Mineralocorticoids

Effect of Spironolactone on Blood Pressure in Subjects With Resistant Hypertension

Neil Chapman, Joanna Dobson, Sarah Wilson, Björn Dahlöf, Peter S. Sever, Hans Wedel, Neil R. Poulter, on behalf of the Anglo-Scandinavian Cardiac Outcomes Trial Investigators

Abstract—Spironolactone is recommended as fourth-line therapy for essential hypertension despite few supporting data for this indication. We evaluated the effect among 1411 participants in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm who received spironolactone mainly as a fourth-line antihypertensive agent for uncontrolled blood pressure and who had valid BP measurements before and during spironolactone treatment. Among those who received spironolactone, the mean age was 63 years (SD: ±8 years), 77% were men, and 40% had diabetes. Spironolactone was initiated a median of 3.2 years (interquartile range: 2.0 to 4.4 years) after randomization and added to a mean of 2.9 (SD: ±0.9) other antihypertensive drugs. The median duration of spironolactone treatment was 1.3 years (interquartile range: 0.6 to 2.6 years). The median dose of spironolactone was 25 mg (interquartile range: 25 to 50 mg) at both the start and end of the observation period. During spironolactone therapy, mean blood pressure fell from 156.9/85.3 mm Hg (SD: ±18.0/11.5 mm Hg) by 21.9/9.5 mm Hg (95% CI: 20.8 to 23.0/9.0 to 10.1 mm Hg; P<0.001); the BP reduction was largely unaffected by age, sex, smoking, and diabetic status. Spironolactone was generally well tolerated; 6% of participants discontinued the drug because of adverse effects. The most frequent adverse events were gynecomastia or breast discomfort and biochemical abnormalities (principally hyperkaliemia), which were recorded as adverse events in 6% and 2% of participants, respectively. In conclusion, spironolactone effectively lowers blood pressure in patients with hypertension uncontrolled by a mean of ≥3 other drugs. Although nonrandomized and not placebo controlled, these data support the use of spironolactone in uncontrolled hypertension. (Hypertension. 2007; 49:839-845.)

Key Words: blood pressure ■ hypertension ■ clinical trial ■ antihypertensive agents ■ aldosterone antagonists ■ spironolactone

In 1988, United Kingdom regulatory authorities directed manufacturers to stop recommending the aldosterone antagonist spironolactone for the treatment of hypertension following unpublished evidence suggesting that a chemically similar compound caused leukemia in rats.1 The drug remained licensed elsewhere for essential hypertension and in the United Kingdom for use in other conditions, such as heart failure and hepatic cirrhosis, for which fewer therapeutic options were available. Since then, despite widespread use, there have been no published reports of associated malignancy in humans.

Spironolactone reduces morbidity and mortality in severe heart failure,2 and effectively lowers blood pressure (BP) in hypertensive patients with and without hyperaldosteronism.3–11 Small uncontrolled studies have also demonstrated its effectiveness in patients with resistant hypertension.12–15 This is reflected in the latest British Hypertension Society guidelines, which recommend spironolactone as fourth-line therapy when other drugs have failed to control BP.16

We conducted an analysis of the effect of spironolactone on BP among participants in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), a large-scale randomized, controlled study of BP-lowering therapy.17,18 Spironolactone was used mainly as fourth-line add-on therapy at the discretion of investigators when study medication had failed to achieve target BP.

Methods

Study Population

ASCOT-BPLA was a multicenter, international, randomized trial, which compared 2 open-label antihypertensive regimens for the prevention of coronary heart disease events in 19,257 hypertensive patients with additional cardiovascular risk factors but no history of coronary heart disease. The study protocol and main results have been published previously.17,18

The BP management algorithm has been described elsewhere17 and is summarized in Table 1. Briefly, participants were randomly assigned an antihypertensive regimen based on either amlodipine or atenolol. At each visit, therapy was titrated to achieve target BP.
TABLE 1. Antihypertensive Treatment Algorithm for the ASCOT Trial

<table>
<thead>
<tr>
<th>Titration Step</th>
<th>Amlodipine-Based Regimen</th>
<th>Atenolol-Based Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steps 1 to 2</td>
<td>Amlodipine</td>
<td>Atenolol</td>
</tr>
<tr>
<td></td>
<td>Dose titration 5 to 10 mg</td>
<td>Dose titration 50 to 100 mg</td>
</tr>
<tr>
<td>Steps 3 to 4</td>
<td>Add perindopril</td>
<td>Add bendroflumethiazide/K*</td>
</tr>
<tr>
<td></td>
<td>Dose titration 4 to 8 mg</td>
<td>Dose titration 1.25 to 2.5 mg</td>
</tr>
<tr>
<td>Steps 5 to 6</td>
<td>Add doxazosin gastrointestinal therapeutic system</td>
<td>Dose titration 4 to 8 mg</td>
</tr>
<tr>
<td>Step 7</td>
<td>Add other antihypertensives at investigator’s discretion*</td>
<td></td>
</tr>
</tbody>
</table>

*Suggested drugs included moxonidine and spironolactone.

<140/90 mm Hg (or <130/80 mm Hg in those with diabetes). If the target BP was not achieved on a combination of 3 study drugs at maximum doses, or if treatment was limited by adverse effects, nonstudy drugs could be added at the discretion of investigators. These analyses include participants in ASCOT-BPLA who were prescribed spironolactone for the management of hypertension during the trial. Participants who received spironolactone for other documented reasons (eg, heart failure or liver disease), and participants diagnosed with hyperaldosteronism during the trial, were excluded.

Follow-Up and BP Measurement
After random assignment, routine follow-up visits took place after 6 weeks, 3 months, 6 months, and every 6 months thereafter, with additional visits as necessary. BP was recorded according to standard protocols. Three seated measurements were made after ≥5 minutes of rest using a validated semiautomatic device (OMRON HEM-705CP), and the mean of the final 2 readings was used in the analyses. For the purpose of these analyses, prespironolactone BP was defined as that recorded on the day that spironolactone was prescribed or the nearest previous measurement. Postspironolactone BP was defined as that recorded at the final study visit or the date that spironolactone was permanently discontinued if this preceded the study end. If no measurement was recorded on either of these dates, the last BP recorded during spironolactone treatment was used. Where spironolactone was prescribed for >1 period, analyses include only the first continuous period of use.

Biochemical Measurements
Blood samples (ideally fasting) were taken from all of the ASCOT participants at study entry, 6 months, and annually thereafter for measurement of sodium, potassium, creatinine, glucose, and lipid profiles. Two central laboratories (in Ireland and Sweden) undertook all of the measurements. The current analyses are limited to participants for whom biochemical data were available before and during spironolactone treatment (selected according to the criteria above); glucose and lipid analyses were further limited to subjects in whom both samples were fasting. Because ASCOT included a lipid-lowering arm, involving a statin or placebo in factorial design, lipid analyses were also performed in a subgroup who took either no lipid-lowering drug or a constant dose for 30 days before the spironolactone blood test until the ontreatment blood sample.

Adverse Events
Information was routinely recorded about adverse events at each ASCOT study visit; investigators were asked to give an opinion on causality (study drug, another drug, or concurrent condition or illness). The current analyses include all of the participants prescribed spironolactone, whatever the indication, but only those events attributed to spironolactone.

Statistical Analysis
The effects of spironolactone on BP and biochemical measurements were evaluated using paired t tests of differences in prespironolactone and postspironolactone values. Additional sensitivity analyses of the BP effects were performed by limiting analyses to subjects whose other antihypertensive drugs did not change during spironolactone treatment and to those with BP recorded within a week of starting and discontinuing spironolactone. Changes in subgroups of participants aged ≥60 years and those >60 years at baseline; men and women; those with and without diabetes; current smokers and ex-/nonsmokers; and those randomly assigned to atenolol-based and amlodipine-based therapy were compared using ANCOVA. Reported subgroup comparisons were adjusted for spironolactone BP levels; adjustments for age, sex, body mass index, and spironolactone treatment duration were also performed. Assumptions of statistical tests and models were assessed.

Results
Study Participants
In total, 1790 individuals were prescribed spironolactone during ASCOT. Of these, 212 received spironolactone for reasons other than BP control or after an in-trial diagnosis of hyperaldosteronism (n=9). A further 167 had no BP measurements recorded on spironolactone (Figure 1). The current BP analyses, therefore, refer to 1411 individuals with available data both before and during spironolactone treatment. Biochemical analyses include available data from among 1578 participants who received spironolactone for BP control; adverse event analyses refer to all 1790 of the participants prescribed spironolactone at any stage.

Table 2 shows characteristics at study entry of participants included in the BP analyses compared with those of all of the ASCOT participants. Those prescribed spironolactone had higher mean systolic BP (SBP) at study entry, were more likely to have left ventricular hypertrophy, to have been randomized to the atenolol-based regimen, and to have diabetes.

Effects of Spironolactone on BP
Spironolactone was prescribed a median of 3.2 years (interquartile range: 2.0 to 4.4 years) after random assignment, and the median treatment duration was 1.3 years (interquartile range: 0.6 to 2.6 years). The median spironolactone starting dose was 25 mg (interquartile range: 25 to 50 mg), and this remained unchanged at the end of the treatment period; mean starting and final doses were 35 mg (SD: ±18 mg) and 41 mg (SD: ±25 mg), respectively. The mean numbers of other antihypertensive drugs taken in addition to spironolactone were 2.9 (SD: ±0.9) and 2.9 (SD: ±1.0) at the start and end of spironolactone treatment, respectively.

During spironolactone treatment, mean BP fell from 156.9/18.8/10.7 mm Hg (SD: ±18.0/11.5 mm Hg) to 135.1/75.8 mm Hg (SD: ±18.8/10.7 mm Hg). The mean reduction in SBP was 21.9 mm Hg (95% CI: 20.8 to 23.0 mm Hg) and diastolic BP was 9.5 mm Hg (95% CI: 9.0 to 10.1 mm Hg; both P<0.001; Figure 2).

Similar results were obtained when analyses were restricted to 591 participants (42%) with no changes in antihypertensive drugs or doses for 30 days before the spironolactone BP measurement until the ontreatment measurement; among this group, mean BP reduction was 21.8/9.5 mm Hg (95% CI: 20.1 to 23.4/8.7 to 10.3 mm Hg). Likewise, when
analyses were restricted to 830 participants (59%) with BP measurements within 1 week of both starting and discontinuing spironolactone (mean reduction: 20.8/9.2 mm Hg; 95% CI: 19.3 to 22.8/5.9 to 9.9 mm Hg).

Broadly similar reductions were observed in subgroups defined according to age, sex, smoking status, diabetic status, and randomized group (atenolol-based or amlodipine-based therapy). However, there were modest but significantly greater reductions in diastolic BP among older compared with younger participants, among women compared with men, and among participants with diabetes compared with those without (Table 3). These differences did not materially differ after adjustment for potential confounding factors. The effect of spironolactone was not modified by concomitant use of thiazide or other diuretics or angiotensin-converting enzyme inhibitors.

Other factors were also evaluated for their value in predicting the effect of spironolactone on SBP. The presence or absence of the metabolic syndrome and baseline weight, body mass index, fasting plasma glucose, total and low-density lipoprotein cholesterol, and triglycerides did not consistently predict response, nor did changes in weight and body mass index during treatment. The only variables that appeared to weakly predict response were baseline high-density lipoprotein cholesterol, baseline serum potassium, and change in potassium during treatment. In regression analyses, each 1 mmol/L lower high-density lipoprotein cholesterol was associated with 3.4 mm Hg greater reduction in SBP (\(P=0.015\)). Each 1 mmol/L lower baseline serum potassium was associated with 2.2 mm Hg greater reduction in SBP (\(P=0.043\)); however, after adjustment for prespironolactone BP, duration of spironolactone treatment, baseline age, sex, and body mass index, this ceased to be significant (\(P=0.165\)). Similarly, each 1-mmol/L increase in potassium during spironolactone treatment was associated

### Table 2. Characteristics at Study Entry of Patients Included in BP Analyses and Whole ASCOT Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Spironolactone Patients (n=1411)</th>
<th>All ASCOT Patients (n=19257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.5 (8.4)</td>
<td>63.0 (8.5)</td>
</tr>
<tr>
<td>Male</td>
<td>1091 (77%)</td>
<td>14 742 (77%)</td>
</tr>
<tr>
<td>White/European</td>
<td>1314 (93%)</td>
<td>18 357 (95%)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>169.3 (19.2)</td>
<td>164.0 (18.0)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>94.6 (10.9)</td>
<td>94.7 (10.4)</td>
</tr>
<tr>
<td>LVH*</td>
<td>386 (27%)</td>
<td>4167 (22%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>570 (40%)</td>
<td>5137 (27%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>370 (26%)</td>
<td>6277 (33%)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.4 (4.6)</td>
<td>28.7 (4.6)</td>
</tr>
<tr>
<td>Allocated amlodipine</td>
<td>350 (25%)</td>
<td>9639 (50%)</td>
</tr>
<tr>
<td>Serum creatinine, µmol/L</td>
<td>99.0 (16.6)</td>
<td>98.7 (16.8)</td>
</tr>
<tr>
<td>Serum potassium, mmol/L</td>
<td>4.18 (0.53)</td>
<td>4.23 (0.47)</td>
</tr>
</tbody>
</table>

*Data are mean (SD) or No. (%). LVH indicates left ventricular hypertrophy; BMI, body mass index.

*Electrocardiographic or echocardiographic LVH identified by study investigators.
with 4.8 mm Hg greater reduction in SBP ($P=0.014$), which was attenuated slightly after adjustment to 4.1 mm Hg ($P=0.037$).

**Biochemical Analyses**

During spironolactone treatment there were small but statistically significant changes in serum electrolytes and creatinine (Table 4). Serum potassium increased by mean 0.41 mmol/L (95% CI: 0.37 to 0.44 mmol/L), sodium decreased by 1.7 mmol/L (95% CI: 1.5 to 1.9 mmol/L), and creatinine increased by 13.2 μmol/L (95% CI: 12.0 to 14.4 μmol/L). Fifty-five participants of 1255 with available data (4%) had serum potassium levels ≥5.5 mmol/L on spironolactone, and 19 (2%) had levels ≥6.0 mmol/L; the percentage with hyperkalemia was identical among participants randomly assigned to the atenolol-based and amldipine-based regimens. Seventeen (1%) of 1256 participants had postspironolactone sodium levels ≥130 mmol/L. Ninety (7%) of 1254 participants had postspironolactone creatinine levels ≥150 μmol/L, of whom 15 (1%) had elevated creatinine levels before starting spironolactone.

Mean prespironolactone fasting plasma glucose levels were high (7.11 mmol/L; SD: ±2.62 mmol/L), reflecting the fact that 40% of those prescribed spironolactone had diabetes at baseline; mean glucose levels were 9.03 mmol/L (SD: ±2.97 mmol/L) and 5.82 mmol/L (SD: ±1.20 mmol/L) among those with and without diabetes, respectively. During treatment, there was a small but significant (mean: 0.19 mmol/L; 95% CI: 0.06 to 0.33 mmol/L; $P=0.005$) increase in glucose levels (Table 4); this increase was similar in magnitude in both randomized treatment arms and among those with and without diabetes. At the same time, there was a small reduction in body weight (mean reduction: 0.5 kg; 95% CI: 0.2 to 0.8 kg; $P=0.001$).

There were small but significant reductions in total and low-density lipoprotein cholesterol and a small rise in high-density lipoprotein cholesterol during spironolactone treatment (Table 4). When analyses were restricted to those

<table>
<thead>
<tr>
<th>Table 3. Estimated Differences in Mean BP Change During Spironolactone Treatment Between Categorical Subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup</strong></td>
</tr>
<tr>
<td>Atenolol</td>
</tr>
<tr>
<td>Amlodipine</td>
</tr>
<tr>
<td>Age ≤60 y</td>
</tr>
<tr>
<td>Age &gt;60 y</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Nondiabetic</td>
</tr>
<tr>
<td>Diabetic</td>
</tr>
<tr>
<td>Nonsmoker</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
</tbody>
</table>

Data are mean differences (95% CI; $t$-test $P$) adjusted for spironolactone BP.
Adverse Effects
Among the 1790 participants who took spironolactone for any cause, investigators ascribed 297 adverse events in 238 participants (13%) to spironolactone, which was discontinued temporarily or permanently as a result in 110 participants (6%). These event rates were identical among 1578 participants prescribed spironolactone for hypertension control.

Among the 1790 participants, the most frequent adverse events were gynecomastia or breast discomfort and biochemical abnormalities (principally hyperkalemia). Gynecomastia or breast discomfort was recorded as an adverse event secondary to spironolactone in 114 male participants and no women (overall 6%), resulting in discontinuation in 52 participants (3%; all men). Similar symptoms were reported in a further 39 participants (2%) who received spironolactone but in whom no suspected causal link was recorded. This compares with a frequency of gynecomastia or breast discomfort of 0.6% among ASCOT participants who did not receive spironolactone at any stage. Biochemical abnormalities were recorded as adverse events secondary to spironolactone in 37 participants (2%), resulting in discontinuation in 15 participants (1%).

Discussion
These analyses from a population of 1411 participants in ASCOT-BPLA show that spironolactone appears to lower BP effectively in patients with uncontrolled BP despite an average of ≈3 existing antihypertensive drugs. Used in modest doses, spironolactone lowered BP by an average of 21.9/9.5 mm Hg and was generally well tolerated.

The observed reductions are large for a single antihypertensive agent, particularly when used fourth line where conventional agents have failed to control BP. The effects were broadly consistent across various subgroups and when the analyses were restricted to participants in whom other antihypertensive drugs and doses remained unaltered during the observation period. The reductions compare favorably with those observed with other drugs used as initial or add-on therapy but are consistent with those observed in smaller uncontrolled studies of spironolactone in essential and resistant hypertension. Although the observed reductions are impressive, we cannot be certain that they translated into reductions in cardiovascular outcomes. However, the best available data suggest that the magnitude of BP reduction rather than choice of antihypertensive agent is the most important factor in reducing most major cardiovascular events.

The major and serious drawback to these analyses is that they are observational and not placebo controlled. Hence, the observed BP reductions may, in theory at least, be explained or influenced by factors other than the treatment itself, including acclimatization, regression to the mean, a placebo-like effect, or selection bias. However, because spironolactone was first administered after a median 3.2 years of follow-up, when ASCOT participants had undergone ≥10 sets of BP readings, acclimatization seems unlikely to explain the reductions observed. Furthermore, regression to the mean is unlikely to be a major contributor, because the SDs of BP levels in the ASCOT Study population were relatively constant after the first 18 months of the trial (N. R. Poulter, unpublished data, 2006). However, selection bias may have occurred in that subjects with resistant hypertension may be particularly prone to salt and water retention and, hence, susceptible to the effects of aldosterone blockade; consequently, the observed effect on BP may be greater than that which might occur if spironolactone were used first line.
Compared with the general ASCOT population, participants who received spironolactone had higher mean SBP and were more likely to have left ventricular hypertrophy at study entry. Recent data suggest that hyperaldosteronism may be more frequent than previously thought, particularly among patients with resistant hypertension. Because participants were not systematically screened for secondary causes of hypertension, ASCOT is likely to have included a number of patients with undiagnosed hyperaldosteronism; however, the similar mean baseline serum potassium in those who did and did not receive spironolactone makes a substantial excess of hyperaldosteronism among the former seem unlikely. Furthermore, whereas spironolactone results in large BP reductions in patients with hyperaldosteronism, a previous study, including subjects both with and without hyperaldosteronism, observed similar reductions in both groups. It, therefore, seems unlikely that undiagnosed hyperaldosteronism accounts for the BP reductions seen here. Nevertheless, the observed associations between BP response to spironolactone and baseline serum potassium and change in potassium during spironolactone treatment do suggest that aldosterone levels may modify the response.

In this population, spironolactone appears to be safe and reasonably well tolerated. Among patients with largely normal renal function, there were small but significant increases in serum creatinine and potassium. However, high levels of each were seen in only a few patients. The increases in creatinine and potassium and the risk of serious hyperkalemia were similar to those seen in previous randomized studies of spironolactone use, although it has been suggested that spironolactone may be associated with excess hyperkalemia-related morbidity when used outside of clinical trials. A modest rise in fasting plasma glucose levels was observed in the current study, unlike previous studies in which no effect was found. In contrast to the overall ASCOT-BPLA cohort, the observed glucose rise did not differ between the 2 antihypertensive drug regimens and may merely reflect the natural increase among an elderly hypertensive population over time. The observed changes in plasma lipids are likely to have been attributable, at least in part, to statin use; previous studies of spironolactone generally observed no effect.

At the modest doses of spironolactone used, adverse events were relatively rarely recorded; only 13% of participants had any adverse event attributed to spironolactone, and temporary or permanent discontinuation of the drug was required in only 6%. The most frequent adverse events were gynecomastia or breast discomfort, which occurred in 6% of the study population, all of whom were men. Others have reported slightly higher rates (~10%) of gynecomastia. However, ASCOT was not designed to identify adverse effects specific to spironolactone and, whereas participants were questioned about adverse events at each visit, the recording of adverse events depended on the investigator identifying spironolactone as a potential cause; therefore, the true frequency of spironolactone-related adverse events is likely to have been underestimated.

**Perspectives**

In conclusion, these data suggest that spironolactone is an effective antihypertensive agent when used in patients whose BP remains uncontrolled on an average of ~3 other medications. Although recognizing the limitations of these uncontrolled observational data, they comprise the largest and best currently available data set to evaluate the impact of spironolactone as add-on therapy for resistant hypertension. As such, they provide unique support for the recent British Hypertension Society recommendations regarding the use of spironolactone as a fourth-line agent. Given the increasing acknowledgement of the need to use ≥2 agents to control hypertension, a prospective randomized, controlled trial of aldosterone blockade in patients with resistant hypertension would perhaps be timely.

**Acknowledgments**

We thank all of the trial doctors, nurses, and practices, but most of all the patients, for their important contribution.

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**Disclosures**

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**References**


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Effect of Spironolactone on Blood Pressure in Subjects With Resistant Hypertension
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