Acute Coronary Syndrome
The Risk of Being Female
Albrecht Elsaesser, MD; Christian W. Hamm, MD

Coronary heart disease is the leading cause of mortality and morbidity in industrialized countries, in men as well as in women. Women have their first cardiac event 6 to 10 years later than men do. Whereas the cardiovascular death rates are declining in men, they remain constant in women. In cardiovascular studies with age limits, women are naturally the minority, amounting to <40%. It is well known that distinct gender differences exist in terms of presentation of symptoms, validity of diagnostic tests, drug side effects, and complications. With respect to cardiac risk factors, women have higher rates of diabetes and hypertension but are less frequently smokers.

Women with acute coronary syndrome (ACS) call later for professional help and present more frequently with atypical symptoms, such as abnormal pain locations, nausea, vomiting, fatigue, and dyspnea. We can only speculate on the reasons for these differences, but they could be related to different pain perception, older age, or other comorbidities.

The type of ischemic event shows gender-specific differences. According to studies such as GUSTO III (Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes),1 TIMI IIIB (Thrombolysis In Myocardial Infarction),2 and the Euro Heart Survey,3 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.

Women seem to be evaluated less intensively, which is possibly related to the perception that coronary artery disease is predominately a male disease. Cardiac-specific biochemical markers, namely troponins, seemed a good tool independent of gender in identifying patients at risk. This view has now been challenged by Wiviott et al4 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.

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.

Troponins in Women
Troponins are today the markers of choice in evaluating the acute risk of patients with ACS without persistent ST elevation and to guide further management. Over the last decade, the analytical quality of troponin T and troponin I assays have been repeatedly improved.5 Accordingly, the diagnostic cutoff levels could be reduced by >10-fold. Elevated troponin levels have been interpreted as the result of irreversible myocardial cell damage resulting from repetitive distal embolization from a ruptured atherosclerotic plaque. The present finding of less frequent elevations of troponins in women is novel and initially irritating. However, several mechanisms may help explain this new finding.

The most simple explanation is related to the fact that female patients with chest pain are a lower-risk population. This is consistent with previous observations that in women coronary angiograms are more frequently normal. Although this was widely ruled out in the present study by identical TIMI risk scores in both gender groups, it cannot be completely excluded. However, the TIMI risk score has not been established to verify gender-related differences in risk.

Another explanation could relate to the improved assay technology for troponin T and I. The question arises whether the low levels measured still represent myocyte necrosis, but are rather leaks from the free cytosolic pool of troponins. It was estimated that 6% of troponin T and 3% of troponin I are not structurally bound and could possibly cross the cell membrane before the contractile apparatus is disintegrated. When cardiac muscle mass corresponding to the number of myocytes is higher in men, small leaks become detectable earlier in men than in women, although this was not evident after correction for body weight. Because so far the analytical cutoffs are generated from predominately male populations, it needs to be investigated after these findings in ACS whether at low levels gender-specific cutoffs must be defined. However, the cutoffs used in the present analysis are considerably lower than the ones achievable in clinical routine.
ingly, the importance of this finding in the “real world” remains open.

Moreover, a pathophysiological finding could be considered responsible for a true gender difference in troponins. In women, coronary plaque erosions as a leading cause of thrombus formation are a more frequent finding than in men. Complete plaque ruptures in men may be a more severe stimulus for repetitive thrombus embolization with consecutive troponins released as compared with plaque erosions in women.6

Whatever the reason is for less frequent troponin elevations in women, this seems not to translate into a different prognostic value. Accordingly, this finding is currently less important for decision making in the emergency room.

**CRP in Women**

CRP measured with high-sensitive assays is an established independent marker of long-term mortality in men and in women.7 The levels are rather stable, provided no other cause of CRP elevation such as infection or trauma is present. In the general population, levels of CRP appear to be remarkably independent of gender. However, in women undergoing hormone replacement therapy, levels are elevated.8 Higher levels of CRP in women with ACS may be linked to different degrees of inflammation as compared with men. However, this is not supported by recent measurements of myeloperoxidase (MPO), an enzyme reflecting acute coronary inflammation processes.9,10 Levels of MPO tended to be even lower or equal in women but had similar prognostic power as in men. The prognostic value of CRP in these studies is reduced when MPO is included in the analysis. Measurements of CD40 ligands reflecting the link between platelets and inflammation so far also have not revealed a gender difference.11 Furthermore, measurements of interleukin 10 as a marker of protective mechanisms do not support a difference in gender.12 Accordingly, the explanation of higher CRP levels in women with ACS must be related to a more general, systemic inflammatory stimulation. In the future, therefore, switching to new acute-phase inflammatory markers that are independent of gender may be considered.

**BNP/NT-proBNP in Women**

Activation of the cardiac neurohormonal system after permanent or transient myocardial dysfunction results in release of BNP and NT-proBNP. This physiological reaction is closely linked to long-term outcome independent of other biochemical markers, ECG findings, and clinical variables.13,14 BNP is the active hormone with a shorter half-life (20 minutes) as compared with the more stable, but inactive, breakdown product NT-proBNP (60 to 100 minutes). In the clinical routine, no superiority of one marker over the others is established. It is well known that levels of BNP and NT-proBNP are gender- and age-dependent. Higher levels in women are independent of other baseline variables such as blood pressure or renal function. Accordingly, the higher levels found in women with ACS are not unexpected. However, as long as the cutoff points for BNP and NT-proBNP are still under debate, the meaning of this finding remains an interesting observation with unclear clinical relevance.

**Use of markers in risk stratification and therapeutic implications.** GP indicates glycoprotein; LMW, low molecular weight; and ACE, angiotensin-converting enzyme.

**A Sequential Multimarker Strategy for All**

Several studies have conclusively shown that the use of several biochemical markers representing different pathophysiological tracks improves risk stratification in patients with ACS.14–16 On the basis of the results of Wiviott et al,4 this multimarker approach is also confirmed to be the best strategy in women. Markers that reflect cell necrosis (troponins), hemodynamic stress (BNP or NT-proBNP), and inflammation (CRP) seem to cover the spectrum needed for acute and long-term clinical decision making. The clinical relevance is paramount when a marker such as troponins determines the therapeutic management in the acute setting. The TACTICS–TIMI 18 study established that the benefit of the early invasive strategy is reserved for women with elevated troponins.17 Earlier studies have established that these are the patients who also benefit from glycoprotein IIb/IIIa antagonists and low molecular weight heparins.18 For the long-term risk assessment, CRP and BNP/NT-proBNP are useful, although the therapeutic consequences are less well established.

All assays for new markers are expensive and should therefore be used rationally. The introduction of biochemical markers to the clinical routine not only will improve the diagnostic workup but also must be cost-effective. Unfortunately, the cost issue is not yet well settled in studies. However, a differentiated use of the markers is deductible from its specific release kinetics and the targeted length for prediction. We propose the following guidelines to be used in women and men equally (Figure). For the initial assessment, troponins are the markers of choice, because they provide the best predictive value for the 30-day risk of myocardial infarction.15 If the initial value is negative, it must be repeated after 6 to 12 hours according to the guidelines.18,19 More measurements are necessary after every new episode of chest pain. The other markers have only little value for the early period, but should be measured during the following course after stabilization. BNP and NT-proBNP seem to predict best the events that occur in the period 30 days after the acute event to the following months. Therefore, it may be suggested to include a measurement, for example, at 72 hours in the diagnostic routine, which appears to deliver excellent prognostic information (Heeschen and Hamm, unpublished data, 2003). As CRP reflects more the chronic disease but has no
acute prognostic value, it may be sufficient to obtain a measurement on discharge or during the early follow-up period. This appears also reasonable with respect to the argument that minor myocardial injury as detected by troponins may itself contribute to the inflammatory reaction.

**Treatment Implications for Women**

Accumulating evidence suggests today that early invasive management reduces the risk of myocardial infarction and death in patients with ACS without ST elevation. Guidelines recommend revascularization within 48 hours in high-risk groups. In contrast, patients without elevated markers or ST depression seem not to benefit from the invasive approach. The outcome in women shows controversial results. The FRISC II (Fragmin and Fast Revascularisation during InStability in Coronary artery disease) and RITA 3 (Randomized Intervention Trial of unstable Angina) studies discourage the invasive management in women, because this was associated with an increased rate of adverse events. However, not all studies in ACS could support this finding. The results of TACTICS-TIMI 18 confirm that women with elevated troponins benefit from early interventions. If markers are not elevated, this strategy has no benefit and may even be harmful.

Complication rates during percutaneous interventions are higher in women. Bleeding rates are elevated, because doses of antiplatelet drugs may have been too high for female patients, although aspirin, clopidogrel, and glycoprotein IIb/IIIa antagonists are similarly effective in women. However, subgroup analyses reveal that glycoprotein IIb/IIIa antagonists in low-risk female patients with negative troponins may be harmful.

**Conclusions**

Measurements of cardiac markers for decision making in women with ACS are at least as essential as in men. Troponins identify the group of patients who benefit from an aggressive approach similarly to men and, in addition and just as important, point out female patients with negative troponin results in whom aggressive treatment could be harmful. Different rates of abnormal values between genders need to be further explored. The multimarker strategy with measurements of troponin, BNP/NT-proBNP, and CRP at optimal time points represents the best acute and overall risk assessment in female and male patients with ACS.

**References**


**Key Words**: Focused Perspectives - women - coronary disease - biological markers
Acute Coronary Syndrome: The Risk of Being Female
Albrecht Elsaesser and Christian W. Hamm

doi: 10.1161/01.CIR.0000116022.77781.26
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/5/565