



## Resistant hypertension—don't forget spironolactone

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### KEY POINTS

- Resistant hypertension is systolic blood pressure of 160 mm Hg despite compliance with three or more anti-hypertensive drugs.
- Spironolactone may be a suitable blood pressure-lowering medicine to consider after ACE inhibitor, thiazide and calcium channel blocker treatment has been optimised.
- Start dosing of spironolactone at 12.5 mg daily and titrate up to 50 mg daily over 4–6 weeks.
- Monitor serum potassium, sodium and creatinine at baseline, 1, 2, 4, 8, 12 and 24 weeks.
- Risk factors for hyperkalaemia include a creatinine clearance less than 45 mL/min, age over 75 years and a serum potassium concentration over 5 mmol/L.

**R**eduction of blood pressure was a focus for the management of cardiovascular disease in the 1980s. The treatment of dyslipidaemia was the focus for the 1990s, followed by the holistic management of cardiovascular risk at the start of this century. Now we need to refocus on managing high blood pressure, not only to reduce cardiovascular events, but also to reduce other end-organ disease, such as chronic kidney disease and retinopathy.

There is healthy debate about the blood pressure target we should be aiming for,<sup>1–4</sup> but general agreement that resistant or refractory hypertension is 'a systolic blood pressure of 160 mm Hg ( $\geq 150$  mm Hg in people with Type 2 diabetes), despite compliance with three or more antihypertensive drugs.'<sup>5</sup> Ideally one of these blood pressure-lowering medicines should be a thiazide,<sup>6</sup> preferably chlorthalidone. Catheter-based renal denervation has increased our awareness of resistant or refractory high blood pressure and the medicines-based management of this. With the publication of the SYMPLICITY HTN-3 study, with no significant difference between renal denervation and medicines-based management,<sup>7</sup> the optimal use of blood pressure-lowering medicines has been highlighted, and in particular the re-emergence of spironolactone as an important blood pressure-lowering medicine that we have neglected lately.

### Spironolactone

After ruling out secondary causes for resistant hypertension, including the use of NSAIDs and non-compliance with blood pressure-lowering medicines, spironolactone is considered after ACE inhibitors, thiazides and calcium

channel blockers have been optimised.<sup>8</sup> Spironolactone is considered for the 10–20% of people with primary aldosteronism, but recent evidence suggests that spironolactone is effective in people with and without primary aldosteronism.<sup>9</sup>

### Blood pressure-lowering benefit

A meta-analysis found that spironolactone may reduce systolic blood pressure by a mean of 20 mm Hg, with a dose response effect up to spironolactone 50 mg daily.<sup>8</sup>

There is increasing evidence that spironolactone may reduce microalbuminuria.<sup>10</sup>

### Dosing

Dosing for spironolactone is usually 12.5–50 mg daily. Due to the long half-life of spironolactone, the maximal effect of spironolactone requires at least four weeks therapy, and dose titration should be every four to six weeks.

Spironolactone should not be used in people with severe renal impairment.

### Monitoring

The risks of spironolactone-induced hyperkalaemia, especially when used in combination with ACE inhibitors, has made prescribers understandably cautious about using spironolactone, but with good monitoring this should not inhibit its use.

Serum potassium, sodium and creatinine concentrations should be done at baseline and

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repeated at week one, two, four, eight, 12 and 24.<sup>11</sup> The extended monitoring is because of the long half-life of spironolactone, although most adverse effects occur in the first four weeks. Spironolactone should be stopped if the serum creatinine increases more than 25%, or the potassium concentration increases over 6 mmol/L.

A randomised controlled trial of 115 people without diabetes, with mild to moderate renal disease (eGFR 30–89 mL/min/1.73m<sup>2</sup>) and on an ACE inhibitor or angiotensin II antagonist, found that after 40 weeks' therapy, less than 1% of people had serious hyperkalaemia. Nine people had a serum potassium between 5.5 and 5.9 mmol/L on one or more occasions, though these people had a baseline potassium concentration of over 5 mmol/L. Risk factors for hyperkalaemia include a creatinine clearance less than 45 mL/min, age over 75 years and a serum potassium concentration over 5 mmol/L.

A longitudinal study found 4% of people stopped spironolactone because of hyperkalaemia and there was a mean serum potassium increase of 0.4 mmol/L.<sup>12</sup>

### Adverse effects

As well as the hyperkalaemia discussed above, gynaecomastia is a well-reported adverse effect of spironolactone. This is usually seen with doses of 50 mg daily or greater.<sup>13</sup> The number of men treated to cause one case of gynaecomastia is approximately 20.

The previous concern that spironolactone may increase the risk of breast cancer appears to be unfounded.<sup>14</sup>

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