Long-Term Antihypertensive Efficacy and Safety of the Oral Direct Renin Inhibitor Aliskiren

A 12-Month Randomized, Double-Blind Comparator Trial With Hydrochlorothiazide

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Background—Diuretics are recommended as first-line agents for the treatment of hypertension. This randomized, double-blind, multicenter study assessed the long-term efficacy and safety of the direct renin inhibitor aliskiren in comparison with the diuretic hydrochlorothiazide in patients with essential hypertension.

Methods and Results—After a 2- to 4-week placebo run-in, 1124 patients (mean sitting diastolic blood pressure [BP] 95 to 109 mm Hg) were randomized to aliskiren 150 mg (n = 459), hydrochlorothiazide 12.5 mg (n = 444), or placebo (n = 221) once daily. Forced titration (to aliskiren 300 mg or hydrochlorothiazide 25 mg) occurred at week 3; at week 6, patients receiving placebo were reassigned (1:1 ratio) to aliskiren 300 mg or hydrochlorothiazide 25 mg. From week 12, amlodipine 5 mg was added and titrated to 10 mg from week 18 for patients whose BP remained uncontrolled. Efficacy variables were analyzed for the intent-to-treat population with the use of the last observation carried forward method. BP reductions (mean sitting systolic BP/mean sitting diastolic BP) were significantly greater with aliskiren-versus hydrochlorothiazide-based treatment at week 26 (−20.3/−14.2 versus −18.6/−13.0 mm Hg; P < 0.05) and were also greater at week 52 (−22.1/−16.0 versus −21.2/−15.0 mm Hg; P < 0.05 for mean sitting diastolic BP). At the end of the monotherapy period (week 12), aliskiren 300 mg was superior to hydrochlorothiazide 25 mg in reducing BP (−17.4/−12.2 versus −14.7/−10.3 mm Hg; P < 0.001). Adverse event rates were similar with aliskiren- (65.2%) and hydrochlorothiazide-based therapy (61.5%). Hypokalemia was more frequent with hydrochlorothiazide-based therapy than aliskiren-based therapy (17.9% versus 0.9%; P < 0.001).

Conclusions—Aliskiren treatment, both as monotherapy and with optional addition of amlodipine, provided significantly greater BP reductions than the respective hydrochlorothiazide regimens. Aliskiren-based therapy was well tolerated. Direct renin inhibition with aliskiren therefore represents an effective option for the long-term treatment of essential hypertension. (Circulation. 2009;119:417-425.)

Key Words: blood pressure ■ direct renin inhibitor ■ diuretics ■ hypertension ■ renin
300 mg. Moreover, aliskiren provides additional BP lowering when used in combination with angiotensin-converting enzyme inhibitors,\textsuperscript{6} angiotensin receptor blockers,\textsuperscript{7} diuretics,\textsuperscript{8} and calcium channel blockers.\textsuperscript{9}

This study is the first to compare the long-term efficacy and safety of an aliskiren regimen with a hydrochlorothiazide regimen in patients with mild to moderate hypertension. Patients entered a 26-week randomized, double-blind, active-controlled, dose-titration phase (including a 12-week monotherapy phase to compare aliskiren versus hydrochlorothiazide head to head) followed by a 26-week blinded extension phase. Patients not achieving goal BP (\(\leq 140/90\) mm Hg) with aliskiren 300 mg or hydrochlorothiazide 25 mg could receive optional amlodipine addition (5 mg titrated to 10 mg, if required).

Methods

Patients

Patients eligible for inclusion were outpatients aged \(\geq 18\) years with essential hypertension (mean sitting diastolic BP [msDBP] \(\geq 90\) mm Hg and \(< 110\) mm Hg at the single-blind placebo run-in visit). At randomization, patients had to have a msDBP \(\geq 95\) mm Hg and \(< 110\) mm Hg and show a difference of \(\leq 10\) mm Hg in msDBP from their previous study visit. Patients with a history of severe cardiovascular or cerebrovascular disease or other severe life-threatening medical conditions were excluded.

The study protocol was approved by the appropriate local ethical review boards and was conducted in accordance with good clinical practice and in compliance with the Declaration of Helsinki. All patients gave written informed consent before undergoing any study procedure.

Study Design

This randomized, double-blind, parallel-group, active-controlled, dose-titration study was performed at 132 study centers in Belgium (11), Finland (6), Germany (34), Italy (43), the Netherlands (20), and Spain (18).

After screening and a 2-week washout period for patients taking antihypertensive treatment, patients entered a 2- or 4-week single-blind, placebo run-in to establish baseline BP and determine eligibility for randomization (Figure 1). Patients not meeting the eligibility requirements for BP after 2 weeks could continue for an additional 2 weeks to establish eligibility, after which patients not meeting the criteria were discontinued from the study.

Eligible patients were randomized in a 2:2:1 ratio to receive once-daily treatment with aliskiren 150 mg, hydrochlorothiazide 12.5 mg, or placebo. After an additional 3 weeks, patients in the placebo group were reassigned (1:1 ratio) to aliskiren 300 mg or hydrochlorothiazide 25 mg for 20 weeks. For patients not achieving goal BP (\(< 140/90\) mm Hg), addition of amlodipine 5 mg was permitted from week 12, and titration to amlodipine 10 mg was permitted from week 18 until study end (week 52; Figure 1).

Randomization by center was performed by the interactive voice response system provider with the use of a validated system that automates the random assignment of patients to randomization numbers. Randomization data were kept strictly confidential until the time of unblinding. Novartis Pharmaceuticals Corporation was responsible for managing the database and conducting audits.

Safety and Tolerability Assessments

Adverse events (AEs) were assessed at each study visit during the double-blind treatment period and at the optional placebo run-in visit. Physical examinations were performed at screening, at randomization, and at the week 26 and week 52 end points. Blood and urine samples for laboratory evaluations (hematology, blood chemistry, and urine measurements) were also obtained at these visits and at the week 12 end point. ECG assessments were performed at screening and at the week 26 and week 52 end points. All safety analyses were performed on the safety population, defined as all randomized patients who received at least 1 dose of study medication and with at least 1 postbaseline safety assessment. A data safety monitoring board was not used for this study because no interim analyses were conducted.

Efficacy Assessments

The primary objectives of this study were (1) to compare the long-term efficacy of an aliskiren-based regimen (with optional addition of amlodipine 5 or 10 mg to aliskiren 300 mg) with that of a hydrochlorothiazide-based regimen (with optional addition of

![Figure 1. Study design. HCTZ indicates hydrochlorothiazide.](http://circ.ahajournals.org/Downloaded from)
Results

Patient Characteristics

In total, 1275 patients entered the single-blind placebo run-in period, of whom 1124 were randomized to treatment with aliskiren 150 mg (n=459), hydrochlorothiazide 12.5 mg (n=444), or placebo (n=221). After 6 weeks, patients receiving placebo were reassigned to aliskiren 300 mg (n=108) or hydrochlorothiazide 25 mg (n=113). During the 6-week double-blind, placebo-controlled treatment period, 67 patients (6.0%) discontinued study treatment. Discontinuations were significantly higher (P<0.05) in the placebo group (21/221 patients, 9.5%) than in the aliskiren group (20/459 patients, 4.4%) but were not significantly greater than in the hydrochlorothiazide group (26/444, 5.9%; P=NS). The main reasons for discontinuation were AEs (aliskiren 8/459 [1.7%], hydrochlorothiazide 5/444 [1.1%], placebo 6/221 [2.7%]) and withdrawal of consent (aliskiren 6/459 [1.3%), hydrochlorothiazide 11/444 [2.5%], placebo 6/221 [2.7%]).

Of the 1124 patients randomized, 978 (87.0%) completed the 26-week double-blind treatment period (Figure 2). The most frequent reasons for discontinuation in this phase of the study were withdrawal of consent and AEs. The overall number of discontinuations was significantly higher with the hydrochlorothiazide regimen than with the aliskiren regimen (88/557, 15.8% versus 58/567, 10.2%; respectively; P<0.01), although no significant difference was found in the rate of discontinuations due to AEs (22/567 [3.9%] versus 29/557 [5.2%]; P=0.317).

In the hydrochlorothiazide group, 49 patients (9%) withdrew from the study from week 6 to week 26, of which 26 patients (4.8%) withdrew from week 12 to week 26. In the aliskiren group, 34 patients (6.1%) withdrew from the study from week 6 to week 26; 15 of these patients (2.7%) withdrew from week 12 to week 26. Data from these patients were analyzed at the respective end points according to the last observation carried forward method.

Of those patients completing the 26-week double-blind treatment period, 965 patients entered the 26-week blinded extension phase of the study. In total, 918 patients (95.1%) completed the 52 weeks of treatment. The main reasons for discontinuation in the extension phase of the study were AEs (aliskiren: 8/501, 1.6%; hydrochlorothiazide: 12/464, 2.6%) and withdrawal of consent (aliskiren: 5/501, 1.0%; hydrochlorothiazide: 8/464, 1.7%). Overall, the proportion of patients discontinuing in this phase of the study was higher with the hydrochlorothiazide regimen than with the aliskiren regimen (31/464, 6.7% versus 16/501, 3.2%, respectively; P<0.05).

No significant differences were found in baseline characteristics between the aliskiren and hydrochlorothiazide treatment groups (Table 1). The majority of patients were white (99.0%), and the mean duration of hypertension was 7.1 years. More than one third of patients (35.2%) were classified...
as obese (body mass index ≥30 kg/m²), and 10.9% of patients had diabetes mellitus (according to medical history). In total, 79.6% of patients received at least 1 concomitant (nonstudy drug) medication during the study. Baseline characteristics of patients who discontinued study treatment were generally similar to those of patients who completed the study. The only statistically significant difference was the duration of hypertension in patients receiving hydrochlorothiazide (least-squares mean difference [95% confidence interval] discontinued versus completed: 1.88 [0.53, 3.23]; P=0.006).

**Effects on msSBP and msDBP**

Substantial reductions in msSBP and msDBP were observed with aliskiren and hydrochlorothiazide monotherapy after 3 weeks of treatment (Figure 3). Further BP reductions observed during the dose-titration and optional add-on amlodipine phases were sustained until week 52 (Figure 3).

**Aliskiren Monotherapy**

At week 6, both the aliskiren and the hydrochlorothiazide monotherapies were superior to placebo in lowering msSBP.
Aliskiren vs Hydrochlorothiazide: 12-Month Study

Table 1. Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Aliskiren (n=567)</th>
<th>Hydrochlorothiazide (n=557)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56.1±10.9</td>
<td>55.7±10.9</td>
<td>0.544</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>307 (54.1)</td>
<td>312 (56.0)</td>
<td>0.529</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td>0.553</td>
</tr>
<tr>
<td>White</td>
<td>561 (98.9)</td>
<td>552 (99.1)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (0.9)</td>
<td>4 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.9±4.6</td>
<td>29.1±4.8</td>
<td>0.378</td>
</tr>
<tr>
<td>Obese patients, n (%)</td>
<td>208 (36.7)</td>
<td>188 (33.8)</td>
<td>0.273</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>231 (40.7)</td>
<td>247 (44.3)</td>
<td>0.545</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>62 (10.9)</td>
<td>60 (10.8)</td>
<td>0.930</td>
</tr>
<tr>
<td>Duration of hypertension, y</td>
<td>7.2±6.6</td>
<td>7.0±6.8</td>
<td>0.706</td>
</tr>
<tr>
<td>msSBP, mm Hg</td>
<td>154.2±11.2</td>
<td>154.3±11.0</td>
<td>0.887</td>
</tr>
<tr>
<td>msDBP, mm Hg</td>
<td>98.9±3.3</td>
<td>99.0±3.4</td>
<td>0.806</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>442 (78.1)</td>
<td>453 (81.2)</td>
<td>0.209</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD unless stated otherwise. Data shown are for the randomized population.

*Body mass index values were missing from 5 patients in the aliskiren group and 2 patients in the hydrochlorothiazide group.
†Obesity was defined as body mass index ≥30 kg/m².
‡Metabolic syndrome was defined according to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) criteria as any 3 of the following: waist circumference >102 cm for men or >88 cm for women; triglycerides ≥150 mg/dL; high-density lipoprotein cholesterol <40 mg/dL for men or <50 mg/dL for women; msSBP ≥130 mm Hg or msDBP ≥85 mm Hg; fasting glucose ≥110 mg/dL.
§By medical history.
||Aliskiren, n=566; hydrochlorothiazide, n=558.

(placebo-subtracted least-squares mean±SEM difference: −7.7±1.0 and −4.7±1.0 mm Hg, P<0.0001 for aliskiren and hydrochlorothiazide, respectively) and msDBP (−3.4±0.6 mm Hg, P<0.0001 and −1.6±0.6 mm Hg, P<0.05).

At week 12, aliskiren monotherapy was statistically superior to hydrochlorothiazide monotherapy in reducing both msSBP (−17.4±0.6 versus −14.7±0.6 mm Hg) and msDBP (−12.2±0.4 versus −10.3±0.4 mm Hg, P<0.001 for both; Figure 4A). Aliskiren monotherapy provided significantly greater BP response (73.8% versus 65.6%, P<0.01; Figure 5) and control rates (60.0% versus 50.6%, P<0.01) compared with hydrochlorothiazide monotherapy.

Combination Therapy

At week 26, 46.4% of patients in the aliskiren group required the addition of amlodipine for BP control compared with 53% of patients in the hydrochlorothiazide group. Similar results were seen at week 52 (47.5% and 52.5% in the aliskiren and hydrochlorothiazide groups, respectively; P=0.119); at this time point, titration to the higher dosage of amlodipine was required by 20.0% and 23.3% of patients in the aliskiren and hydrochlorothiazide groups, respectively (P=0.225).

At week 26, the aliskiren regimen provided significantly superior reductions from baseline in msSBP (least squares mean±SEM: −20.3±0.6 versus −18.6±0.6 mm Hg, P<0.05) and msDBP (−14.2±0.4 versus −13.0±0.4 mm Hg, P<0.01) compared with the hydrochlorothiazide regimen (Figure 4B). The superior reduction in msDBP with the aliskiren regimen compared with the hydrochlorothiazide regimen was maintained at week 52 (−16.0±0.4 versus −15.0±0.4 mm Hg, P<0.05); reductions in msSBP with the aliskiren regimen were not inferior to those with the hydrochlorothiazide regimen at this time point but were not statistically superior (−22.1±0.6 versus −21.2±0.6 mm Hg, P<0.0001 for noninferiority; Figure 4C). Responder rates were significantly greater with the aliskiren regimen than with the hydrochlorothiazide regimen at both week 26 (85.5%
versus 80.3%, \( P<0.05 \) and week 52 (88.8% versus 82.5%, \( P<0.01 \)) (Figure 5).

**Effect of Age on BP-Lowering Efficacy of Treatment**

A post hoc analysis showed a significant age-treatment interaction for msSBP at week 52 (\( P<0.045 \)) but not at week 26. No significant age-treatment interaction was detected at either week 26 or week 52 for msDBP. Analysis of BP changes by age group showed that at week 52, the aliskiren regimen provided significantly greater reductions in msSBP (but not msDBP) in elderly (\( \geq 65 \) years) and very elderly (\( \geq 75 \) years) patients than in younger patients (Table 2). Reductions in msSBP and msDBP with the hydrochlorothiazide regimen were similar across all age groups (Table 2).

**Safety and Tolerability**

The proportion of patients who experienced AEs during the 6-week placebo-controlled period was similar in the aliskiren monotherapy, hydrochlorothiazide monotherapy, and placebo groups (26.4%, 24.5%, and 28.5%, respectively). During the 52-week double-blind treatment period (excluding the 6-week placebo-controlled period), AEs were reported by a similar proportion of patients receiving the aliskiren and hydrochlorothiazide regimens (Table 3). Most AEs were mild or moderate in intensity.

Three serious AEs were considered by the investigator to be related to the study medications (dyspepsia, aliskiren 150 mg; myocardial infarction, placebo; moderate hypokalemia, hydrochlorothiazide 25 mg); all 3 patients were discontinued from the study. No deaths occurred during the 52-week, double-blind treatment period. One patient died from a stroke after discontinuing from the single-blind placebo run-in period; 1 patient in the aliskiren group died from acute...
were observed in the hydrochlorothiazide group than in the aliskiren group (change from baseline to week 26: 30.4 versus 4.9 μmol/L; least-squares mean difference: -0.03, P<0.0001).

Discussion
This study is the first to compare the antihypertensive efficacy, safety, and tolerability of the direct renin inhibitor aliskiren with the diuretic hydrochlorothiazide. The major finding of the study was that aliskiren 300 mg monotherapy was superior to hydrochlorothiazide 25 mg monotherapy in lowering BP. In addition, during long-term treatment, aliskiren-based therapy (with optional addition of amlodipine) provided significantly greater BP reductions than hydrochlorothiazide-based therapy. Responder rates were significantly higher with aliskiren treatment, either alone or with amlodipine addition, compared with the respective hydrochlorothiazide treatments.

Hydrochlorothiazide was chosen as the comparator in this study because JNC 7 guidelines recommend thiazide-type diuretics as the preferred initial agent for the treatment of hypertension.1 In the present study, the aliskiren regimen was statistically superior to the hydrochlorothiazide regimen in lowering SBP and DBP after 6 months of treatment. After 1 year, aliskiren-based therapy provided superior reductions in DBP and numerically greater reductions in SBP compared with the hydrochlorothiazide regimen. Furthermore, before the optional addition of amlodipine, treatment for 12 weeks with aliskiren 300 mg monotherapy provided significantly superior reductions in office SBP and DBP than hydrochlorothiazide 25 mg monotherapy. In a previous study of similar design, aliskiren 300 mg monotherapy was more effective than ramipril 10 mg monotherapy in reducing BP after 12 weeks of treatment; after an additional 14 weeks, aliskiren-based treatment (with optional addition of hydrochlorothiazide) provided superior reductions in SBP and DBP over ramipril-based therapy, despite a lower frequency of add-on treatment (46.4% versus 49.5% in the aliskiren and ramipril groups, respectively).11

Treatment with ≥2 antihypertensive agents is commonly required to achieve BP control, and a recent survey of nearly 4000 US patients with hypertension reported that 64% were receiving combination therapy.2 The present study shows that an aliskiren regimen provides effective BP lowering that is maintained during long-term treatment in patients with mild to moderate hypertension and also demonstrates that amlo-
dipine (which was administered in nearly half [47.5%] of patients) is an effective add-on agent for a renin system inhibitor. Furthermore, the tolerability profile of the aliskiren/amlodipine combination, which is as important as efficacy, was similar to other aliskiren-based regimens.7,11

A significant age-treatment interaction was demonstrated for msSBP at week 52, and a post hoc analysis showed that long-term treatment with the aliskiren regimen was particularly effective for reducing SBP in elderly and very elderly patients. In contrast, reductions in SBP with the hydrochlorothiazide regimen were similar across all age groups. SBP increases with age and is associated with increased cardiovascular morbidity and mortality.12 Moreover, clinical trials have shown that lowering SBP lowers the risk of stroke, myocardial infarction, and other cardiovascular events in elderly patients.13

Aliskiren treatment, either as monotherapy or in combination with amlodipine, was well tolerated over 12 months; the overall incidence of AEs was similar with the aliskiren and hydrochlorothiazide treatment regimens. However, the proportion of patients with hypokalemia (serum potassium <3.5 mmol/L) was significantly greater with the hydrochlorothiazide regimen; hypokalemia is a well-established side effect of thiazide diuretics and has been associated with the development of impaired glucose tolerance.14 Elevated levels of serum potassium (>5.5 mmol/L), a known effect of renin system inhibitors, occurred at a higher frequency with the aliskiren regimen, although no patients discontinued the study because of hyperkalemia. After 6 weeks (end of the placebo phase), the incidence of AEs in the aliskiren monotherapy group was similar to placebo; this is consistent with previous aliskiren studies, in which once-daily aliskiren doses up to 300 mg demonstrated an overall tolerability profile comparable to placebo.15,16

It is important to note the limitations of the study. First, this was a study of achieved BP reductions and not a comparison of clinical outcomes. Because the selection criteria were based on DBP rather than SBP, the mean age of the study population was relatively low (55.9 years). This contrasts with the majority of patients seen in the physician’s clinic who tend to be older individuals with systolic hypertension. However, a post hoc analysis demonstrated the antihypertensive efficacy of the aliskiren regimen in the subgroup of elderly patients and showed that aliskiren provided significantly greater reductions in msSBP in elderly patients than in younger patients. Although hydrochlorothiazide is most commonly used at doses of 12.5 to 25 mg/d for the treatment of hypertension, the drug can be used at doses up to 50 mg/d. In this study, no comparisons were made with hydrochlorothiazide doses >25 mg/d, and therefore no conclusions can be drawn in regard to the effects of higher doses of hydrochlorothiazide relative to aliskiren. This was a predominantly white population, and it may therefore not be appropriate to extrapolate the results of the present study to other racial subgroups. However, a pooled analysis of aliskiren studies conducted in a total of 7045 patients with hypertension showed no effect of race on the antihypertensive efficacy and safety of aliskiren.5 Finally, although mandated by health authorities during the design of the present study, the last observation carried forward method of analysis could be considered a limitation.

In conclusion, aliskiren-based therapy (with optional add-on amlodipine) provided significantly greater BP reductions than hydrochlorothiazide-based therapy during long-term (6 months) treatment in patients with hypertension. Furthermore, aliskiren 300 mg monotherapy was superior to hydrochlorothiazide 25 mg monotherapy in lowering BP. Aliskiren treatment therefore provides more effective BP lowering than a thiazide-type diuretic, the drug class recommended by JNC 7 guidelines as first-line therapy for the treatment of hypertension.

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CLINICAL PERSPECTIVE

Low-dose diuretics, either alone or in combination with other classes of antihypertensive agents, are recommended by US Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines as initial therapy for patients with stage 1 hypertension. Aliskiren is the first in a new class of direct renin inhibitors and has been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of hypertension at once-daily doses of 150 and 300 mg. This study in 1124 patients with mild to moderate hypertension is the first to compare the long-term antihypertensive efficacy, safety, and tolerability of an aliskiren-based regimen with a hydrochlorothiazide-based regimen. We showed that aliskiren 300 mg monotherapy was superior to hydrochlorothiazide 25 mg monotherapy in lowering blood pressure. In addition, an aliskiren-based regimen (with optional addition of amlodipine as needed to achieve blood pressure control) provided significantly greater blood pressure reductions and responder rates than a hydrochlorothiazide-based regimen (also with optional amlodipine addition) over long-term treatment. The incidence of adverse events was similar in the 2 treatment groups, but aliskiren-based treatment was associated with a markedly lower incidence of clinically significant hypokalemia than hydrochlorothiazide-based treatment. This study demonstrates that aliskiren-based treatment is a highly effective and well-tolerated option for the long-term treatment of hypertension.
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SUPPLEMENTAL MATERIAL

Appendix

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