

Sex and Outcomes After Percutaneous Coronary Intervention: A Cause for Concern for Young Women and Those With ST-Segment Elevation Myocardial Infarction?

Jacqueline E. Tamis-Holland, MD, FAHA

Since the first reports describing mortality differences in women and men with acute myocardial infarction nearly 25 years ago,¹ there has been a plethora of information regarding sex differences in the presentation, management, and outcomes of patients with coronary artery disease (CAD). The data are overwhelming and not uncommonly, the results are often discrepant. So, what do we *know* about CAD in women? We know that there are clear differences by sex in the presentation of patients with CAD. Women are typically about 5 to 10 years older than men and are significantly more likely to have a history of hypertension and diabetes mellitus and to be in heart failure on presentation to the hospital. Fewer women than men are smokers.^{1–18} Women are less aggressively treated.^{2,17–20} As such, women have a higher in-hospital, 30-day, and long-term mortality as compared with men. Yet, many of the differences in outcomes have been attributed to sex differences in the presentation and treatment of these patients. Although most studies have shown that after adjusting for the higher rate of comorbidities and therapies given, women and men have similar outcomes, some reports have suggested persistently higher adjusted odds for adverse events in women as compared with men.^{2,6–10,18–21}

In this issue of *JAHA*,²² the authors looked at sex differences in procedural events and hospital mortality among women and men referred for percutaneous coronary intervention (PCI) in 218 hospitals in Germany from 2007 to 2009. The advantage of

this analysis relates to the robustness of the data collected, providing detailed information regarding procedural characteristics and outcomes for 185 312 patients. Since the analysis is inclusive of all patients referred for PCI, it avoids some of the potential for treatment bias and permits a more uniform comparison of women and men with CAD undergoing revascularization for predefined clinical scenarios. Because of the extremely large sample size, the authors were able to compare sex differences in outcome among patients presenting with myriad disease conditions including stable ischemic heart disease, non ST-elevation acute coronary syndrome, and ST-segment elevation myocardial infarction (STEMI) as well as patients getting PCI for cardiogenic shock. In addition, the authors were able to examine difference in outcome for women and men in different age groups. The study demonstrated that PCI success rates were generally higher in women than men (although success of PCI was similar in women and men with STEMI). However, women were less likely to undergo a complex PCI procedure. Irrespective of the clinical scenario, vascular complications following PCI were higher in women. As compared to men, age-adjusted hospital mortality was significantly higher in women undergoing PCI for STEMI or cardiogenic shock, but mortality in women and men undergoing PCI for stable symptoms or non ST-elevation acute coronary syndrome was similar. When outcomes in women and men were compared for patients in discrete age groups, mortality was higher in younger women undergoing PCI as compared with younger men, while older women and men had similar mortality.

The findings in this study emphasize 3 very important and consistent themes noted in the literature regarding the sex differences in outcome of patients with CAD:

1. Women referred for PCI have more vascular complications than men.
2. Women with STEMI have a worse prognosis than men.
3. Younger women with CAD have a worse outcome than younger men.

This report lends further (and stronger) support to earlier studies demonstrating a worse prognosis for women as compared with men with STEMI,^{6–10,13,14,17,19,21} and for younger women as

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From Mount Sinai Saint Luke's Hospital, New York, NY.

Dr Tamis-Holland is a co-founder and former Director of Mount Sinai Heart's Women's Heart NY.

Correspondence to: Jacqueline E. Tamis-Holland, MD, FAHA, Department of Cardiology, Mount Sinai Saint Luke's Hospital, 1111 Amsterdam Ave, New York, NY 10025. E-mail: jacqueline.tamis-holland@mountsinai.org

J Am Heart Assoc. 2017;6:e005739. DOI: 10.1161/JAHA.117.005739.

© 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley Blackwell. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

compared with younger men.^{2,7,12–14,19,20} Even among a select group of patients referred for primary PCI (the guideline recommended reperfusion therapy for STEMI), women have a higher in-hospital and 30-day mortality than men^{7,8,10,14,21} and this is particularly notable among younger women as compared with younger men.¹⁴ The big question is *Why?*

As stated earlier, women (particularly younger women) have more comorbidities than men, including more diabetes mellitus, hypertension, peripheral artery disease, and chronic kidney disease.^{2,19} It has been suggested that traditional cardiovascular risk factors including diabetes mellitus, smoking, and the metabolic syndrome appear to have a greater influential risk for cardiovascular events in women.^{23–25} Furthermore, studies have shown that women, especially younger women, are less likely than younger men to receive guideline-recommended care.^{2,17,19,20} However, it appears that these differences by sex in presentation and treatment appear to account for only one third of the mortality risk difference noted in younger patients.² Even after adjusting for baseline presenting features and therapies administered, younger women with acute infarction are nearly twice as likely as younger men to die before hospital discharge.²

Women with acute coronary syndromes (ACS) are more likely than men to have no chest pain or to have atypical symptoms,^{2,4,18,20} and this is particularly prominent in younger women.^{2,4,20} Women, especially younger women, take longer to arrive after symptom onset.^{2,3,6,20} This is likely because of a combination of factors including the lack of recognition that symptoms are related to a heart event, and the tendency to call a doctor, before calling 911. This will inevitably lead to a delay in hospital diagnosis and subsequent treatment. Unlike patients with stable ischemic heart disease, or non ST-elevation acute coronary syndrome, total ischemic time in STEMI is an important determinant of outcomes, and therefore these delays will have a stronger adverse impact on outcome for patients presenting with STEMI as compared with other forms of ischemic heart disease. Although delays to hospital presentation, as well as use of emergency medical services in STEMI have improved over time, there remains a gap in presentation times for women.²⁶ This highlights the importance of continuing efforts toward raising awareness of heart disease and related symptoms. While there has been a great improvement in heart disease awareness in women over the past 15 years, awareness of heart disease, symptoms related to heart disease, and cardiovascular risk factors remains suboptimal in minority women and younger women.²⁷

Bleeding^{2,6,8,9,12,16,28} and vascular complications^{12,16,28,29} are higher in women and are independent of baseline variables. Bleeding (and vascular complications) are associated with advanced age, lower body weight, and overdosing of anticoagulant medications, all of which are more common in women than men. A prespecified subgroup analysis of the Radial Vs

femorAL access for coronary intervention (RIVAL) Trial²⁹ demonstrated a similar proportional reduction in vascular complications with radial artery access as compared to femoral artery access in women and men. In the Study of Access Site for Enhancement of PCI for Women (SAFE-PCI) Trial, which randomized women undergoing PCI to radial or femoral artery access, radial artery access resulted in a significantly lower rate of vascular complications and bleeding.³⁰ Unfortunately, women are more likely than men to have failed radial artery access, with higher rates of radial artery vasospasm and arterial tortuosity, leading to difficulties with catheter advancement.²⁹ Although the introduction of bleeding avoidance strategies including the use of bivalirudin in lieu of alternative anticoagulant/antiplatelet regimens, “safe-zone arteriotomy,” and radial artery access has resulted in decreased bleeding events over time, bleeding and vascular complications remain higher in women compared with men, and this is particularly notable in young women and women undergoing emergency PCI such as in STEMI or for cardiogenic shock.¹³ It is important to note that the use of radial artery access in the current study by Heer et al²² was estimated to be very low.

Women, especially younger women, with ACS (including STEMI) are less likely than men to have extensive CAD and a larger proportion of younger women have nonobstructive CAD as compared with younger men.^{5,7,9,10,12,18} This implies that there may be alternative mechanisms leading to the manifestation of CAD in some women, extending beyond atherosclerosis. While the overwhelming majority of women with ACS or stable ischemic heart disease have coronary atherosclerosis, one needs to consider alternative nonatherosclerotic causes of CAD in some of the younger women or in a select group of women with STEMI. Vasospasm, vasculitis, fibromuscular dysplasia, and spontaneous coronary artery dissection are all reportedly more common in women. In addition, plaque erosion leading to an ACS is more commonly seen in women than men. It is important to always have a wide differential for other causes of CAD, especially in young women without cardiac risk factors who present with severe stenosis, or in women with ACS who do not have obstructive CAD. These conditions sometimes respond differently to the standard therapies used to treat atherosclerotic heart disease. The use of optical coherence tomography or intravascular ultrasound imaging can aid in diagnosing some of these conditions, thereby supporting the use of additional therapies to treat the underlying disease process, including vasodilating agents or anti-inflammatory drugs.

The overarching point we must remember is that young women and women with STEMI have a worse outcome, and this is likely a combination of factors. When evaluating women presenting with symptoms suggestive of ACS (or even atypical symptoms), we need to maintain a high index of suspicion so that we can make an early diagnosis and begin treatment as soon as possible. Furthermore, we need to be aggressive about

administering guideline-recommended therapies to women with CAD, while employing maneuvers to minimize bleeding and vascular complications. Finally, we must always maintain a solid clinical acumen, especially in the younger cohort of women, to help identify the rare case (or maybe not so rare) in which there is an unusual etiology of CAD.

References

- Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1,524 women after myocardial infarction. Comparison with 4,315 men. *Circulation*. 1991;83:484–491.
- Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. *N Engl J Med*. 1999;341:217–225.
- Cheng CI, Yeh KH, Chang HW, Yu TH, Chen YH, Chai HT, Yip HK. Comparison of baseline characteristics, clinical features, angiographic results, and early outcomes in men vs women with acute myocardial infarction undergoing primary coronary intervention. *Chest*. 2004;126:47–53.
- De Luca G, Suryapranata H, Dambrink JH, Ottervanger JP, van 't Hof AW, Zijlstra F, Hoorntje JC, Gosselink AT, de Boer MJ. Sex-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty: data from the Zwolle Myocardial Infarction Study. *Am Heart J*. 2004;148:852–856.
- Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, Aylward P, Topol EJ, Califf RM. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global use of strategies to open occluded coronary arteries in acute coronary syndromes IIB investigators. *N Engl J Med*. 1999;341:226–232.
- Weaver WD, White HD, Wilcox RG, Aylward PE, Morris D, Guerci A, Ohman EM, Barbash GI, Betriu A, Sadowski Z, Topol EJ, Califf R. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. GUSTO-I Investigators. *JAMA*. 1996;275:777–782.
- de Boer SP, Roos-Hesselink JW, van Leeuwen MA, Lenzen MJ, van Geuns RJ, Regar E, van Mieghem NM, van Domburg R, Zijlstra F, Serruys PW, Boersma E. Excess mortality in women compared to men after PCI in STEMI: an analysis of 11,931 patients during 2000–2009. *Int J Cardiol*. 2014;176:456–463.
- Gevaert SA, De Bacquer D, Evrard P, Convens C, Dubois P, Boland J, Renard M, Beauloye C, Coussement P, De Raedt H, de Meester A, Vandecasteele E, Vranckx P, Sinnaeve PR, Claeys MJ. Gender, TIMI risk score and in-hospital mortality in STEMI patients undergoing primary PCI: results from the Belgian STEMI Registry. *EuroIntervention*. 2014;9:1095–1101.
- De Luca G, Marini M, Gonzini L, Boccellini A, Casella G, Chiarella F, De Servi S, Di Chiara A, Di Pasquale G, Olivari Z, Caretta G, Lenatti L, Massimo Gilizia M, Savonitto S. Contemporary trends and age-specific sex differences in management and outcome for patients with ST-segment elevation myocardial infarction. *J Am Heart Assoc*. 2016;5:e004202. DOI: 10.1161/JAHA.116.004202.
- Bavishi C, Bangalore S, Patel D, Chatterjee S, Trivedi V, Tamis-Holland JE. Short and long-term mortality in women and men undergoing primary angioplasty: a comprehensive meta-analysis. *Int J Cardiol*. 2015;198:123–130.
- Berger JS, Elliot L, Gallup D, Roe M, Granger CB, Armstrong PW, Simes J, White HD, Van de Werf F, Topol EJ, Hochman JS, Newby LK, Harrington RA, Califf RM, Becker RC, Douglas PS. Sex differences in mortality following acute coronary syndromes. *JAMA*. 2009;302:874–882.
- Khera S, Kolte D, Gupta T, Subramanian KS, Khanna N, Aronow WS, Ahn C, Timmermans RJ, Cooper HA, Fonarow GC, Frishman WH, Panza JA, Bhatt DL. Temporal trends and sex differences in revascularization and outcomes of ST-segment elevation myocardial infarction in younger adults in the United States. *J Am Coll Cardiol*. 2015;66:1961–1972.
- Lichtman JH, Wang Y, Jones SB, Leifheit-Limson EC, Shaw LJ, Vaccarino V, Rumsfeld JS, Krumholz HM, Curtis JP. Age and sex differences in in-hospital complication rates and mortality after percutaneous coronary intervention procedures: evidence from the NCDR. *Am Heart J*. 2014;167:376–383.
- Zhang Z, Fang J, Gillespie C, Wang G, Hong Y, Yoon PW. Age-specific gender differences in in-hospital mortality by type of acute myocardial infarction. *Am J Cardiol*. 2012;109:1097–1103.
- Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, Brogan GX, Boden WE, Rose MT, Ohman EM, Gibler WB, Newby LK; CRUSADE Investigators. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol*. 2005;45:832–837.
- Hess C, McCoy LA, Duggirala HJ, Tavis DR, O'Callaghan K, Douglas PS, Peterson ED, Wang TY. Sex-based differences in outcomes after percutaneous coronary intervention for acute myocardial infarction: a report from TRANSLATE-ACS. *J Am Heart Assoc*. 2014;3:e000523. DOI: 10.1161/JAHA.113.000523.
- Jneid H, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, LaBresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L; for the Get With the Guidelines Steering Committee and Investigators. Sex differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008;118:2803–2810.
- Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, FitzGerald G, Jackson EA, Eagle KA; for the GRACE investigators. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart*. 2009;95:20–26.
- Bangalore S, Fonarow GC, Peterson ED, Hellkamp AS, Hernandez AF, Laskey W, Peacock WF, Cannon CP, Schwamm LH, Bhatt DL; Get with the Guidelines Steering Committee, Investigators. Age and gender differences in quality of care and outcomes for patients with ST-segment elevation myocardial infarction. *Am J Med*. 2012;125:1000–1009.
- Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V, Kiefe CI, Frederick PD, Sopko G, Zheng Z; for the NCDR Investigators. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307:813–822.
- Jackson EA, Moscucci M, Smith DE, Share D, Dixon S, Greenbaum A, Grossman PM, Gurm HS. The association of sex with outcomes among patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction in the contemporary era: insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). *Am Heart J*. 2011;161:106–112.e1.
- Heer T, Hochadel M, Schmidt K, Mehilli J, Zahn R, Kuck KH, Hamm C, Böhm M, Ertl G, Hoffmeister HM, Sack S, Senges J, Massberg S, Gitt AK, Zeymer U. Sex differences in percutaneous coronary intervention—insights from the coronary angiography and PCI registry of the German Society of Cardiology. *J Am Heart Assoc*. 2017;6:e004972. DOI: 10.1161/JAHA.116.004972.
- Prescott E, Hippe M, Schnohr P, Ole Hein H, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ*. 1998;316:1043–1051.
- Marroquin OC, Kip KE, Kelley DE, Johnson BD, Shaw LJ, Bairey MERZ CN, Sharaf BL, Pepine CJ, Sopko G, Reis SE; for the Women's Ischemia Syndrome Evaluation Investigators. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women. A report from the Women's Ischemia Syndrome Evaluation. *Circulation*. 2004;109:714–721.
- Lee WL, Cape D, Cheung AM, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care*. 2000;23:962–968.
- Kaul P, Armstrong PW, Sookram S, Leung BK, Brass N, Welsh RC. Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction. *Am Heart J*. 2011;161:91–97.
- Mosca L, Mochari-Greenberger H, Dolor RJ, Newby LK, Robb KJ. Twelve-year follow-up of American women's awareness of cardiovascular disease risk and barriers to heart health. *Circ Cardiovasc Qual Outcomes*. 2010;3:120–127.
- Ahmed B, Piper WD, Malenka D, VerLee P, Robb J, Ryan T, Herne M, Phillips W, Dauerman HL. Significantly improved vascular complications among women undergoing percutaneous coronary intervention: a report from the Northern New England Percutaneous Coronary Intervention Registry. *Circ Cardiovasc Interv*. 2009;2:423–429.
- Pandey S, Mehta SR, Cantor WJ, Cheema AN, Gao P, Madan M, Niemela K, Rao SV, Schwalm JD, Valentin V, Veilaniou JL, Jolly SS. Radial versus femoral access for coronary angiography/intervention in women with acute coronary syndromes: insights from the RIVAL trial (Radial Vs femoral access for coronary intervention). *JACC Cardiovasc Interv*. 2015;8:505–512.
- Rao SV, Hess CN, Barham B, Rao SV, Aberle LH, Anstrom KJ, Patel TB, Jorgensen JP, Mazzaferri EL, Jolly SS, Jacobs A, Newby LK, Gibson CM, Kong DF, Mehran R, Waksman R, Gilchrist IC, McCourt BJ, Messenger JC, Peterson ED, Harrington RA, Krucoff MW. A registry-based randomized trial comparing radial and femoral approaches in women undergoing percutaneous coronary intervention: the SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) trial. *JACC Cardiovasc Interv*. 2014;7:857–867.

Key Words: Editorials • complication • mortality • percutaneous coronary intervention • ST-segment elevation myocardial infarction • women



Sex and Outcomes After Percutaneous Coronary Intervention: A Cause for Concern for Young Women and Those With ST–Segment Elevation Myocardial Infarction?

Jacqueline E. Tamis-Holland

J Am Heart Assoc. 2017;6:e005739; originally published March 20, 2017;
doi: 10.1161/JAHA.117.005739

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://jaha.ahajournals.org/content/6/3/e005739>