

Importance of Gender Differences in the Diagnosis and Management of Patients with Acute Coronary Syndromes: The GRACE Study in an Argentine Population

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Coronary heart disease is the leading cause of mortality and morbidity in industrialized countries, in men as well as in women. Whereas the cardiovascular death rates are declining in men, they remain constant in women. Women with acute coronary syndrome (ACS) usually present later at hospitals for professional help and show more frequently with atypical symptoms, such as abnormal pain locations, nausea, vomiting, fatigue, and dyspnea. So far there are only speculations to explain these differences, but they could be related to different pain perception, older age, or other comorbidities (1).

The misperception that females are somehow protected against cardiovascular disease may be one factor at the moment to evaluate the risk of heart disease women that is often underestimated. Recent data from the National Health and Nutrition Examination Surveys (NHANES) have shown that over the past two decades the prevalence of myocardial infarctions has increased in midlife (35 to 54 years) women, while declining in similarly aged men (1). This view has also been challenged by Wiviott et al on the basis of an analysis from the TACTICS (Treat angina with Aggrastat and determine Costs of Therapy with Invasive or Conservative Strategies)-TIMI 18 study population (2).

The under-recognition of heart disease and differences in clinical presentation in women lead to less aggressive treatment strategies.

According to studies such as GUSTO IIb (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes) (3), TIMI IIIB (Thrombolysis In Myocardial Infarction) (4), and the Euro Heart Survey (5), women present more frequently with unstable angina and non-ST-elevation myocardial infarction (NSTEMI), whereas men have ACS with ST elevation (STEMI). The outcome in NSTEMI appears equal, but in STEMI, mortality is higher in women.

Cardiac-specific biochemical markers, like troponins, seemed a good tool independent of gender in identifying patients at risk. In patients with non-ST-elevation ACS,

biomarkers today play a central role in establishing or ruling out a diagnosis and assessing the risk. A great number of markers have been under investigation, but only the following 3 currently qualify for the clinical routine: troponins as markers of cell injury, C-reactive protein (CRP) as inflammatory marker, and B-type natriuretic peptides (BNP) and N-terminal proBNP (NT-proBNP) as parameters of hemodynamic function. For CRP and BNP measurements but not for troponins, gender differences have been reported.

Accumulating evidence suggests that early invasive management reduces the risk of myocardial infarction and death in patients with ACS without ST elevation. Still, the outcome in women shows controversial results. The FRISC II (FRagmin and Fast Revascularisation during InStability in Coronary artery disease) (6) and RITA 3 (Randomized Intervention Trial of unstable Angina) (7) studies discourage the invasive management in women, because this was associated with an increased rate of adverse events.

In this issue of the Journal, Barros et al. (8), present the results from the GRACE study from an Argentinean population. The study evaluated a cohort of 4708 men and 2027 woman and the two years as well as follow up results are deeply discussed on this article. As previously reported, the study showed that women in Argentina were exposed to fewer interventions during hospitalization. The proportions of ischemic ECG changes and abnormal cardiac enzymes were similar among both sexes. The use of aspirin, clopidogrel and beta blockers was significantly lower in women, who had 50% the chance of undergoing either percutaneous coronary intervention (OR= 0.55; 95% CI 0.48-0.62) or coronary artery bypass graft surgery (OR= 0.49; 95% CI 0.36-0.67). The crude incidences of mortality and reinfarction during hospitalization and at two years of follow up were higher in women with no differences in the relative risk of major events

Persistent sex disadvantage results have been a

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common factor from more than two decades of acute coronary syndrome (ACS) studies. Most of these results support the view that women have higher mortality and morbidity despite the introduction of new medical therapies and devices. Even in contemporary practice in development countries like US and the EU community countries, women continue to have longer delays in presentation and treatment. Selection bias in unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) trials allows inclusion of large numbers of women with clinically insignificant coronary disease and may mistakenly shift results toward apparent benefit of a less aggressive approach. Other aspects that may account for differences in outcomes between women and men are related to vascular biological factors such as a smaller atheroma burden and slower progression in women, a smaller vessel size, less collateral flow, lower coronary flow reserve, more vascular stiffness, differences in remodeling, and functional differences of smooth muscle cells in the vessel wall. Enrollment of more women in clinical trials and timely sex-specific analysis would promote a better understanding of the role of female gender in ACS and would facilitate better care of all patients. Identification of their cardiovascular risk factors in women needs special consideration and further clinical studies which should result in a better prevention of cardiovascular events.

The evaluation of gender differences in the use of diagnostic and therapeutic methods between men and women with non-ST segment elevation acute coronary syndromes and the incidence of major events were presented on this study. The importance of the present study relay on the fact that in Argentina as well as other regions around the world, coronary angiography, PCI, CABG, antiplatelet therapy and beta blockers were less frequently indicated to women. This clinical trial should encourage other countries to initiate similar studies that can contribute to create an international task force to create women treatment oriented guidelines and promote cardiovascular health in women.

Conflicts of interest

None declared

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