



New evidence for gender disparities in cardiac interventions: 'CREATE'-ing some clarity?

"Standfirst"

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Globally, the burden of cardiovascular disease, especially coronary artery disease (CAD) is increasing in low- and middle-income countries (LMICs). In addition, mortality from CAD in these nations in epidemiological transition strikes relatively younger people [1]. CAD has seen a disturbing rise in its incidence among women and has become the leading cause of mortality. The WHO states that nearly one-third of all deaths among women are caused by cardiovascular disease [2]. Despite this, women in even developed nations are treated less well than men [3]. There are no data from LMICs, from representative studies, on gender disparities in the treatment of CAD.

This editorial focuses on gender disparities in treatments and outcomes following an acute coronary event based on findings from a multicenter hospital-based registry in India; the CREATE Registry [4].

Gender-based societal and health disparities are prominent in India. This is illustrated by a skewed sex ratio (940 women per 1000 men) and by the country's high maternal mortality rate (212 per 100,000 live births) [5]. The 2011 Global Gender Gap report used an index, introduced by the Global Economic Forum in 2006, to benchmark national gender gaps in four critical areas – economic parity, political empowerment, education and health. Even though India has seen an explosive economic growth and efforts are being made to increase women's political participation, it is ranked below several sub-Saharan African countries. India ranked 105 overall among 135 countries. This low ranking is due to poor health indicators amongst women [6].

Gender disparity & acute coronary syndromes

Globally, the notion that heart disease is a 'man's disease' has changed in the last decade

[7]. Advances in the treatment of acute coronary syndromes (ACS) do not seem to have impacted the outcomes among women [8]. _ENref_6 ACS registries in western countries have shown that women receive fewer invasive cardiac procedures compared with men [3].

There is a paucity of data on gender-based differences in the treatment and outcomes of ACS, especially from developing countries such as India. We analyzed data from the CREATE Registry to assess disparities in ACS treatments and outcomes between women and men.

The CREATE Registry

The CREATE Registry was a prospective hospital-based registry of patients with ACS involving 89 hospitals across the country. Participating hospitals were represented geographically, and had equal proportions by type of hospital (tertiary, secondary, government, private, teaching and nonteaching) and type of care (secondary and tertiary). Over a 4-year period, between 2001 and 2005, 20,468 patients were enrolled into CREATE across the spectrum of ACS (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction and UA). Data on demographics, clinical presentation, time to reach hospital from symptom onset and door to needle time, interventions, if any, and other treatments were recorded. Outcomes were captured at discharge and at 30 days from admission.

Gender-based findings in the CREATE Registry

The registry enrolled 4826 (23.6%) women among the 20,468 patients with ACS. Women were older (60.90 vs 56.46 years; $p < 0.0001$), and had higher rates of diabetes (37.9 vs 28.3%; $p < 0.0001$) and hypertension (52.3 vs 33.3%; $p < 0.0001$). At presentation, more women (18.2 vs 15.3%; $p < 0.0001$) were in heart failure

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(killip class >1). Women reached hospital later after symptom onset than men (median time in minutes 415 vs 340) and formed a higher proportion amongst those that took >12 h to reach hospital (38.3 vs 32.9%; $p < 0.0001$). In hospital the time to first intervention was delayed among women (median time 35 vs 30 min).

In hospitals, the use of antiplatelet drugs (97.6 vs 98.3%; $p = 0.004$), lipid-lowering drugs (50.6 vs 53.0%; $p = 0.006$) angiotensin converting enzyme inhibitors or angiotensin receptor blockers (54.7 vs 56.5%; $p = 0.024$) was lower compared with men. Women also received fewer revascularization therapies, such as thrombolysis (30.9 vs 44.9%; $p < 0.0001$), coronary angiography (19.3 vs 24.0%; $p < 0.0001$), percutaneous transluminal coronary angioplasty (6.1 vs 7.7%; $p = 0.0002$) and coronary artery bypass grafting (2.4 vs 3.9%; $p = 0.016$). Overall, any revascularization intervention was performed less frequently in women compared with men (37.5 vs 52.7%; $p < 0.0001$). There was no difference in the use of β -blockers and anticoagulants.

“Quote.”

The unadjusted all-cause mortality rate at 30 days was significantly higher in women (odds ratio [OR]: 1.42; 95% CI: 1.26–1.60; $p < 0.0001$). Adjustment for age and risk factors reduced, but did not abolish, this higher mortality; OR: 1.21 (95% CI: 1.07–1.37; $p = 0.003$). After adjusting for treatment-related factors (time to hospital, revascularization, evidence-based medications), the increased mortality was abolished (OR: 1.02, 95% CI: 0.76–1.38; $p = 0.892$). This indicates that the decrease in mortality was explained entirely by the inferior treatment that women received compared with men. In other words, after accounting for age and risk factors, if women received the same treatments as men, about 20% could have been saved at 30 days.

How do the findings in CREATE compare with available literature?

Observations in the CREATE Registry are consistent with findings from other countries [3]. In 14,196 Canadian patients with non-ST-segment elevation ACS recruited into the Acute Coronary Syndrome I (ACSI), ACSII, Global Registry of Acute Coronary Events (GRACE/GRACE2), and Canadian Registry of Acute

Coronary Events (CANRACE) prospective multicenter registries women were found to be significantly older than men and were more likely to have a history of heart failure, diabetes or hypertension. Fewer women were treated with thienopyridines, heparin and glycoprotein IIb/IIIa inhibitors compared with men in GRACE and CANRACE. Women were independently associated with a lower in-hospital use of coronary angiography (adjusted OR: 0.76; 95% CI: 0.69–0.84; $p < 0.001$) and higher in-hospital mortality (adjusted OR: 1.26; 95% CI: 1.02–1.56; $p = 0.036$), irrespective of age. (p for interaction = 0.76) [3].

“Quote.”

The CRACE trial reported women to be older and have higher rates of risk factors that determine a poor prognosis after ACS. Women had lower rates of reperfusion therapy (37.1 vs 26.8%; $p = 0.013$ for ST-segment elevation myocardial infarction; 53.6 vs 37.2%; $p < 0.0001$ for NSTEMI-ACS) compared with men.

The MIDAS study group concluded that women are less likely to undergo invasive cardiac procedures and have a higher 3-year adjusted death rate up to 70 years of age [9].

In a Korean study enrolling 6636 ACS patients (66.2% men), women were older, had higher rates of hypertension, diabetes and sedentariness, presented more often with atypical symptoms and underwent revascularization procedures less often [10].

A smaller study in Egyptian ACS patients, that enrolled 1204 ACS subjects confirmed similar findings. In addition the study found that women were less likely to be prescribed aspirin or statins at discharge [11].

Possible explanations & solutions for this disparity

Data from CREATE adds to the body of literature to indicate that women in India have increased risk of mortality following an ACS event compared with men. This is associated with their clinical condition on presentation (older age, presence of heart failure and delayed presentation), higher prevalence of cardiovascular risk factors (hypertension and diabetes) and because of inferior treatment.

Solutions to reduce the disparity must begin with increasing awareness among women and their healthcare providers. Women need to

acknowledge that heart disease is a preventable cause of death. This awareness has increased only in recent years, even amongst American women [12]. More research into lowering levels of their risk factors using culturally tailored nutrition and physical activity programs, which have shown promising results in lowering rates of hypertension, is needed [13].

Early detection of cardiovascular risk factors in internal medicine and obstetrics – gynecology clinics, which are more frequently accessed by women, can further reduce the prevalence of hypertension and other modifiable cardiovascular risk factors [14]. Dissemination and implementation of treatment guidelines like the American Heart Association 'effectiveness – based guidelines' on prevention of cardiovascular diseases amongst women [15] could improve control of lipids, blood sugars and blood pressure.

Misdiagnosis or delay in diagnosis of ACS in women reaching the emergency department is generally cited as a reason for delayed intervention. The presentation of ACS amongst women is less characterized compared with men. Women have a tendency to report atypical ACS symptoms, like absence of chest discomfort and may present with just shortness of breath. Increasing age is a factor for atypical symptoms and triaging them effectively can potentially minimize delays [16].

Women are less represented in clinical trials of interventions for managing an ACS event. Regulators and federal funding agencies of developed countries now mandate greater representation of women in clinical trials or research [17]. This could potentially lead to an increased use of evidence-based effective interventions amongst women. LMICs can implement similar regulations to gather evidence from women.

Eliminating gender disparity in treatments offered to women with ACS has the potential to reduce the burden of cardiovascular mortality.

Efforts are needed in LMICs to empower women with awareness and better access to healthcare.

Conclusion

The CREATE Registry shows evidence of gender disparity in presentation and treatments, among women suffering an ACS event in India. This is consistent with data reported from developed and other LMICs. Even though women were older and had higher levels of risk factors, if they were given similar treatments, many more lives could potentially have been saved.

Future perspective

Gender disparity has the potential to evolve with time and is subject to change with increasing levels of education and economic stability. The last decade has seen increased awareness being created among the general public and among the medical community. There are efforts on a global scale to make women more aware of the incidence of this number one killer. International agencies are addressing clinicians around the world to reduce the gap in gender disparity of treating patients with ACS. In the next decade, we anticipate increased representation of women in trials evaluating the use of revascularization interventions and gathering evidence on its benefits. International and national professional bodies will advocate policy changes, to reach women suffering from an ACS event, to ensure that they are sent to a hospital early and receive immediate intervention.

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