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## The Effect of Aliskiren on Exercise Capacity in Older Patients with Heart Failure and Preserved Ejection Fraction: A Randomized, Placebo-Controlled, Double-Blind Trial

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### Abstract

In older patients (70±7 years) with chronic well-compensated heart failure with preserved ejection and controlled blood pressure, 6 months treatment with aliskiren (direct renin inhibitor) showed non-significant trends for modest improvements in peak exercise oxygen consumption (14.9±0.2 ml/kg/min versus 14.4±0.2 ml/kg/min; p=0.10, trend) and ventilatory anaerobic threshold (888±19 m//min versus 841±18ml/min; p=0.08).

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.<sup>1</sup> 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-

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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.<sup>2,3</sup> 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,<sup>4</sup> and those used by Rich et al,<sup>5</sup> and verified by a board-certified cardiologist.<sup>2,3</sup> The NHANES-1 criteria have been shown to have 94% specificity for HF, similar to the Framingham criteria.<sup>6</sup> 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 contraindication to aliskiren; current treatment with antidepressant medication in the monoamine oxidase or selective serotonin 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.<sup>3,7</sup> Metabolic gas exchange was measured continuously during exercise and averaged over 15-second intervals (Medgraphics Ultima, Medical Graphics Corp., St. Paul, Minnesota). Peak VO<sub>2</sub> was defined as the average of the 2 highest VO<sub>2</sub> values for a given 15-second interval within the last 90 seconds of exercise.<sup>7</sup> We have shown peak VO<sub>2</sub> measurements to be highly reproducibly specifically in HFpEF patients using these methods.<sup>7</sup> Exercise time, VO<sub>2</sub> at the ventilatory threshold (VAT), a key measure of submaximal exercise performance,<sup>7</sup> 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.<sup>3</sup>

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 300mg 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<0.05.

Fifty-two patients were enrolled. Patient characteristics were typical of HFpEF and had severely reduced exercise capacity (Table 1 and Table 2) 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 1). 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 in 18 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  $\text{VO}_2$  was 0.5 ml/kg/min higher in aliskiren compared to placebo ( $14.9 \pm 0.2$  ml/kg/min versus  $14.4 \pm 0.2$  ml/kg/min;  $p=0.10$ , trend, Figure 1). VAT was 5% higher in aliskiren compared to placebo ( $888 \pm 19$  m<sup>3</sup>/min versus  $841 \pm 18$  m<sup>3</sup>/min;  $p=0.08$ , Figure 1). There was a small but significant reduction in resting systolic BP ( $-8$  mmHg;  $p=0.01$ ) and pulse pressure ( $-7$  mmHg;  $p=0.01$ , supplemental Table 2). However, there was no relationship between change in systolic BP and change in peak  $\text{VO}_2$  ( $r: -0.12$ ,  $p=0.41$ ). There were no significant differences in exercise time, 6-MWD, QOL, or LV structure and function. There were no significant changes in safety blood labs (supplemental Table 3).

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 HF<sub>rEF</sub>. In the ALOFT study,<sup>8</sup> 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 HF<sub>rEF</sub> patients.<sup>9</sup> 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.<sup>10</sup> Thus, although direct renin inhibition did not reduce clinical events in HF<sub>rEF</sub> patients, it reduced RAAS escape, natriuretic peptides and adverse LV remodeling.<sup>8;9;11</sup>

In this trial, we observed a trend ( $p=0.10$ ) for improvement in peak  $\text{VO}_2$  with an effect size of 0.5 ml/kg/min. Although relatively modest, this is similar in magnitude to that achieved with exercise training (0.6 ml/kg/min) in HF-ACTION, the largest trial of exercise outcomes in HF patients and is similar to that often achieved in pharmacological trials HF<sub>rEF</sub> patients.<sup>12</sup> In addition, since older HF<sub>pEF</sub> 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 HF<sub>pEF</sub> 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 criteria yielded a patient group that was typical of HF<sub>pEF</sub> seen in population-based studies, and who had severe exercise intolerance, impaired diastolic function, and reduced QOL. The enrollment rate was reasonably efficient

(4.7 patients per month), there was a good safety profile, and retention and compliance were excellent. A future trial should also utilize the Kansas City Cardiomyopathy Questionnaire, which recent reports suggest is more sensitive for assessing QOL in HFpEF patients than the instrument we used.<sup>3</sup>

### Limitations:

The p-values for peak VO<sub>2</sub> (0.10) and for VAT (0.08) suggest the study may have been underpowered, particularly for the effect size we observed which was less than our sample size estimate. We performed additional analyses which indicated that if the number of completed patients in the trial had been 119, and other results remained the same (such as effect size and variability), then the study would have been positive on peak VO<sub>2</sub> at the 0.05 level of significance. Of course, that includes some key assumptions that might not be met in a subsequent study, so this additional analysis results should be interpreted with caution. However, these results do provide valuable data for sample size calculations for a subsequent, larger, definitive trial. Similarly we cannot exclude the possibility that a longer duration of treatment may have shown a statistically significant improvement in exercise capacity. Because this was a single-center study, results require confirmation in a larger, multicenter trial.

Another limitation of our study is lack of more detailed hemodynamic measures. Even though patients had controlled BP at baseline, and aliskiren treatment was accompanied by only a small (but significant) reduction in systolic BP that did not appear related statistically to the improved exercise performance, we cannot definitively exclude a role for improved arterial function and / ventricular-vascular coupling, since we did not perform detailed assessments of central arterial hemodynamics (aortic stiffness, aortic distensibility, stroke volume/pulse pressure) particularly during exercise. These should be examined in future studies.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

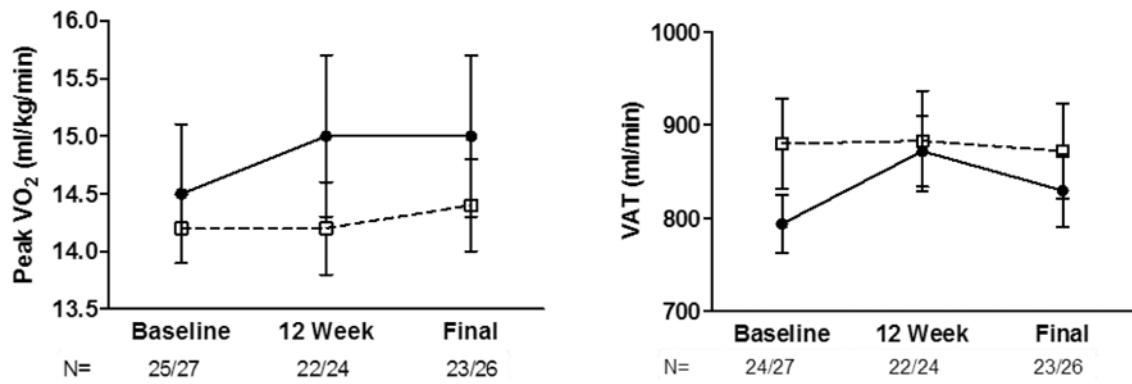
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**Figure 1.**

Raw, unadjusted means  $\pm$ 1 SE at baseline and 3-month and 6-month follow-up visits for aliskiren (circles) and placebo (squares) for peak exercise VO<sub>2</sub> by expired gas analysis. The number of evaluable patients is shown for the specific outcome at each visit (aliskiren versus placebo).

**Table 1.**

## Baseline Characteristics of the Study Population

Characteristic	Aliskiren (n=25)	Placebo (n=27)	p-value
Age(years)	69.3±6.3	70.6±7.7	0.52
Sex, Women	19(76)	23(85)	0.49
Race, Caucasian	17(68)	14(52)	0.27
Body weight (kg)	87.0±12.9	90.4±19.6	0.46
BSA(m <sup>2</sup> )	1.91±0.15	1.95±0.23	0.43
BMI(kg/m <sup>2</sup> )	33.3±4.9	33.7±6.6	0.79
LVEF(%)	59±8	61±8	0.30
Sinus rhythm	24(96)	25(93)	1.0
NYHA class			
II	20(80)	17(63)	0.23
III	5(21)	10(39)	
Diabetes mellitus	11(44)	10(37)	0.78
History of hypertension	24(96)	26(96)	1.0
Systolic BP(mmHg)	130±15	130±21	0.97
Diastolic BP(mmHg)	73±7	73±9	0.99
Diastolic Filling Pattern			
Normal	0(0)	0(0)	0.74
Delayed	18(75)	20(80)	
Pseudonormal	6(25)	5(20)	
Current Medication			
ACE-Inhibitors	9(36)	11(41)	0.78
Beta-blockers	11(44)	13(48)	0.79
CA channel blockers	9(36)	10(37)	1.0
Digoxin	0(0)	1(4)	1.0
Diuretics	17(68)	20(74)	0.76
ARBs	7(28)	6(22)	0.75
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 2.

## Exercise Performance

	Aliskiren				Placebo				p-value
	Baseline	12 Week	Final	LS mean*	Baseline	12 week	Final	LS mean*	
<b>Peak Exercise</b>									
Indexed VO <sub>2</sub> (ml/kg/min)	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	0.10
VO <sub>2</sub> (ml/min)	1228±230	1279±255	1281±256	1304±16	1278±336	1303±332	1293±369	1275±15	0.19
Time(sec)	621±120	628±135	624±151	607±13	580±126	602±137	579±145	605±12	0.90
Heart rate(bpm)	131±25	135±23	132±25	130±2	125±24	126±22	122±23	127±2	0.17
Respiratory rate(bpm)	34±5	34±6	35±6	35±1	35±7	35±6	34±7	34±1	0.67
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	0.72
VCO <sub>2</sub> (ml/min)	1433±288	1492±318	1477±323	1474±24	1422±399	1476±418	1445 ±451	1465±23	0.79
VE(l/min)	47±9	49±10	49±10	47±1	45±11	46±11	45±12	46±1	0.53
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	0.91
VE/VCO <sub>2</sub> 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	0.61
VAT(ml/min)	794±151	872±180	830±187	888±19	880±248	883±267	872±258	841±18	0.08
<b>6 Minute walk(feet)</b>	1364±169	1378±172	1372±188	1360±15	1321±198	1366±180	1302±198	1348±16	0.58

Data represented are mean ± SD.

\* LS means ± SE represents combined follow-up visits following adjustment for the baseline value, age and gender. P-value represents comparison of LS means.

Abbreviations: VO<sub>2</sub>: oxygen consumption; VCO<sub>2</sub>: carbon dioxide production; VE: minute ventilation; RER: respiratory exchange ratio; VAT: ventilatory anaerobic threshold