Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Heart Failure With Outcomes Among Patients With Peripheral Artery Disease: Insights From EUCLID

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BACKGROUND: Peripheral artery disease (PAD) and heart failure (HF) are each independently associated with poor outcomes. Risk factors associated with new-onset HF in patients with primary PAD are unknown. Furthermore, how the presence of HF is associated with outcomes in patients with PAD is unknown.

METHODS AND RESULTS: This analysis examined risk relationships of HF on outcomes in patients with symptomatic PAD randomized to ticagrelor or clopidogrel as part of the EUCLID (Examining Use of Ticagrelor in Peripheral Arterial Disease) trial. Patients were stratified based on presence of HF at enrollment. Cox models were used to determine the association of HF with outcomes. A separate Cox model was used to identify risk factors associated with development of HF during follow-up. Patients with PAD and HF had over twice the rate of concomitant coronary artery disease as those without HF. Patients with PAD and HF had significantly increased risk of major adverse cardiovascular events (hazard ratio [HR], 1.31; 95% CI, 1.13–1.51) and all-cause mortality (HR, 1.39; 95% CI, 1.19–1.63). In patients with PAD, the presence of HF was associated with significantly less bleeding (HR, 0.65; 95% CI, 0.45–0.96). Characteristics associated with HF development included age ≥66 (HR, 1.29; 95% CI, 1.18–1.40 per 5 years), diabetes mellitus (HR, 1.85; 95% CI, 1.41–2.43), and weight (bidirectionally associated, ≥76 kg, HR, 0.77; 95% CI, 0.64–0.93; <76 kg, HR, 1.12; 95% CI, 1.07–1.16).

CONCLUSIONS: Patients with PAD and HF have a high rate of coronary artery disease with a high risk for major adverse cardiovascular events and death. These data support the possible need for aggressive treatment of (recurrent) atherosclerotic disease in PAD, especially patients with HF.

Key Words: heart failure ■ outcomes ■ peripheral artery disease

Peripheral artery disease (PAD) and chronic heart failure (HF) are systemic diseases, each with an increasing incidence and repeatedly associated with progressive functional limitation as well as increased morbidity and mortality.[1–5] Expectedly, PAD and HF often coexist in patients with atherosclerotic vascular disease.[6,7] The presence of PAD has been associated with increased morbidity and mortality in patients with HF.[8,9] However, the association of chronic HF with clinical and safety outcomes in patients with atherosclerotic vascular disease, particularly PAD, remains undefined. Several of the recently published clinical trials studying antiplatelet and antithrombotic therapies in patients with PAD do not report the baseline rates of concomitant HF and are therefore unlikely to incorporate this important comorbidity into prediction modeling for clinical or safety events.[10–13]

The EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) trial randomly assigned patients with symptomatic PAD to receive either ticagrelor

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018684

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Peripheral artery disease (PAD) and chronic heart failure (HF) are each independently associated with adverse events and death, yet outcomes for patients with both comorbidities are poorly defined.
- For patients with PAD, risk factors associated with development of de novo HF are unknown.
- This post hoc analysis of the EUCLID (Examining Use of Ticagrelor in Peripheral Arterial Disease) trial demonstrates that patients with PAD and HF have a high rate of concomitant coronary artery disease with an associated high risk for major adverse cardiovascular events and death; age, concomitant diabetes mellitus, and low weight were the strongest predictors of new HF for patients with PAD during follow-up in EUCLID.

What Are the Clinical Implications?

- These data support the possible need for aggressive treatment of (recurrent) atherosclerotic disease in patients with PAD, especially those with concomitant HF.

Nonstandard Abbreviations and Acronyms

EUCLID	Examining Use of Ticagrelor in Peripheral Artery Disease
HF-ACTION	Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training
MACE	major adverse cardiovascular event
MALE	major adverse limb event
PEGASUS-TIMI 54	Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54
TIMI	Thrombolysis in Myocardial Infarction

or clopidogrel to determine optimal antiplatelet therapy for patients with symptomatic PAD. We conducted this analysis to examine the association of HF with clinical outcomes and safety events in patients with PAD. We intended to identify a high-risk cohort of patients who are tolerant of guideline-directed medical therapy without an increased risk of harm. We hypothesized that compared with patients without HF, those with concomitant HF are at increased risk of adverse clinical outcomes. We further hypothesized that patients with HF would have no difference in rates of adverse outcomes and tolerance of antiplatelet therapy without differences in rates of bleeding.

Finally, progressive atherosclerotic coronary artery disease (CAD) is the strongest risk factor for development of HF.[13–16] We were also interested in identifying risk factors for development of HF (defined as HF-related death or HF hospitalization) in a cohort of patients with known atherosclerotic disease but without a high burden of concomitant CAD. We therefore used EUCLID, which uniquely included a relatively small proportion of patients with CAD.

METHODS

Study Design and Population

The design and primary results of the EUCLID (NCT01732822) trial have been previously published.[12,17] EUCLID was a double-blind, multicenter, randomized controlled trial comparing the efficacy and safety of ticagrelor (90 mg twice daily) with clopidogrel (75 mg once daily) for the treatment of major adverse cardiovascular events (MACEs) in patients with symptomatic PAD. Inclusion criteria for EUCLID were as follows: (1) symptomatic PAD defined as an ankle-brachial index (ABI) ≤0.80 with claudication (n=6010) or (2) prior lower-extremity revascularization (n=7875). Key exclusion criteria were planned use of dual antiplatelet therapy, requirement for aspirin, history of bleeding diathesis, treatment with anticoagulation, or poor metabolizer status for cytochrome P450 2C19 (possessing a known genotype of 2 loss-of-function alleles). A total of 13 885 patients were randomized and followed for all clinical end points and serious adverse events until the end of the study. For this analysis, a patient was included in the HF group if "prior congestive heart failure" was answered as "Yes" on the EUCLID case report form at the time of enrollment. Additional information on HF findings and duration were not available.

All patients provided written informed consent. Institutional review boards at each participating center approved the protocol. The authors had access to all data and are responsible for statistical analysis, drafting, critical review, content control, and submission of this article. The data that support the findings of this study are available from the corresponding author upon reasonable request.

End Points

The end points for this analysis were derived from the primary efficacy and safety end points of the EUCLID

trial. Efficacy end points included: MACE including combined cardiovascular death, myocardial infarction (MI), and ischemic stroke. Major adverse limb events (MALEs) were defined as a combination of major amputation and acute limb ischemia requiring hospitalization. Patients were considered to have new-onset HF if they did not have HF at baseline and the patient died with the adjudicated cause of death as HF/cardiogenic shock; the patient was hospitalized with a primary discharge diagnosis of HF (nonadjudicated); or the patient had a serious adverse event labeled as "heart failure signs and symptoms, left ventricular failure, or right ventricular failure." Outcome analyses, including development of new-onset HF, were conducted using the intention-to-treat population in EUCLID, and all events that occurred after randomization through the end of the study were included. Efficacy end points were measured from randomization to the censoring date for the primary analysis or the date of last trial contact (whichever came first). Safety end points included TIMI (Thrombolysis in Myocardial Infarction) major bleeding and combined TIMI major and minor bleeding. In EUCLID, safety end points were measured during the on-treatment period plus an additional 7 days, unless treatment ended in patient death. Patients who died during this 7-day follow-up period were censored at the time of death.

Statistical Methods

For descriptive summaries, all patients with data for history of HF were included (N=13 883). Categorical variables are presented as percentage counts and compared between groups with Pearson's chi-squared tests. Continuous variables are presented as medians (Q1–Q3) and compared between groups with Wilcoxon rank-sum tests.

For the efficacy and safety outcomes Kaplan-Meier curves were created with patients stratified on the basis of HF status. To examine risk relationships of HF with outcomes, we used previously developed Cox models from EUCLID for the MACE, MALE, and major and minor bleeding outcomes.[12,18] For all-cause hospitalization, an additional Cox model was created using predictors chosen on the basis of stepwise selection with significance level of P=0.05. Age, weight, kidney function, and ABI were fit using restricted cubic splines, consistent with the other models as part of EUCLID. Despite not being statistically significant, treatment assignment was retained in all models.

Given the interest in ascertaining whether outcomes from EUCLID were modified by the presence of concomitant HF, we chose to test the interaction between presence of HF at baseline with previously identified significant predictors for each outcome. To achieve this, an additional Cox model was also used to assess a differential treatment effect between assigned treatment in EUCLID and presence of HF. For all models, patients with complete covariate data (N=12 767) were included.

Among patients without HF at baseline and with complete covariate data (N=10 948), an additional Cox model was developed, using the same method as the model for all-cause hospitalization. For this model, the outcome was first hospitalization for HF. Predictors were again identified using stepwise selection with a prespecified significance cut point of P=0.05. Assigned EUCLID treatment remained in the model, regardless of significance level.

Rates of missing were low in EUCLID. Among the analysis cohort, for the 22 baseline variables (aside from randomized treatment) used or considered as covariates for ≥1 end points, rates of missing were weight, 3.8% (n=482); renal function, 3.1% (n=434); ABI, 1.7% (n=231); tobacco use, <1% (n=80), diabetes mellitus, <1% (n=1); and Rutherford classification, <1% (n=1), for a total of 1116 patients (8%). Given these low rates, only complete cases were used in each model, which is consistent with previous EUCLID publications. Mean follow-up in EUCLID was 30.4 months.

RESULTS

Demographics and Associations With Clinical Outcomes

A total of 13 883 (99.9%) patients with completed details regarding history of HF were included from EUCLID. Demographics of patients according to whether they had a history of HF at the time of enrollment are shown in Table 1. The average age of each group was 66 years, and there was no difference in sex between the groups. Patients with HF had significantly worse renal function (estimated glomerular filtration rate, 69.4 versus 76.1; P<0.001) and significantly lower ABI compared with patients without HF (0.68 versus 0.71; P<0.001). Patients with HF were more likely to have CAD (53.6% versus 25.1%; P<0.001), prior MI (39.7% versus 14.7%; P<0.001), carotid stenosis/revascularization (24.5% versus 16.6%; P<0.001), and polyvascular disease defined by >1 arterial bed (P<0.001). Patients with HF were more likely to enroll on the basis of ABI criteria (54.9%) rather than a history of lower-extremity revascularization (45.1%), while patients without HF were more likely to have undergone prior PAD revascularization procedures (58.6% prior revascularization versus 41.4% noninvasive criteria; P<0.001). Forty percent of patients with HF reported claudication symptoms of Rutherford category ≥3,

Table 1. Baseline Characteristics by History of HF

Variable	HF (n=1928)	No HF (n=11 955)	*P* Value
Randomized to ticagrelor, %	50.8	49.8	0.41
Age, y	66 (60–73)	66 (60–72)	0.02
Female, %	27.0	28.2	0.3
BMI	27.8 (24.8–31.2)	26.6 (23.8–29.9)	<0.001
eGFR, mL/min per 1.73 m^2 (MDRD)	69.4 (55.5–83.9)	76.1 (61.1–92.0)	<0.001
Geographic region, %			<0.001
Central/South America	6.7	13.5	
Europe	71.8	51.1	
Asia	3.8	12.8	
North America	17.6	22.6	
Inclusion criteria for randomization, %			<0.001
Prior revascularization	45.1	58.6	
ABI or TBI criteria	54.9	41.4	
ABI	0.68 (0.55–0.77)	0.71 (0.58–0.84)	<0.001
Limb symptoms (Rutherford classification), %			<0.001
Asymptomatic (0)	10.5	20.1	
Mild or moderate claudication (1/2)	49.2	54.1	
Severe claudication (3)	32.2	21.8	
Rest pain (4)	6.0	2.2	
Distal ischemic ulcers (5)	1.8	1.4	
Severe ischemic ulcers or gangrene (6)	0.4	0.4	
Medical history, %			
Major amputation (above ankle)	2.7	2.4	0.35
Minor amputation	4.6	4.3	0.63
NYHA class, %			
I	39.1	2.2	
II	50.3	0.6	
III	6.8	0.1	
IV	0.2	0	
No heart failure	3.6	97.1	
Prior stroke, %	11.4	7.7	<0.001
Prior TIA, %	4.0	3.6	0.39
CAD, %	53.6	25.1	<0.001
Prior MI, %	39.7	14.7	<0.001
Carotid stenosis or carotid revascularization, %	24.5	16.6	<0.001
Number of vascular beds affected, %			<0.001
1	35.1	59.6	
2	43.4	32.2	
3	21.6	8.2	
Diabetes mellitus, %	39.7	38.3	0.25
Hypertension, %	87.3	76.7	<0.001
Hyperlipidemia, %	80.6	74.7	<0.001

(*Continued*)

Table 1. Continued

Variable	HF (n=1928)	No HF (n=11 955)	*P* Value
Tobacco use, %			<0.001
Never	28.1	20.6	
Former smoker	43.5	47.9	
Current smoker	28.5	31.5, %	
Medications within 30 d before randomization, %			
Aspirin	67.1	66.7	0.74
Clopidogrel	34.8	31.8	0.01
ACE inhibitor	49.7	39.1	<0.001
Beta blocker	59.1	37.6	<0.001
ARB	23.5	25.4	0.09
Statin	77.0	72.7	<0.001
Cilostazol	7.5	16.3	<0.001

Covariates used for modeling. Cardiovascular death/MI/stroke: age, female, geographic region, weight, eGFR, inclusion criteria, ABI, Rutherford classification, previous major amputation, previous minor amputation, number of vascular beds, tobacco use, diabetes mellitus, prior MI, prior stroke, statin use. Cardiovascular death: age, female patient, weight, eGFR, ABI, Rutherford classification, major amputation, minor amputation, prior MI, prior stroke, ARB use, statin use. Ischemic stroke: age, region, Rutherford classification, minor amputation, tobacco use, prior stroke. MI: age, female patient, geographic region, eGFR, inclusion criteria, Rutherford classification, number of diseased vascular beds, tobacco use, prior percutaneous coronary intervention, prior MI, aspirin use. Death: age, female patient, geographic region, weight, eGFR, inclusion criteria, ABI, Rutherford classification, previous major amputation, previous minor amputation, diabetes mellitus, prior MI, prior stroke, ARB use, statin use. Major amputation/acute limb ischemia hospitalization: geographic region, weight, inclusion criteria, ABI, Rutherford classification, previous major amputation, previous minor amputation, diabetes mellitus, prior coronary artery bypass grafting, ARB use, statin use. Hospitalization: age, geographic region, weight, eGFR, inclusion criteria, ABI, Rutherford classification, previous minor amputation, number of vascular beds, prior carotid revascularization, tobacco use, diabetes mellitus, prior percutaneous coronary intervention, prior MI, prior stroke, randomized treatment assignment. Major bleed: age, female patient, geographic region, aspirin use. Combined major/minor bleed: age, female patient, geographic region, weight, inclusion criteria, ABI, Rutherford classification, aspirin use. ABI indicates ankle-brachial index; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; NYHA, New York Heart Association; TBI, toe-brachial index; and TIA, transient ischemic attack.

while 25% of patients without HF reported symptoms of Rutherford category ≥3. Discontinuation of the study drug was consistent in patients with HF compared with those without (26% versus 28%, respectively).

Crude event rates for the overall population and by HF status for each outcome are shown in Table 2. Associations of HF with clinical outcomes are shown in the Figure. Patients with HF had significantly increased risk of experiencing MACE (hazard ratio [HR], 1.31; 95% CI, 1.13–1.51) and all-cause mortality (HR, 1.39; 95% CI, 1.19–1.63) compared with patients without HF. There was a significantly increased risk of cardiovascular death for patients with HF (HR, 1.59; 95% CI, 1.31–1.92) and all-cause death (HR, 1.9; 95% CI, 1.19–1.63). Patients with HF had an increased risk of ischemic stroke and MI, though these did not meet the prespecified threshold for significance. Presence of HF was associated with significantly less combined TIMI major and minor bleeding (HR, 0.65; 95% CI, 0.45–0.96). The presence of HF was not significantly associated with risk of MALE (HR, 0.84; 95% CI, 0.60–1.16).

Interaction Between Heart Failure and Predictors of MACE

Table 3 shows significant interactions between HF and baseline variables and outcomes of interest. There were 3 variables (geographic region, weight, and ABI) significantly associated with HF and clinical outcomes. When compared with North Americans, patients with HF from Central/South America and Europe had lower risk of MACE than patients without HF (HR, 0.51 versus 0.64; and HR, 0.51 versus 0.84, respectively). Compared with North Americans, patients from Asia with HF had higher risk of MACE compared with patients without HF (HR, 0.75 versus 0.72) (interaction *P*=0.013).

We found a U-shaped relationship between weight and risk of MACE for patients with HF (HR, 0.90; 95% CI, 0.85–0.96 per 5 kg up to 85 kg; and HR, 1.05; 95% CI, 0.99–1.12 per 5 kg above 85 kg). For patients without HF, there was consistently a decreased risk of MACE across all weights (HR, 0.96; 95% CI, 0.93–1.00 per 5 kg ≤85 kg; and HR, 1.01; 95% CI, 0.97–1.05 per 5 kg >85 kg) (Figure S1).

For patients with HF, risk of MACE decreased with increasing ABIs ≤0.6 (HR, 0.93; 95% CI, 0.82–1.05 per ABI 0.1), at which point risk of MACE did not change (HR, 1.00; 95% CI, 0.92–1.08). For patients without HF, there was an inverse relationship between risk of MACE and ABI (HR, 0.88; 95% CI, 0.82–0.95 per 0.1 ≤ ABI 0.6; and HR, 0.95; 95% CI, 0.91–0.99 >ABI 0.6) (Figure S2).

Interaction Between Heart Failure and Predictors of MALE

There were 3 significant interactions between HF and predictors of MALE (inclusion criteria, ABI, and

Table 2. Association of HF With Clinical and Safety Outcomes

Outcome	Events/100 Patient-Years (Total Events)			Unadjusted Model		Adjusted Model	
	All Patients	HF	No HF	HF vs No HF HR (95% CI)	*P* Value	HF vs No HF HR (95% CI)	*P* Value
Number	12 767	1819	10 948				
Efficacy							
MACE	4.41 (1350)	6.65 (279)	4.05 (1071)	1.63 (1.43–1.87)	<0.001	1.31 (1.13–1.51)	<0.001
Cardiovascular death	2.03 (644)	3.69 (162)	1.76 (482)	2.08 (1.74–2.49)	<0.001	1.59 (1.31–1.92)	<0.001
Ischemic stroke	0.88 (274)	1.18 (51)	0.83 (223)	1.45 (1.07–1.97)	0.017	1.36 (0.99–1.87)	0.058
MI	1.97 (610)	2.81 (119)	1.84 (491)	1.52 (1.25–1.86)	<0.001	1.20 (0.97–1.48)	0.096
All-cause mortality	3.58 (1145)	5.35 (237)	3.30 (908)	1.62 (1.40–1.87)	<0.001	1.39 (1.19–1.63)	<0.001
MALE	1.13 (351)	1.07 (46)	1.14 (305)	0.93 (0.68–1.26)	0.631	0.84 (0.60–1.16)	0.288
Hospitalization	22.57 (5410)	25.00 (809)	22.19 (4601)	1.12 (1.04–1.20)	0.004	1.06 (0.98–1.15)	0.161
Safety							
TIMI major bleed	0.75 (203)	0.50 (19)	0.79 (184)	0.61 (0.37–0.99)	0.046	0.67 (0.41–1.10)	0.112
TIMI major/minor bleed	1.26 (340)	0.79 (30)	01.33 (310)	0.59 (0.40–0.86)	0.006	0.65 (0.45–0.96)	0.030

Covariates used for modeling. Cardiovascular death/MI/stroke: age, female patient, geographic region, weight, eGFR, inclusion criteria, (ABI, Rutherford classification, previous major amputation, previous minor amputation, number of vascular beds, tobacco use, diabetes mellitus, prior MI, prior stroke, statin use. Cardiovascular death: age, female patient, weight, eGFR, ABI, Rutherford classification, major amputation, minor amputation, prior MI, prior stroke, ARB use, statin use. Ischemic stroke: age, region, Rutherford classification, minor amputation, tobacco use, prior stroke.MI: age, female patient, geographic region, estimated GFR, inclusion criteria, Rutherford classification, number of diseased vascular beds, tobacco use, prior percutaneous coronary intervention, prior MI, aspirin use. Death: age, female patient, geographic region, weight, eGFR, inclusion criteria, ABI, Rutherford classification, previous major amputation, previous minor amputation, diabetes mellitus, prior MI, prior stroke, ARB use, statin use. Major amputation/acute limb ischemia hospitalization: geographic region, weight, inclusion criteria, ABI, Rutherford classification, previous major amputation, previous minor amputation, diabetes mellitus, prior coronary artery bypass grafting, ARB use, statin use. Hospitalization: age, geographic region, weight, eGFR, inclusion criteria, ABI, Rutherford classification, previous minor amputation, number of vascular beds, prior carotid revascularization, tobacco use, diabetes mellitus, prior percutaneous coronary intervention, prior MI, prior stroke, randomized treatment assignment. Major bleed: age, female patient, geographic region, aspirin use. Combined major/minor bleed: age, female, geographic region, weight, inclusion criteria, ABI, Rutherford classification, aspirin use. ABI indicates ankle brachial index; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event (combined cardiovascular death, myocardial infarction, ischemic stroke); MALE, major adverse limb event (combined major amputation and acute limb ischemia requiring hospitalization); MI, myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

angiotensin II receptor blocker use) (Table 3). There was an elevated risk of MALE based on inclusion criteria in EUCLID, which was less pronounced in patients with HF (HF HR, 1.43; 95% CI, 0.79–2.58 versus no HF HR, 2.73; 95% CI, 2.06–3.62; interaction *P*=0.048). We found a U-shaped relationship between risk of MALE and ABI for patients with HF (HR, 0.66; 95% CI, 0.53–0.82 per ABI, 0.1≤0.6 versus HR, 1.18; 95% CI, 1.02–1.38 per ABI 0.1>0.6). For patients without HF, the risk of MALE decreased with increasing ABI until the threshold of ABI=0.6, after which the risk remained stable (HR, 0.71; 95% CI, 0.63–0.79 per ABI 0.1≤0.6 versus HR, 0.94; 95% CI, 0.87–1.02 per ABI 0.1>0.6). There was a significant interaction found between angiotensin II receptor blocker use before enrollment and presence of HF regarding MALE (HF HR, 2.07; 95% CI, 1.11–3.85 versus no HF HR, 0.66; 95% CI, 0.49–0.89; interaction *P*=0.001) (Figure S3).

Interaction Between HF and Predictors of All-Cause Hospitalization

There were 3 significant interactions between HF and all-cause hospitalization (geographic region, ABI, and Rutherford score). When compared with North Americans, patients from Central/South America and Europe had a decreased risk of all-cause hospitalization, regardless of HF. Patients from Asia had an increased risk of all-cause hospitalization compared with North Americans, regardless of HF (interaction *P*<0.001). There was a U-shaped relationship between risk of all-cause hospitalization and ABI for patients with HF (HR, 0.93; 95% CI, 0.86–1.01 per 0.1 ≤ ABI =0.6 versus HR, 1.03; 95% CI, 0.98–1.08 per 0.1 > ABI=0.6). For patients without HF, the risk of hospitalization decreased with increasing ABI (HR, 0.92; 95% CI, 0.88–0.96 per 0.1 ≤ ABI=0.6 versus HR, 0.98; 95% CI, 0.96–1.00 per 0.1 > ABI=0.6; interaction *P*=0.039) (Figure S4). For patients without HF, compared with asymptomatic patients, increasing risk of all-cause hospitalization occurred with increasing Rutherford score (Rutherford score 1–2: HR, 1.04; 95% CI, 0.96–1.13; 3: HR, 1.24; 95% CI, 1.12–1.37; 4–6: HR, 1.58; 95% CI, 1.36–1.84). This relationship was not present for patients with HF (Rutherford score 1–2: HR, 0.99; 95% CI, 0.79–1.25; 3: HR, 1.17; 95% CI, 0.92–1.48; 4–6: HR, 0.92; 95% CI, 0.66–1.28; interaction *P*=0.012) (Table 3).

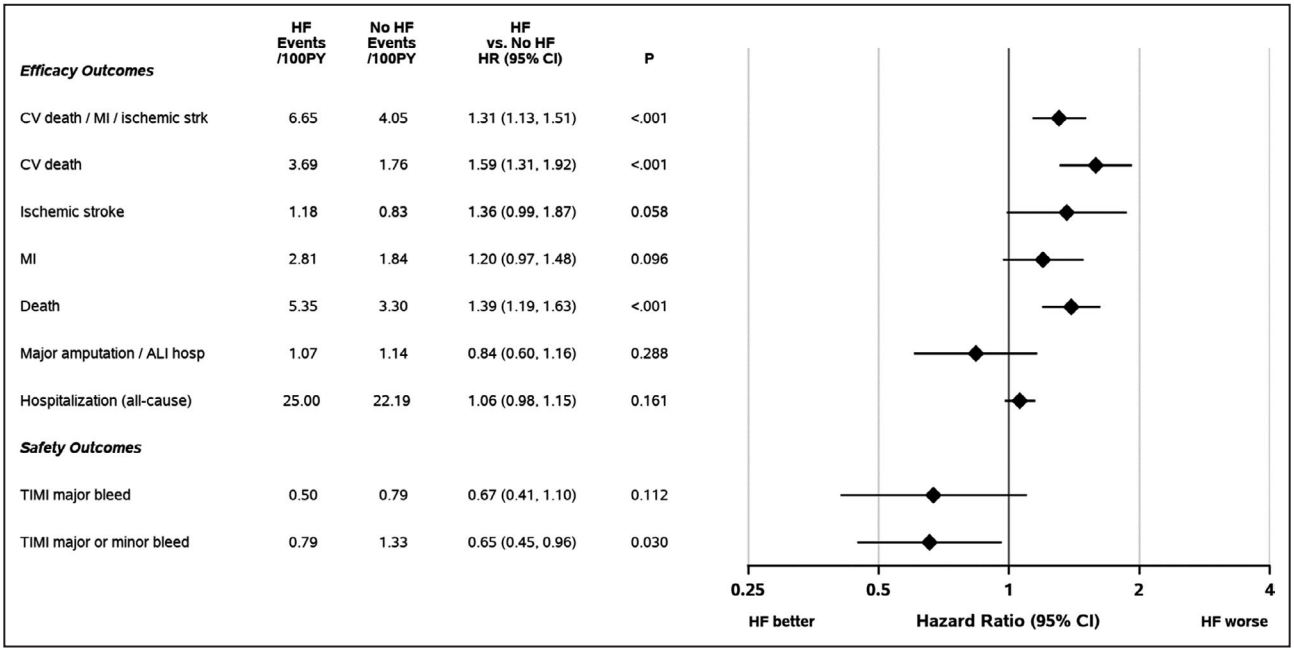

Figure 1. Association of HF with outcomes.
Forest plot of HRs for history of HF for efficacy outcomes. ALI hosp indicates acute limb ischemia hospitalization; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PY, patient years; strk, stroke; and TIMI, Thrombolysis in Myocardial Infarction.

Development of New-Onset HF During Trial Follow-Up

Of the 10 948 patients from EUCLID without baseline HF and with complete covariate data present, 235 (0.87%) developed HF during follow-up. Table 4 lists characteristics and event rates for development of new-onset HF during the EUCLID trial. Table S1 includes event rates, unadjusted univariate model results, full model results, and final (selected) model results for all candidate predictors. The following clinical characteristics, listed in decreasing order of contribution to the model, were associated with development of new-onset HF: age, weight, presence of diabetes mellitus, previous MI, renal function, previous minor amputation, increasing number of diseased vascular beds, increased Rutherford category, and major amputation were all associated with development of new-onset HF. Other variables that were assessed but dropped because of lack of significance included sex, geographic region, inclusion criteria, ABI, prior carotid revascularization, tobacco use, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior stroke, and medication use before enrollment.

DISCUSSION

In this post hoc analysis from EUCLID, we present the largest and most contemporary analysis directly examining the added risk of HF on clinical outcomes in patients with PAD. There are several novel findings of this analysis, which should be considered hypothesis generating. First, patients with symptomatic PAD and concomitant HF were more likely to have an increased burden of vascular disease as well as a history of MI and stroke. Second, the presence of HF was potentially associated with increased risk of MACE and all-cause death but not MALE or hospitalization. Finally, we identified increasing age, increasing weight, diabetes mellitus, and known CAD as the clinical attributes most strongly associated with development of postrandomization HF in patients with symptomatic PAD.

With regard to clinical outcomes of patients with PAD and HF, our findings build on data from the HF-ACTION (Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training) trial.[19,20] In patients with chronic HF from HF-ACTION, PAD was an independent predictor of all-cause death or all-cause hospitalization.[8] In the larger EUCLID trial, which was conducted in patients with PAD rather than patients with HF, those with PAD and concomitant HF had a significantly increased risk of MACE and all-cause mortality compared with patients with PAD in the absence of HF. Furthermore, there was a trend toward a significantly increased risk of ischemic stroke and MI in patients with HF. These results are potentially explained by the significantly increased burden of multibed atherosclerotic cardiovascular disease, hypertension, and diabetes mellitus in the patients with PAD and HF. The

Table 3. Significant Interactions Between HF and Baseline Variables* for Risk of MACE, MALE, and All-Cause Hospitalization

	HR Represents	HF HR (95% CI)	No HF HR (95% CI)	Interaction *P* Value
MACE				
Region†	Central/South America vs North America	0.51 (0.30–0.87)	0.64 (0.51–0.80)	0.013
	Europe vs North America	0.51 (0.38–0.67)	0.81 (0.69–0.94)	
	Asia vs North America	0.75 (0.44–1.26)	0.72 (0.58–0.90)	
Weight (2-part spline)	Per 5 kg, up to 85 kg	0.90 (0.85–0.96)	0.96 (0.93–1.00)	0.014
	Per 5 kg, above 85 kg	1.05 (0.99–1.12)	1.01 (0.97–1.05)	
ABI (2-part spline)	Per 0.1, up to 0.6	0.93 (0.82–1.05)	0.88 (0.82–0.95)	0.042
	Per 0.1, above 0.6	1.00 (0.92–1.08)	0.95 (0.91–0.99)	
MALE				
Inclusion criteria	Revascularization vs ABI	1.43 (0.79–2.58)	2.73 (2.06–3.62)	0.048
ABI (2-part spline)	Per 0.1, up to 0.6	0.66 (0.53–0.82)	0.71 (0.63–0.79)	0.026
	Per 0.1, above 0.6	1.18 (1.02–1.38)	0.94 (0.87–1.02)	
ARB	Yes vs no	2.07 (1.11–3.85)	0.66 (0.49–0.89)	0.001
All-cause hospitalization				
Region†	Central/South America vs North America	0.75 (0.55–1.01)	0.66 (0.59–0.74)	<0.001
	Europe vs North America	0.62 (0.52–0.74)	0.93 (0.86–1.00)	
	Asia vs North America	1.34 (0.98–1.83)	1.10 (1.00–1.23)	
ABI (2-part spline)	Per 0.1, up to 0.6	0.93 (0.86–1.01)	0.92 (0.88–0.96)	0.039
	Per 0.1, above 0.6	1.03 (0.98–1.08)	0.98 (0.96–1.00)	
Rutherford	Mild/moderate vs asymptomatic	0.99 (0.79–1.25)	1.04 (0.96–1.13)	0.012
	Severe vs asymptomatic	1.17 (0.92–1.48)	1.24 (1.12–1.37)	
	Pain/ulcers vs asymptomatic	0.92 (0.66–1.28)	1.58 (1.36–1.84)	

Covariates used for modeling. MACE: presence of HF, age, female patient, geographic region, weight, eGFR, inclusion criteria, ABI, Rutherford classification, previous major amputation, previous minor amputation, number of vascular beds, tobacco use, diabetes mellitus, prior MI, prior stroke, statin use, randomized treatment. MALE: major amputation/acute limb ischemia hospitalization: presence of HF, geographic region, weight, inclusion criteria, ABI, Rutherford classification, previous major amputation, previous minor amputation, diabetes mellitus, prior coronary artery bypass grafting, ARB use, statin use, randomized treatment. All-cause hospitalization: presence of HF, age, geographic region, weight eGFR, inclusion criteria, ABI, Rutherford classification, previous minor amputation, number of vascular beds, prior carotid revascularization, tobacco use, diabetes mellitus, prior percutaneous coronary intervention, prior MI, prior stroke, randomized treatment. ABI indicates ankle-brachial index; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; EUCLID, Examining Use of Ticagrelor in Peripheral Artery Disease; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular event (combined cardiovascular death, myocardial infarction, ischemic stroke); MALE, major adverse limb event (combined major amputation and acute limb ischemia requiring hospitalization); MI, myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

*There were no significant interactions between HF and baseline variables for mortality, TIMI major bleeding, and combined TIMI major/minor bleeding. Furthermore, when testing for an interaction between assigned treatment in EUCLID and presence of HF, there were no significant interactions found.

†Three separate region/HF interaction terms were included in the model. They were jointly tested in a single, 3-degrees-of-freedom overall test.

significant interactions in geographic region with presence of HF on clinical outcomes may be explained by an increased prevalence of concomitant CAD in these regions. Efforts were made to limit enrollment of patients with known CAD in the United States to reduce overlap with the simultaneously enrolling PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54) trial.

Objectively, patients with PAD and HF had significantly worse measures of arterial disease, and a greater proportion of patients with HF had at least Rutherford category 3 claudication. Despite more advanced PAD in patients with HF, we did not identify a difference in MALEs between patients with and without HF. This finding was somewhat surprising considering that patients with more advanced PAD have been shown to have increased rates of MALEs.[1,5]

We found that treatment with single antiplatelet agent therapy (clopidogrel or ticagrelor without the concomitant use of aspirin) in patients with PAD and HF was well tolerated. In fact, there was less combined TIMI major or minor bleeding in patients with PAD and HF compared with patients with PAD without HF. This is driven by the minor bleeding events, as there were no significant differences in TIMI major bleeding between patients with and without HF. The findings of no difference in MALEs and decreased bleeding in patients with PAD and HF are hypothesis generating and

Table 4. Baseline Variables Associated With New-Onset HF

Baseline Variable*	Categories†	N	Events/100 Patient-Years (Total Events)	Multivariable Model		
				Chi-Square	HR (95% CI)	*P* Value
Overall		10 948	0.87 (235)			
Age, y	≥66	5771	1.16 (163)	34.60	1.29 (1.18–1.40)	<0.001
	<66	5177	0.56 (72)		Per 5 y	
Weight, kg‡	≥76	5514	1.03 (140)	29.24	0.77 (0.64–0.93) Up to 60 kg, per 5	<0.001
	<76	5434	0.72 (95)		1.12 (1.07–1.16) Above 60 kg, per 5	
Diabetes mellitus	Yes	4181	1.40 (141)	19.64	1.85 (1.41–2.43)	<0.001
	No	6767	0.56 (94)			
Prior MI	Yes	1614	1.87 (73)	15.76	1.88 (1.38–2.56)	<0.001
	No	9334	0.70 (162)			
GFR, mL/min per 1.73 m^2	≥76	5509	0.59 (81)	15.59	0.94 (0.91–0.97)	<0.001
	<76	5439	1.17 (154)		Per 5 mL/min per 1.73 m^2	
Minor amputation	Yes	455	2.34 (24)	14.30	2.32 (1.50–3.59)	<0.001
	No	10 493	0.81 (211)			
Vascular beds	3	909	2.39 (53)	11.78	1.83 (1.30–2.59)	<0.001
	1 or 2	10 039	0.74 (182)		3 vs 1 or 2	
Rutherford	3 or higher§	2803	1.29 (86)	7.35	1.45 (1.11–1.90)	0.007
Score	0–2	8145	0.74 (149)		Score ≥3 vs 0–2	
Major amputation	Yes	237	2.01 (11)	6.68	2.24 (1.22–4.14)	0.010
	No	10 711	0.85 (224)			

Patients without baseline HF and with complete covariate data are included (n=10 948). Variables are shown in order of decreasing model Wald chi-square (ie, importance in the model). ABI indicates ankle-brachial index; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; and MI, myocardial infarction.

*Only variables significant in the final model are shown in the table. Other variables that were assessed but were dropped from the model with $P>0.05$ were sex; geographic region; inclusion criteria (ABI or revascularization); ABI; prior carotid revascularization; tobacco use; prior percutaneous coronary intervention; prior coronary artery bypass grafting; prior stroke; and use of aspirin, angiotensin II receptor blocker, statin, or clopidogrel in the 30 days before enrollment.

†Continuous variables are divided at the median for the purpose of showing event rates (which require groups defined in some way) but are included in their continuous form in the model.

‡Weight has a nonlinear relationship with HF risk and is fit in the model as a piecewise linear spline with a single knot at 60. Over the range of weights up to 60 kg, the HR is 0.77 for each 5-kg increase, while over the range of weights >60 kg, the HR is 1.12 for each 5-kg increase. That is, the relationship is approximately V-shaped, with the highest risk of HF at the extreme weights and the lowest risk near 60 kg.

§Rutherford category ≥3 includes severe claudication, rest pain, ischemic ulceration, or gangrene. Categories 0–2 include no leg symptoms or mild or moderate claudication.

may be attributable to lower overall blood pressure in patients with PAD and HF.

Confirming our a priori hypotheses, we identify a clinically significant cohort of patients, those with PAD and concomitant HF, at potentially increased risk of MACEs and all-cause mortality. Furthermore, treatment with antiplatelet agents including ticagrelor or clopidogrel was well tolerated. Finally, we identified increasing age, increasing weight, diabetes mellitus, and known CAD as the clinical attributes most strongly associated with development of postrandomization HF (defined as HF-related death or hospitalization) in patients with symptomatic PAD. These risk factors mirror those that are routinely referenced in the HF guidelines and cardiovascular disease prevention literature.[13–16] Taken together, data from our analysis should provide reassurance to the practicing clinician that aggressive secondary prevention of atherosclerotic events with a single antiplatelet agent in this high-risk population is safe. Whether this is true for dual antiplatelet therapy was not studied. The high event rate in this population also reinforces the importance of medical therapy for both HF and secondary prevention of atherosclerotic cardiovascular disease.

Limitations

Data were not available regarding left ventricular ejection fraction or duration of HF. There was also potential risk for misclassification of HF given the relatively little information regarding HF disease severity collected. Furthermore, there was a relatively low HF event rate in EUCLID, which may have been a result of underdetection of incident HF. This analysis was therefore underpowered to detect any potential differences. Finally, while controlling for type I error is important for the main findings of clinical trials, we have not implemented this in secondary analysis

manuscripts from EUCLID, which are considered hypothesis generating.

CONCLUSIONS

Patients with symptomatic PAD and concomitant HF are at increased risk of MACEs and all-cause mortality compared with patients with PAD without HF. Despite worse objective and subjective measures of arterial disease in patients with HF, there was no difference in MALEs between patients with PAD stratified by presence of HF. Furthermore, treatment with antiplatelet agents was well tolerated with respect to bleeding events. These data possibly support the need for aggressive treatment of recurrent atherosclerotic disease in patients with PAD, especially those with HF.

ARTICLE INFORMATION

Received October 10, 2020; accepted March 4, 2021.

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Sources of Funding

EUCLID was supported by AstraZeneca.

Disclosures

Dr Samsky reports salary support via National Institutes of Health T32 training grant (T32 HL069749) and research support from Boston Scientific. Dr Hiatt reports institutional research grants from Bayer, Janssen, Amgen, AstraZeneca, and the National Institutes of Health. Dr Fowkes reports member of advisory boards for AstraZeneca, Bayer, Merck. Dr Baumgartner reports institutional research grants from Abbott Vascular, Cook, and Boston Scientific. Dr Berger reports institutional research grants from Astra Zeneca; the National Heart, Lung, and Blood Institute; and American Heart Association. Dr Berger reports consulting fees from Janssen, Merck, and Takeda. Dr Katona is an employee of AstraZeneca. Dr Mahaffey's disclosures are available at https://profiles.stanford.edu/kenneth-mahaffey?tab=research-and-scholarship. Dr Norgren reports honoraria/Advisory Board/Steering Committees from AnGes, Bayer, Cesca, and Pluristem. Dr Blomster reports consultation and prior employment by AstraZeneca. Dr Rockhold reports research funding from the National Institutes of Health, Patient Centered Outcomes Research Institute, Duke Clinical Research Institute, Alzheimers Drug Discovery Foundation, AstraZeneca, ReNeuron, Luitpold, Bristol Myers Squib, and Janssen; Consulting/Honoraria from California Institute for Regenerative Medicine, the Patient Centered Outcomes Research Institute, BARDA, Merck Serono, Janssen, resTORbio, Eidos Therapeutics, FuturaMedical, AbbVie, Amgen, Complexa, Adverum Biotechnologies, AstraZeneca, Aldeyra, KLSMC, Merck Research Laboratories, and Chimerix; equity interest in GlaxoSmithKline, DataVant, M3 Biotechnology. Dr DeVore reports research funding through his institution from the American Heart Association; Amgen; AstraZeneca; Bayer; Intra-Cellular Therapies; American Regent, Inc; the National Heart, Lung, and Blood Institute; Novartis; and the Patient Centered Outcomes Research Institute. He also provides consulting services for AstraZeneca. Dr Patel reports institutional research grants from AstraZeneca, CSL, HeartFlow, and Janssen Research. Dr Jones reports research grants from Boehringer Ingelheim, Doris Duke Charitable Foundation, the National Institutes of Health, and the Patient-Centered Outcomes Research Institute; and honorarium/other from Bayer, Bristol-Myers Squibb, and Janssen Pharmaceuticals. Dr Hellkamp has no disclosures to report.

Supplementary Material

Table S1
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Covariates used for examining risk relationship of heart failure with outcomes.

	MACE	Death	MALE	Hospitalization	Major Bleed	Major/minor Bleed
Demographics						
Age	x	x		x	x	x
Female	x	x			x	x
Region	x	x	x	x	x	x
Physical exam						
Weight	x	x	x	x		x
Estimated GFR	x	x		x		
PAD history						
Incl. crit. (ABI/prior revasc)	x	x	x	x		x
ABI	x	x	x	x		x
Rutherford classification	x	x	x	x		x
Major amputation	x	x	x			
Minor amputation	x	x	x	x		
Number of vascular beds	x			x		
Prior carotid revascularization				x		
Medical history						
Tobacco use	x			x		
Diabetes	x	x	x	x		
Prior PCI				x		
Prior CABG			x			
Prior MI	x	x		x		
Prior stroke	x	x		x		
Medications in 30 days prior						
ASA					x	x
ARB		x	x			
Statin	x	x	x			

MACE (major adverse cardiovascular event) = Cardiovascular death, MI, or ischemic stroke

MALE (major adverse limb event) = Major amputation or hospitalization for acute limb ischemia. This predictor list is a combination of the lists from separate major amputation and acute limb ischemia models.

For major/minor bleeding, this is a combination of the lists from separate major and minor bleeding models.

Identification of predictors for all endpoints was carried out in the diabetes analysis, except for acute limb ischemia hospitalization, which was done in the critical limb ischemia analysis.

Figure S1. Interaction between presence of heart failure and weight for MACE.

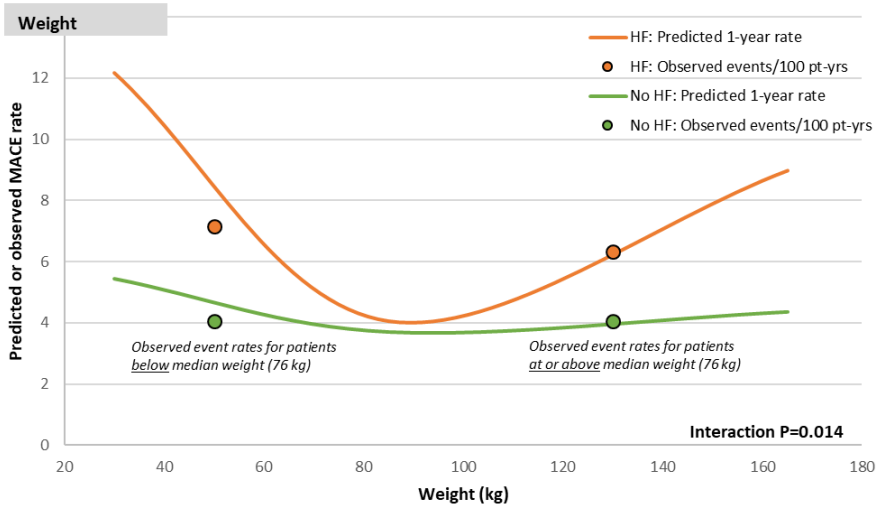

Figure S2. Interaction between presence of heart failure and ABI on MACE.

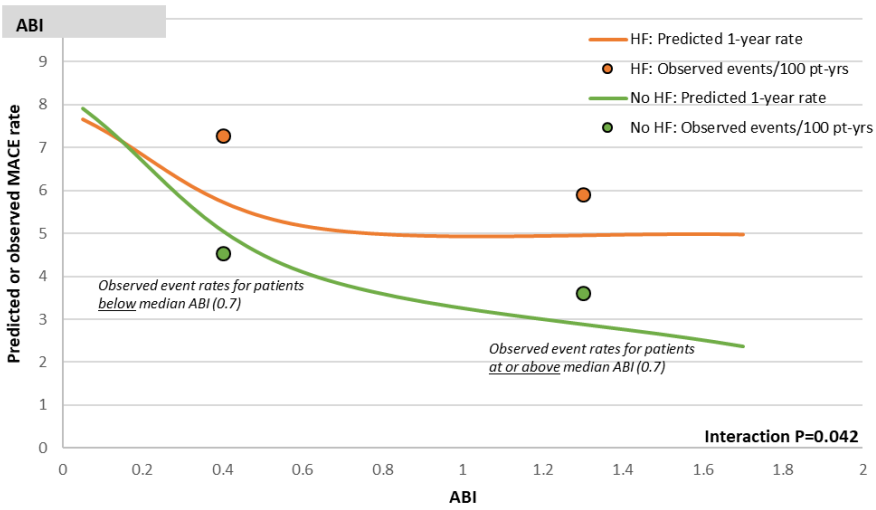

Figure S3. Interaction between presence of HF and ARB use on MALE.

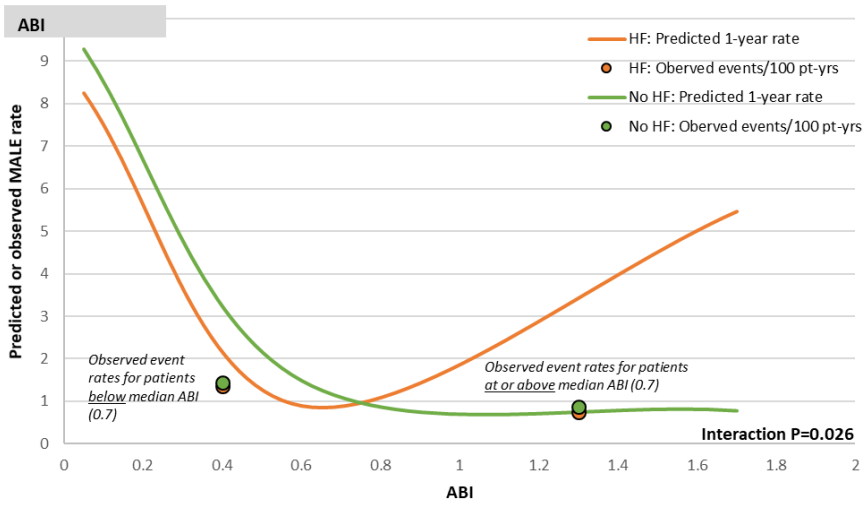

Figure S4. Interaction between presence of HF and ABI on all-cause hospitalization.