The Spironolactone, Amiloride, Losartan, and Thiazide (SALT) Double-Blind Crossover Trial in Patients With Low-Renin Hypertension and Elevated Aldosterone-Renin Ratio

Susan J. Hood, RGN; Kevin P. Taylor, MSc; Michael J. Ashby, BSc; Morris J. Brown, FMedSci

Background—There is continuing variation in diagnosis and estimated prevalence of primary hyperaldosteronism. The higher estimates encourage search for adrenal adenomas in patients with elevated ratios of plasma aldosterone to renin. However, it is more likely that patients with normal plasma K⁺ and aldosterone belong to the polygenic spectrum of low-renin hypertension rather than have the same monogenic syndrome as classic Conn’s. Our primary hypothesis was that in low-renin patients with normal plasma K⁺ and aldosterone, a thiazide diuretic, bendroflumethiazide, would be as effective as spironolactone in overcoming the Na⁺ retention and lowering blood pressure. Secondary objectives were to compare the dose response for each diuretic and to evaluate amiloride as an alternative to spironolactone.

Methods and Results—Fifty-seven patients entered and 51 patients completed a placebo-controlled, double-blind, randomized crossover trial. Entry criteria included low plasma renin, normal K⁺, elevated aldosterone-renin ratio, and a previous systolic blood pressure response to spironolactone of 20 mm Hg. Two doses each of spironolactone and bendroflumethiazide were compared. The crossover also included amiloride and losartan. Outcome measures were blood pressure, plasma renin, and other biochemical markers of diuretic action. Spironolactone 100 mg and bendroflumethiazide 5 mg caused similar falls in systolic blood pressure, whereas bendroflumethiazide 2.5 mg was 5/2 mm Hg less effective in reducing blood pressure than either bendroflumethiazide 5 mg or spironolactone 50 mg (P<0.005). Amiloride 40 mg was as effective as the other diuretics. Biochemical indices of natriuresis showed bendroflumethiazide to be less effective than either spironolactone or amiloride; plasma renin rose 4-fold on spironolactone but only 2-fold on bendroflumethiazide (P=0.003).

Conclusions—In hypertensive patients with a low plasma renin but normal K⁺, bendroflumethiazide 5 mg was as effective as spironolactone 100 mg in lowering blood pressure, despite patients being selected for a previous large fall in blood pressure on spironolactone. Because this result differs from that expected in primary hyperaldosteronism, our finding argues against low-renin hypertension including a large, undiagnosed pool of primary hyperaldosteronism. However, spironolactone was the more effective natriuretic agent, suggesting that inappropriate aldosterone release or response may still contribute to the Na⁺ retention of low-renin hypertension. (Circulation. 2007;116:11001–11007)

Key Words: aldosterone ▪ atrial natriuretic factor ▪ diuretics ▪ pharmacology ▪ renin

In recent years, several studies have suggested that primary hyperaldosteronism (PHA) is much more common than previously thought, occurring in at least 10% of all patients with hypertension.1,2 The proportion in whom hypertension is cured by removal of a unilateral adrenal adenoma remains much smaller, at 1% to 2% of hypertension; instead, the major practical outcome of diagnosing PHA has been greater use of spironolactone for patients who have appeared resistant to more conventional drugs.3,4 The test that led to increased diagnosis of PHA has been the aldosterone-renin ratio, which seemed to permit detection of PHA in patients with an apparently normal plasma aldosterone level.5,6

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be at least as useful as increased aldosterone-renin ratio in predicting response to spironolactone and noted that the logarithmic distribution of plasma renin explains the previously noted dominance of a low plasma renin in determining the ratio.\textsuperscript{13,15} The question therefore is whether there is truly noninferiority for amiloride at the small doses present in current diuretic formulations.

There have been few formal comparisons of diuretics in the patients in whom a suppressed plasma renin indicates Na\textsuperscript{+} retention to be the principal cause of hypertension. Anecdotial observations in the rare monogenic syndromes suggest that such patients can differ markedly in their response to differing diuretics, depending on the site within the nephron where elevated Na\textsuperscript{+} reabsorption occurs.\textsuperscript{16} Thiazide responsiveness has been the clinical hallmark of low-renin hypertension,\textsuperscript{17} whereas “true PHA” is classically resistant to thiazides but responsive to spironolactone.\textsuperscript{18} If, therefore, there is a common subgroup of patients with low-renin hypertension in whom further investigations for PHA should be performed, we hypothesized that hypertension in such patients would respond well to spironolactone and that a comparison of the 2 types of diuretic would show spironolactone to be superior. If, on the other hand, a higher than usual dose of thiazide is as effective as spironolactone, even when patients have been selected for elevated aldosterone-renin ratio and a previous good response to spironolactone, we may be able to conclude that it is dose rather than type of diuretic that is critical in reducing the Na\textsuperscript{+} load responsible for most low-renin hypertension.\textsuperscript{19}

The practical problem with higher doses of thiazides is the metabolic side effects. Spironolactone is also problematic, partly because of the cumulative burden of gynecomastia at modest long-term doses. A possible alternative is amiloride. This has been compared previously with thiazides but generally at the small doses present in current diuretic formulations rather than the higher doses used in patients with genetic causes of low-renin hypertension or as an alternative to spironolactone in PHA.\textsuperscript{20–25} The primary objective of the present study, therefore, was to establish whether there is a common group of patients in whom spironolactone is superior to bendroflumethiazide in overcoming renin suppression and reducing blood pressure. The secondary objectives were to determine whether low-dose thiazide is submaximal in low-renin hypertension and whether we could establish noninferiority for amiloride against either of the other diuretics.

### Methods

The Spironolactone, Amiloride, Losartan, and Thiazide (SALT) study compared responses to 3 diuretics in patients with low-renin hypertension and elevated, aldosterone-renin ratio, who had responded well to previous treatment with spironolactone. The design was a double-blind, placebo-controlled, randomized crossover with 5-week cycles of treatment. In addition to the placebo, we included an active, nondiuretic control.

### Patients

The inclusion criteria were as follows: (1) clinic seated blood pressure of 140/90 to 170/110 mm Hg while either untreated for at least 1 month or receiving a calcium channel blocker, if untreated blood pressure was expected to exceed the inclusion limits; (2) plasma renin of \( \leq 12 \, \text{mU/L} \), measured off \( \beta \)-blockade; this is equivalent to the limit of 0.65 ng/mL per hour commonly used as a cutoff for low-renin hypertension;\textsuperscript{26,27} (3) plasma aldosterone-renin ratio \( > 750 \), when renin activity is measured or calculated from renin mass;\textsuperscript{28} (4) previous fall in systolic blood pressure (SBP) of at least 20 mm Hg after 1 month of open-label treatment with spironolactone 50 mg daily.

Patients with known secondary causes of hypertension, contraindications to trial drugs, or history of hypokalemia were excluded. All patients gave informed written consent to participate in the study, which was approved by the Cambridge Research Ethics Committee.

### Drugs and Randomization

Patients began the study with a single-blind placebo run-in phase lasting 1 month (see schema in Figure 1). The dose of any open-label

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**Figure 1.** Study schema. Each visit was the last day of treatment shown in the previous column. Thus, measurements listed in the bottom row relate to treatment in the top row of the previous column. Higher doses of each diuretic and placebo were randomly assigned to 1 of the cycles ending on an even-numbered visit. Lower doses of each diuretic and losartan were randomly assigned to 1 of the cycles ending on an odd-numbered visit. At least 3 cycles separated the 2 doses of each diuretic. The drugs are listed by their initial in the row of doses. BP indicates blood pressure; CCB, calcium channel blocker; Amlo, amlodipine; Lerc, lercanidipine; Elecs, electrolites; Bendro, bendroflumethiazide; and ABPM, ambulatory blood pressure monitor.

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### BP Measurements

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**TABLE 1. Patient Demographics and Entry Criteria**

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<td>Age, y</td>
<td>59.5 (11.9)*</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>151.0/96.5 (12.4/9.7)*</td>
</tr>
<tr>
<td>White/black</td>
<td>56/1</td>
</tr>
<tr>
<td>Previously treated (1, 2, &gt;2 drugs)</td>
<td>57 (16, 27, 14)</td>
</tr>
<tr>
<td>Receiving calcium channel blocker at study entry (amlodipine/lenercandipine)</td>
<td>51 (30/21)</td>
</tr>
<tr>
<td>24-h Na(^+), mmol/L</td>
<td>148 (37)*</td>
</tr>
<tr>
<td>Plasma K(^-), mmol/L</td>
<td>4.0 (3.0)</td>
</tr>
<tr>
<td>Plasma renin, mU/L</td>
<td>6.3 (3.4 to 13.0)†</td>
</tr>
<tr>
<td>Aldosterone-renin ratio</td>
<td>960 (551 to 1723)†</td>
</tr>
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*Normally distributed traits are expressed as mean (SD).†Logarithmic distributions are shown as median (range).*

blood background treatment (amlodipine 5 to 10 mg or lercandipine 10 to 20 mg) was titrated before this phase and continued unchanged for the rest of the study. Patients then received 10 cycles of double-blind treatment comprising spironolactone 50 to 100 mg, amiloride 20 to 40 mg, bendroflumethiazide 2.5 to 5 mg at the 2 doses shown, losartan 100 mg, and placebo. Order of drugs and doses were randomized, except that the higher doses of diuretic and the placebo were administered in alternate cycles, and the 2 doses of each diuretic were separated by at least 3 intervening cycles. Each cycle of treatment lasted 5 weeks. There were no washout periods, and the entire study lasted 44 weeks for each patient.

Randomization was performed by an in-house program that randomly ordered the 48 possible permutations of the even-numbered phases (high-dose diuretics and placebo), with the use of blocks of 12 in which all permutations of the first 2 of these phases were covered. A similar block was generated for the final 12 patients. The program then randomly assigned the odd-numbered phases, rejecting any assignment of the same diuretic to sequential phases. Over the 8 phases, each patient had a unique sequence of drugs.

**Measurements**

Seated blood pressure was measured in triplicate with the use of the A&D 767 at the same time of day at the end of run-in and each subsequent cycle. At the even-numbered visits (end of high-dose and placebo treatment), blood samples were taken after completion of blood pressure measurement for analysis of plasma electrolytes, renin, aldosterone, and atrial natriuretic peptide (ANP). After sampling, patients were fitted with an A&D 24-hour ambulatory blood pressure monitor. Blood samples were separated for immediate assay of electrolytes and batched assay of hormone immunoassay. Renin was measured as renin mass by the Nichols Advantage assay and log-normalized for statistical analyses.

**Analyses**

The primary outcomes were the difference in SBP and plasma renin between the end of high-dose spironolactone and high-dose bendroflumethiazide. Secondary blood pressure outcomes were the differences in SBP between amiloride and the other diuretics and between lower and higher doses of each diuretic; secondary biochemical outcomes were indices, additional to plasma renin, of Na\(^+\) loss during diuretic treatment. The study was powered for the primary clinical outcome, namely, blood pressure, for which previous data enabled a precise prediction of plausible difference and SD if the primary hypothesis was correct. Given the variety of available tests and definitions for normokalemic PHA, our cohort is intended to satisfy some but not all suggested criteria for this diagnosis.28–31

Thus, we considered that, if PHA was a common component of low-renin hypertension, at least half of the patients selected for a previous ≥20 mm Hg fall in SBP on spironolactone should show a ≥10 mm Hg greater fall on spironolactone than on bendroflumethiazide. We therefore wished to detect a mean (for all patients in the study) of ≥5 mm Hg greater fall on spironolactone than bendroflumethiazide. Because patients were selected 1-sidedly, ie, for a previous large fall in SBP on only 1 of the trial drugs, we considered that large falls on spironolactone in half of the patients were unlikely to be cancelled by similarly larger falls on bendroflumethiazide in the other half of the patients. We used the sample size module of WSTATA to calculate that in a 1-sample (crossover) test, assuming SD for blood pressure of 10 mm Hg, 60 patients would give us the necessary power (α=0.01, β=0.9). Because, however, full analysis of a crossover trial is limited to those completing all randomized treatment, we calculated that 43 completed patients were adequate for α=0.05, β=0.9. The primary analysis was undertaken by paired t test, followed by repeated-measures ANOVA incorporating age, gender, background treatment, and drug order as factors. For noninferiority to be established of 1 diuretic against another, we required that the upper 95% CI of the difference in SBP should be no more than 2.5 mm Hg, this being half the expected difference for superiority and equating to a difference in 5-year stroke risk of <10%.32

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

Fifty-seven patients were recruited, of whom 51 completed all cycles of the study. Their demographics are shown in Table 1. In 30 patients, the month’s trial of open-label spironolactone was part of our previous study investigating prevalence of PHA33; in the remainder, spironolactone had been tried as an option for treating patients referred to our clinics with difficult hypertension.

**Blood Pressure**

In brief, all diuretics achieved substantial reduction in placebo-corrected SBP. On this outcome, the superiority hypothesis for spironolactone over higher-dose bendroflumethiazide was not supported, whereas the secondary hypothesis of a dose response for bendroflumethiazide was confirmed. Amiloride had efficacy similar to that of the other diuretics, meeting the preset noninferiority hypothesis against bendroflumethiazide.

In more detail, the placebo-corrected falls for each drug are shown in Table 2, and absolute values are shown in Figure 2. Spironolactone 50 mg reduced SBP more than bendroflumethiazide 2.5 mg (t=2.95, P=0.005), but at their higher doses

**TABLE 2. Blood Pressure Responses**

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<tr>
<th>Dose</th>
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<th>Spironolactone</th>
<th>Amiloride</th>
<th>Losartan</th>
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<tr>
<td>Low</td>
<td>−4.9 (−8.4, −1.4)</td>
<td>−10.1 (−13.7, −6.4)</td>
<td>−8.3 (−11.4, −5.2)</td>
<td>−5.9 (−10.7, −1)</td>
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<tr>
<td>High</td>
<td>−10.5 (−13.3, −7.6)</td>
<td>−11.6 (−15.4, −7.8)</td>
<td>−11.5 (−15.1, −7.6)</td>
<td>−3.1 (−5.9, −0.4)</td>
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Results are shown as ∆SBP (95% CI)/Δdiastolic blood pressure (95% CI) for each dose of the 3 diuretics and single dose of losartan. The ∆ values are calculated by subtracting the value on active drug from the value in the double-blind placebo phase. Significant differences (SBP only) are shown between doses as *P<0.05, †P<0.01, and from bendroflumethiazide as ‡P<0.05, §P<0.01.
there was no significant difference between the mean placebo-corrected falls in clinic SBP of 10.5 mm Hg on bendroflumethiazide 5 mg and 11.6 mm Hg on spironolactone 100 mg (t=0.77, P=0.44). This was because bendroflumethiazide 2.5 mg was submaximal, with a 5.5/2.6 mm Hg greater fall in blood pressure on 5 mg (t=3.7, P=0.0005). The repeated-measures ANOVA on SBPs and diastolic blood pressures at both doses excluded order effect and showed no overall difference between spironolactone and bendroflumethiazide (F=2.00, P=0.16).

Amiloride 20 to 40 mg was similar in efficacy to both bendroflumethiazide and spironolactone, with a dose response midway between that of the other diuretics for steepness. The noninferiority analyses, shown for the higher dose of each diuretic in Table 3, permit a claim of noninferiority for amiloride 40 mg compared with bendroflumethiazide 5 mg.

We found that the 24-hour ambulatory blood pressure monitor performed on placebo and the higher doses of diuretic showed no significant differences between the latter. However, satisfactory tracings were obtained for all time points in only 26 of 51 patients completed.

Biochemistry
In brief, spironolactone was substantially more effective than bendroflumethiazide in reversing the suppression of plasma renin. Of the secondary indices of natriuresis, spironolactone caused greater increase in plasma urea and greater falls in plasma Na⁺ and ANP. The effects of amiloride were similar to those of spironolactone, except for a rise in plasma ANP (Table 4, Figures 3 to 5). More detail is given below for each measurement.

Renin
Renin was log-normalized for analysis. Levels increased 2-fold on bendroflumethiazide but 4-fold on spironolactone (t=3.1 for the comparison, P=0.003) (Figure 3). Amiloride increased renin in a manner similar to that of spironolactone.

Other Indices of Natriuresis
Plasma urea rose by almost 1 mmol/L on spironolactone, twice as much as on bendroflumethiazide (t=3.1, P=0.003), and the pattern for plasma Na⁺ was similar, falling by >2 mmol/L on spironolactone compared with <1 mmol/L on bendroflumethiazide (t=2.35, P=0.02) (Figure 4). Plasma ANP also fell more on spironolactone than on bendroflumethiazide (t=2.35, P=0.02). Small falls in weight mirrored the other differences in natriuretic indices (Figure 5). Amiloride had effects similar to those of spironolactone except that it caused a significant increase in plasma ANP (t=2.6, P=0.01).

K⁺ and Aldosterone
There were the expected differences in plasma K⁺, which fell by 0.4 mmol/L on bendroflumethiazide but rose by 0.5 mmol/L on spironolactone and even more on amiloride. Plasma aldosterone rose 3-fold on the K⁺-sparing diuretics but was unchanged on bendroflumethiazide.

Discussion
The primary hypothesis was that if PHA was a common cause of low-renin hypertension in our cohort of previous spironolactone responders, we would find spironolactone superior to bendroflumethiazide in reducing Na⁺ retention and blood pressure. Although we did indeed find a greater effect of spironolactone on all indices of Na⁺ retention, there was no significant difference in blood pressure reduction. The secondary hypotheses were that, in low-renin patients, an increase from the usual dose of bendroflumethiazide would cause a further reduction in blood pressure and that amiloride would be noninferior to bendroflumethiazide and spironolactone. The dose response for bendroflumethiazide was confirmed, and amiloride met the preset noninferiority hypothesis against bendroflumethiazide.

What conclusions and caveats should be applied to these findings? Having selected a group of low-renin patients who would include many of the candidates for the putative diagnosis of normokalemic PHA, we did not find the hypothesized superiority of spironolactone over bendroflumethiazide. Although our higher doses of both primary diuretics were higher than current usage in hypertension, even higher doses of both have been used in the past. We cannot therefore completely exclude the possibility of a common group of patients in whom a maximal dose of spironolactone would be superior to maximal-dose thiazide. However, doses of spironolactone >100 mg seem most likely, in theory, to be

**TABLE 3. Noninferiority Comparisons Between Diuretics**

<table>
<thead>
<tr>
<th></th>
<th>ΔSBP</th>
<th>95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride vs bendroflumethiazide</td>
<td>-0.90</td>
<td>-4.22 to 2.42</td>
</tr>
<tr>
<td>Amiloride vs spironolactone</td>
<td>0.08</td>
<td>-2.97 to 3.11</td>
</tr>
<tr>
<td>Bendroflumethiazide vs spironolactone</td>
<td>1.17</td>
<td>-1.85 to 4.23</td>
</tr>
</tbody>
</table>

The table shows the mean differences between SBP on the higher doses of each diuretic and the 95% CIs around these. The previous hypothesis was that noninferiority was established if the upper limit of the CI was ≥2.5 mm Hg. This was met for the planned comparison of amiloride vs bendroflumethiazide.
required when aldosterone secretion is elevated, and our blood pressure dose response (Figure 2) suggests that, if anything, a higher dose of diuretics would have favored bendroflumethiazide. Moreover, it is the apparent efficacy of spironolactone 25 to 50 mg in patients with resistant hypertension, and the consequent suspicion of underlying PHA, that stimulated the present study. Although there has not been a similar study of different diuretics in patients with proven Conn’s adenomas, such patients have the reputation of being resistant to thiazides, best documented in a review from the Mayo Clinic conducted at a time when thiazides were commonly used in higher doses than is now usual. Our patients were selected for having a high aldosterone-renin ratio and minimum fall in SBP of 20 mm Hg on previous open-label exposure to spironolactone 50 mg. We considered that if these were also selection criteria for PHA, at least half of our cohort would have a 10 mm Hg fall on bendroflumethiazide. As expected, placebo correction and regression on the mean led to generally 20 mm Hg falls on double-blind rechallenge with spironolactone. Because currently patients with true PHA are unlikely to have received bendroflumethiazide 5 mg (or an equivalent dose of hydrochlorothiazide) before diagnosis and prospective testing is unlikely to receive ethical approval, we will probably have to rely on likelihood rather than proof that the similar blood pressure response of our patients to spironolactone 50 mg and bendroflumethiazide 5 mg is different from that of true PHA.

Although we had only 1 primary and 2 secondary hypotheses, the number of comparisons (and therefore the potential for spurious results) was increased by the number of drugs and doses and by the inclusion of both blood pressure and biochemical end points. The purpose of the latter was to permit any superiority of spironolactone in blood pressure reduction to be ascribed to a difference in natriuretic efficacy rather than postulated extrarenal effects of aldosterone blockade. In the present study, we found a difference in the biochemical but not blood pressure response to spironolactone, and the interpretation will be discussed below. The main secondary finding was the substantial dose response for the blood pressure fall on bendroflumethiazide. At 5 mm Hg for SBP, this was the same as we had hypothesized might exist between bendroflumethiazide and spironolactone. It is therefore tempting to conclude that the clinical efficacy of spironolactone in patients apparently resistant to thiazides, for instance, to atenolol 100 mg and bendroflumethiazide 2.5 mg

### TABLE 4. Biochemical Data

<table>
<thead>
<tr>
<th></th>
<th>Na⁺, mmol/L</th>
<th>K⁺, mmol/L</th>
<th>Urea, mmol/L</th>
<th>Aldosterone, pmol/L</th>
<th>Renin, mU/L</th>
<th>ANP, pmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>140.0 (139.2 to 140.8)</td>
<td>4.0 (3.9 to 4.1)</td>
<td>5.3 (5 to 5.7)</td>
<td>357 (276 to 438)</td>
<td>7.4 (6.3 to 8.4)</td>
<td>6.2 (5.3 to 7)</td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
<td>138.8 (138.0 to 139.6)</td>
<td>3.6 (3.4 to 3.8)</td>
<td>5.7 (5.3 to 6.1)</td>
<td>374 (330 to 419)</td>
<td>24.5 (11.7 to 37.3)</td>
<td>5.7 (5.1 to 6.4)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>137.5 (136.3 to 138.7)</td>
<td>4.5 (4.4 to 4.6)</td>
<td>6.4 (5.9 to 6.8)</td>
<td>1116 (893 to 1339)</td>
<td>61.4 (48.6 to 74.2)</td>
<td>5.2 (4.9 to 5.6)</td>
</tr>
<tr>
<td>Amiloride</td>
<td>137.9 (137.0 to 138.9)</td>
<td>4.8 (4.6 to 4.9)</td>
<td>6.3 (5.8 to 6.8)</td>
<td>963 (797 to 1129)</td>
<td>47.4 (29.8 to 65)</td>
<td>7.6 (6.7 to 8.5)</td>
</tr>
</tbody>
</table>

Values are mean (95% CI). Except for the increases in urea and aldosterone on bendroflumethiazide, all other changes from placebo are significant. Differences between the primary drugs are shown in Figures 3 to 5.

![Figure 3](image1.png)  
**Figure 3.** Effects of bendroflumethiazide (Bendro) and spironolactone (Spiro) on plasma renin. Renin was log-normalized and plotted as log-renin. Error bars are 95% CIs. The probability value refers to repeated-measures ANOVA across the 3 values.

![Figure 4](image2.png)  
**Figure 4.** Effects of bendroflumethiazide (Bendro) and spironolactone (Spiro) on plasma sodium and urea. Error bars are 95% CIs. The probability value refers to repeated-measures ANOVA across the 3 values.
in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), could be achieved alternatively by increasing the dose of thiazide.

In recent years, there has been a view that low-dose thiazides achieve maximal blood pressure reduction. However, the studies that led to this conclusion, mainly in younger patients with mild hypertension, are likely to have included only small numbers of low-renin patients in whom hypertension is due in part to inappropriate renal Na+ retention. In older or low-renin patients, studies using hydrochlorothiazide have suggested that 25 or even 50 mg is not maximal. In the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study, for instance, in which the average patient’s age was 65 years, the increase in dose from hydrochlorothiazide 25 to 50 mg was associated with a larger fall in blood pressure than from nifedipine 30 to 60 mg. The present study, in which dose and duration of treatment were separated as factors, appears to confirm that in low-renin patients, bendroflumethiazide 2.5 mg is submaximal. There are few head-to-head comparisons of bendroflumethiazide with hydrochlorothiazide (which is not available in the United Kingdom except in fixed-dose combinations), but the 2.5-mg dose is probably equivalent to between 12.5 and 25 mg hydrochlorothiazide. This statement is based on common usage and meta-analysis of their dose response in different trials. A Cochrane Review is in progress. If correct, and if treatment with a renin-angiotensin system blocker effectively converts a patient’s hypertension to a functionally low-renin type, it is notable that none of the angiotensin-converting enzyme inhibitor plus thiazide fixed-dose combinations includes a maximal dose of thiazide. This impression is supported by data for recently introduced angiotensin receptor blocker combinations with hydrochlorothiazide 25 mg, showing greater blood pressure reduction than the same angiotensin receptor blocker with hydrochlorothiazide 12.5 mg.

We included a renin-angiotensin system blocker, losartan, as a negative control. This was because we expected a number of patients to require background treatment with a calcium channel blocker. We therefore wished to confirm that patients with a low plasma renin measured while on a calcium channel blocker still behaved like low-renin patients, responding better to a diuretic than to a renin-angiotensin system blocker. As seen in Figure 2, this was indeed the case. The study was not powered or intended to compare losartan with the individual diuretics or doses.

One of the stimuli to rediscover or reinvestigate diuretics and doses has been the advent of high-throughput immunoluminometric assays for plasma renin mass. Thus, recognition of low-renin status in resistant hypertension is not just a research activity but is potentially cost-effective in the routine clinic. The “reinvention” of low-renin hypertension as normokalemic PHA could have discouraged renin measurement because the simultaneous assay for aldosterone remains a slower, more expensive radioimmunoassay. The reporting of elevated aldosterone-renin ratios in older low-renin patients also leads to an unnecessary burden of diagnostic tests—fludrocortisone suppression, computed tomographic/magnetic resonance imaging scan, adrenal vein sampling—in the search for curable adrenal adenomas, with the need for even further investigations in the 4% (at least) of patients with adrenal incidentalomas. Our previous study, in which screening of 846 community-based patients identified 119 with an elevated aldosterone-renin ratio and led to adrenal computed tomographic/magnetic resonance imaging in 78 of these, discovered only 2 adenomas. Some investigators have reported adrenal lesions that are detected only by adrenal vein sampling, but removal of such adrenals from normokalemic patients does not usually cure the hypertension. Others have therefore favored long-term medical treatment of normokalemic PHA with spironolactone. However, SALT suggests that the excellent blood pressure response to spironolactone predicted by a high aldosterone-renin ratio is no better than can be achieved by a diuretic acting upstream of the aldosterone receptor in the nephron. The ratio is driven by log-normally distributed renin rather than aldosterone, and SALT would seem to demote value of the ratio. A normal value may have use in excluding the diagnosis of PHA in low-renin, hypokalemic patients. A high ratio in the absence of hypokalemia is probably an expensive and misleading way of describing low-renin hypertension. Because it was impracticable in such a number, we did not
confirm nonsuppression by fludrocortisone in our patients. Because, however, the ratio has previously been shown to predict nonsuppression, and our patients came from the top decile of aldosterone-renin ratio in an unslected primary care population, they can be assumed to include virtually all patients who might have been diagnosed with normokalemic PHA in that population.3,15

Crossover studies offer the opportunity of comparing drugs in small numbers of selected subjects. Had we found, as hypothesized, that half of the patients responded better to spironolactone than bendroflumethiazide, we could have discovered who these patients were. However, although crossovers can lead to changes in treatment, as we saw in the United Kingdom after the Angiotensin-converting enzyme inhibitor, β-adrenergic blocker, Calcium channel blocker, Diuretic (ABCD) studies, there is usually a lag and a need for them to predict similar findings in larger, parallel group studies of less selected patients before their conclusions are adopted by guidelines.45–49,50 Clearly, neither spironolactone nor amiloride has the outcome data of thiazides in hypertension, even if most of the latter is for doses of thiazide closer to bendroflumethiazide 5 mg or hydrochlorothiazide 50 mg than for the lower doses used currently.32 Confirmation of our findings may lead to an expanded choice of diuretics and a possible return to using higher doses of thiazides as one of the choices. Key questions for further study will be whether K+-sparing diuretics avoid the glucose intolerance associated with thiazides and, if so, whether this translates into improved cardiovascular outcome.38,51

Finally, what if anything should be read into the apparently greater natriuretic responses to spironolactone than bendroflumethiazide? Because of the concordance both among all our indices of natriuresis and between the 2 K+-sparing diuretics, we think that the multiple results support the validity of the observation rather than its being a spurious product of the multiple testing. It has long been thought that thiazides work in part as vasodilators, although the mechanism remains uncertain.52 Our head-to-head comparison of a thiazide with other diuretics now seems to confirm this supposition, with possible further evidence being an apparently greater fall in diastolic blood pressure on bendroflumethiazide. If the diuretics acting downstream of thiazides in the nephron are indeed more effective at eliminating Na+ in low-renin patients, this finding suggests a role for aldosterone in causing the Na+ retention. The lack of hypokalemia, compared with true PHA, is to be expected because low-renin hypertension is almost certainly polygenic and aldosterone is but 1 of many players. Rather than diagnostic tests aimed at finding an unlikely cure for individual patients, systematic research can be encouraged that is directed at the many pathways controlling either aldosterone secretion or response.

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Disclosures
Dr Brown has received honoraria from and has served as a consultant for or on the advisory board of MSD. The other authors report no conflicts.

References
2. Lim PO, Jung RT, MacDonald TM. Screening for primary hyperaldosteronism in a hospital hypertensive population: is it the commonest form of secondary hypertension? J Hypertens. 1997;15:1531–1532.


**CLINICAL PERSPECTIVE**

The present study addressed 2 related questions. The first was whether low-dose thiazides are really adequate to achieve maximal blood pressure reduction. We considered this unlikely in patients with low-renin (salt-dependent) hypertension and hypothesized that underdosage contributes to apparent treatment resistance. The second question was whether primary hyperaldosteronism is frequently the cause of low-renin hypertension; in this case, treatment with an aldosterone antagonist should be more effective than a thiazide and prompt investigations for a possible adrenal adenoma. We designed a head-to-head comparison of diuretics in a group in which suspicion of primary hyperaldosteronism often arises: those with suppressed plasma renin but normal plasma K+ and aldosterone. In a 40-week double-blind, crossover rotation, bendroflumethiazide 2.5 mg (=hydrochlorothiazide 25 mg) was 5/2 mm Hg less effective in reducing blood pressure than either bendroflumethiazide 5 mg, spironolactone 50 mg, or amiloride 40 mg (P<0.005). These results show that doubling the thiazide dose is as effective as switching to spironolactone; the choice among effective diuretics in individual patients can be influenced by their tolerability. Because spironolactone was not superior in our patients despite their having an elevated aldosterone-renin ratio, the study supports abandonment of the ratio as a useful predictor of primary hyperaldosteronism in patients with normal K+ and aldosterone. It is likely that, even without renin measurement, our conclusions apply broadly to the 3 (overlapping) groups whose hypertension is often salt dependent: older patients, blacks, and patients receiving renin-system blockers. Clearly, further study is required, which can provide important information on the influence of diuretics on glucose tolerance.