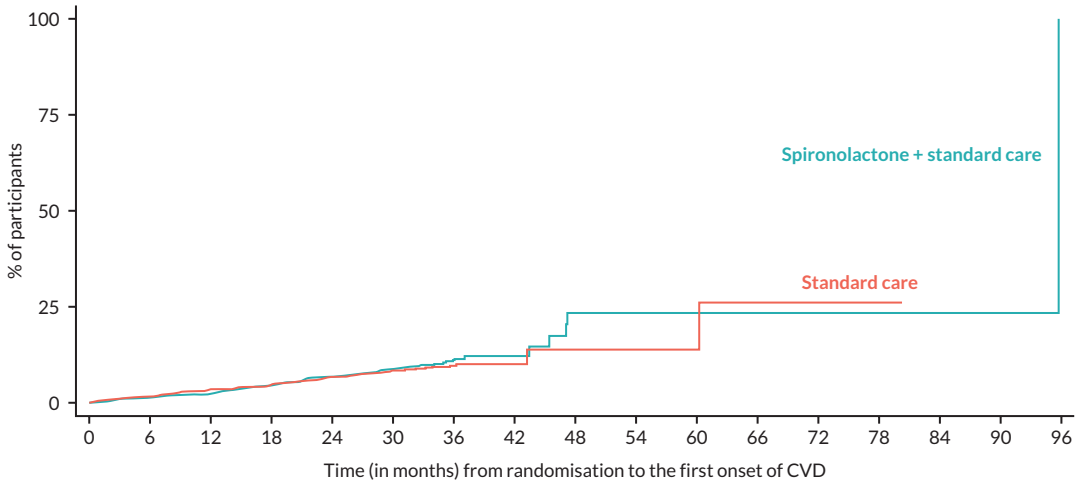
		Treatment and follow-up																
Week		**B**		**1**	**2**	**4**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**	**117**	**130**	**143**	**156**
Visit	**S**	**V**	**0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
HbA1c		X						X		X				X				X
Fasting blood sugar		X						X		X				X				X
BNP (where local labs allow)		X						X		X				X				X
Future analysis (where applicable)		X								X				X				X
Intensively phenotype group only																		
PWV		X						X		X				X				X
24-hour ambulatory BP estimation		X						X		X				X				X

Appendix 4 Kaplan–Meier curves for the primary end-point components



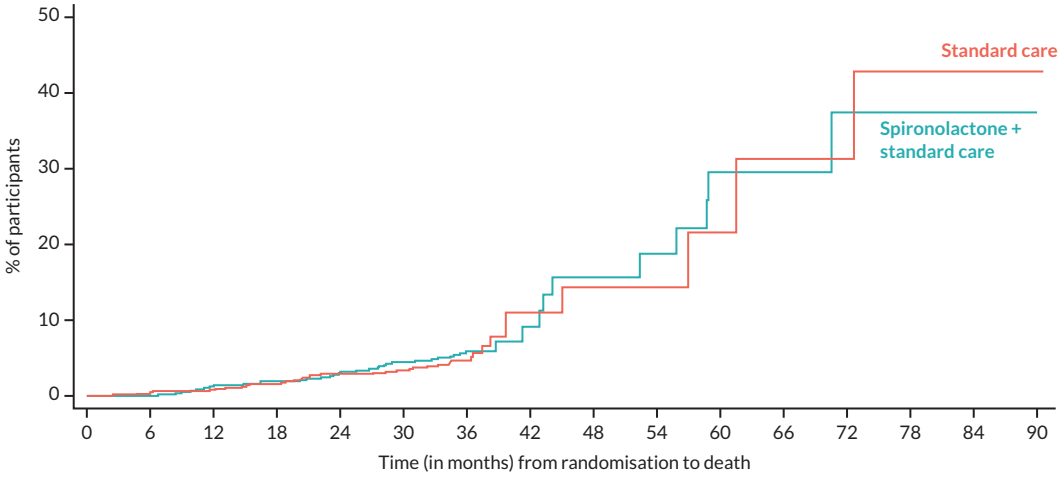
Spironolactone + standard care																
At risk	661	588	556	529	509	483	308	39	29	22	16	13	9	6	3	1
Censored	16	86	112	130	143	161	332	601	609	616	622	625	629	632	635	637
Events	0	3	9	18	25	33	37	37	39	39	39	39	39	39	39	39
Standard care																
At risk	687	638	610	571	553	529	301	29	15	8	7	4	3	2	0	0
Censored	8	44	69	101	112	129	352	624	638	645	646	649	650	651	653	653
Events	0	13	16	23	30	37	42	42	42	42	42	42	42	42	42	42

FIGURE 13 Kaplan–Meier curve for the time (in months) from randomisation to the first occurrence of hospitalisation.



Spironolactone + standard care																	
At risk	661	585	550	519	492	461	289	36	26	20	16	13	10	7	4	2	0
Censored	16	84	112	132	147	168	329	580	586	592	592	599	602	605	608	610	611
Events	0	8	15	26	38	48	59	61	65	65	65	65	65	65	65	65	66
Standard care																	
At risk	687	640	604	561	540	512	287	28	15	8	7	4	3	1	0	0	0
Censored	8	44	68	103	113	131	350	608	620	627	628	630	631	633	634	634	634
Events	0	11	23	31	42	52	58	59	60	60	60	61	61	61	61	61	61

FIGURE 14 Kaplan–Meier curve for the time (in months) from randomisation to the first onset of CVD.



Spironolactone + standard care																
At risk	661	597	572	552	534	509	327	44	33	25	16	14	8	5	2	0
Censored	16	80	98	114	125	143	318	599	607	614	620	622	627	630	633	635
Events	0	0	7	11	18	25	32	34	37	38	41	41	42	42	42	42
Standard care																
At risk	687	652	630	595	579	561	319	34	19	13	11	7	6	3	1	1
Censored	8	41	60	90	98	113	348	627	641	647	648	651	654	654	656	656
Events	0	2	5	10	18	21	28	34	35	35	36	37	38	38	38	38

FIGURE 15 Kaplan–Meier curve for the time (in months) from randomisation to death.

Appendix 5 Log–log plots and Kaplan–Meier predicted survival plots testing the proportional hazards assumption for the primary analysis

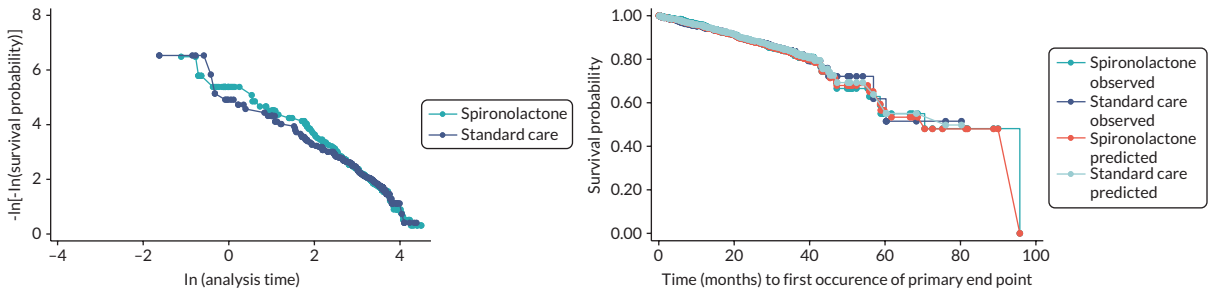


FIGURE 16 Model residuals for the primary end point.

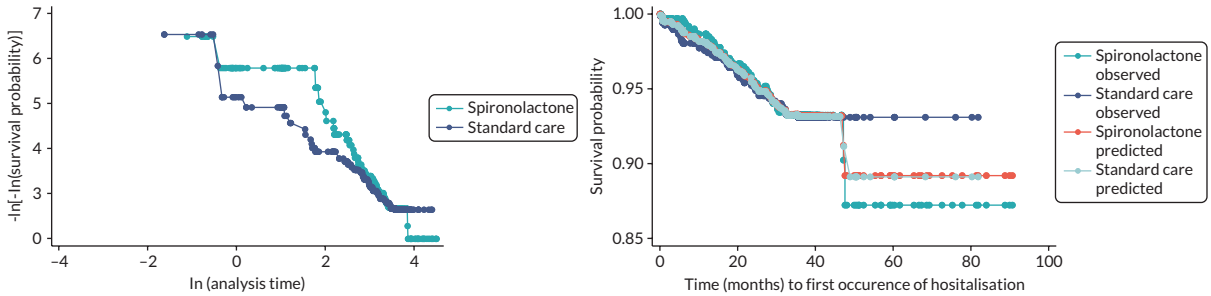


FIGURE 17 Model residuals for the primary end-point component: hospitalisation.

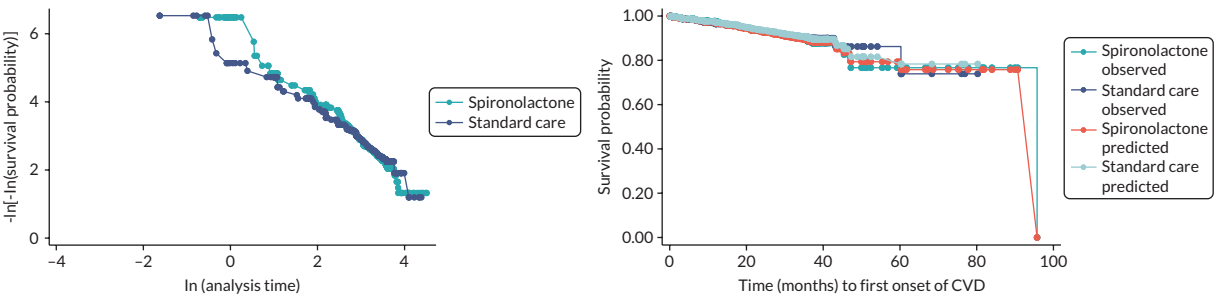


FIGURE 18 Model residuals for the primary end-point component: CVD.

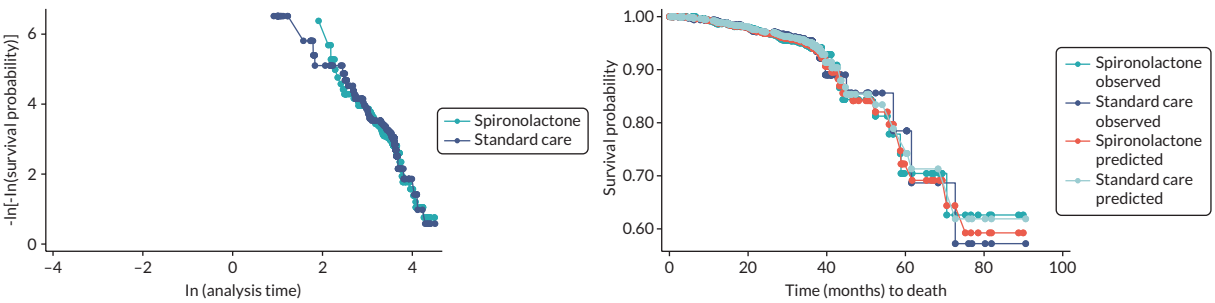


FIGURE 19 Model residuals for the primary end-point component: death.

Appendix 6 Histograms of the secondary end points by randomised arm at each assessment time point and post estimate plots of the model residuals from the linear mixed-effects models

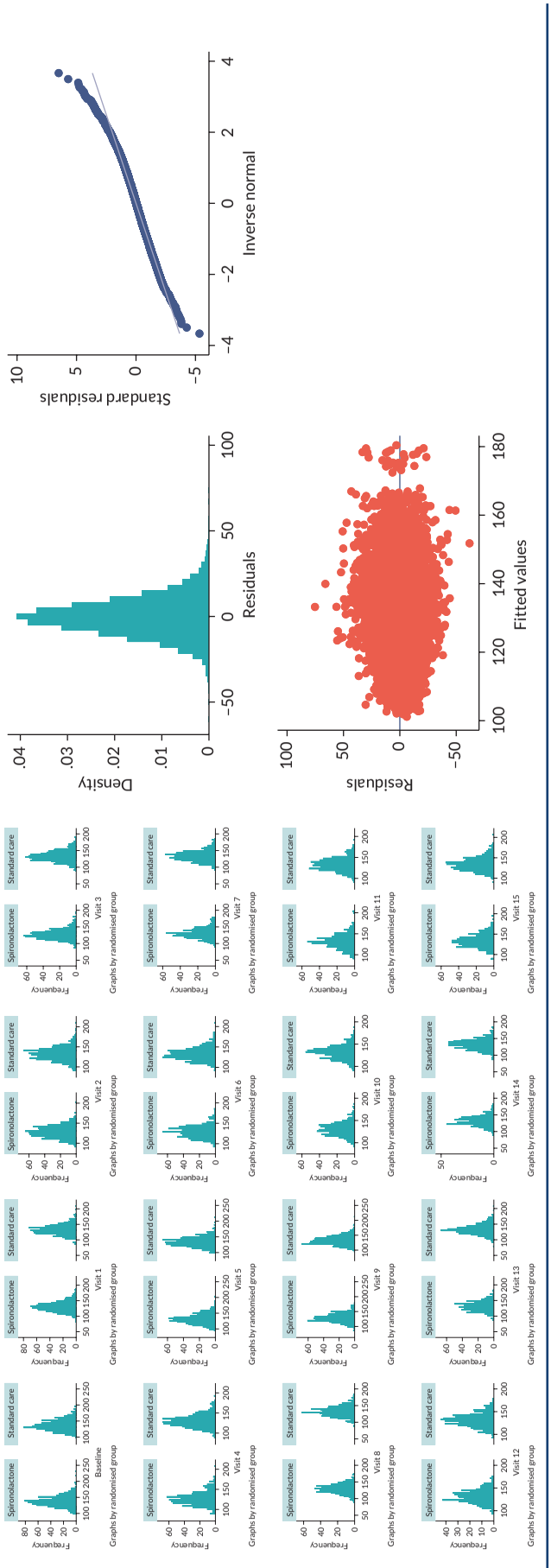


FIGURE 20 Histograms and model residuals for office measurements of systolic BP.

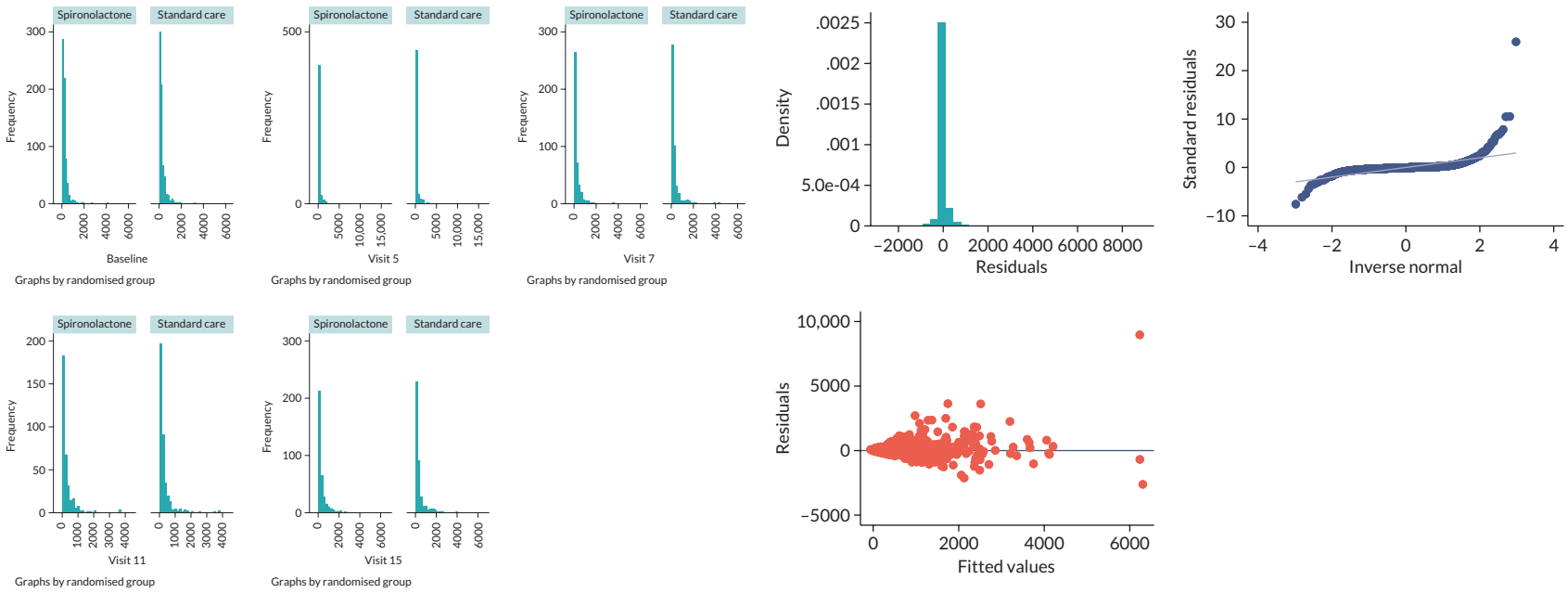


FIGURE 21 Histograms and model residuals for NP.

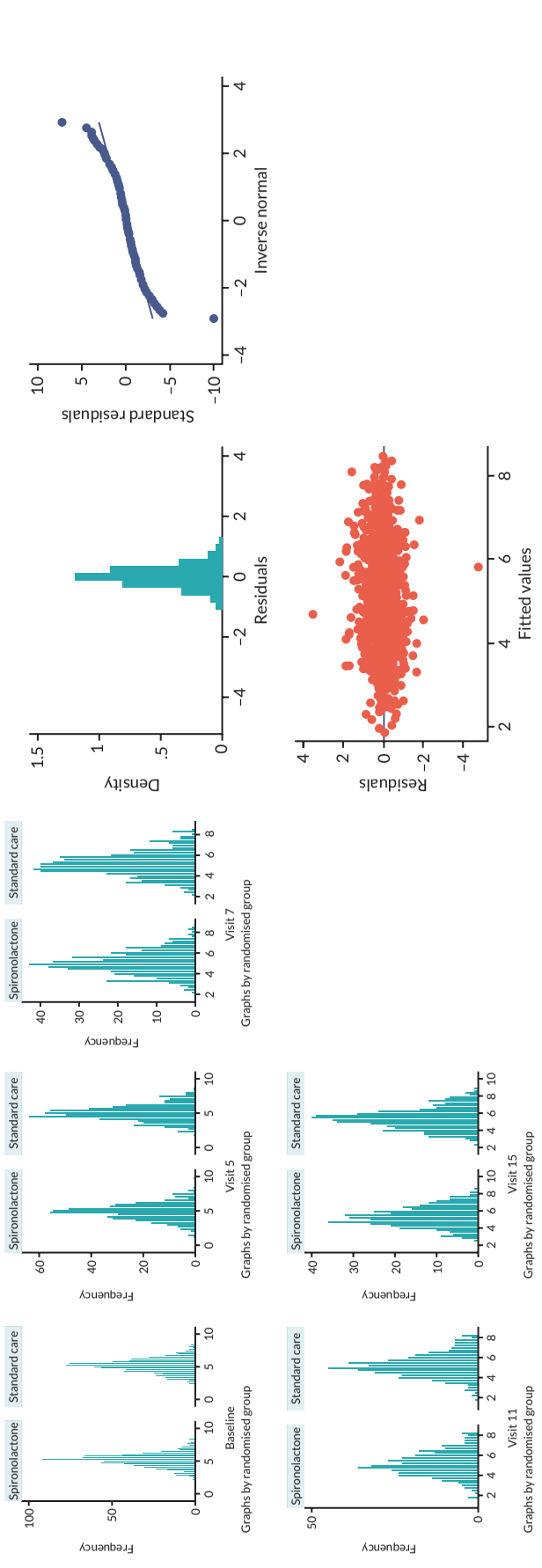


FIGURE 22 Histograms and model residuals for the logarithmic transformation of NP.

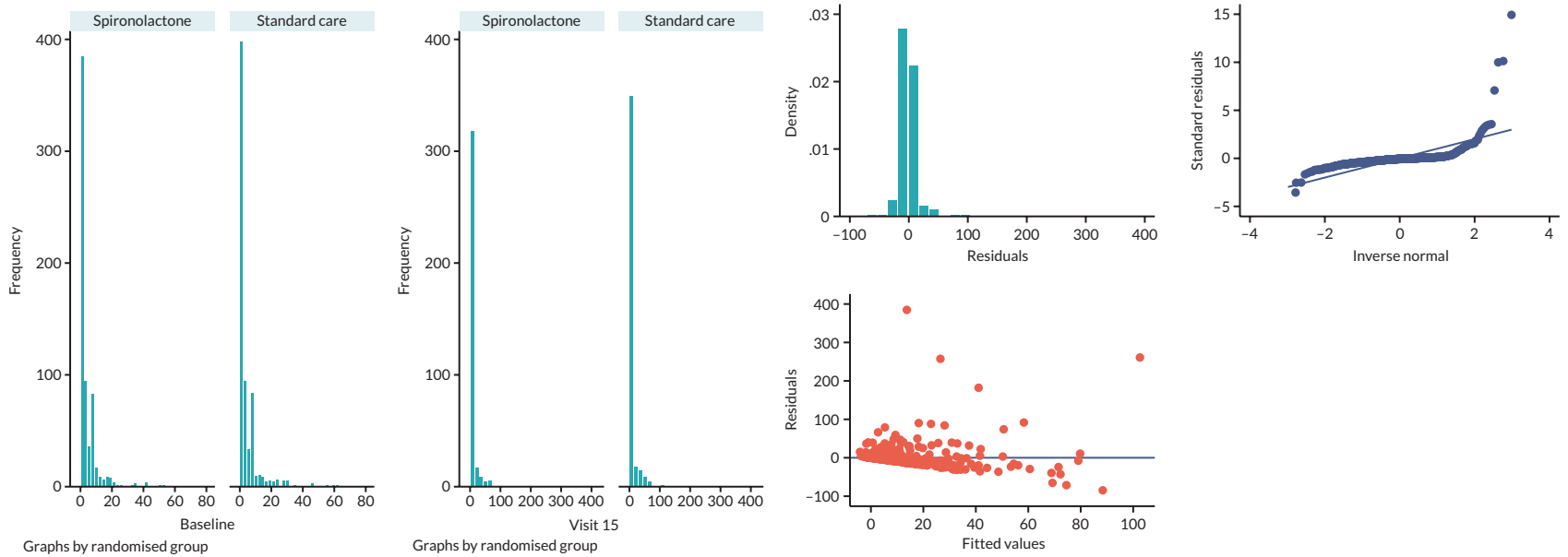


FIGURE 23 Histograms and model residuals for ACR.

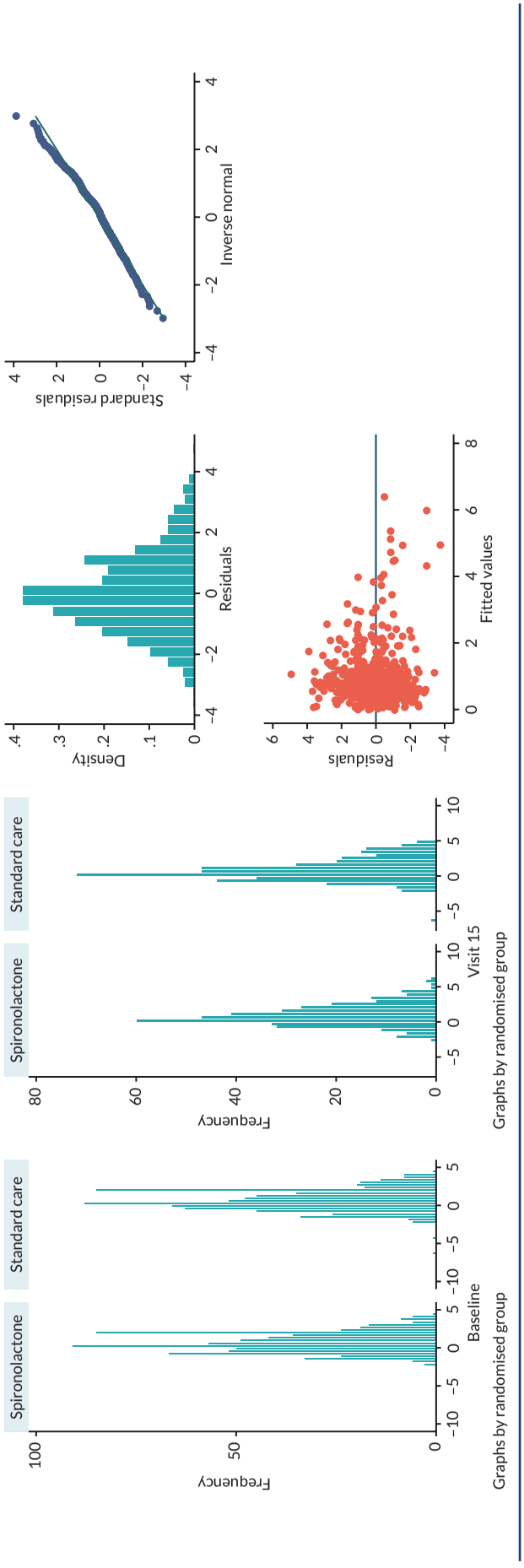


FIGURE 24 Histograms and model residuals for the logarithmic transformation of ACR.

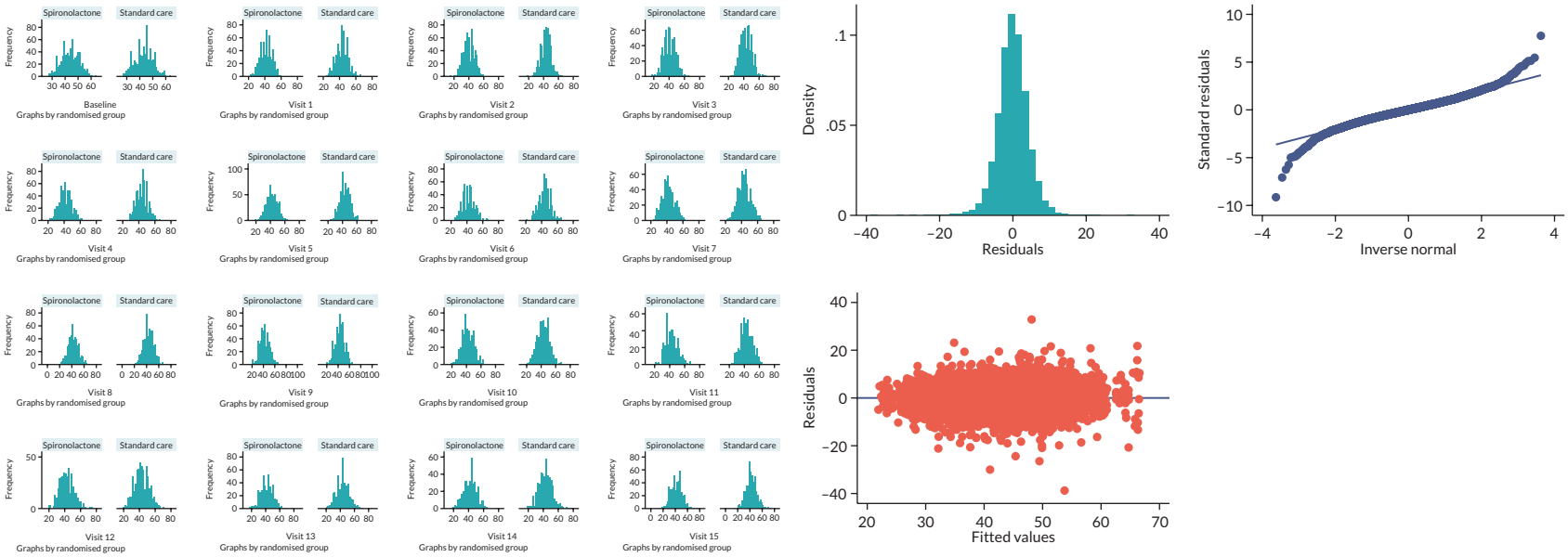


FIGURE 25 Histograms and model residuals for eGFR.

Appendix 7 Adverse events coded by MedDRA system organ class and preferred term

System organ class Preferred term, *number of participants (%) number of events*	Spironolactone (*N* = 677)	Standard care (*N* = 757)	Overall (*N* = 1434)
Blood and lymphatic system disorders			
Anaemia	4 (0.6) 4	1 (0.1) 2	5 (0.3) 6
Iron deficiency anaemia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Cardiac disorders			
Acute MI	1 (0.1) 1	3 (0.4) 3	4 (0.3) 4
Angina pectoris	3 (0.4) 3	5 (0.7) 6	8 (0.6) 9
Angina unstable	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Aortic valve disease	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Aortic valve sclerosis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Atrial fibrillation	9 (1.3) 9	9 (1.2) 10	18 (1.3) 19
Atrial tachycardia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Atrioventricular block	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Atrioventricular block second degree	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Bradyarrhythmia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Bradycardia	1 (0.1) 2	0 (0.0) 0	1 (0.1) 2
Bundle branch block left	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Cardiac failure	1 (0.1) 1	5 (0.7) 5	6 (0.4) 6
Cardiac failure congestive	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Cardiac flutter	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Cardiogenic shock	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Coronary artery disease	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Heart valve incompetence	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
LV dysfunction	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
LV failure	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
MI	1 (0.1) 1	3 (0.4) 3	4 (0.3) 4
Myocardial ischaemia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Palpitations	7 (1.0) 7	3 (0.4) 4	10 (0.7) 11
Sinus arrhythmia	1 (0.1) 1	2 (0.3) 2	3 (0.2) 3
Supraventricular tachycardia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Tachycardia	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Ventricular extrasystoles	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1

continued

System organ class Preferred term, *number of participants (%) number of events*	Spironolactone (*N* = 677)	Standard care (*N* = 757)	Overall (*N* = 1434)
Congenital, familial and genetic disorders			
Birt–Hogg–Dube syndrome	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Ear and labyrinth disorders			
External ear inflammation	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Hearing impaired	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Otorrhoea	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Vertigo	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Vertigo positional	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Endocrine disorders			
Hyperparathyroidism primary	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Eye disorders			
Amaurosis fugax	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Cataract	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Chalazion	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Conjunctival haemorrhage	3 (0.4) 3	1 (0.1) 1	4 (0.3) 4
Conjunctivitis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Eye discharge	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Eye pruritus	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Macular degeneration	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Retinal artery embolism	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Vision blurred	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Visual impairment	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Gastrointestinal disorders			
Abdominal adhesions	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Abdominal discomfort	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Abdominal distension	3 (0.4) 3	2 (0.3) 2	5 (0.3) 5
Abdominal pain	7 (1.0) 7	6 (0.8) 8	13 (0.9) 15
Abdominal pain lower	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Abdominal pain upper	7 (1.0) 7	4 (0.5) 6	11 (0.8) 13
Abdominal tenderness	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Anorectal discomfort	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Colitis ischaemic	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Constipation	5 (0.7) 5	4 (0.5) 5	9 (0.6) 10
Crohn's disease	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Defaecation urgency	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Diarrhoea	25 (3.7) 30	6 (0.8) 9	31 (2.2) 39

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Diverticulum	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Dry mouth	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Duodenal ulcer	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Dyspepsia	3 (0.4) 3	0 (0.0) 0	3 (0.2) 3
Dysphagia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Faeces discoloured	1 (0.1) 1	2 (0.3) 2	3 (0.2) 3
Food poisoning	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Frequent bowel movements	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Gastritis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Gastro-oesophageal reflux disease	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Gastrointestinal haemorrhage	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Gastro-oesophageal reflux disease	2 (0.3) 3	1 (0.1) 1	3 (0.2) 4
Glossodynia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Haematemesis	1 (0.1) 1	2 (0.3) 2	3 (0.2) 3
Haematochezia	1 (0.1) 1	2 (0.3) 2	3 (0.2) 3
Hematemesis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Hiatus hernia	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Ileus paralytic	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Inflammatory bowel disease	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Intestinal obstruction	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Irritable bowel syndrome	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Large intestine perforation	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Melena	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Nausea	17 (2.5) 17	4 (0.5) 4	21 (1.5) 21
Necrotising pancreatitis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Oesophageal spasm	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Pancreatic necrosis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Pancreatitis	1 (0.1) 2	3 (0.4) 4	4 (0.3) 6
Pancreatitis acute	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Pouchitis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Rectal haemorrhage	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Rectal polyp	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Small bowel obstruction	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Small intestinal obstruction	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Upper gastrointestinal haemorrhage	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Vomiting	13 (1.9) 15	6 (0.8) 7	19 (1.3) 22

continued

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
General disorders and administration site conditions			
Adverse drug reaction	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Asthenia	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Chest discomfort	5 (0.7) 6	0 (0.0) 0	5 (0.3) 6
Chest pain	3 (0.4) 4	5 (0.7) 5	8 (0.6) 9
Chills	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Condition aggravated	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Death	10 (1.5) 10	10 (1.3) 10	20 (1.4) 20
Drug intolerance	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Fatigue	23 (3.4) 27	6 (0.8) 7	29 (2.0) 34
Feeling abnormal	3 (0.4) 3	0 (0.0) 0	3 (0.2) 3
Feeling hot	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Gait disturbance	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Gravitational oedema	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Hernia obstructive	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Local swelling	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Malaise	6 (0.9) 6	1 (0.1) 1	7 (0.5) 7
Non-cardiac chest pain	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Oedema peripheral	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Pain	6 (0.9) 6	1 (0.1) 1	7 (0.5) 7
Peripheral swelling	1 (0.1) 1	2 (0.3) 2	3 (0.2) 3
Pyrexia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Sudden death	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Suprapubic pain	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Swelling	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Thirst	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Hepatobiliary disorders			
Biliary colic	1 (0.1) 1	1 (0.1) 2	2 (0.1) 3
Cholecystitis	0 (0.0) 0	1 (0.1) 2	1 (0.1) 2
Cholecystitis acute	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Cholelithiasis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Jaundice	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Immune system disorders			
Hypersensitivity	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Seasonal allergy	0 (0.0) 0	1 (0.1) 2	1 (0.1) 2

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Infections and infestations			
Acute sinusitis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Appendicitis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Breast abscess	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Bronchitis haemophilus	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Cellulitis	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Cystitis	1 (0.1) 2	1 (0.1) 1	2 (0.1) 3
Diarrhoea infectious	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Diverticulitis	4 (0.6) 4	0 (0.0) 0	4 (0.3) 4
Gastroenteritis	0 (0.0) 0	1 (0.1) 2	1 (0.1) 2
Gastroenteritis viral	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Hepatitis E	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Herpes zoster	4 (0.6) 4	2 (0.3) 2	6 (0.4) 6
Infected bite	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Influenza	2 (0.3) 2	2 (0.3) 2	4 (0.3) 4
Intraspinal abscess	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Labyrinthitis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Lobar pneumonia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Localised infection	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Lower respiratory tract infection	8 (1.2) 8	13 (1.7) 13	21 (1.5) 21
Mastitis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Nasopharyngitis	5 (0.7) 5	4 (0.5) 4	9 (0.6) 9
Neutropenic sepsis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Oral candidiasis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Otitis externa	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Otitis media acute	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Peritonitis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Pharyngitis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Pneumonia	6 (0.9) 6	6 (0.8) 6	12 (0.8) 12
Pyelonephritis	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Respiratory tract infection viral	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Rhinitis	1 (0.1) 1	2 (0.3) 2	3 (0.2) 3
Sepsis	4 (0.6) 4	2 (0.3) 2	6 (0.4) 6
Sinusitis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Staphylococcal infection	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Tooth abscess	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1

continued

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Tooth infection	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Upper respiratory tract infection	2 (0.3) 2	3 (0.4) 3	5 (0.3) 5
Urinary tract infection	18 (2.7) 18	15 (2.0) 21	33 (2.3) 39
Urosepsis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Viral infection	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Viral upper respiratory tract infection	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Injury, poisoning and procedural complications			
Ankle fracture	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Contusion	1 (0.1) 2	0 (0.0) 0	1 (0.1) 2
Drug dispensing error	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Fall	17 (2.5) 19	11 (1.5) 11	28 (2.0) 30
Femoral neck fracture	1 (0.1) 1	4 (0.5) 4	5 (0.3) 5
Femur fracture	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Foot fracture	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Fracture	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Gastrointestinal stoma complication	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Hand fracture	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Head injury	0 (0.0) 0	3 (0.4) 3	3 (0.2) 3
Hip fracture	3 (0.4) 3	0 (0.0) 0	3 (0.2) 3
Humerus fracture	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Injection-related reaction	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Joint injury	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Laceration	1 (0.1) 1	2 (0.3) 3	3 (0.2) 4
Ligament sprain	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Limb crushing injury	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Lower limb fracture	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Muscle strain	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Radius fracture	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Stress fracture	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Thermal burn	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Urinary retention postoperative	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Wound	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Investigations			
Biopsy	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Blood creatinine increased	9 (1.3) 10	0 (0.0) 0	9 (0.6) 10
Blood glucose increased	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Blood potassium decreased	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Blood potassium increased	118 (17.4) 155	70 (9.2) 85	188 (13.1) 240
Blood pressure decreased	3 (0.4) 3	3 (0.4) 3	6 (0.4) 6
Blood pressure diastolic decreased	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Blood pressure increased	2 (0.3) 2	3 (0.4) 3	5 (0.3) 5
Blood pressure systolic decreased	14 (2.1) 15	8 (1.1) 8	22 (1.5) 23
Blood sodium decreased	5 (0.7) 5	2 (0.3) 2	7 (0.5) 7
Blood sodium increased	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Blood urea increased	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Brain NP abnormal	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Brain NP increased	5 (0.7) 5	9 (1.2) 10	14 (1.0) 15
Cardiac function diagnostic procedures	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Cardiac murmur	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Colonoscopy	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Echocardiogram	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Echocardiogram normal	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Electrocardiogram ST segment elevation	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Electrocardiogram normal	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Emergency care examination	0 (0.0) 0	4 (0.5) 4	4 (0.3) 4
Endoscopy upper gastrointestinal tract	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Glomerular filtration rate decreased	288 (42.5) 350	201 (26.6) 253	489 (34.1) 603
Glycosylated haemoglobin increased	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Haemoglobin decreased	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Heart rate irregular	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Hepatobiliary scan abnormal	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
N-terminal prohormone brain NP increased	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Nuclear magnetic resonance imaging	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Prostatic specific antigen increased	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Renal function test abnormal	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Sigmoidoscopy	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Stool analysis abnormal	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Temperature difference of extremities	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Troponin increased	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Ultrasound biliary tract abnormal	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Ultrasound scan	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1

continued

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Urine ACR increased	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Urodynamics measurement abnormal	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Waist circumference increased	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Weight decreased	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Weight increased	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
White blood cell count increased	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Metabolism and nutrition disorders			
Decreased appetite	2 (0.3) 2	1 (0.1) 2	3 (0.2) 4
Dehydration	1 (0.1) 1	4 (0.5) 4	5 (0.3) 5
DM inadequate control	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Gout	7 (1.0) 7	2 (0.3) 2	9 (0.6) 9
Hypercalcaemia	0 (0.0) 0	1 (0.1) 2	1 (0.1) 2
Hyperkalaemia	29 (4.3) 34	11 (1.5) 11	40 (2.8) 45
Hypokalaemia	3 (0.4) 4	1 (0.1) 1	4 (0.3) 5
Hyponatraemia	5 (0.7) 6	0 (0.0) 0	5 (0.3) 6
Impaired fasting glucose	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Polydipsia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Type 2 diabetes mellitus	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Musculoskeletal and connective tissue disorders			
Arthralgia	9 (1.3) 11	6 (0.8) 8	15 (1.0) 19
Back pain	12 (1.8) 13	5 (0.7) 5	17 (1.2) 18
Bursitis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Coccydynia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Fibromyalgia	0 (0.0) 0	1 (0.1) 2	1 (0.1) 2
Joint dislocation	1 (0.1) 2	0 (0.0) 0	1 (0.1) 2
Joint swelling	4 (0.6) 4	2 (0.3) 3	6 (0.4) 7
Leg discomfort	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Ligament sprain	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Muscle spasms	24 (3.5) 26	1 (0.1) 1	25 (1.7) 27
Muscular weakness	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Musculoskeletal chest pain	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Musculoskeletal pain	3 (0.4) 3	1 (0.1) 1	4 (0.3) 4
Musculoskeletal stiffness	1 (0.1) 2	0 (0.0) 0	1 (0.1) 2
Myalgia	4 (0.6) 4	1 (0.1) 1	5 (0.3) 5
Myopathy	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Neck mass	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Neck pain	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Osteoarthritis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Pain in extremity	2 (0.3) 2	3 (0.4) 4	5 (0.3) 6
Polymyalgia rheumatica	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Rheumatoid arthritis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Rotator cuff syndrome	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Sciatica	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Shoulder deformity	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Spinal osteoarthritis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Temporomandibular joint syndrome	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Trigger finger	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Acute myeloid leukaemia	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Basal cell carcinoma	2 (0.3) 2	2 (0.3) 2	4 (0.3) 4
Bladder cancer recurrent	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Bowen's disease	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Breast cancer	1 (0.1) 2	2 (0.3) 2	3 (0.2) 4
Breast cancer metastatic	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Breast cancer recurrent	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Burkitt's lymphoma	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Cholangiocarcinoma	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Chronic lymphocytic leukaemia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Colon cancer	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Gallbladder cancer	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Gastric cancer	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Glioblastoma	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Glomerular filtration rate decreased	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Glomus tumour	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Hepatic cancer metastatic	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Leukaemia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Lipoma	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Lung carcinoma cell type unspecified stage 0	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Lung neoplasm malignant	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Lymphoma	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Lymphoplasmacytoid lymphoma/immunocytoma	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Meningioma	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1

continued

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Metastases to bone marrow	1 (0.1) 2	0 (0.0) 0	1 (0.1) 2
Metastases to central nervous system	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Metastases to lung	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Metastatic neoplasm	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Metastatic renal cell carcinoma	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Neoplasm malignant	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Oesophageal adenocarcinoma	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Oesophageal cancer metastatic	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Pancreatic carcinoma	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Pheochromocytoma	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Plasma cell myeloma	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Prostate cancer	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Rectal cancer	1 (0.1) 2	0 (0.0) 0	1 (0.1) 2
Renal cell carcinoma	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Seborrhoeic keratosis	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Squamous cell carcinoma	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Nervous system disorders			
Ataxia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Balance disorder	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Carpal tunnel syndrome	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Cerebral infarction	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Cerebral microhaemorrhage	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Cerebrovascular accident	6 (0.9) 8	7 (0.9) 7	13 (0.9) 15
Convulsion	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Dementia Alzheimer's type	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Dizziness	37 (5.5) 40	8 (1.1) 8	45 (3.1) 48
Dizziness postural	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Drug withdrawal headache	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Dysarthria	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Epilepsy	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Headache	12 (1.8) 13	1 (0.1) 1	13 (0.9) 14
Hemiparesis	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Hypoaesthesia	3 (0.4) 4	0 (0.0) 0	3 (0.2) 4
Intracranial hypotension	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Lacunar infarction	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Lethargy	9 (1.3) 9	1 (0.1) 1	10 (0.7) 10

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Loss of consciousness	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Migraine	3 (0.4) 3	0 (0.0) 0	3 (0.2) 3
Neuralgia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Neuropathy peripheral	1 (0.1) 2	0 (0.0) 0	1 (0.1) 2
Nystagmus	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Paraesthesia	3 (0.4) 3	1 (0.1) 1	4 (0.3) 4
Parkinson's disease	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Presyncope	2 (0.3) 2	2 (0.3) 2	4 (0.3) 4
Seizure	1 (0.1) 2	0 (0.0) 0	1 (0.1) 2
Sensory loss	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Somnolence	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Syncope	3 (0.4) 3	6 (0.8) 6	9 (0.6) 9
TIA	1 (0.1) 1	9 (1.2) 9	10 (0.7) 10
Vascular dementia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Vertigo	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Psychiatric disorders			
Confusional state	3 (0.4) 3	1 (0.1) 1	4 (0.3) 4
Depressed mood	4 (0.6) 4	0 (0.0) 0	4 (0.3) 4
Depression	3 (0.4) 3	0 (0.0) 0	3 (0.2) 3
Emotional distress	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Fear of death	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Insomnia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Renal and urinary disorders			
Acute kidney injury	2 (0.3) 2	5 (0.7) 5	7 (0.5) 7
Calculus bladder	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Cystitis-like symptom	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Gastroenteritis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Glomerular filtration rate decreased	6 (0.9) 6	0 (0.0) 0	6 (0.4) 6
Haematuria	1 (0.1) 1	3 (0.4) 4	4 (0.3) 5
Hydronephrosis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Microalbuminuria	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Nephrolithiasis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Nocturia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Pollakiuria	9 (1.3) 9	1 (0.1) 1	10 (0.7) 10
Renal failure	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Renal failure acute	5 (0.7) 5	4 (0.5) 4	9 (0.6) 9

continued

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Renal impairment	21 (3.1) 21	6 (0.8) 7	27 (1.9) 28
Renal mass	1 (0.1) 1	2 (0.3) 2	3 (0.2) 3
Urethral stenosis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Urinary incontinence	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Urinary retention	2 (0.3) 2	3 (0.4) 3	5 (0.3) 5
Reproductive system and breast disorders			
Atrophic vulvovaginitis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Balanitis	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Breast enlargement	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Breast mass	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Breast pain	5 (0.7) 5	0 (0.0) 0	5 (0.3) 5
Breast swelling	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Breast tenderness	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Cystocele	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Erectile dysfunction	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Gynaecomastia	11 (1.6) 11	1 (0.1) 1	12 (0.8) 12
Haematospermia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Nipple pain	5 (0.7) 5	0 (0.0) 0	5 (0.3) 5
Nipple swelling	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Prostatomegaly	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Rectocele	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Uterine polyp	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Respiratory, thoracic and mediastinal disorders			
Asthma	2 (0.3) 2	1 (0.1) 1	3 (0.2) 3
Chronic obstructive pulmonary disease	2 (0.3) 2	3 (0.4) 3	5 (0.3) 5
Cough	6 (0.9) 6	1 (0.1) 1	7 (0.5) 7
Dry throat	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Dysphonia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Dyspnoea	8 (1.2) 8	3 (0.4) 3	11 (0.8) 11
Epistaxis	2 (0.3) 3	1 (0.1) 1	3 (0.2) 4
Exertional dyspnoea	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Haemoptysis	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Hypoxia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Increased upper airway secretion	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Nasopharyngitis	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Oropharyngeal pain	3 (0.4) 3	7 (0.9) 8	10 (0.7) 11

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Pleural effusion	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Pleuritic pain	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Pneumonia aspiration	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Productive cough	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Pulmonary embolism	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Pulmonary oedema	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Rhinorrhoea	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Wheezing	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Skin and subcutaneous tissue disorders			
Actinic keratosis	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Alopecia	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Blister	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Dermatitis allergic	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Dermatitis contact	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Eczema	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Erythema	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Hair growth abnormal	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Hair texture abnormal	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Hyperhidrosis	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Pruritus	4 (0.6) 4	0 (0.0) 0	4 (0.3) 4
Rash	3 (0.4) 4	0 (0.0) 0	3 (0.2) 4
Skin lesion	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Social circumstances			
Treatment non-compliance	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Surgical and medical procedures			
Amputation	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Aneurysm repair	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Arterial stent insertion	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Bladder catheter temporary	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Bladder neoplasm surgery	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Cardiac operation	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Cardiac pacemaker insertion	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Cataract operation	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Chemotherapy	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Cholecystectomy	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Colectomy	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1

continued

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Colostomy	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Colporrhaphy	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Coronary arterial stent insertion	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Coronary artery bypass	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Dupuytren's contracture operation	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Hepatectomy	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Hip arthroplasty	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Hospice care	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Hospitalisation	9 (1.3) 9	12 (1.6) 13	21 (1.5) 22
Hysterectomy	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Inguinal hernia repair	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Joint arthroplasty	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Kidney ablation	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Knee arthroplasty	3 (0.4) 3	0 (0.0) 0	3 (0.2) 3
Limb operation	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Parathyroidectomy	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Percutaneous coronary intervention	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Peripheral endarterectomy	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Proctocolectomy	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Resection of rectum	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Skin lesion excision	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Tooth extraction	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Ureteral catheterisation	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Ureteral stent insertion	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Vaginal prolapse repair	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Venipuncture	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Vascular disorders			
Aneurysm ruptured	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Aortic stenosis	0 (0.0) 0	2 (0.3) 2	2 (0.1) 2
Blood pressure inadequately controlled	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Circulatory collapse	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Femoral artery occlusion	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Flushing	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Haematoma	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Hot flush	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Hypertension	3 (0.4) 3	0 (0.0) 0	3 (0.2) 3

System organ class	Spironolactone	Standard care	Overall
Preferred term, ***number of participants (%) number of events***	**(*N* = 677)**	**(*N* = 757)**	**(*N* = 1434)**
Hypotension	45 (6.6) 46	25 (3.3) 33	70 (4.9) 79
Intermittent claudication	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Orthostatic hypotension	6 (0.9) 7	2 (0.3) 2	8 (0.6) 9
Peripheral artery aneurysm	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Peripheral coldness	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Peripheral ischaemia	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Peripheral vascular disorder	1 (0.1) 1	1 (0.1) 1	2 (0.1) 2
Phlebitis superficial	1 (0.1) 1	0 (0.0) 0	1 (0.1) 1
Popliteal artery aneurysm	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Raynaud's phenomenon	2 (0.3) 2	0 (0.0) 0	2 (0.1) 2
Shock	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1
Missing			
Lacunar stroke	0 (0.0) 0	1 (0.1) 1	1 (0.1) 1

Appendix 8 List of serious adverse events

Serious adverse event	Intervention received
On 11/1/15 attended Emergency Dept John Radcliffe with (R) Flank pain. Diagnosis RLL pneumonia and dehydration + AKI (Creat 260). discharged? 14/1/15 (No summary yet) and missed 2 days of antibiotics ('not available to patient') Re-admitted 19/1/15 with haemoptysis ascribed to resolving RLL pneumonia. Antibiotics continued and discharged same day. Limited information first received by GP 16/1/15, reviewed at home 21/1/15 - much improved.	Standard care
Admitted with vomiting and abdominal pain. CT abdo showed large abdominal hernia with mild small bowel dilatation. Not clear if obstruction or ileus. Rx NBM + IV fluids + laxative + NG tube + analgesia. Also given antibiotics for suspected aspiration pneumonia.	Standard care
Admitted for 4 days with acute exacerbation of COPD, treated with Prednisolone and antibiotics. Was hypotensive on admission so his antihypertensive therapies Lisinopril/and Doxazosin were stopped. Four days post discharge developed ankle swelling likely related to chronic obstructive pulmonary disease (COPD) and to cessation of Lisinopril. GP colleague added Furosemide which helped together with resumption of Lisinopril and Doxazosin. One year ago an echo showed LV diastolic dysfunction and we conclude he has developed heart failure with a preserved ejection fraction (HFpEF) related to COPD.	Standard care
Admitted 04/08/17 with a 3-week history of worsening dyspnoea, abdominal and leg swelling. Creatinine had risen to 295 and acute coronary syndrome could not be ruled out (Troponin positive 1.46) Decompensated heart failure diagnosed and managed by ambulatory unit attendances and hospital at home intravenous injections of furosemide. Not doing well – had to defer Barack Visit 14. Still under ambulatory care. DM comment, additional information received: Admitted 04/08/17 with decompensated heart failure and Acute kidney injury fluid overload managed with intravenous furosemide and lisinopril stopped. When echocardiogram eventually performed on 17/08/17 Atrial Fibrillation also diagnosed.	Standard care
On day when BARACK–D study review due (15/9/15) did not attend appointment. GP phoned and established unwell for 6 weeks with chest pain anorexia and progressive weakness. Admitted to hospital where raised inflammatory markers and subtle CXR appearance interpreted as 'pneumonia'. 'Improved with antibiotics'. Discharged 16/9/15 Reports no improvement – under GP review. Visit booked for 30/9/15	Standard care
Admitted following referral via 2 weeks wait to chest clinic as clearly unwell with proximal myopathy, hypercalcaemia, Wt loss, iron deficiency anaemia, possible primary hyperparathyroidism (still awaiting definitive diagnosis) but to date occult malignancy not identified	Standard care
Drop in renal function most likely due to uncontrolled Hypercalcaemia due in turn to primary hyperparathyroidism. Endocrine team informed with request to expedite definitive treatment given that malignancy has been ruled out. DM update: Query response to the associated AE states on 19/07/2019 that primary hyperparathyroidism persists as it was not treated; hypercalcaemia has resolved as of 16/05/2018	Standard care
Assessed in Emergency Dept and admitted overnight 12/4/17 for pain relief following development of acute back pain after pushing motorbike up a ramp. No neurological disability, no imaging required. Pain settled with analgesia, and resolved.	Spironolactone
Developed rest pain and cool left foot in April 2017. Referred to vascular team and admitted for elective femoral endarterectomy and endovascular placement of two metallic stents. Good recovery	Spironolactone
Diabetic patient with toe infection – amputation (admitted to hospital on unknown date, still in hospital currently)	Spironolactone
Patient found deceased at home (29/1/17, I was informed 2/2/17) in discussion with the coroner thought to be due to ischaemic heart disease (pre-existing)	Spironolactone
Admitted to A&E 21 /9/16 then admitted to medical team having suffered posterior circulation stroke. Discharged home 26/9/16. DM comment: Query response confirmed dates entered on SAE form – 21/9/2016 – sent to A&E for suspected stroke; 24/9/2016 – transferred from A&E to medical ward for stroke.	Standard care

Serious adverse event	Intervention received
10/7/17 Started taking spironolactone. 18/7/17 Visit 1 – K raised 5.9 Creat raised 120 – Spiro reduced to alternate days. 31/7/17 Visit 2 – K reduced 5.38 Creat reduced 103 - 4/8/17 Spiro stopped following discussion with Dr Anon (BARACK-D) 18/8/17 Visit 3 Potassium 5.2 Creat raised 243 – Biochem alert, likely AKI pt called into kidney EMU seen daily. 25/8/17 Creat 202 29/8/17 Discharged from Witney EMU 13/8/17 AE form sent. Asked via data query to send SAE form on 6 entered on AE form. This patient was never admitted to hospital and has recovered well. e-mail advice from nephrology consultant suggests unexplained AKI. Latest bloods on 17th Oct Creat 127 Potassium 4.5 eGFR 36	Spironolactone
Spironolactone started 03/08/16 Feverish illness started 07/08/2016; antibiotics for suspected urine infection started 09/08/16. No better by 12/08/16 so antibiotic started. Deteriorated and admitted on 13/08/16 to the hospital with pneumonia. Verbal report from daughter today: no written details available.	Standard care
Hyperkalaemia 6.36 – no symptoms. In view of his diabetes and ischaemic heart disease he was admitted to hospital for observations, monitoring and treatment.	Spironolactone
Fall resulting in hospitalisation.	Standard care
Attended day unit for elective blood transfusion for CLL but presented with SOB, hypoxia, wheezy, CXR showed LRTI. Admitted 23/05/16 – 01/06/16. Treated with nebulisers and IV antibiotics	Spironolactone
A relapse of CLL (enlarged cervical and supraclavicular lymphadenopathy) requiring chemotherapy.	Spironolactone
Hospital admission for fall and sepsis treated with IV and oral antibiotics known CLL patient. 17/10/16–21/10/16	Spironolactone
Admitted to ward with chest infection. Intravenous antibiotics given. 07/01/17–08/01/17	Spironolactone
Admitted to hospital on 27/02/2020 with history of being unsteady on feet and needing support when walking.? Cerebellar infarct. CT scan and MRI taken. No clear cause for symptoms.? Anxiety related.	Standard care
Patient admitted to hospital 21/11/14 and died 27/11/14. Await postmortem report. DM update on 14/8/2019: The cause of death has been provided as ischaemic and hypertensive heart disease. Non-Hodgkin's lymphoma on the end-point form.	Standard care
7/5/2015 – Patient was staggering and dragging his feet, lost use of his left arm and speech was slurred. 8/5/2015 – Home visit by G.P. speech more slurred with left facial nerve palsy. Diagnosed with right cerebrovascular accident. Hospital admission under care of stroke team.	Standard care
Patient was admitted to A/E on 19/11/2015 with dragging left foot, unable to lift arm and reduced grip. Patient died 20/11/2015 following right lacunar infarction. Awaiting post mortem results.	Standard care
History of osteoarthritis. Elective admission on 20/12/2016 for R Exeter total hip prosthesis. Discharged 28/12/2016.	Standard care
Patient had a glomus tumour which developed in October 2015. This was excised 02 February 2016 as an intervention procedure.	Standard care
She was admitted on 21/12/16 with breathlessness + malaise + fever. She was started on antibiotics + higher doses of furosemide. Discharged on 22/12/16 – diagnosis was pneumonia + congestive cardiac failure.	Standard care
See discharge letter. She was admitted with collapse + low BP and her medications were reduced on discharge	Standard care
SAE – Acute Kidney Injury Stage 1. Patient collapsed at home several times. Admitted to hospital 27/3/2016. Investigations led to diagnosis of acute kidney injury. Discharged 30/3/2016.	Standard care
SAE – Sepsis patient collapsed at home several times. Admitted to hospital 27/3/2016. Discharged 30/3/2016.	Standard care
Patient woke with chest pain, sweaty, clammy. Saw GP, ECG performed (attached). Hospitalised overnight for observation. Admitted 30/3/2017, Discharged 31/3/2017.	Standard care
L arm weakness A&E 26/3/18 CT scan diagnose R lacunar stroke TIA (complete occlusion of R internal carotid artery) admitted as inpatient. Discharged on 28/3/18 with Aspirin/Clopidogrel and increased dose of statin	Standard care

continued

Serious adverse event	Intervention received
Discussed with (Anon, trial team). Patient was not hospitalised. Event happened on 17/3/2017. Patient was seen in hospital via referral from P.I. Subsequent Doppler showed anterior circulation atheroma. Doppler report attached.	Standard care
Admitted via A&E on 20/1/18 following three epileptic seizures in 24 hours (new diagnosis). Treated with sedation and anticonvulsants (midazolam, Lorazepam, Ketamine & Phenytoin) CT scan done. Oral anti-convulsant meds started Discharged on 21/1/18	Spironolactone
Patient died in James Paget Hospital DM update – A query response completed on 11/10/18 indicated glioblastoma and aortic valve disease as the cause of death	Standard care
Death – sepsis secondary to pneumonia	Standard care
Patient was admitted to A&E with palpitations on 27/05/2018	Standard care
Patient was admitted to A&E due to atrial fibrillation on 01/04/2018	Standard care
Patient died due to other medical conditions	Standard care
Pt went to GWH with low back pain severe around her kidneys she says and fever – rigors. They admitted her 14/02/15 and she was discharged with antibiotics 17/02/15 with oral Co-amoxiclav. Treatment while admitted – stat Gentamicin, IV fluids, Analgesia and IV Co-amoxiclav – Probable UTI. USS – shows simple cysts within both kidneys.	Standard care
Pt was admitted 10/11/16 with chest pain, tachycardia, hypoxic + a raised respiratory rate. Pt had a recent Hartmann's procedure mid October 2016, and was diagnosed as having an acute kidney injury during her admission. Discharged 09/12/16.	Standard care
During study bloods K+ was 6.03 @ week 4 after randomised to have spironolactone colleague referred to ED. Diagnosis hyperkalaemia and AKI. Spironolactone and Lisinopril stopped.	Spironolactone
Admitted to hospital on 24/4/19 with SDB + cough. No response to IV antibiotics. Discharged home as E OF L (? End of Life). Pt died at home on 02/05/2019.	Standard care
Hospital admission for acute confusion and ataxia. Ultrasound scan of the renal tract revealed suspicious suprarenal mass of the right kidney ~ under investigation.	Standard care
Emergency hospital admission for transient incoherent speech – diagnosed TIA. CT head – small vessel disease. Whole body CT scan arranged for 31/05/2016	Standard care
Emergency hospital admission Saw GP – episode of disorientation. O/E weak, not eating, vomits if tries to. BP 95/60 sitting, unable to stand for standing BP -? postural hypotension. Not safe to mobilize – ambulance booked – hospital.	Standard care
Admitted to hospital 27/04/18 discharged 02/05/18.Diagnosis = uncomplicated UTI. Presented UTI, abdominal pain, fever & rigors, increased urine frequency. Treated with IV antibiotics to oral and furosemide for leg oedema which is to continue 40 mg mane. Urinary tract ultrasound = nil evidence of anything acute.	Spironolactone
Hospital admission 24/06/18–27/06/18 for infective diarrhoea. Treated with 1 week course of Metronidezole and an increase is dose of prescribed oral steroids. Stool C.diff negative, blood culture negative. Discharged home.	Spironolactone
Emergency hospital admission 23/06/18–25/06/18 – diagnosed with meningioma following sudden onset of vertigo followed by light-headedness and unsteadiness on feet; generally unwell and developed left sided weakness. MRI showed 3.5 rounded lesion in right frontal lobe.	Spironolactone
Participant admitted to hospital with right iliac fossa pain. CT scan performed suggests diverticulitis. Treated with IV antibiotics for raised CRP. Admitted – 07 /11/2017. Discharged 11/11/2017.	Standard care
Admitted with abdominal pain – CT abdomen focal acute appendicitis with inflammatory rectocaecal component. Continuous caecal oedema – booked for outpatient colonoscopy and treated conservatively with Co-amoxiclav 625 mg tds x 4 days	Spironolactone
Patient diagnosed Ca oesophagus for stretch + stent on 11/7/2018 – pain at home and readmitted for pain control and further investigation discharged 23/7/18	Spironolactone
Patient diagnosed with adenocarcinoma of oesophagus. Stent fitted 11/7/18. Pain and vomiting necessitated hospital admission where she deteriorated and died 6/10/18	Spironolactone

Serious adverse event	Intervention received
Attended A+E dept with abdominal pain – constipated 13 days – admitted for observation – B.O + sent home with ongoing investigations for Ca Oesophagus to follow.	Standard care
Two episodes of bringing up small amount of bright red blood and associated dark stools.	Standard care
Admission for symptom control of retrosternal chest pain, constipation, hiccups and fatigue. Admitted to local hospice – known Ca oesophagus.	Standard care
Admitted to A+E following a fall on 07/02/17 – X-ray closed fracture neck of femur (Right).	Spironolactone
Abdominal pain resulting in hospital admission. Still awaiting further information. DM* Updates: CT scan showed adhesive small bowel obstruction which was treated with fluids and antibiotics due to raised WBC. Outcome and end date provided for the related AE	Standard care
Admitted with abdominal pain. Underwent CTAP which showed pancreatitis and a walled-off area of necrosis. Bloods showed raised CRP and WCC. Managed with tazocin and fluconazole.	Standard care
Treated for pancreatic necrosis with infection. Treated with IV Tazocin, IV fluids, analgesia and bowel rest.	Standard care
Epigastric pain – USS showed gallbladder wall polyp or stone. MRCP showed potential lesion at sphincter of Oddi. For ERCP as outpatient. ERCP showed (26/01/18) no intraductal stones seen, likely spontaneously passed.	Standard care
16/07/2018 mechanical fall sustaining left Colles' fracture – cast and left fractured neck of femur – hemiarthroplasty discharged 23/07/18 to home	Spironolactone
Hospitalised due to gastrointestinal bleed secondary to newly diagnosed colonic carcinoma. Anaemia 67 g/L	Spironolactone
Hyponatraemia – Drug induced (not trial drug) Na 123 on admission. Fluid restricted and several drugs stopped (bendroflumethiazide, candesartan, omeprazole).	Spironolactone
Admitted with a headache and found to be hypertensive 205/105. Treated with extra candesartan and doxazosin and symptoms resolved and blood pressure normalised.	Spironolactone
Cough, coryzal symptoms and developed chest pain + dyspnoea – called 999 and admitted to hospital -See discharge summary	Standard care
Admitted with chest pain 29/10/19 ECE subtle changes in inferior leads. [illegible] high at 17000. Had angiogram and stent inserted in left anterior descending coronary artery.	Standard care
Complaining of chest pain 31/12/18 Admitted on 01/01/19 with troponin negative chest pain. An angiogram showed stenosis of his left circumflex graft and he had 2 stents inserted.	Standard care
Pt. died not due to the research medication as was not on any research med. Rather died natural cause.	Standard care
Onset of diarrhoea, abdominal pain (diverticular flare-up) on 20/12/18 continued to get worse. Attended walk centre – A&E and admitted as inpatient on 23/12/18 for rehydration and blood tests. Acute episode resolved but SX continue as before. Discharged 24/12/18.	Spironolactone
22/02/19 Fell – ankle injury, attended A&E. Admitted with cellulitis R ankle and gout. Treated with urate lowering meds and antibiotics. Discharged 24/02/19.	Standard care
Developed episodes of red painful swellings of feet – recurrent.? Gout urate 0.51 (normal 0.14––0.36) so gout, diagnosed + started on allopurinol at 100 mg	Spironolactone
Admitted via A&E with exacerbation of asthma due to viral illness. H/O pains in legs and back pain – no DVT found. Total admission time 15 hours.	Spironolactone
Presented at A&E with chest pain 12/04/2018 – had an angiogram which showed mild plaque disease. Discharged on 13/04/18 with cardiac follow-up diagnosed with angina on 30/05/18.	Spironolactone
AE – Fall in bath 21/12/16 and stuck for 20 hours (found by postman). On admission found to have AKI and Pneumonia and rhabdomyolysis D/C summary received – raised troponin 3.31 – 'likely' due to T2 MI. Echo completed. Mildly impaired LV function w/moderately dilated atria, mild TR with fast AF (known AF)	Standard care

continued

Serious adverse event	Intervention received
Patient attended BARACK-D visit 9 as planned on 01/08/2019. Lab report from biochemistry issued on 02/08/2019 revealed a potassium result of 2.7. Result viewed and acted on by a locum GP and coded hypokalaemia and medication deemed necessary to prevent patient hospitalisation a further harm.	Spironolactone
(SAE 297) Patient attended BARACK-D study visit 13 as planned 06/08/20. Samples collected as per protocol returned a K+ 6.29. Result was renewed by site PI on 07/08/20 and issue of treatment (K+ supplements) was deemed necessary to correct electrolyte abnormality to prevent hospital admission (should it have further decreased) or further harm sample collected on 6th Aug was collected on a warm day and was haemolysed.	Spironolactone
Seizure	Standard care
This patient had a stroke. The symptoms completely resolved without any medical intervention. The patient was admitted to hospital overnight, then discharged and is no longer symptomatic.	Standard care
Pt under investigation for anaemia on entry into trial. Investigation on 03/05/14 show large mass. Diagnosis 'Cancer' given 14/05/14 and surgery booked for 11/06/14. Brought to attention of research nurse 30/05/14.	Standard care
Pt diagnosed with hairy cell leukaemia 22/03/99. Routine bone marrow biopsy showed deterioration of his condition 18/08/14. Pt. informed researcher 20/08/14.Chemotherapy treatment begins 28/08/14. Classed as SAE by duty Dr (anonymised) 21/08/14 due to definition(s): Intervention required to prevent hospitalisation	Standard care
Admitted to A+E on 26/09/15 Then admitted to hospital ward – for urethral stricture and chronic urine retention. Discharged on 3/10/15. Not well. Confused.	Standard care
Pt was admitted to hospital with hyponatraemia. Pt spend 5 days in hospital and symptoms resolved with treatment.	Standard care
Pt had chest infection and fall. Pt was admitted to hospital. Pt is not on spironolactone and is in control group.	Standard care
Hypotension causing dizziness requiring A&E admission BP 84/60 Then seen by GP who suggested stopping spironolactone	Standard care
Patient had ultrasound scan on 04/03/21 which diagnosed with gallstones. Patient referred themselves to the A+E Dept with abdominal pain on 15/03/21. Admitted to hospital with perforated gall bladder, peritonitis. Surgical team performed sub low cholecystectomy. Hospital notes report no change to patients regular medications. Patient was declared fit for discharge on 17/03/21.	Standard care
Liver function tests abdominal – USS showed possible pancreatic mass. Admitted to hospital on 09/07/15 following ERCP – discharged 16/07/15. Readmitted 19/07/15–31/07/15 – blocked drain + stent fitted awaiting Whipple's procedure	Standard care
Had fall at home admitted to hospital sustained a fractured left femur and injury to elbow – had open reduction and internal fixation of femur on 14/02/17.	Standard care
Patient fell in bathroom at home – taken by paramedics to hospital and admitted for urinary tract infection and falls for 4 days.	Standard care
Admitted to hospital 13/09/15 for diuretic induced dehydration + AKI. (Not on study drug – standard care). Given intravenous fluids, furosemide stopped, lisinopril withheld and then reduced dose recommended. Discharged home 15/09/15.	Standard care
24/11/16 Admitted to hospital with angina at rest (known ischaemic heart disease). Angiogram performed, circumflex lesion was predilated and stented with drug eluting stent. Previous stent showed restenosis and was re-stented. Anticoagulants to continue. Discharged home 29/11/16 Patient in control group – NOT on study medications.	Standard care
09/03/18 Vomiting + severe abdo pain. Admitted to hospital. Diagnosis pancreatitis. Listed for cholecystectomy 25/04/18. Discharged 26/03/18.	Standard care
Initially patient came into GP practice on 02/12/16 with chesty cough, feeling short of breath and wheezey, underlying COPD. She was given antibiotics and prednisolone. Patient came in again on 09/12/16 for more antibiotics which were given to her. She had worsening shortness of breath over weekend and seen by GP on 12/12/16 who admitted her to hospital via ambulance.	Standard care
Patient felt unwell with bloating and Nausea. He is a diabetic and had uncontrolled blood sugars. Admitted to Yeovil hospital on 09/10/18 and discharged from hospital on 12/10/18 with diagnosis of pancreatic cancer T2, N0, M0	Standard care

Serious adverse event	Intervention received
Admitted to Musgrove Park Hospital A+E department on 26/03/18. Found fractured neck of femur. Left hemi arthroplasty performed in hospital. Patient discharged home on 12/04/18	Standard care
Patient was hospitalised with viral gastroenteritis yesterday, was treated and self-discharged home. Patient feels much better today + has booked his next visit.	Standard care
Anterior resection of rectum + exteriorisation of bowel.	Standard care
Pt went into hospital for reversal of colostomy. Became unwell after procedure with? LRTI progressed to pneumonia and sepsis.	Standard care
Pt admitted to hospital with severe heart failure.	Standard care
Pt had stroke on 11/04/17.	Standard care
Admitted to hospital with exacerbation of asthma secondary to influenza B infection, complicated by evidence of pulmonary oedema – treated with diuretic therapy.	Standard care
Bradyarrhythmia. Admitted to hospital with 'dizziness'. Heart rate (ECG) recording reveal bradycardia HR dropping to 14 and symptomatic permanent pacemaker inserted 11/05/20.	Spironolactone
Myocardial infarction.	Standard care
Admitted 22/06/20 with slurred speech and facial drop. Diagnosed with 'mild' stroke.	Standard care
Drop in eGFR from 32 to 19	Standard care
Fractured neck of femur requiring dynamic hip screw.	Standard care
Patient broke his right leg as he slipped on ice in front of his house on 29/12/16. He was admitted to Yeovil hospital on 29/12/16 and had surgery on 30/12/16 to his right leg. He is waiting in hospital to be discharged home with plaster on his right leg.	Spironolactone
(Anon) was admitted to Musgrove Park Hospital with urosepsis, haematuria +++. Temperature 39.7 and confusion. Found left renal mass 19 cm – probable malignancy, hypercalcaemia, delirium, vit K deficiency secondary to sepsis + diet. Admitted on 19/03/18 and discharged on 04/04/18. Also myeloma diagnosed recently.	Spironolactone
Patient slipped in the street and fractured left hip. Admitted to hospital 02/10/17. Operation on 03/10/17 was left hip hemiarthroplasty. Stopped taking spironolactone on 02/10/17 on admission. Discharged on 11/10/17. GP and review medications as patient happy to restart spironolactone.	Spironolactone
Patient was admitted to hospital for abdominal pain stayed in overnight at Musgrove Park Hospital 05/07/16, she had a CT Scan performed on 05/07/16 did not find anything so told to have a colonoscopy. Discharged from hospital on 06/07/16. Prior to hospital admission patient given antibiotics. Overcome was? Diverticulitis.	Spironolactone
Had a fall and developed haematoma on thigh, knee swelling and shoulder injury (? old) Warfarin stopped in hospital – Discharged on 30/09/16 but District nurses have referred back to hospital and wound? Infected & breaking down	Spironolactone
Admitted with collapse on 20/0717. Discharged 31/07/17. Discharge summary and cardiology follow-up details: NSTEMI, cardiogenic shock with pulmonary oedema, AKI, LVF (referred to heart failure team; EF < 15%), paroxysmal AF, *Escherichia coli* UTI.	Standard care
While on holiday in Cyprus, admitted with severe pneumonia, diagnosed with acute myeloid leukaemia. Two weeks in hospital in Cyprus, transferred back to UK 16/09/16 to Musgrove Park Hospital. Condition continued to deteriorate and she died on 23/09/16.	Spironolactone
02/19/14 Attended GP on 03/06/16 c/o unwell past 4/7 with sweats and rigors. Collapsed in GP surgery. Admitted for further assessment of location of infection.	Spironolactone
Patient's eGFR declined to 25, which was less than 1% above a between visit 20% decrease and baseline to any visit 25% decrease. Also, their potassium was on an upward trend. Baseline 4.8, V1 5.2, V2 5.3, V4 5.4, 15/09/16 5.8. Spironolactone was stopped on 15/09/16, prior to patient taking an extended holiday to Australia. Advice was sought from the trial team who have advised patient should remain off spironolactone permanently.	Spironolactone

continued

Serious adverse event	Intervention received
Death of patient. Recent hospitalisation as per previous SAE. Discharged 26/03/20. General deterioration. End-of-life care commenced 21/05/20. Cared for at home by family, GP and district nurses. Died at home 29/05/20. Entry in EMIS record: Death certificate issued: 1. Frailty of old age 2. Dementia	Standard care
Admitted to the hospital with leg swelling. No correspondence as yet from hospital. Patient's wife reports likely infection of the leg. Reports has developed mobility problems and likely to community hospital for rehabilitation. Standard care arm of BARACK-D.	Standard care
Patient had pain in left leg of calf. he was admitted to Musgrove Park Hospital for Doppler scan + CT scan. He stayed in overnight for observations. He has blockage in the artery (femoral artery). He will probably need an operation.	Standard care
Patient went into Musgrove Park Hospital on Wednesday 01/11/17 Stayed overnight for his planned operation on 02/11/17. He has left iliac system occlusion plus left femoral occlusion. Also looks like an ectatic right common iliac segment. Operation cancelled on day because of concerns about reduced kidney function. Blood pressure tablets changed to improve renal function.	Standard care
Patient investigated for anaemia found lung cancer, (stage IV non-small cell lung cancer). Investigated with PET scan confirmed avid lesions. Right lung lesions. For palliative care. He had previous diagnosis of lung hamartoma. Wishes to stay in BARACK-D trial for time being.	Standard care
Fall (slip on wet floor) resulted in fracture ankle and admission. Not thought related to study drug.	Standard care
Patient had a fall in the supermarket and hit his head. Was admitted to hospital – CT scan performed – small contusion within right frontal lobe. Due for discharge on 27/09/17.	Standard care
Unexpected Death. Coroner's report – 1a Ischaemic heart disease 1b Coronary Artery Atheroma 2. Hypertension.	Standard care
Postural hypotension possibly caused by Tamsulosin.	Spironolactone
Malignant neoplasm of gallbladder – 13/07/17 Biliary sepsis 13/07/17 Patient died at home 20/07/17.	Standard care
Patient developed acute kidney Injury secondary to urinary retention caused by constipation. Spironolactone thought to have contributed to AKI in context of urinary retention. Spironolactone was withheld, awaiting recovery of renal function.	Standard care
Admitted at Musgrove Park Hospital on 08/06/16 for sepsis and AKI (line illegible) 20/05/16 in Southmead Hospital. Patient treated with antibiotics and discharged 13/06/16. I should have completed form on 08/08/16 but did not, apologies.	Spironolactone
Patient presented with 3–4-week history of worsening headache, associated with facial drop and slurred speech. MRI showed Metastases in Brain. Oncology team suspect there maybe recurrence of bladder cancer. Patient admitted to Musgrove Park Hospital on 13/01/17 and discharged 16/01/17	Spironolactone
On 07/03/17 Patient fell over at home and cut her left wrist and arm in the fall. First of all she went to West Mendip Hospital A+E and then sent via ambulance to Yeovil District Hospital. She was admitted on 07/03/17 and discharged on 10/03/17	Standard care
Admitted to Royal United Hospital Bath with chest pain. Positive test for pulmonary embolism identified and treated. Admitted to hospital on 23/09/17 and discharged on 27/09/17.	Standard care
Admitted to A + E with abdominal pains transferred to ITU with AKI on CKD. Sepsis MRSA colonised, macrocytic anaemia, thrombocytopenia. Possible linelozid induced marrow suppression and delirium.	Standard care
Patient went into hospital for booked angiogram – Angiogram performed 23/09/16. Pt sent home and then admitted via 999 ambulance that evening at 20.00 hrs. SOB, sweaty. Seen in A&E Great Western Hospital, Swindon. Bloods, CXR, ECG performed. Diagnosed with hyperkalaemia, reaction to dye from angiogram. Discharged home 24/09/16 18.00.	Standard care
Patient admitted as elective procedure for PCI to LCX (09/11/16) Patient stayed in Great Western Hospital and was discharged the following day 10/11/16	Standard care
Pt had blood taken at Visit 07/03/18 +Hb 61 g/dl repeated today. Pt has been short of breath and has been admitted to Great Western Hospital Swindon today 08/03/18	Standard care
Pt noted on blood test at Visit 8. eGFR 12. Creat 299. Feeling tired + inc thirst for 2 weeks not mentioned at visit. Admitted to RUH Bath 10/08/17. Renal u/s. Normal kidneys. iv. fluids Discharged 14/08/17. eGFR 17. Creat 222 Commenced Amlodipine 5mg OD 21/08/17 Repeat blood Creat. 200 + eGFR 19.	Standard care

Serious adverse event	Intervention received
Pt admitted to hospital for total hip replacement. 14/02/18 discharged home 18/02/18. Booked admission following increasing pain from previous THR 2009.	Standard care
15/11/16 Admitted via ambulance to A&E Royal United hosp. Bath with chest pain after ballroom dancing. ECG sinus arrhythmia (not available) troponin 36 > 40. CXR – pulmonary oedema. Echo cardiogram good LV function mild LVH. Aortic stenosis + mitral regurgitation – Good RV function. Discharged 17/11/16. No change in con meds.	Standard care
Chest pain.	Standard care
Acute non-ST segment elevation MI.	Standard care
Hospital-acquired pneumonia.	Standard care
Pt. felt unwell 24/08/18. Taken by 999 ambulance, where has had a stent fitted (percutaneously) Discharged home 29/08/18. No further details as no discharged letter as yet.	Standard care
Sudden death at home No coroner's report available.	Standard care
Left knee replacement, routine at Royal United Hospital, Bath admitted on the 11/04/18 and discharged on the 14/04/18.	Spironolactone
He fell over on left arm and fractured humerus in 3 places while on holiday in Australia. It happened on 25/02/17 and he was admitted to Alfred hospital in Melbourne via A + E. He was discharged on 28/02/17 from hospital. Arm put in brace to immobilise.	Spironolactone
Patient has been self-catheterising. He was admitted to Royal united hospital Bath with haematuria overnight. Admitted on the 23/08/18 and discharged 24/08/18 from hospital. He was discharged home on antibiotics and to continue to self-catheterise.	Standard care
Patient was admitted to royal united hospital bath with urinary tract infection. The participant was admitted on 12/12/18 and discharged from hospital home on 16/12/18. He was treated with antibiotics meropenem and ciprofloxacin.	Standard care
Patient went to A&E at Royal United Hospital Bath with haematemesis and blood in stools. Admitted on 19/12/16 had gastroscopy. Severe reflux oesophagitis with contact bleeding diagnosed. Patient discharged on 24/12/16 after several blood transfusions. Problem resolved on 24/12/16.	Standard care
Admitted at Royal United Hospital following a vacant episode and a month of diarrhoea every day. The admission was on the 14/01/2018 and she was discharged on 15/01/18-referred for colonoscopy.	Standard care
Admitted at Royal United Hospital on 19/01/18 as collapsed at home (vacant episode of 3 minutes) chronic diarrhoea for 6 weeks outcome was pre-syncopal episode secondary to dehydration from diarrhoea. Patient discharged from hospital on 23/01/18.	Standard care
Unexpected and unexplained death. Has done to coroner for PM – result pending.	Standard care
Fall while getting out of a car. Left intracapsular neck of femur fracture resulting in a left total hip replacement.	Standard care
Acute presentation of spinal abscess. Presented on 14/11/20. Required emergency surgery.	Standard care
06/06/2019 Self-referral to Emergency Department due to Frank Haematuria. Treated for UTI but symptoms remain. Has been referred by urology for urgent CT urogram.	Spironolactone
Unexpected death at home. Post-mortem report not yet sent to practice. Patient had stopped study medication on 18/09/18.	Standard care
Admitted to Lister Hospital with palpitations and unsteadiness on her feet Reports dizziness, nausea, tremor and generally feeling unwell all day. Discharged home on the same day (4th Nov).	Standard care
Presented to the GP on 24/10/19 with a 4–6-week history of unsteady gait. Admitted to hospital on 28/10/19 with dizziness. MRI showed a left parietal single micro haemorrhage. (No follow-up required.) Discharged home on 29/10/19. Candesartan stopped.	Standard care
Patient had BARACK-D ECG + found to be in heart block. Advised to stop B blocker + was referred to cardiology. Fall 11/7; 31/7l -NSTEMI; pacemaker inserted. Unwell since. 23/08/18. Found to have raised K+ 6.4 -> admitted to hospital for tests.	Standard care

continued

Serious adverse event	Intervention received
Elective surgery booked for June 2019 for malignant neoplasm of rectum. Had colorectal surgery 5 weeks ago (exact date unknown). Admission unexpectedly increased due to post op complications. Visit 7 due today. Unable to attend as remains in hospital. Discharge date unknown. Pre-op, patient wanted to remain in BARACK-D trial.	Spironolactone
Patient admitted for acute asthma exacerbation. Noted decline in renal function hence spironolactone stopped. Further details to follow.	Standard care
Patient admitted with Rt sided diagnosed CVA infarct. Residual weakness and incapacity.	Standard care
Admitted 13/02/17 with generalised abdominal pain radiating to his back. Confirmed pancreatitis on ultrasound. Discharged after resolution. No further investigations showed problem.	Standard care
Admission to hospital due to stroke.	Standard care
Pt been unwell, admitted to hospital with pneumonia.	Standard care
Admitted with chest pain, recent chest infection treated with antibiotics. No evidence of MI. Some pulmonary oedema and was noted to be in fast atrial fibrillation. Was discharged and advised for review in community with regards to optimum control of his IHD an AF.	Standard care
Seen 19/02/16 with epididymitis – prostate examined as part of assessment – firm lump found + raised PSA on blood test – referred to Urology – biopsy showed carcinoma of prostate – on treatment with Zoladex NoI.	Standard care
06/11/15 – 09/11/15 admission to hospital with suspected upper gastrointestinal bleed secondary to Naproxen 10 days previously (on top as Aspirin).	Standard care
The 2-week renal profile showed dramatic rise in creatinine necessitating discontinuation of spironolactone and all other medications – Renal profile rapidly improved.	Spironolactone
Iron deficiency anaemia – Investigated with OGD – Polypoidal mass at gastro-oesophageal junction – likely malignant. Patient is undergoing further investigations pending possible radical treatment.	Standard care
Patient had gastrointestinal bleed on Sunday 19th July requiring admission to A+E IV fluids given blood tests checked allowed home next morning (practice only notified today 23/07/15).	Spironolactone
Admitted to hospital with abdominal pain + rectal bleeding on 13/03/17 discharged on 21/03/17.	Spironolactone
Admitted to hospital 23/02/17 presenting with haematuria with clots causing urinary retention. Known atrial fibrillation and takes Warfarin. Radical prostatectomy 2006. Urinary catheter placed on admission and bladder washouts performed. Haematuria resolved – discharged 24/02/17. Follow up as an outpatient. *Update to SAE (received 28/03/16): A subsequent CT scan has revealed a 9 cm left renal mass consistent with a renal cell carcinoma. Waiting renal surgical referral for consideration of laparoscopic radical nephrectomy.	Standard care
Admitted to hospital 28/05/17–29/05/17. Presented with reoccurrence of haematuria. Previous reported SAE episode 23/02/17–24/02/17. Haematuria resolved spontaneously. Known 9 cm left renal mass consistent with a renal cell carcinoma. Recent left laparoscopic radical nephrectomy. (SAE previously reported and updated today) (19/06/17).	Standard care
Admitted to hospital 23/02/17 with haematuria which resolved spontaneously (previously reported SAE). A subsequent CT scan has revealed a 9 cm left renal mass consistent with a renal cell carcinoma. Waiting renal surgical referral for consideration of laparoscopic radical nephrectomy. 19/06/17 SAE Update; left laparoscopic nephrectomy on 09/06/17. Admitted to hospital for elective surgery on 09/06/17 discharged 13/06/17. Histology pending. 21/09/17 SAE Update Left laparoscopic nephrectomy for Fuhrman Grade 3 clear cell carcinoma. Tumour measured 8 cm with necrosis and vascular invasion and invasion into perinephric fat. There was a separate 15 mm papillary renal carcinoma. Overall he has a high risk of reoccurrence. Under surveillance for fluctuating eGFR consultant nephrologist suggest may require renal placement therapy either short or long term for the management of his CKD following removal of kidney.	Standard care
13/01/15 presented with chest pain; and a history of nausea + diarrhoea [unknown] pulse 54 bpm (r) BP 154/78 mmHg. Not dehydrated peripherally shut down and feeling cold Admitted- blood values attached. Negative. Troponin 1; Potassium 4.3 mmol/L.	Spironolactone
02/06/15 Admitted with chest pain + altered bowel habit. Acute coronary syndrome excluded. Awaiting to have a pacemaker fitted investigations initiated into altered bowel habit to exclude diverticulitis. Discharged 04/06/15.	Spironolactone

Serious adverse event	Intervention received
20/12/15: Patient was admitted via Accident & Emergency dept with shortness of breath, dry cough x 4 days. Prednisolone and nebulizer given stat, then prescribed prednisolone and doxycycline x 1 week course. ECG = normal, bloods = normal, chest X-ray = Bi-Basal Atelectasis, otherwise lungs clear. Discharged 23/12/15. Recovered.	Spironolactone
Patient diagnosed with prostate cancer on the 31/05/16.	Spironolactone
Patient underwent a cystoscopy for haematuria. Incidental findings of soft tissue on gallbladder. Subsequent MRI scans suggest cancer of gallbladder and intraductal cholangiocarcinoma and patient has been referred.	Spironolactone
Diagnosed with prostate cancer in June 2016, haematuria in January 2018, CT scan performed showing thickening of gall bladder wall. Cholesystectomy in July 2018 with histology revealing Burkitt's lymphoma diagnosed in August 2018.	Spironolactone
Admitted to emergency department at the local hospital with increased breathlessness, central chest pain and whitish productive cough on 16/09/16. Patient treated with Doxycycline, clinically improved and discharged home 20/09/16.	Standard care
Admitted 05/03/16 with right TACS – thrombolysed. Still swallowing problems.	Standard care
Admitted to hospital with suspected stroke and then passed away – see attached docs.	Standard care
Accidental fall resulting in hip fracture 22/11/15.	Spironolactone
Found dead at home on 08/04/19 by police last seen 03/04/19.	Standard care
Hyperkalaemia K – 6.1.	Standard care
Patient was admitted with collapse, 5 presyncopal episodes in last 12/12. He has background os severe degenerative AS, good LV function. His device was checked showed no pauses or high-grade AV block, he was reviewed by Dr Banks who stopped ramipril, allowed discharge home with catheter coronary angiogram and CT thorax (aorta) as an outpatient. Also advised to refer for TAVI assessment.	Spironolactone
Admitted with abdominal pain thought to be cholecystitis. Symptoms resolved. Discharged 13/07/16.	Standard care
He was admitted with non-specific illness – infection unknown source. Treated with IV antibiotics and discharged 20/06/16.	Standard care
Reported vomiting once last night at least 10 times – dark/black vomit. No Hx of malaria. No adbs pain reported. B/P 93/59 sitting B/P 80/57 standing HRT 88. Altert: Cap refill < 2 seconds. 8/3 duty Dr -? GI bleed. Referred for review 2/52 colorectal exam for change in bowel habit on 13/11/15. Note: eGFR dropped to 26 ml/minute at last study visit (visit 2). Randomised into standard care. eGFR at visit 1 26 ml/minute 27/10/15 Baseline 29 ml/minute 25/09/15 30ml/minute 11/06/15 34 ml/m 24/09/15 H/o Hydronephrosis.	Standard care
Acute ST segment elevation MI 30/01/17 requiring hospitalisation, cardiac catheterisation, PCI of mid-LAD artery.	Standard care
Referred to haematology following Wt loss and Pancytopenia subsequent diagnosis Lymphoplasmacytoid Lymphoma commenced chemo February 2016, but keen to continue in study.	Standard care
Secondary malignant neoplasm of lung.	Spironolactone
3 year history of paroxysmal atrial fibrillation. 26/0915 attended A&E, feeling 'unwell' Diagnosis Fast AF atrial fibrillation (AF) commenced on Bisoprolol. 30/09/15 '23 hour stay' Poole Hospital exacerbation Fast AF. 18 started on Rivaroxaban. 18/11/15 Angiography – No obstructive coronary disease. 19/11/15 Cardioversion to sinus rhythm.	Spironolactone
Attended A+E with dizziness, palpitations and cough. Atrial fibrillation for 5 hours 15 minutes Has reveal implant reverted back to sinus rhythm on initial ECG in A+E. Troponin 222, Echo normal LV + RV sizes with good diastolic function. Mildly thickened septal appearance. Moderately dilated LA. Angiogram shows mild bridging in LAD, No change since 2015.	Spironolactone
Admitted to hospital 19.7.16 @ 14:15 with suspected Cauda Equina syndrome. Subsequent imaging excluded this.	Standard care
Admission to hospital with chest pain. Still in hospital waiting for inpatient angiogram. Admitted 30/01/17. Transferred to cardiac unit on 01/02/17. Troponin T, echocardiogram + ECG normal.	Standard care

continued

Serious adverse event	Intervention received
Epistaxis requiring admission to hospital.	Standard care
Hospitalised with epistaxis. 23/12/16 to 25/12/16 Hb dropped from 105 to 94. Required packing.	Standard care
Patient had fall. GP sent to A&E with possible shoulder dislocation or humeral head fracture.	Standard care
TURP on 29/05/18. Discharged on 31/05/18. Returned for catheterisation on 05/06/18 in urinary retention. Planned review at 2 weeks.	Standard care
Entered BARACK-D and randomised to spironolactone in July 2018. Developed right upper quadrant discomfort/bloating in January 2019, which resulted in CT scan showing right adrenal mass 27 mm on 25/01/19, with subsequent blood tests by endocrinologists confirming a diagnosis of right sided solitary adrenal pheochromocytoma. While I am not aware of any known causal link, I cannot exclude the possibility given mechanism of action and timeline.	Spironolactone
Admitted for TIA on 11/06/16 - Discharged home 23/06/16: Please see attached summary for details. Site aware on 20/07/16.	Standard care
Admitted to hospital with gastroenteritis 17/11/17. Rehydrated with IV fluids – discharged 19/11/17.	Standard care
Tripped due to left leg neuropathy sustained forehead laceration, no bony injuries. Suture removed and healing well.	Standard care
Admitted with history of diarrhoea and vomiting. IV fluids for rehydration. Noro and C diff stools negative. Discharged home 13/12/17	Standard care
03/03/16 Incidental finding of 3.5 cm AAA- for annual surveillance. 07/09/17 symptomatic rapidly extending AAA - emergency EVAR 08/09/17. Discharged 10/09/17.	Spironolactone
Pt fell following dizzy episode related to UTI. Fall resulted in broken ankle.	Spironolactone
Admitted to hospital with hypokalaemia. Seru potassium 2.3. Furosemide and indapamide stopped on admission. Given IV fluids with potassium. Discharged next day.	Spironolactone
Ileostomy for Crohn's disease for 20 years. Woke with abdominal pain admitted to hospital for assessment. Blocked stoma-flushed Discharged with no follow-up.	Standard care
CVA – reported by daughter No further information yet available.	Standard care
Fell in a supermarket and appeared confused. Admitted to hospital overnight – discharged with antibiotics & diuretics.	Standard care
Fall at home on admission also found to have chest infection so admitted 08/12/16 Discharged 12/12/16 Site aware on 15/02/17	Standard care
Admitted to hospital with urinary tract infection and noted to be in fast AF. All relevant correspondence/paperwork attached to study visit.	Standard care
Admitted to hospital 13/04/19 with upper abdominal pain in RUQ. USS – gallstones. Awaiting cholescystectony Discharged summary attached	Standard care
Admitted to hospital 22/12/18 with LRTI. Treated with antibiotics IV fluids but swabs positive to Influenza A so stopped.	Standard care
Angiogram carried out late afternoon on 08 /09/17 so observation of insertion site (radial artery) post procedure necessitated an overnight stay.	Standard care
AE of left sided chest pain 30/08–31/08/15. Hospital overnight stay. Diagnosis of muscular pain. Aware of A/E 19/10/15.	Standard care
Admitted to hospital 22/10/20 following abnormal bloods, had bone marrow aspirate, immunophenotyping and cytogenics. Diagnosed with Acute myeloid leukaemia – for palliative management. Had blood transfusion. Condition progressing rapidly. Symptoms being managed at home.	Standard care
Pt presented to ED with (R) arm weakness and numbness lasting 30 minutes. Labs – Nil acute. ECG – 1st degree heart block referred to TIA clinic – high risk. MRI – Brain – see attached doc. Diagnosis small (L) CVA.	Standard care

Serious adverse event	Intervention received
This patient's wife rang into the surgery 9 a.m. this morning to say her husband who is in the trial has been admitted to hospital last night. He was seen yesterday at visit 6 and had lost weight now down to 7 stone 9lb. no other details known. Hyperkalaemia secondary to Spironolactone required urgent hospital admission.	Spironolactone
Patient passed away 01/05/16. He was admitted 12th February and diagnosed. Hyperkalaemia oncology then diagnosed metastatic oesophageal adenocarcinoma affecting the gastric tube and left adrenal gland. He was on palliative care until time of death at home.	Spironolactone
Patient admitted to hospital as emergency to date no information as to the reason for admission or date of discharge. *DM additional information provided: Patient died in Hospital on the 16/08/16 – cause of death serious aortic stenosis.	Standard care
Admitted to hospital with UTI/? pyelonephritis and acute chronic kidney impairment on 09/07/18. Discharged on 13/07/18.	Standard care
Ca breast requiring mastectomy and reconstruction.	Standard care
Urinary retention, UTI, vomiting, fever, epigastric pain.	Spironolactone
Deranged LfT's Acute Hep E infection.	Spironolactone
Presented to GP with episode of transient left arm and leg weakness (mild) – was transferred to stroke unit for same day assessment as presumed TIA -All symptoms (weakness) resolved.	Spironolactone
Patient was admitted to hospital with AF. This patient is not taking spironolactone. Was discharged the next day.	Standard care
Patient admitted with hospital acquired pneumonia. Treated with IV antibiotics and discharged 3 days later.	Standard care
Hospital admission 26/07/20–05/08/20 with urinary tract infection + acute kidney injury.	Standard care
Patient report of hospital admission on 22/02/18 due to cardiac event. Diagnosed with bundle branch block, discharged on 23/02/18 awaiting further investigation and? surgery GP (PI)to F/U with further details once hospital discharge summary received.	Standard care
Admitted to hospital 22/02/18 with angina. Discharged 23/02/18.	Standard care
01/08/19 Admitted to hospital with stable angina + underwent coronary artery bypass grafting to treat this. Discharged 09/08/19. Operation complicated by atrial fibrillation.	Spironolactone
3 days history epigastric pain, cramping pain, lightheaded. Admitted to Poole General Hospital – treated with oral ciprofloxacin and PPI. Discharged and per OPD OGD.	Standard care
Re-admitted with abdominal pain and vomiting. USS – thin walled gallbladder containing 2 gallstones one of which appears to be stuck in the neck. Discharged 30/03/18 on PPI and oral antibiotics.	Standard care
Admitted via A+E. Colonoscopy as in-patient. Diagnosed malignant tumour small intestine. RT hemi-colectomy 02/06/18. Has now commenced chemotherapy.	Standard care
Patient died. 1a UTI 1b Metastatic carcinoma.	Standard care
Bi-lateral PE secondary to vasculitis. Seen by GP with increasing SOB over 1 week. Under rheumatology team with large vessel vasculitis. Admitted to hospital. CTPA – bilateral PE. ECG – sinus tachy. 3 days Dalteparin IM – then started NDAC. Discharged home on Rivaroxaban.	Standard care
Unplanned hospital admission for pleural effusion and pneumonia.	Standard care
Passed away at home – unexpected Unknown cause, awaiting further information.	Standard care
Right lower zone pneumonia. Suspicious middle lobe lesion ?infective ?malignancy. Haemoptysis, SOB, night sweats. Admitted to hospital 15/05/20–22/05/20. Treatment – IV then PO antibiotics, oxygen. Follow-up CT was arranged for nodule.	Spironolactone
Presented with SOB + pleuritic chest pain. GP admitted to A+E with? pulmonary embolism. Investigated at hospital, hiatus hernia found to be the cause of pain + SOB. Pt has increased esomeprazole and states is feeling much better now. Hospital letters attached.	Standard care

continued

Serious adverse event	Intervention received
Had a fall which led to a periprosthetic fracture of L femur and 36 hours lie.	Standard care
Small bowel obstruction which required an unplanned hospital admission and an in-patient stay.	Standard care
A+E attendance followed by emergency admission + surgical intervention for bladder + kidney stones.	Standard care
See attached summary. Admission with pyelonephritis (unplanned via A + E). Septic on admission. Treated with IV abx + fluids	Standard care
Emergency hospital admission, postural hypotension and dehydration. Discharging diagnosis: acute renal failure (see A+E report). The patient has progressive spread of colonic carcinoma.	Standard care
Nausea + central chest pain, III sent ambulance who took pt to A+E. Diagnosis lower respiratory tract infection.	Spironolactone
Attended ED with neck lump 3 cm mass, Rt.mid-clavical? Neutropenic sepsis. Further investigations detected? lymphoplasmacytic lymphoma. Histology sent to Derriford for second opinion.	Spironolactone
New? diagnosis as impatient -? Lymphoplasmatic lymphoma secondary to breast cancer.	Spironolactone
New diagnosis of metastatic breast cancer with bone marrow involvement.	Spironolactone
Patient died 13/08/19 Cause of death: IA: Sepsis IB: Breast cancer, bone marrow lymphoma mets.	Spironolactone
Unplanned hospital admission with breathlessness. Admitted by GP. Diagnosis on dischargeL Hyponatraemia secondary to indapaminde. Breathlessness ?secondary to viral infection.	Spironolactone
Admission to hospital with obstructed hernia.	Spironolactone
Ruptured aneurysm.	Standard care
Initial report: Diagnosed with relapsed metastatic renal cell cancer, lymphadenopathy and lung lesion. For consideration for chemotherapy under urologist. Follow-up report: Metastatic renal cell cancer. Ongoing.	Standard care
Patient attended for last visit. Bloods possibly delayed in processing. Potassium was 8. Patient admitted via out of hours to Torbay hospital. CH repeat potassium was 4.4. Patient remained well throughout. Discharge summary states blood test repeated. No treatment mentioned. Patient not on study drug but had been commenced on Ramipril 10/09/20 (U&Es 08/10/20 normal potassium 5.2) High K could have been Ramipril effect or delay in processing sample.	Standard care
Ventricular tachycardia admitted and had DC cardioversion, something happened again and again cardioverted in A + E. Awaiting cardiology. On Beta blockers.	Standard care
Admitted with chest pain on 21/09/17. Following PCI which showed normal coronary arteries patient was diagnosed with non-cardiac chest pain. Discharged on 22/09/17.	Standard care
Epistaxis.	Standard care
See attached sheet. Patient is on the spironolactone arm of the study. On 02/08/18 patient collapsed, was sweaty, clammy and nauseous, loss of consciousness < 1 minute. Admitted to hospital and was diagnosed with having experienced a Vasovagal Episode which may have been due to Hypotension as patient was on 3 antihypertensive medications. BP recorded in hospital was 112/70. Amlodipine was stopped but continues on ramipril and spironolactone. Other investigations - CT of head and abdomen/ pelvis NAD. Patient was discharged home on 04/08/18. Unscheduled visit to trial clinic on 06/08/18 – BP (R) arm 114/70. (L) arm 112/66. No further episodes since discharge from hospital.	Spironolactone
Pneumonia treated in hospital and now fully recovered. Not on spironolactone.	Standard care
Patient admitted to Worthing hospital with aortic stenosis and died.	Standard care
Admitted to hospital on 02/01/18 for elective admission for right hepatectomy. Solitary Segment VII hepatocellular carcinoma on the background of a non-cirrhotic liver. Discharged on 18/01/18.	Standard care
Pt died on 31/07/18 – liver CA + METS.	Standard care
Admitted to A+R following a fall, injured R arm. Hypotensive in A+E – resolved before discharge.	Standard care
Admitted with abdominal pain on 11/04/19 and discharged on 04/05/19 with necrotising pancreatitis. Had flare up on 11/06/19 and attended A/E. -Discharged home, now has cellulitis of arm (due to canula) and URTI. Currently unable to contact pt.	Standard care

Serious adverse event	Intervention received
18/09/18 Patient reported falling/losing balance/drooling over past year. ACT scan requested and performed 24/11/18 showed established left frontal infart. Patient put on secondary prevention medication & had physio.	Standard care
Patient developed an exacerbation of COPD requiring hospital admission resolving with a course of steroids and antibiotics (patient not on study drug).	Standard care
Patient fell sustaining a fractured neck of L Femur – fixed with dynamic hip screws on 22/08/16. Discharged home on 01/09/16.	Standard care
Admitted to hospital with acute kidney injury (patient not on spironolactone) (see discharge letter).	Standard care
Admitted to hospital with shortness of breath related to heart failure (cor pulmonale).	Standard care
Patient had a stroke (CVA) while getting dressed on 02/11/16. Ambulance crew noticed slight weakness to grip in left hand, and he was confused. Patient was taken to A+E then referred to the stroke ward. Research team only notified of this the day before BARACK-D appointment on 23/11/16.	Spironolactone
Patient had a stroke on 2nd November 2016 and subsequently died on 30/11/16. Cause of death on the death certificate State Intracerebral Haemorrhage and Aspiration Pneumonia.	Spironolactone
Patient collapsed (18/12/14) loss of consciousness 2 minutes, Admitted to A + E. Now on short stay ward, possible discharge post lying + standing BP. Diagnosis is vaso vagal syncopy post dehydration, decrease in BP. Con medications reviewed, fluids orally, GP review follow-up.	Standard care
Patient had a vasovagal event. Called an ambulance + was referred to A + E by rapid response team from where she was admitted. Diagnosis UTI, discharged after 5 days. (21/02/19–25/02/19).	Spironolactone
Patient attended A+E on 27/07/18 with bilateral leg oedema. He was admitted the same day with suspected LV failure. He is still hospitalised, no further information available.	Standard care
Patient died on 21/02/21, cause of death cardiopulmonary arrest due to community-acquired pneumonia.	Standard care
Collapse secondary to dehydration. Flu-like illness for 2 weeks, been to gym, collapse in town. Recovered with intravenous fluid and discharged same day.	Standard care
He has a (L) renal tumour under surveillance long-term. It is related to his Birt–Hogg–Dube syndrome. Recent biopsy + ablation as raised in size. No complications from procedure. Well. Will continue under surveillance.	Standard care
Operation and hospital stay following small bowel obstruction secondary to adhesions. Significantly dehydrated suffering AKI stage 2 prior to surgery due to bowel obstruction. Fast heart rate and episodes of AF prior to and shortly after surgery, resolved in ICU with Amiodarone. Tachycardia has remained. Normal ECG, regular pulse. GP advised no need for ECG as pulse 96/minute. Low potassium and calcium, now resolved. Mild confusion – for referral to memory clinic. Weight loss since admission with obstruction. If continues, rule out melanoma/prostate cancer.	Standard care
Hospital admission on 29/12/20 – 05/01/21 for critical ischaemia secondary to occluded graft on right leg. Thrombectomy right fem-pop bypass graft (PTFE). Jump graft to TPT from PTFE graft with arm vein.	Standard care
Admitted to A+E with abdominal pain + rectal bleeding – Diagnosed with Acute Colitis – treated with oral antibiotics. Discharged from A+E with OP colonoscopy f/up. Colonoscopy 11/05/20 – NAD sigmoidoscopy 15/07/20 – NAD.	Standard care
3 days H/o epigastric tenderness H/o pancreatitis May 2018 Attended GP surgery with significant abdo pain – admitted to hospital and diagnosed with acute mild pancreatitis.	Standard care
Sudden onset of severe epigastric pain and vomiting M/O pancreatitis 11/2018 Admitted to hospital 04/03/19 with suspected pancreatitis.	Standard care
Recurrent episode of pancreatitis. Study med was discontinued due to previous episodes of pancreatitis 11/03/19.	Standard care
Participant presented to A&E on 27/09/18 with head pain and blurred vision. CT head performed the same day NAD. Repeat CT 28/09/18 showed an acute left PCA territory infarct. Discharged 11/10/18.	Standard care
Lower respiratory tract infection leading to hospitalisation for 4 days. Fully recovered with iv + oral antibiotics.	Spironolactone

continued

Serious adverse event	Intervention received
Initial report: Emergency hospital admission 21/04/21 with shortness of breath. Currently on ITU. Diagnosis provisionally pneumonia + acute cholecystitis Follow-up report: Emergency hospital admission with pneumonia/acute kidney injury & biliary sepsis – hospital admission 21/04/21 – 09/06/21. Patient went to ITU from A + E inotropes/filtration + intubation – recovery with antibiotics and gallstones removed via ERCG. Discharged from ITU to ward on 20 /05/21.	Spironolactone
Admitted to hospital with abdominal pain, vomiting, constipation on 30/12/18 ?cause. Currently still an inpatient.	Standard care
Emergency hospital 21/11/18 → 14/12/18 due to incarcerated abdominal wall hernia requiring emergency surgery.	Standard care
Recent hospital admissions x 2 for bowel obstruction/constipation. Readmitted 13/01/19 with abdo pain/constipation. Currently still in hospital.	Standard care
Initial report: Blood test done 16/05/18 for routine practice annual review. Rise in creatinine (from 160 baseline to 248) repeat test 25/05/18 – further deterioration in renal function – Creatinine 307 – admitted to hospital – still an inpatient. Follow-up report: Follow up report (SAE submitted 01/06/18 & 29/05/18).	Spironolactone
Fall down stairs 07/05/2018 Multiple injuries – soft tissue Currently still hospital inpatient.	Standard care
Hospital admission with H/O right lower chest wall pain. Discharge same day investigation negative.	Standard care
Sudden onset of palpitations. Hospitalised from 8th to 12th April. Discharge with OPD follow-up and investigations See discharge letter (post)	Spironolactone
Patient had UTI – eGFR dropped and cr raised. Did not improve and pt required hospitalisation for fluids and monitoring renal function. Other medications, irbesartan, doxazosin and furosemide temporarily stopped.	Standard care
Myocardial infarct and upper GI bleed + heart failure. – Pt admitted to A+E with upper GI bleed + chest pain – assessed, not a candidate for coronary angio or PCI so medically managed. Renal deterioration ongoing. End diagnosis – gi bleed causing M.I., pt had had symptoms of gi bleed for 3 weeks.	Spironolactone
Patient diagnosed with gastric cancer delayed diagnosis, 02/06/20. Patient had GI bleed and vomiting and died 29/06/20	Spironolactone
eGFR dropped from 46 18/03/19, to 37 23/04/19, repeated eGFR 30/04/19 – dropped to 34. Seen on 02/05/19 – tender pelvis,? mass? UTI ordered ultrasound. Urine test back 04/05/19 – showed urine infection, hasn't had ultrasound yet, not sure if cancelled. eGFR has not improved since.	Spironolactone
Had a fall at home on 12/02/21 appeared to be more confused and drowsy -> admitted via 999. Also attended the PDWH A&E 29/01/21 found to have fracture (L) greater trochanter treated conservatively. Currently still an inpatient in hospital.	Standard care
History of collapse with WC on 06/12/18 required hospital admission (6/12 - 9/12/18 at POWH). Investigations ECG/echo/bloods nil acute. Had flu with cardiology final diagnosis vasovagal syncope.	Standard care
Patient admitted to hospital with worsening chronic renal failure and cardiac failure. Sadly died. Cause of death stated as acute chronic renal failure, cardiac failure and frailty.	Spironolactone
Patient admitted to hospital with hip fracture following a fall. The patient had surgery to the hip on 15/07/20. Patient anaemic Hb 86 g/L 17/07/20. Chest X-ray 19/07/20 appearance consistent with infection. Patient suffered sudden cardiac death 19/07/20.	Standard care

Appendix 9 Log–log plots and Kaplan–Meier predicted survival plots testing the proportional hazards assumption for the post hoc analysis

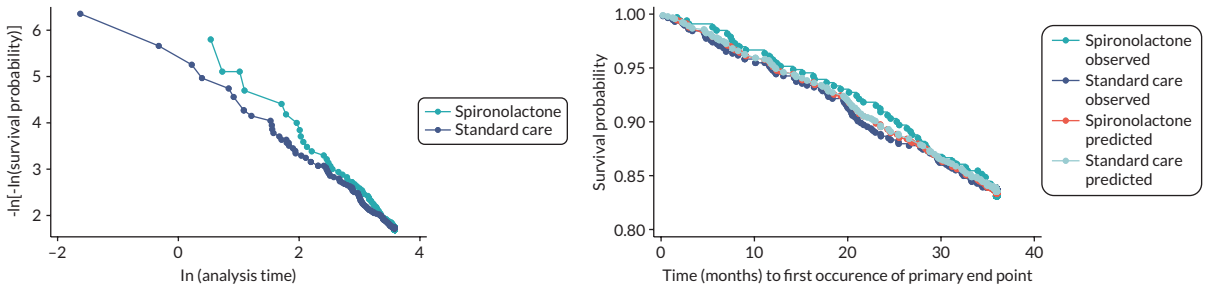


FIGURE 26 Model residuals for the post hoc analysis based on a per-protocol principle and an on-treatment population.

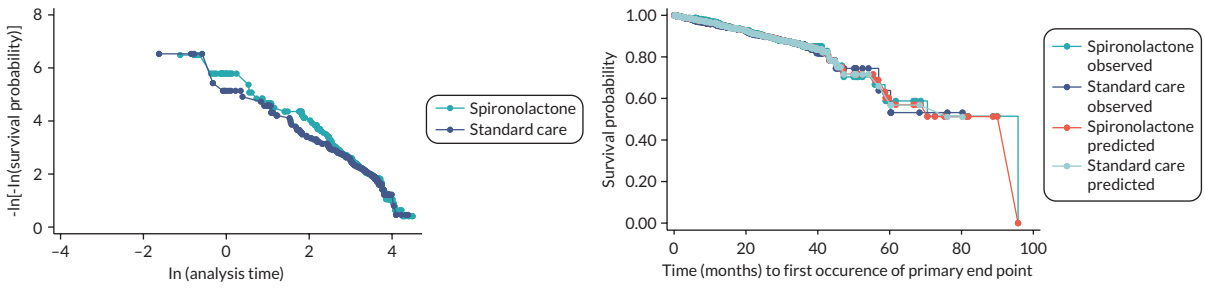


FIGURE 27 Model residuals for the post hoc analysis excluding PAD.

Appendix 10 Economic evaluation

TABLE 21 Availability of resource use data for health economic analysis by time point and treatment group

	Spironolactone: *N* = 677 eligible at baseline				Standard care: *N* = 695 eligible at baseline			
			Attrition from previous to given time point				Attrition from previous to given time point	
	Available at given time point *N* (%)	Missing at given time point *N* (%)	Withdrawal *N* (%)	Death *N* (%)	Available at given time point *N* (%)	Missing at given time point *N* (%)	Withdrawal *N* (%)	Death *N* (%)
Year 1	476 (70.3)	94 (13.9)	91 (13.4)	16 (2.4)	555 (79.9)	78 (11.2)	50 (7.2)	12 (1.7)
Year 2	473 (69.9)	56 (8.3)	31 (4.6)	10 (1.5)	540 (77.7)	39 (5.6)	43 (6.2)	11 (1.6)
Year 3	463 (68.4)	32 (4.7)	26 (3.8)	8 (1.2)	533 (76.7)	15 (2.2)	23 (3.3)	8 (1.2)

TABLE 22 Availability of EQ-5D-5L data for health economic analysis by time point and treatment group

	Spironolactone: *N* = 677 eligible at baseline				Standard care: *N* = 695 eligible at baseline			
			Attrition from previous to given time point				Attrition from previous to given time point	
	Available at given time point *N* (%)	Missing at given time point *N* (%)	Withdrawal *N* (%)	Death *N* (%)	Available at given time point *N* (%)	Missing at given time point *N* (%)	Withdrawal *N* (%)	Death *N* (%)
Baseline	651 (96.2)	26 (3.8)	N/A	N/A	664 (95.5)	31 (4.5)	N/A	N/A
Month 6	517 (76.4)	82 (12.1)	72 (10.6)	6 (0.9)	605 (87.1)	49 (7.1)	35 (5.0)	6 (0.9)
Year 1	491 (72.5)	79 (11.7)	19 (2.8)	10 (1.5)	583 (83.9)	50 (7.2)	15 (2.2)	6 (0.9)
Year 2	466 (68.8)	63 (9.3)	31 (4.6)	10 (1.5)	510 (73.4)	69 (9.9)	43 (6.2)	11 (1.6)
Year 3	459 (67.8)	36 (5.3)	26 (3.8)	8 (1.2)	502 (72.2)	46 (6.6)	23 (3.3)	8 (1.2)

TABLE 23 Healthcare resource use frequency by time point and treatment group

Time point	Spironolactone		Standard care	
	Available cases (ACs): *N* = 476		Available cases (ACs): *N* = 555	
Year 1	*N*	Rate per AC	*N*	Rate per AC
Family doctor (GP)	432	0.908	479	0.863
Practice nurse	392	0.824	440	0.793
Home visit – family doctor (GP)	26	0.055	33	0.059
Home visit – practice nurse	18	0.038	11	0.020
Dietitian	9	0.019	13	0.023
Occupational therapist	21	0.044	26	0.047
Counselling/psychological support	5	0.011	6	0.011

TABLE 23 Healthcare resource use frequency by time point and treatment group (*continued*)

Time point	Spironolactone		Standard care	
	Available cases (ACs): *N* = 476		Available cases (ACs): *N* = 555	
Year 1	***N***	**Rate per AC**	***N***	**Rate per AC**
Community/district nurse	16	0.034	10	0.018
Hospital outpatient department	339	0.712	361	0.650
Hospital inpatient department	64	0.134	69	0.124
Hospital A&E department	80	0.168	77	0.139
ITU	1	0.002	4	0.007
HDU	1	0.002	2	0.004
Total number of medications	667	1.401	686	1.236
	Available cases (ACs): *N* = 473		Available cases (ACs): *N* = 540	
Year 2	*N*	**Rate per AC**	*N*	**Rate per AC**
Family doctor (GP)	289	0.611	347	0.643
Practice nurse	286	0.605	312	0.578
Home visit – family doctor (GP)	23	0.049	14	0.026
Home visit – practice nurse	10	0.021	9	0.017
Dietitian	5	0.011	8	0.015
Occupational therapist	14	0.030	19	0.035
Counselling/psychological support	4	0.008	5	0.009
Community/district nurse	13	0.027	12	0.022
Hospital outpatient department	215	0.455	259	0.480
Hospital inpatient department	40	0.085	52	0.096
Hospital A&E department	50	0.106	48	0.089
ITU	1	0.002	1	0.002
HDU	2	0.004	0	0.000
Total number of medications	496	1.049	579	1.072
	Available cases (ACs): *N* = 463		Available cases (ACs): *N* = 533	
Year 3	*N*	**Rate per AC**	*N*	**Rate per AC**
Family doctor (GP)	240	0.518	294	0.552
Practice nurse	203	0.438	236	0.443
Home visit – family doctor (GP)	20	0.043	20	0.038
Home visit – practice nurse	9	0.019	13	0.024
Dietitian	8	0.017	2	0.004
Occupational therapist	11	0.024	12	0.023
Counselling/psychological support	3	0.006	3	0.006
Community/district nurse	6	0.013	13	0.024

continued

TABLE 23 Healthcare resource use frequency by time point and treatment group (*continued*)

	Available cases (ACs): *N* = 463		Available cases (ACs): *N* = 533	
Year 3	***N***	**Rate per AC**	***N***	**Rate per AC**
Hospital outpatient department	168	0.363	206	0.386
Hospital inpatient department	23	0.050	42	0.079
Hospital A&E department	43	0.093	47	0.088
ITU	0	0.000	0	0.000
HDU	0	0.000	1	0.002
Total number of medications	517	1.117	564	1.058

A&E, accident and emergency; HDU, high dependency unit; ITU, intensive therapy unit.

TABLE 24 Unit costs used for healthcare resource use costing

Resource use	Unit cost (£ 2021 price)[a]	Unit	Reference
Family doctor (GP)	30.9	Per consultation	PSSRU 2021[107]
Practice nurse	44	Per hour	PSSRU 2021[107]
Home visit – family doctor (GP)	45.6	Per visit	PSSRU 2018[122]
Home visit – practice nurse	78	Per hour	PSSRU 2010[123]
Dietitian	65	Per hour	PSSRU 2021[107]
Occupational therapist	65	Per hour	PSSRU 2021[107]
Counselling/psychological support	51	Per hour	PSSRU 2021[107]
Community/district nurse	44	Per hour	PSSRU 2021[107]
Hospital outpatient department	175	Per day	NHS reference costs 19/20[124]
Hospital inpatient department	561.5755	Per day	NHS reference costs 19/20[124]
Hospital A&E department	313.3575	Per attendance	NHS reference costs 19/20[124]
ITU[b]	874.7889	Per day	NHS reference costs 19/20[124]
HDU[c]	625.6164	Per day	NHS reference costs 19/20[124] and acute kidney injury (AKI) in England report[125]
Spironolactone 25 mg	0.5	Per day	British National Formulary[106]

A&E, accident and emergency; HDU, high dependency unit; ITU, intensive therapy unit.
a Costs were inflated to 2021 prices using the Hospital and Community Health Services Pay and Prices Inflation Index reported in the *Unit Costs of Health and Social Care 2021* compendium.[107]
b Based on average 4.2 days from National Chronic Kidney Disease Audit.
c Based on median 12 days from UK Kidney Association._ENREF_122[125]

TABLE 25 EuroQol-5 Dimensions, five-level version dimension responses from available cases by time point and treatment group

		Spironolactone: *N* = 677						Standard care: *N* = 695					
		Item response level N (% of *N* = 677)						Item response level *N* (% of *N* = 695)					
Time point	Dimension[a]	1	2	3	4	5	Missing	1	2	3	4	5	Missing
Baseline	M	308 (45.5)	167 (24.7)	145 (21.4)	36 (5.3)	1 (0.1)	20 (3.0)	321 (46.2)	173 (24.9)	127 (18.3)	50 (7.2)	2 (0.3)	22 (3.2)
	SC	579 (85.5)	49 (7.2)	23 (3.4)	3 (0.4)	1 (0.1)	22 (3.2)	581 (83.6)	51 (7.3)	33 (4.7)	4 (0.6)	0 (0.0)	26 (3.7)
	UA	371 (54.8)	184 (27.2)	80 (11.8)	17 (2.5)	5 (0.7)	20 (3.0)	382 (55.0)	172 (24.7)	84 (12.1)	28 (4.0)	5 (0.7)	24 (3.5)
	P	226 (33.4)	239 (35.3)	138 (20.4)	46 (6.8)	5 (0.7)	23 (3.4)	222 (31.9)	241 (34.7)	150 (21.6)	46 (6.6)	12 (1.7)	24 (3.5)
	AD	510 (75.3)	108 (16.0)	34 (5.0)	3 (0.4)	1 (0.1)	21 (3.1)	515 (74.1)	115 (16.5)	35 (5.0)	3 (0.4)	2 (0.3)	25 (3.6)
Month 6	M	263 (38.8)	132 (19.5)	97 (14.3)	30 (4.4)	1 (0.1)	154 (22.7)	306 (44.0)	140 (20.1)	113 (16.3)	47 (6.8)	2 (0.3)	87 (12.5)
	SC	465 (68.7)	38 (5.6)	19 (2.8)	1 (0.1)	0 (0.0)	154 (22.7)	533 (76.7)	50 (7.2)	25 (3.6)	1 (0.1)	0 (0.0)	86 (12.4)
	UA	332 (49.0)	112 (16.5)	59 (8.7)	17 (2.5)	3 (0.4)	154 (22.7)	347 (49.9)	133 (19.1)	103 (14.8)	22 (3.2)	4 (0.6)	86 (12.4)
	P	192 (28.4)	175 (25.8)	111 (16.4)	44 (6.5)	4 (0.6)	151 (22.3)	203 (29.2)	214 (30.8)	136 (19.6)	51 (7.3)	6 (0.9)	85 (12.2)
	AD	390 (57.6)	101 (14.9)	26 (3.8)	4 (0.6)	1 (0.1)	155 (22.9)	457 (65.8)	103 (14.8)	40 (5.8)	7 (1.0)	1 (0.1)	87 (12.5)
Year 1	M	233 (34.4)	122 (18.0)	100 (14.8)	34 (5.0)	0 (0.0)	188 (27.8)	275 (39.6)	139 (20.0)	117 (16.8)	47 (6.8)	2 (0.3)	115 (16.5)
	SC	417 (61.6)	50 (7.4)	22 (3.2)	1 (0.1)	0 (0.0)	187 (27.6)	491 (70.6)	56 (8.1)	29 (4.2)	2 (0.3)	2 (0.3)	115 (16.5)
	UA	275 (40.6)	121 (17.9)	72 (10.6)	17 (2.5)	6 (0.9)	186 (27.5)	312 (44.9)	147 (21.2)	87 (12.5)	25 (3.6)	5 (0.7)	119 (17.1)
	P	155 (22.9)	174 (25.7)	120 (17.7)	38 (5.6)	3 (0.4)	187 (27.6)	181 (26.0)	218 (31.4)	124 (17.8)	45 (6.5)	13 (1.9)	114 (16.4)
	AD	367 (54.2)	90 (13.3)	29 (4.3)	5 (0.7)	0 (0.0)	186 (27.5)	432 (62.2)	95 (13.7)	45 (6.5)	8 (1.2)	1 (0.1)	114 (16.4)
Year 2	M	198 (29.2)	109 (16.1)	80 (11.8)	26 (3.8)	2 (0.3)	262 (38.7)	224 (32.2)	121 (17.4)	88 (12.7)	42 (6.0)	1 (0.1)	219 (31.5)
	SC	365 (53.9)	37 (5.5)	14 (2.1)	2 (0.3)	0 (0.0)	259 (38.3)	409 (58.8)	43 (6.2)	25 (3.6)	0 (0.0)	0 (0.0)	218 (31.4)
	UA	224 (33.1)	114 (16.8)	60 (8.9)	16 (2.4)	1 (0.1)	262 (38.7)	255 (36.7)	118 (17.0)	75 (10.8)	25 (3.6)	4 (0.6)	218 (31.4)
	P	125 (18.5)	156 (23.0)	105 (15.5)	29 (4.3)	2 (0.3)	260 (38.4)	145 (20.9)	168 (24.2)	118 (17.0)	39 (5.6)	6 (0.9)	219 (31.5)
	AD	309 (45.6)	86 (12.7)	20 (3.0)	2 (0.3)	0 (0.0)	260 (38.4)	342 (49.2)	99 (14.2)	29 (4.2)	4 (0.6)	0 (0.0)	221 (31.8)
Year 3	M	176 (26.0)	106 (15.7)	68 (10.0)	37 (5.5)	0 (0.0)	290 (42.8)	196 (28.2)	111 (16.0)	93 (13.4)	51 (7.3)	3 (0.4)	241 (34.7)
	SC	336 (49.6)	36 (5.3)	15 (2.2)	0 (0.0)	0 (0.0)	290 (42.8)	366 (52.7)	56 (8.1)	24 (3.5)	6 (0.9)	2 (0.3)	241 (34.7)

continued

TABLE 25 EuroQol-5 Dimensions, five-level version dimension responses from available cases by time point and treatment group (*continued*)

		Spironolactone: *N* = 677						Standard care: *N* = 695					
		Item response level N (% of *N* = 677)						Item response level *N* (% of *N* = 695)					
Time point	Dimension[a]	1	2	3	4	5	Missing	1	2	3	4	5	Missing
	UA	213 (31.5)	97 (14.3)	63 (9.3)	9 (1.3)	5 (0.7)	290 (42.8)	235 (33.8)	112 (16.1)	78 (11.2)	21 (3.0)	7 (1.0)	242 (34.8)
	P	113 (16.7)	159 (23.5)	81 (12.0)	32 (4.7)	1 (0.1)	291 (43.0)	118 (17.0)	169 (24.3)	119 (17.1)	38 (5.5)	9 (1.3)	242 (34.8)
	AD	280 (41.4)	82 (12.1)	20 (3.0)	6 (0.9)	0 (0.0)	289 (42.7)	317 (45.6)	100 (14.4)	28 (4.0)	7 (1.0)	0 (0.0)	243 (35.0)

a Dimension acronyms: M, mobility; SC, self-care; UA, usual activities; P, pain; AD, anxiety and depression.

TABLE 26 EuroQol-5 Dimensions, five-level version dimension responses from complete cases by time point and treatment group

		Spironolactone: *N* = 309					Standard care: *N* = 365				
		Item response level *N* (% of *N* = 309)					Item response level *N* (% of *N* = 365)				
Time point	Dimension[a]	1	2	3	4	5	1	2	3	4	5
Baseline	M	153 (49.5)	78 (25.2)	66 (21.4)	11 (3.6)	1 (0.3)	197 (54.0)	88 (24.1)	54 (14.8)	26 (7.1)	0 (0.0)
	SC	278 (90.0)	24 (7.8)	7 (2.3)	0 (0.0)	0 (0.0)	319 (87.4)	28 (7.7)	15 (4.1)	3 (0.8)	0 (0.0)
	UA	189 (61.2)	80 (25.9)	35 (11.3)	5 (1.6)	0 (0.0)	227 (62.2)	81 (22.2)	39 (10.7)	16 (4.4)	2 (0.5)
	P	115 (37.2)	115 (37.2)	57 (18.4)	21 (6.8)	1 (0.3)	135 (37.0)	124 (34.0)	77 (21.1)	21 (5.8)	8 (2.2)
	AD	250 (80.9)	41 (13.3)	17 (5.5)	1 (0.3)	0 (0.0)	292 (80.0)	50 (13.7)	20 (5.5)	1 (0.3)	2 (0.5)
Month 6	M	168 (54.4)	71 (23.0)	53 (17.2)	17 (5.5)	0 (0.0)	195 (53.4)	77 (21.1)	65 (17.8)	28 (7.7)	0 (0.0)
	SC	281 (90.9)	20 (6.5)	8 (2.6)	0 (0.0)	0 (0.0)	315 (86.3)	33 (9.0)	17 (4.7)	0 (0.0)	0 (0.0)
	UA	208 (67.3)	61 (19.7)	30 (9.7)	10 (3.2)	0 (0.0)	216 (59.2)	78 (21.4)	55 (15.1)	13 (3.6)	3 (0.8)
	P	119 (38.5)	108 (35.0)	56 (18.1)	24 (7.8)	2 (0.6)	126 (34.5)	128 (35.1)	81 (22.2)	24 (6.6)	6 (1.6)
	AD	242 (78.3)	51 (16.5)	15 (4.9)	1 (0.3)	0 (0.0)	280 (76.7)	56 (15.3)	24 (6.6)	4 (1.1)	1 (0.3)
Year 1	M	165 (53.4)	73 (23.6)	54 (17.5)	17 (5.5)	0 (0.0)	191 (52.3)	79 (21.6)	68 (18.6)	26 (7.1)	1 (0.3)
	SC	272 (88.0)	30 (9.7)	7 (2.3)	0 (0.0)	0 (0.0)	312 (85.5)	35 (9.6)	15 (4.1)	2 (0.5)	1 (0.3)
	UA	180 (58.3)	75 (24.3)	44 (14.2)	8 (2.6)	2 (0.6)	204 (55.9)	96 (26.3)	47 (12.9)	15 (4.1)	3 (0.8)
	P	107 (34.6)	109 (35.3)	71 (23.0)	21 (6.8)	1 (0.3)	125 (34.2)	137 (37.5)	71 (19.5)	26 (7.1)	6 (1.6)
	AD	240 (77.7)	51 (16.5)	16 (5.2)	2 (0.6)	0 (0.0)	276 (75.6)	58 (15.9)	25 (6.8)	5 (1.4)	1 (0.3)
Year 2	M	154 (49.8)	81 (26.2)	51 (16.5)	21 (6.8)	2 (0.6)	172 (47.1)	89 (24.4)	72 (19.7)	32 (8.8)	0 (0.0)
	SC	274 (88.7)	25 (8.1)	8 (2.6)	2 (0.6)	0 (0.0)	312 (85.5)	32 (8.8)	21 (5.8)	0 (0.0)	0 (0.0)
	UA	174 (56.3)	83 (26.9)	41 (13.3)	10 (3.2)	1 (0.3)	193 (52.9)	85 (23.3)	66 (18.1)	18 (4.9)	3 (0.8)
	P	95 (30.7)	118 (38.2)	73 (23.6)	23 (7.4)	0 (0.0)	112 (30.7)	122 (33.4)	97 (26.6)	29 (7.9)	5 (1.4)
	AD	232 (75.1)	61 (19.7)	14 (4.5)	2 (0.6)	0 (0.0)	264 (72.3)	73 (20.0)	25 (6.8)	3 (0.8)	0 (0.0)
Year 3	M	144 (46.6)	84 (27.2)	52 (16.8)	29 (9.4)	0 (0.0)	166 (45.5)	80 (21.9)	77 (21.1)	41 (11.2)	1 (0.3)
	SC	270 (87.4)	30 (9.7)	9 (2.9)	0 (0.0)	0 (0.0)	293 (80.3)	46 (12.6)	20 (5.5)	5 (1.4)	1 (0.3)
	UA	175 (56.6)	77 (24.9)	47 (15.2)	8 (2.6)	2 (0.6)	191 (52.3)	83 (22.7)	68 (18.6)	19 (5.2)	4 (1.1)
	P	93 (30.1)	132 (42.7)	61 (19.7)	22 (7.1)	1 (0.3)	94 (25.8)	139 (38.1)	96 (26.3)	27 (7.4)	9 (2.5)
	AD	225 (72.8)	61 (19.7)	17 (5.5)	6 (1.9)	0 (0.0)	256 (70.1)	81 (22.2)	22 (6.0)	6 (1.6)	0 (0.0)

a Dimension acronyms: M, mobility; SC, self-care; UA, usual activities; P, pain; AD, anxiety and depression.

TABLE 27 EuroQol visual analogue scale scores from available cases by time point and treatment group

Time point	Spironolactone	Standard care	Mean difference	*p*-value	Bootstrap 95% CI
Baseline	77.580	77.587	−0.007	0.994	−1.903 to 1.863
Month 6	77.451	75.780	1.671	0.103	−0.251 to 3.755
Year 1	76.585	76.048	0.538	0.620	−1.484 to 2.600
Year 2	76.524	76.029	0.495	0.670	−1.870 to 2.709
Year 3	81.478	78.039	3.439	0.376	−3.778 to 11.219

TABLE 28 EuroQol visual analogue scale scores from complete cases by time point and treatment group

Time point	Spironolactone	Standard care	Mean difference	*p*-value	Bootstrap 95% CI
Baseline	79.356	79.637	−0.282	0.815	(−2.381 to 2.173)
Month 6	78.763	76.200	2.563	0.041	(0.163 to 4.864)
Year 1	77.942	76.259	1.684	0.192	(−0.692 to 4.131)
Year 2	76.693	75.227	1.466	0.272	(−1.107 to 4.002)
Year 3	82.891	74.683	8.208	0.026	(1.992 to 17.935)

TABLE 29 Kidney Disease Quality of Life - Short Form scale scores from available cases by time point and treatment group

Time point	Spironolactone	Standard care	Mean difference	*p*-value	Bootstrap 95% CI
KDQoL symptoms of kidney disease scale					
Baseline	85.804 (*N* = 631)	85.091 (*N* = 644)	0.713	0.318	−0.590 to 2.161
Month 6	84.002 (*N* = 498)	84.116 (*N* = 578)	−0.115	0.887	−1.695 to 1.511
Year 1	84.482 (*N* = 460)	83.661 (*N* = 550)	0.821	0.357	−1.041 to 2.405
Year 2	83.239 (*N* = 244)	84.193 (*N* = 272)	−0.954	0.428	−3.342 to 1.323
Year 3	83.290 (*N* = 359)	83.530 (*N* = 429)	−0.240	0.808	−2.312 to 1.713
KDQoL effects of kidney disease scale					
Baseline	95.940 (*N* = 605)	95.692 (*N* = 613)	0.248	0.507	−0.750 to 1.264
Month 6	95.127 (*N* = 456)	95.315 (*N* = 527)	−0.188	0.761	−1.507 to 0.886
Year 1	94.881 (*N* = 428)	95.303 (*N* = 507)	−0.422	0.509	−1.724 to 0.820
Year 2	94.852 (*N* = 224)	94.413 (*N* = 250)	0.440	0.673	−1.524 to 2.425
Year 3	94.823 (*N* = 329)	94.662 (*N* = 394)	0.161	0.831	−1.307 to 1.625
KDQoL burden of kidney disease scale					
Baseline	92.504 (*N* = 667)	91.760 (*N* = 672)	0.744	0.374	−0.915 to 2.515
Month 6	91.920 (*N* = 509)	92.912 (*N* = 589)	−0.991	0.283	−2.789 to 0.866
Year 1	90.965 (*N* = 478)	93.255 (*N* = 556)	−2.290	0.017	−4.015 to −0.346

continued

TABLE 29 Kidney Disease Quality of Life - Short Form scale scores from available cases by time point and treatment group (*continued*)

Time point	Spironolactone	Standard care	Mean difference	*p*-value	Bootstrap 95% CI
Year 2	91.860 (*N* = 248)	91.725 (*N* = 284)	0.135	0.927	−2.942 to 3.068
Year 3	91.222 (*N* = 361)	92.460 (*N* = 436)	−1.238	0.274	−3.680 to 1.082
KDQoL composite kidney scale					
Baseline	91.208 (*N* = 691)	90.530 (*N* = 699)	0.678	0.559	−0.356 to 1.812
Month 6	90.085 (*N* = 530)	90.240 (*N* = 618)	−0.155	0.811	−1.421 to 1.105
Year 1	89.766 (*N* = 494)	90.250 (*N* = 579)	−0.484	0.489	−1.813 to 0.911
Year 2	89.744 (*N* = 257)	89.780 (*N* = 294)	−0.036	0.972	−2.079 to 1.964
Year 3	89.353 (*N* = 381)	89.799 (*N* = 454)	−0.446	0.571	−1.896 to 1.099
KDQoL physical composite scale					
Baseline	42.252 (*N* = 639)	41.632 (*N* = 637)	0.620	0.323	−0.759 to 1.755
Month 6	42.159 (*N* = 484)	41.536 (*N* = 566)	0.623	0.371	−0.784 to 1.924
Year 1	41.544 (*N* = 457)	41.468 (*N* = 543)	0.076	0.916	−1.131 to 1.482
Year 2	40.744 (*N* = 239)	40.630 (*N* = 274)	0.114	0.908	−1.863 to 2.040
Year 3	41.413 (*N* = 330)	39.894 (*N* = 408)	1.519	0.069	−0.010 to 3.079
KDQoL mental composite score					
Baseline	53.119 (*N* = 639)	52.946 (*N* = 637)	0.173	0.725	−0.820 to 1.098
Month 6	52.583 (*N* = 484)	51.966 (*N* = 566)	0.617	0.295	−0.509 to 1.765
Year 1	52.092 (*N* = 457)	52.035 (*N* = 543)	0.057	0.924	−1.088 to 1.290
Year 2	52.797 (*N* = 239)	52.010 (*N* = 274)	0.787	0.324	−0.744 to 2.324
Year 3	52.261 (*N* = 330)	51.559 (*N* = 408)	0.703	0.325	−0.593 to 2.117

TABLE 30 Kidney Disease Quality of Life - Short Form scale scores from complete cases by time point and treatment group

Time point	Spironolactone	Standard care	Mean difference	*p*-value	Bootstrap 95% CI
KDQoL symptoms of kidney disease scale: spironolactone (N = 153); standard care (N = 186)					
Baseline	87.189	85.667	1.522	0.272	−1.239 to 4.160
Month 6	84.923	85.055	−0.132	0.928	−2.981 to 2.723
Year 1	85.893	84.346	1.547	0.306	−1.370 to 4.488
Year 2	85.011	84.790	0.220	0.878	−2.311 to 2.943
Year 3	83.832	84.372	−0.540	0.717	−3.266 to 2.434
KDQoL effects of kidney disease scale: spironolactone (N = 128); standard care (N = 146)					
Baseline	95.898	95.890	0.008	0.995	−2.551 to 2.340
Month 6	95.215	95.826	−0.611	0.622	−3.142 to 1.724
Year 1	95.825	95.184	0.641	0.576	−1.373 to 2.871

TABLE 30 Kidney Disease Quality of Life - Short Form scale scores from complete cases by time point and treatment group (*continued*)

Time point	Spironolactone	Standard care	Mean difference	*p*-value	Bootstrap 95% CI
Year 2	95.776	94.777	0.999	0.448	−1.699 to 3.274
Year 3	95.972	94.884	1.087	0.322	−0.923 to 3.030
KDQoL burden of kidney disease scale: spironolactone (N = 176); standard care (N = 202)					
Baseline	93.146	91.151	1.995	0.206	−1.036 to 5.086
Month 6	93.040	93.688	−0.648	0.651	−3.378 to 2.482
Year 1	92.791	92.358	0.434	0.780	−2.485 to 3.217
Year 2	91.406	91.863	−0.456	0.793	−4.360 to 2.574
Year 3	91.264	91.584	−0.320	0.847	−3.623 to 2.888
KDQoL composite kidney scale: spironolactone (N = 207); standard care (N = 238)					
Baseline	92.090	90.232	1.857	0.061	−0.090 to 3.734
Month 6	90.552	90.861	−0.309	0.760	−2.226 to 1.648
Year 1	90.503	89.531	0.972	0.387	−1.386 to 3.014
Year 2	89.856	89.692	0.164	0.883	−2.007 to 2.378
Year 3	88.993	89.305	−0.312	0.781	−2.783 to 1.908
KDQoL physical composite scale: spironolactone (N = 144); standard care (N = 178)					
Baseline	44.127	43.315	0.812	0.502	−1.835 to 3.294
Month 6	43.686	42.151	1.535	0.206	−0.821 to 3.689
Year 1	42.903	41.958	0.946	0.436	−1.565 to 3.037
Year 2	42.649	40.644	2.005	0.105	−0.326 to 4.204
Year 3	42.862	39.567	3.295	0.008	0.963 to 5.616
KDQoL mental composite score: spironolactone (N = 144); standard care (N = 178)					
Baseline	54.019	53.142	0.877	0.355	−1.030 to 2.683
Month 6	53.606	53.271	0.335	0.729	−1.562 to 2.221
Year 1	53.323	52.633	0.690	0.502	−1.301 to 2.639
Year 2	53.321	52.641	0.680	0.484	−1.229 to 2.550
Year 3	53.120	51.466	1.654	0.125	−0.438 to 3.653

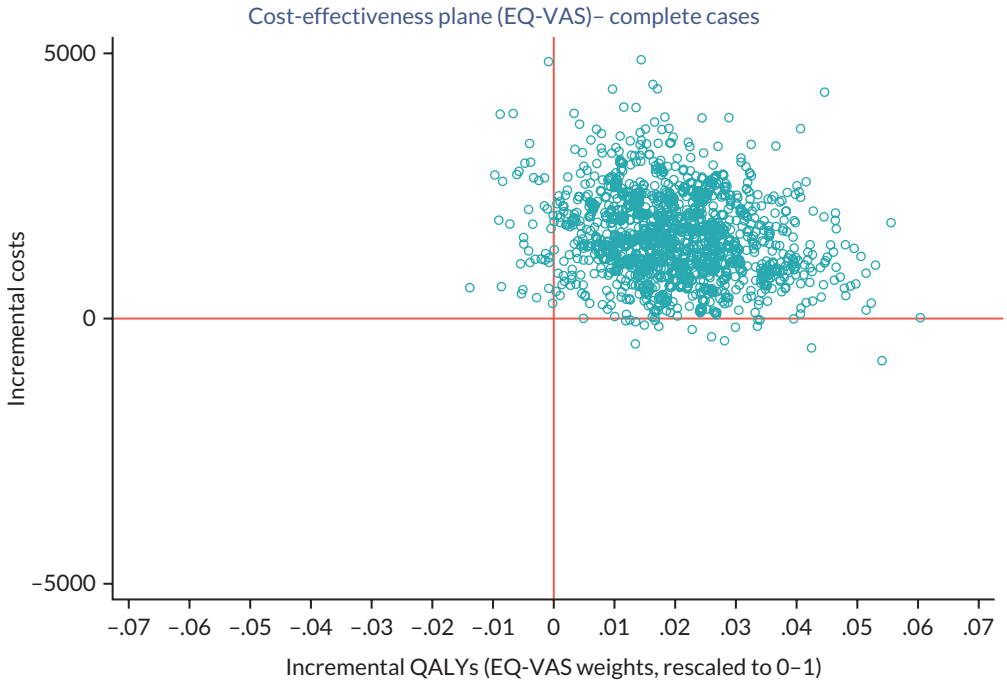


FIGURE 28 Cost-effectiveness plane for spironolactone vs. standard care under complete case analysis with EQ-VAS weights for QALY.

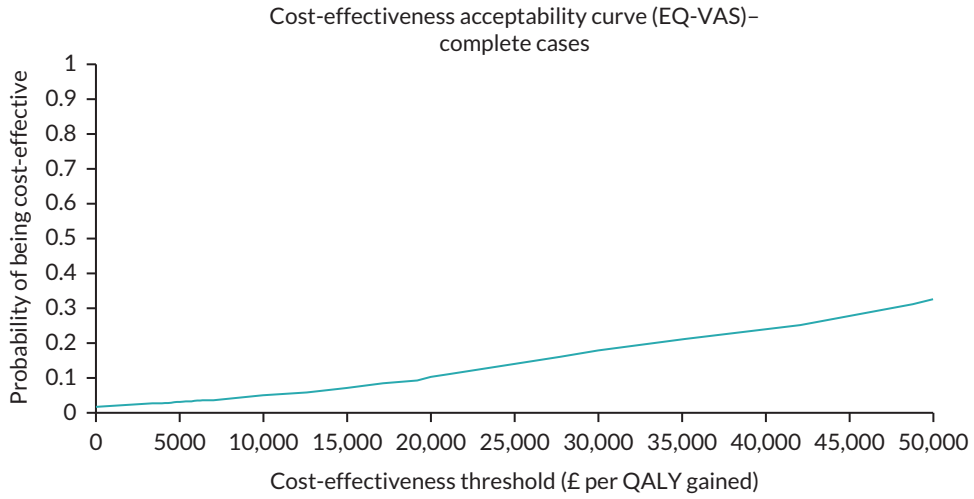


FIGURE 29 Cost-effectiveness acceptability curve for spironolactone vs. standard care under complete case analysis with EQ-VAS weights for the QALY.

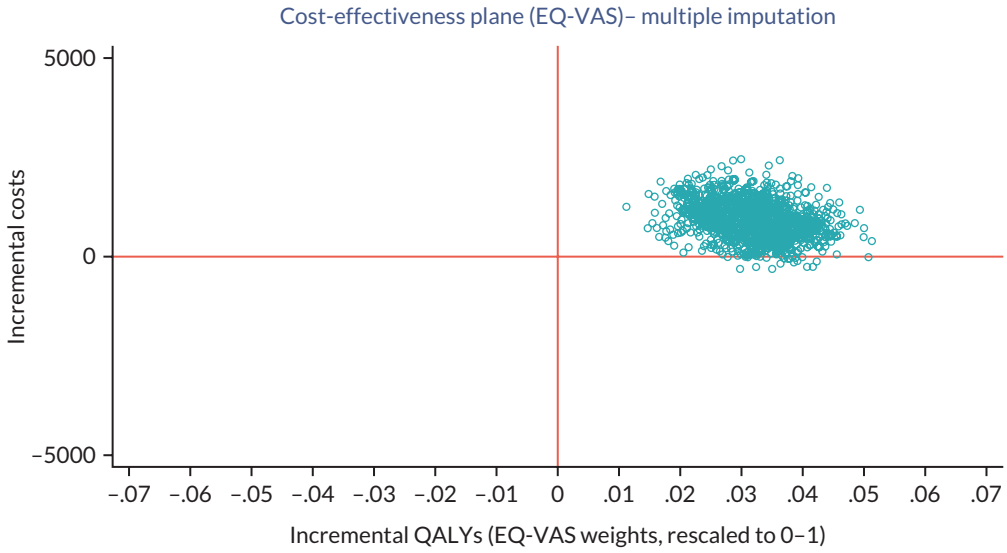


FIGURE 30 Cost-effectiveness plane for spironolactone vs. standard care with imputed resource use and QALY values and EQ-VAS weights for the QALY.

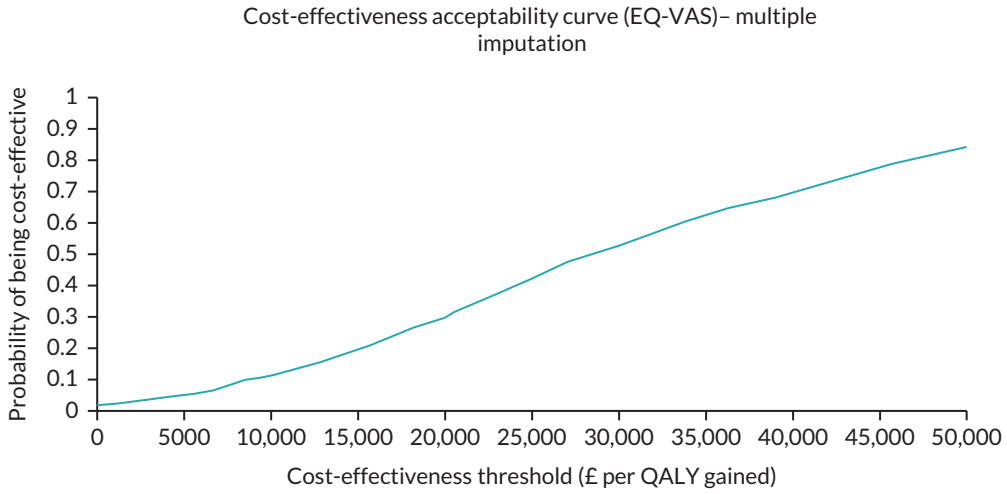


FIGURE 31 Cost-effectiveness acceptability curve for spironolactone vs. standard care with imputed resource use and QALY values and EQ-VAS weights for the QALY.

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