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Women, Bleeding, and Coronary Intervention

Bina Ahmed, MD; Harold L. Dauerman, MD

Bleeding initiates a cascade of events that increase morbidity and mortality among patients undergoing percutaneous coronary intervention (PCI).¹⁻⁵ Acute loss of blood impacts circulatory volume and can potentiate and perpetuate shock. In addition, bleeding leads to anemia and transfusion of blood products, which promote inflammation and untoward cardiovascular effects, especially in the setting of acute coronary syndrome.⁶⁻⁸ Finally, bleeding results in cessation of dual antiplatelet therapy, which increases risk of recurrent ischemic events such as stent thrombosis and myocardial infarction.^{9,10}

Registries and randomized trials have shown the impact of bleeding on outcomes. Patient in the Global Registry of Acute Coronary Events were noted to have a 4.0% incidence of major bleeding across the spectrum of acute coronary syndrome (ACS). Furthermore, major bleeding was an independent predictor of in-hospital mortality (adjusted odds ratio, 1.64 [95% confidence interval, 1.18-2.28]).¹¹ Ndrepepa et al² evaluated 4 randomized control trials of patients undergoing PCI and identified major bleeding as the strongest independent predictor of 1-year mortality. Similarly, Mehran et al¹² performed a patient level pooled analysis of >17000 patients in 3 ACS trials: the occurrence of a major bleed within 30 days of hospitalization was associated with a 4-fold higher risk of mortality at 1 year. Finally, in patients with ST segment elevation myocardial infarction enrolled in the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction trial, bleeding related to PCI was an independent predictor of mortality after 3 years of follow-up (hazard ratio, 2.80 [95% confidence interval, 1.89-4.16]).¹³

Increased focus on the morbidity and mortality associated with PCI-related bleeding has led to pharmacological, procedural, and technological advances,¹⁴ which have resulted in improvement in post-PCI bleeding rates over the past decade (Figure 1).¹⁵⁻¹⁸ The 2011 American College of Cardiology-American Heart Association PCI Guidelines formally recognize the quality improvement goal of reducing bleeding complications: "All patients should be evaluated for risk of bleeding complications before PCI" (class I, level of evidence C).¹⁹

Absolute event rates for bleeding have improved over time for both men and women undergoing PCI and, as reviewed below, major bleeding occurs in <3% of both sexes. In this Review article, we highlight the risk of bleeding complications in women compared with men, the differences in platelet biology and potential ischemic risk, and the guideline-recommended pharmacology that may benefit women undergoing coronary intervention. Ongoing quality improvement focuses

on prevention of bleeding complications among high-risk patients but cannot come at the cost of increased thrombotic events. Thus, discussion of the interaction of female sex and bleeding risk must be balanced by potential interactions of sex and ischemic risk (ie, platelet biology).

Female Sex and the Risk of Bleeding Complications

As compared with men, women undergoing PCI are older and have a higher prevalence of renal insufficiency, anemia, and diabetes mellitus.²⁰⁻²² As demonstrated in 2 large registry studies, women with ACSs have higher unadjusted mortality and less use of guideline recommended therapies (an early invasive approach, thienopyridines and glycoprotein inhibitors [GPIs]) than men.^{21,22} In the setting of this heightened cardiovascular risk, the decision to withhold guideline-recommended antiplatelet therapy because of enhanced bleeding risk among women should be considered using an individualized risk-benefit analysis. Although it is unclear whether the sex-specific risk of increased cardiovascular events persists after adjustment for comorbidities,²² the association between bleeding and female sex persists after adjustment for confounding clinical factors.

The risk of bleeding complications can be assessed using integer scoring systems involving clinical variables associated with a heightened risk.²³⁻²⁵ Risk prediction tools have been validated using both observational cohorts and large, randomized ACS trials. Although the use of integer scoring systems goes beyond sex in providing an overall estimation of bleeding risk, common to all scores is the independent association between female sex and risk of bleeding complications (Figure 2).

Analysis from the Northern New England PCI registry of >13 000 women undergoing PCI compared with 30 000 men emphasized the importance of female sex in assessment for bleeding risk before PCI. Despite improvement in bleeding events over time, female sex remained a strong independent predictor of bleeding and vascular complications over a 6-year period (Figures 3 and 4).¹⁷ Similarly, the CathPCI Registry examined 570 777 patients between 2008 and 2011 and found that women had a near 2-fold increased risk of bleeding compared with men (7.8% versus 3.7%; odds ratio, 1.95 [95% CI, 1.91-2.02]) despite adjusting for baseline clinical and procedural variables.²⁶ Thus, although bleeding complications have improved for men and women, female sex remains a potent predictor of increased risk for bleeding.

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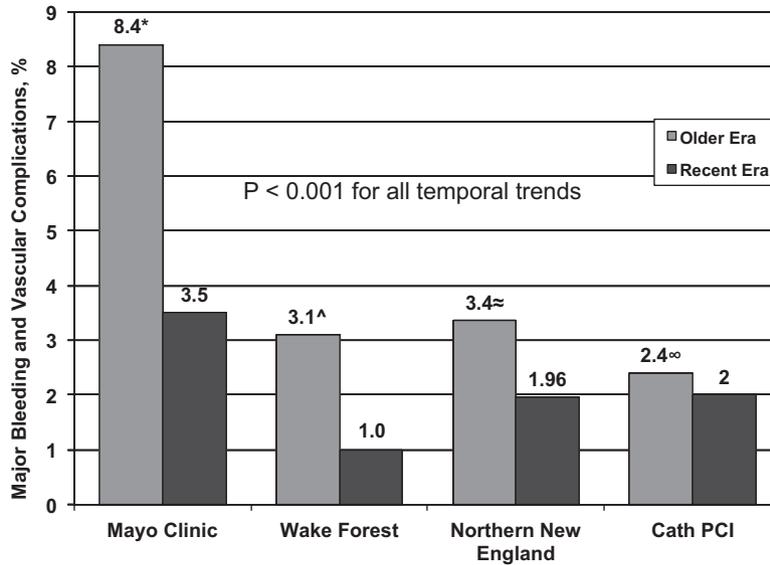


Figure 1. Trends in bleeding and vascular complication rates from large registries. There has been a significant improvement in overall rates of percutaneous coronary intervention (PCI)-related bleeding.¹⁴ *Older era: 1994-1995. New era: 2000-2005. Bleeding was defined as femoral hematoma >4 cm in diameter that required blood transfusion, surgery, or prolonged hospital stay; femoral bleed such as external bleeding from the femoral artery requiring blood transfusion or surgery; and retroperitoneal hematoma identified with abdominal ultrasound or computed tomography scan. ^Older era: 1998. New era: 2007. Vascular complications are defined as follows: minor vascular complications: hematoma >10 cm, arteriovenous fistulae, or pseudoaneurysm; and major vascular complications: death caused by vascular complications, vascular repair, major vascular bleeding (>3 g hemoglobin decrease because of access site bleeding or retroperitoneal bleeding), vessel occlusion, or loss of pulse. ~Older era: 2002. New era: 2007. Bleeding/vascular complication was defined as any access site-related bleeding requiring a transfusion or an access site complication requiring surgical or procedural intervention, such as access artery dissection, perforation, arteriovenous fistula, pseudoaneurysm, or embolism, during the index hospitalization. ∞Older era: 2005. New era: 2009. Major bleeding was defined as follows: (1) bleeding requiring a blood transfusion or prolonged hospitalization; (2) a decrease in hemoglobin >3.0 g/dL from any location, including percutaneous entry site, retroperitoneal, gastrointestinal, genitourinary, and other/unknown location; or (3) percutaneous entry site hematoma >10 cm for femoral access, >2 cm for radial access, or >5 cm for brachial access. Adapted from and reprinted with permission from Dauerman et al.¹⁴

Unlike broadly inclusive registries, PCI and ACS trials show significant evidence of sex bias in enrollment of women in clinical trials. Although women compose 40%

of patients with ACS or PCI, women represent only 25% of the patient pool enrolled in trials of ACS.²⁷ Despite a more selected enrollment of women, data from randomized

Variable	Points Assigned
ACS Type	
ST elevation MI	10
Non-ST Elevation MI	3
Cardiogenic Shock	8
Female Gender	6
Previous CHF	5
No Previous PCI	4
NYHA class IV CHF	4
PAD	2
Age	
66-75	2
76-85	5
>85	8
Estimated glomerular filtration rate	1 (per 10 unit decrease if < 90)

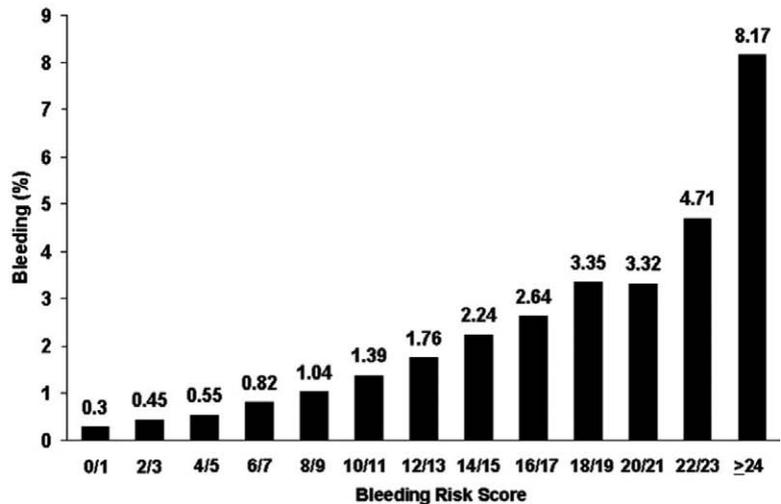


Figure 2. Bleeding risk score from the National Cardiovascular Data Registry. **A**, Weighted variables used to calculate a bleeding risk score. **B**, Prevalence of percutaneous coronary intervention (PCI)-related bleeding based on clinical risk score.²⁵ ACS indicates acute coronary syndrome; CHF, congestive heart failure; MI, myocardial infarction; NYHA, New York Heart Association; and PAD, peripheral arterial disease. Reprinted with permission from Mehta et al.²⁵ Copyright Wolters Kluwer Health, 2009.

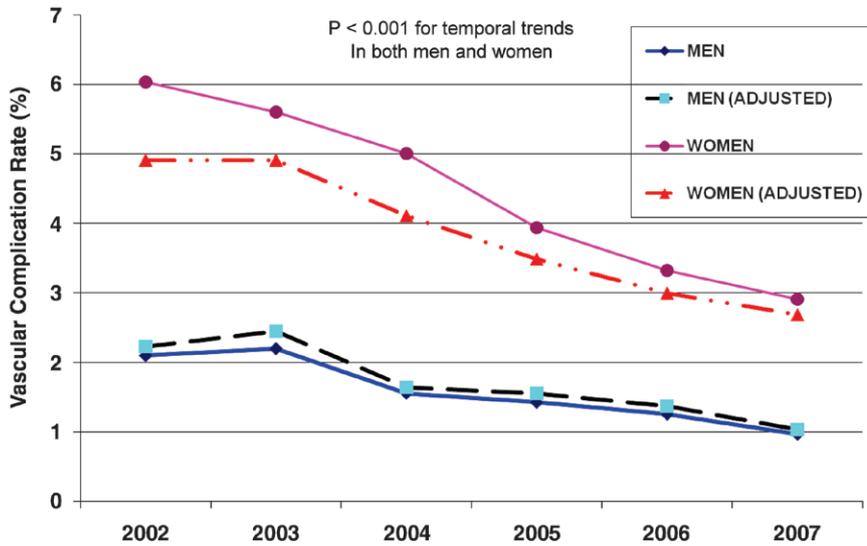


Figure 3. Temporal trends in bleeding and vascular complication rates among men and women undergoing percutaneous coronary intervention in the Northern New England PCI Registry from 2002 to 2007.¹⁷ Bleeding/vascular complication was defined as any access site-related bleeding requiring a transfusion or an access site complication requiring surgical or procedural intervention, such as access artery dissection, perforation, arteriovenous fistula, pseudoaneurysm, or embolism, during the index hospitalization. Adapted from Ahmed et al.¹⁷

control trials, such as the Acute Catheterization and Urgent Intervention Triage Strategy, study continue to highlight the female predisposition for bleeding.^{28,29} Similarly, evaluation of a more potent P2Y12 antagonist in the TRITON TIMI 38 trial found women to be 77% more likely than men to have a major bleeding complication.³⁰ Given the selection bias of randomized clinical trials, it is not surprising to see that the sex-related relative risk of bleeding complications is, in general, higher in registry studies (2.0–2.5) as compared with clinical trials (1.5–1.9; Table).^{11,17,26,28,30–32}

What mechanisms drive this bleeding disparity between men and women? Clinical factors, such as older age, renal failure, cardiogenic shock, and use of larger sheaths, have been specifically identified as predictors of risk in women.¹⁷ However, the female propensity for bleeding persists beyond these risk factors. Sex-specific mechanisms surrounding body mass index (BMI), access vessel anatomy, platelet biology, and PCI-related pharmacotherapy may play a role (Figure 5).

Sex and Platelet Biology

Differences in platelet function between men and women uncover a paradoxical relationship between biology and bleeding-related clinical outcomes. Surprisingly, the majority

of studies report higher baseline platelet reactivity in response to agonists among women compared with men, implicating female sex as a risk for ischemic (not bleeding) events.³³ For example, female platelets bind more fibrinogen and have higher plasma thromboxane levels.³⁴ Becker et al reported that in unaffected individuals from families with premature coronary artery disease, female platelets were more reactive compared with male platelets after the application of low-dose aspirin for 14 days.³⁵ Thus, female platelets have an increased propensity to thrombosis without biological evidence to support the higher propensity for bleeding.

If female platelets are more prone to aggregation and increased platelet reactivity, is it possible then that women bleed more because of a hyperresponsiveness to antiplatelet therapy as compared with men? The potential for sex interaction in antiplatelet therapies has been demonstrated previously: in a meta-analysis of 6 clinical trials of GPIs, death/myocardial infarction was reduced by 20% compared with heparin alone in men (odds ratio, 0.81 [95% confidence interval, 0.75–0.89]); on the other hand, women show a strikingly opposite efficacy interaction—risk of death/myocardial infarction was 15% higher among women treated with GPI therapy compared with heparin alone (odds ratio, 1.15 [95%

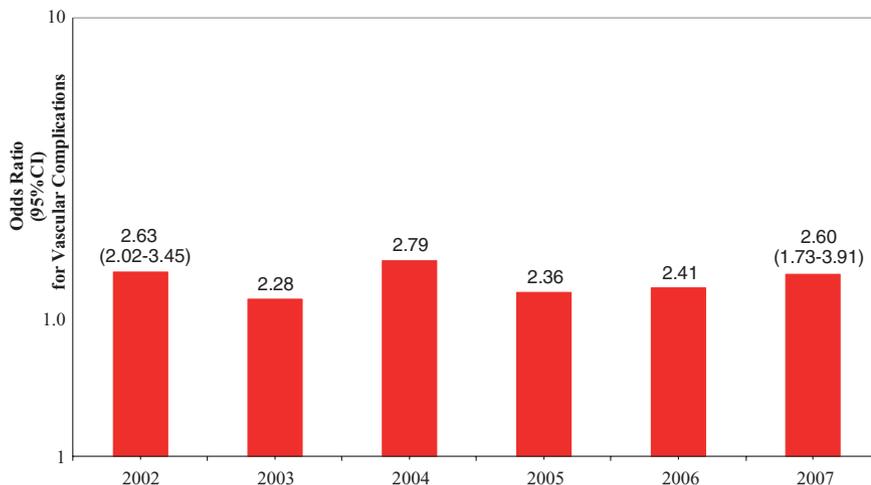


Figure 4. Adjusted risk of female sex predicting bleeding and vascular complications over a 6-year period. Despite improvement in overall bleeding event rates, female sex persists to carry a 2.6-fold increased risk of bleeding with no change appreciable from 2002 (odds ratio, 2.63 [95% confidence interval {CI}, 2.02–3.45] to 2007 (odds ratio, 2.60 [95% CI, 1.73–3.91]).¹⁷ Adapted from Ahmed et al.¹⁷

Table. Impact of Female Sex (vs Male Sex) on Risk of Bleeding Complications After Percutaneous Coronary Intervention

Trial	Author	Female Sex-Adjusted OR	95% CI
Multicenter Registries			
ACC-NCDR Registry (1998–2003) ³¹	Tavris et al	2.41	2.19–2.65
GRACE (1999–2002) ¹¹	Moscucci et al	1.43	1.23–1.66
NNE PCI Registry (2002–2007) ¹⁷	Ahmed et al	2.60	1.74–3.91
Cath PCI Registry (2008–2011) ²⁶	Daugherty et al	1.96	1.91–2.02
Randomized Clinical Trials			
REPLACE-2 (2001–2002) ³²	Feit et al	1.54	1.12–2.10
ACUITY (2004) ²⁸	Manoukian et al	1.92	1.61–2.29
TRITON-TIMI 38 (2007) ³⁰	Hochholzer et al	1.77	1.44–2.18

CI indicates confidence interval; and OR, odds ratio.

confidence interval, 1.01–1.30)].³⁶ This finding of lower efficacy may be driven by the significant higher bleeding events seen in women as compared with men treated with GPI therapy (15.7% versus 7.3%; $P < 0.0001$).³⁷ On the other hand, there appear to be selected women for who GPI therapy may be appropriate and effective: when evaluating patients that were troponin positive, the efficacy of treatment between men and women was similar.

Platelet reactivity testing shows that, although heightened platelet suppression in response to antiplatelet therapy increases the risk of PCI-related bleeding, there is no evidence to suggest stronger suppression in women compared with men. Patti et al³⁸ studied 310 patients (22% women) on antiplatelet therapy undergoing PCI and evaluated the relationship between platelet reactivity using the VerifyNow P2Y12 assay and bleeding outcomes at 30 days. Patients with heightened platelet suppression were noted to have a 4.5-fold higher risk of bleeding complications. However, female sex

was not reported as being predictive of heightened platelet suppression. Another recent study assessed platelet reactivity in 1331 patients treated with aspirin and clopidogrel: surprisingly, female sex was significantly associated with high-on-treatment platelet reactivity (odds ratio, 1.71 [95% confidence interval, 1.12–2.62]; Figure 6) consistent with a potentially increased risk of thrombotic, not bleeding, events.³⁹ These contradictory findings of higher in vivo platelet reactivity and a simultaneously higher risk of bleeding among women remain unexplained. A recent review by Wang et al⁴⁰ highlights the major knowledge gaps that continue to exist in our current understanding of sex-specific platelet biology and antiplatelet therapy. The roles of sex-based differences in non-platelet mediators of coagulation, sex-specific hormones, and post-PCI inflammation need to be better defined.

Sex, Anatomy, and BMI

Sex differences in femoral artery anatomy may explain enhanced female risk of bleeding, but bleeding risk is generally not confined to the access site alone. For example, in the Radial Versus Femoral Access for Coronary Intervention trial, access site major bleeding composed only 30% of all major bleeding events.⁴¹ Thus, interactions between sex and access site bleeding are likely to play only a partial role in mediating the overall risk of bleeding.

Safe zone arteriotomy, puncture between the lower border of inferior epigastric artery and above common femoral artery (CFA) bifurcation,⁴² has been associated with a lower risk of access site related bleeding.⁴³ Safe arterial access may be more challenging in women: studies have shown that women have smaller and shorter CFA compared with men⁴⁴ (Figure 7). Measures of height and weight correlate with CFA size.^{45,46} More recently, comparisons among patients undergoing transcatheter aortic valve replacement have confirmed the sex interaction with CFA diameter even when patients are being selected based on having ideal femoral calibers.⁴⁷ In a single-center case-control study examining sex differences in bleeding incorporating CFA anatomy as a variable, women with a bleeding event had a smaller CFA reference vessel diameter compared with men (5.9 ± 1.4 versus 6.9 ± 1.5 mm; $P < 0.01$).⁴⁸

Although women have smaller arteries than men, the excess risk of access site bleeding does not clearly link these smaller

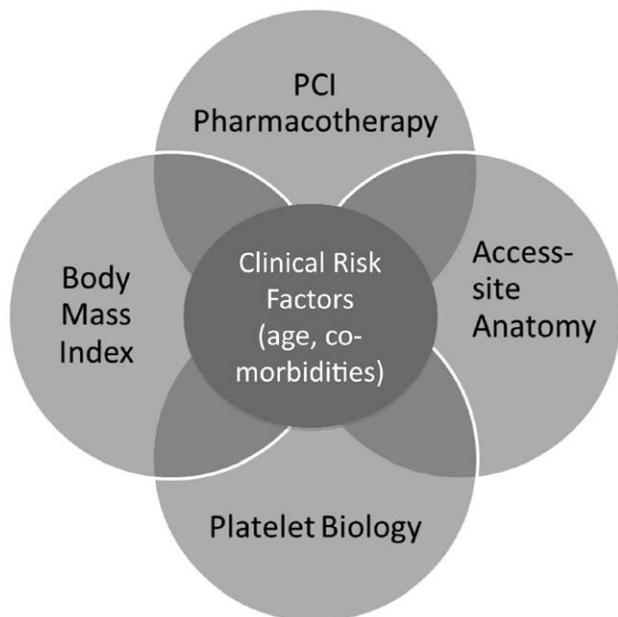


Figure 5. The female predisposition to bleeding. There may be an overlapping relationship among sex-specific differences in body mass index, access vessel anatomy, percutaneous coronary intervention (PCI) pharmacotherapy, and inherent biological risk.

Variable	Univariate OR 95% CI	P-value	Multivariate OR 95% CI	P-value
Age >75 years	2.58 (1.76–3.79)	<0.0001	1.83 (1.16–2.87)	0.009
Creatinine clearance <60ml/min	2.58 (1.86–3.58)	<0.0001	1.80 (1.23–2.64)	0.002
Female gender	2.28 (1.55–3.34)	<0.0001	1.71 (1.12–2.62)	0.01
Diabetes	1.64 (1.18–2.28)	0.003	1.47 (1.03–2.11)	0.03
Hypertension	1.51 (1.11–2.05)	0.009	—	NS
PPI	1.47 (1.07–2.00)	0.01	1.59 (1.13–2.23)	0.008
Dyslipidaemia	1.24 (0.90–1.70)	0.18	—	NS
Previous ACS	0.74 (0.55–1.01)	0.06	—	NS
Smoker	0.60 (0.43–0.86)	0.005	—	NS
BMI >30 (kg/m ²)	1.17 (0.78–1.76)	0.44	—	—
Familial history of CAD	0.92 (0.64–1.32)	0.66	—	—

Figure 6. Predictors of high on treatment platelet reactivity (Platelet Reactivity Units >235) among patients treated with clopidogrel 75 mg. ACS indicates acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; OR, odds ratio; and PPI, proton-pump inhibitor. Female sex was a strong predictor of increased platelet reactivity (not enhanced platelet suppression) while on dual antiplatelet therapy.³⁹ Reprinted with permission from Silvain et al.³⁹ Copyright Wolters Kluwer Health, 2011.

arteries to less effective arterial punctures. A large registry identified female sex and lack of safe zone arteriotomy as independent predictors of retroperitoneal bleeding.⁴⁹ Our case-control study confirmed the independence of these 2 observations: being a woman does not predict lack of safe zone arteriotomy, and a higher incidence of bleeding is predicted in women independent of site of arteriotomy. Although arteriotomy outside the safe zone strongly predicted bleeding, this association was seen in men only.⁵⁰ Thus, although we can confirm that women have smaller femoral arteries than men, there is no clear anatomic mechanism (ie, lack of safe zone arteriotomy) that explains the heightened risk of access site bleeding in women.

Women undergoing PCI are smaller than men, and lower BMI increases risk of PCI-related bleeding among women¹⁷ (Figure 8). Other studies have also shown an independent relationship between low BMI and procedure-related bleeding. Cox et al⁵¹ found that patients with low BMI had twice the rate of bleeding compared with obese patients in a cohort of >5000 patients undergoing cardiac catheterization and PCI. Similarly, Ellis et al⁵² reported a higher rate of blood transfusions in patients with a low BMI (<25 kg/m²) compared with those with normal or high BMI in a cohort of patients

presenting with ACS. Gurm et al⁵³ pooled data from 4 GPI trials and found that patients with low BMI had significantly higher rates of death, MI, and bleeding. The association between BMI and increased risk of bleeding may be linked via platelet function. Bonello et al⁵⁴ studied platelet function among patients with ACS on antiplatelet therapy. The authors found that higher BMI was an independent predictor of high-on-treatment platelet reactivity. Similarly, Barker et al⁵⁵ evaluated patients with increased platelet reactivity on standard treatment and found that higher BMI was independently and negatively associated with the degree of incremental inhibition provided by the higher doses of antiplatelet therapy. Thus, it is plausible that patients (selected women) with lower BMI have enhanced platelet suppression.

Given the inability of optimal femoral artery puncture technique to ameliorate the increased risk of bleeding in women, should women preferentially have a nonfemoral approach? Although this is an attractive option, radial artery anatomy also differs among men and women. Radial artery dimensions are significantly smaller in women compared with men (2.43±0.38 versus 2.69±0.40 mm),⁵⁶ and female sex is a potent predictor of radial artery occlusion after PCI.⁵⁷ In studies evaluating the safety of radial artery approach for

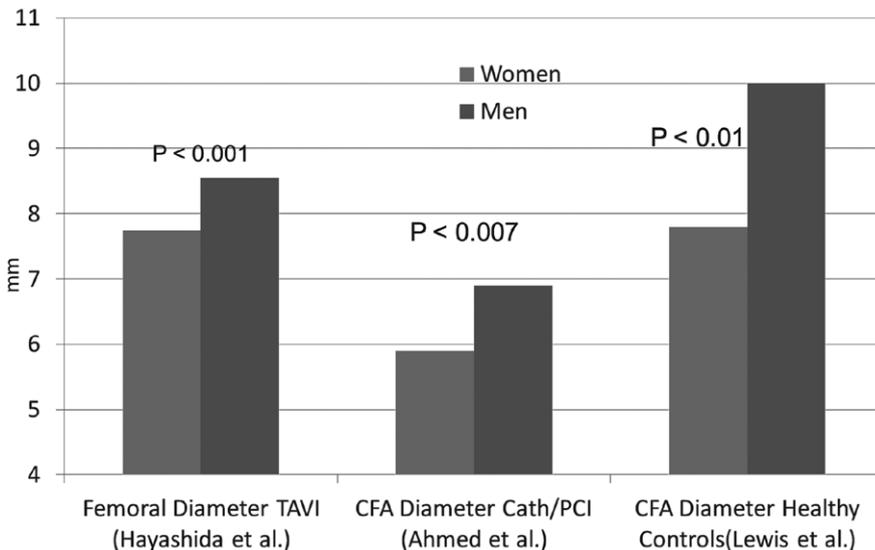


Figure 7. Comparison of common femoral artery (CFA) diameter measurement between men and women from patients enrolled in transcatheter aortic valve replacement (TAVR) trials, CathPCI Registry, and healthy control population. Women have significantly smaller CFA diameter versus men. PCI indicates percutaneous coronary intervention.^{46–48}

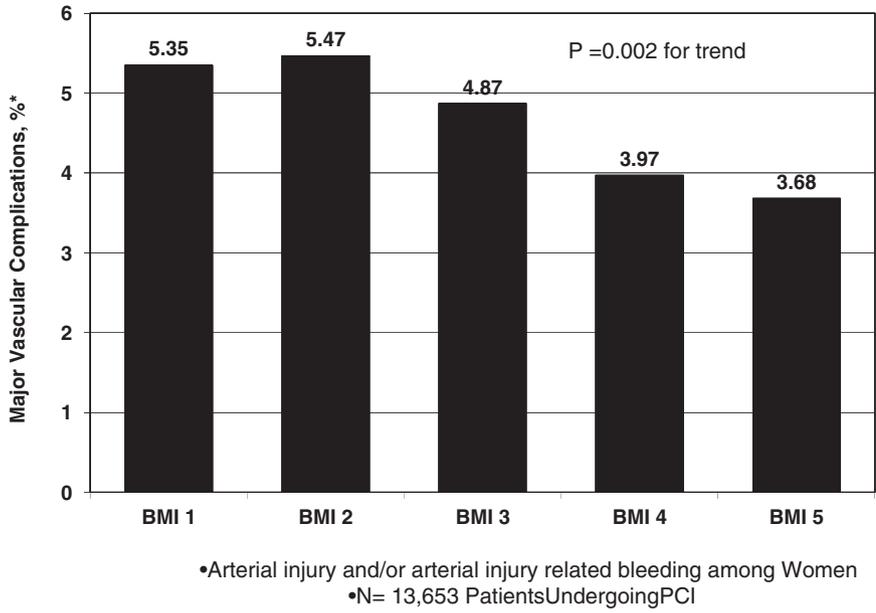


Figure 8. Relationship between body mass index (BMI) and bleeding and vascular complications. Women with the smallest BMI (quintile 5) have the highest risk of bleeding. PCI indicates percutaneous coronary intervention. Adapted from Ahmed et al.¹⁷

cardiac catheterization, sex still confers a higher risk of access site bleeding in women compared with men.⁵⁸

Still, there are some data to suggest that radial access may be particularly beneficial in women. In an observational comparison between men and women undergoing cardiac catheterization via the radial and femoral approach, the radial artery approach was significantly more protective for women as compared with men.⁵⁹ Similarly, in the Radial Versus Femoral Access for Coronary Intervention trial, the odds ratio for the primary end point in men is nearly unity (0.99). On the other hand, there is a nonstatistically significant trend toward improvement with radial approach seen specifically in women (odds ratio, 0.78 [95% confidence interval, 0.50–1.20]).⁴¹ The Study of Access Site for Enhancing PCI trial is currently randomizing 1800 women to radial versus femoral access for elective and urgent PCI and should explore the proper role of access approaches in

mediating the risk of bleeding among women (Figure 9). In summary, both anatomic differences and difference in body mass composition between men and women play a role in the sex disparity seen in bleeding risk. Our understanding of clear mechanisms, such as the role of platelet function in mediating this risk, remains incomplete.

Female Sex and PCI Pharmacotherapy

An enhanced interaction between female sex and PCI pharmacotherapy may not be discernible in randomized clinical trials. A large meta-analysis comparing effect of aspirin in men and women showed aspirin treatment similarly increased the risk of bleeding in women and in men.⁶⁰ For clopidogrel treatment, an analysis from 5 large trials found that the odds ratio for bleeding was numerically higher among women than men, but there was no evidence of heterogeneity of effect between women and men for major bleeding.⁶¹

Study of Access site For Enhancing PCI for Women (SAFE-PCI for Women)*

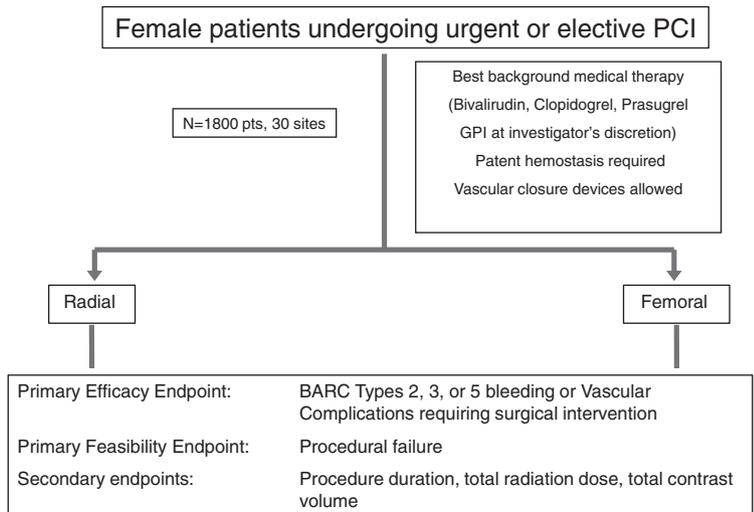


Figure 9. Design of the Study of Access Site for Enhancing (SAFE) Percutaneous Coronary Intervention (PCI) Trial. BARC indicates Bleeding Academic Research Consortium.

*Planned in collaboration with ACC, CSRC, FDA Office of Women's Health

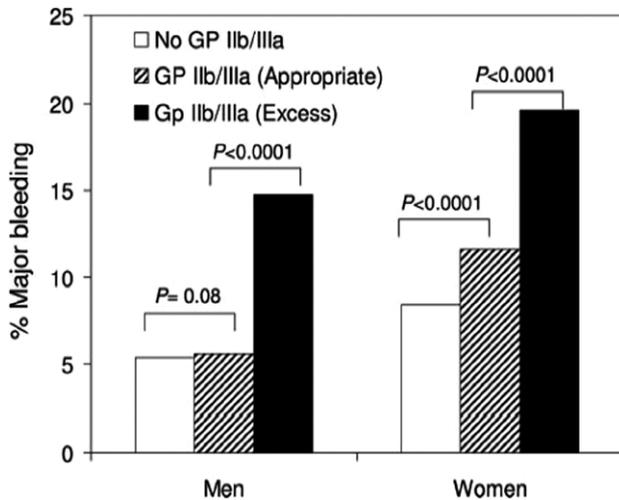


Figure 10. Glycoprotein (GP) inhibitor (GPI) therapy and bleeding. Women receiving GPI therapy were significantly more likely to bleed versus men. Women were also more likely to receive an inappropriately high dose of GPI and had almost a 4-fold higher risk of bleeding versus men. Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation major bleeding was defined as intracranial hemorrhage, transfusion >2 U of red blood cells, or an absolute drop in hematocrit of >0.12 from baseline to nadir. Reprinted with permission from Alexander et al.³⁷ Copyright Wolters Kluwer Health, 2006.

A sex-specific analysis from the Prospective Randomized Platelet Inhibition and Platelet Outcomes trial found women treated with ticagrelor to derive similar ischemic benefit without a noticeable excess in bleeding risk.⁶²

Still, there is concern that female sex may confer enhanced bleeding risk related to specific PCI pharmacology via difference in drug bioavailability and distribution as influenced by the ratio of lean to fat tissue. Women have lower body mass and higher circulating lipid levels, which may impact drug exposure and volume of distribution.⁶³ In addition, renal function as measured by glomerular filtration rate is weight based and therefore relatively lower in women. Thus, there is a potential for drug dosing issues that may be enhanced in women as compared with men.

In the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines registry, Alexander et al³⁷ explored the relationship among patient sex, GPI use, GPI dose, and bleeding in 32 601 patients with ACSs. Women had higher rates of major bleeding compared with men among those treated with GPI (15.7% versus 7.3%; $P<0.0001$) and among those not treated with GPI (8.5% versus 5.4%; $P<0.0001$). Despite similar serum creatinine levels, creatinine clearance averaged 20 points lower among treated women than men. Thus, women were more likely to receive excess GPI doses than men, and excessive dosing was correlated with bleeding risk (Figure 10). Thus, unlike the platelet biology and anatomic data, the interaction among PCI pharmacotherapy, female sex, and bleeding complications appear clearly demonstrated and linked to drug dosing.

Female Sex and Modification of Bleeding Risk

Bleeding can be avoided. In a recent report, Daugherty et al²⁶ examined sex and bleeding risk associated with the use of bleeding avoiding strategies of bivalirudin, closure devices, and radial artery access among patients undergoing PCI from 2008 to 2011. Among >185 000 women undergoing PCI, the bleeding rate was reduced 50% (12.5% versus 6.2%) if any bleeding avoidance strategy was used. Similarly, our study of women in northern New England undergoing PCI found use of bivalirudin (as opposed to nonbivalirudin strategies) and vascular closure devices to confer a decreased risk of bleeding complications, even after multivariable adjustment for confounding factors.¹⁷

Randomized clinical trials support some of these sex-specific strategies to reduce bleeding in women. For example, the reduction in bleeding complications with bivalirudin compared with unfractionated heparin/GPI in the Acute Catheterization and Urgent Intervention Triage Strategy trial was identical for both men and women.²⁹ On the other hand, the benefit of vascular closure devices in reducing complications in either men or women remains controversial and unproven in adequately powered multicenter randomized clinical trials.¹⁴ Although there is clear evidence that the radial artery approach confers decreased access site complications in both men and women,⁶⁴ the impact of the radial artery approach on total bleeding complications specific to female sex awaits completion of the Study of Access Site for Enhancing PCI trial.

Conclusions

Although bleeding complications among women undergoing PCI have improved over time, the sex gap remains constant and independent. Nonmodifiable sex-associated factors, such as lower BMI and lower creatinine clearance, and anatomic differences, such as smaller vessel size, may contribute to the excess risk seen in women; further study is required to delineate whether there are sex-attributable risks beyond these factors. In addition, clinical trials are ongoing to understand the role of alternative access sites (radial versus femoral), and there is a need to understand sex-specific platelet biology. On the other hand, sex-specific modifiable risk factors have been identified, including drug dosing based on renal function and use of anticoagulant strategies associated with lower bleeding risk. Women may be at heightened cardiovascular ischemic risk; thus, the decision to withhold guideline-recommended antiplatelet therapy because of enhanced bleeding risk among women should be considered using an individualized risk-benefit analysis. As we move forward, the next generation of clinical trials should ensure adequate enrollment of women; the current care of patients should recognize the enhanced risk of bleeding in women, and bleeding avoidance strategies should be used aggressively in women undergoing PCI.

Disclosures

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