





ORIGINAL RESEARCH

# Recurrent Admissions for Acute Decompensated Heart Failure Among Patients With and Without Peripheral Artery Disease: The ARIC Study

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**BACKGROUND:** Peripheral artery disease (PAD) is both a common comorbidity and a contributing factor to heart failure. Whether PAD is associated with hospitalization for recurrent decompensation among patients with established heart failure is uncertain.

**METHODS AND RESULTS:** Since 2005, the ARIC (Atherosclerosis Risk in Communities) study has conducted active surveillance of hospitalized acute decompensated heart failure (ADHF), with events verified by physician review. From 2005 to 2016, 1481 patients were hospitalized with ADHF and discharged alive (mean age, 78 years; 69% White). Of these, 207 (14%) had diagnosis of PAD. Those with PAD were more often men (55% versus 44%) and smokers (17% versus 8%), with a greater prevalence of coronary artery disease (72% versus 52%). Patients with PAD had an increased risk of at least 1 ADHF readmission, both within 30 days (11% versus 7%) and 1 year (39% versus 28%) of discharge from the index hospitalization. After adjustments, PAD was associated with twice the hazard of ADHF readmission within 30 days (HR, 2.02; 95% CI, 1.14–3.60) and a 60% higher hazard of ADHF readmission within 1 year (HR, 1.60; 95% CI, 1.25–2.05). The 1-year hazard of ADHF readmission associated with PAD was stronger with heart failure with reduced ejection fraction (HR, 2.01; 95% CI, 1.29–3.13) than preserved ejection fraction (HR, 1.04; 95% CI, 0.69–1.56); *P* for interaction=0.05.

**CONCLUSIONS:** Patients with ADHF and concomitant PAD have a higher likelihood of ADHF readmission. Strategies to prevent ADHF readmissions in this high-risk group are warranted.

**Key Words:** epidemiology ■ heart failure ■ peripheral artery disease

Peripheral artery disease (PAD) and heart failure (HF) share many risk factors in common, and frequently coexist in patient populations.<sup>1</sup> Both conditions are characterized by exercise intolerance, possibly contributing to the reported increase in mortality and all-cause hospitalizations for patients with HF with concomitant PAD.<sup>2,3</sup> Prospective studies suggest that PAD is a risk factor for the development of incident HF<sup>4–7</sup>; however, it is unknown whether PAD is associated with increased likelihood of acute decompensation among patients with established HF. Further, as a manifestation of atherosclerotic disease,

concomitant PAD may differentially impact HF secondary to coronary artery disease versus HF arising from a non-ischemic etiology, or HF with reduced ejection fraction (HFrEF) versus HF with preserved ejection fraction (HFpEF). In the present study, we analyze recurrent hospitalizations for acute decompensated heart failure (ADHF) among patients with HF with and without a clinical diagnosis of PAD using hospital surveillance data captured by the cohort component of the ARIC (Atherosclerosis Risk in Communities) study. We examine whether associations differ for HFpEF and HFrEF, or are modified by demographics, extent

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## CLINICAL PERSPECTIVE

### What Is New?

- Whether peripheral artery disease is associated with recurrent hospitalization for acute decompensated heart failure (ADHF) is uncertain.
- In this population-based cohort of patients hospitalized with ADHF, concomitant peripheral artery disease was associated with a higher adjusted likelihood of ADHF readmission.
- The associated hazard of ADHF readmission was stronger for patients with heart failure with reduced ejection fraction than preserved ejection fraction.

### What Are the Clinical Implications?

- Our findings contribute to understanding the association of peripheral artery disease with ADHF readmission in a population-based cohort encompassing 4 geographic regions of the United States.
- Targeted interventions or secondary preventive measures combined with exercise therapy may help reduce readmission for ADHF in patients with coexisting peripheral artery disease.

## Nonstandard Abbreviations and Acronyms

|              |  |
|--------------|--|
| <b>ADHF</b>  | acute decompensated heart failure              |
| <b>ARIC</b>  | Atherosclerosis Risk in Communities Study      |
| <b>HFpEF</b> | heart failure with preserved ejection fraction |
| <b>HFrEF</b> | heart failure with reduced ejection fraction   |

of atherosclerotic burden (prevalent coronary artery disease, history of myocardial infarction, or history of stroke), or other comorbidities. As secondary outcomes, we investigate the relationship between PAD and mortality, and the composite outcome of mortality and/ or ADHF readmissions.

## METHODS

The ARIC study's data and materials are publicly available to qualified investigators with an approved manuscript proposal and data use agreement. The authors will not distribute the data, analytic methods, and study materials to other researchers for purposes of reproducing the results or replicating the procedure.

## ARIC Study

The ARIC study is an observational, population-based cohort of 15 792 mostly White or Black adults in 4 US communities: Forsyth County, NC; Washington County, MD; Jackson, MS; and Minneapolis, MN. Study participants were recruited with informed consent and have been prospectively followed since enrollment (1987–1989). To date, participation in the ARIC cohort study has involved 7 completed in-person study visits, with annual telephone contact during interim years and surveillance of hospitalized events. All research activities are approved by local institutional review boards within the 4 ARIC communities.

## Data Abstraction

In 2005, the ARIC study began abstracting medical records for cohort members hospitalized with heart failure, as previously described.<sup>8</sup> At the time of this writing, hospitalized HF events were adjudicated through December 31, 2017. Demographics, comorbidities, laboratory data, and medications were abstracted from the patient medical record by trained abstractors following a standardized protocol. Laboratory values were abstracted by recording the worst and last values over the course of the hospitalization. For the purposes of our study, the last laboratory values were analyzed, because these are temporally closer to hospital discharge and likely more pertinent to subsequent outcomes. Similarly, we considered medications if prescribed at hospital discharge. Ejection fraction was abstracted from in-hospital echocardiography reports. PAD was defined by documented evidence from the medical record, which included any of the following: diagnosis of PAD, diagnosis of intermittent claudication, diagnosis of lower extremity artery disease, or history of peripheral vascular bypass graft surgery or revascularization.

## ADHF Adjudication

Using standardized criteria, hospitalizations were classified by physician reviewers as definite ADHF, probable ADHF, stable chronic HF, not HF, or unclassifiable, based on diagnostic reports from the hospital record, physician notes, and discharge summaries.<sup>8</sup> ADHF was differentiated from stable, chronic HF by evidence of new onset or worsening paroxysmal nocturnal dyspnea, orthopnea, hypoxia, edema, or shortness of breath. For the purposes of this analysis, we defined HFrEF by an ejection fraction <40% and considered an ejection fraction ≥40% to be HFpEF.

## Recurrent ADHF Hospitalizations

We considered the first hospitalization for definite or probable ADHF captured by active surveillance

in 2005 to 2016 to be the “index” hospitalization, with follow-up for subsequent hospitalizations adjudicated through 2017. Hospitalizations for definite or probable ADHF within 30 days and 1 year of the index hospitalization discharge date were considered ADHF readmissions, with follow-up time administratively censored at the end of each time interval. Transfers were defined by relocation to another acute care hospital or relocation to a rehabilitation unit of the same hospital generating a separate admission. Transfer hospitalizations with admission dates on the day of discharge from a previous ADHF hospitalization were not considered as readmission and were excluded from the analysis.

### Statistical Analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Continuous variables were assessed for normality and compared using t tests or Wilcoxon rank sums tests, as appropriate. Categorical variables were compared using  $\chi^2$  test. The Kaplan–Meier cumulative incidence of ADHF readmission, death, or composite (whichever first) was calculated within 30 days and 1 year of discharge from the index hospitalization. Hazard ratios of ADHF readmissions were analyzed using standard Cox regression, competing-risk Cox regression,<sup>9</sup> and repeat-events Cox regression. Standard and competing-risk Cox regression models were censored after the first occurring ADHF readmission. Repeat-events Cox regression models counted each recurrent ADHF readmission per patient within 30 days and 1 year of the index hospitalization discharge date, with censoring only at death or the end of the observation period. The discharge date of the index hospitalization served as the common origin for all events, with robust variance estimators accounting for within-subject correlation between recurrent readmissions.<sup>10</sup> Hazard ratios were adjusted for demographics (age, race, sex, year of admission and hospital of admission), as well as comorbidities thought to influence ADHF readmissions (chronic obstructive pulmonary disease, current smoking, diabetes mellitus, chronic kidney disease, coronary artery disease, and history of stroke/transient ischemic attack). As a sensitivity analysis, models were further adjusted for obesity, history of myocardial infarction, and length of hospital stay (a surrogate for acuity of the hospitalization). Modification of the association between PAD and ADHF readmission was explored by constructing stratified models and testing multiplicative interactions. A  $P < 0.10$  was considered suggestive of statistical interaction, to account for the diminished power inherent with stratification.<sup>11</sup> Death and the composite of death and/ or ADHF readmission were

analyzed as secondary outcomes, using standard and repeat-events Cox regression.

## RESULTS

From 2005 to 2016, there were 1481 index hospitalizations for ADHF among participants of the ARIC cohort study. The mean age at admission was 76 years, most were White (69%), and slightly over half were women (54%). A total of 207 (14%) had a diagnosis of PAD at the index hospitalization. Smoking was more prevalent with PAD (17% versus 8%), as was coronary artery disease (72% versus 52%), chronic obstructive pulmonary disease (39% versus 28%), history of myocardial infarction (31% versus 19%), and history of stroke/transient ischemic attack (29% versus 17%), but the prevalence of obesity was lower (33% versus 42%), Table 1. Known history of HF before the index hospitalization for ADHF was common for both groups, but more prevalent among patients with PAD than those without (64% versus 55%). At the index hospitalization, patients with PAD had higher laboratory values for serum creatinine (1.4 versus 1.2 mg/dL) but left ventricular ejection fraction was similar for the 2 groups (45% and 44%), as was mean length of stay (7.5 days for both). Medications at hospital discharge were largely comparable between the 2 groups, with the exception of diuretics, which were less often prescribed to patients with PAD (68% versus 75%).

The maximum number of recurrent ADHF readmissions per patient within 30 days of discharge ranged from 0 to 2, both for patients with and without PAD. However, the likelihood of being readmitted at least once was disproportionately higher for patients with PAD (Kaplan–Meier cumulative incidence: 11% versus 7%), Figure 1. Mortality within 30 days of discharge was 6%, irrespective of concomitant PAD. When examined as a composite outcome, the cumulative incidence of at least 1 ADHF readmission or death (whichever first) was 16% for patients with PAD, versus 13% for those without. In multivariable models adjusted for demographics (age, race, sex, year of admission, hospital of admission) and comorbidities (current smoking, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, coronary artery disease, and history of stroke), PAD was associated with a higher 30-day hazard of ADHF readmission, whether analyzed by standard Cox regression (HR, 2.01; 95% CI, 1.14–3.54), competing-risk Cox regression (HR, 2.04; 95% CI, 1.12–3.72), or repeat-events models counting all recurrent ADHF readmissions per patient within 30 days (HR, 2.02; 95% CI, 1.14–3.60), Table 2. Additional adjustments for obesity, myocardial infarction, diuretics prescribed at discharge, and length of

**Table 1. Demographics, Clinical Characteristics, and Medications Administered at Index Hospitalization for Acute Decompensated Heart Failure Among Patients Discharged Alive**

| Characteristic               | Peripheral Artery Disease<br>(n=207) | No Peripheral Artery Disease<br>(n=1274) | P Value |
|------------------------------|--------------------------------------|--|---------|
|                              | No. (%) or Mean±SD                   | No. (%) or Mean±SD                       |         |
| Demographics                 |                                      |  |         |
| Age, y                       | 77±7                                 | 78±6                                     | 0.2     |
| Men                          | 113 (55%)                            | 564 (44%)                                | 0.006   |
| White                        | 151 (73%)                            | 865 (68%)                                | 0.1     |
| Health insurance             | 196 (95%)                            | 1218 (96%)                               | 0.6     |
| Admission y, median (Q1, Q3) | 2010 (2007, 2013)                    | 2010 (2007, 2014)                        | 0.1     |
| Medical history              |                                      |  |         |
| Previous diagnosis of HF*    | 126 (64%)                            | 670 (55%)                                | 0.03    |
| Current smoking*             | 33 (17%)                             | 101 (8%)                                 | 0.002   |
| Obesity*                     | 60 (33%)                             | 473 (42%)                                | 0.02    |
| Hypertension                 | 185 (89%)                            | 1116 (88%)                               | 0.5     |
| Diabetes mellitus            | 106 (51%)                            | 584 (46%)                                | 0.2     |
| Coronary artery disease      | 148 (72%)                            | 665 (52%)                                | <0.0001 |
| Myocardial infarction        | 65 (31%)                             | 246 (19%)                                | <0.0001 |
| Chronic bronchitis/COPD      | 80 (39%)                             | 358 (28%)                                | 0.002   |
| Sleep apnea                  | 21 (10%)                             | 140 (11%)                                | 0.7     |
| Chronic kidney disease†      | 70 (46%)                             | 359 (40%)                                | 0.2     |
| Atrial fibrillation/flutter  | 59 (29%)                             | 421 (33%)                                | 0.2     |
| Stroke/TIA                   | 59 (29%)                             | 220 (17%)                                | 0.0001  |
| Depression                   | 27 (13%)                             | 191 (15%)                                | 0.5     |
| Hospital visit               |                                      |  |         |
| Ejection fraction, %*        | 44±16                                | 45±16                                    | 0.3     |
| Systolic BP, mm Hg           | 145±34                               | 144±32                                   | 0.5     |
| Diastolic BP, mm Hg          | 79±21                                | 78±19                                    | 0.3     |
| Hemoglobin, g/dL             | 11.3±1.7                             | 11.4±1.9                                 | 0.6     |
| Serum creatinine, mg/dL      | 1.4 (1.1–2.0)                        | 1.2 (1.0–1.7)                            | 0.002   |
| Sodium, mEq/L                | 139±4                                | 138±4                                    | 0.5     |
| Length of stay, d            | 7.5±10                               | 7.5±12                                   | 1.0     |
| Medications at discharge     |                                      |  |         |
| Lipid-lowering agent‡        | 128 (62%)                            | 752 (59%)                                | 0.4     |
| Beta blocker                 | 163 (79%)                            | 938 (74%)                                | 0.1     |
| ACEi/ARB                     | 117 (57%)                            | 672 (53%)                                | 0.3     |
| Aldosterone blocker          | 18 (9%)                              | 100 (8%)                                 | 0.7     |
| Diuretics                    | 141 (68%)                            | 955 (75%)                                | 0.03    |

The ARIC (Atherosclerosis Risk in Communities) study, 2005 to 2016. ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; HF, heart failure; Q1, first quartile; Q3, third quartile; and TIA, transient ischemic attack.

\*Previous diagnosis of heart failure missing for 73 patients (5%), smoking not abstracted for 90 patients (6%), obesity not abstracted for 177 patients (12%), ejection fraction limited to 1078 (73%) of patients with echocardiography data.

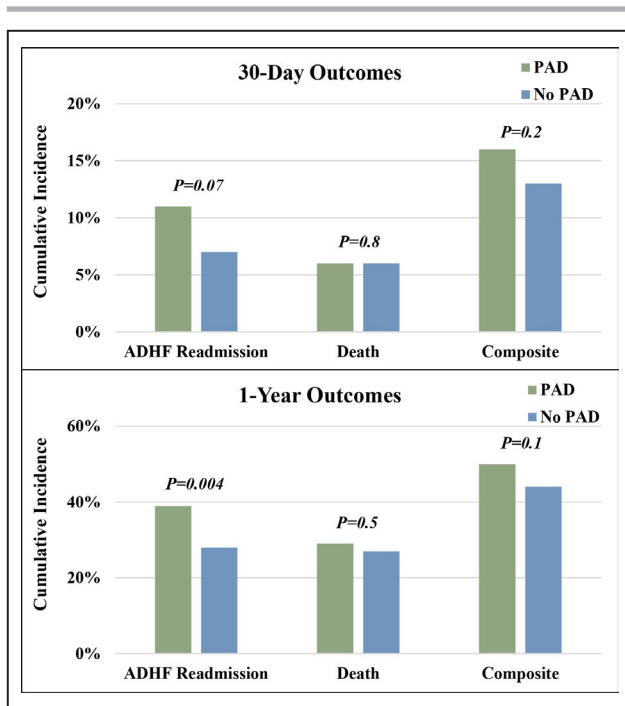
†Chronic kidney disease defined by an estimated glomerular filtration rate <45 mL/min per 1.73 m<sup>2</sup> or receipt of dialysis. Serum creatinine abstraction missing for 436 patients (29%).

‡Lipid-lowering agents include statins, niacin, and fibrates.

hospital stay yielded a similar hazard ratio of recurrent ADHF readmission (HR, 1.88, 95% CI, 1.00–3.54).

A greater likelihood of recurrent ADHF admission among patients with PAD was also observed within 1 year of discharge from the index hospitalization. Patients with PAD were disproportionately

readmitted at least once for ADHF (Kaplan–Meier cumulative incidence: 39% versus 28%), Figure 1. The maximum number of recurrent ADHF readmissions ranged from 0 to 5 for patients with PAD, and from 0 to 8 for patients without PAD; however, the average number of ADHF hospitalizations among readmitted



**Figure 1.** Kaplan–Meier cumulative incidence of first occurring acute decompensated heart failure readmission, death, or composite (whichever first) within 30 days or 1 year of hospital discharge.

The ARIC (Atherosclerosis Risk in Communities) study. ADHF indicates acute decompensated heart failure; and PAD, peripheral artery disease.

patients was 1.5 for both groups. Mortality within 1 year of discharge from the index hospitalization was comparable for patients with versus without PAD (Kaplan–Meier cumulative incidence: 29% versus 27%). Figure 1. Among the fatalities, the average time to death was 133±106 days for those with PAD, and 140±108 days for those without PAD (*P* for

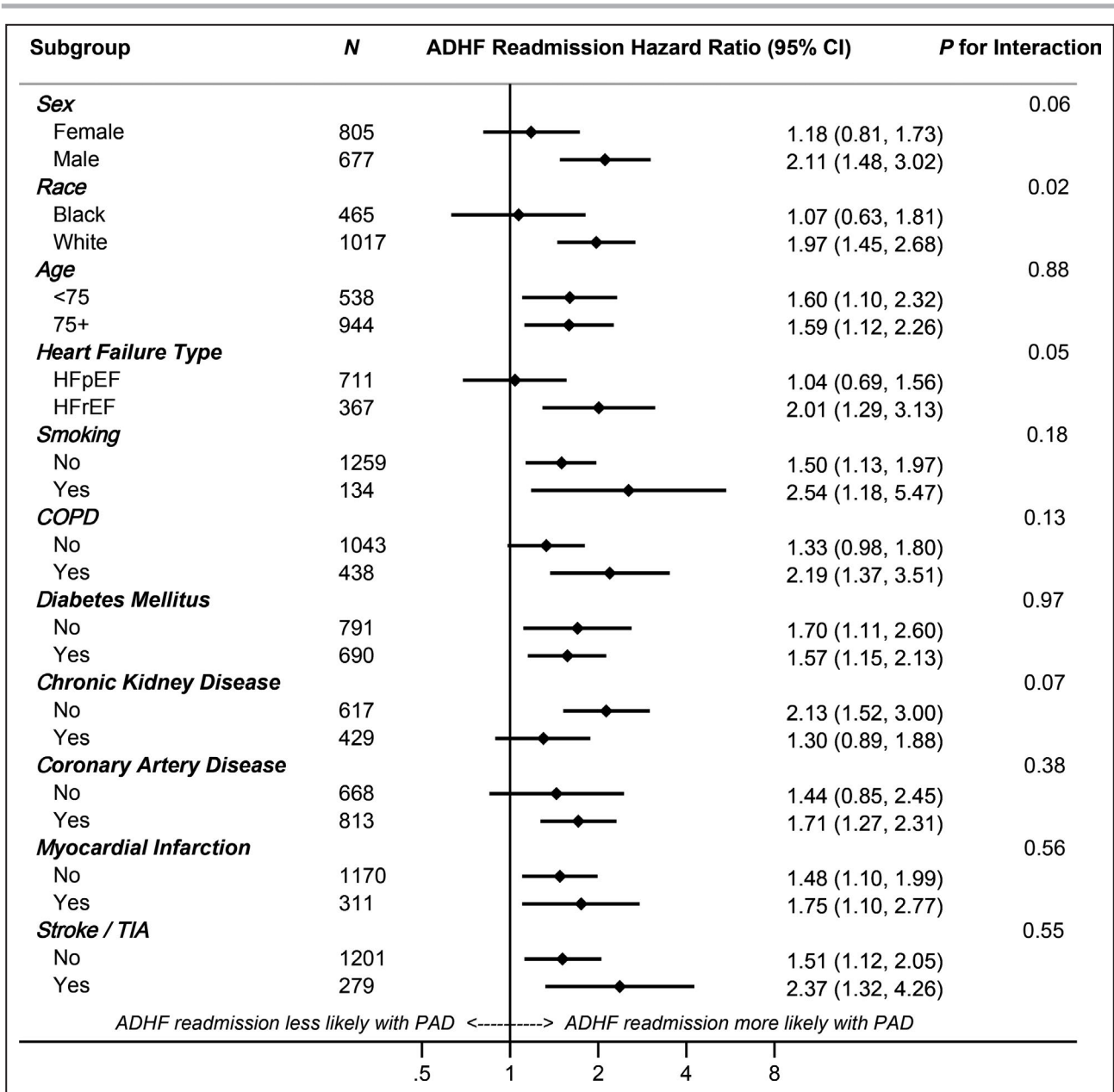
comparison, 0.9). When examined as a composite outcome, the cumulative incidence of at least 1 ADHF readmission or death (whichever first) within 1 year of discharge was 50% for patients with PAD, versus 44% for those without. After adjustments, PAD was associated with a greater hazard of ADHF readmission, whether analyzed by standard Cox regression (HR, 1.64; 95% CI, 1.21–2.22), competing risk regression (HR, 1.64; 95% CI, 1.21–2.23), or repeat-events models counting all recurring ADHF hospitalizations during the 1-year interval (HR, 1.60; 95% CI, 1.25–2.05). The composite outcome of recurrent ADHF readmissions and/ or death was also higher among patients with PAD (HR, 1.32; 95% CI, 1.07–1.64), Table 2. In sensitivity analyses, the hazard ratios of recurrent ADHF readmissions (HR, 1.53; 95% CI, 1.17–1.99) and composite of ADHF readmissions and/ or death (HR, 1.32; 95% CI, 1.04–1.67) were not greatly altered by additional adjustments for obesity, myocardial infarction, diuretics prescribed at discharge, and length of hospital stay. Further adjustment for diagnosis of HF before the index ADHF hospitalization yielded similar associated hazards of ADHF readmissions (HR, 1.45; 95% CI, 1.10–1.91) or composite of readmissions and/ or death (HR, 1.26; 95% CI, 0.99–1.60).

To explore potential modification by demographics or comorbid conditions, we examined the association between PAD and 1-year ADHF readmission within several subgroup stratifications (Figure 2). Models were adjusted identically to the primary analysis. PAD was more strongly associated with ADHF readmission among men (HR, 2.11; 95% CI, 1.48–3.02) than women (HR, 1.18; 95% CI, 0.81–1.73); *P* for interaction=0.06, and among White patients (HR, 1.97; 95% CI, 1.45–2.68) compared with Black patients (HR, 1.07; 95% CI, 0.63–1.81); *P* for interaction=0.02.

**Table 2.** Adjusted Hazard Ratios of Recurrent Acute Decompensated Heart Failure Readmission, Death, or Composite Within 30 Days or 1 Year of Discharge From Index Hospitalization for ADHF, Comparing Patients With Versus Without Peripheral Artery Disease

| Outcome          | Model 1          | Model 2          | Model 3          |
|------------------|------------------|------------------|------------------|
|                  | HR (95% CI)      | HR (95% CI)      | HR (95% CI)      |
| 30 d             |                  |                  |                  |
| ADHF readmission | 1.53 (0.97–2.42) | 1.62 (1.02–2.58) | 2.02 (1.14–3.60) |
| Death            | 0.91 (0.50–1.67) | 0.87 (0.47–1.62) | 0.79 (0.35–1.78) |
| Composite        | 1.24 (0.86–1.77) | 1.26 (0.87–1.83) | 1.41 (0.89–2.23) |
| 1 y              |                  |                  |                  |
| ADHF readmission | 1.38 (1.12–1.70) | 1.49 (1.20–1.84) | 1.60 (1.25–2.05) |
| Death            | 1.10 (0.84–1.44) | 1.15 (0.87–1.51) | 1.11 (0.80–1.54) |
| Composite        | 1.24 (1.04–1.48) | 1.31 (1.09–1.57) | 1.32 (1.07–1.64) |

Model 1: unadjusted. Model 2: adjusted for demographics (age, race, sex, hospital, and year of admission). Model 3: adjusted for demographics and comorbidities (chronic obstructive pulmonary disease, smoking, diabetes mellitus, chronic kidney disease, coronary artery disease, and stroke). ADHF indicates acute decompensated heart failure; and HR, hazard ratio.



**Figure 2. Adjusted hazard ratios\* of recurrent acute decompensated heart readmission within 1 year of hospital discharge, stratified by various demographic groups and comorbid conditions.**

The ARIC (Atherosclerosis Risk in Communities) study. \*Models adjusted for age, race, sex, year of admission, hospital of admission, smoking, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, coronary artery disease, and stroke/transient ischemic attack. ADHF indicates acute decompensated heart failure; COPD, chronic obstructive pulmonary disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PAD, peripheral artery disease; and TIA, transient ischemic attack.

The hazard of ADHF readmission associated with PAD was not significantly modified by diabetes mellitus or smoking, or by extent of atherosclerotic burden (coronary artery disease, history of myocardial infarction, or history of stroke/transient ischemic attack). However, PAD was differentially associated with recurrent ADHF hospitalization by concomitant chronic kidney disease. The association was stronger among patients without chronic kidney disease

(HR, 2.13; 95% CI, 1.52–3.00), compared with those with chronic kidney disease (HR, 1.30; 95% CI, 0.89–1.88); *P* for interaction=0.07. In the subset of patients with available echocardiography, an increased hazard of ADHF readmission was observed in association with PAD, but only in patients with HFrEF (HR, 2.01; 95% CI, 1.29–3.13). In contrast, no association was observed in patients with HFpEF (HR, 1.03; 95% CI, 0.69–1.56); *P* for interaction=0.05).

## DISCUSSION

In this population-based cohort study surveilling ADHF hospitalizations from 2005 to 2017, we observed the following: (1) Out of 1481 patients who were hospitalized with ADHF and discharged alive, 207 (14%) had a clinical diagnosis of PAD at the index hospitalization. (2) Those with PAD were more often White, men, and smokers, with a greater prevalence of obesity, coronary artery disease, chronic obstructive pulmonary disease, and history of myocardial infarction and stroke. (3) Patients with PAD had an increased risk of ADHF readmission both within 30 days and 1 year of discharge from the index hospitalization, but mortality was comparable with patients without PAD. (4) After adjustments, PAD was associated with twice the hazard of ADHF readmission within 30 days and 60% higher hazard of readmission within 1 year. (5) The increased 1-year hazard of ADHF readmission associated with PAD was not modified by extent of atherosclerotic burden but was primarily observed among patients with HFrEF.

Previous investigations of PAD and ADHF hospitalization among patients with established HF have been inconsistent and limited to post-hoc analyses from clinical trials. The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study reported a 30% higher adjusted hazard of hospitalization for worsening heart failure over  $\approx 3$  years of follow-up for patients with HFrEF with versus without intermittent claudication.<sup>12</sup> In contrast, a propensity-matched analysis of patients with chronic HFrEF enrolled in the BEST (Beta-Blocker Evaluation of Survival Trial) reported no difference in ADHF hospitalization among patients with versus without clinical diagnosis of PAD (HR, 1.05), across 4 years of follow-up.<sup>2</sup> A small study from Japan reported an increase in ADHF hospitalizations over 2 years for patients with either HFrEF or HFpEF and concomitant PAD (HR, 1.37), but the association was non-significant.<sup>13</sup> Similarly, the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, which was limited to patients with HFpEF, reported a non-significant increase in ADHF hospitalization across  $\approx 3.5$  years of follow-up for patients with versus without PAD (HR, 1.29).<sup>3</sup> Interestingly, the association was stronger (HR, 1.51) and attained significance among the subset of chronic HF patients who had a prior history of ADHF hospitalization. In contrast to these clinical trials, our study population from the ARIC cohort was unselected and may be a better reflection of real-world scenarios. The mean length of stay at the index ADHF hospitalization exceeded 1 week, irrespective of concomitant PAD. Moreover, the 1-year mortality in our patient population was high, both for patients with and without

PAD (29% versus 27%). We observed a greater risk of recurrent ADHF hospitalizations among patients with PAD, both at 30 days and 1 year following discharge from the index ADHF hospitalization.

PAD is associated with a high prevalence of comorbid conditions,<sup>14</sup> which are likely to increase the risk of cardiovascular events. Consistent with prior reports, patients with PAD in our study population had a greater comorbidity burden. However, after adjustment for comorbidities, the association between PAD and recurrent decompensation persisted. Surprisingly, the increased hazard of recurrent ADHF hospitalization among patients with PAD was not modified by prevalent coronary artery disease or history of myocardial infarction, nor by prevalent diabetes mellitus or current smoking. Of note, PAD was more strongly associated with ADHF readmission among patients free of chronic kidney disease. One explanation may be that chronic kidney disease itself is a risk factor for ADHF readmission, irrespective of PAD; hence the impact of PAD may be more noticeable among patients without chronic kidney disease who otherwise may have a relatively low likelihood of ADHF readmission. Interestingly, in the subgroup of patients with available echocardiography, the increased hazard of recurrent ADHF hospitalization associated with PAD was solely observed among patients with HFrEF. In previous studies, a higher incidence of recurrent ADHF readmissions has been reported with HFrEF relative to HFpEF,<sup>15</sup> an outcome which may be influenced by coexisting PAD.

One potential explanation for the association between PAD and recurrent ADHF may be the exacerbation of functional impairment. PAD is known to accelerate functional decline leading to physical disability.<sup>16,17</sup> Patients with HF and coexisting PAD walk shorter distances on 6-minute walk tests compared with those without PAD, have worse cardiopulmonary fitness as assessed by VO<sub>2</sub> testing, and score lower on the short form-36 physical function inventory.<sup>13,18–20</sup> There is also evidence to suggest that concomitant PAD is associated with worse New York Heart Association class,<sup>19</sup> potentially increasing the risk of ADHF hospitalization. One possible strategy to reduce ADHF readmissions in patients with coexisting PAD may be structured exercise programs. In 2014, the Centers for Medicare and Medicaid services approved national coverage of supervised exercise therapy for medically stable patients with HFrEF,<sup>21</sup> and in 2017 extended coverage to symptomatic patients with PAD.<sup>22</sup> Exercise therapy combined with comprehensive secondary prevention has the potential to benefit patients with PAD by preserving or improving functional capacity and reducing cardiovascular events.<sup>23</sup> Structured and at-home exercise programs have also been shown to reduce long-term

mortality, all-cause hospitalization, and HF-related hospitalization in patients with HF<sub>r</sub>EF and HF<sub>p</sub>EF.<sup>24</sup> Although symptomatic PAD is often an exclusion factor for exercise interventions targeting HF populations, a post-hoc analysis of HF<sub>r</sub>EF patients with versus without PAD in HF-ACTION (Heart Failure—A Controlled Trial Investigating Outcomes of Exercise Training) reported a significant increase in mean exercise duration for patients randomized to structured exercise, irrespective of concomitant PAD.<sup>18</sup>

Although many patients are unaware of PAD and may not receive preventive therapy,<sup>25</sup> in our study population, PAD was clinically diagnosed before the index hospitalization for ADHF. Upon prospective follow-up, diagnosed PAD was shown to be associated with increased risk of recurrent ADHF readmission. However, demographic differences in PAD management may exist in HF populations, with the potential to influence functional impairment and possibly the likelihood of recurrent decompensation. Administrative claims data suggest Black patients with PAD are more often managed by amputation than by limb revascularization<sup>26,27</sup>; a strategy associated with poor functional outcomes. Functional impairment, as assessed by the peripheral artery questionnaire, is also reported to be worse for women compared with men with PAD.<sup>28</sup> In this analysis of patients hospitalized with ADHF, however, the risk of ADHF readmission associated with PAD was higher among White and male patients, possibly reflecting the stronger association between PAD and ADHF readmission among patients with HF<sub>r</sub>EF.

Inpatient management of ADHF mainly depends on the precipitating factors and the signs and symptoms of congestion.<sup>29</sup> While differences in ADHF management and administration of guideline-directed medications may influence ADHF readmissions, the medications prescribed at discharge were comparable for patients with and without PAD. One exception, however, was the prescription of diuretics, which was lower among patients with PAD than those without (68% versus 75%). The reason for the differential management is uncertain, but 1 possibility is that PAD complicates the assessment of lower extremity edema, particularly in the event of lower extremity amputation. On the other hand, the association between PAD and recurrent ADHF hospitalization was not substantially altered by additional adjustment for diuretics at discharge.

Although our study originates from the well-designed ARIC cohort, there are some limitations. This was an observational study, and data collection was limited to availability in the medical record and abstraction priority. Echocardiography and serum creatinine assessments were available for 73% and 71% of the index hospitalizations. Clinical diagnosis of PAD was not verified or adjudicated by standard ARIC physician review

of the medical record, and we were unable to consider PAD severity. Similarly, in administrative claims records, the majority (60%) of cases of PAD are coded as “unspecified”, rather than as intermittent claudication or critical limb ischemia.<sup>27</sup> We also lacked information on cilostazol use or antiplatelet medications. Furthermore, in some patients, it is possible that PAD went undetected or was masked by coexisting HF symptoms. Although ADHF medications at discharge did not appear to differ by PAD diagnosis, we were unable to consider differences in dietary counseling and encouragement to implement healthy lifestyle changes, daily exercise, or smoking cessation. We were also unable to consider medication compliance, follow-up care, and at-home telemonitoring. Despite these limitations, our study has several noteworthy strengths. The ARIC study is a large population-based cohort representing 4 geographically diverse regions of the United States. Clinical data were abstracted from the medical record by a standardized protocol and all hospitalizations for ADHF were verified by physician review of the medical record.

In conclusion, patients with ADHF and concomitant PAD have a greater cardiovascular comorbidity burden and higher likelihood of ADHF readmission. The association is stronger among patients with HF<sub>r</sub>EF, who may represent a high-risk group suitable for targeted intervention.

## ARTICLE INFORMATION

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Author contributions: Drs Caughey and Chunawala interpreted the data and wrote the article. Dr Caughey conceptualized the study and performed the statistical analysis. Drs Chang, DeFilippis, Hall, and Matsushita interpreted the data and revised the article critically.

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