Sex, Death and the Diagnosis Gap

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Cardiovascular disease (CVD) continues to kill more women than men annually in the US\textsuperscript{1}, a female death epidemic which emerged rapidly in 1984 and persists in 2014. This mortality shift was not accompanied by explanatory sex-specific changes in known risk factors\textsuperscript{2}, and was too rapid to be due to sex-linked genetic/genomic change. While 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 to an \textit{increase} in younger women\textsuperscript{2}. While overall female CVD death rates began to decline in the 2000s\textsuperscript{1}, we continue to have both a surplus of female s 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\textsuperscript{1}. Said another way, while women comprise over half of CVD deaths, they account for only one-third of the CHD and MI burden. A simple look the daily CCU or cath lab roster tells the story – we continue to have sex ratios of 30:70% - women:men - diagnosed with CHD and MI. While 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\textsuperscript{1}. How do women die from IHD without a diagnosis of MI or CHD?

In this issue of Circulation, a new analysis by Buchholz et al\textsuperscript{3} adds to the confusion. Examining sex differences in 39 studies with longer term 5 and 10 year mortality following acute myocardial infarction (AMI), overall less than 1/3 of the subjects were women. While a meta-analysis was planned, significant heterogeneity across study design precluded this. The populations, outcomes and covariates differed too widely to be pooled statistically – qualitative results are presented. Not surprisingly, the authors report variable sex differences with studies
demonstrating higher, similar and lower mortality in women compared to men. Qualitatively, overall, age-adjustment accounted for much of the sex-death difference, although younger women paradoxically had a higher mortality than younger men, consistent with prior literature. In the 22 (56%) studies which adjusted for other covariates, the majority demonstrated the same or lower longer term AMI adjusted mortality in women compared to men. Notably, revascularization treatment, which is more protocolized, had similar female and male mortality.

Only one (3%) study included medical treatment and reported higher female mortality.

Why 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; 3) cardiac biomarker evidence of myocardial cell death. Among these, the most objective criteria are cardiac biomarkers. The widely varying time frames, from 1951-2008, when serologic criteria for AMI progressively changed precludes 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 CPK and troponin assays clearly demonstrate sex differences in reference thresholds for AMI diagnosis in women versus men; e.g. lower thresholds are appropriate for women, yet male-standard thresholds are used in practice, resulting 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. The associated higher female mortality 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 CAD 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 in males\textsuperscript{9}, yet this has not been repeated or incorporated into clinical care. Many ECG variables demonstrate sex differences. Women have a longer QTc and greater sensitivity to QT prolonging medications\textsuperscript{10}, while left ventricular hypertrophy (LVH) criteria differ by sex \textsuperscript{11}. Despite these published data, ECG reference standards used in practice for ischemia, QT and LVH are all male thresholds. Do these ECG differences impact clinical outcomes? A recent publication suggests that it can. Women with left bundle branch block benefit from cardiac resynchronization therapy (CRT) at a shorter QRS duration than men\textsuperscript{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 msec), which is a male standard, CRT is underused in appropriate women compared to men\textsuperscript{12}.

More analyses have evaluated sex differences in AMI symptoms. Studies can be cited which support or refute that women and men substantially differ in symptom presentation\textsuperscript{13}. This controversy is explained by case selection in clinical registries and trials, whereby patients in with more “typical” AMI symptoms are selected for diagnostic testing. Pre (ECG and troponin) and post (stress test, cath) testing “referral bias” selects the population studied and impacts the diagnostic accuracy of testing\textsuperscript{14}. Said 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, while broad-net symptom analyses support important sex differences. Canto et al, for example, in a large meta-analysis of more than 470,000 patients with acute coronary syndrome found significant sex differences in symptoms, including that 37.5\% of women compared to 27.4\% of men presented without chest pain\textsuperscript{15}.

Do others factors contribute to women dying from 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 CAD despite being older with a higher risk factor burden compared to men\[^16\]. We have demonstrated a female-specific pattern of IHD characterized by coronary microvascular dysfunction (CMD) in symptomatic women without obstructive CAD which has an adverse prognosis\[^17\], and is not routinely recognized with current male-pattern diagnostic angiographic strategies. In short, existing diagnostic AMI and CHD strategies developed in men, for men and by men, fail to diagnose approximately 20-30% of women with IHD.

Why do we care about sex differences in diagnosis of AMI? Without a diagnosis, patients are not treated. Failure to diagnosis AMI results in the obvious lack of AMI treatment and elevated death rates\[^18\], while a failure to diagnose CHD is associated with lower rates of aspirin, lipid lowering agents and beta blockers use after a “no obstructive CAD” angiography than before\[^19\]. The presence or absence of AMI or CHD, e.g. “male-pattern” IHD, remains a key decision point for treatment by practicing physicians. Prior work has demonstrated that women with ACS are less likely to receive appropriate guidelines therapy, and implementation of strategies to close guideline gaps preferentially saves women’s lives\[^20\]. These findings argue against misogynistic “gender-based” sexism as a driving force for the sex-death-diagnosis gap, and support the concept that lack of recognition of biological “sex-based” differences in IHD diagnosis resulting in failure to treat is the root cause.

How can we improve IHD outcomes for women? We currently have sufficient evidence to implement sex-specific thresholds for AMI and CHD diagnosis, as well as address knowledge gaps (Figure 1). Guidelines should incorporate “female-pattern IHD” to improve diagnosis, appropriate therapy use and IHD mortality, including 1) \textit{sex-specific troponin thresholds} and 2)
strategies that explicitly incorporate assessment of common non–chest pain symptoms. An important knowledge gap for research is to investigate sex differences in the ECG diagnosis of AMI using sex-specific biomarker standards. Women comprise 51% of the population – addressing IHD as their leading killer must be one of our highest priorities.

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long-term mortality after myocardial infarction: A systematic review. *Circulation.* 2014;130:XX-XXX.


**Figure Legend:**

**Figure 1.** Acute Myocardial Infarction (AMI) - Sex Differences in Diagnosis and Knowledge Gaps.
Symptoms

- Chest, upper extremity, mandibular or epigastric discomfort (with exertion or at rest) or an ischemic equivalent such as dyspnea or fatigue (7). Non-chest symptoms in 27.4% vs 37.5% in women (15)
- Will explicit elicitation of common non-chest symptoms improve outcomes? – knowledge gap

ECG

- New or presumed new significant ST segment-T wave changes or new left bundle branch block (LBBB); development of pathological Q waves (7)
- Do sex differences in ST, LVH and QT (11,12) impact ECG AMI diagnosis? – knowledge gap

Cardiac Biomarker

- Detection of a rise and/or fall in of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) (7); 1.2-2.5 fold cTn and 1.2-2.6 fold higher CKMB 99th percentile thresholds male vs female (6) with 20% of AMI in women not detected (8)
- Will sex-specific cardiac biomarker URL improve AMI detection? – knowledge gap
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