ORIGINAL ARTICLE

Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

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ABSTRACT

BACKGROUND

This study was undertaken to determine whether use of the direct renin inhibitor aliskiren would reduce cardiovascular and renal events in patients with type 2 diabetes and chronic kidney disease, cardiovascular disease, or both.

METHODS

In a double-blind fashion, we randomly assigned 8561 patients to aliskiren (300 mg daily) or placebo as an adjunct to an angiotensin-converting–enzyme inhibitor or an angiotensin-receptor blocker. The primary end point was a composite of the time to cardiovascular death or a first occurrence of cardiac arrest with resuscitation; nonfatal myocardial infarction; nonfatal stroke; unplanned hospitalization for heart failure; end-stage renal disease, death attributable to kidney failure, or the need for renal-replacement therapy with no dialysis or transplantation available or initiated; or doubling of the baseline serum creatinine level.

RESULTS

The trial was stopped prematurely after the second interim efficacy analysis. After a median follow-up of 32.9 months, the primary end point had occurred in 783 patients (18.3%) assigned to aliskiren as compared with 732 (17.1%) assigned to placebo (hazard ratio, 1.08; 95% confidence interval [CI], 0.98 to 1.20; P=0.12). Effects on secondary renal end points were similar. Systolic and diastolic blood pressures were lower with aliskiren (between-group differences, 1.3 and 0.6 mm Hg, respectively) and the mean reduction in the urinary albumin-to-creatinine ratio was greater (between-group difference, 14 percentage points; 95% CI, 11 to 17). The proportion of patients with hyperkalemia (serum potassium level, ≥6 mmol per liter) was significantly higher in the aliskiren group than in the placebo group (11.2% vs. 7.2%), as was the proportion with reported hypotension (12.1% vs. 8.3%) (P<0.001 for both comparisons).

CONCLUSIONS

The addition of aliskiren to standard therapy with renin–angiotensin system blockade in patients with type 2 diabetes who are at high risk for cardiovascular and renal events is not supported by these data and may even be harmful. (Funded by Novartis; ALTITUDE ClinicalTrials.gov number, NCT00549757.)

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MORTALITY ASSOCIATED WITH TYPE 2 diabetes remains nearly twice that when diabetes is absent.[1] Complications of diabetes, particularly renal and cardiovascular disease, substantially increase the risk of subsequent severe illness and death. When a patient has both renal and cardiovascular disease, the risk is magnified further.[2,3] Blood-pressure lowering is beneficial in slowing renal-disease progression, reducing cardiovascular disease events, and preventing premature death.[4] Renin–angiotensin–aldosterone system (RAAS) blockers are highly effective, with apparent benefits extending beyond simple blood-pressure lowering[5-8]; such agents have become the preferred first-line interventions in high-risk persons with diabetes.

Theoretically, dual RAAS blockade should be more effective than a single agent, yet the results of both the Valsartan in Acute Myocardial Infarction Trial and the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial did not support combined therapy with an angiotensin-converting–enzyme (ACE) inhibitor and an angiotensin-receptor blocker (ARB).[9,10] The lack of benefit could be due to the deleterious effects of aldosterone escape and compensatory renin activation.[11-13] Aliskiren is a renin inhibitor that reduces plasma renin activity, and aliskiren combined with an ARB, as compared with an ARB alone, has been shown to result in a greater decrease in albuminuria in diabetic renal disease.[14] The effect of dual therapy on hard renal outcomes (e.g., end-stage renal disease and death from kidney failure) and on cardiovascular disease itself is unknown.

The present trial was designed to determine the effectiveness and safety of direct renin inhibition with aliskiren, as compared with placebo, with respect to fatal and nonfatal renal and cardiovascular events in patients with type 2 diabetes who were at high risk for these complications and were already taking an ACE inhibitor or an ARB per standard practice. Thus, our trial was designed to evaluate the safety of dual RAAS blockade.

METHODS

STUDY DESIGN

The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE) was a randomized, double-blind, placebo-controlled trial conducted at 853 centers in 36 countries. Details of the trial design and methods have been published previously,[15] and the protocol and its amendments are available with the full text of this article at NEJM.org. The trial was approved by the ethics committee or institutional review board at each participating center. All patients provided written informed consent. We enrolled men and women 35 years of age or older with type 2 diabetes and evidence of microalbuminuria, macroalbuminuria, or cardiovascular disease, as described in Table S1 in the Supplementary Appendix, available at NEJM.org.

The primary outcome was a composite of death from cardiovascular causes or the first occurrence of cardiac arrest with resuscitation; nonfatal myocardial infarction; nonfatal stroke; unplanned hospitalization for heart failure; end-stage renal disease, death attributable to kidney failure, or the need for renal-replacement therapy with no dialysis or transplantation available or initiated; or a serum creatinine value that was at least double the baseline value and that exceeded the upper limit of the normal range (>80 μmol per liter [0.9 mg per deciliter] in women and >106 μmol per liter [1.2 mg per deciliter] in men), sustained for at least a month.[15] The secondary cardiovascular outcome was a composite of all five cardiovascular components of the primary composite end point. Similarly, the secondary renal outcome was a composite of the renal components of the primary composite end point. Confirmatory data for all potential study end points were collected from the study investigators and adjudicated by a central adjudication committee at Brigham and Women's Hospital, whose members were not aware of the study-group assignments. End points were adjudicated according to standard criteria, as described previously[15] (Table S2 in the Supplementary Appendix).

The executive committee designed the trial and wrote the study protocol in collaboration with coauthors who are employees of Novartis. The first author drafted the report with contributions from all authors, who also reviewed and approved the manuscript. All authors jointly decided to submit the manuscript for publication, and all authors vouch for the accuracy of the data and the fidelity of the study to the protocol. The sponsor (Novartis) collected and managed the data with oversight by the executive committee. Independent statisticians at Axio Research prepared the

interim unblinded reports for the independent data and safety monitoring committee, which oversaw patient safety and the quality of trial conduct. The full data set was transferred to Brigham and Women's Hospital at study completion. The statistical analysis was performed by the sponsor and verified by the independent group at Brigham and Women's Hospital.

RUN-IN PERIOD, RANDOMIZATION, AND FOLLOW-UP

Eligible patients entered a 4-to-12-week screening period and were subsequently randomly assigned to receive aliskiren or placebo in addition to standard treatment and were followed for a median of 32.9 months, as described in detail in the Methods section in the Supplementary Appendix. The initial dose of aliskiren, 150 mg once daily, was increased to 300 mg once daily at 4 weeks after randomization if there were no safety concerns. The investigators adhered to clinical-practice guidelines for hyperkalemia management (Table S3 in the Supplementary Appendix).

INTERIM ANALYSES AND DATA MONITORING

An independent data and safety monitoring committee (see the Acknowledgments section in the Supplementary Appendix) met twice yearly; two formal interim analyses were conducted when approximately one third and two thirds of the total primary composite events had occurred. At the second interim efficacy analysis and the seventh interim safety analysis (December 14, 2011), the independent data and safety monitoring committee recommended termination of the study medication, on the basis of their assessment that the excess risk of adverse events in the aliskiren group could not be offset by a reduction in major cardiovascular and renal events (Table S4 and letter from the data and safety monitoring committee in the Supplementary Appendix). A futility analysis was neither planned for the trial nor included in the charter of the data and safety monitoring committee. However, the statistician on the committee performed a futility analysis and calculated the conditional power. The supply of study medication was stopped immediately, and all investigators were instructed to stop trial medication in each patient no later than January 6, 2012. All end points occurring before or on January 31, 2012, are noted in this report. After trial termination, patients were asked to return for a safety-assessment visit and were invited to participate in a yearlong safety-extension study (without the use of the study drugs).

STATISTICAL ANALYSIS

The trial was designed to enroll 8600 patients and to continue until 1620 patients reached the primary composite end point, with the assumption of an annual event rate of 8% in the placebo group, in order to provide 90% power to detect a reduction in risk of 15% or more at a significance level of 5%. The sample size was adjusted to include an assumed 8% total dropout rate, with two equally spaced interim analyses based on the Lan–DeMets alpha spending function approximating the O'Brien–Fleming boundaries.

The main analysis used the time-to-first-event approach, based on the Cox proportional-hazards model stratified according to history of cardiovascular disease (yes or no) and baseline urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 or higher (yes or no), as prespecified in the protocol. Confidence intervals, hazard ratios, and nominal P values were obtained on the basis of the above model. All primary outcome analyses were confirmed by an independent statistician at Brigham and Women's Hospital. All reported P values are two-sided and have not been adjusted for multiple comparisons. Holm's multiple-comparison procedure was used for the comparisons of secondary end points. Estimates of cumulative event rates are shown as Kaplan–Meier curves. All comparisons were based on the intention-to-treat principle (with data from the full analysis set). The consistency of the study-drug effect in prespecified subgroups was assessed with the use of the same Cox model, with an additional test for the interaction between study drug and each subgroup covariate.

For the principal analysis of the primary and secondary composite end points, 0.046 was established as the threshold for statistical significance after accounting for the two interim efficacy analyses (performed when 35% and 69% of the events had occurred). For other analyses, 0.05 was considered to indicate statistical significance. Assessments of safety were based on data from the patients who received at least one dose of the study drug. A repeated-measure analysis of covariance was used to assess the overall difference in mean systolic blood pressure and mean diastolic blood pressure between the study groups.

RESULTS

STUDY POPULATION

Of 21,157 patients screened at 838 centers in 36 countries, 8606 (40.7%) were randomly assigned to aliskiren or placebo between October 10, 2007, and June 23, 2010. After randomization, 45 participants were excluded from the analysis (22 underwent randomization by mistake, and 23 were excluded because of violations in Good Clinical Practice guidelines at two sites, resulting in the closure of both sites), leaving a study population

of 8561 patients who could be evaluated (Fig. S1 in the Supplementary Appendix).

Baseline characteristics were similar in the aliskiren and placebo groups (Table 1, and Table S5 in the Supplementary Appendix). Eighty-two percent of patients in each group had had diabetes for at least 5 years, and 8086 patients (94.5%) had received a diagnosis of hypertension. Overall, 3619 patients (42.3%) had known cardiovascular diseases other than hypertension, mainly coronary artery disease. Nearly all patients had chronic kidney disease (98.0%), and 84.1% had proteinuria. A total of 40.8% of patients had a baseline systolic blood pressure higher than 140 mm Hg, and 12.2% had a diastolic blood pressure higher than 85 mm Hg. Participants with cardiovascular disease were receiving more intensive treatment at baseline than those without such disease — 71.2% were taking diuretics (vs. 57.3% of those without cardiovascular disease), 80.5% were receiving antiplatelet agents (vs. 48.1%), 69.5% were taking beta-blockers (vs. 35.9%), and 79.6% were taking statins (vs. 54.6%). An exception was that fewer patients with cardiovascular disease were taking calcium-channel blockers (55.7% vs. 65.5%). A total of 56.7% of all patients were taking insulin. Medications at baseline are shown in Table S6 in the Supplementary Appendix. During the trial, the use of most concomitant antihypertensive drugs remained nearly unchanged (Table S7 in the Supplementary Appendix), as did the dose of the most commonly used ACE inhibitors and ARBs (data not shown).

At 2 months after randomization, 84.1% of patients in the aliskiren group were taking the higher dose (300 mg daily), and 86.3% of patients in the placebo group were taking the study medication (P=0.006). At 1 year, 84.6% of surviving participants assigned to aliskiren were taking the study medication, as compared with 87.3% of those assigned to placebo (P<0.001). At 2 years, these percentages were 74.1% and 78.7% (P<0.001), respectively, and at 3 years, 65.7% and 70.1% (P=0.009).

STUDY FOLLOW-UP

A total of 123 patients in the aliskiren group (2.9%) and 99 in the placebo group (2.3%) were lost to follow-up (including withdrawal of consent) (Fig. S1 in the Supplementary Appendix); information on vital status was available for

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Aliskiren (N=4274)	Placebo (N=4287)
Age — yr	64.6±9.6	64.4±9.9
Female sex — no. (%)	1393 (32.6)	1342 (31.3)
Current smoker — no. (%)	557 (13.0)	571 (13.3)
Body-mass index†	29.9±5.8	29.9±5.9
Blood pressure in the sitting position — mm Hg		
Systolic	137.3±16.2	137.3±16.7
Diastolic	74.1±9.8	74.3±9.9
Glycated hemoglobin — %	7.8±1.6	7.8±1.6
Estimated GFR‡		
Mean — ml/min/1.73 m²	57.0±21.9	57.0±23.0
Category — no. (%)		
<30 ml/min/1.73 m²	92 (2.2)	118 (2.8)
≥30 to <45 ml/min/1.73 m²	1244 (29.1)	1294 (30.2)
≥45 to <60 ml/min/1.73 m²	1534 (35.9)	1494 (34.8)
≥60 ml/min/1.73 m²	1402 (32.8)	1381 (32.2)
Missing data	2 (<0.1)	0
Urinary albumin-to-creatinine ratio		
Geometric mean — mg/g	206	208
Interquartile range — mg/g	57–866	58–912
Category — no. (%)		
<20 mg/g	614 (14.4)	620 (14.5)
≥20 to <200 mg/g	1105 (25.9)	1089 (25.4)
≥200 mg/g	2486 (58.2)	2517 (58.7)
Missing data	69 (1.6)	61 (1.4)

* Plus–minus values are means ±SD unless otherwise noted. There were no significant differences (at P<0.05) between the two groups for any of the variables listed.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The estimated glomerular filtration rate (GFR) was calculated with the use of the modified Modification of Diet in Renal Disease formula for isotope dilution mass spectrometry–traceable serum creatinine values.[16]

Table 2. Prespecified Primary and Secondary Composite Outcomes and Deaths.*

Outcome	Aliskiren (N=4274)	Placebo (N=4287)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Primary composite outcome	783 (18.3)	732 (17.1)	1.08 (0.98–1.20)	0.12
Death from cardiovascular causes	246 (5.8)	215 (5.0)	1.16 (0.96–1.39)	0.12
Cardiac arrest with resuscitation	19 (0.4)	8 (0.2)	2.40 (1.05–5.48)	0.04
Myocardial infarction (fatal or nonfatal)	147 (3.4)	142 (3.3)	1.04 (0.83–1.31)	0.72
Stroke (fatal or nonfatal)	147 (3.4)	122 (2.8)	1.22 (0.96–1.55)	0.11
Unplanned hospitalization for heart failure	205 (4.8)	219 (5.1)	0.95 (0.78–1.14)	0.56
ESRD, death attributable to kidney failure, or loss of kidney function‡	121 (2.8)	113 (2.6)	1.08 (0.84–1.40)	0.56
Doubling of baseline serum creatinine	210 (4.9)	217 (5.1)	0.97 (0.80–1.17)	0.75
Cardiovascular composite outcome	590 (13.8)	539 (12.6)	1.11 (0.99–1.25)	0.09
Renal composite outcome	257 (6.0)	251 (5.9)	1.03 (0.87–1.23)	0.74
Death from any cause	376 (8.8)	358 (8.4)	1.06 (0.92–1.23)	0.42

* A patient may have had multiple cardiovascular and renal events of different types. All composite outcomes reflect only the first occurrence of any of the components.
† P values have not been adjusted for multiple comparisons.
‡ Loss of kidney function was defined by the need for renal-replacement therapy with no dialysis or transplantation available or initiated. ESRD denotes end-stage renal disease.

98.3% of the maximum possible follow-up time in both study groups. The median follow-up periods for vital status for the primary cardiorenal composite outcome, the cardiovascular composite outcome, and the renal composite outcome were 2.8, 2.8, and 2.7 years, respectively.

PRIMARY CARDIORENAL COMPOSITE OUTCOME

The primary outcome occurred in 783 participants in the aliskiren group (18.3%) and 732 in the placebo group (17.1%) (Table 2 and Fig. 1A). The hazard ratio for this outcome in the aliskiren group as compared with the placebo group was 1.08 (95% confidence interval [CI], 0.98 to 1.20; P=0.12). The study-drug effect was consistent across all prespecified subgroups except for baseline serum potassium concentration and status with respect to biguanide use (Fig. S2 in the Supplementary Appendix). Patients with a baseline potassium level of 5.0 mmol per liter or higher had a greater risk of the primary composite outcome with aliskiren than with placebo, as compared with patients with a potassium level below 5.0 mmol per liter (Table S8 in the Supplementary Appendix).

SECONDARY CARDIOVASCULAR COMPOSITE OUTCOME

The secondary cardiovascular composite outcome occurred in 590 participants in the aliskiren group (13.8%) and 539 in the placebo group (12.6%);

the hazard ratio in the aliskiren group was 1.11 (95% CI, 0.99 to 1.25; P=0.09) (Table 2 and Fig. 1B). All components of the cardiovascular outcome, with the exception of unplanned hospitalization for heart failure, occurred more frequently in the aliskiren group, and the excess of patients who had cardiac arrest with resuscitation (19 in the aliskiren group vs. 8 in the placebo group) was nominally significant (Table 2).

SECONDARY RENAL COMPOSITE OUTCOME

The secondary renal composite outcome occurred in 257 participants in the aliskiren group (6.0%) and 251 in the placebo group (5.9%); the hazard ratio in the aliskiren group was 1.03 (95% CI, 0.87 to 1.23; P=0.74) (Table 2 and Fig. 1C). There were no significant differences between study groups for any component of the renal outcome (Table 2).

DEATHS

The number of deaths from any cause did not differ significantly between the study groups (Table 2). The number of adjudicated deaths that were sudden (or presumed to be sudden) was 119 in the aliskiren group and 102 in the placebo group.

CHANGES IN BLOOD PRESSURE AND KIDNEY FUNCTION

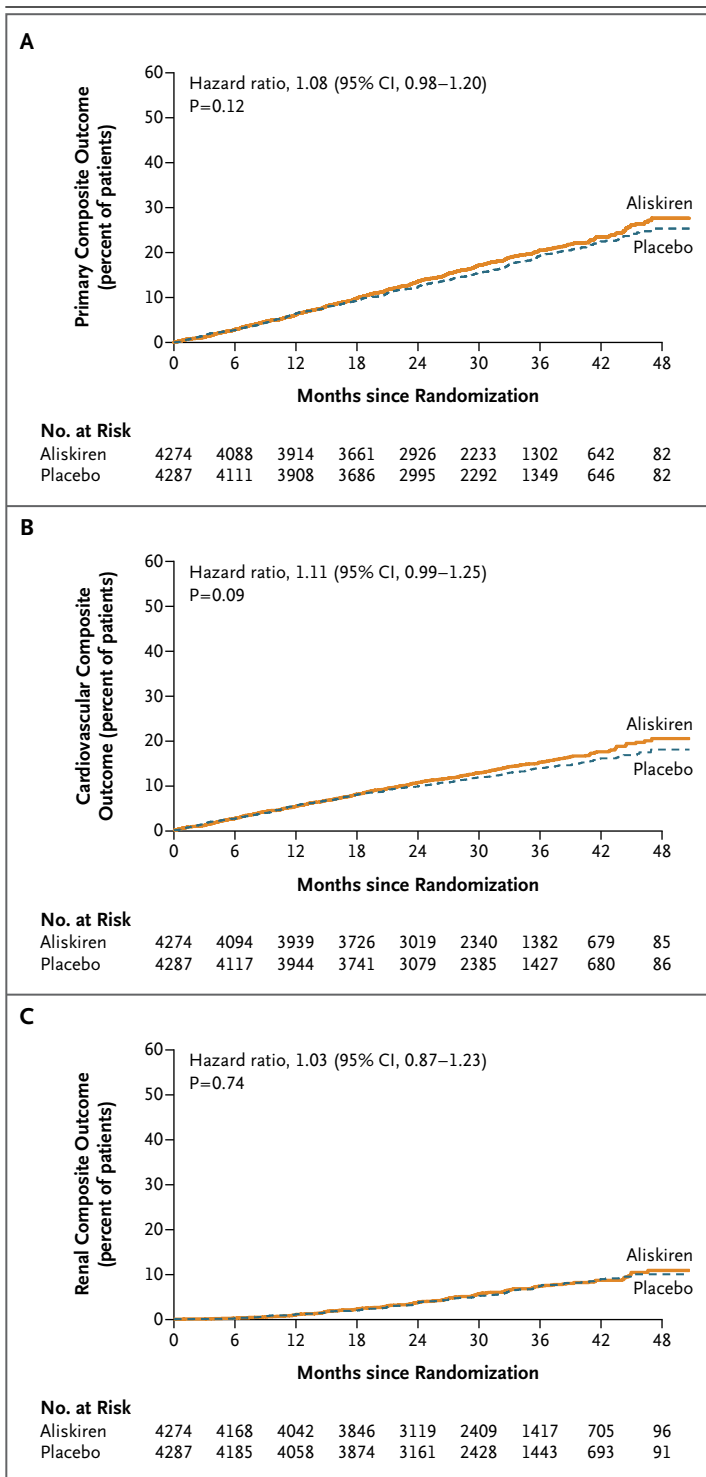Blood pressure increased during follow-up, but the overall increase was smaller with aliskiren

Figure 1. Kaplan–Meier Curves for the Primary Composite Outcome, Secondary Cardiovascular Composite Outcome, and Secondary Renal Composite Outcome.

The primary composite outcome was the time to cardiovascular death or the first occurrence of cardiac arrest with resuscitation, nonfatal myocardial infarction, nonfatal stroke, unplanned hospitalization for heart failure, end-stage renal disease or death from renal causes, or a doubling of the baseline serum creatinine concentration that was sustained for at least a month (Panel A). The secondary cardiovascular outcome was a composite of all five cardiovascular elements in the primary composite end point (Panel B). Similarly, the secondary renal outcome was a composite of the renal elements in the primary composite end point (Panel C).

tween baseline and 6 months was 1.5 mm Hg (95% CI, 1.0 to 2.0) with aliskiren versus 3.4 mm Hg (95% CI, 2.9 to 3.9) with placebo, for a difference of 1.9 mm Hg (95% CI, 1.2 to 2.6; P<0.001). The change in diastolic pressure was −0.2 mm Hg (95% CI, −0.5 to 0.0) versus 0.7 mm Hg (95% CI, 0.5 to 1.0), for a difference of 1.0 mm Hg (95% CI, 0.6 to 1.4; P<0.001).

The overall urinary albumin-to-creatinine ratio decreased more with aliskiren than with placebo (between-group difference, 14 percentage points; 95% CI, 11 to 17) (Fig. S3 in the Supplementary Appendix). The decrease between baseline and 6 months was 16% (95% CI, 13 to 18) with aliskiren versus 5% (95% CI, 3 to 8) with placebo, for a difference of 11 percentage points (95% CI, 7 to 15; P<0.001).

The adjusted least-squares mean decrease in the estimated glomerular filtration rate (GFR) between baseline and 6 months was 2.45 ml per minute per 1.73 m² of body-surface area (95% CI, 2.11 to 2.78) with aliskiren versus 1.29 ml per minute per 1.73 m² (95% CI, 0.95 to 1.62) with placebo, for a difference of 1.16 ml per minute per 1.73 m² (95% CI, 0.69 to 1.63; P<0.001) (Fig. S3 in the Supplementary Appendix).

ADVERSE EVENTS AND DISCONTINUATION OF THE STUDY DRUG

During the trial, 1445 patients assigned to aliskiren (33.8%) and 1218 assigned to placebo (28.4%) discontinued the study drug permanently for a reason other than death (P=0.001). In the aliskiren group, 563 patients (13.2%) discontinued the study drug because of an adverse event, as compared with 437 patients (10.2%) in the placebo group (P<0.001).

than with placebo (between-group differences, (1.3 mm Hg systolic and 0.6 mm Hg diastolic) (Fig. S3 in the Supplementary Appendix). The adjusted least-squares mean increase in systolic pressure be-

Table 3. Most Commonly Reported Adverse Events and Study-Drug Discontinuation.*

Event	Any Event Reported		P Value	Event Leading to Permanent Study-Drug Discontinuation		P Value
	Aliskiren (N=4272)	Placebo (N=4285)		Aliskiren (N=4272)	Placebo (N=4285)	
	no. of patients (%)			*no. of patients (%)*		
Hyperkalemia	1670 (39.1)	1244 (29.0)	<0.001	205 (4.8)	111 (2.6)	<0.001
Peripheral edema	686 (16.1)	706 (16.5)	0.60	11 (0.3)	7 (0.2)	0.34
Hypotension	519 (12.1)	357 (8.3)	<0.001	28 (0.7)	13 (0.3)	0.02
Diarrhea	417 (9.8)	312 (7.3)	<0.001	11 (0.3)	7 (0.2)	0.34
Hypertension	429 (10.0)	469 (10.9)	0.17	3 (0.1)	9 (0.2)	0.15
Renal impairment	418 (9.8)	371 (8.7)	0.07	65 (1.5)	54 (1.3)	0.30
Nasopharyngitis	405 (9.5)	383 (8.9)	0.39	1 (<0.1)	0	NA
Hypoglycemia	393 (9.2)	341 (8.0)	0.04	1 (<0.1)	3 (0.1)	NA
Back pain	363 (8.5)	353 (8.2)	0.67	1 (<0.1)	2 (<0.1)	NA
Dizziness	327 (7.7)	314 (7.3)	0.57	4 (0.1)	4 (0.1)	NA
Urinary tract infection	326 (7.6)	288 (6.7)	0.10	4 (0.1)	2 (<0.1)	NA
Anemia	316 (7.4)	307 (7.2)	0.68	0	0	—
Pain in extremity	302 (7.1)	317 (7.4)	0.56	1 (<0.1)	2 (<0.1)	NA
Arthralgia	302 (7.1)	313 (7.3)	0.67	0	1 (<0.1)	NA
Cough	265 (6.2)	283 (6.6)	0.45	1 (<0.1)	1 (<0.1)	NA
Bronchitis	242 (5.7)	239 (5.6)	0.86	0	0	—
Dyspnea	223 (5.2)	213 (5.0)	0.60	6 (0.1)	5 (0.1)	0.76
Upper respiratory tract infection	223 (5.2)	229 (5.3)	0.80	1 (<0.1)	0	NA
Cataract	229 (5.4)	223 (5.2)	0.75	0	0	—
Constipation	203 (4.8)	241 (5.6)	0.07	0	1 (<0.1)	NA
Headache	200 (4.7)	220 (5.1)	0.33	2 (<0.1)	4 (0.1)	NA

* Events reported in 5% or more of either study group are shown. There were no predefined criteria for the adverse events listed. The investigators provided the reasons listed for the discontinuation of study drugs. Study groups were compared with the use of the chi-square test, where appropriate. Information on other relevant adverse events is available in the Supplementary Appendix. NA denotes not applicable.

Hyperkalemia was the most common adverse event reported by investigators and the most common adverse event leading to discontinuation of the study drug (Table 3). Serum potassium was also measured at regular intervals during the trial. The number of patients with a maximum unconfirmed postbaseline potassium level of 5.5 to less than 6.0 mmol per liter was 907 in the aliskiren group (21.2%) and 723 in the placebo group (16.9%); for a potassium level of 6.0 mmol per liter or higher, these figures were 479 (11.2%) and 308 (7.2%), respectively (P<0.001 for both comparisons). The frequency of a maximum serum potassium level above 5.0 mmol per liter during the study was 15% higher among pa-tients with a baseline estimated GFR below 45 ml per minute per 1.73 m² than among those with a higher estimated GFR.

As expected, renal impairment and hypotension were more commonly reported in the aliskiren group than in the placebo group; they were the second and third most common adverse events leading to study-drug discontinuation (Table 3). The next most commonly recorded cause of study-drug discontinuation was stroke (in 25 patients in the aliskiren group and 18 in the placebo group). Reported hypotension was more frequent in elderly patients (>65 years of age), those with a pulse pressure below the median (68 mm Hg), and those receiving treatment with

loop diuretics at baseline (data not shown). Reported hypoglycemia was slightly more frequent in the aliskiren group than in the placebo group, whereas overall glycemic control from baseline to the end of the study remained nearly identical between the two groups (data not shown). Diarrhea was a common adverse event but an infrequent cause of study-drug discontinuation.

At the interim analysis, there was an apparently higher risk of stroke in the aliskiren group than in the placebo group (hazard ratio, 1.34; 95% CI, 1.01 to 1.77; nominal P=0.044). With the subsequent orderly closeout of the study and the identification of an additional 392 patients with a primary event, including 72 patients with an adjudicated stroke, the overall neutral effect of aliskiren was confirmed, the effect size for stroke was reduced, and the nominal P value was no longer significant. (Table S9 in the Supplementary Appendix compares the rates of stroke in our trial with those in three other trials.) Additional adverse events are described in the Supplementary Appendix.

DISCUSSION

We found that the direct renin inhibitor aliskiren, when added to standard-of-care renin–angiotensin blockade in high-risk patients with type 2 diabetes, did not reduce cardiovascular or renal outcomes, as compared with placebo, and resulted in an increased number of adverse events. On average, blood pressure rose over the course of the trial in both groups, but slightly less with aliskiren (between-group differences, 1.3/0.6 mm Hg). However, no improvement in the primary composite outcome was observed, suggesting that factors such as hyperkalemia, renal dysfunction, and hypotension play a role in offsetting any beneficial effect of the treatment.[17] When used individually, both ACE inhibitors and ARBs have been shown to reduce the incidence of major cardiovascular and renal events in patients with a variety of cardiovascular disorders and those with nephropathy.[6,7,18-20] However, with the exception of two trials involving patients with chronic heart failure,[21,22] the combination of these agents has not incrementally improved cardiovascular or renal outcomes as compared with monotherapy, and combination therapy has been associated with an increased incidence of hyperkalemia, hypotension, and renal dysfunction.[9,10,23]

Aliskiren inhibits the renin–angiotensin axis at the most proximal step, offering the theoretical advantage of preventing the compensatory rise in plasma renin activity, which has been associated with cardiovascular events.[11,24] Aliskiren is an effective antihypertensive agent[25] and, when added to either an ACE inhibitor or an ARB, has improved surrogate markers for clinical outcomes in some, but not all, studies. Specifically, aliskiren reduced urinary albumin excretion in patients with diabetic nephropathy[14] and reduced plasma levels of B-type natriuretic peptides in patients with heart failure[26] but did not improve left ventricular remodeling in patients with acute myocardial infarction.[27]

The results of the Aliskiren in the Evaluation of Proteinuria in Diabetes study, which compared aliskiren with placebo in patients with diabetic renal disease who were also receiving losartan therapy, are particularly pertinent here.[14] The addition of aliskiren to the recommended dose of losartan resulted in an incremental 20% reduction in the urinary albumin-to-creatinine ratio. This improvement was greater than anticipated from the small reduction in systolic blood pressure (2 mm Hg). Data relating the degree of proteinuria or albuminuria to the risk of adverse cardiovascular events[28] and renal events[29] and analyses in clinical trials suggesting that the extent of pharmacologically produced reductions in proteinuria could be linked to improved outcomes provided a rationale for our trial.[30] The increased risks of hyperkalemia and hypotension with dual therapy with an ACE inhibitor and an ARB were known from prior studies.[9,10,17,23]

The recommendation by the independent data and safety monitoring committee for early termination of aliskiren was based on the members' assessment that the excess risk of adverse events in the aliskiren group could not be offset by a reduction in major cardiovascular and renal events. At the time of the recommendation, with approximately 69% of the projected events, the point estimate for the primary composite outcome (hazard ratio, 1.09; 95% CI, 0.97 to 1.22) favored placebo (single RAAS blockade). An increase in the risk of stroke in the aliskiren group was apparent at the time of the interim analysis, but the nominal P value was no longer significant at the closeout of the study. Three other major outcome trials comparing a different combination of renin–angiotensin system in-

hibitors (an ACE inhibitor plus an ARB) with monotherapy[9,10,17,22,23,31] that were not restricted to patients with diabetes did not show an increased incidence in stroke.

The overall lack of benefit with regard to the primary composite cardiovascular and renal outcome was observed across all the predefined subgroups. Although a serum potassium level higher than 5.0 mmol per liter was an exclusion criterion (with the measurement performed at a central laboratory 1 to 2 weeks before randomization), the results among patients with an elevated potassium value at randomization raised a particular safety concern. Of those who underwent randomization with a serum potassium level higher than 5 mmol per liter, the patients assigned to the aliskiren group were more likely to have at least one of the major cardiovascular or renal events reflected in the primary composite outcome than were those assigned to the placebo group.

Two trials in which aliskiren is being added to another renin–angiotensin system blocker in patients with heart failure are continuing under the supervision and at the recommendation of the data and safety monitoring committees of the trials.[32,33] However, the sponsor has discontinued a trial of aliskiren in elderly patients with mild hypertension, contrary to the recommendation from the data and safety monitoring committee.

A number of studies of various drugs have shown favorable changes in surrogate markers of disease progression, with subsequent studies of morbidity and mortality documenting a lack of clinical benefit or even harm.[34,35] The present study documented more adverse events in the aliskiren group than in the placebo group without clinical benefits to offset them, which underscores the need to go beyond surrogate biomarkers and obtain risk–benefit data from clinical end-point trials to better inform clinical decisions.[36]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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