Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Effects of the Oral Direct Renin Inhibitor Aliskiren in Patients With Symptomatic Heart Failure

John J.V. McMurray, Bertram Pitt, Roberto Latini, Aldo P. Maggioni, Scott D. Solomon, Deborah L. Keefe, Jessica Ford, Anil Verma, Jim Lewsey and for the Aliskiren Observation of Heart Failure Treatment (ALOFT) Investigators

Circ Heart Fail 2008;1;17-24
DOI: 10.1161/CIRCHEARTFAILURE.107.740704
Circulation: Heart Failure is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-3289. Online ISSN: 1941-3297

Effects of the Oral Direct Renin Inhibitor Aliskiren in Patients With Symptomatic Heart Failure

John J.V. McMurray, MD; Bertram Pitt, MD; Roberto Latini, MD; Aldo P. Maggioni, MD; Scott D. Solomon, MD; Deborah L. Keefe, MD; Jessica Ford, MSc; Anil Verma, MD; Jim Lewsey, PhD; for the Aliskiren Observation of Heart Failure Treatment (ALOFT) Investigators

Background—Loss of negative feedback inhibition of renin release during chronic treatment with an angiotensin-converting enzyme (ACE) inhibitor leads to a compensatory rise in renin secretion and downstream components of the renin-angiotensin-aldosterone (RAAS) cascade. This may overcome ACE inhibition but should be blocked by a direct renin inhibitor. We studied the effects of adding the direct renin inhibitor aliskiren to an ACE inhibitor in patients with heart failure.

Methods and Results—Patients with New York Heart Association class II to IV heart failure, current or past history of hypertension, and plasma brain natriuretic peptide (BNP) concentration >100 pg/mL who had been treated with an ACE inhibitor (or angiotensin receptor blocker) and β-blocker were randomized to 3 months of treatment with placebo (n=146) or aliskiren 150 mg/d (n=156). The primary efficacy outcome was the between-treatment difference in N-terminal pro-BNP (NT-proBNP). Patients' mean age was 68 years, mean ejection fraction was 31%, and mean±SD systolic blood pressure was 129±17.4 mm Hg. Sixty-two percent of the patients were in New York Heart Association functional class II, and 33% were taking an aldosterone antagonist. Plasma NT-proBNP rose by 762±6123 pg/mL with placebo and fell by 244±2025 pg/mL with aliskiren (P=0.0106). BNP and urinary (but not plasma) aldosterone were also reduced by aliskiren. Clinically important differences in blood pressure and biochemistry were not seen between aliskiren and placebo.

Conclusions—Addition of aliskiren to an ACE inhibitor (or angiotensin receptor blocker) and β-blocker had favorable neurohumoral effects in heart failure and appeared to be well tolerated. **(*Circ Heart Fail*. 2008;1:17-24.)**

Key Words: heart failure ■ renin ■ angiotensin ■ pharmacology

The value of inhibiting the renin-angiotensin-aldosterone system (RAAS) in heart failure was first demonstrated with the angiotensin-converting enzyme (ACE) inhibitor enalapril in 1987.[1] Since then, there have been 2 major aims of therapeutic research with inhibitors of the RAAS in heart failure.[2] The first has been to determine whether alternative agents offered superior efficacy, tolerability, or both as a result of their distinctive pharmacological actions. In the only head-to-head comparison, the angiotensin receptor blocker (ARB) losartan was not superior to the ACE inhibitor captopril.[3] The second aim, based on the pathophysiological observations of aldosterone "escape" in patients treated with an ACE inhibitor and of non-ACE generation of angiotensin II, was to determine whether the combination of RAAS inhibitors could improve clinical outcomes further than with ACE inhibitor monotherapy. This has been shown to be the case for both an aldosterone antagonist[4] and ARBs.[5,6]

Clinical Perspective p 24

Direct renin inhibitors (DRIs) offer another pharmacologically distinct means of suppressing the RAAS, with the theoretical advantages of blocking an enzyme with only one known substrate (angiotensinogen), inhibiting the rate-limiting step in the RAAS cascade, and reducing synthesis of all subsequent components of the cascade.[7] As with ARBs, DRIs may offer an alternative to an ACE inhibitor or could be used in combination with an ACE inhibitor (or ARB).[2] The rationale for the latter approach is that ACE inhibitors (and ARBs) induce a compensatory rise in renin and downstream RAAS components that may eventually overcome their RAAS-blocking effect. A DRI should block this compensatory increase in RAAS activity. Conversely, the addition of an ACE inhibitor (or ARB) to a DRI may be valuable in view of the possibility of nonrenin production of angiotensin I

Received September 18, 2007; accepted February 8, 2008.

From the BHF Cardiovascular Research Centre (J.J.V.M.) and Department of Public Health and Health Policy (J.L.), University of Glasgow, Glasgow, Scotland, United Kingdom; University of Michigan School of Medicine (B.P.), Ann Arbor, Mich; Department of Cardiovascular Research (R.L.), Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; ANMCO Research Center (A.P.M.), Florence, Italy; Brigham & Women's Hospital (S.D.S., A.V.), Boston, Mass; and Novartis Pharmaceuticals Corporation (D.L.K., J.F.), East Hanover, NJ.

Clinical trial registration information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00219011.

Correspondence to Professor John J.V. McMurray, BHF Cardiovascular and Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, United Kingdom. E-mail j.mcmurray@bio.gla.ac.uk

Circ Heart Fail **is available at http://circheartfailure.ahajournals.org** **DOI: 10.1161/CIRCHEARTFAILURE.107.740704**

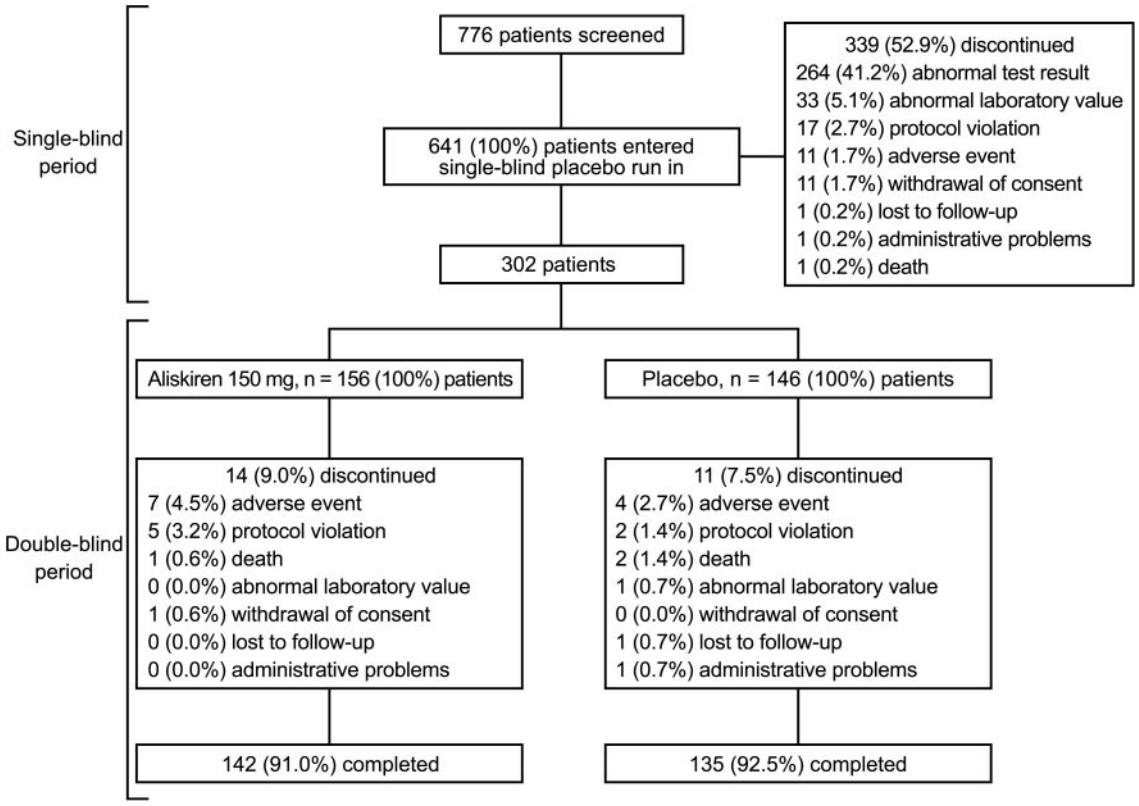

Figure. Patient disposition.

through enzymes such as cathepsin D and tonin.[8–10] We studied the effects of adding the DRI aliskiren to an ACE inhibitor or ARB in patients with chronic symptomatic heart failure.

Methods

Patients

Men and women ≥18 years of age were eligible if they fulfilled each of the following criteria and provided written informed consent: (1) stable New York Heart Association class II to IV heart failure for at least 1 month; (2) past or current diagnosis of essential hypertension; (3) stable dose of an ACE inhibitor (or ARB) and a β-blocker (unless there was a contraindication or intolerance to such therapy); and (4) plasma brain natriuretic peptide (BNP) >100 pg/mL (28.9 pmol/L). There was no left ventricular ejection fraction (LVEF) inclusion criterion. The key exclusion criteria included treatment with both an ACE inhibitor and an ARB (combination of either with an aldosterone antagonist was permitted); heart failure related to obstructive valve disease or hypertrophic, restrictive, or infective cardiomyopathy, pregnancy, or lung disease; systolic blood pressure <90 mm Hg; serum potassium ≥5.1 mmol/L; creatinine >2.0 mg/dL (177 μmol/L) or history of dialysis or nephrotic syndrome; myocardial infarction, cerebrovascular accident or transient ischemic attack, or coronary revascularization within 6 months; cardiac resynchronization device or implantable cardioverter defibrillator; and prior malignancy or other disease likely to greatly limit life expectancy, adherence to the protocol, or absorption of study drug.

Procedures

Patients were enrolled at 75 sites in 9 countries (Figure). The study consisted of 2 phases: a 2-week single-blind placebo run-in period (to assess eligibility, particularly BNP concentration, and patient adherence to study drug), and a 12-week randomized, double-blind, parallel-group phase in which patients received either placebo or aliskiren 150 mg once daily in an equal ratio (Figure). The randomization list was generated by Novartis Drug Supply Management (Basel, Switzerland) with a validated system that automated the random assignment of treatment groups to randomization numbers. The randomization scheme was reviewed by a biostatistics quality assurance group at Novartis and locked by that group after approval. Placebo and drug tablets and capsules were matched in size, shape, and color to maintain blinding.

Randomization was done by a telephonic interactive voice response system with stratification by center and locally determined LVEF at baseline (stratum 1: > 40%; stratum 2: ≤40%) to ensure a balanced LVEF distribution within each treatment group. Within a stratum (LVEF within center), a block size of 4 was used. Within centers, the number of patients randomized to the 2 treatment groups never differed by more than 3 patients. For the 2 centers where the difference between groups was 3 patients, the randomization was 2 versus 5 and 3 versus 0.

Patients were evaluated at 2, 4, 8, and 12 weeks after randomization. Blood chemistry was checked at each of these time points. The protocol specified that any patient admitted to a hospital because of worsening heart failure or with serum potassium >5.5 mmol/L or serum creatinine >3 mg/dL (265 μmol/L), confirmed by the central laboratory (CRL Medinet Inc, Lenexa, Kan, and CRL Medinet BV, Breda, the Netherlands), should be withdrawn from the study.

The primary objective of the present study was to assess the tolerability and safety of aliskiren, specifically the incidence of renal dysfunction (any relevant Medical Dictionary for Regulatory Activities adverse event term or increase in creatinine to >3.0 mg/dL [267 μmol/L]), symptomatic hypotension (any relevant Medical Dictionary for Regulatory Activities adverse event term), and hyperkalemia (potassium >5.5 mmol/L, confirmed by the central laboratory or Medical Dictionary for Regulatory Activities adverse event term for hyperkalemia), in hierarchical order. Efficacy assessments were also prespecified. The aims were to evaluate the effect of aliskiren, compared with placebo, on N-terminal pro-BNP (NT-proBNP), BNP, aldosterone, signs and symptoms of heart failure (and New

York Heart Association class), echocardiographic measures of cardiac size and ventricular function, blood pressure, heart rate variability, quality of life (Kansas City Cardiomyopathy Questionnaire), neurohumoral and inflammatory biomarkers (including urinary biomarkers), and glycemic measures (in the order specified).

Echocardiograms were obtained at the sites after centralized site training at investigator meetings. All echocardiographic studies were obtained digitally or on videotape and transferred to the core echocardiography laboratory at the Brigham and Women's Hospital (Boston, Mass) for analysis. Echocardiograms were digitized and analyzed by trained echocardiographers blinded to treatment assignment. Endocardial borders were traced manually in multiple views, left ventricular volumes were measured by the Simpson's rule method,[11] and ejection fraction was calculated in the standard fashion. Mitral regurgitation was assessed semiquantitatively by calculating the ratio of mitral regurgitant jet area to left atrial area in apical 2- and 4-chamber views. Doppler parameters, including peak early (E) transmitral flow velocity, peak atrial (A) transmitral flow velocity, and tissue Doppler E′ and S′, representing annular relaxation and contraction velocity, respectively, were measured. The ratio of transmitral E wave to tissue Doppler E′ was calculated, as was Tei's index.[12]

Statistical Analysis

Although this was primarily a safety study, we calculated a sample size on the basis of the ability to detect a difference between treatment groups in the change from baseline to the end of the study in NT-proBNP, which was also the first of the prespecified secondary efficacy assessments. Inspection of existing data on BNP suggested that assumption of a normal distribution was most appropriate for log-transformed data. Assuming a standard deviation of 0.65 for the logarithmized NT-proBNP ratio of end of study to baseline, an α-level for statistical significance of 0.05 (2 sided), a dropout rate of 10%, and 250 patients, the study had 72% power to detect a 20% reduction and 89% power to detect a 25% reduction in NT-proBNP.

The change from baseline to end of study was analyzed with a 2-way ANCOVA model with adjustment for treatment, region of the world, and core laboratory LVEF (<40% and ≥40%). For parameters for which the data were highly skewed and did not fit a normal distribution (including NT-proBNP, BNP, and aldosterone), the analysis was performed on the change from end of study to baseline with log-transformed data. The least-squares means of the treatment effects were back-transformed (antilog) and, given the properties of logarithms, are an estimate of the ratio of the end point to baseline. This is comparable to the ratio of end point to baseline of the geometric means. The treatment comparisons presented are the ratio of the 2 treatment effects.

Prespecified hypothesis tests with the Fisher exact test were performed on the primary safety parameters, as well as additional tests that compared the incidence of adverse events. Treatment comparisons were investigated with a Cochran-Mantel-Haenszel χ^2 test, with adjustment for LVEF (>40% or ≤40%).

All statistical analyses were performed with SAS version 8.2 (or higher) by the sponsor (J.F.) and checked by an independent statistician at Glasgow University (J.L.). Because the efficacy assessments were exploratory, no adjustment was made for multiple statistical comparisons.

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

The baseline characteristics of the 302 patients randomized (Figure) are shown in Table 1. The majority were male. All had a history of hypertension according to the inclusion criteria, but baseline seated blood pressure was 129±17.4 mm Hg systolic and 77±9.5 mm Hg diastolic. Although a low LVEF was not an inclusion criterion, 79% of

Table 1. Baseline Characteristics

	Placebo (n=146)	Aliskiren 150 mg (n=156)
Age, y	68±10	67±11
Male sex	111 (76)	125 (80)
White	144 (99)	150 (96)
Physiological measurements		
LVEF, %*	31.1±5.5	30.6±5.5
Body mass index, kg/m^2	27.3±4.8	27.8±4.8
Systolic blood pressure, mm Hg		
Seated	128±16.4	130±18.3
Standing	126±15.6	129±19.1
Diastolic blood pressure, mm Hg		
Seated	76.4±8.4	78.1±10.4
Standing	75.9±9.2	78.8±11.3
Heart rate, bpm		
Seated	70±11.3	70±12.1
Standing	72±12.0	72±13.1
Heart failure history		
Duration, y	4.9±5.4	4.1±3.9
Etiology†		
Ischemic	79 (54)	86 (55)
Hypertensive	25 (17)	25 (16)
Idiopathic	29 (20)	36 (23)
Other	13 (9)	9 (6)
LVEF		
≤40%*	113 (77)	125 (80)
>40%	33 (23)	31 (20)
New York Heart Association class		
I	1 (0.7)	0 (0)
II	87 (60)	98 (63)
III	58 (40)	56 (36)
IV	0 (0)	2 (1)
Medical history		
Myocardial infarction	72 (49)	71 (46)
Angina pectoris	30 (21)	32 (21)
Diabetes mellitus	43 (30)	48 (31)
Atrial fibrillation	47 (32)	50 (32)
Laboratory measurements		
Estimated glomerular filtration rate, mL·min^{-1}·1.73 m^{-2}	67.8±19.1	70.0±21.3
Creatinine, μmol/L	97.3±39.4	92.4±36.1
Urea, mmol/L	8.89±5.31	9.15±5.94
Potassium, mmol/L	4.41±0.43	4.48±0.62
Treatment		
ACE inhibitor	123 (84)	130 (83)
ARB	21 (14)	25 (16)
Aldosterone antagonist	49 (34)	52 (33)
β-Blocker	138 (95)	147 (94)

Values are provided as mean±SD or number (percentage).
*As measured locally.
†Investigator reported.

Table 2. Neurohumoral Measurements (Plasma Unless Stated Otherwise)

Neurohumoral Measure	Baseline		End of Study		Ratio: End of Study/Baseline Geometric Mean (95% CI)	Ratio: Aliskiren/Placebo (95% CI)	*P*
	Mean±SD	Geometric Mean (95% CI)	Mean±SD	Geometric Mean (95% CI)			
NT-proBNP, pg/mL							
Aliskiren	2158±2269	1389 (1159, 1664)	1915±2373	1087 (888, 1331)	0.73 (0.57, 0.93)	0.75 (0.61, 0.94)	0.0106
Placebo	2123±3858	1233 (1019, 1492)	2885±6393	1419 (1190, 1691)	0.96 (0.75, 1.24)		
BNP, pg/mL							
Aliskiren	301±269	204 (175, 240)	240±307	135 (112, 163)	0.64 (0.48, 0.84)	0.75 (0.59, 0.95)	0.0160
Placebo	273±246	189 (162, 220)	261±272	168 (141, 200)	0.85 (0.64, 1.12)		
Aldosterone, pmol/L							
Aliskiren	334±364	208 (176, 247)	285±281	184 (157, 216)	0.99 (0.81, 1.22)	0.99 (0.93, 1.18)	0.9064
Placebo	307±316	190 (159, 226)	276±273	177 (149, 210)	1.00 (0.82, 1.23)		
Urinary aldosterone, nmol/d							
Aliskiren	38±43	24 (20, 28)	29±33	18 (16, 21)	0.81 (0.65, 1.00)	0.79 (0.66, 0.96)	0.0150
Placebo	37±41	23 (19, 27)	31±33	21 (18, 24)	1.02 (0.82, 1.26)		
Plasma renin concentration, ng/L							
Aliskiren	69±112	26 (20, 33)	155±177	63 (49, 81)	2.61 (1.87, 3.63)	2.60 (1.97, 3.44)	<0.0001
Placebo	79±120	31 (24, 39)	74±116	28 (22, 37)	1.00 (0.73, 1.38)		
Plasma renin activity, $ng \cdot mL^{-1} \cdot h^{-1}$							
Aliskiren	7.32±11.70	1.80 (1.32, 2.46)	1.61±3.47	0.42 (0.33, 0.54)	0.18 (0.12, 0.26)	0.23 (0.17, 0.31)	<0.0001
Placebo	8.38±12.98	2.24 (1.65, 3.05)	7.42±11.54	2.04 (1.50, 2.76)	0.78 (0.54, 1.13)		

patients had an LVEF ≤40%, and the mean±SD LVEF was 31±5.5%. Thirty-five percent of patients had a history of diabetes mellitus. Ninety percent of patients had a plasma BNP concentration >150 pg/mL (43 pmol/L), and the mean±SD value was 291±265 pg/mL (Table 2). Most patients were in New York Heart Association functional class II (61%) or III (38%) and were treated with neurohumoral blockers. Ninety-four percent were treated with an ACE inhibitor (or ARB) and β-blocker and 32% with an aldosterone antagonist as well. Of the 302 patients randomized, 277 (92%) completed the double-blind treatment phase.

Plasma NT-proBNP rose by a mean±SD of 762±6123 pg/mL over the 12 weeks of treatment in the placebo group and fell by a mean±SD of 244±2025 pg/mL with aliskiren treatment (between-treatment difference in change from baseline $P=0.0106$; Table 2). BNP decreased by a mean±SD of 12.2±243 pg/mL in the placebo group and by 61.0±257 pg/mL in the aliskiren group ($P=0.0160$). Plasma aldosterone did not differ between groups, but urinary aldosterone excretion decreased more in the aliskiren group; the decrease with aliskiren was 9.24±42.9 nmol/d, and the decrease with placebo was 6.96±38.5 nmol/d ($P=0.0150$; Table 2). Plasma renin activity decreased more with aliskiren (decrease of 5.71 ± 11.27 ng $\cdot$ $mL^{-1} \cdot h^{-1}$ with aliskiren compared with a decrease of 0.97 ± 9.96 ng $\cdot$ $mL^{-1} \cdot h^{-1}$ with placebo; $P<0.0001$; Table 2).

There was no difference between treatments for change in symptoms or signs between baseline and the end of the study. There were no differences in echocardiographic measurements of wall thickness, chamber volumes, or LVEF. We observed significant reductions in the degree of mitral regurgitation, transmitral E velocity, and ratio of mitral velocity to early diastolic velocity of the mitral annulus in patients treated with aliskiren, although no adjustment was made for the multiple comparisons that were performed (Table 3).

The mean±SD decrease in seated systolic blood pressure was 1.7±13.2 mm Hg in the placebo group and 4.1±14.5 mm Hg in the aliskiren group ($P=0.2257$). The corresponding decreases in diastolic blood pressure were 0.2±8.6 mm Hg in the placebo group and 2.9±9.0 mm Hg in the aliskiren group ($P=0.0599$). The mean increase in heart rate was 0.2±10.3 bpm in the placebo group and 1.1±13.6 bpm in the aliskiren group ($P=0.6774$). Mean standing systolic blood pressure decreased by 1.7±13.1 mm Hg in the placebo group and by 3.5±16.1 mm Hg in the aliskiren group ($P=0.497$). The corresponding changes in diastolic blood pressure were a 0.7±8.3-mm Hg increase with placebo and a 3.5±10.7-mm Hg decrease with aliskiren ($P=0.0045$). Standing heart rate decreased by 0.3±11.4 bpm in the placebo group and increased by 0.7±13.8 bpm in the aliskiren group ($P=0.466$). There were no differences between treatments in any of the other prespecified comparisons, including autonomic measurements, the Kansas City Cardiomyopathy questionnaire, inflammatory and other plasma and urinary biomarkers (including urinary protein excretion), or measurements of glucose/insulin metabolism.

Eleven (7.5%) placebo-treated and 14 (9.0%) aliskiren-treated patients discontinued use of the study drug prematurely. Of these, 2 placebo-treated and 1 aliskiren-treated patient died, and 4 placebo-treated and 7 aliskiren-treated patients discontinued use of the drug because of an adverse event. Discontinuations related to the primary end point (renal dysfunction, symptomatic hypotension, or hyperkalemia) and worsening heart failure occurred in 4 aliskiren-

Table 3. Echocardiographic Measurements

Measure	Baseline	End of Study	Change	*P*
End-diastolic volume index, mL/m^2				0.56
Aliskiren	124±24	123±24	−2.7±6.7	
Placebo	123±30	121±28	−3.4±12.9	
End-systolic volume index, mL/m^2				0.67
Aliskiren	87.2±22	84.9±22	−4.0±8.1	
Placebo	85.4±25	82.4±24	−4.3±10.7	
LVEF, %				0.96
Aliskiren	30.6±5.5	31.5±5.5	1.7±3.1	
Placebo	31.1±5.5	32.5±5.6	1.6±2.9	
Left ventricular internal diastolic dimension, cm				0.93
Aliskiren	6.3±0.6	6.3±0.5	−0.08±0.2	
Placebo	6.2±0.6	6.2±0.6	−0.07±0.1	
Left ventricular internal systolic dimension, cm				0.66
Aliskiren	5.3±0.6	5.2±0.6	−0.14±0.2	
Placebo	5.2±0.6	5.1±0.6	−0.12±0.2	
Left atrial volume, mL				0.55
Aliskiren	109±27	109±27	−3.4±5.9	
Placebo	99±22	97±22	−2.7±5.2	
Mitral regurgitation area, cm^2				0.0017
Aliskiren	8.6±4.3	7.1±3.1	−1.3±2.9	
Placebo	7.8±3.5	8.3±3.3	0.13±2.6	
Mitral regurgitation area/left atrium area ratio				0.0006
Aliskiren	30.2±13.8	26.0±12.1	−4.1±10.1	
Placebo	29.5±13.1	32.3±13.0	1.3±10.1	
Peak early (E) transmitral flow velocity, cm/s				0.0012
Aliskiren	79.0±24.3	72.8±26.2	−6.6±22.0	
Placebo	78.0±26.3	80.8±26.0	2.9±19.3	
Peak atrial (A) transmitral flow velocity, cm/s				0.51
Aliskiren	58.6±28.8	64.7±26.9	4.3±20.0	
Placebo	63.6±28.2	67.0±27.0	0.7±17.8	
E/A ratio				0.032
Aliskiren	1.9±1.5	1.4±1.1	−0.4±1.1	
Placebo	1.6±1.1	1.5±1.1	0.01±0.8	
Deceleration time, ms				0.04
Aliskiren	219±87	210±72	−10.0±80.0	
Placebo	210±83	230±75	10.0±68.0	
Early diastolic peak velocity of the mitral annulus, cm/s				0.81
Aliskiren	7.1±3.1	6.9±2.9	−0.07±3.1	
Placebo	6.3±2.7	6.3±2.8	0.15±2.6	
Ratio of mitral velocity to early diastolic velocity of the mitral annulus				0.047
Aliskiren	13.1±2.7	12.2±5.9	−0.83±8.0	
Placebo	14.6±7.2	14.5±7.3	0.11±6.9	
Right ventricular fractional area change, %				0.59
Aliskiren	39.9±5.9	41.4±4.9	1.06±2.3	
Placebo	40.2±5.7	41.4±5.6	0.9±1.8	
Tei's index				0.26
Aliskiren	0.58±0.3	0.59±0.3	0.03±0.3	
Placebo	0.58±0.3	0.56±0.2	−0.03±0.2	

All results are shown as mean±SD. The statistical tests performed were not adjusted for testing of multiple end points.

Table 4. Prespecified Safety Assessments and Adverse Events

	Placebo (n=146)	Aliskiren (n=156)
Prespecified safety assessment, n (%)		
Renal dysfunction‡	2 (1.4)	3 (1.9)
Symptomatic hypotension†§	2 (1.4)	5 (3.2)
Hyperkalemia‖	7 (4.8)	10 (6.4)
Any of the above¶	11 (7.5)	17 (10.9)
Adverse events occurring in ≥3% of patients, n (%)*		
Nasopharyngitis	4 (2.7)	6 (3.8)
Asthenia	2 (1.4)	5 (3.2)
Diarrhea	2 (1.4)	5 (3.2)
Hyperuricemia	2 (1.4)	5 (3.2)
Hypotension	1 (0.7)	5 (3.2)
Nausea	0 (0.0)	5 (3.2)
Cardiac failure	6 (4.1)	4 (2.6)
Dyspnea	5 (3.4)	3 (1.9)
Dizziness	5 (3.4)	2 (1.3)

No statistically significant differences were found in any assessment.

*In either treatment group.

†Orthostatic hypotension (defined as a decrease of ≥10 mm Hg diastolic or ≥20 mm Hg in systolic blood pressure when changing from the sitting to the standing position) occurred in 25 (17.4%) placebo-treated and 27 (17.4%) aliskiren-treated patients at any time after randomization.

Fisher exact test *P* for ‡1.000, §0.4495, ‖0.4989, and ¶0.3294; all nonsignificant.

treated patients (2 hypotension, 1 hyperkalemia, and 1 worsening heart failure) and 3 placebo-treated patients (all due to worsening heart failure). One placebo-treated patient (and no aliskiren-treated patients) discontinued the study drug because of an abnormal laboratory value. The remaining 4 placebo-treated and 6 aliskiren-treated patients discontinued the study drug because of a protocol violation, withdrawal of consent, or administrative problems or because they were lost to follow-up (1 placebo-treated patient).

The primary safety assessments are shown in Table 4, along with the most commonly reported adverse events. Important biochemical changes are described in Table 5. The following cardiovascular serious adverse events occurred: sudden death (1 placebo, 0 aliskiren), sudden cardiac death (0 placebo, 1 aliskiren), cardiac arrest (0 placebo, 1 aliskiren), ventricular tachycardia (0 placebo, 1 aliskiren), cerebrovascular accident or transient ischemic attack (0 placebo, 2 aliskiren), heart failure (including cardiac failure, left ventricular failure, pulmonary edema, and paroxysmal nocturnal dyspnea; 2 placebo, 3 aliskiren), unstable angina (0 placebo, 1 aliskiren), atrial fibrillation (0 placebo, 1 aliskiren), tachyarrhythmia (0 placebo, 1 aliskiren), and pulmonary embolism (1 placebo, 0 aliskiren). One aliskiren-treated patient accounted for 3 events—ie, that patient had unstable angina, ventricular tachycardia, and a cardiac arrest.

Table 5. Important Biochemical Abnormalities

Biochemical Abnormalities n, %	Placebo (n=146)	Aliskiren (n=156)
Urea, mmol/L		
>14.3	15 (10.4)	13 (8.3)
Creatinine, μmol/L		
>177	8 (5.6)	11 (7.1)
>265	3 (2.1)	0 (0.0)
Potassium, mmol/L		
<3.5	7 (4.9)	2 (1.3)
>5.5	12 (8.3)	13 (8.3)
≥6.0	6 (4.2)	3 (1.9)

Values are provided as number (percentage). There were no statistically significant differences in any assessment. To convert urea to urea-nitrogen (mg/dL), multiply by 2.8; to convert creatinine to mg/dL, divide by 88.8.

Discussion

The potential therapeutic value of DRIs has been recognized since 1957, but problems with bioavailability, potency, duration of action, and cost of production hindered their development.[7] Aliskiren, the first of a new class of nonpeptide, orally active, transition-state DRIs, is a potent and specific agent with a plasma half-life of ≈24 hours that has recently been approved as a treatment for hypertension in a dose of up to 300 mg.[7,10,13,14] We added 150 mg of aliskiren to the treatment regimen of patients with chronic symptomatic heart failure treated with a stable dose of an ACE inhibitor (or ARB) and a β-blocker for at least 1 month. The present study design is important because it tested the effect of a DRI in patients who had experienced the compensatory rise in plasma renin (and other downstream RAAS components) caused by ACE inhibitor–induced (or ARB–induced) loss of negative feedback inhibition of renin secretion. This compensatory response may partially overcome the RAAS-blocking effect of ACE inhibitors. A DRI has not been used in this way previously. In this setting, aliskiren was well tolerated and had favorable neurohumoral effects, reducing the plasma concentration of both natriuretic peptides. Such changes have been associated with improved clinical outcomes in therapeutic trials and observational studies, although no outcome data are available with aliskiren in heart failure.

The decrease in BNP with aliskiren (by 61 pg/mL from a baseline of 301 pg/mL, compared with a rise of 12 pg/mL from a baseline of 273 pg/mL with placebo) was somewhat larger than observed with the addition of ARBs in prior heart failure trials.[15–17] For example, in the Valsartan Heart Failure Trial (Val-HeFT), BNP decreased from a baseline concentration of 181±230 pg/mL by 34 pg/mL in the valsartan group at 4 months (compared with an increase of 2 pg/mL in the placebo group).[15] In the African-American Heart Failure Trial (A-HeFT), the combination of hydralazine and isosorbide dinitrate reduced BNP by 39 pg/mL (from a baseline of 283 pg/mL), compared with a decrease of 8 pg/mL in the placebo group.[16]

Reductions in BNP have consistently been associated with improved outcome in heart failure.[18–20] For example, in Val-HeFT, an increment of 10 pg/mL in BNP was associated with a 1.2% increase in risk of death (and an identical increase in the risk of hospitalization for heart failure).[18]

In addition, aliskiren reduced urinary aldosterone excretion, although it did not reduce plasma aldosterone concen-

tration. Prior experience with "add-on" therapy and plasma aldosterone is less clear-cut. In Val-HeFT, aldosterone fell by 35 pg/mL from a baseline of 144±143 pg/mL after 4 months of treatment with valsartan (compared with an increase of 10 pg/mL with placebo).[21] In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study, aldosterone decreased by 20 to 25 pg/mL from a baseline of 114 mg/mL after 17 weeks of treatment with candesartan and enalapril, but this reduction was similar to that observed with 16 mg of candesartan alone (there was no change with enalapril).[22] Measurement of 24-hour urinary aldosterone excretion, however, better quantifies aldosterone secretion than does a single plasma measurement. Reduction in aldosterone secretion can be regarded as a favorable neurohumoral effect of aliskiren, in light of the postulated detrimental pathophysiological role of aldosterone and the beneficial clinical effects of aldosterone antagonists in heart failure.[2]

As expected, aliskiren also reduced plasma renin activity (and increased plasma renin concentration). Patients in the present study were treated with a β-blocker, which inhibits renin secretion.[23] It was of interest, therefore, that the size of the effect of aliskiren on plasma renin activity was as large in the present trial as in prior studies in which patients were not treated with β-blockers. It is also notable that plasma renin activity is itself predictive of mortality and morbidity in patients with heart failure.[18]

Aliskiren had no effect on left ventricular wall thickness and volumes or LVEF, probably because of the short duration of treatment and relatively small sample size, although a larger, longer-term study is needed to prove or disprove this hypothesis. Aliskiren did, however, reduce the amount of mitral regurgitation and the ratio of mitral velocity to early diastolic velocity of the mitral annulus, a Doppler measure of left ventricular filling pressure (although the latter analysis was added retrospectively).[24] These findings are in keeping with acute hemodynamic studies with the intravenous renin inhibitors enalkiren and remikiren that showed that those agents reduced pulmonary capillary wedge pressure.[25,26] They are also consistent with the reduction we observed in BNP and NT-proBNP concentration, although these peptides are thought to give a more integrated measure of "left ventricular stress," and in the present study, the effects were seen with chronic rather than acute therapy; ie, they were sustained over 3 months.[27] Multiple echocardiographic parameters were assessed, and no statistical correction was made for the multiple end points.

There are, however, still some uncertainties about the actions of renin inhibitors. Recently, a receptor that binds renin and prorenin has been identified.[28,29] Binding of renin to this receptor increases its enzymatic activity, and inert prorenin is converted to active renin when bound. Binding of either peptide to this receptor is also thought to activate intracellular mitogen activated protein kinases and increase synthesis of transforming growth factor-β, independent of angiotensin formation (possibly stimulating fibrosis).[30] It is uncertain whether DRI-induced increases in renin concentration activate this receptor, whether this receptor is downregulated when renin concentration is increased, and whether aliskiren binds to or blocks this receptor.[30,31]

The addition of aliskiren 150 mg/d to standard therapy for heart failure that includes an ACE inhibitor (or ARB), a β-blocker, and an aldosterone antagonist, if indicated, appeared to be well tolerated, with only slightly (but not statistically significantly) higher rates of hypotension and hyperkalemia. There was no notable increase in renal dysfunction, although patients in the present study had been carefully selected, and patients with hypotension, hyperkalemia, or a significantly elevated creatinine at baseline were excluded from this trial (nevertheless, a high proportion had a baseline estimated glomerular filtration rate <60 mL · min^{-1} · 1.73 m^{-2}, and one third were taking an aldosterone antagonist). Of possible relevance here is the suggestion that DRIs increase renal blood flow more than other inhibitors of the RAAS.

In summary, these findings in patients with stable New York Heart Association class II and III heart failure and elevated BNP support further trials to test the safety and efficacy of aliskiren in patients with heart failure, either as an alternative to an ACE inhibitor or in combination with other blockers of the RAAS.[31]

Acknowledgment

Novartis was involved in the design of the study and the collection and analysis of the data. The corresponding author had access to all the study data, and all authors took part in the analysis and interpretation of the data and wrote the manuscript. We thank J. Chung, B. Smith, and M. Prescott (all with Novartis) for their assistance during this trial.

Source of Funding

This trial was funded by Novartis, which also funded the core echocardiography laboratory at the Brigham and Women's Hospital. All authors (with the exception of Dr Keefe and Ms Ford) or their institutions were paid for time spent on trial-related activities and traveling/accommodation expenses related to Steering Committee meetings, as required.

Disclosures

Drs McMurray, Pitt, Latini, Maggioni, and Solomon have received consulting and lectures fees from Novartis related to aliskiren and valsartan and from other pharmaceutical companies that market drugs that inhibit the RAAS. Dr Keefe and Ms Ford are employees of Novartis. Drs Verma and Lewsey have no conflicts of interest to disclose.

References

1. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987; 316:1429–1435.
2. McMurray JJ, Pfeffer MA, Swedberg K, Dzau VJ. Which inhibitor of the renin-angiotensin system should be used in chronic heart failure and acute myocardial infarction? *Circulation*. 2004;110:3281–3288.
3. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial: the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000;355:1582–1587.
4. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J; Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709–717.
5. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667–1675.

6. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003;362:767–771.
7. Staessen JA, Li Y, Richart T. Oral renin inhibitors. *Lancet*. 2006;368: 1449–1456.
8. Katwa LC, Tyagi SC, Campbell SE, Lee SJ, Cicila GT, Weber KT. Valvular interstitial cells express angiotensinogen and cathepsin D, and generate angiotensin peptides. *Int J Biochem Cell Biol*. 1996;28:807–821.
9. Borges JC, Silva JA Jr, Gomes MA, Lomez ES, Leite KM, Araujo RC, Bader M, Pesquero JB, Pesquero JL. Tonin in rat heart with experimental hypertrophy. *Am J Physiol Heart Circ Physiol*. 2003;284:H2263-H2268.
10. Birkenhager WH, Staessen JA. Dual inhibition of the renin system by aliskiren and valsartan. *Lancet*. 2007;370:195–196.
11. Schiller NB, Acquatella H, Ports TA, Drew D, Goerke J, Ringertz H, Silverman NH, Brundage B, Botvinick EH, Boswell R, Carlsson E, Parmley WW. Left ventricular volume from paired biplane two-dimensional echocardiography. *Circulation*. 1979;60:547–555.
12. Tei C, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ, Tajik AJ, Seward JB. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function: a study in normals and dilated cardiomyopathy. *J Cardiol*. 1995;26: 357–366.
13. Wood JM, Maibaum J, Rahuel J, Grutter MG, Cohen NC, Rasetti V, Ruger H, Goschke R, Stutz S, Fuhrer W, Schilling W, Rigollier P, Yamaguchi Y, Cumin F, Baum HP, Schnell CR, Herold P, Mah R, Jensen C, O'Brien E, Stanton A, Bedigian MP. Structure-based design of aliskiren, a novel orally effective renin inhibitor. *Biochem Biophys Res Commun*. 2003;308:698–705.
14. Nussberger J, Wuerzner G, Jensen C, Brunner HR. Angiotensin II suppression in humans by the orally active renin inhibitor Aliskiren (SPP100): comparison with enalapril. *Hypertension*. 2002;39:E1–E8.
15. Latini R, Masson S, Anand I, Judd D, Maggioni AP, Chiang YT, Bevilacqua M, Salio M, Cardano P, Dunselman PH, Holwerda NJ, Tognoni G, Cohn JN; Valsartan Heart Failure Trial Investigators. Effects of valsartan on circulating brain natriuretic peptide and norepinephrine in symptomatic chronic heart failure: the Valsartan Heart Failure Trial (Val-HeFT). *Circulation*. 2002;106:2454–2458.
16. Cohn JN, Tam SW, Anand IS, Taylor AL, Sabolinski ML, Worcel M; A-HeFT Investigators. Isosorbide dinitrate and hydralazine in a fixed-dose combination produces further regression of left ventricular remodeling in a well-treated black population with heart failure: results from A-HeFT. *J Card Fail*. 2007;13:331–339.
17. Rousseau MF, Gurne O, Duprez D, Van Mieghem W, Robert A, Ahn S, Galanti L, Ketelslegers JM; Belgian RALES Investigators. Beneficial neurohormonal profile of spironolactone in severe congestive heart failure: results from the RALES neurohormonal substudy. *J Am Coll Cardiol*. 2002;40:1596–1601.
18. Latini R, Masson S, Anand I, Salio M, Hester A, Judd D, Barlera S, Maggioni AP, Tognoni G, Cohn JN; for the Val-HeFT Investigators. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. *Eur Heart J*. 2004;25: 292–299.
19. Latini R, Masson S, Wong M, Barlera S, Carretta E, Staszewsky L, Vago T, Maggioni AP, Anand IS, Tan LB, Tognoni G, Cohn JN; Val-HeFT Investigators. Incremental prognostic value of changes in B-type natriuretic peptide in heart failure. *Am J Med*. 2006;119:70.e23–e30.
20. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, Aupetit JF, Aumont MC, Galinier M, Eicher JC, Cohen-Solal A, Juilliere Y. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol*. 2007;49:1733–1739.
21. Cohn JN, Anand IS, Latini R, Masson S, Chiang YT, Glazer R; Valsartan Heart Failure Trial Investigators. Sustained reduction of aldosterone in response to the angiotensin receptor blocker valsartan in patients with chronic heart failure: results from the Valsartan Heart Failure Trial. *Circulation* 2003;108:1306–1309.
22. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, Tsuyuki RT, White M, Rouleau J, Latini R, Maggioni A, Young J, Pogue J; the RESOLVD Pilot Study Investigators. Comparison of candesartan, enalapril, and their combination in congestive heart failure: evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. *Circulation*. 1999;100:1056–1064.
23. The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy: the randomized evaluation of strategies for left ventricular dysfunction pilot study. *Circulation*. 2000; 101:378–384.
24. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol*. 1997;30:1527–1533.
25. Neuberg GW, Kukin ML, Penn J, Medina N, Yushak M, Packer M. Hemodynamic effects of renin inhibition by enalkiren in chronic congestive heart failure. *Am J Cardiol*. 1991;67:63–66.
26. Kiowski W, Beermann J, Rickenbacher P, Haemmerli R, Thomas M, Burkart F, Meinertz T. Angiotensinergic versus nonangiotensinergic hemodynamic effects of converting enzyme inhibition in patients with chronic heart failure: assessment by acute renin and converting enzyme inhibition. *Circulation*. 1994;90:2748–2756.
27. Nicholls MG, Richards AM; Christchurch Cardioendocrine Research Group. Disease monitoring of patients with chronic heart failure. *Heart* 2007;93:519–523.
28. van Kesteren CA, Danser AH, Derkx FH, Dekkers DH, Lamers JM, Saxena PR, Schalekamp MA. Mannose 6-phosphate receptor-mediated internalization and activation of prorenin by cardiac cells. *Hypertension*. 1997;30:1389–1396.
29. Nguyen G, Delarue F, Burckle C, Bouzhir L, Giller T, Sraer JD. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest*. 2002;109:1417–1427.
30. Luft FC. Renin and its putative receptor remain enigmas. *J Am Soc Nephrol*. 2007;18:1989–1992.
31. Fisher ND, Hollenberg NK. Renin inhibition: what are the therapeutic opportunities? *J Am Soc Nephrol*. 2005;16:592–599.

CLINICAL PERSPECTIVE

Inhibition of the renin-angiotensin system with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is beneficial in heart failure. We studied a new approach to blocking this system using the direct renin inhibitor aliskiren. Our primary aim was to assess the safety of adding aliskiren to conventional treatment. Aliskiren was generally well tolerated in the selected patients randomized in the present study. It also reduced plasma B-type natriuretic peptide concentrations and urinary aldosterone excretion, which suggests it might be of therapeutic benefit in heart failure. This hypothesis, however, needs to be tested in an appropriately designed and sized prospective study.