

Sex-Based Differences in Outcomes After Percutaneous Coronary Intervention for Acute Myocardial Infarction: A Report From TRANSLATE-ACS

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Background—Data regarding sex-based outcomes after percutaneous coronary intervention (PCI) for myocardial infarction are mixed. We sought to examine whether sex differences in outcomes exist in contemporary practice.

Methods and Results—We examined acute myocardial infarction patients undergoing PCI between April 2010 and October 2012 at 210 US hospitals participating in the Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) observational study. Outcomes included 1-year risk of major adverse cardiac events and bleeding according to Global Utilization of Strategies To Open Occluded Arteries (GUSTO) and Bleeding Academic Research Consortium (BARC) definitions. Among 6218 patients, 27.5% (n=1712) were female. Compared with men, women were older, had more comorbidities, and had lower functional status. Use of multivessel PCI and drug-eluting stents was similar between sexes, while women received less prasugrel. Unadjusted cumulative incidence of 1-year major adverse cardiac events was higher for women than for men (15.7% versus 13.6%, $P=0.02$), but female sex was no longer associated with higher incidence of major adverse cardiac events after multivariable adjustment (hazard ratio 0.98, 95% CI 0.83 to 1.15). Female sex was associated with higher risks of post-PCI GUSTO bleeding (9.1% versus 5.7%, $P<0.0001$) and postdischarge BARC bleeding (39.6% versus 27.9%, $P<0.0001$). Differences persisted after adjustment (GUSTO: hazard ratio 1.32, 95% CI 1.06 to 1.64; BARC: incidence rate ratio 1.42, 95% CI 1.27 to 1.56).

Conclusions—Female and male myocardial infarction patients undergoing PCI differ regarding demographic, clinical, and treatment profiles. These differences appear to explain the higher observed major adverse cardiac event rate but not higher adjusted bleeding risk for women versus men. (*J Am Heart Assoc.* 2014;3:e000523 doi: 10.1161/JAHA.113.000523)

Key Words: acute myocardial infarction • major adverse cardiac events • percutaneous coronary intervention • sex-based outcomes

Cardiovascular disease is the leading cause of mortality for women and men in the United States, accounting for approximately 1 in 4 deaths.^{1,2} According to the American Heart Association, 42% of patients hospitalized for acute myocardial infarction (MI) and 34% of patients undergoing percutaneous coronary intervention (PCI) are women. Although the overall rate of death attributable to cardiovascular disease has declined by >30% from 1999 to 2009, the

rate of decline for women compared with men has been slower,¹ prompting investigation into this discrepancy.

Prior comparisons of outcomes according to sex in the MI and PCI populations have produced mixed results. After adjustment for clinical and procedural characteristics, female sex has been variably associated with mortality.^{3–9} However, these studies did not account for functional characteristics, such as lower physical function and depression, which may be more prevalent among women and are associated with adverse outcomes in patients with cardiovascular disease.¹⁰ Furthermore, many studies were conducted before the availability and routine use of newer antithrombotic agents such as bivalirudin and prasugrel. It is unknown whether sex-based differences in outcomes still exist in contemporary practice and whether these differences persist after accounting for additional clinical and functional variables.

The Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns

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and Events after Acute Coronary Syndrome (TRANSLATE-ACS) study is a prospective, longitudinal, observational study of patients with ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) who were treated with PCI and adenosine diphosphate (ADP) receptor inhibitor therapy in community practice in the United States. The TRANSLATE-ACS study offers the opportunity to (1) describe clinical and treatment characteristics of women and men presenting with acute MI who are treated with PCI in contemporary practice and (2) compare the long-term risks of major adverse cardiac events (MACE) and bleeding between women and men with MI.

Methods

Data Source and Study Population

Details regarding TRANSLATE-ACS (clinical trial NCT01088503) have been previously published.¹¹ The study is broadly inclusive, excluding only patients unable or unwilling to provide written consent for longitudinal follow-up and those simultaneously participating in a research study directing use of an investigational or approved ADP receptor inhibitor within the first 12 months after the acute MI. The latter exclusion allowed us to examine contemporary antiplatelet therapy management patterns among PCI-treated MI patients. TRANSLATE-ACS did not direct treatment intervention or use of specific agents. Informed consent was obtained before study enrollment. Participating hospitals collected information on baseline demographics, clinical characteristics, processes of care, and in-hospital outcomes using a standardized set of data elements and definitions aligned with those of the National Cardiovascular Data Registry CathPCI Registry.¹¹ After discharge from their index hospitalization, patients were interviewed via telephone at 6 weeks, 6 months, 12 months, and 15 months by trained personnel at the Duke Clinical Research Institute. For this analysis, 6218 patients enrolled at 210 hospitals between April 4, 2010, and October 4, 2012, had complete 12-month data available.

Outcomes

Full definitions of each end point have been previously described.¹¹ Briefly, MACE was defined as the composite of all-cause death, MI, stroke, or unplanned revascularization at 1 year. In-hospital MACE events were standardized to CathPCI Registry definitions, which are available at <https://www.ncdr.com/webncdr/cathpci/home/datacollection>. Post-discharge MACE were independently validated by study physicians at the Duke Clinical Research Institute using medical records. A diagnosis of NSTEMI or STEMI was made if ischemic symptoms and ≥ 1 of the following were reported:

cardiac biomarkers greater than the local laboratory reference range; new ST-T wave changes, new left bundle branch block, pathologic Q waves on the electrocardiogram; or new imaging evidence of loss of viable myocardium or regional wall motion abnormality. Stroke was defined as loss of neurological function caused by an ischemic or hemorrhagic event with residual symptoms ≥ 24 hours after onset or leading to death. Unplanned coronary revascularization included any unplanned PCI or coronary artery bypass graft surgery (CABG) occurring after the index PCI. Staged revascularization procedures planned at the time of index PCI and occurring within 60 days were not considered unplanned revascularization events unless a documented recurrent ischemic episode determined the timing of the follow-up procedure.

Bleeding events during the index hospitalization or subsequent rehospitalizations were stratified according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria into the following categories: mild (not meeting criteria for moderate or severe bleeding), moderate (bleeding requiring blood transfusion but not causing hemodynamic compromise), or severe (intracranial hemorrhage or bleeding causing hemodynamic compromise).¹² All GUSTO bleeding events were independently validated by study physicians via medical record review. To capture less severe postdischarge bleeding that may not have required rehospitalization, we also assessed bleeding events according to Bleeding Academic Research Consortium (BARC) criteria. Full BARC definitions have been previously described.¹³ Briefly, BARC bleeding was classified into the following categories: type 1 (bleeding that is not actionable), type 2 (overt, actionable bleeding not meeting criteria for higher BARC bleeding types that requires nonsurgical, medical intervention by a health care professional; leads to hospitalization or increased level of care; or prompts evaluation), type 3a (overt bleeding requiring transfusion with related hemoglobin drop >3 and <5 g/dL), type 3b (cardiac tamponade or bleeding with related hemoglobin drop ≥ 5 g/dL or bleeding requiring surgical intervention for control), type 3c (intracranial hemorrhage, intraocular bleeding compromising vision), type 4 (CABG-related bleeding), or type 5 (fatal bleeding). Patient-reported BARC type 2 or higher bleeding events that involved a hospital stay were also validated via medical record review. Patient reports of BARC type 1 bleeding that, by definition, were not brought to medical attention could not be validated.

Statistical Analyses

Patient and procedure characteristics were examined according to sex. Categorical variables were presented as frequencies, and differences were assessed using χ^2 tests. Continuous variables were presented as medians with

interquartile ranges; differences were assessed using Wilcoxon rank-sum tests. For all outcomes except BARC bleeding, time 0 was considered the date of PCI. Kaplan–Meier cumulative incidence curves were plotted, and cumulative incidences were compared using log-rank tests. These outcomes were examined using Cox proportional hazards models. Cubic spline plots were fitted to assess for nonlinear associations with continuous variables but were ultimately not included in models due to linear associations between variables and outcomes. Hazard ratios (HRs) and associated 95% CIs were reported.

Since the CathPCI Registry does not capture index hospitalization bleeding not brought to medical attention (BARC type 1), time 0 for BARC bleeding was set to the date of index hospital discharge. In contrast to hospitalized bleeding events for which exact dates were available, the timing of patient-reported bleeding events was not collected. Therefore, BARC bleeding was examined using Poisson regression with an offset for person-time to account for variable follow-up due to deaths and variation in 12-month interview times. The person-time offset was defined as the number of follow-up days from discharge to the first event date (if known) or to the date of the interview during which the event was reported; patients who died before their 12-month interview only contributed time while alive. Incidence rate ratios (IRRs) and associated 95% CIs were reported for BARC bleeding outcomes.

Both Cox proportional hazards and Poisson regression models were adjusted for preselected variables deemed clinically relevant or significantly different between groups in univariate comparisons. The following variables were used to assess adjusted risk of composite MACE and individual components: age, body mass index, race, employment status, marital status, insurance status, education status, EuroQol-5 Domain (EQ-5D) quality of life index, Patient Health Questionnaire-2 (PHQ-2) depression score, previous MI, previous PCI, previous CABG, previous stroke or transient ischemic attack (TIA), cerebrovascular disease, peripheral artery disease, congestive heart failure, atrial fibrillation/flutter, diabetes, hypertension, dyslipidemia, chronic lung disease, current/recent smoker, use of dialysis, gastrointestinal or genitourinary bleeding within past 6 months, presentation with STEMI, cardiac arrest within 24 hours, cardiogenic shock within 24 hours, admission heart rate, admission systolic blood pressure, ejection fraction $\leq 40\%$, baseline creatinine, baseline hemoglobin, preprocedure peak troponin, multivessel disease, multivessel PCI, bifurcation lesion, graft lesion, lesion success, drug-eluting stent (DES) use, and hospital region. Adjustment variables used in the bleeding model included age, weight, EQ-5D index, PHQ-2 depression score, cerebrovascular disease, previous stroke/TIA, peripheral artery disease, diabetes, current/recent smoker, congestive heart

failure, gastrointestinal or genitourinary bleeding within past 6 months, presentation with STEMI, cardiogenic shock within 24 hours, admission heart rate, admission systolic blood pressure, baseline creatinine, baseline hemoglobin, in-hospital CABG, other surgery in-hospital, in-hospital MI, in-hospital cardiogenic shock, in-hospital heart failure, in-hospital stroke/TIA, discharge warfarin, other discharge anticoagulant, discharge aspirin, and hospital region.

Secondary analyses for composite MACE and any GUSTO bleeding outcomes were performed among the following patient subgroups: those with creatinine clearance < 60 mL/min, treatment with DES, age ≥ 65 years, use of ADP receptor inhibitor before index admission, and presentation with STEMI. A 2-way *P* value < 0.05 was considered statistically significant. All data analyses were performed independently by statisticians at the Duke Clinical Research Institute using SAS version 9.3 (SAS Institute).

Results

Patient Characteristics

Among 6218 acute MI patients treated with PCI, 27.53% ($n=1712$) were women. Demographic variables were significantly different between the sexes (Table 1). Compared with men, women were of lower body weight but similar body mass index, older, more often of non-white race, less frequently uninsured, and less often married or employed. Women also scored lower on all EQ-5D domains than men, and were more likely to report symptoms of depression than men, as assessed with PHQ-2 scores. Compared with men, women had a significantly greater burden of comorbid conditions, including hypertension, diabetes, previous stroke/TIA, peripheral artery disease, and worse renal function. Women more frequently presented with a first-time MI, whereas a higher percentage of men had histories of MI and revascularization. Women were less likely than men to present with STEMI (versus NSTEMI; 46.96% versus 54.35%, $P<0.0001$).

During the index MI hospitalization, women were treated more often with clopidogrel or bivalirudin, while men more frequently received prasugrel or glycoprotein IIb/IIIa inhibitors (Table 2). The use of radial access for catheterization and arterial closure device was similar between the sexes, as was the rate of multivessel PCI and DES use. Women were less frequently prescribed prasugrel at discharge.

Major Adverse Cardiovascular Outcomes

The unadjusted cumulative incidence of 1-year MACE was significantly higher for women than men (15.7% versus 13.6%, $P=0.02$, Figure 1), yet after multivariable adjustment, female

Table 1. Patient Characteristics

	Female (n=1712)	Male (n=4506)	P Value
Demographic features			
Age, median (IQR), y	64.0 (55.0 to 72.0)	59.0 (52.0 to 67.0)	<0.0001
Weight, median (IQR), kg	76.8 (66.0 to 90.7)	91.0 (81.6 to 104.5)	<0.0001
BMI, median (IQR), kg/m ²	29.3 (25.3 to 34.4)	29.3 (20.1 to 33.0)	0.58
Nonwhite race, %	14.1	8.8	<0.0001
No health insurance, %	10.7	14.2	0.0003
Married, %	48.9	71.2	<0.0001
High school graduate, %	84.8	88.4	<0.0001
Employed, %	34.5	55.0	<0.0001
Functional characteristics			
EQ-5D index, median (IQR)	0.83 (0.77 to 1.0)	0.86 (0.81 to 1.00)	<0.0001
Mobility: no problems walking	68.0	80.9	<0.0001
Self-care: no problems with self-care	88.2	93.3	<0.0001
Usual activities: no problems performing usual activities	67.2	76.9	<0.0001
Pain/discomfort: no pain/discomfort	57.5	68.6	<0.0001
Anxiety/depression: not anxious/depressed	63.4	75.4	<0.0001
Visual analogue scale	70 (50 to 80)	75 (60 to 85)	<0.0001
PHQ2 depression score >3, %	11.2	6.1	<0.0001
Medical comorbidities			
Current/recent smoker, %	37.9	35.8	0.14
Hypertension, %	73.6	65.3	<0.0001
Dyslipidemia, %	70.3	66.8	0.01
Cerebrovascular disease, %	9.6	5.8	<0.0001
Prior stroke or TIA	7.2	4.3	<0.0001
Peripheral artery disease, %	7.6	5.8	0.01
Chronic lung disease, %	12.0	8.9	0.0003
Diabetes mellitus, %	31.1	23.4	<0.0001
Prior MI, %	17.1	20.4	0.003
Prior PCI, %	18.6	22.6	0.001
Prior CABG, %	7.6	10.4	0.001
Prior HF, %	7.2	5.6	0.02
GI/GU bleeding within 6 months, %	1.6	0.8	0.01
Creatinine clearance, median (IQR), mL/min	56.7 (41.8 to 72.5)	77.7 (62.1 to 94.7)	<0.0001
Dialysis, %	1.8	0.9	0.01

BMI indicates body mass index; CABG, coronary artery bypass graft surgery; EQ-5D, EuroQoL-5 Domain; GI, gastrointestinal; GU, genitourinary; HF, heart failure; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; PHQ-2, Patient Health Questionnaire-2; TIA, transient ischemic attack.

sex was no longer significantly associated with a higher risk of MACE (HR 0.98, 95% CI 0.83 to 1.15, $P=0.78$). Individually, the unadjusted cumulative incidence of death or MI within 1 year of the index MI event was significantly higher among women than among men (Figure 2A through D). In contrast, rates of stroke and unplanned revascularization were similar.

All observed differences in individual outcomes were no longer significant after adjustment for patient and procedure characteristics: HR 0.79, 95% CI 0.56 to 1.09, $P=0.15$ for death; HR 1.37, 95% CI 0.99 to 1.89, $P=0.06$ for MI; HR 0.44, 95% CI 0.17 to 1.17, $P=0.10$ for stroke; and HR 1.06, 95% CI 0.88 to 1.26, $P=0.54$ for unplanned revascularization.

Table 2. In-Hospital Treatment

	Female (n=1712)	Male (n=4506)	P Value
In-hospital medications, %			
Aspirin	97.5	98.4	0.09
Clopidogrel	82.6	76.2	<0.0001
Prasugrel	23.4	31.7	<0.0001
Ticagrelor	0.6	0.3	0.24
Unfractionated heparin	74.7	75.7	0.57
Low molecular weight heparin	21.3	18.9	0.08
Bivalirudin	48.7	44.9	0.01
Glycoprotein IIb/IIIa inhibitor	42.0	48.9	<0.0001
Procedural features			
Radial artery access, %	8.2	8.9	0.68
Arterial closure device, %	34.8	35.3	0.65
Multi-vessel PCI, %	9.6	10.6	0.26
Drug-eluting stent use, %	70.6	70.0	0.64
Discharge medications			
Aspirin, %	97.5	98.6	0.002
Clopidogrel, %	76.2	68.4	<0.0001
Prasugrel, %	22.3	30.6	<0.0001
Ticagrelor, %	0.5	0.3	0.16
Anticoagulant, %	4.4	5.6	0.06

PCI indicates percutaneous coronary intervention.

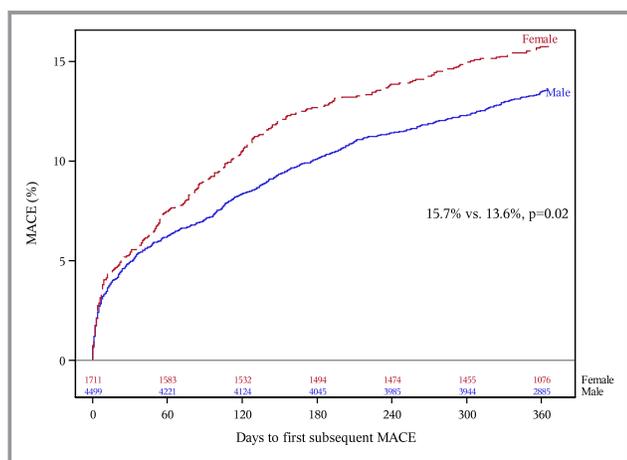


Figure 1. Unadjusted cumulative incidence of major adverse cardiac events according to sex. The Kaplan–Meier curve for 1-year post-PCI MACE is shown. MACE indicates major adverse cardiac events; PCI, percutaneous coronary intervention.

Bleeding Outcomes

We examined the cumulative incidence of any GUSTO-defined bleeding event within 1 year post index PCI. Women had a higher risk of any GUSTO bleeding (9.1% versus 5.7%,

$P<0.0001$; Figure 3A) as well as a higher risk of GUSTO moderate/severe bleeding (5.1% versus 2.0%, $P<0.0001$; Figure 3B) than men. The curves diverged early after the index PCI. After multivariable adjustment, female sex remained significantly associated with any GUSTO bleeding event (HR 1.32, 95% CI 1.06 to 1.64, $P=0.01$) and GUSTO moderate or severe bleeding (HR 1.63, 95% CI 1.19 to 2.24, $P=0.003$).

Postdischarge bleeding, including patient-reported bleeding not brought to clinical attention, was examined according to the BARC definition. Overall rates of any BARC bleeding were significantly higher for women than men (39.6% versus 27.9%, $P<0.0001$). This higher risk of bleeding in women persisted after adjustment for patient and procedural characteristics (IRR 1.42, 95% CI 1.27 to 1.56, $P<0.0001$). Figure 4 shows the distribution of events according to specific BARC bleeding types. In general, there were few severe (BARC type ≥ 3) bleeding events for both men and women. The adjusted IRRs for women versus men were significantly higher for BARC type 1 (IRR 1.46, 95% CI 1.26 to 1.70, $P<0.0001$) and BARC type 2 (IRR 1.71, 95% CI 1.36 to 2.14, $P<0.0001$) bleeding. The risk of postdischarge BARC type ≥ 3 bleeding was not significantly different between the sexes (IRR 1.14, 95% CI 0.75 to 1.75, $P=0.54$).

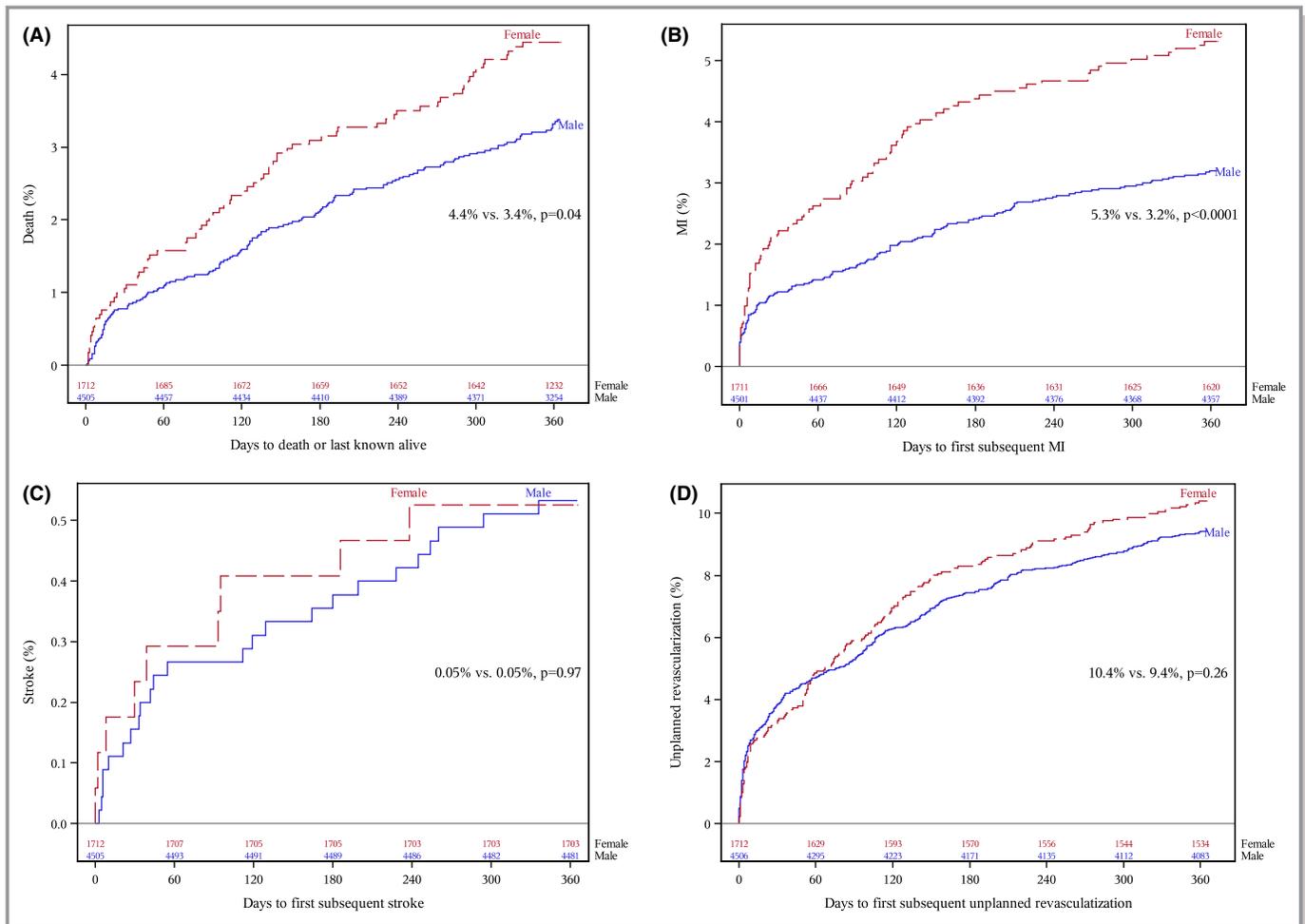


Figure 2. Unadjusted cumulative incidence of ischemic outcomes according to sex. Shown are Kaplan–Meier curves for 1-year post-PCI: (A) all-cause mortality; (B) MI; (C) stroke; and (D) unplanned repeat revascularization. MI indicates myocardial infarction; PCI, percutaneous coronary intervention.

Secondary Analyses

After adjustment, the association of female sex with risk of 1-year MACE was similar between patients with versus those without renal impairment (creatinine clearance cutoff <60 mL/min), patients treated with DES versus bare metal stent, older (≥ 65 years) versus younger patients, patients with versus those without preadmission ADP receptor inhibitor use, and patients presenting with STEMI versus NSTEMI (Figure 5A; P for interaction >0.05 for all subgroups). Similarly, as shown in Figure 5B, interactions between sex and these subgroup characteristics for bleeding were not statistically significant.

Discussion

In this study of acute MI patients undergoing PCI, we found that women presented with a significantly different profile

than men with respect to demographic, clinical, and functional features. While observed 1-year MACE rates were higher among women, this difference in risk was mitigated after adjustment for baseline characteristics. In contrast, women remain at higher bleeding risk than men even after multivariable adjustment. Our data further suggest that women are at an increased risk of more severe bleeding (GUSTO moderate or severe bleeding) than men, with the curves diverging early after PCI. After discharge, women are also more likely than men to have bleeding that is not brought to their clinician's attention.

Previous analyses of outcomes by sex in PCI and MI populations have found mixed results. In some studies, female sex independently predicted mortality after acute coronary syndrome and PCI after adjustment for baseline differences,^{3,4,6} while in others, these differences appeared to explain most (if not all) of the variation in outcome between the sexes.^{5,7,9,14–16} Some data even suggest that female sex

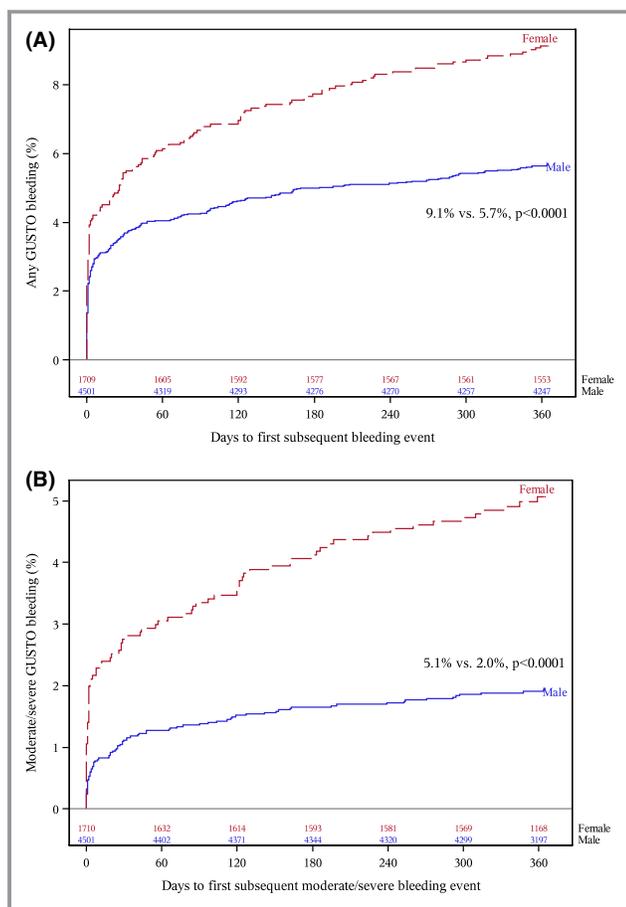


Figure 3. Cumulative incidence of GUSTO bleeding according to sex. Kaplan–Meier curves for: (A) any GUSTO bleeding; and (B) moderate or severe GUSTO bleeding at 1 year post-PCI are shown. GUSTO indicates Global Use of Strategies to Open Occluded Coronary Arteries; PCI, percutaneous coronary intervention.

may be associated with better survival after PCI.^{8,17} In contrast, women remain consistently at higher risk than men for bleeding complications after MI and PCI, despite overall reduced rates of these events over time.^{5,6,8,9,18,19}

Our study expands current knowledge of post-MI sex-based differences in outcomes in several ways. First, beyond traditional risk factors, we included additional baseline quality of life, functional status, depression, and demographic variables. Sex differences among these factors have been historically observed, and these factors have been associated with worse outcomes in patients with coronary artery disease,^{10,20,21} yet they have not been included in previous studies examining sex and post-MI outcomes. Second, we included postdischarge patient-reported bleeding outcomes. These bleeding events may not be severe enough to trigger review by a clinical trial events committee or require rehospitalization captured by administrative data, but they could still impact patient quality of life and medication adherence. Finally, these data represent outcomes of

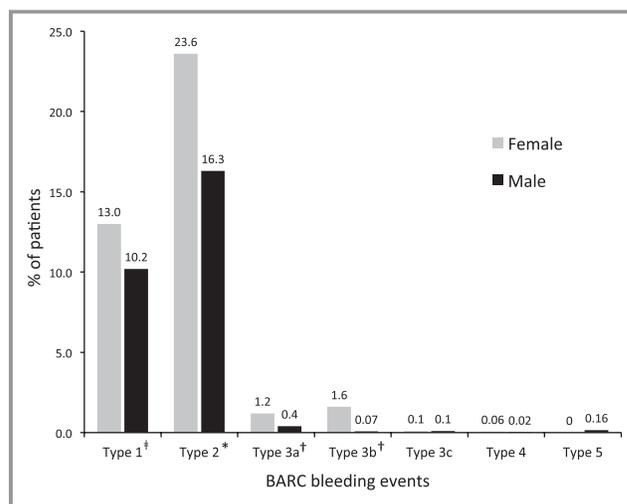


Figure 4. Distribution of Bleeding Academic Research Consortium (BARC) bleeding according to sex. Bleeding events according to BARC definitions for women vs men are shown. The most severe BARC was counted per patient. **P* value <0.0001; †*P* value <0.001; ‡*P* value <0.01 for pairwise comparisons.

contemporary community-based MI patients treated with PCI who are exposed to novel therapies (eg, prasugrel or bivalirudin) recently adopted into routine practice.

Previous investigators have described sex-based differences in patient characteristics in MI populations and observed less frequent referral of women for coronary revascularization.^{22,23} Our study focused on patients who all underwent PCI and found significant differences in clinical and treatment characteristics between male and female MI patients. In particular, women are older and are more likely to present with comorbid conditions such as peripheral arterial or cerebrovascular disease, even as they are less likely to have had previous MI or previous coronary revascularization. Substantial differences between men and women exist in baseline functional status and quality of life, as well as a higher rate among women of depression and disparities in demographic features and social support. In this study, higher 1-year rates of MACE (15.7% versus 13.6%), death (4.4% versus 3.4%), and MI (5.3% versus 3.2%) for women versus men were no longer significant after adjusting for measured differences between sexes. Furthermore, we did not find significant interactions between sex and outcomes among high-risk subgroups.

In contrast, we found that the adjusted long-term risk of bleeding was greater in women than in men. Women are at higher risk of any GUSTO-defined bleeding and, specifically, GUSTO moderate or severe bleeding within 1 year after PCI. This difference in bleeding risk was noted early post PCI, suggesting greater risk of procedural or periprocedural bleeding. After discharge, women remained at higher risk of

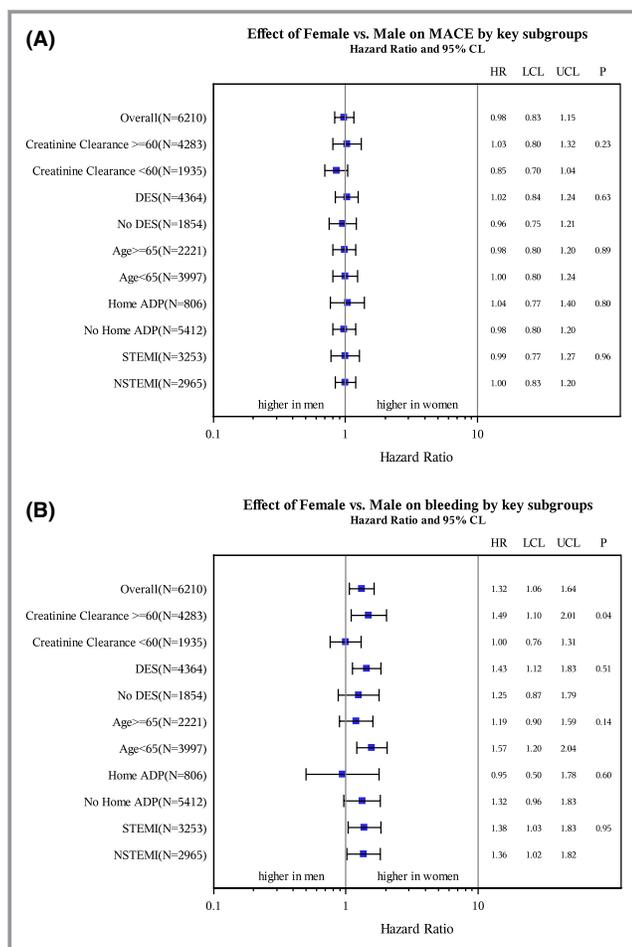


Figure 5. MACE and bleeding outcomes by sex among subgroup populations. HRs for composite of: (A) MACE; and (B) any GUSTO bleeding events are shown for pre-specified subgroups. *P* values correspond to the test for interaction between sex and the specific subgroup of interest. *P* values < 0.05 indicate that the effect of sex differs significantly between levels of the subgroup, while *P* values ≥ 0.05 indicate no significant difference in the effect of sex by levels of the subgroup. ADP indicates adenosine diphosphate; CrCl, creatinine clearance; DES, drug-eluting stent; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; HR, hazard ratio; LCL, lower 95% confidence limit; MACE, major adverse cardiac events; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UCL, upper 95% confidence limit.

bleeding according to the BARC definition. BARC type ≥ 2 bleeding has been significantly associated with 1-year post-PCI mortality and has been found to outperform existing bleeding definitions with respect to mortality prediction in this setting.²⁴ Women are also more likely to have BARC type 1 bleeding than are men. These bleeding events may not be brought to medical attention but could still affect patient quality of life and medication adherence.^{25,26} Investigation into the clinical significance of our findings, such as whether mild bleeding is associated with premature discontinuation of antiplatelet therapy and stent thrombosis, is warranted.

Female sex has been consistently identified as a predictor of major bleeding after PCI and in acute coronary syndromes,^{27,28} and several factors may explain these sex-specific differences in bleeding risk. Overall increased bleeding risk for women may be due to sex-based variation in platelet biology and response to antiplatelet therapies—particularly when multiple antiplatelet and anticoagulants are coadministered in the periprocedural acute MI setting.^{14–16,29,30} Differences in patient age and comorbidities associated with bleeding, such as renal impairment, which is more common in women, or in drug safety profiles and provider choice of antithrombotic agents, may also contribute to increased risk of bleeding.^{31–33} In clinical trials, bivalirudin was noninferior for efficacy but reduced bleeding compared with heparin plus a glycoprotein IIb/IIIa inhibitor; prasugrel reduced ischemic outcomes but at the cost of more bleeding compared with clopidogrel.^{34–36} In our study, we found that bivalirudin was more frequently used during PCI in women than in men, and women received prasugrel less frequently than did men during the hospitalization and at discharge. Provider concern over increased bleeding risk in women and prasugrel labeling, which prohibits use in patients with previous stroke or TIA and recommends cautionary use in patients ≥ 75 years old or < 60 kg, all of which we observed to be more common in women than men, may have motivated these therapeutic decisions. Notably, 42% of women were treated with a glycoprotein IIb/IIIa inhibitor, a drug that is frequently incorrectly dosed in women.³⁷ Excess antithrombotic drug dosing—especially common among women, older patients, and those with lower body weight—has been shown to contribute to bleeding risk.^{5,32,38} Given the adjunctive use of antithrombotic agents at the time of PCI, bleeding risk associated with these therapies may explain the increased female frequency and severity of bleeding around the time of MI and PCI observed in our analysis.

Our findings may have important regulatory implications. The US Food and Drug Administration Office of Women's Health has expressed an interest in assessing sex differences in the safety and effectiveness of Food and Drug Administration-regulated products, with a focus on obtaining a more generalizable understanding of the risks and benefits associated with “real-world” antiplatelet therapy use.³⁹ Here, we examined sex-based differences in both effectiveness and safety outcomes among MI patients undergoing PCI and treated with dual-antiplatelet therapy. Information gained from this study and further similar comparative effectiveness research investigations may aid the agency in determining whether labeling changes (ie, modifications to indications for use) for products regulated by the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health are warranted. Results of this research may also affect the design of future trials in which antithrombotic therapy regimens are prescribed,

which includes many of the cardiovascular device trials evaluated by the Center for Devices and Radiological Health. In this current analysis, although adjusted rates of MACE were not found to be higher in the female group, the increased adjusted rates of bleeding complications are of concern. These findings will need to be further evaluated with close attention to the contribution of other factors to sex differences in clinical outcomes in this population.

Several limitations should be acknowledged. First, although our study was prospective, it was observational and did not randomize treatments; therefore, unmeasured sex-based differences may exist. Second, we did not capture the rationale for specific drug choice or treatment dosing for certain drugs, such as heparin or glycoprotein IIb/IIIa inhibitors. Third, while MACE and GUSTO-defined bleeding events were independently validated by study physicians using medical records, BARC-defined bleeding was patient reported, and less severe BARC bleeding events not requiring rehospitalization could not be validated. Fourth, this study is not powered to examine relationships between sex and individual MACE end points. Finally, although observational, TRANSLATE-ACS could track only long-term outcomes for patients who provided informed consent and were enrolled in the study.

In conclusion, in this study of contemporary community-based acute MI patients undergoing PCI, we found that women are older, more likely to have comorbid conditions, and more frequently have lower functional status and depression than men. After adjustment for these differences, we found a similar risk of 1-year MACE between women and men. In contrast, women are consistently at higher risk of bleeding than men, even after multivariable adjustment. Furthermore, our data suggest that women are both at higher risk of more severe bleeding than men and more likely than men to have postdischarge bleeding not brought to their clinician's attention. Further investigation is needed regarding whether these findings can be modified, such as through choice of antiplatelet therapy.

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