The Yentl syndrome is alive and well

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This editorial refers to ‘Are we using cardiovascular medications and coronary angiography appropriately in men and women with chest pain?’, by N. Johnston et al., on page 1331 and ‘Factors influencing underutilization of evidence-based therapies in women’, by R. Bugiardini et al., on page 1337

More women than men die annually from ischaemic heart disease (IHD) in the developed world. This represents a reversal of fortune from previous decades and places women firmly as the new majority now impacted. Notably, the adverse IHD gender gap is the widest in relatively young women, where myocardial infarction (MI) mortality is 2-fold higher in women under 50 years compared with age-matched men. While it is now clear that there are many gender differences in IHD outcomes, including more frequent angina diagnosis, more office visits, more avoidable hospitalizations, higher MI mortality, and higher rates of heart failure in women compared with men, the aetiologies contributing to these differences are less clear.

A number of paradoxes are evident with regard to sex differences in IHD. First, women have a higher prevalence of angina compared with men, yet have an overall lower prevalence of obstructive coronary artery disease (CAD). Second, symptomatic women undergoing coronary angiography have less extensive and severe obstructive CAD, despite being older with a higher risk factor burden compared with men. Third, despite relatively less obstructive CAD, women have a more adverse prognosis compared with men. We have hypothesized an alternative, female-specific pattern of IHD due to the relatively high frequency of microvascular coronary dysfunction (MCD) in symptomatic women with and without obstructive CAD which we have linked with symptoms, ischaemia, and adverse outcomes. This alternative ‘female pattern’ of IHD is not easily recognized, given our male-pattern strategies aimed at detection and treatment of obstructive CAD.

What relevance does this have to the adverse gender gaps for IHD in women? The literature suggests that when women look like men (with ‘male-pattern’ obstructive CAD), they are more likely to be diagnosed and treated like men. As characterized by the ‘Yentl syndrome’ depicted in the Barbra Streisand movie of the same name, Dr Bernadine Healy used this term in 2001 to call attention to the paradox of adverse outcomes of women with IHD, as well as the underdiagnosis and undertreatment of women.

Two new analyses suggest that the Yentl syndrome is alive and well 10 years later. Johnson and colleagues compare utilization of medication and diagnostic coronary angiography in 12,000 women and men with stable signs and symptoms of IHD and 2 year outcomes in Sweden between 2006 and 2008. Bugiardini and colleagues summarize 6558 women and men with acute coronary syndrome (ACS) with 1 year outcomes from the Canadian ACS Registry I and II between 1999 and 2003. Both studies add insight into aetiologies contributing to the IHD gender gap. Both studies demonstrate medical undertreatment of women, including lower rates of aspirin and angiotensin-converting enzyme (ACE) inhibitor use in stable women compared with men, and lower rates of ACE inhibitor, β-blocker, and statin medication in women with ACS compared with men. Both studies also show gender differences in use of procedures, where interestingly stable women undergo more repeat angiography, while women with ACS undergo fewer angiograms, percutaneous coronary interventions (PCIs), and coronary artery bypass grafts (CABGs) compared with their male counterparts. The adverse outcomes described in these new works are consistent with earlier literature—both studies demonstrate adverse gender differences for women whereby stable women have more MIs, and women with ACS have higher death rates compared with men.

Is there evidence of progress in closing these gender gaps and improving IHD outcomes for women over the last 10 years? Potentially—the Swedish data are more contemporary, and report equivalent use of the four life-saving medication strategies (ACE inhibitors, β-blockers, aspirin, and statins) among the stable women and men after angiographic diagnosis of obstructive CAD. Importantly, this appropriate medication utilization was accompanied by equivalent mortality between the sexes, although event rates were predictably lower in this stable lower risk...
population and therefore the sensitivity to detect differences is more limited compared with an ACS population. The large Swedish sample size, however, argues somewhat reassuringly for similar outcomes in stable obstructive CAD patients treated similarly with guideline therapy. While previous work has shown an improvement of prognosis in women over time, nevertheless, other contemporary data demonstrate persistently more adverse outcomes for women compared with men. The Canadian Registry analysis adds to the accumulated literature that women with ACS remain less likely than men to receive the indicated diagnostic tests, medication, and procedures and then suffer the not unexpected higher rates of adverse outcomes.

So why are women less likely to receive appropriate IHD guideline therapy? Both studies provide a similar clue—the Canadian Registry data demonstrate that female sex, despite adjustment for multiple associated variables, independently remains associated with underutilization of guideline therapy for ACS patients. The Swedish data demonstrate that while before diagnostic coronary angiography there are relatively large differences in treatment between women and men, these differences for guideline medication vanished following demonstration of obstructive CAD at angiography. These consistent findings argue against cultural ‘gender-based’ factors including misogyny and sexism as a driving force for drug underutilization in women, and suggest alternatively that biological ‘sex-based’ differences are key contributors. We can conclude from these and other studies that the presence or absence of obstructive CAD, e.g. ‘male-pattern’ IHD, remains a key decision point for medication prescribing for practising physicians. Because higher proportions of women with IHD present without obstructive CAD or undergo less coronary angiography, relatively fewer women will be treated, including those with evident ACS (for which guideline medication is not related to angiography), resulting in relatively more female deaths (Figure 1).

How can we incorporate this new knowledge to improve IHD outcomes for women? Our group has estimated the prevalence of signs and symptoms of IHD in the absence of obstructive CAD using the US NCDR database to be 2–3 million women, placing it as a larger healthcare threat to women than breast cancer, and comparable with the highly prevalent 6 million women with clinically documented obstructive CAD in the USA alone. Accordingly, two US guidelines now specify strategies for women, i.e. the AHA/ACC Prevention of Cardiovascular Disease in Women and the AHA/ACC Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction. Moreover, IHD strategies that provide guideline-driven infrastructure support to physicians, such as the AHA ‘Get With The Guidelines’ and the ACC ‘Guidelines Applied in Practice’, appear to have the largest impact on closing therapeutic gender gaps that disadvantage women.

Do we have a sufficient fund of knowledge to close the persistent gender gap in IHD and vanquish the Yentl syndrome to history? While increasing knowledge exists regarding pathophysiological mechanistic pathways for ‘female-pattern IHD’, translational studies aimed at developing practical diagnosis and therapeutics with both traditional and novel treatments are needed. Further closure of knowledge gaps related to the paradox and the pathophysiology of IHD in women is one of our highest priorities to improve the health of the 51% of the population that is female and represent currently the majority of deaths.

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References


