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Research Letter

The effect of Aliskiren on exercise capacity in older patients with heart failure and preserved ejection fraction: A randomized, placebo-controlled, double-blind trial

Targeting the renin–angiotensin–aldosterone system (RAAS) pathways has long been considered a logical intervention for heart failure (HF) with preserved ejection fraction (HFpEF), due to its hypothesized link to left ventricular (LV) hypertrophy and fibrosis, and observations that HFpEF patients have abnormal activation of the RAAS. Aliskiren, as a direct renin inhibitor, functions through inhibition of angiotensin II effects as well as angiotensin II-independent effects mediated via the prorenin receptor.[1] Direct renin inhibition has the theoretical benefit of upstream RAAS inhibition at the point of pathway activation. Furthermore, renin is a key variable in hypertension which is the most common risk factor for HFpEF, preceding the diagnosis ~80% of HFpEF patients. We hypothesized that the severe exercise intolerance experienced by older patients with HFpEF can be improved with direct renin inhibition. To begin testing of this hypothesis, we performed a 6-month prospective, randomized, double-blind, placebo-controlled pilot trial with detailed measurements of exercise performance, health-related quality- of-life (QOL) scores, and cardiac structure and function.

As previously described, and in accord with the 2013 American College of Cardiology HF Guideline, HFpEF was defined as symptoms and signs of HF, a preserved LVEF(≥50%), and no other medical condition that could mimic HF symptoms, including significant ischemic, infiltrative, valvular, pericardial, or pulmonary disease, anemia or thyroid dysfunction.[2,3] HF diagnosis was based on clinical criteria as previously described, including HF clinical score ≥3 from the National Health and Nutrition Examination Survey(NHANES)-I of,[4] and those used by Rich et al.,[5] and verified by a board-certified cardiologist.[2,3] The NHANES-1 criteria have been shown to have 94% specificity for HF, similar to the Framingham criteria.[6] Patients were excluded if they had: peripheral artery revascularization or acute cerebrovascular syndrome within past 3 months; known significant bilateral renal artery stenosis; seated blood pressure (BP) ≥160/90 mmHg at baseline screening; prior treatment with, intolerance of or contra-indication to aliskiren; current treatment with antidepressant medication in the monoamine oxidase or selective serotine reuptake inhibitor class; baseline serum potassium >5.0 mEq/L or serum creatinine ≥2.5 mg/dL.

Exercise testing was performed on a treadmill using the modified Naughton protocol and conducted by the same master's exercise physiologist as previously described.[3,7] Metabolic gas exchange was measured continuously during exercise and averaged over 15-second intervals (Medgraphics Ultima, Medical Graphics Corp, St Paul, MN). Peak VO_2 was defined as the average of the 2 highest VO_2 values for a given 15-second interval within the last 90 seconds of exercise.[7] We have shown peak VO_2 measurements to be highly reproducibly specifically in HFpEF patients using these methods.[7] Exercise time, VO_2 at the ventilatory threshold (VAT), a key measure of submaximal exercise performance,[7] and 6-minute walk distance (6MWD) were also assessed. Echo-Doppler examinations, including mitral annulus tissue and blood flow Doppler, were performed during supine rest at baseline and follow-up and analyzed as previously described in detail.[3]

Participants were randomly assigned to receive either aliskiren or placebo in a 1:1 ratio using permuted blocks and stratification by current angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB). Aliskiren vs placebo was initiated at 300 mg or placebo, with no dose titrations. Outcomes were assessed using an intention-to-treat analysis. Comparisons of outcome measures between intervention groups were made by repeated measures analysis of covariance procedures. Analyses were adjusted for pre-randomization values of the outcome measure and other factors significantly associated with the outcome variable after adjusting for the other terms in the model. Data were presented as raw, unadjusted mean +/− standard deviation at each visit for each group, along with the P-value corresponding to the adjusted least squares outcomes means from the analysis of covariance procedures accounting for all data at all follow-up visits. Significance was set at $P < .05$.

Fifty-two patients were enrolled. Patient characteristics were typical of HFpEF and had severely reduced exercise capacity (Tables I and II) and typical echo-Doppler findings, including LV hypertrophy, concentric LV remodeling, abnormal indices of diastolic function including reduced mitral annulus velocity and increased early filling to annulus velocity, and mildly increased left atrial size (Supplemental Table I). Twenty-four patients in the aliskiren group and 27 in the placebo group completed the 6-month follow-up. Compliance by pill count was excellent (94%). All patients tolerated full dose and there were no reductions in dose needed. Retention was excellent. There were 22 adverse events in18 individual patients, 6 in aliskiren and 16 in the placebo group: 3 acute exacerbations of HF in 3 separate patients, all in the placebo group; 5 hospitalizations, all in the placebo group (1 for viral gastroenteritis, 1 for small bowel obstruction, 1 for dehydration, and 2 for dyspnea; the remaining adverse events were minor.

At 6-month follow-up, peak VO_2 was 0.5 mL kg^{-1} min^{-1} higher in aliskiren compared to placebo (14.9 ± 0.2 mL kg^{-1} min^{-1} versus 14.4 ± 0.2 mL kg^{-1} min^{-1}; $P = .10$, trend, Figure). VAT was 5% higher in aliskiren compared to placebo (888 ± 19 m//min versus 841 ± 18 mL/min; $P = .08$, Figure). There was a small but significant reduction in resting systolic BP (-8 mmHg; $P = .01$) and pulse pressure (-7 mmHg; P = .01, Supplemental Table II). However, there was no relationship between change in systolic BP and change in peak VO_2 (r: −0.12, $P = .41$). There were no significant differences in exercise time, 6-MWD, QOL, or LV structure

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Table I
Baseline characteristics of the study population

Characteristic	Aliskiren (n = 25)	Placebo (n = 27)	*P*
Age (years)	69.3 ± 6.3	70.6 ± 7.7	.52
Sex, Women	19 (76)	23 (85)	.49
Race, Caucasian	17 (68)	14 (52)	.27
Body weight (kg)	87.0 ± 12.9	90.4 ± 19.6	.46
BSA (m^2)	1.91 ± 0.15	1.95 ± 0.23	.43
BMI (kg/m^2)	33.3 ± 4.9	33.7 ± 6.6	.79
LVEF (%)	59 ± 8	61 ± 8	.30
Sinus rhythm	24 (96)	25 (93)	1.0
NYHA class			
II	20 (80)	17 (63)	.23
III	5 (21)	10 (39)	
Diabetes mellitus	11 (44)	10 (37)	.78
History of hypertension	24 (96)	26 (96)	1.0
Systolic BP (mmHg)	130 ± 15	130 ± 21	.97
Diastolic BP (mmHg)	73 ± 7	73 ± 9	.99
Diastolic Filling Pattern			
Normal	0 (0)	0 (0)	.74
Delayed	18 (75)	20 (80)	
Pseudonormal	6 (25)	5 (20)	
Current Medication			
ACE-Inhibitors	9 (36)	11 (41)	.78
Beta-blockers	11 (44)	13 (48)	.79
CA channel blockers	9 (36)	10 (37)	1.0
Digoxin	0 (0)	1 (4)	1.0
Diuretics	17 (68)	20 (74)	.76
ARBs	7 (28)	6 (22)	.75
Nitrates	3 (12)	3 (11)	1.0

Data represented are mean ± SD or count (%).
Abbreviations: BSA: body surface area; BMI: body mass index; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; BP: blood pressure; Ea: early mitral annulus velocity; E: early mitral flow velocity; ACE: angiotensin converting enzyme; CA: calcium; ARB: angiotensin receptor blocker.

Table II
Exercise Performance

	Aliskiren				Placebo				*P*
	Baseline	12 Week	Final	LS mean*	Baseline	12 week	Final	LS mean*	
Peak Exercise									
Indexed VO_2 ($mL\ kg^{-1}\ min^{-1}$)	14.4 ± 2.9	15.0 ± 3.2	15.0 ± 3.2	14.9 ± 0.2	14.2 ± 1.8	14.2 ± 2.0	14.4 ± 2.1	14.4 ± 0.2	.10
VO_2 (mL/min)	1228 ± 230	1279 ± 255	1281 ± 256	1304 ± 16	1278 ± 336	1303 ± 332	1293 ± 369	1275 ± 15	.19
Time (s)	621 ± 120	628 ± 135	624 ± 151	607 ± 13	580 ± 126	602 ± 137	579 ± 145	605 ± 12	.90
Heart rate (bpm)	131 ± 25	135 ± 23	132 ± 25	130 ± 2	125 ± 24	126 ± 22	122 ± 23	127 ± 2	.17
Respiratory rate (bpm)	34 ± 5	34 ± 6	35 ± 6	35 ± 1	35 ± 7	35 ± 6	34 ± 7	34 ± 1	.67
Oxygen pulse (mL/beat)	9.8 ± 3.4	10.0 ± 3.6	10.1 ± 3.3	10.4 ± 0.1	10.5 ± 2.9	10.5 ± 2.6	10.7 ± 2.8	10.3 ± 0.1	.72
VCO_2 (mL/min)	1433 ± 288	1492 ± 318	1477 ± 323	1474 ± 24	1422 ± 399	1476 ± 418	1445 ± 451	1465 ± 23	.79
VE (L/min)	47 ± 9	49 ± 10	49 ± 10	47 ± 1	45 ± 11	46 ± 11	45 ± 12	46 ± 1	.53
RER	1.17 ± 0.05	1.17 ± 0.07	1.15 ± 0.06	1.14 ± 0.01	1.11 ± 0.07	1.13 ± 0.09	1.11 ± 0.08	1.14 ± 0.01	.91
VE/VCO_2 slope	32.2 ± 4.3	31.5 ± 4.8	31.8 ± 4.9	30.9 ± 0.5	30.2 ± 4.7	30.5 ± 3.8	29.4 ± 4.4	30.5 ± 0.5	.61
VAT (mL/**min**)	794 ± 151	872 ± 180	830 ± 187	888 ± 19	880 ± 248	883 ± 267	872 ± 258	841 ± 18	.08
6 min walk (**feet**)	1364 ± 169	1378 ± 172	1372 ± 188	1360 ± 15	1321 ± 198	1366 ± 180	1302 ± 198	1348 ± 16	.58

Data represented are mean ± SD.
Abbreviations: VO_2: oxygen consumption; VCO_2: carbon dioxide production; VE: minute ventilation; RER: respiratory exchange ratio; VAT: ventilatory anaerobic threshold.
* LS means ± SE represents combined follow-up visits following adjustment for the baseline value, age and gender. *P*-value represents comparison of LS means.

and function. There were no significant changes in safety blood labs (Supplemental Table III).

The effect of aliskiren on exercise intolerance, which is an independent, clinically meaningful outcome, has not to our knowledge been examined in any type of HF. There are some data regarding the effect of aliskiren on other outcomes in patients with HFrEF. In the ALOFT study,[8] plasma N-terminal-pro brain natriuretic peptide level was significantly reduced by aliskiren compared with placebo and there was reduction in echocardiographic parameters of LV remodeling. However, the ASTRONAUT trial showed no reduction in cardiovascular death or HF rehospitalization with the addition of aliskiren to standard therapy in hospitalized HFrEF patients.[9] In the ATMOSPHERE study, the addition of aliskiren to enalapril did not result in a lower risk of death or HF hospitalization compared to aliskiren or enalapril monotherapy.[10] Thus, although direct renin inhibition did not reduce clinical events in HFrEF patients, it reduced RAAS escape, natriuretic peptides and adverse LV remodeling.[8,9,11]

In this trial, we observed a trend ($P = .10$) for improvement in peak VO_2 with an effect size of 0.5 $mL\ kg^{-1}\ min^{-1}$. Although relatively modest, this is similar in magnitude to that achieved with exercise training (0.6 $mL\ kg^{-1}\ min^{-1}$) in HF-ACTION, the largest trial of exercise outcomes in HF patients and is similar to that often achieved in pharmacological trials HFrEF patients.[12] In addition, since older HFpEF patients have such markedly impaired exercise capacity, even modest effects sizes (in absolute units) can be proportionally substantial and clinically meaningful. Furthermore, since trials of drug therapy for improving exercise capacity in HFpEF have been negative to date, this finding is worth pursuing further.

The present study also provides other valuable information to facilitate the design of a subsequent, definitive trial. The inclusion/exclusion