Sex, Death, and the Diagnosis Gap

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Cardiovascular disease (CVD) continues to kill more women than men annually in the United States,1 a female death epidemic that emerged rapidly in 1984 and persists in 2014. This mortality shift was not accompanied by explanatory sex-specific changes in known risk factors2 and was too rapid to be caused by sex-linked genetic/genomic change. Although the aging epidemic combined with female longevity is a convenient putative explanation, CVD death rates have actually declined in older women, concomitant with the declines in older and young men, compared with an increase in younger women.2 Although overall female CVD death rates began to decline in the 2000s,1 we continue to have both a surplus of female deaths and an absence of understanding as to root causes.

Ischemic heart disease (IHD) accounts for the majority of CVD death. Notably, the female-majority CVD death epidemic has occurred in the absence of a female-majority coronary heart disease (CHD) and myocardial infarction (MI) mortality epidemic.1 Said another way, although women constitute more than half of all CVD deaths, they account for only one third of the CHD and MI burden. A simple look at the daily cardiac care unit or catheterization laboratory roster tells the story: We continue to have sex ratios of 30% women to 70% men diagnosed with CHD and MI. Although higher burdens of stroke and heart failure mortality in women explain a portion of the female excess CVD mortality, it does not fully explain the gap.3 How do women die of IHD without a diagnosis of MI or CHD?

In this issue of Circulation, a new analysis by Bucholz et al4 adds to the confusion. When sex differences in 39 studies with longer-term 5- and 10-year mortality after acute MI (AMI) were examined, overall fewer than one third of the subjects were women. Although a meta-analysis was planned, significant heterogeneity across studies precluded this; the populations, outcomes, and covariates differed too widely to be pooled statistically, so qualitative results are presented. Not surprisingly, the authors report variable sex differences, with studies demonstrating higher, similar, and lower mortality in women compared with men. Qualitatively, overall, age adjustment accounted for much of the sex-related death difference, although younger women paradoxically had a higher mortality than younger men, consistent with prior literature.4 In the 22 studies (56%) that adjusted for other covariates, the majority demonstrated the same or lower longer-term AMI adjusted mortality in women compared with men. Notably, revascularization treatment, which is more protocolized, had similar female and male mortality. Only 1 study (3%) included medical treatment and reported higher female mortality.

Why was there so much heterogeneity, and what does this teach us about the sex-death-MI diagnosis gap? AMI is diagnosed by the triad of (1) symptoms, (2) ECG, and (3) cardiac biomarker evidence of myocardial cell death. Among these, the most objective criteria are cardiac biomarkers. The widely varying time frames, from 1951 to 2008, when serological criteria for AMI progressively changed, preclude not only meta-analyses but also qualitative analysis conclusions. This new work, however, does call attention to an issue long ignored in both science and practice. Established normative standard studies for creatine kinase5 and troponin6 assays clearly demonstrate sex differences in reference thresholds for AMI diagnosis in women versus men; for example, lower thresholds are appropriate for women, yet male-standard thresholds are used in practice,7 which results in lower detection of AMI in women. Indeed, an initial report suggests that the current high-sensitivity troponin threshold failed to detect 20% of AMI in women.8 The associated higher female mortality4 argues against a “troponitis” explanation.

What do we know about sex differences in ECG criteria for AMI? ECG abnormalities are less likely to be diagnostic for obstructive coronary artery disease in women than in men, but there is little work evaluating ECG AMI criteria stratified by sex. One study reported that post-MI ST-segment elevation in anterior leads was a significant predictor of events in females, whereas ST depression in lateral leads predicted events in males,9 yet this has not been repeated or incorporated into clinical care. Many ECG variables demonstrate sex differences. Women have a longer corrected QT interval and greater sensitivity to QT-prolonging medications,10 whereas left ventricular hypertrophy criteria differ by sex.11 Despite these published data, ECG reference standards used in practice for ischemia, QT, and left ventricular hypertrophy are all male thresholds. Do these ECG differences impact clinical outcomes? A recent publication suggests that they can. Women with left bundle-branch block benefit from cardiac resynchronization therapy at a shorter QRS duration than men,12 yet because the current US guidelines have a Class IIa recommendation (benefit >> risk; additional studies with focused objectives needed for patients with QRS duration of 130–149 ms), which is a male standard, cardiac resynchronization therapy is underused in appropriate women compared with men.12

More analyses have evaluated sex differences in AMI symptoms. Studies can be cited that support or refute that women

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and men differ substantially in symptom presentation. This controversy is explained by case selection in clinical registries and trials, whereby patients with more typical AMI symptoms are selected for diagnostic testing. Pretesting (ECG and troponin) and posttesting (stress test, catheterization) referral bias selects the population studied and impacts the diagnostic accuracy of testing. Stated another way, if fewer women have typical AMI symptoms, fewer women will be tested, and typical symptoms will have a lower specificity in women, all of which are true in the literature. Accordingly, studies using convenient but biased populations will not accurately assess AMI sex differences, whereas broad-net symptom analyses support important sex differences. Canto et al, for example, in a large meta-analysis of >470,000 patients with acute coronary syndrome, found significant sex differences in symptoms, including that 37.5% of women compared with 27.4% of men presented without chest pain.

Do others factors contribute to women dying of IHD without a diagnosis of CHD or MI? Prior work suggests that sex differences in IHD presentation contribute to the death-diagnosis CHD gap. Women at coronary angiography have less obstructive angiographic coronary artery disease despite being older with a higher risk factor burden than men. We have demonstrated a female-specific pattern of IHD characterized by coronary microvascular dysfunction in symptomatic women without obstructive coronary artery disease despite being older with a higher risk factor burden than men. We have demonstrated a female-specific pattern of IHD characterized by coronary microvascular dysfunction in symptomatic women without obstructive coronary artery disease despite being older with a higher risk factor burden than men. We have demonstrated a female-specific pattern of IHD characterized by coronary microvascular dysfunction in symptomatic women without obstructive coronary artery disease despite being older with a higher risk factor burden than men.
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