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Outcomes of Individuals With and Without Heart Failure Presenting With Acute Coronary Syndrome

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Abstract

Major adverse cardiac event (MACE) and bleeding risks following percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS) are not well defined in individuals with heart failure (HF). We followed 1,145 individuals in the Pharmacogenomic Resource to improve Medication Effectiveness Genotype Guided Antiplatelet Therapy cohort for MACE and bleeding events following PCI for ACS. We constructed Cox proportional hazards models to compare MACE and bleeding in those with vs. without HF, adjusting for sociodemographics, comorbidities, and medications. We also determined predictors of MACE and bleeding events in both groups. 370 (32%) individuals did and 775 (68%) did not have HF prior to PCI. Mean age was 61.7 ± 12.2 years, 31% were female, and 24% were African American. After a median follow-up of 0.78 years, individuals with HF had higher rates of MACE compared to those without HF (48 vs. 24 events per 100 person years) which remained significant after multivariable adjustment (hazard ratio [HR] 1.31, 95% confidence interval [CI] 1.00-1.72). Similarly, bleeding was higher in those with vs. without HF (22 vs. 11 events per 100 person years), although this was no longer statistically significant after multivariable adjustment (HR 1.29, 95% CI 0.86-1.93). Diabetes and peripheral vascular disease were predictors of MACE, and ESRD was a predictor of bleeding among participants with HF. MACE risk is higher in individuals with vs. without HF following

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

PCI for ACS. However, the risk of bleeding, especially among those with ESRD, must be considered when determining post-PCI anticoagulant strategies.

Keywords

heart failure; acute coronary syndrome; bleeding; major adverse cardiac events

Introduction

Ischemic heart disease is a leading cause of death among those living in the United States,[1] and is associated with both an almost 8-fold increased risk of developing heart failure (HF).[2] It is an important cause of HF hospitalization and death, as patients with HF and coronary artery disease (CAD) have a higher 10 year mortality than HF patients without concomitant CAD.[3,4] HF patients who experience an ischemic event have an almost 3-fold increased risk of recurrent ischemic events as compared to HF patients who do not experience an event,[5] and preventing these events has been the rationale for long-term dual-antiplatelet therapy (DAPT) regimens.[6] Major bleeding is the most common complication of DAPT therapy with a 3 to 4 times higher risk of all-cause mortality[7], an increase in the rate of in-hospital mortality, and 30-day major adverse cardiac events (MACE).[8] Understanding the predictors of MACE and major bleeding in individuals receiving PCI for ACS is imperative to mitigate the risks associated with PCI and the medical therapy that follows. MACE events are most often associated with traditional cardiovascular risk factors; however, prior history of HF is an often under-represented cohort in the ACS literature.[9] Advanced age, female sex, and renal insufficiency have been associated with an increased risk of bleeding while taking DAPT,[10] however, the risk of bleeding while on DAPT in patients with HF is unknown. In this study, we sought to compare the risk and characterize predictors of MACE and major bleeding events for patients with and without HF.

Methods

The Pharmacogenomic Resource to improve Medication Effectiveness Genotype Guided Antiplatelet Therapy is a prospective cohort study conducted under the approval of the Institutional Review Board of the University of Alabama at Birmingham (UAB). Patients eligible for enrollment included those who underwent PCI and were subsequently admitted to UAB Hospital. As a component of the study genetic data was obtained, and thus participants must be willing and able to provide consent. A total of 1,596 participants were enrolled between April 2014 and November 2019. Of these, 1,145 participants received PCI for an ACS indication and were included in this analysis. ACS, defined as unstable angina, non-ST segment elevation MI, or ST segment elevation Ml, was determined by a fellow in the cardiovascular disease fellowship under direct supervision of a board-certified cardiology faculty.

After enrollment, a trained coordinator completed a structured case report form. Demographic information was abstracted from the medical record, including each participant's age, sex, race, past medical history, and cardiovascular risk factors. An interview was conducted to document the participant's health insurance status, level of

education, smoking history, current employment, home medications, medication adherence, physical activity, marital status, and home ownership.

Procedural characteristics were obtained at the time of PCI. These included indication for PCI, vital signs, access site, contrast volume, number of obstructed coronary arteries, type of stents placed, and number of stents placed. Information about the severity of each participant's coronary disease was obtained via chart abstraction, with obstructed coronary disease classified as >70% stenosis.

Medications given during and after the PCI procedure, including antiplatelet therapy, were documented.

Participants were classified based on the presence or absence of HF prior to undergoing PCI. HF was defined as having an echocardiogram showing a left ventricular ejection fraction of <50% prior to PCI, if there was no EF documented, then H F was defined as a medical history of H F or a brain naturietic peptide level of ≥400 mg/dl prior to PCI.[11]

Participants were followed for up to 1 year after PCI. UAB medical records were reviewed, and changes in medication use, laboratory parameters, hospitalizations, MACE, and major hemorrhage (HEM) during follow-up were documented. We requested physical and/or electronic medical records from participants' primary care physicians, cardiologists, and/or outside hospital records in case of hospitalization. This was done to ensure encounters outside of the UAB health system were obtained and recorded. All potential MACE and HEM events were adjudicated by expert clinician adjudicators after review of all available medical records.

MACE events were defined as the composite of death (both cardiovascular and non-cardiovascular), non-fatal myocardial infarction (MI), non-fatal ischemic stroke or transient ischemic attack (TIA), and stent thrombosis. MI was diagnosed based on an increase in the cardiac troponin above the 99th percentile upper reference limit in addition to ischemic symptoms or new electrocardiographic findings suggestive of myocardial ischemia. Stent thrombosis was defined as evidence of thrombosis on invasive angiogram. Stroke and TIA were diagnosed based on the presence of a focal neurologic deficit plus imaging evidence of new focal lesion, or new focal deficit defined as TIA by a neurologist. Death was determined through both the inpatient and outpatient medical record.

HEM events were defined as a composite of intracranial hemorrhage, gastrointestinal (GI), or other hemorrhage that resulted in significant hemodynamic compromise requiring treatment, as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) criteria.[12] The GUSTO criteria classified intracerebral hemorrhage and hemodynamic compromise as evidence of severe or life-threatening bleeding, with the identifier of major bleeding being hemodynamic compromise.

The data were summarized using absolute number and percent of total for categorical variables and mean and standard deviation for continuous variables. To compare differences between groups, we used T tests for continuous variables and χ^2-tests for categorical variables. Next, we calculated incidence rates for MACE and major bleeding events in those

with and without HF and compared these rates in those with vs. without HF using incident rate ratios (IRR) and 95% confidence intervals (CI).

In order to determine the independent association of HF status with MACE and major bleeding events, we constructed Cox proportional hazards models to calculate hazard ratios (HR) and 95% CI for participants with vs. without HF. All covariates listed in Table 1 were added to the model if they varied by HF status in bivariate analyses using a p value of <0.05. In model 1, we added demographics, including age, black race, female sex as well as past medical history, including hypertension, diabetes mellitus, atrial fibrillation, CAD, end-stage renal disease (ESRD), and peripheral vascular disease (PVD), insurance status, and alcohol use. Then, in model two, we included components of the first model plus medications prescribed at discharge, including DAPT (aspirin with clopidogrel or aspirin with ticagrelor), calcium-channel blocker, aldosterone inhibitor, diuretics, and oral anticoagulation (warfarin, rivaroxaban, or apixaban). Finally, we constructed Cox proportional hazards models, separately in those with and without HF, to determine which factors predicted MACE and major bleeding events. Factors included in the multivariable model were those known to influence MACE and bleeding (age[13], race[14], gender[15], DAPT therapy[6,16]), in addition to factors listed in Table 1 that were associated with the outcome of interest in univariate analyses with a p-value <0.20.[17] All analyses were performed using SAS version 9.4.

Results

The baseline characteristics, demographic information, and medications prescribed at discharge for our study population are shown in Table 1. Of the 1,145 participants with ACS, 370 had evidence of HF before PCI. The HF and non-HF populations did not differ in terms of female gender and black race. Participants with HF had a lower mean ejection fraction, lower mean systolic blood pressure, and higher mean brain natriuretic peptide levels than those without HF. In addition, as compared to those without HF, participants with HF had a higher prevalence of hypertension, diabetes mellitus, atrial fibrillation, CAD, ESRD, and PVD. However, participants without HF were more likely to consume alcohol than those with HF. In terms of medications, participants with and without HF were similarly likely to receive aspirin at discharge, although individuals with HF were more likely to receive clopidogrel and less likely to receive ticagrelor than those without HF.

The rates of both MACE and bleeding events over a median follow-up of 0.78 years for individuals with and without HF are shown in Table 2. Participants with HF were nearly twice as likely to have MACE than participants without HF. This unadjusted increased risk was related to an increase in all-cause mortality and non-fatal myocardial infarction in those with as compared to without HF. The increased risk for MACE and all-cause mortality remained significant after multivariable adjustment.

Participants with HF were also almost twice as likely to have major bleeding events than participants without HF. This unadjusted risk was driven mainly by differences in GI and other bleeding events, with a 2 times higher risk of GI bleeding for participants with as compared to without HF. Although this increased bleeding risk remained significant when

adjusting for medical history, it was no longer statistically significant after adjustment for medications prescribed at discharge.

The predictors of MACE and major bleeding in individuals with and without HF are shown in Table 3. Among those with HF, prior history of CAD, diabetes mellitus, ESRD, PVD, private insurance, having less than a high school education, use of diuretics, calcium channel blockers, ACE-inhibitors, warfarin, and statins were associated with MACE in univariate analyses. Of these, diabetes remained statistically significant after multivariable adjustment. PVD trended towards elevated risk, however, was not statistically significant. For participants without HF, black race, hypertension, atrial fibrillation, diabetes, ESRD, PVD, private insurance, ACE inhibitor, aldosterone antagonist, insulin, warfarin, and diuretic use were associated with MACE in univariate analyses. Black race, ESRD, PVD, and diuretic use remained statistically significant after multivariable adjustment. For major bleeding, ESRD was associated with a four to five times higher risk of major bleeding in those with and without HF and remained a statistically significant predictor of bleeding after multivariable adjustment in both populations.

Discussion

In this analysis, as compared to those without HF, participants with a history of HF who underwent PCI for the treatment of ACS were more likely to experience MACE and major bleeding events over 1 year of follow-up. The risk of MACE remained significant after multivariable adjustment, although the risk of major bleeding was no longer significant after adjustment for medication use. These data suggest that there is an inherent risk for MACE and major bleeding complications following PCI in those with HF, and this inherent risk should be considered when managing these individuals in clinical practice. Additionally, predictors of MACE and bleeding outcomes differed in those with and without HF, highlighting the importance of patient specific characteristics when evaluating secondary prevention measures for individuals with ACS and further magnifying the inherent risk associated with HF for both outcomes.

In addition to revascularization, the management of patients following ACS focuses on the prevention of future ischemic events, and the hallmark of this prevention strategy is the use of dual antiplatelet therapy (DAPT).[6] After an event, there is a Class 1 indication for a minimum time of 6 to 12 months, with discretion for longer use given a class 2b recommendation.[18] It is important to notice that even in this cohort, where >90% of participants were discharged with DAPT therapy, there were still a significant number of MACE related events. In this analysis, in those without HF, black race, PVD, and ESRD were the strongest risk predictors of MACE, similar to what has been previously described in this cohort.[14] Interestingly, however, these factors were not predictors of MACE in participants with HF. Rather, diabetes was the strongest predictors of MACE in those with a history of HF, and PVD trended towards significance. These findings highlight the importance of risk factor identification given that even with reliable DAPT therapy, a significant number of events still occurred.

Understanding what co-morbidities are associated with an increased risk of MACE in HF patients following ACS could influence decisions about strategies for duration of DAPT following ACS as well as other potential strategies to reduce MACE following ACS in these patients. We observed that diabetes was the strongest predictors of MACE following ACS in patients with HF, similar to previous findings in other populations with ACS.[19,20] In our population, this finding was in the setting of multivariable modeling with other risk factors, highlighting the importance of diabetes in an ACS population. Diabetes is an established risk factor for CAD events and HF has recently become a focus of therapy in the prevention of cardiovascular disease events.[21] Sodium-Glucose Cotransporter 2 (SGLT 2) Inhibitors have been shown to reduce the risk of recurrent events in individuals with established cardiovascular disease, including decreased rates of hospitalization for HF and death,[22] and our findings only strengthen the case for intensive diabetes control in the setting of cardiovascular disease.

PVD was strongly associated with an increased risk of MACE in patients without HF following ACS and trended towards significance in patients with HF. DAPT therapy has been shown to reduce MACE risk in individuals with PVD, and many trials of DAPT show a substantial risk reduction in PVD subgroups.[23] Additionally, anticoagulation use reduces MACE rates in individuals with concomitant CAD and PVD. The use of rivaroxaban was shown to reduced MACE and PVD outcomes for individuals in the PVD subgroup of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial when compared to aspirin monotherapy.[24] In our cohort, anticoagulation use was low (16% in non-HF group and 6% in the HF group), and with PVD emerging as a predictor in multivariable modeling, highlights the importance of this comorbid condition in managing patients with ACS. These findings, coupled with our observation that PVD is a strong predictor of MACE following ACS, can guide clinicians as they determine which patients need more intensive antiplatelet and anticoagulant regimens following ACS.

However, with more intensive medical therapy, the risk of major bleeding increases. Often, the patients at highest risk for recurrent MACE events are also at highest risk of bleeding events and are therefore often not included in large randomized trials of DAPT therapy. In addition, clinical risk prediction scores, like CRUSADE,[25] do not discern true bleeding risk among ACS and post-PCI patients.[26] Additionally, patients with chronic HF are often not included in risk modeling, and our study highlights the significant risk participants with HF face when PCI is used to treat ACS. In our study, we observed that individuals with HF were almost twice as likely as those without HF to experience a major bleeding event following PCI for ACS. Our findings remained statistically significant after adjustment for sociodemographic factors and other comorbidities but were no longer significant following adjustment for medication use. Interestingly, we observed that individuals with HF were 2-3 times more likely to be taking warfarin or apixaban following PCI for ACS than those without HF, likely a result of increased prevalence of atrial fibrillation among those with HF. This highlights the medical complexity of patients with HF, and the higher rates of so-called triple therapy (DAPT plus an anticoagulant) may have contributed to our observed findings of increased bleeding risk.

In addition, renal insufficiency is an established risk factor associated with an elevated risk of major bleeding.[27] In our study, ESRD was a powerful predictor of bleeding following PCI for ACS in both individuals with and without HF, but was not associated with MACE in those with a history of HF. These findings suggest that shorter durations of DAPT following PCI for ACS for ESRD patients, especially in those with a history of HF who also require an anticoagulant, may be able to reduce bleeding risk without increasing MACE. This strategy deserves further investigation. When balancing the risks associated with MACE and major bleeding, it is important to note that bleeding is an independent predictor of mortality for patients undergoing PCI,[28] and both bleeding and MACE should be considered in decisions about medical therapy following PCI.

Our current study does have some limitations. This study is observational and from a single center, thus we are unable to establish causality. The relatively small sample size limits our power to fully assess the relationship between HF and bleeding. Additionally, we are unable to separate EFs obtained during the index encounter vs. during the preceding 3 months. While this does make the study group heterogeneous, it does reflect the differential outcomes of those patients with a degree of LV dysfunction, manifested by either a low EF or clinical HF, putting them at increased risk for MACE and major bleeding. Given that our study is observational, and despite adjusting for important past medical history and medications at discharge, unmeasured and residual confounding is always possible.

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Table 1:

Demographics, Comorbidities, and Medications by Heart Failure Status among Individuals Undergoing Percutaneous Coronary Interventions for Acute Coronary Syndromes in the Pharmacogenomic Resource to improve Medication Effectiveness Genotype Guided Antiplatelet Therapy Cohort, April 2014 – November 2019.

Variable	Heart Failure		
	Yes (N=370)	No (N=775)	P Value
Age (years)	62.7 ± 11.82	61.0 ± 12.29	0.029
Women	109 (29%)	250 (32%)	0.340
Black Race	94 (25%)	181 (23%)	0.448
Left Ventricular Ejection Fraction (%)	36.9 ± 9.4	58.0 ± 5.7	<0.001
Systolic Blood Pressure (mmHg)	138.6 ± 22	144.1 ± 24.3	<0.001
Diastolic Blood Pressure (mmHg)	83.2 ± 14.4	84.6± 15.2	0.138
Brain Naturietic Peptide (pg/dl)	1022.9 ± 1902.1	294.3 ± 723.3	<0.001
Hypertension	326 (88%)	648 (84%)	0.046
Dyslipidemia	271 (73%)	546 (70%)	0.329
Diabetes Mellitus	293 (79%)	189 (24%)	<0.001
Atrial Fibrillation	66 (18%)	71 (9%)	<0.001
Coronary Heart Disease	279 (75%)	404 (52%)	<0.001
Chronic Kidney Disease	89 (24%)	112 (14%)	<0.001
End-Stage Renal Disease	32 (9%)	21 (3%)	<0.001
Peripheral Vascular Disease	58 (16%)	74 (10%)	0.002
Insurance Status			
Private	139 (38%)	373 (48%)	<0.001
Medicare	170 (46%)	258 (33%)	<0.001
Medicaid	144 (39%)	61 (8%)	<0.001
Education Level			
<High-School	199 (54%)	404 (52%)	0.244
>High-School	142 (38%)	311 (40%)	0.571
Alcohol Use	92 (25%)	253 (33%)	0.006
Smoker	104 (28%)	223 (29%)	0.690
Income <$50,000	148 (40%)	301 (39%)	0.385
Medications at Discharge			
Aspirin	352 (95%)	753 (97%)	0.183
DAPT	336 (93%)	732 (96%)	0.046
DAPT using Clopidogrel	233 (63%)	454 (59%)	0.044
DAPT using Ticagrelor	103 (28%)	278 (36%)	0.009
Statin Therapy	336 (91%)	710 (92%)	0.922
Beta-Blocker	314 (85%)	652 (84%)	0.454
Calcium Channel Blocker	61 (16%)	192 (24%)	0.002

Variable	Heart Failure		
	Yes (N=370)	No (N=775)	P Value
ACEi/ARB	187 (52%)	404 (53%)	0.737
Spironolactone	51 (14%)	40 (5%)	<0.001
Diuretic	183 (51%)	220 (29%)	<0.001
Insulin at Discharge	93 (26%)	127 (16%)	<0.001
Oral Anticoagulant	57 (16%)	47 (6%)	<0.001
Warfarin	36 (10%)	28 (4%)	<0.001
Apixaban	21 (6%)	19 (3%)	0.005

All values expressed as mean ± standard deviation or number (percent).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHF, congestive heart failure; DAPT, dual anti-platelet therapy

Diuretics: indapamide, methazolamide, metolazone, acetazolamide, bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, triamterene, chlorothiazide, or chlorthalidone.

Oral Anticoagulation: warfarin, apixaban

Table 2:

Major Adverse Cardiovascular Event and Major Bleeding Event Rates by Heart Failure Status among Individuals Undergoing Percutaneous Coronary Interventions for Acute Coronary Syndromes in the Pharmacogenomic Resource to improve Medication Effectiveness Genotype Guided Antiplatelet Therapy Cohort, April 2014 – November 2019.

	Heart Failure				IRR (95% CI)	Model 1 HR (95% CI)[1]	Model 2 HR (95% CI)[2]
	Yes (n=370)		No (n=775)				
Follow-up (years)	264.96		627.54				
	N	Incidence rate*	N	Incidence rate*			
MACE	126	47.8	150	23.9	1.99 (1.57-2.52)	1.44 (1.11-1.86)	1.31 (1.00-1.72)
All-Cause Mortality	43	16.2	37	5.9	2.75 (1.77-4.27)	1.93 (1.19-3.13)	1.76 (1.04-2.99)
Non-Fatal Myocardial Infarction	82	31.0	99	15.8	1.96 (1.46-2.63)	1.39 (1.01-1.90)	1.29 (0.93-1.81)
Non-Fatal Ischemic Stroke/TIA	9	3.4	20	3.2	1.07 (0.49-2.34)		
Stent Thrombosis	8	3.0	11	1.8	1.72 (0.69-4.28)		
Major Bleeds	58	21.9	70	11.2	1.96 (1.39-2.78)	1.73 (1.89-2.52)	1.29 (0.86-1.93)
Intracranial	3	1.1	5	0.8	1.42 (0.34-5.95)		
Gastrointestinal	25	9.4	27	4.3	2.19 (1.27-3.78)	2.06 (1.14-3.73)	1.70 (0.89-3.26)
Other	30	11.3	38	6.1	1.87 (1.16-3.02)	1.60 (0.95-2.68)	1.17 (0.68-2.03)

*Incidence rate per 100 patient years.

Abbreviations: CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; N, number; TIA, transient ischemic attack.

[1]Adjusted for age, female sex, black race, hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, end-stage renal disease, peripheral vascular disease, insurance status, and alcohol use.

[2]Adjusted for covariates included in model 1 plus the following medications prescribed at discharge: DAPT (dual-antiplatelet therapy), calcium-channel blockers, aldosterone inhibitors, diuretics, or anticoagulation (warfarin or apixaban).

Table 3:

Independent Predictors of Major Adverse Cardiovascular Events and Major Bleeding Events by Heart Failure Status among Individuals Undergoing Percutaneous Coronary Interventions for Acute Coronary Syndromes in the Pharmacogenomic Resource to improve Medication Effectiveness Genotype Guided Antiplatelet Therapy Cohort, April 2014 – November 2019.

	Heart Failure			
	Yes (N=370)		No (N=775)	
	Univariate HR (95% CI)	Multivariable HR (95% CI)	Univariate HR (95% CI)	Multivariable HR (95% CI)
MACE				
Black Race	1.24 (0.77-2.00)	1.27 (0.59-2.77)	2.10 (1.35-3.25)	2.07 (1.32-3.22)
Diabetes Mellitus	1.70 (1.09-2.66)	2.55 (1.04-6.25)	1.93 (1.25-2.96)	1.32 (0.77-2.29)
ESRD	3.01 (1.93-4.95)	2.36 (0.55-10.11)	3.59 (1.64-7.85)	2.67 (1.10-6.25)
PVD	1.90 (1.18-3.07)	2.34 (0.92-5.95)	2.86 (1.66-4.91)	1.95 (1.07-3.57)
Alcohol Use	0.91 (0.50-1.63)	*	0.42 (0.25-0.73)	0.55 (0.33-0.90)
Diuretic Use	1.46 (0.92-2.31)	1.31 (0.46-3.69)	2.07 (1.34-3.20)	1.63 (1.00-2.67)
Major Bleeding				
ESRD	4.31 (1.88-9.89)	3.27 (1.32-8.12)	5.42 (2.62-11.23)	4.17 (1.37-12.74)

Abbreviations: CHF, congestive heart failure; CI, confidence interval; ESRD, end stage renal disease; HR, hazard ratio; MACE, major adverse cardiovascular event; PVD, peripheral vascular disease;

*Represents a variable that did not reach a p value of <0.20 in univariate analysis and was not included in the multivariable model.