BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2011.04102.x

The safety and tolerability of spironolactone in patients with mild to moderate chronic kidney disease

Nicola C. Edwards,[1] Richard P. Steeds,[2] Colin D. Chue,[2] Paul M. Stewart,[3] Charles J. Ferro[4] & Jonathan N. Townend[2]

Departments of [1]Cardiovascular Medicine, [2]Cardiology, [3]Medicine and [4]Nephrology, University Hospital and University of Birmingham, Edgbaston, Birmingham, UK

Correspondence
Dr Nicola C. Edwards, Department of Cardiovascular Medicine, University Hospital and University of Birmingham, Edgbaston, Birmingham B15 2TH, UK.
Tel.: +44 1213714035
Fax: +44 1213714175
E-mail: n.c.edwards@bham.ac.uk

Keywords
aldosterone, chronic kidney disease, mineralocorticoid receptor blockade, potassium

Received
13 June 2011

Accepted
16 September 2011

Accepted Article Published Online
28 September 2011

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Spironolactone has recently been shown to exert beneficial effects on the cardiovascular and renal systems. To date, its use in patients with chronic kidney disease has been limited due to potential risks of hyperkalaemia and declining renal dysfunction.

WHAT THIS STUDY ADDS

- Non-diabetic patients with early stage chronic kidney disease (CKD) on concomitant therapy with angiotensin converting enzyme (ACE) inhibition or angiotensin II receptor blockade with a serum potassium of <5.5 mmol/L and no history of hyperkalaemia who were randomized in a trial to treatment with spironolactone for 40 weeks had low rates of serious hyperkalaemia (<1%) and worsening renal function (<3%). Frequent biochemical monitoring is required for the initial 4 weeks but only routine monitoring is needed thereafter.

AIM

Mineralocorticoid receptor blockade (MRBs) in combination with angiotensin converting enzyme (ACE) inhibitors and angiotensin-II receptor blockade (ARBs) improve prognostic markers of cardiovascular and renal disease in early stage chronic kidney disease (CKD). Concerns relating to the safety and tolerability of MRBs in CKD may limit their use in a non clinical trial setting.

METHODS

In the Chronic Renal Impairment in Birmingham II study, 115 patients with non-diabetic early stage CKD (eGFR 30–89 ml/min/1.73m^2) received 25 mg daily of spironolactone for 4 weeks before randomization to continuing treatment or placebo for a further 36 weeks. All patients were on ACE inhibitors and/or ARB therapy. Potassium and renal function were checked at weeks 1, 2, 4, 8, 16, 28 and 40. The incidence of hyperkalaemia, significant renal dysfunction (reduction eGFR ≥25%) and adverse effects was assessed.

RESULTS

After 40 weeks of treatment the incidence of serious hyperkalaemia (K^+ ≥6.0 mmol/L) was <1%. A potassium 5.5–5.9 mmol/L occurred on ≥1 occasion over follow-up in 11 patients (nine on spironolactone) and was predicted by baseline potassium ≥5.0 mmol/L and eGFR ≤45 ml/min/1.73m^2. Over follow-up, three patients experienced significant renal dysfunction but no patients withdrew due to intolerance or side effects. Changes in potassium, eGFR and systolic blood pressure were most apparent in the first 4 eeks.

CONCLUSION

Spironolactone was well tolerated in selected patients with early stage CKD. Strict monitoring over the first month of treatment followed by standard surveillance as for ACE inhibitors and ARBs is suggested.

Introduction

There has been a major increase in the use of mineralocorticoid receptor blockade (MRBs) over the past decade following the demonstration of their efficacy in the treatment of heart failure, left ventricular dysfunction following myocardial infarction and resistant hypertension [1–4]. However, an increased risk of hyperkalaemia and decline in renal function with these drugs, particularly when used in combination with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockade (ARBs) [5, 6] has led to an avoidance of such treatment in a non-clinical trial setting in patients with chronic kidney disease (CKD).

Paradoxically, although co-existing CKD is present in up to 60% of patients with heart failure the use of MRBs is usually well tolerated. There is also now a small but increasing body of evidence showing that MRBs exert beneficial renal and cardiovascular effects in patients with CKD [7, 8]. A number of investigators have shown a slowing in the decline in renal function using MRBs in CKD [8, 9]. In the Chronic Renal Impairment in Birmingham II (CRIB-II) study we have demonstrated beneficial effects of spironolactone on LV mass and arterial stiffness, probably as a result of anti-inflammatory and anti-fibrotic effects in the heart and vasculature [10, 11]. It is postulated that the efficacy of MRBs reflects further suppression of the renin-angiotensin-aldosterone system. In patients with CKD aldosterone concentrations are often high due to aldosterone 'escape' and despite chronic treatment with ACE inhibitors or ARBs, concentrations remain elevated in up to 50% of patients, a phenomenon known as aldosterone 'breakthrough'. This provides a rationale for the increasing use of MRBs in CKD and emphasizes the urgent need for data on their safety and tolerability in this setting [12].

In this retrospective sub-analysis of the CRIB-II study we report in detail the effects on renal function, potassium, blood pressure and tolerability that occurred over 40 weeks of treatment with spironolactone.

Methods

The CRIB-II study was a double-blind, randomized, placebo controlled trial investigating the effect of low dose spironolactone (25 mg daily) in early CKD. The design and clinical characteristics of the patients have been published previously [13]. In brief, inclusion criteria for the study were: stage 2 or 3 CKD (estimated glomerular filtration rate (eGFR) 30–89 ml/min/1.73m^2 using the Modification of Diet in Renal Disease (MDRD) equation) [13], established treatment with ACE inhibitors and/or ARBs at maximally tolerated doses for at least 6 months before enrolment into the study and controlled blood pressure (24 h ambulatory ≤135/85 mmHg) on standard therapy. Exclusion criteria included symptomatic cardiovascular disease, uncontrolled blood pressure (≥135/85 mmHg), diabetes mellitus and a serum potassium ≥5.5 mmol/L. The protocol was approved by South Birmingham Local Research Ethics Committee and all patients gave written informed consent. Drug nomenclature in this manuscript conforms to British Journal of Pharmacology guidelines [14].

Protocol

After baseline clinical and biochemical assessment, patients received 4 weeks of open label treatment with spironolactone 25 mg once a day. Surveillance of renal function and serum potassium were performed after weeks 1, 2 and 4 of treatment. All samples were collected in the hospital and processed by the core laboratory within 30 min of collection. Intra-assay variation for serum potassium in the core laboratory was 1.0% with a standard deviation of 0.1 mmol/L. The protocol for management of hyperkalaemia is described in Table 1. Patients were also withdrawn if eGFR was reduced by ≥30% compared with a previous sample or if they were intolerant of the study medication. Patients unwell with vomiting or diarrhoeal illnesses had study medication temporarily suspended. Patients were maintained on their normal diet throughout the study and were not given any additional advice on dietary sodium or potassium restriction

At the end of week 4, patients were randomized to double-blinded treatment with either continued spironolactone at their current dose or to placebo for a further 36 weeks. Renal function and potassium were measured after week 8, 16, 28 and on final review at week 40. Adjustments to spironolactone/placebo dose during the double-blinded treatment phase were made as above according to serum potassium concentration. Ambulatory 24 h blood pressure and proteinuria [assessed by urinary albumin : creatinine ratio (ACR)] were made at baseline, week 4 and week 40 prior to discontinuation of treatment. At each study visit, patients were actively questioned as to possible side effects including disturbed menstrual cycle, breast tenderness, erectile dysfunction and gynaecomastia.

Statistical analysis

All data were analyzed using SPSS version 16 (SPSS Inc, Chicago, Il, USA). Data are mean or absolute/percentage

Table 1

Management of hyperkalaemia in the CRIB II study [10]

Serum potassium (mmol/L)	Action
≥6.5 mmol/L	Appropriate treatment and withdrawal from study
6.0–6.4 mmol/L	Abstain for 1 week, recommence at 25 mg spironolactone on alternate days
≥6.0 mmol/L on repeat testing	Withdrawal from study
≥5.5–5.9 mmol/L	Change to 25 mg spironolactone on alternate days
<5.4 mmol/L	No action

change ± 95% confidence intervals (95% CI) or SD. Non-normally distributed data are presented as median (inter-quartile range) and were log-transformed for analysis. Continuous variables over the first 4 weeks of treatment were compared between groups using paired *t*-tests and quartiles using one way analysis of variance with Tukey *post hoc* test. Between weeks 0–40 groups were compared using repeated measures analysis of variance. Odds ratios (OR) and 95% CI for a reduction in eGFR (>10%), serum potassium ≥5.5 mmol/L and reduction in systolic blood pressure (≥10%) were derived using logistic regression. Multiple linear regression models were used to assess the predictors of change in eGFR, potassium and blood pressure. Models included baseline demographic and clinical features known to increase the risk of occurrence (age, male gender, concurrent ACE inhibitor, ARB or spironolactone use, eGFR ≥45 ml/min/1.73m^2 and baseline potassium ≥5 mmol/L) [15]. Analysis was adjusted for baseline differences. Co-linearity between explanatory variables was assessed by examining the variance inflation factor. A *P* value <0.05 was considered significant.

Results

One hundred and seventeen patients were consented to participate in CRIB-II. The three primary aetiologies were glomerular disease (55%), quiescent vasculitis (13%) and adult polycystic disease (8%). Two patients were excluded prior to the open labelled treatment due to uncontrolled blood pressure and baseline serum potassium ≥5.5 mmol/L. Baseline demographic and biochemical data for both treatment groups are presented in Table 2.

Open label treatment with spironolactone

Three patients were withdrawn during the 4 weeks of open label spironolactone treatment; two patients for safety reasons: one with serious hyperkalaemia (potassium 6.8 mmol/L) at week 3, and one with symptomatic hypotension and significant deterioration of eGFR (≥30%) at week 3. One patient withdrew consent.

After 4 weeks of spironolactone the mean eGFR was reduced by 3%, an absolute change of –1.6 ml/min/1.73m^2 (95% CI –2.5, 0.8, $P < 0.01$). Serum creatinine increased by +7 µmol/L (95% CI 5 9, $P < 0.01$). The change in mean eGFR was not different between quartiles of baseline GFR ($P = 0.80$) (Figure 1), quartiles of age ($P = 0.07$) or gender ($P = 0.9$) or predicted by any variable in a multivariate regression model (Table 3).

Mean serum potassium was increased by 0.22 mmol/L (95% CI 0.14, 0.30, $P < 0.01$) over the first 4 weeks of treatment with spironolactone. In accordance with our protocol, five patients with mild hyperkalaemia (5.5–5.9 mmol/L) were switched to alternate day spironolactone at week 1 and one further patient was switched to alternate day treatment at week 2. The patients in the lowest quartile of potassium at baseline showed the greatest absolute change over the first 4 weeks (Figure 2 and Table 3). Predictors of the change in potassium in multivariate regression were baseline potassium (each 0.1 mmol/L increase predicted a –0.47 mmol/L decrease at week 4), baseline eGFR (each 10 mmol/L ml/min/1.73m^2 increase predicted

Table 2

Baseline characteristics of patients randomized to treatment with placebo or spironolactone

	Placebo (n = 56)	Spironolactone (n = 56)
Age (years)	53 ± 12	54 ± 12
Male gender (%)	59	57
Body surface area (m^2)	1.9 ± 0.2	1.9 ± 0.2
Office systolic blood pressure (mmHg)	130 ± 19	130 ± 16
Office diastolic blood pressure (mmHg)	77 ± 10	77 ± 10
Biochemistry		
eGFR (ml/min/1.73m^2)	53 ± 11	49 ± 12
Serum creatinine (µmol/L)	124 ± 34	133 ± 35
Serum potassium (mmol/L)	4.3 ± 0.3	4.4 ± 0.8
ACR (mg/mmol)	8.2 (48.4)*	9.5 (34.9)*
Total number medications per patient	1.6	2.1
ACE inhibitor	37	37
ARB	17	18
ACE inhibitor + ARB	2	1
Calcium channel blockade	17	13
β-adrenoceptor blockade	8	15
Diuretics†	13	18

Mean ± SD, *median (inter-quartile range). †Diuretics; bendroflumethiazide 3 *vs.* 5, furosemide 10 *vs.* 13, placebo and spironolactone respectively. No significant differences between baseline characteristics. ACR, urinary albumin : creatinine ratio; ARB, angiotensin receptor blocker.

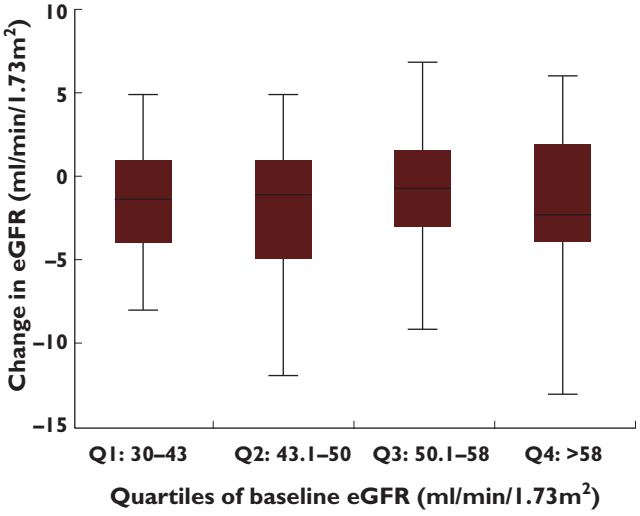

Figure 1

Change in eGFR over the first 4 weeks of open labelled treatment with spironolactone by quartiles of baseline eGFR. Data are median, upper and lower quartiles (box) and range using one way analysis of variance with *post hoc* Tukey test

Table 3

Linear regression models for change in eGFR, potassium and systolic blood pressure after 4 weeks of spironolactone treatment

Variables	Change in eGFR β coefficient + (SE)	Change in potassium β coefficient + (SE)	Change in systolic BP β coefficient + (SE)
Age	–0.003 (0.005) $P = 0.96$	0.01 (0.003) $P < 0.01$	–0.02 (0.10) $P = 0.82$
Male gender	0.61 (1.27) $P = 0.63$	0.07 (0.07) $P = 0.35$	–5.78 (2.61) $P = 0.03$
Baseline eGFR	–0.02 (0.05) $P = 0.64$	–0.01 (0.003) $P < 0.01$	0.08 (0.08) $P = 0.34$
Baseline 24 h systolic BP	0.04 (0.06) $P = 0.45$	0.002 (0.003) $P = 0.43$	–0.25 (0.11) $P = 0.03$
Baseline potassium	N/A	–0.50 (0.08) $P < 0.01$	N/A
ACE inhibitor*	–1.56 (1.34) $P = 0.25$	–0.02 (0.07) $P = 0.75$	2.05 (2.26) $P = 0.37$

Three models are shown: the first the 4 weeks of open labelled treatment with spironolactone. Estimates for all models are adjusted for the variables listed and also for use of β-adrenoceptor blockade, statins, diuretics, calcium channel blockade. *ACE inhibitor and ARB were used in separate models in view of co-linearity. Substituting ARBs did not significantly alter the data (not shown). β coefficient, unstandardized β-coefficient; SE, standard error; BP, blood pressure; N/A, variable not known to influence dependent variable.

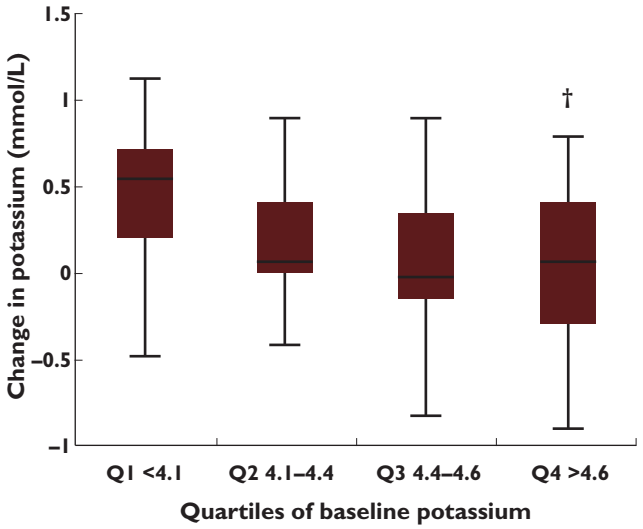

Figure 2

Change in serum potassium concentrations over the first 4 weeks of open labelled treatment with spironolactone by quartiles of baseline potassium. Data are median, upper and lower quartiles (box) and range †$P <$ 0.01, using one way analysis of variance with *post hoc* Tukey test

a –0.11 mmol/L reduction) and age (each increase of 10 years predicted an increase 0.10 mmol/L). However, the only predictor for the development of hyperkalaemia (potassium ≥5.5 mmol/L) during weeks 0–4 in a logistic regression model was baseline potassium ≥5.0 mmol/L (OR 5.0; 95% CI 1.0, 25, $P = 0.04$).

Ambulatory systolic and diastolic blood pressures were reduced at week 4 compared with baseline: systolic –7 mmHg (95% CI –10, –5, $P < 0.01$), diastolic blood pressure –5 mmHg (95% CI –7, –4, $P < 0.01$). In multivariate regression, the change in ambulatory systolic blood pressure was predicted by baseline systolic blood pressure (each 10 mmHg increase in baseline systolic predicted –2.5 mmHg reduction at week 4) and gender (Table 3).

Urinary ACR was also significantly reduced after 4 weeks of spironolactone therapy from median 7.4 mg/mmol (95% CI 0, 603) to 4.1 mg/mmol (95% CI 0, 518, $P <$ 0.01). Thirty-nine patients (35%) had a reduction in ACR of ≥50% from baseline. Comparing these patients with those with a lower percentage reduction in ACR, there were no differences in age, baseline eGFR, baseline ACR, baseline blood pressure or medication usage. In logistic regression, the single independent predictor of the change in ACR was a reduction in systolic office blood pressure over the first 4 weeks of treatment (OR 4.4, 95% CI 1.4, 14.0, $P < 0.01$). There was no association between change in ACR and change in eGFR.

Randomized treatment with spironolactone or placebo

In total, 112 patients were randomized equally to spironolactone or placebo. Two patients were withdrawn during the double-blind randomized phase of the study; one patient randomized to spironolactone withdrew consent in week 6 and one patient randomized to placebo had a symptomatic relapse of Wegener's granulomatosis in week 15. No patients were withdrawn for iatrogenic complications or side effects.

Compared with baseline, eGFR was reduced in patients on spironolactone at week 40 (49 ml/min/1.73m^2 *vs.* 46 ml/min/1.73m^2, $P < 0.01$) (Figure 3). On placebo, baseline eGFR did not change significantly over follow-up (53 ml/min/1.73m^2 *vs.* 52 ml/min/1.73m^2, $P = 0.48$). Estimated GFR measured as per protocol at weeks 8, 16 and 28 was lower on spironolactone compared with placebo but there was no significant difference by week 40 (46.1 ml/min/1.73m^2 *vs.* 52.3 ml/min/1.73m^2, $P = 0.09$) (Figure 3). Four patients (three on spironolactone) experienced a clinically significant reduction in eGFR (25–29%) but with such small numbers it was not possible to identify co-variates which were predictive in a logistic regression model. Minor reductions in eGFR (10–20%) were more common with spironolactone, 17 patients *vs.* nine patients on placebo. In a logistic regression model, a reduction in eGFR of ≥10% was predicted by baseline eGFR ≤45 ml/min/1.73m^2 and treatment assignment to spironolactone (Table 4).

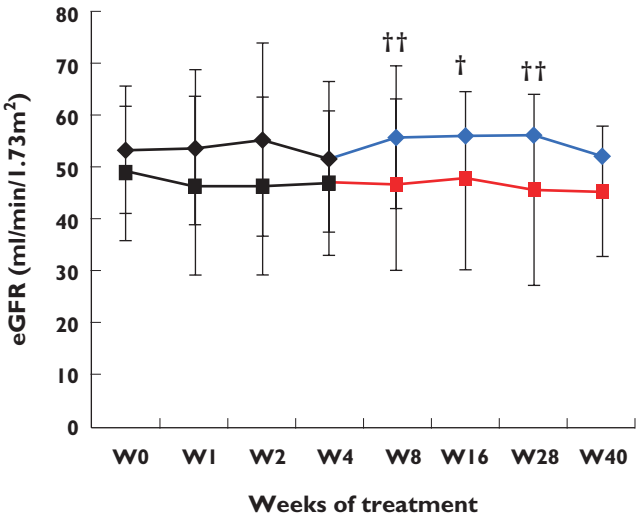

Figure 3

Change in eGFR over 40 weeks of follow-up with spironolactone and placebo. Data are mean ± SD. †$P < 0.05$, ††$P < 0.01$, repeated measures analysis of variance. Spiro open labeled (■); Spiro randomized (■); Placebo randomized (■)

Compared with patients with ≤10% reduction in eGFR, these patients had a greater reduction in office systolic blood pressure (–7 mmHg ± 8 *vs.* 2 mmHg ± 8, $P = 0.01$) and lower baseline eGFR (47 ml/min/1.73m^2 ± 13 *vs.* 53 ml/min/1.73m^2 ± 12, $P < 0.01$).

After randomization mean serum potassium concentrations were persistently higher ($P < 0.05$) with spironolactone than with placebo but remained stable over the 36 weeks of follow-up (Figure 4). No patients experienced serum potassium ≥6 mmol/L and only four patients had a potassium ≥5.5 mmol/L; two with spironolactone and two with placebo. Nine patients on spironolactone and two on placebo had a potassium ≥5.5 mmol/L on at least one occasion over 40 weeks of treatment. The risk of developing a serum potassium ≥5.5 mmol/L during 40 weeks of treatment was increased if baseline potassium was ≥5.0 mmol/L and baseline eGFR ≤45 ml/min/1.73m^2 (Table 4).

At week 40, spironolactone significantly reduced ambulatory systolic blood pressure (–6 mmHg [95% CI –8, –3] *vs.* –1 mmHg [95% CI –3, 1], $P < 0.01$) and pulse pressure (–2 mmHg [95% CI –4, –1] *vs.* 0 mmHg [95% CI –2, 1], $P < 0.05$) compared with placebo. Diastolic blood pressure (–3 mmHg [95% CI 5, –1] *vs.* –1 [95% CI –3, 0], $P = 0.20$) and mean arterial pressure (–3 mmHg [95% CI, 5, –1] *vs.* –1 [95% CI –3, 1], $P = 0.12$) were reduced but did not reach statistical significance. In multivariate regression, the changes in ambulatory systolic blood pressure and pulse pressure were predicted by baseline ambulatory systolic blood pressure (Table 4).

Urinary ACR was significantly reduced with spironolactone (–3.2 mg/mmol/L (–38 to +11) *vs.* –0.6 (–14 to +5) compared with placebo ($P < 0.05$). Thirty patients on spironolactone and 14 on placebo experienced a reduction in ACR of greater than 50%. This reduction was predicted in logistic regression by treatment with spironolactone (OR 4.5, 95% CI 1.6, 12.2, $P < 0.01$), a reduction in 24 h systolic blood pressure (OR 3.4, 95% CI, 1.1, 10.5, $P < 0.05$) and treatment with an ACE inhibitor (OR 4.8, 95% CI 1.5, 15.7, $P < 0.01$) and ARBs (OR 1.3, 95% CI 1.1, 1.9, $P < 0.05$) but no other variables in the model including number of antihypertensives, age and baseline eGFR.

Tolerability

There were no reports of disturbed menstrual cycle, breast tenderness, erectile dysfunction or gynaecomastia.

Discussion

These results provide support for the safety and tolerability of low dose spironolactone with concurrent ACE inhibitor or ARB treatment in selected patients with non-diabetic early stage CKD. In a cohort of patients with well characterized renal disease treated with spironolactone, the incidence of serious hyperkalaemia (>6 mmol/L) was <1% and that of a clinically significant (≥25%) reduction in eGFR was <5% over the 40 weeks of treatment. Changes in potassium, eGFR and systolic blood pressure were most apparent in the first month of treatment but only 2% of patients required treatment discontinuation within 4 weeks. Of the 56 patients randomized to continuing therapy with spironolactone, all remained stable thereafter with no serious adverse events occurring during 36 weeks of follow-up.

In our study a pre-treatment serum potassium ≥5 mmol/L was predictive for the development of hyperkalaemia and thus we would agree with the original RALES criterion [1] and not recommend spironolactone in such patients. It is important to note that our patient population was selected to minimize the chances of serious iatrogenic hyperkalaemia; patients with a history of hyperkalaemia, diabetes and CKD stages 4 and 5 were excluded. Spironolactone did reduce proteinuria but this effect was modest and was associated, perhaps causatively, with blood pressure reduction. However, these data are encouraging, with plentiful available evidence linking even minor reductions in proteinuria with both improved renal and cardiovascular outcomes [16].

Following publication of the RALES study, several studies raised safety concerns about MRBs in combination with ACE inhibitors and ARBs in patients with heart failure [5, 17, 18]. A population based study of patients aged ≥66 years treated for heart failure reported a three-fold increase in prescriptions for spironolactone after RALES and a two-fold increase in hospital admissions with hyperkalaemia and associated mortality [17]. Analysis identified poor patient selection as a major contributory factor for

Table 4

Logistic regression models for change in eGFR, potassium and systolic blood pressure over 40 weeks of treatment

Variables	eGFR reduction >10% OR (95% CI)	Potassium >5.5 mmol/L anytime OR (95% CI)	Systolic BP reduction >10% OR (95% CI)
Age	1.0 (0.1, 1.1) $P = 0.40$	1.0 (0.9, 1.0) $P = 0.10$	0.96 (0.9, 1.0) $P = 0.19$
Male gender	1.2 (0.4, 3.5) $P = 0.86$	0.4 (0.1, 2.4) $P = 0.33$	3.3 (0.8, 13) $P = 0.10$
eGFR <45 ml/min/1.73m^2	3.2 (1.1, 9.4) $P = 0.04$	5.8 (1.1, 29.0) $P = 0.04$	1.0 (0.2, 4.6) $P = 0.96$
Baseline 24 h SBP	1.0 (1.0, 1.1) $P = 0.56$	1.0 (0.9, 1.0) $P = 0.40$	1.1 (1.0, 1.3) $P < 0.01$
Baseline K >5 mmol/L	NA	16.5 (4.4, 61.0) $P < 0.01$	NA
ACE inhibitor*	2.0 (0.6, 6.9) $P = 0.25$	0.7 (0.1, 4.1) $P = 0.69$	0.8 (0.2, 3.3) $P = 0.80$
Spironolactone	6.1 (1.9, 19.7) $P = 0.01$	0.7 (0.1, 3.5) $P = 0.63$	1.2 (0.2, 6.3) $P = 0.3$

Three models are shown: 40 weeks of treatment with spironolactone and placebo. Estimates for all models are adjusted for the variables listed and also for use of β-adrenoceptor blockade, statins, diuretics, calcium channel blockade. Baseline potassium was not thought to contribute to reduction in eGFR or BP and is not examined in the model. *ACE inhibitor and ARB were used in separate models in view of co-linearity. Substituting ARBs did not significantly alter the data (not shown). K, serum potassium; OR, Odds ratio (95% CI); SBP, systolic blood pressure.

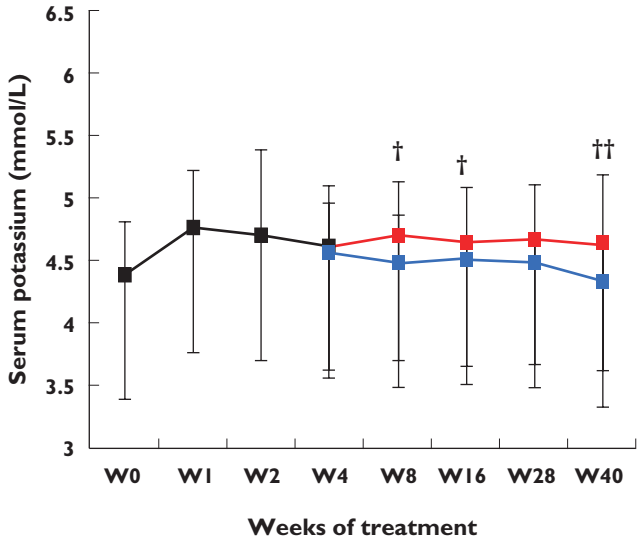

Figure 4

Change in serum potassium over 40 weeks of follow-up with spironolactone and placebo. Data are mean ± SD. †$P < 0.05$, ††$P < 0.01$, repeated measures analysis of variance. Spiro open labeled (■); Spiro randomized (■); Placebo randomized (■)

the adverse events observed in the 'real world'. Indeed, over a third of patients prescribed spironolactone after RALES did not meet the study inclusion criteria at the time of discharge from hospital. Specifically, 17% of patients had severe renal impairment (eGFR <30 ml/min/1.73m^2), 23% had discharge potassium of >5 mmol/L and 17% were still receiving potassium supplements. Other factors which increased the risk of hyperkalaemia included inadequate monitoring of potassium concentrations, neglect of predisposing factors to hyperkalaemia including diabetes, concomitant mediations such as β-adrenoceptor blockade and inappropriately high doses of spironolactone. It is therefore reassuring that a recent publication reporting the use of spironolactone in Scotland between 1994 and 2007, reported a similar marked increase in prescriptions without an increase in hospital admissions for hyperkalaemia and low rates of serious hyperkalaemia. These data reflect appropriate patient selection and an increase in the rates of monitoring of serum potassium and creatinine. Indeed rates of mild hyperkalaemia (5.0–6.0 mmol/L) were increased but without an increase in the incidence of serious hyperkalaemia (≥6.0 mmol/L) [19].

To date, safety data on the use of MRBs in patients with CKD have been limited to small studies investigating their role in reducing proteinuria and have been reassuring [8, 9, 20, 21]. Bomback *et al.* published a systematic review of the effect of adding a MRB to an ACE inhibitor and ARBs for proteinuria [8]. In the 15 studies and 436 patients reviewed, a serum potassium ≥5.5 mmol/L was identified in 5.5% of patients. Post treatment mean eGFR was reduced in three studies with study durations up to 12 months, although these reductions were considered clinically insignificant (74 to 67, 87 to 74, 57 to 54 ml/min/1.73m^2). A recent randomized controlled trial in patients with idiopathic glomerular disease and an eGFR of >30 ml/min/1.73m^2 provided information on long term (3 years) treatment with a MRB. Spironolactone was combined with both an ACE inhibitor and an ARB plus a statin in the 'intensive' treatment group [22]. While mean serum potassium increased only slightly in comparison with the control group, the rate of hyperkalaemia (potassium ≥5.5 mmol/L after dose frequency reduction) was 9/64 in the intensive regimen compared with 3/64 in the conventional group. This may have been due to the concomitant use of both ARBs and ACE inhibitors, a treatment strategy not commonly employed. In the spironolactone group, eGFR fell approximately 2% over the first 3 months before subsequently improving and was not significantly different from the baseline value at the end of follow-up. This change is consistent with our own findings of a mean 3% reduction in eGFR over the first month of open-label treatment before improving over further

follow-up and is similar to that observed following initiation of ACE inhibitors [23].

Mild hyperkalaemia (5.5–5.9 mmol/L) during MRB therapy is common but is probably of no adverse clinical significance [24]. In our study, 8% of patients on spironolactone and 2% on placebo had a potassium ≥5.5 mmol/L on one or more occasion over 40 weeks of treatment. In a recent prospective observational study of 820 patients with CKD stages 3–5, a potassium concentration between 5.5 and 5.9 mmol/L was not associated with an increased mortality rate or progression to end-stage CKD over an average follow-up of 2.6 years [24]. Indeed, there was an increased risk of end-stage CKD and death with serum potassium concentrations ≤4.0 mmol/L. Thus there may be a U-shaped relationship between potassium and mortality in CKD, with an optimum 'eukalaemic' range for serum potassium concentration of between 4.1 and 5.5 mmol/L. In CRIB-II, 16 patients randomized to placebo had a serum potassium ≤4 mmol/L during follow-up compared with eight patients with spironolactone.

An early reduction in eGFR can be anticipated with spironolactone just as it can be following treatment with ACE inhibitors and ARBs, and renal function should be monitored [23]. The frequency of monitoring in CRIB-II was greater in the first month of treatment than is commonly employed following initiation of ACE inhibitors and ARBs but does not differ significantly from protocols used for anticoagulants such as warfarin where the importance of frequent monitoring is accepted. This decision reflected concurrent treatment with an ACE inhibitor and/or ARB and the significant range of renal function; 34% of patients in CRIB-II had an eGFR ≤45 ml/min/1.73m^2. After randomization, we observed no increase in the risk of hyperkalaemia or reduction in eGFR compared with placebo. Thus monitoring for adverse effects of spironolactone after 4 weeks of therapy is probably required no more frequently than is recommended for monitoring of patients on ACE inhibitor/ARB therapy. Attention to the risk factors for the development of hyperkalaemia (eGFR ≤45 ml/min/1.73m^2 and baseline potassium ≥5.0 mmol/L) and clear advice to suspend spironolactone temporarily with acute illnesses such as diarrhoea and vomiting should help reduce such risks along with careful patient selection.

We acknowledge that the optimum dosing and monitoring strategies are still to be determined and data from large scale prospective studies will be required. Eminent figures in this area have suggested a role for very low dose spironolactone 12.5 mg daily [12] or using a titration schedule of 25 mg on alternate days for 1 month with an increase to daily treatment if potassium remains ≤5 mmol/L [25]. We believe that a dose of 25 mg once daily can be used safely providing adequate monitoring is employed.

There are limitations to this study. Patients with diabetic CKD appear to be at high risk of hyperkalaemia [26]. Such patients were excluded from recruitment into CRIB-II and it is important to emphasize that our data provide no support for use of MRBs in this population. Patients were recruited from specialist nephrology clinics limiting the applicability of these data to those treated in primary care who represent the majority of patients with CKD. Doses of ACE inhibitors and ARBs were titrated to those maximally tolerated but were not the same in all patients. Finally, we can report only 40 weeks of follow-up data and cannot, therefore, draw any conclusions as to the frequency of later adverse event rates. Such adverse events can be precipitated by acute illness or surgery occurring during treatment and these events are unlikely during short treatment periods.

In conclusion, low dose spironolactone is well tolerated in selected patients with early stage CKD. The risks of serious hyperkalaemia or significant renal deterioration appear to be low, particularly after the first month of treatment. Careful patient selection and biochemical monitoring should ensure these adverse effects are minimized and may be an early and 'acceptable price' in reducing cardiovascular events and preventing the progression of renal disease in these high risk patients. These data serve to heighten the need for a large scale clinical outcome trial from which much needed further safety data would be available.

Competing Interests

There are no competing interests to declare.

The study was funded by a British Heart Foundation Project Grant

The authors thank Peter Nightingale for statistical support.

REFERENCES

1 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. 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.

2 Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003; 348: 1309–21.

3 Pitt B, Reichek N, Willenbrock R, Zannad F, Phillips RA, Roniker B, Kleiman J, Krause S, Burns D, Williams GH. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. Circulation 2003; 108: 1831–8.

4 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. BMJ 2004; 328: 634–40.

5 Cruz CS, Cruz AA, Marcilio de Souza CA. Hyperkalaemia in congestive heart failure patients using ACE inhibitors and spironolactone. Nephrol Dial Transplant 2003; 18: 1814–9.

6 Schepkens H, Vanholder R, Billiouw JM, Lameire N. Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. Am J Med 2001; 110: 438–41.

7 Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. Nat Clin Pract Nephrol 2007; 3: 486–92.

8 Bomback AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am J Kidney Dis 2008; 51: 199–211.

9 Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. Kidney Int 2006; 70: 2116–23.

10 Edwards NC, Steeds RP, Stewart PM, Ferro CJ, Townend JN. Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. J Am Coll Cardiol 2009; 54: 505–12.

11 Rocha R, Martin-Berger CL, Yang P, Scherrer R, Delyani J, McMahon E. Selective aldosterone blockade prevents angiotensin II/salt-induced vascular inflammation in the rat heart. Endocrinology 2002; 143: 4828–36.

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 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.

14 Alexander SPH, Mathie A, Peters JA. Guide to receptors and channels (GRAC). Br J Pharmacol 2009; 158 (Suppl. 1): S1–254.

15 de Denus S, Tardif JC, White M, Bourassa MG, Racine N, Levesque S, Ducharme A. Quantification of the risk and predictors of hyperkalemia in patients with left ventricular dysfunction: a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trials. Am Heart J 2006; 152: 705–12.

16 Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, de Zeeuw D, de Jong PE, van Veldhuisen DJ, van Gilst WH. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation 2004; 110: 2809–16.

17 Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004; 351: 543–51.

18 Masoudi FA, Gross CP, Wang Y, Rathore SS, Havranek EP, Foody JM, Krumholz HM. Adoption of spironolactone therapy for older patients with heart failure and left ventricular systolic dysfunction in the United States, 1998–2001. Circulation 2005; 112: 39–47.

19 Wei L, Struthers AD, Fahey T, Watson AD, Macdonald TM. Spironolactone use and renal toxicity: population based longitudinal analysis. BMJ 2010; 340: c1768.

20 Chrysostomou A, Becker G. Spironolactone in addition to ACE inhibition to reduce proteinuria in patients with chronic renal disease. N Engl J Med 2001; 345: 925–6.

21 Sato A, Hayashi K, Naruse M, Saruta T. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. Hypertension 2003; 41: 64–8.

22 Bianchi S, Bigazzi R, Campese VM. Intensive versus conventional therapy to slow the progression of idiopathic glomerular diseases. Am J Kidney Dis 2010; 55: 671–81.

23 Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000; 160: 685–93.

24 Korgaonkar S, Tilea A, Gillespie BW, Kiser M, Eisele G, Finkelstein F, Kotanko P, Pitt B, Saran R. Serum potassium and outcomes in CKD: insights from the RRI-CKD cohort study. Clin J Am Soc Nephrol 2010; 5: 762–9.

25 Pitt B. Pharmacotherapy: cardiovascular effects of aldosterone blockade in CKD. Nat Rev Cardiol 2009; 6: 679–80.

26 Khosla N, Kalaitzidis R, Bakris GL. Predictors of hyperkalemia risk following hypertension control with aldosterone blockade. Am J Nephrol 2009; 30: 418–24.