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## Effect of Peripheral Arterial Disease on Functional and Clinical Outcomes in Patients with Heart Failure From HF-ACTION

W. Schuyler Jones, MD<sup>a,b</sup>, Robert Clare, MS<sup>c</sup>, Stephen J. Ellis, PhD<sup>c</sup>, James S. Mills, MD<sup>a</sup>, David L. Fischman, MD<sup>d</sup>, William E. Kraus, MD<sup>a</sup>, David J. Whellan, MD<sup>d</sup>, Christopher M. O'Connor, MD<sup>a,c</sup>, and Manesh R. Patel, MD<sup>a,c</sup>

<sup>a</sup>Department of Medicine, Duke University Medical Center, Durham, North Carolina

<sup>b</sup>Department of Medicine, Durham VA Medical Center, Durham, North Carolina

<sup>c</sup>Duke Clinical Research Institute, Durham, North Carolina

<sup>d</sup>Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania

### Abstract

Patients with peripheral arterial disease (PAD) have lower functional capacity and worse clinical outcomes than age and gender matched patients. Few data exist on the relationship of PAD with functional and clinical outcomes in heart failure (HF) patients. We sought to compare HF patients with and without PAD for baseline functional capacity, response to exercise training, and clinical outcomes. HF-ACTION was a randomized controlled trial comparing usual care to structured exercise training plus usual care in HF patients with an ejection fraction  $\leq 35\%$  and NYHA class II – IV heart failure symptoms. Cardiopulmonary exercise (CPX) testing occurred at enrollment, 3 months, and 1 year. Clinical follow-up occurred up to 4 years. Of the 2331 HF-ACTION patients, 157 (6.8%) had PAD. At baseline, HF patients with PAD had a lower exercise duration (8.0 vs. 9.8 minutes,  $p < 0.001$ ), lower peak oxygen consumption ( $VO_2$ ) (12.5 vs. 14.6 mL/kg/min,  $p < 0.001$ ), and shorter six minute walking distance (306 vs. 371 meters,  $p < 0.001$ ) compared to HF patients without PAD. At three months, HF patients with PAD had less improvement on CPX testing [exercise duration (0.5 vs. 1.1 minutes;  $p = 0.002$ ) and peak  $VO_2$  (mean change; 0.1 vs. 0.6 mL/kg/min;  $p = 0.04$ )] compared to HF patients without PAD. PAD was an independent predictor of all-cause death or hospitalization [hazard ratio (95% CI); 1.31 (1.06 – 1.62),  $p = 0.011$ ]. PAD patients with HF have depressed baseline exercise capacity and decreased response to exercise training. In conclusion, PAD is an independent predictor of all-cause death or hospitalization in HF patients.

### Keywords

Peripheral Arterial Disease; Heart Failure; Exercise Training

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Evaluation of the influence of PAD on HF patients is warranted to better understand the response to exercise training and clinical outcomes in patients with these disease states. We hypothesized that the presence of PAD in HF patients would be associated with worse baseline exercise capacity, a limited response to exercise training in an exercise training

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**Corresponding Author:** W. Schuyler Jones MD Mailing Address: Duke University Medical Center Box 3126, Durham, NC 27710 jones298@mc.duke.edu Telephone Number: 919-286-0411 ext. 5214 Fax Number: 919-681-7223.

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study, more hospitalizations, and a higher morbidity and mortality than HF patients without PAD.

## Methods

The design of the HF-ACTION clinical trial has been described previously.<sup>1</sup> Briefly, HF-ACTION was a multinational, randomized controlled trial investigating outpatients with a left ventricular (LV) ejection fraction (EF)  $\leq$  35% and New York Heart Association (NYHA) class II to IV heart failure symptoms. These patients were randomized to a usual care plus structured exercise training group or a usual care group. Enrollment occurred from 2003 to 2007 in the United States, Canada, and France. Patients were excluded if they had major co-morbidities or limitations that would interfere with exercise training, recent ( $\leq$  6 weeks) or planned major cardiovascular events or procedures, performed regular exercise training, or used devices that limited the ability to achieve target heart rates. The study protocol was reviewed and approved by the institutional review board or ethics committee for each enrolling center and by the coordinating center's institutional review board. All patients provided written informed consent prior to randomization.

All patients were treated with evidence-based medical therapies for heart failure at enrollment. Enrolled patients were to undergo a baseline cardiopulmonary exercise (CPX) test and eligible patients were then randomized in a 1:1 fashion using permuted block randomization which was stratified by clinical site and heart failure etiology (ischemic vs. non-ischemic). Patients with a history of PAD as documented on the case report form were included in the PAD cohort. If patients did not have a diagnosis of PAD, they were included in the 'no PAD' cohort.

Patients randomized to the usual care plus exercise training group participated in a supervised exercise program with a goal of 36 sessions over 3 months. Full details of the exercise training protocol have been reported.<sup>2</sup> Patients were to begin home-based exercise after completing 18 supervised sessions and were to fully transition to home exercise after 36 supervised sessions. Patients in the usual care group were not provided with formal exercise instructions. All patients received a detailed HF educational booklet at the time of enrollment, including information on medications, fluid management, symptom exacerbation, sodium intake, and activity level of 30 minutes of moderate-intensity activity on most days of the week, consistent with the guidelines from the American College of Cardiology and the American Heart Association.<sup>3</sup>

All patients were asked to return for clinic visits every 3 months for the first 2 years and yearly thereafter for up to 4 years. CPX testing and a 6-minute walk test were to be performed at the 3-, 12-, and 24-month follow-up visits, while the 6-minute walk test was also to be performed at the 3-year and final visits. Patients made their final visit at the end of the study follow-up period or at 4 years. For patients lost to follow-up, searches of the Social Security Death Index and the National Death Index were performed to assess whether any of these patients had died during the follow-up period.

The primary end point for this study was a composite of all-cause death or all-cause hospitalization. All-cause death, the composite of cardiovascular death or cardiovascular hospitalization, and the composite of cardiovascular death or heart failure hospitalization were secondary endpoints. In addition, data were collected to measure the change from baseline in peak oxygen consumption (peak  $\text{VO}_2$ ) on a progressive exercise test to exhaustion at 3 months and 1 year and change in distance from baseline in the 6-minute walk test at 3 months and 1 year. A clinical end point committee adjudicated deaths and many cardiovascular hospitalizations for each patient.

Statistical analyses were performed by the coordinating center (Duke Clinical Research Institute, Durham, North Carolina) using SAS software version 8.2 (SAS Institute Inc, Cary, North Carolina). Baseline patient characteristics were summarized using medians for continuous variables and percentages for categorical variables. All statistical tests were 2-tailed. Cumulative event rates were calculated using the Kaplan-Meier method and a plot of unadjusted Kaplan-Meier rates for the primary endpoint by PAD status was produced.

Cox proportional hazards modeling was used to statistically compare the two study groups with respect to the time until the first occurrence of either component of the primary composite end point and the secondary time-to-event outcomes, adjusting for covariates identified in models developed by the process described below. Relative risks were expressed as hazard ratios (HR) with 95% confidence intervals (C.I.) and were calculated using the Cox proportional hazards model.

The baseline predictors of the primary and secondary outcomes were objectively selected using a stepwise variable selection based on a bootstrap-backward selection process (see Supplementary Appendix). Multiple imputation was used to replace missing data for covariates. A mixed model analysis was used to estimate changes from baseline to specified repeated measures time points in physiologic variables (6-minute walk (meters), CPX exercise time (minutes), and peak  $\text{VO}_2$  (mL/kg/min)) at 3 months and 12 months among PAD and non-PAD patients. Comparisons of change at these time points between the two groups were made as contrasts within the model.

## Results

Of the 2331 HF-ACTION patients, 2320 (99.5%) patients had baseline data on PAD and 157 (6.8%) patients had a diagnosis of PAD. Table 1 demonstrates the baseline demographic characteristics, exercise capacity, and randomized treatment assignment of the PAD and non-PAD patients. The mean modeled change from baseline in peak  $\text{VO}_2$ , exercise duration and the 6-minute walk distance at 3 months are presented in Table 2.

Data for the primary and secondary endpoints are presented in Table 3. The one-year Kaplan-Meier rate of the primary endpoint (all-cause death or all-cause hospitalization) was 53.5% vs. 41.0% of HF patients with and without PAD, respectively. PAD remained an independent predictor of the primary endpoint after adjustment (HR (95% C.I.): 1.31 (1.06 – 1.62);  $p=0.011$ ; Figure 1). The one-year Kaplan-Meier rate of the secondary endpoint of all-cause death was 11% vs. 4.5% of HF patients with and without PAD, respectively. However, PAD only trended towards significance for this endpoint after adjustment (HR (95% C.I.) = 1.36 (0.98 – 1.91);  $p=0.07$ ). Incidence of the composite secondary endpoints cardiovascular (CV) death / CV hospitalization and CV death / HF hospitalization was also increased among PAD patients, with PAD making a significant contribution to previously defined adjusted models for CV death / CV hospitalization (HR (95% C.I.) = 1.41 (1.12 – 1.76);  $p=0.003$ ) and CV death / HF hospitalization (HR (95% C.I.) = 1.72 (1.31 – 2.26);  $p<0.001$ ).

## Discussion

This analysis of PAD patients in the HF ACTION study identifies several important findings. The first is that patients with HF and PAD have decreased baseline functional capacity when compared to HF patients without PAD. The second is that patients with HF and PAD may not obtain the same benefits from structured exercise training afforded routine HF patients without PAD. Finally, patients with HF and PAD have substantially worse

clinical outcomes when compared to patients without PAD. We believe these findings could have important clinical and health policy implications.

The decreased baseline functional capacity in HF patients with PAD is not surprising as these patients were more likely to be older, current smokers, to have an ischemic etiology of HF, and more likely to have a history of diabetes, hypertension, MI, and stroke. Multivariable adjustment was performed to control for these differences in baseline characteristics, and PAD remained an independent predictor of all-cause mortality or hospitalization in this study population. This is similar to a recent sub-study from the Beta-Blocker Evaluation of Survival Trial (BEST) dataset that showed that PAD was associated with increased mortality and hospitalization in a propensity-matched cohort of chronic HF patients.<sup>4</sup>

Importantly, we evaluated the response to exercise training in HF patients with PAD. Currently, supervised exercised training is a class I recommendation in PAD patients, based on moderate sized randomized controlled trials to increase walking distance.<sup>5-7</sup> In HF publications, prior studies have observed that a lack of improvement in exercise capacity after exercise training has strong prognostic significance for clinical events.<sup>8,9</sup> To date no study has described the functional limitations in HF patients with PAD and the lack of functional improvement after exercise training in this population. The current study shows that a diagnosis of PAD is associated not only with an elevated risk of mortality and hospitalization in HF, but also with limited functional benefit after exercise training in this population.

The mechanism leading to the association of PAD with poorer outcomes and lack of improvement with exercise training in a large HF population is unknown. The lack of improvement with exercise training has been separately described in the PAD and HF literature, and it may relate to skeletal muscle abnormalities or a mixture of central and peripheral hemodynamic abnormalities.<sup>10-16</sup> There are unfortunately no data on skeletal muscle changes or hemodynamic changes with exercise in this study. The association of PAD with poor outcomes may be related to more extensive atherosclerosis or a higher frequency of myocardial infarction or sudden cardiac death in this subpopulation of the HF-ACTION cohort. Additionally, patients with PAD are known to undergo more endovascular revascularization procedures than similar patients without PAD, and the associated hospitalizations and complications could contribute to the findings in our study. Unfortunately, our study was not designed to interrogate these factors.

The standard of care for management of HF patients consists of lifestyle modification, utilization of evidence-based medications, and a walking program at home.<sup>3</sup> The current study finds that, despite standard HF care, patients who carry a diagnosis of PAD do poorly. Approximately 50% of patients with a confirmed diagnosis of PAD are asymptomatic, thus the prevalence of PAD in this HF population is likely underestimated.

Taken together, these facts imply that simple diagnostic testing such as ankle-brachial index (ABI) testing may identify HF patients at higher risk for poorer outcomes. When PAD is identified, the medical treatment of PAD in HF patients is limited due to the current FDA black box warning against the use of cilostazol, a phosphodiesterase inhibitor proven to mildly improve walking distance in PAD patients. Further investigation into the influence of other co-morbid conditions, use of disease-specific medications, and evaluation of invasive treatment options for PAD should be considered in this population.

Several limitations of this study must be recognized. This is a post-hoc analysis of a randomized controlled trial, and the representation of patients may not be generalizable to a “real world” HF population. We relied on an existing diagnosis of PAD rather than on a

screening diagnostic test, such as ankle-brachial index testing, for inclusion in the PAD cohort. Since PAD is often asymptomatic and under-diagnosed, the prevalence of PAD may be underestimated in this study population, possibly leading to overestimated hazard ratios for PAD. Furthermore, the extent of PAD was not defined in our cohort. Missing data may have biased the follow-up exercise testing results. Unmeasured confounding factors may have affected the results of the Cox modeling as well as the results on the three-month change in exercise testing.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

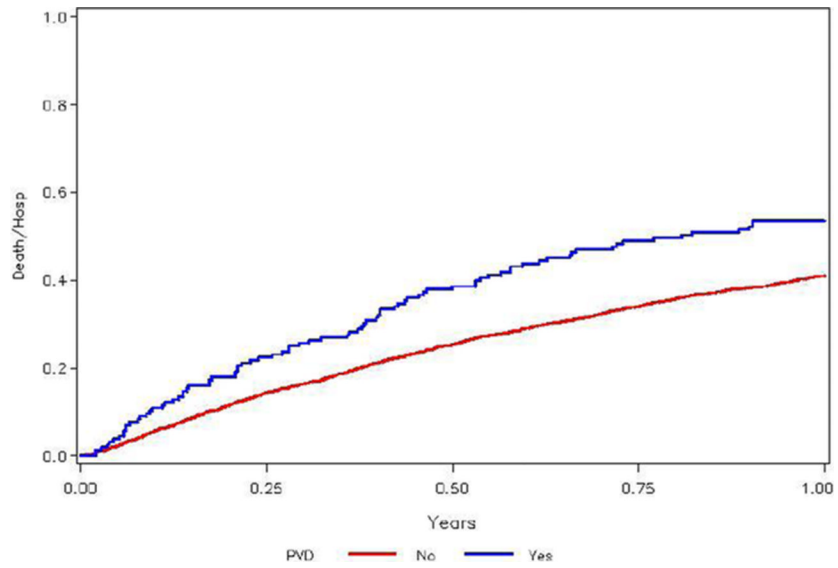
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**Figure 1. Unadjusted Kaplan-Meier Curve Demonstrating Time to All-Cause Death or All-Cause Hospitalization by Presence or Absence of PAD**  
Unadjusted Kaplan-Meier curve that demonstrates the time to all-cause death or all-cause hospitalization based on presence or absence of PAD.



**Table 1**

Baseline Demographic and Clinical Characteristics, Exercise Testing Results, and Randomized Treatment Assignments

<b>Patient Characteristics</b>	<b>All HF Patients (N=2320)</b>	<b>HF with PAD (N=157)</b>	<b>HF no PAD (N=2163)</b>
Age (years, median)	59	67	59
Female Sex	28%	10%	30%
United States	89%	89%	89%
Canada	8%	10%	8%
France	3%	1%	3%
Body Mass Index (kg/m <sup>2</sup> , median)	30	28	30
Ischemic Etiology of HF	51%	83%	49%
Current Angina Pectoris Class			
None	84%	79%	84%
I	9%	9%	9%
II–IV	8%	12%	7%
Moderate to Severe or Severe Mitral Regurgitation	11%	12%	11%
Rest Electrocardiographic Ventricular Conduction			
Normal	43%	35%	44%
Left Bundle Branch Block	17%	17%	17%
Right Bundle Branch Block	4%	6%	4%
Intraventricular Conduction Delay	13%	13%	13%
Paced	23%	29%	23%
Creatinine in mg/dL (median)	1.2	1.4	1.2
Baseline Beta Blocker Dose Using Carvedilol Equivalent (mg/day, median)	27	31	27
Baseline Loop Diuretic Dose Using Furosemide Equivalent (mg/day, median)	40	40	40
KCCQ Overall Summary Score at Baseline (median)	68	65	68
Smoking Status			
Never	37%	19%	39%
Current	17%	28%	16%
Past	46%	53%	46%
Left Ventricular Ejection Fraction (% , median)	25%	25%	25%
History of Hypertension	60%	77%	59%
History of Diabetes Mellitus	32%	45%	31%
Prior Myocardial Infarction	42%	68%	40%
Prior Chronic Obstructive Pulmonary Disease	11%	30%	9%
Prior Stroke	10%	17%	10%
<b>Baseline Exercise Testing Medians (Q1, Q3)</b>			
Exercise Duration on Cardiopulmonary Exercise Test (minutes)	9.6 (6.9, 12.0)	8.0 (5.7, 10.0)	9.8 (7.0, 12.1)
Peak Oxygen Consumption (mL/kg/min)	14.4 (11.4, 17.7)	12.5 (10.0, 15.0)	14.6 (11.6, 17.8)
6 Minute Walk Distance (meters)	370 (299, 435)	306 (235, 393)	375 (302, 438)



<b>Patient Characteristics</b>	<b>All HF Patients (N=2320)</b>	<b>HF with PAD (N=157)</b>	<b>HF no PAD (N=2163)</b>
<b>Randomized Treatment Assignment</b>			
Usual Care	50%	54%	50%
Exercise Training + Usual Care	50%	46%	50%

**Table 2**

Change in Exercise Testing Results from Baseline to 3 Months

Mean Modeled Change in Exercise Testing from Baseline to 3 Months Means (95% CI)	HF with PAD (N=157)	HF no PAD (N=2163)	p value
Exercise Duration on Cardiopulmonary Exercise Test (minutes)	0.5 (0.1, 0.9)	1.1 (1.0, 1.2)	0.002
Peak Oxygen Consumption (mL/kg/min)	0.1 (-0.4, 0.5)	0.6 (0.4, 0.7)	0.04
6 Minute Walk Distance (meters)	10.1 (-3.0, 23.1)	14.4 (11.1, 17.7)	0.53

Unadjusted Kaplan-Meier Event Rates, Unadjusted and Adjusted Effect of Peripheral Arterial Disease for Primary and Secondary Endpoints.

**Table 3**

Endpoint	Kaplan-Meier 1 year Rate Estimates		PAD Effect in Unadjusted Cox Proportional Hazards Model			PAD Effect in Adjusted Cox Proportional Hazards Model		
	No PAD	PAD	Wald Chi-Square	P-Value	HR (95% CI)	Wald Chi-Square	P-Value	HR (95% CI)
All-Cause Death or All-Cause Hospitalization	0.410	0.535	17.9	<0.001	1.49 (1.24-1.79)	6.4	0.011	1.31 (1.06-1.62)
All-Cause Death	0.045	0.110	21.9	<0.001	2.07 (1.53-2.81)	3.3	0.070	1.36 (0.98-1.91)
Cardiovascular Death or Cardiovascular Hospitalization	0.318	0.414	14.4	<0.001	1.47 (1.20-1.79)	8.8	0.003	1.41 (1.12-1.76)
Cardiovascular Death or Heart Failure Hospitalization	0.149	0.210	21.5	<0.001	1.76 (1.39-2.24)	15.2	<0.001	1.72 (1.31-2.26)