EuroIntervention

# Gender outcomes in acute myocardial infarction: are women from Venus and men from Mars?

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*R. Mehran is an Advisory Board member for Abbott Vascular, AstraZeneca, OrthoMcNeil, Regado Biosciences and has received a research grant – BMS/sanofi-aventis. J. Sweeney has no conflict of interest to declare.*

Mortality rate differences observed between men and women presenting with acute myocardial infarction (AMI) have been the focus of clinical trials and registry analyses over the past two decades. Despite advances in cardiovascular therapies over this time, studies have shown that women presenting with AMI have increased early mortality compared to their male counterparts[1,2]. The cause of mortality discrepancy after AMI in women has been the subject of much debate and has become one of many areas of interest regarding sex-specific outcomes in cardiovascular disease (CVD). Research suggests potential baseline risk profile differences and treatment biases among women compared to men as a reason for the AMI mortality gap. While the exploration of gender differences in coronary artery disease (CAD) has increased, the low proportion of female patients included in CVD trials as well as the lack of published studies results sorted by sex, leaves this an area in need of further study.

The current issue of EuroIntervention includes two papers addressing this topic. Both studies assessed different European populations for gender-related differences in mortality after ST-segment elevation myocardial infarction (STEMI) and come to the conclusions that female gender is an independent predictor of in-hospital mortality following AMI. Benamer et al analysed 16,760 patients (3,664 women) treated by PCI for STEMI from 2003 to 2007 in the CARDIO-ARHIF registry and determined that women tended to be older, had more diabetes, were more likely to present in cardiogenic shock and had a lower success rate of PCI when compared to men. After multivariate logistic regression adjusted for these risks, the authors concluded female gender was associated with higher in-hospital mortality (OR 1.38 [1.16-1.63], p=0.0002) but only after age of 75.

Sadowski and colleagues analysed 26,035 consecutive patients (8,989 women) with STEMI enrolled in the Polish Registry of Acute Coronary Syndromes (PL-ACS). Like Benamer's study, Sadowski et al determined these women were older with higher incidences of comorbidities such as hypertension, diabetes, obesity (BMI>30kg/m$^2$) and cardiogenic shock at presentation compared to males, and found a higher in-hospital mortality (1.13 [1.01-1.26], $p$<0.03), but not 12-month mortality (1.02 [0.96-1.09], p=NS) after multivariate adjustment.

Given the data presented from these two studies, three important issues need further discussion. First, CVD is the most common cause of death among women[3], yet women remain poorly represented in randomised clinical trials investigating cardiovascular disease and treatment. As a society we have enjoyed a steady reduction in age-adjusted mortality for CVD, but only recently has the rate of mortality decline for women approached that of men[4]. Reasons for this delay may include less frequent use of revascularisation procedures or evidence-based therapies in female patients with CVD[5]. Others postulate an overall lack of awareness of the prevalence of CVD in women, on the part of patients, policy makers and healthcare professionals[6]. A 2005 online survey of primary care physicians, gynaecologists and cardiologists found that fewer than 20% of physicians were aware that more women die annually of CAD than men[7] – a finding that highlights the need for awareness campaigns among healthcare providers[8]. There is a paucity of well-designed clinical trials assessing outcomes in women with cardiovascular disease and as a result, women have been under-represented in CVD clinical trials. In early studies investigating therapies employed in the treatment of AMI, fewer than 20% of subjects were women[9]. Reasons for this

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"gender-bias" are speculative, but may include the concern by Clinical Trialists that female patients have been associated with more adverse events. In order to avoid such gender-bias, many present-day studies investigating women and CVD (included the two published in this issue) are registry based. However, even with a registry design, both Benamer and Sadowski's studies enrolled few women, (22% and 34%, respectively), further underscoring the contemporary exclusion of females in CVD studies. One should also consider that this may be secondary to the fact that there are fewer women presenting with AMI than men.

Second, women presenting with AMI have higher cardiovascular risk profiles compared to males. Similar to prior databases[2,10], women enrolled in these two studies were older at presentation and had higher prevalence of traditional cardiovascular risk factors such as hypertension, diabetes and hypercholesterolaemia. The rationale for higher CV risk levels among women is likely multifactorial, involving complex social barriers to healthcare as well as possible physiological explanations. As mentioned previously, lack of awareness among both women and healthcare providers has certainly contributed to an unchecked progression of CVD and its risk factors. In numerous studies, women have been shown to receive suboptimal CVD preventative care[11,12]. In addition, women are more likely to have non-specific chest pain syndromes compared to men as well as unpredictable accuracy on available cardiovascular diagnostic testing[13] contributing to missed diagnoses and later presentations of CVD in women. Even when identified and appropriately treated, women may still not achieve the same benefit as men from evidence based pharmacological therapies used to reduce cardiovascular risks. It has been shown that women indeed respond differently to preventative medications such as aspirin, lipid lowering agents, ß-blockers and ACE inhibitors secondary to physiological, pharmacokinetic and pharmacodynamic differences compared to men[14]. Lastly, due to the loss of protective vascular effects of oestrogen, menopause contributes to an adverse impact on cardiovascular risk factors in women by delaying the onset of CVD. As a consequence, women tend to be 10 years older than men at the time of presentation with CVD, and more likely to have extensive disease[15].

Lastly, despite being at greater risk, according to the literature, it appears women are less likely to undergo life-saving revascularisation procedures in the setting of ACS. This was evident in Sadowski's study where 57.4% of males underwent primary PCI compared to 47.8% of females, but not in Benemer's study (88.9% PCI rate among females). These differences could partially be explained by geographical practice patterns and adherence to current guidelines. Despite the evidence supporting the benefit of early revascularisation in AMI and the burden of CVD in women, female patients analysed in the National Registry of Myocardial Infarction (NRMI) were significantly less likely to undergo revascularisation compared to male patients[16]. A similar treatment pattern was found among women presenting with NSTEMI as well[17]. Potential reasons for suboptimal treatment of female patients presenting with AMI include diagnostic uncertainty (in the case of NSTEMI), and increased incidence of complications. Retrospective analyses of female patients undergoing PCI show women are more likely than men to suffer access site complications such as pseudoaneurysms and bleeding[6], potentially influencing operators to avoid invasive procedures in this group. More data on this area is anticipated in the Xience V SPIRIT Women's Health Study, an ongoing prospective, multicentre trial specifically designed to evaluate women undergoing PCI.

Statistics show that 42% of women who have acute coronary syndrome die within one year compared with only 24% of men[14]. While the reasons for this are not completely clear, it seems that women may not be diagnosed or treated as aggressively compared to men. How this translates into mortality outcomes in women presenting with acute myocardial infarction requires further study using well designed clinical trials that enrol adequate numbers of females. In the meantime, we are left with the possibility that men and women are different regarding mortality outcomes in the setting of AMI – a disparity likely stemming from different cardiovascular care leading up to, during and after the acute event.

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