The Swedish paradox: or is there really no gender difference in acute coronary syndromes?

Helge Möllmann, Christoph Liebetrau, Holger M. Nef, and Christian W. Hamm*

Kerckhoff Klinik, Heart and Thorax Center, Benekestrasse 2–8, D-61231 Bad Nauheim, Germany and Medical Clinic I, Cardiology and Angiology, University Hospital Giessen, Giessen, Germany

Online publish-ahead-of-print 14 October 2011

This editorial refers to 'Similar outcome with an invasive strategy in men and women with non-ST-elevation acute coronary syndromes', by J. Alfredsson et al., on page 3128

Over many years, gender differences in medical care have been reported, particularly in the context of cardiovascular disease (CVD). Across the industrialized world, CVD shows a continuous increase over the last decades and is the major cause of morbidity and mortality for men as well as for women. Moreover, the impact of CVD on overall mortality rates in Europe is even higher for women than it is for men. Nonetheless, women today outlive men by ≏ 5–10 years, a fact that may be explained by different arguments. One reason for women's longevity is the delay in onset of CVD. Women developing coronary artery disease (CAD) are usually 10 years older than men, who typically develop CAD at the age of 50–60. The risk factors for CAD are well established and do not differ between genders. However, given the older age of onset of clinically relevant CAD, women presenting with acute coronary syndrome (ACS) have a higher frequency of diabetes, hypertension, heart failure, and other co-morbidities. Women with ACS are more likely to have had prior episodes of angina pectoris or congestive heart failure, whereas men with ACS are more likely to have had prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting. Despite the fact that an early invasive strategy over many years is the treatment of choice in patients with non-ST-elevation acute coronary syndromes (NSTE-ACS), findings of subanalyses have fostered the attitude that women should in general be treated rather conservatively. How can this perception be explained? A subanalysis of the FRISC II (Fragmin and fast Revascularization during InStability in Coronary artery disease II) study reported that an early invasive strategy did not reduce the risk for future events in women. These findings could be confirmed in RITA 3 (Randomized Intervventional Trial of unstable Angina 3) when women in the conservative group had an even better outcome compared with women in the early invasive group. The results of these two trials are conclusive. However, these data have been challenged by the results of the large-scale TACTICS-TIMI 18 trial (Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18), which found a trend towards a beneficial effect of early invasive treatment for death or myocardial infarction in both women and men. Women with elevated troponin T levels, in particular, clearly had a benefit from early intervention. On the other hand, women with ACS are found to have high-risk angiographic features less often. Following coronary angiography, women and men are referred equally to revascularization, but women have to face higher complication rates, mostly related to a higher frequency of bleeding. Furthermore, the mortality rate after myocardial infarction during hospitalization has been reported to be higher in young women compared with men of the same age.

Does the prognosis differ between women and men?

Differences between women and men with ACS in terms of diagnostic work-up, treatment, and outcome have been reported, but available data are conflicting.

While ACS is quite common in women, nonetheless they receive less optimal medical therapy, are less likely to be admitted to hospital with catheterization capabilities, and consequently undergo coronary angiography less often than men. Despite the fact that an early invasive strategy over many years is the treatment of choice in patients with non-ST-elevation acute coronary syndromes (NSTE-ACS), findings of subanalyses have fostered the attitude that women should in general be treated rather conservatively. How can this perception be explained? A subanalysis of the FRISC II (Fragmin and fast Revascularization during InStability in Coronary artery disease II) study reported that an early invasive strategy did not reduce the risk for future events in women. These findings could be confirmed in RITA 3 (Randomized Interventional Trial of unstable Angina 3) when women in the conservative group had an even better outcome compared with women in the early invasive group. The results of these two trials are conclusive. However, these data have been challenged by the results of the large-scale TACTICS-TIMI 18 trial (Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18), which found a trend towards a beneficial effect of early invasive treatment for death or myocardial infarction in both women and men. Women with elevated troponin T levels, in particular, clearly had a benefit from early intervention. On the other hand, women with ACS are found to have high-risk angiographic features less often. Following coronary angiography, women and men are referred equally to revascularization, but women have to face higher complication rates, mostly related to a higher frequency of bleeding. Furthermore, the mortality rate after myocardial infarction during hospitalization has been reported to be higher in young women compared with men of the same age.

Taken together, women with ACS seem to be underdiagnosed and undertreated. This is also confirmed by two meta-analyses. However, one has to consider that these data are taken from subgroups of randomized trials with strict inclusion criteria that do not necessarily reflect the real world. Therefore, the time has come to look at registries, and the Swedish investigators have repeatedly helped out here with solid data. The gender imbalance does not obviously exist in Sweden. Alfredsson et al. studied gender differences in the outcome of
patients with NSTE-ACS treated either with an early invasive or an early non-invasive strategy. The authors examined an impressive cohort of 46,455 consecutive NSTE-ACS patients [14,819 women (32%)] from the SWEDEHEART registry. The key finding of the study is that the early invasive strategy is associated with a mortality reduction during 1-year follow-up in both women [hazard ratio (HR) 0.46, 95% confidence interval (CI) 0.38–0.55] and men (HR 0.45, 95% CI 0.40–0.52), without interaction in gender. More importantly, the authors could clearly exclude differences in mortality between women and men after adjusting for different variables, including age and classical risk factors. How does the Swedish diagnostic and treatment approach compare with those which have previously been reported and which result in worse outcome for women with ACS? Is this result perhaps related to better gender equality in Swedish daily medical practice?

Gender differences in diagnostic work-up

Swedish physicians seem better prepared for the fact that CAD is also a frequent disease among women, especially when they are older, and that symptoms may vary. Women more often present with atypical symptoms than men in the setting of ACS, such as dyspnoea, nausea, abdominal pain, and arm pain (Figure 1). In particular, the lack of typical angina may be misleading and causes delays in hospital admission, risk stratification, diagnosis, funding, and treatment. Women have to wait longer before a first electrocardiogram (ECG) is requested. Furthermore, women present significantly more often than men with NSTE-ACS but initially no elevation of biomarkers (cardiac troponin, creatine kinase-MB), which may cause further time delays. Moreover, separate female and male cut-off concentrations for cardiac troponins have been discussed recently. Taken together, longer delays may contribute to higher morbidity and mortality after revascularization. Therefore, the identification of these women within the large proportion of patients presenting with chest discomfort to the emergency department is more challenging, but apparently better understood in Sweden.

Gender differences in treatment approaches

Women with ACS are older, which might explain a priori that women are less likely to be treated with evidence-based medication, because older patients are more likely to be under-treated. Interestingly, this fact also holds true for the SWEDEHEART registry, which revealed that women with ACS received beta-blockers, statins, and aspirin less often. Furthermore, the awareness of the increased bleeding risk in women may result in an inappropriate use of anticoagulation during hospitalization and aggressive new dual antiplatelet therapies. Finally, women eventually undergoing angiography often present with a typical morphology with smaller size coronary arteries, which are less inviting for interventional treatment on the one hand and less promising for a beneficial long-term outcome on the other.

Lessons to learn

We have to face the fact that there are gender differences in patients with ACS. Some factors, such as age and the prevalence of co-morbidities, cannot be modified. However, differences related to the diagnostic work-up and to interventional and/or medical treatment are modifiable. They do not, however, all necessarily translate into a worse outcome, as shown in the SWEDEHEART registry. In particular, if the invasive concept is kept equal, any gender difference in medical management seems to disappear.

The under-representation of women in randomized clinical trials carries the risk that the interpretation for female patients is skewed when the result is driven by the male patients. Accordingly, subanalyses of randomized clinical trials related to women should be carefully interpreted and confirmed in large registries as in SWEDEHEART. Therefore, the SWEDEHEART registry is not a Swedish paradox, but rather represents real world management and is a valuable tool for improving our understanding of the role of gender in ACS.

Conflict of interest: none declared.

References


