Tolerability of spironolactone as adjunctive treatment for heart failure in patients over 75 years of age

SIR—Following the RALES (Randomised Aldactone Evaluation) study of 1999 [1, 2], guidelines recommend adjunctive treatment of moderate to severe heart failure with spironolactone, in addition to angiotensin-converting enzyme (ACE) inhibitors [3].

The RALES study, a randomised placebo-controlled trial of spironolactone in 1,663 heart failure patients already taking ACE inhibitors, found that spironolactone reduced heart failure symptoms, hospitalisations and mortality, and there was no major increase in renal failure or life-threatening hyperkalaemia. However, the mean age of patients enrolled in RALES was only 66 ± 12 years, whereas heart failure is predominantly a syndrome of older people, the average age at diagnosis being 76 years. Adverse drug events are often more common in older populations. Since the publication of RALES, several case reports have raised concerns about the risks of hyperkalaemia and renal failure with adjunctive spironolactone treatment for heart failure in clinical practice, especially in older patients [4–7]. A time-series analysis of hospitalisation and prescription data in Ontario reported an increase in hyperkalaemia-associated morbidity and mortality, following the publication of RALES [8].

We audited the prescribing of spironolactone to patients aged ≥75 years, to see whether patients prescribed spironolactone are being monitored in accordance with RALES study guidelines, and to determine the incidence of renal failure and life-threatening hyperkalaemia in a district general hospital setting. We also hoped to identify predictors of spironolactone adverse events.

Methods

This was a retrospective case note review for which local research ethics committee approval was granted. All those over 75 years of age, with a clinical diagnosis of heart failure, who had been prescribed spironolactone in conjunction with an ACE inhibitor between September 1999 (the date of publication of the RALES study) and the end of July 2003 were studied.

Patients were identified from the hospital’s inpatient and outpatient databases. Demographic and clinical data were recorded as well as adverse events.

Baseline serum potassium and creatinine concentrations at spironolactone initiation, as well as follow-up values on treatment were recorded from case notes and the hospital laboratory database. Given that serum creatinine concentration is a relatively poor marker of renal function in older people, baseline creatinine clearances were also calculated using the Cockcroft–Gault equation [9].

The definitions for severe hyperkalaemia and renal failure were taken as potassium ≥6.0mmol/l and creatinine ≥354μmol/l, since these were the cut-off levels at which spironolactone treatment was withdrawn in RALES [1, 2]. Potassium concentrations above 5.5mmol/l and the absolute and percentage rises in creatinine for all patients were also recorded. Intercurrent illnesses consisting of sepsis, vomiting or diarrhoea were noted. Adverse events were expressed as proportions of the total number of patients on treatment.

Results

Subjects

Sixty-six patients aged 75 years or over (age range 75–94 years), with heart failure, taking ACE inhibitor and spironolactone were identified. Altogether 3,703 patients


doi:10.1093/ageing/afi088
received inpatient treatment for heart failure during the same period, in a total of 5,553 hospital admissions. Two patients were excluded as they had only been initiated on spironolactone in the preceding 10 days. Sixty-four patients were therefore studied.

The most obvious difference between the study group and RALES treatment group was the marked discrepancy in patient mean age: 85±5.7 years in the study group, compared to 66±12 years in RALES (Table 1). Our patients’ mean baseline serum creatinine was 125±30 µmol/l, and 37.5% (24/64) of our patients sustained a >50% rise in creatinine concentration. In the RALES treatment group, a median rise in serum creatinine of only 4–9 µmol/l was documented. There was no obvious temporal pattern to the occurrence of adverse events in our patients.

Thirty-four per cent of patients had spironolactone discontinued because of hyperkalaemia or worsening renal function and 9% because of hypotension/postural hypotension compared with discontinuation in RALES of only 8% (66/822). Interestingly, two patients were able to continue taking adjunctive spironolactone at a reduced dose of 12.5 mg, and one patient was able to successfully restart treatment after recovery from a severe intercurrent illness. Three deaths in our study group appeared to be drug related.

### Adverse event predictors

Only the presence of severe intercurrent illness predicted the adverse outcomes, hyperkalaemia (odds ratio 4.05, P<0.05) and the development of renal insufficiency (odds ratio 4.05, P<0.05) on univariate logistic regression analysis. There was no significant relationship between any of the possible predictors (age, baseline creatinine, creatinine clearance, ACE inhibitor dose, NYHA class, diabetes mellitus, intensity of monitoring, co-morbidity, number of medications) and the outcomes, hyperkalaemia and development of renal insufficiency.

### Discussion

The RALES study, a landmark trial, showed excellent tolerability for adjunctive spironolactone in patients with heart failure [1, 2]. However, in this retrospective study of

### Table 1. Patient characteristics

| Age (years) | 85±5.7 | 66±12 |
| Gender (%) | Male 55/73 | Female 45/27 |
| Mean baseline creatinine (µmol/l) | 125±30 (excluded if creatinine >221) |
| Mean creatinine clearance (ml/min) | 39±12 |
| NYHA class (%) | 26/27 |
| Mean age (years) | 85±5.7 66±12 |
| Echo findings (%) | No echo 5 |
| Mod. LV impairment | 27 |
| Sev. LV impairment | 21 25.6±6.7 |
| Good LV. function | 3 |
| Diastol. dysfunction | 2 |
| 1st valve lesion (%) | 20 Excluded |
| Mean number of drugs per patient | 8±2 n/r |
| Mean number of hospital admissions | 1.4±1.4 n/r |
| Patients with diabetes mellitus (%) | 26.5 n/r |
| Patients on long-term NSAIDs (%) | 3 n/r |

Unwise otherwise stated, numbers refer to mean ± s.d.

### Table 2. Patient medication

<table>
<thead>
<tr>
<th>Medication (%)</th>
<th>Study cohort (n=64)</th>
<th>RALES trial (n=822)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretic</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>Diurals</td>
<td>20</td>
<td>75</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>K supp./K sparer</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Mean dose ACEI (mg/day ± s.d.)</td>
<td>100±0 63.4</td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>30±0</td>
<td>13.5</td>
</tr>
<tr>
<td>Enalapril</td>
<td>23±10</td>
<td>15.5</td>
</tr>
<tr>
<td>Lisnopr</td>
<td>7.5±3 n/r</td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td>5±2 n/r</td>
<td></td>
</tr>
<tr>
<td>Fosinopril</td>
<td>29±10 n/r</td>
<td></td>
</tr>
<tr>
<td>Mean dose of spironolactone (mg/day)</td>
<td>25±0 26</td>
<td></td>
</tr>
</tbody>
</table>

with a small number being monitored in day hospital (6% of those monitored). Fifty-five per cent were not monitored as frequently as in RALES.

### Adverse events

Thirty-six per cent (23/64) of patients in our study developed hyperkalaemia of ≥5.5 mmol/l, and 11% (7/64) severe hyperkalaemia of >6.0 mmol/l. In the RALES treatment arm, the incidence of ‘serious hyperkalaemia’ (value not specified) was only 2% (14/822).

The incidence of severe renal failure (creatinine ≥354 µmol/l) was 11% and 37.5% (24/64) of our patients sustained a >50% rise in creatinine concentration. In the RALES treatment group, a median rise in serum creatinine of only 4–9 µmol/l was documented. There was no obvious temporal pattern to the occurrence of adverse events in our patients.

Thirty-four per cent of patients had spironolactone discontinued because of hyperkalaemia or worsening renal function and 9% because of hypotension/postural hypotension compared with discontinuation in RALES of only 8% (66/822). Interestingly, two patients were able to continue taking adjunctive spironolactone at a reduced dose of 12.5 mg, and one patient was able to successfully restart treatment after recovery from a severe intercurrent illness. Three deaths in our study group appeared to be drug related.

### Adverse event predictors

Only the presence of severe intercurrent illness predicted the adverse outcomes, hyperkalaemia (odds ratio 4.05, P<0.05) and the development of renal insufficiency (odds ratio 4.05, P<0.05) on univariate logistic regression analysis. There was no significant relationship between any of the possible predictors (age, baseline creatinine, creatinine clearance, ACE inhibitor dose, NYHA class, diabetes mellitus, intensity of monitoring, co-morbidity, number of medications) and the outcomes, hyperkalaemia and development of renal insufficiency.
‘real-life’ elderly patients, we found a high incidence of adverse events, severe hyperkalaemia (11%) and renal insufficiency in 38%. The most obvious limitation of our work was the small number of subjects, representing the entire cohort of older patients on spironolactone treatment at our hospital. Bozkurt et al. [10] reported severe hyperkalaemia in 12% and renal insufficiency in 25% of 104 USA cardiology patients (mean age 66 ± 10 years) taking therapeutic doses of ACE inhibitor and spironolactone, and a Danish study [11] found severe hyperkalaemia in 10% and renal insufficiency (50% increase in serum creatinine) in 25% of 125 patients on spironolactone, mean age 72.9 years, attending a specialist heart failure clinic. Despite our patients being significantly older (mean age 85 years), these are remarkably similar findings to our own. A criticism of the RALES study was that the doses of ACE inhibitor used were much lower than those recommended for clinical use in heart failure. It has been postulated that this is why such low adverse event rates were documented in RALES.

Our study is the first to be conducted in a district general hospital, non-specialist setting with all patients cared for by general physicians. The majority of our patients had moderate/severe disease (85%), and no patients with elevated potassium or severe renal impairment (measured as serum creatinine) were commenced on spironolactone. In our study, electrolyte monitoring of spironolactone therapy was found to be patchy at best. Schepkens et al. [6] have found that hyperkalaemia occurs most frequently at 14–36 weeks. Our experience was of wide variation in timing of adverse events, and we therefore recommend that adjunctive spironolactone treatment is monitored throughout the duration of treatment.

Age, low left ventricular ejection fraction (lvef), NYHA class and diabetes have been found to be predictors of renal failure and hyperkalaemia [11, 12]. We did not replicate these findings, possibly due to the high age and severity of failure in the group as a whole. We did, however, find a relationship between intercurrent illness (sepsis, and dehydration secondary to vomiting or diarrhoea) and occurrence of both renal failure and hyperkalaemia. This confirms what others have hypothesised, namely that intercurrent illnesses which involve dehydration are clinically important in heart failure, and may precipitate adverse events to heart failure treatment [13].

In conclusion, the incidence of hyperkalaemia and renal failure in elderly patients treated with ACE inhibitor and spironolactone in clinical practice is high. Severe intercurrent illness involving dehydration is a significant predictor of hyperkalaemia and renal failure, and consideration should be given to withholding spironolactone during such illnesses. Combining aldosterone blockade with ACE inhibition remains an important evidence-based therapeutic strategy in heart failure [14], but patients need to be monitored closely throughout treatment.

Key points
- 37.5% of patients aged ≥75 years treated for heart failure with spironolactone combined with ACE inhibitor and diuretics developed renal insufficiency (>50% rise in creatinine), despite having mean baseline creatinine of 125 µmol/l.
- 36% developed hyperkalaemia (K ≥ 5.5 mmol/l) and 11% developed severe hyperkalaemia (K ≥ 6.0 mmol/l).
- Intercurrent illness involving dehydration was associated with adverse events and consideration should be given to stopping spironolactone during such illnesses.
- If adverse events are to be minimised, patients should be monitored for the entire duration of treatment.

Acknowledgements
The authors would like to thank the Consultant Physicians at Morriston Hospital, Swansea for permitting their patients to be studied and Mrs Helen Gallivan for her help in obtaining patient case notes.

Claire Dinsdale1,3, Mishtaq Wani1, John Steward2, M. Sinead O’Mahony3*
1Department of Elderly Medicine, Morriston Hospital, Morriston, Swansea SA6 6NL, UK
2Welsh Cancer Intelligence and Surveillance Unit, Cardiff, UK
3University Department of Geriatric Medicine, Landough Hospital, Penarth CF64 2XX, UK
*To whom correspondence should be addressed
E-mail: omahonyms@cf.ac.uk

Research letters

Are depression, anxiety and health beliefs important predictors of older people’s primary care consulting?

SIR—Evidence is lacking on the importance of psychological factors in predicting older peoples’ primary care consulting, despite their high and increasing consultation rates. A questionnaire survey of patients aged ≥65 years from two London practices assessed physical health and psychological factors. Seventy-five per cent (1,704/2,276) of invitees responded and 92% (1,565/1,704) of responders consented to linkage of their survey and primary care record data. Anxiety and a belief in powerful others predicted consulting independently of physical ill-health. Other health beliefs were not independent predictors of consulting. The association between depression and consulting was explained by physical ill-health, underlining the importance of treating coexisting physical illness in older people with depression.

Introduction

Recent analyses show high and increasing primary care contact by older people (≥65 years), with major workload implications [1]; yet consulting predictors remain unclear. Several UK studies have assessed the relative importance of psychological factors and physical ill-health in predicting older peoples’ consulting. Anxiety [2] and health beliefs [3] appear to predict consulting independently of physical ill-health, but have not been extensively studied. Depression findings are inconsistent; some studies show no association with consulting after controlling for subjects’ poorer physical health [2, 4, 5], others do show an independent association, but are limited by inadequately controlling for physical ill-health [6] or having no effect estimates [7]. The main criticism of all these studies is their reliance on self-report consultations, making them prone to recall bias [8], particularly in the presence of depression or anxiety. Studies with more robust consultation measures from patient records show depressive symptoms to be the major predictor of frequent attendance [9], but are based on adults and not specific to older people. Studies of different healthcare systems may not be directly applicable to the UK, and USA studies in particular may suffer from selection bias into medical care [10]. A large Canadian population-based study avoiding such bias and using robust consulting data found that a high depression score predicted primary care contact independently of physical health [10]. However, findings were again not reported separately for older people.

This paper examines the effects of depression, anxiety and health beliefs on primary care consulting by older people, whilst taking account of their physical health. Importantly, we linked survey and primary care record data [11], thus providing robust consultation measures.

Methods

Participants were aged ≥65 years (n=2,843), registered with two fully computerised London practices. Practices identified those with terminal illness or dementia (to exclude) or more appropriate to interview (e.g. frailty, poor vision). A postal survey was conducted, and assistance in completion offered. Non-responders were re-mailed after 4 weeks. The questionnaire included measures for depression (Geriatric Depression Score 15-item (GDS-15) [12]), anxiety (the four-item version of the Anxiety Disorder Scale [13]) and a health locus of control instrument for measuring health beliefs [14]. The latter instrument gives scores on three scales: internality (belief that you control your own health), chance (belief that your health is controlled by fate), and powerful others (belief that your health is controlled by others, including doctors). All of these psychological measures have been validated for use in primary care. Standardised measures of physical health were also included: general health, long-standing illness and limiting long-standing illness, disability, pain, and chronic disease score. Full details have been published previously [11, 15] and sources of questionnaire measures are given in Table 1.

Consultation data were downloaded for those giving written informed consent, 1 year after survey completion at that practice (2001–2002). The outcome variable was total consultations per person, for the year following the questionnaire return date. Total consultations included home visits, surgery contacts and telephone contacts with general practitioners and practice nurses (see Table 2).

Analysis

Consultation rates did not follow Poisson or negative binomial distributions. Therefore, associations between psychological factors and consultations were modelled using ordered logistic regression, with multiple cuts to increase power [11]. Results were expressed as odds ratios with 95% confidence intervals. Initial adjustments were for age, sex and practice. We were interested in whether psychological factors predicted consulting independently of physical ill-health. We therefore used forward stepwise ordered logistic regression (P<0.05) with all the physical health factors available for inclusion, to select the most important for a physical health model (general health, disease score and pain were selected). We then adjusted the psychological