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Original Article

Impact of Panvascular Disease on Exercise Capacity and Clinical Outcomes in Patients with Heart Failure with Reduced Ejection Fraction

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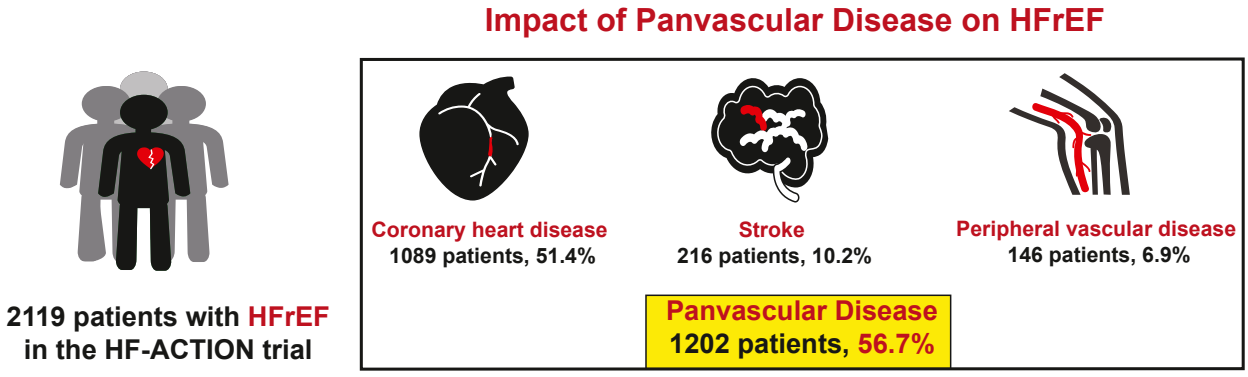

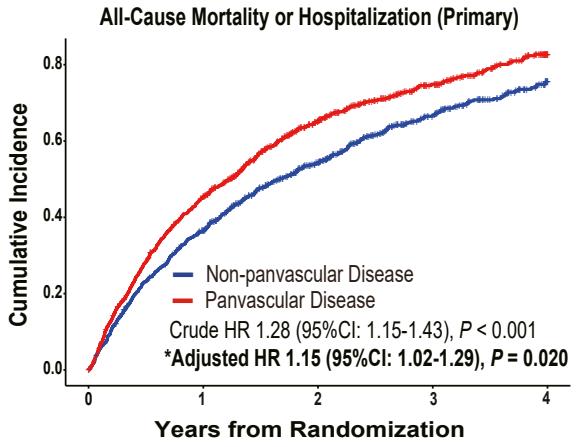

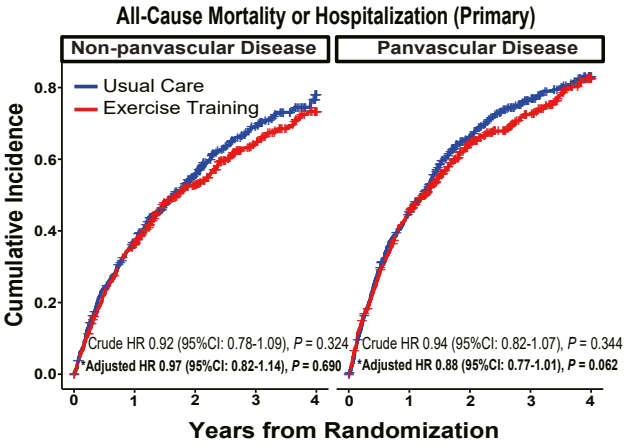

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ABSTRACT

Background: The aim of this study was to assess the impact of panvascular disease (PVD) on quality of life (QOL), exercise capacity, and clinical outcomes, in patients with heart failure (HF) with reduced ejection fraction (HFrEF).

Methods: We performed a post hoc analysis of the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION; NCT00047437). Patients with PVD were defined as those having coronary heart disease, stroke, or peripheral vascular disease at baseline. Multivariable Cox proportional hazard models were constructed to evaluate the effect of PVD on the primary endpoint (all-cause mortality or hospitalization) and secondary endpoints (all-cause mortality, cardiovascular (CV) mortality or CV hospitalization, and CV mortality or HF hospitalization). Generalized estimating-equation models were constructed to evaluate the effect of PVD on QOL (Kansas City Cardiomyopathy Questionnaire score) and exercise capacity (peak oxygen consumption and 6-minute walk test distance).

Results: Of 2119 patients with chronic HFrEF, 1202 (56.7%) had comorbid PVD. PVD was associated significantly with reduced exercise capacity ($P < 0.001$). Patients with PVD had a higher risk of all-cause mortality or hospitalization (hazard ratio [HR] 1.15, 95% confidence interval [CI]: 1.02-1.29), CV mortality or CV hospitalization (HR 1.22, 95% CI: 1.07-1.39), and CV mortality or HF hospitalization (HR 1.25, 95% CI: 1.05-1.48), compared with the risk for patients without PVD. Aerobic exercise training did not significantly improve the prognosis of HFrEF patients, in either the PVD or the non-PVD subgroups.

Conclusions: PVD may adversely affect the QOL, exercise capacity, and prognosis of patients with chronic HFrEF.

RÉSUMÉ

Contexte : Cette étude visait à évaluer les répercussions de la maladie panvasculaire (PV) sur la qualité de vie, la capacité d'effort et les résultats cliniques de patients atteints d'insuffisance cardiaque avec fraction d'éjection réduite (ICFER).

Méthodologie : Nous avons procédé à une analyse a posteriori des données de l'étude HF-ACTION (*Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training*; NCT00047437). Les patients considérés comme présentant une maladie PV au départ étaient atteints d'une maladie coronarienne ou d'une maladie vasculaire périphérique, ou avaient subi un accident vasculaire cérébral. On a utilisé des modèles de régression à risques proportionnels de Cox pour évaluer les effets de la maladie PV sur le principal paramètre d'évaluation (mortalité ou hospitalisation toutes causes confondues) et les paramètres d'évaluation secondaires (mortalité toutes causes confondues, mortalité d'origine cardiovasculaire [CV]) ou hospitalisation d'origine CV, et mortalité d'origine CV ou hospitalisation liée à une insuffisance cardiaque). Des modèles d'analyse par équation d'estimation généralisée (EEG) ont été construits pour évaluer les effets de la maladie CV sur la qualité de vie (score au questionnaire *Kansas City Cardiomyopathy Questionnaire*) et la capacité d'effort (consommation maximale d'oxygène et distance parcourue à l'épreuve de marche de 6 minutes).

Résultats : Sur les 2 119 patients atteints d'ICFER chronique, 1 202 (56,7 %) présentaient une maladie PV concomitante. La maladie PV a été associée à une réduction significative de la capacité d'effort ($p <$ 0,001). Les patients atteints d'une maladie PV présentaient un risque accru de mortalité ou d'hospitalisation toutes causes confondues (rapport des risques instantanés [RRI] = 1,15; intervalle de confiance [IC] à 95 % : 1,02-1,29), de mortalité d'origine CV ou d'hospitalisation d'origine CV (RRI = 1,22; IC à 95 % : 1,07-1,39), et de mortalité d'origine CV ou d'hospitalisation liée à une insuffisance cardiaque (RRI = 1,25; IC à 95 % : 1,05-1,48), comparativement au risque observé chez les patients ne présentant pas de maladie PV. L'exercice aérobique n'a pas amélioré de façon significative le pronostic des patients atteints d'ICFER, et ce, que les patients soient atteints ou non d'une maladie PV.

Conclusions : La maladie PV peut avoir des répercussions négatives sur la qualité de vie, la capacité d'effort et le pronostic des patients atteints d'ICFER chronique.

Panvascular disease (PVD) is a systemic disease based on atherosclerosis and often involves multiple vascular beds throughout the body, including the coronary, cerebrovascular, and peripheral arteries.[1] Although PVDs share common underlying arterial pathology, risk factors, and preventive treatments, they rarely are studied concurrently.[2] As an emerging discipline, panvascular medicine is proposed to establish a comprehensive management model, including prevention, diagnosis, therapy, and prognosis.[3] PVD is the most common cause or comorbidity of heart failure (HF), and in-depth study of PVD can help in the prevention and management of HF. However, most current studies related to PVD have focused on major adverse cardiovascular (CV) events, such as myocardial infarction, stroke, and CV death.[4-6] Fewer studies have been done on the relationship between PVD and HF, focusing on HF risk prediction in patients with PVD.[7,8] For patients who have developed HF, an observational study found that PVD increased the risk of death from acute decompensated HF.[9] In addition, the impact of PVD on quality of life (QOL) and exercise capacity in patients with HF is unclear.

HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) was the largest clinical trial of aerobic exercise training (ET) in outpatients with chronic stable HF with reduced ejection fraction (HFrEF).[10] We performed a secondary analysis of the HF-ACTION trial to assess the impact of PVD on QOL, exercise

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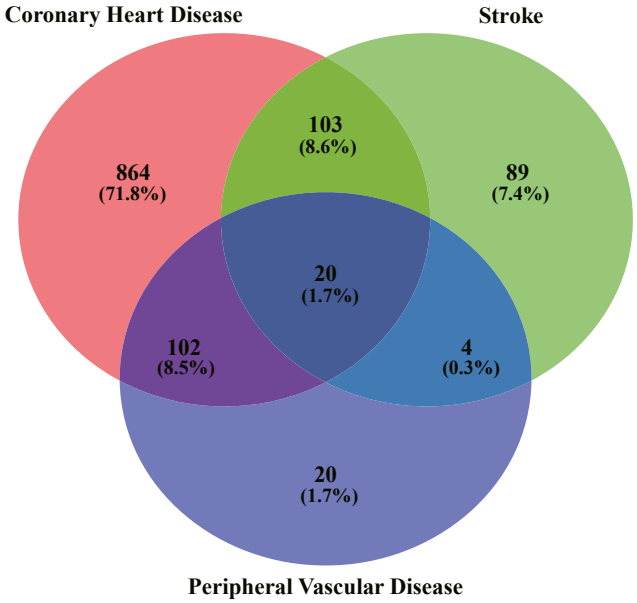

Figure 1. Prevalence of panvascular disease in patients with chronic heart failure with reduced ejection fraction.

capacity, and clinical outcomes, in patients with chronic HFrEF, and to explore the effectiveness of aerobic ET in HF patients with comorbid PVD.

Methods

Study design and participants

The study design and principal results of HF-ACTION have been reported previously.[10,11] In brief, HF-ACTION was a multicentre, randomized controlled trial designed to evaluate the long-term efficacy and safety of aerobic ET in patients with chronic HF (left ventricular ejection fraction $\leq$ 35% and New York Heart Association class II-IV). The trial recruited 2331 participants between April 2003 and February 2007, from 82 medical centres, who were randomized in a 1:1 ratio to either aerobic ET or usual care. The exercise intervention consisted of 36 sessions of supervised aerobic ET and follow-up home-based exercise. All participants, regardless of treatment group, received detailed HF treatment and self-management instruction consistent with the American College of Cardiology & American Heart Association guidelines.

The study protocol was approved by the ethics committee of each participating centre, and all participants provided written informed consent. Deidentified, publicly available data from the trial were obtained from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center.

Definition of PVD

PVD was defined as the presence of coronary heart disease (CHD), stroke, or peripheral vascular disease at baseline, and it was classified further into single-bed vascular disease vs polyvascular disease (coexisting disease in $\geq$ 2 arterial beds), based on the number of vascular beds affected.[3,4] PVD information was collected through medical history records in the case-report form.

Outcomes of interest

Consistent with HF-ACTION, the primary outcome for our analysis was a composite of all-cause mortality or all-cause hospitalization. Secondary endpoints included all-cause mortality, the composite of CV mortality or CV hospitalization, and the composite of CV mortality or HF hospitalization. QOL was assessed by the 23-item self-administered Kansas City Cardiomyopathy Questionnaire (KCCQ). Exercise capacity was assessed per the 6-minute walk test distance (6-MWD) test and peak oxygen consumption (Vo_2). Differences in QOL and exercise capacity were analyzed at baseline, and at 3-month and 12-month follow-up.

Statistical analysis

Baseline characteristics of the study participants were summarized as medians and interquartile ranges (continuous variables), or as frequencies and percentages (categorical variables). Differences in baseline characteristics across groups were evaluated using the Mann–Whitney *U* test or the Kruskal–Wallis H test, for continuous variable, and the χ^2 test, for categorical variables. Missing rates were calculated for variables, and multiple imputation was performed for variables with $<$ 10% missingness (Supplemental Table S1). The Kaplan–Meier method was used to calculate cumulative event rates, and comparisons of differences between groups were performed using the log-rank test. Multivariable Cox proportional hazard models were constructed to evaluate the effect of PVD status on the primary and secondary endpoints. Generalized estimating-equation models were constructed to evaluate the effect of PVD status on QOL and exercise capacity. All models were adjusted for the following covariates: age, sex, race, treatment group,

Table 1. Baseline characteristics of study participants, stratified by panvascular disease status

Characteristics	Overall (N = 2119)	Nonpanvascular disease (n = 917)	Panvascular disease (n = 1202)	*P*
Age, y	59.0 (51.0, 68.0)	54.0 (45.0, 62.0)	63.0 (55.0, 71.0)	< 0.001
Female sex	598 (28.2)	372 (40.6)	226 (18.8)	< 0.001
Race				< 0.001
Black or African American	669 (32.1)	380 (42.3)	289 (24.3)	
White	1311 (62.8)	484 (53.8)	827 (69.6)	
Other	107 (5.1)	35 (3.9)	72 (6.1)	
Exercise training	1055 (49.8)	454 (49.5)	601 (50.0)	0.823
Ischemic etiology of heart failure	1089 (51.4)	0 (0.0)	1089 (90.6)	< 0.001
Peripheral vascular disease	146 (6.9)	0 (0.0)	146 (12.1)	< 0.001
Stroke	216 (10.2)	0 (0.0)	216 (18.0)	< 0.001
Hypertension	1254 (59.5)	463 (50.8)	791 (66.1)	< 0.001
Diabetes mellitus	673 (31.8)	233 (25.4)	440 (36.6)	< 0.001
Atrial fibrillation or atrial flutter	440 (20.8)	156 (17.0)	284 (23.6)	< 0.001
Smoking				< 0.001
Never	778 (36.9)	446 (48.7)	332 (27.8)	
Former	359 (17.0)	154 (16.8)	205 (17.2)	
Current	973 (46.1)	316 (34.5)	657 (55.0)	
New York Heart Association class				0.003
II	1345 (63.5)	613 (66.8)	732 (60.9)	
III	754 (35.6)	300 (32.7)	454 (37.8)	
IV	20 (0.9)	4 (0.4)	16 (1.3)	
Body mass index, kg/m^2	29.8 (25.9, 35.1)	31.3 (26.3, 37.4)	29.2 (25.6, 33.3)	< 0.001
Heart rate, beats/min	70.0 (63.0, 77.0)	72.0 (64.0, 80.0)	68.0 (62.0, 76.0)	< 0.001
Systolic blood pressure, mm Hg	110.0 (100.0, 126.0)	110.5 (100.0, 125.0)	110.0 (100.0, 126.0)	0.948
Diastolic blood pressure, mm Hg	70.0 (60.0, 78.0)	70.0 (62.0, 80.0)	70.0 (60.0, 78.0)	< 0.001
Beck Depression Inventory II score	8.0 (4.0, 15.0)	8.0 (4.0, 16.0)	8.0 (4.0, 14.0)	0.350
KCCQ overall summary score	68.0 (51.0, 83.0)	68.0 (51.0, 83.0)	69.0 (51.0, 84.0)	0.261
Left ventricular ejection fraction	24.8 (20.0, 30.2)	24.7 (20.0, 30.7)	24.9 (20.1, 30.0)	0.899
Sodium, mEq/L	139.0 (137.0, 141.0)	139.0 (137.0, 141.0)	139.0 (137.0, 141.0)	0.698
Blood urea nitrogen, mg/dL	20.0 (15.0, 28.0)	18.0 (14.0, 25.0)	22.0 (16.0, 30.5)	< 0.001
eGFR, mL/min per 1.73 m^2	66.3 (50.7, 81.3)	72.1 (57.2, 87.7)	62.9 (47.3, 77.5)	< 0.001
Functional measures				
Distance of 6-min walk, m	371.2 (300.0, 435.9)	384.0 (314.3, 448.1)	361.9 (285.9, 426.0)	< 0.001
Cardiopulmonary exercise time, min	9.7 (7.0, 12.0)	10.1 (7.5, 12.8)	9.0 (6.7, 11.6)	< 0.001
Peak oxygen consumption, mL/kg/min	14.5 (11.5, 17.7)	15.3 (12.2, 18.4)	14.0 (11.2, 17.0)	< 0.001
Baseline use of medications and devices				
ACE-I or ARB	2000 (94.4)	877 (95.6)	1123 (93.4)	0.029
β-blocker	2004 (94.6)	874 (95.3)	1130 (94.0)	0.190
Aldosterone receptor antagonist	954 (45.0)	458 (49.9)	496 (41.3)	< 0.001
Loop diuretic	1654 (78.1)	711 (77.5)	943 (78.5)	0.613
Digoxin	956 (45.1)	437 (47.7)	519 (43.2)	0.040
Aspirin	1358 (64.1)	449 (49.0)	909 (75.6)	< 0.001
HMG-CoA reductase inhibitor	1006 (47.5)	263 (28.7)	743 (61.8)	< 0.001
Implantable cardioverter-defibrillator	859 (40.5)	270 (29.4)	589 (49.0)	< 0.001
Biventricular pacemaker	390 (18.4)	166 (18.1)	224 (18.6)	0.754

Data are presented as median (interquartile range), for continuous measures, and n (%), for categorical measures.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; eGFR, estimated glomerular filtration rate; HMG-CoA, hydroxymethylglutaryl-CoA; KCCQ, Kansas City Cardiomyopathy Questionnaire.

duration of cardiopulmonary exercise test, left ventricular ejection fraction, Beck Depression Inventory II score, and history of atrial fibrillation or flutter. The adjustment covariates were selected based on the HF-ACTION trial, which were prespecified and used consistently in previous analyses.[10,12] All analyses were performed using R, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). A *P* value of < 0.05 was considered statistically significant.

Results

Of the 2130 participants who consented to data use, 11 were excluded, due to missing information on peripheral vascular disease. This analysis finally included 2119 participants with a median age of 59 years; 28.2% of the participants were female, and 62.8% were of White race. A total of 1202 participants (56.7%) had combined PVD at baseline, of whom 973 (45.9%) had single-bed vascular disease, and 229 (10.8%) had polyvascular disease. Combined atherosclerotic involvement of all 3 vascular territories was rare (Fig. 1).

Patients with HFrEF and PVD were older (aged 63 vs 54 years), were more often male (81% vs 59%), and were more frequently White (70% vs 54%) than those without PVD. At baseline, they had worse New York Heart Association functional class, renal function, and exercise capacity, a higher burden of atherosclerosis-related risk factors (smoking, hypertension, and diabetes mellitus), and higher rates of antiatherosclerotic medication use (Table 1). Differences in baseline characteristics among participants with non-PVD, single-bed vascular disease, and polyvascular disease are shown in Supplemental Table S2.

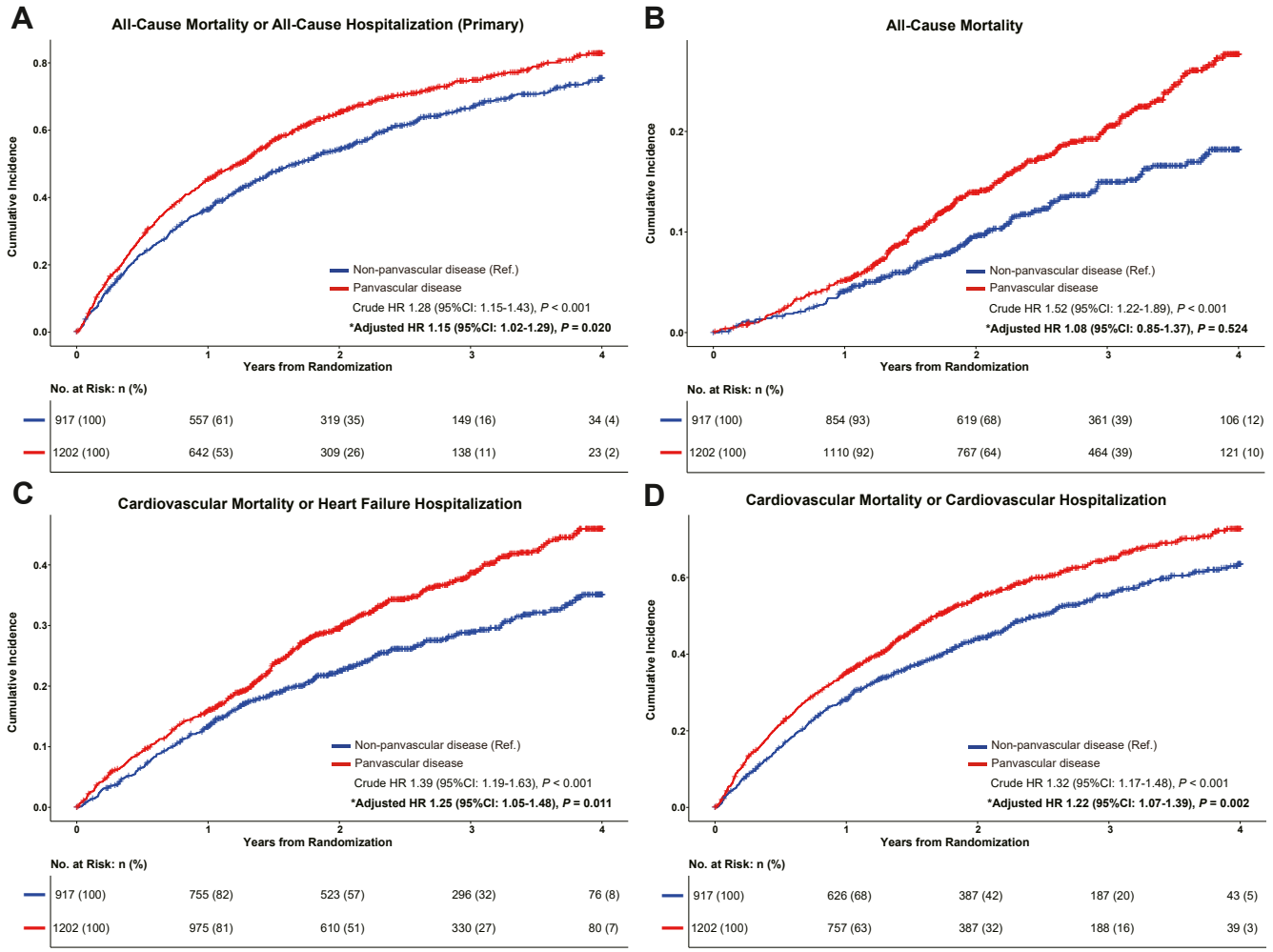

Figure 2. Cumulative incidence of the primary and secondary endpoints, stratified by panvascular disease status. Shown are the following: (**A**) all-cause mortality or all-cause hospitalization; (**B**) all-cause mortality; (**C**) cardiovascular (CV) mortality or heart failure hospitalization; and (**D**) CV mortality or CV hospitalization. CI, confidence interval; HR, hazard ratio; Ref., referent. *Adjusted for age, sex, race, treatment group, duration of cardiopulmonary exercise test, left ventricular ejection fraction, Beck Depression Inventory II score, and history of atrial fibrillation or flutter.

Impact of PVD on clinical outcomes in patients with HFrEF

During a median follow-up of 2.9 years (interquartile range, 2.0-3.8), 1417 patients (66.9%) developed a primary composite endpoint event. Of these, 847 (40.0%) had comorbid PVD. Univariate survival analysis showed that patients with PVD had a higher risk of the primary endpoint, and of all secondary endpoints, than did patients without PVD (all $P < 0.001$; Fig. 2). After adjustment for covariates, patients with PVD had a higher risk of the primary endpoint (hazard ratio [HR] 1.15, 95% confidence interval [CI]: 1.02-1.29), CV mortality or CV hospitalization (HR 1.22, 95% CI: 1.07-1.39), and CV mortality or HF hospitalization (HR 1.25, 95% CI: 1.05-1.48) than did patients without PVD. The difference in the risk of all-cause mortality (HR 1.08, 95% CI: 0.85-1.37) between the 2 groups was not significant. Patients with HFrEF and polyvascular disease had the highest risk of both the primary endpoint and all secondary endpoints (Supplemental Fig. S1).

Impact of PVD on QOL and exercise capacity in patients with HFrEF

No significant difference occurred in KCCQ scores at baseline, vs 3-month follow-up vs 12-month follow-up for patients with PVD vs patients without PVD (Supplemental Table S3). The 6-MWD and the peak Vo_2 of patients with PVD at baseline, and at 3-month and 12-month follow-up, were lower than these measures for those without PVD (all $P < 0.001$). After adjustment for covariates, the difference in KCCQ scores between the 2 groups was not significant ($\beta = -0.34$, 95% CI:-1.73 to 1.05, $P = 0.632$). Patients with PVD had a lower 6-MWD ($\beta = -13.5$, 95% CI: -21.2 to -5.94, $P < 0.001$) and peak Vo_2 ($\beta = -0.83$, 95% CI: -1.11 to -0.55, $P < 0.001$) than did patients without PVD (Fig. 3).

Effects of aerobic ET on clinical outcomes, QOL, and exercise capacity in patients with vs without PVD

As shown in Table 2, aerobic ET did not significantly reduce the risk of either the primary endpoint or any of the

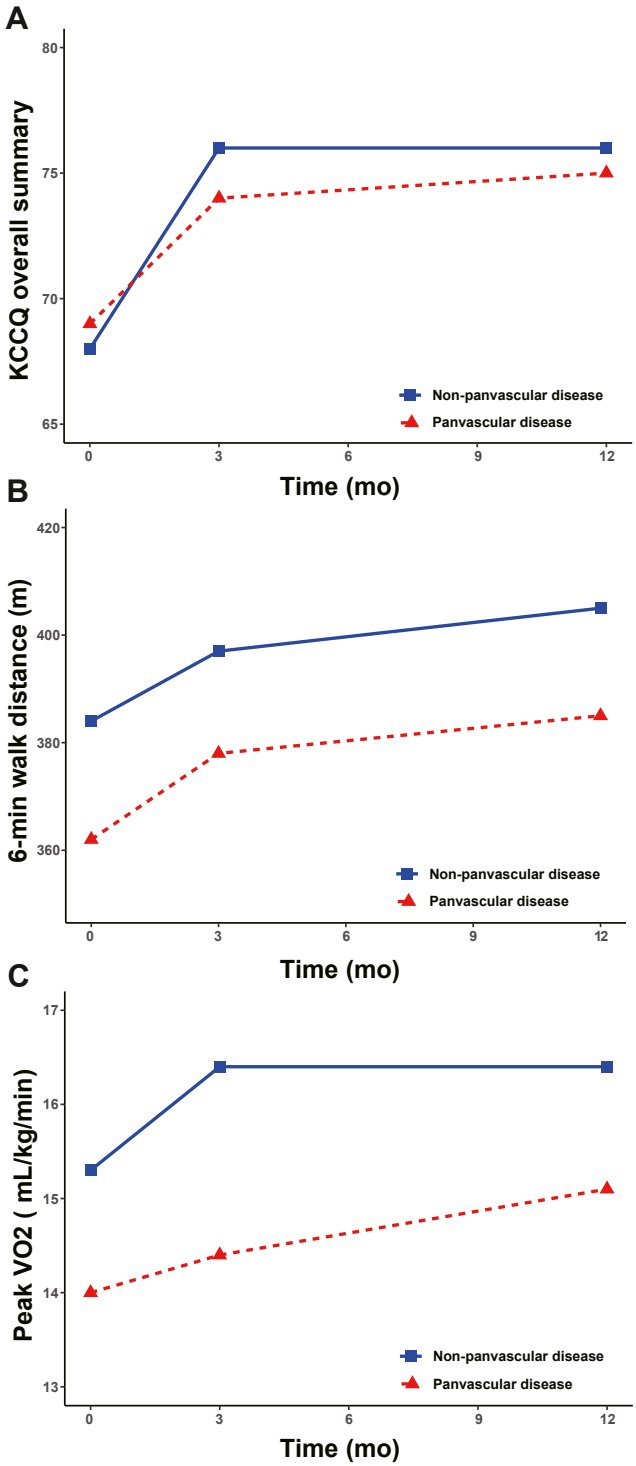

Figure 3. Changes in Kansas City Cardiomyopathy Questionnaire (KCCQ) score, peak oxygen consumption (VO_2), and 6-minute walk distance, stratified by panvascular disease status. Shown are: (**A**) KCCQ overall summary score; (**B**) 6-minute walk distance; and (**C**) peak VO_2.

secondary endpoints, in patients with HFrEF, in both the PVD and the non-PVD subgroups. In the PVD subgroup, aerobic ET was associated with improvement of KCCQ scores ($\beta = 1.96$, 95% CI: 0.34-3.57, $P = 0.017$), but not with the changes in 6-MWD ($\beta = 4.14$, 95% CI: −4.72 to 13.00, $P = 0.360$) and peak Vo_2 ($\beta = 0.23$, 95% CI: −0.10 to 0.55, $P = 0.167$). In the non-PVD subgroup, aerobic ET was associated with an increase in 6-MWD ($\beta = 11.28$, 95% CI: 0.83-21.72, $P = 0.034$), but not with the changes in the KCCQ scores ($\beta = 1.09$, 95% CI: −0.81 to 2.99, $P = 0.261$) and peak Vo_2 ($\beta = 0.19$, 95% CI: −0.19 to 0.57, $P = 0.326$).

Table 2. Effects of aerobic exercise training (ET) on clinical outcomes in patients with vs without panvascular disease (PVD)

Outcomes of interest	Subgroup	Usual care	ET	Crude		Interaction	Adjusted*		Interaction
		Events, n (%)	Events, n (%)	HR (95% CI)	*P*	*P*†	HR (95% CI)	*P*	*P*†
Primary composite endpoint	PVD	435 (72.4)	412 (68.6)	0.94 (0.82−1.07)	0.344	0.898	0.88 (0.77−1.01)	0.062	0.382
	NVD	292 (63.1)	278 (61.2)	0.92 (0.78−1.09)	0.324		0.97 (0.82−1.14)	0.690	
All-cause mortality	PVD	115 (19.1)	115 (19.1)	1.01 (0.78−1.31)	0.943	0.204	0.98 (0.76−1.27)	0.874	0.496
	NVD	68 (14.7)	52 (11.5)	0.76 (0.53−1.09)	0.131		0.86 (0.60−1.24)	0.432	
CV mortality or heart failure hospitalization	PVD	219 (36.4)	202 (33.6)	0.93 (0.77−1.12)	0.442	0.293	0.91 (0.75−1.10)	0.335	0.508
	NVD	137 (29.6)	109 (24.0)	0.78 (0.61−1.01)	0.058		0.83 (0.64−1.07)	0.146	
CV mortality or CV hospitalization	PVD	372 (61.9)	346 (57.6)	0.93 (0.81−1.08)	0.361	0.793	0.88 (0.76−1.02)	0.087	0.407
	NVD	242 (52.3)	224 (49.3)	0.90 (0.75−1.08)	0.272		0.97 (0.81−1.17)	0.772	

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; NVD, nonpanvascular disease.

*Adjusted for age, sex, race, duration of cardiopulmonary exercise test, left ventricular ejection fraction, Beck Depression Inventory II score, and history of atrial fibrillation or flutter.

†A multiplicative interaction term (treatment arm × PVD status) was added to the model for the overall cohort.

Discussion

In this post hoc analysis of HF-ACTION, we observed that 56.7% of patients with chronic HFrEF had PVD, and 10.8% had polyvascular disease. HF patients with comorbid PVD had a worse prognosis, with a significantly increased risk of all-cause mortality or all-cause hospitalization; CV mortality, or CV hospitalization; and CV mortality or HF hospitalization. Of these, patients with polyvascular disease had the worst clinical outcomes. During the course of chronic HF, exercise capacity consistently was lower in patients with comorbid PVD than it was in those without PVD, despite their having similar measures of QOL.

PVD is associated with a poor prognosis. **Imp**roved **R**eduction of **O**utcomes: **V**ytorin **E**fficacy **I**nternational **T**rial (IMPROVE-IT),[13] the **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk (FOURIER) trial,[14,15] and the **C**ardiovascular **O**utcomes for **P**eople Using **A**nticoagulation **S**trategies (COMPASS) trial[16,17] all demonstrated that PVD increased patients' risk of major adverse CV events. PVD also can increase the risk of HF and can affect the prognosis of patients with HF adversely. In the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) registry, a greater extent of arterial disease was significantly associated with prior congestive HF (CHF), signs of CHF on hospital admission, and a diminished ejection fraction.[18] The rate of CHF increased with the number of affected vascular beds. Data from the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events—Thrombolysis in Myocardial Infarction 50 (TRA 2°P-TIMI 50) trial showed the following: 2070 patients (8%) with stable atherosclerosis had a prior history of HF; hospitalization for HF risk was associated highly with the burden of symptomatic atherosclerosis; and patients with 3, 2, and 1 symptomatic vascular territory, respectively, experienced hospitalization for HF event rates of 6.5%, 3.2%, and 0.9%, at 3 years.[8] The Atherosclerosis Risk in Communities (ARIC) study found that being hospitalized with acute decompensated HF and coexisting polyvascular disease was associated with an increased risk of all-cause mortality.[9] The present study found that PVD also increases the risk of adverse outcomes in patients with chronic stable HFrEF, and that this risk increases with the number of vascular beds involved.

PVD also can impact QOL and exercise capacity. Previous studies have shown that CHD, stroke, peripheral arterial disease, and HF all can lead to reduced QOL and exercise capacity.[19-23] This study found that PVD further exacerbates exercise limitation in HF patients, but its impact on QOL may be "masked" by chronic HF symptoms. ET is beneficial for both HF and PVD. In HF-ACTION, aerobic ET produced modest significant reductions for both all-cause mortality or hospitalization, and for CV mortality or HF hospitalization, after adjusting for highly prognostic predictors of the primary endpoint.[10] The Cochrane systematic review confirmed that ET not only improves QOL and reduces the risk of hospitalization in patients with HF, but also reduces the risk of myocardial infarction, hospitalization, and CV mortality in patients with CHD.[24,25] The benefit of ET in patients with stroke and peripheral arterial disease mainly is an improvement in their functional indices.[26,27] Although the aforementioned studies have confirmed the value of ET in the management of HF and PVD, we found that when chronic HF coexisted with PVD, ET could improve only the QOL of patients.

Limitations

The present study has the following limitations. First is that this is a post hoc analysis of HF-ACTION, and although adjustments were made for highly prognostic predictors, other unknown or unmeasured factors may have influenced these results. Second, the percentage of missing data for KCCQ score, 6-MWD, and peak Vo_2 was > 10% (13%-37%), at both 3-month and the 12-month follow-up assessment, which may reduce the accuracy of QOL and exercise capacity measures. Third, a lower level of adherence to exercise recommendations in the intervention group, and the presence of exercise crossovers in the usual-care group, may have reduced the benefits of aerobic ET. Finally, the participants in HF-ACTION were outpatients with HFrEF, who were recruited from 2003 to 2007. They were relatively young, had a relatively modest burden of comorbidities, such as atrial fibrillation, were stable enough for aerobic ET at baseline, and received guideline-directed medical therapy, which was different from the current guideline recommendations. Therefore, our findings may not be generalizable to patients

with HFrEF who do not meet the study's inclusion and/or exclusion criteria, and the study's significance is in helping to provide valuable clinical hypotheses for subsequent studies.

Conclusions

In HF-ACTION, more than half of the patients with chronic HFrEF had comorbid PVD, which may affect their QOL, exercise capacity, and prognosis adversely.

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Ethics Statement

The study protocol was approved by the ethics committee of each participating centre, and all participants provided written informed consent. Deidentified, publicly available data from the HF-ACTION trial were obtained from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center.

Patient Consent

The authors confirm that patient consent forms have been obtained for this article.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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