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REVIEW ARTICLE

Gender-specific differences in biomarkers responses to acute coronary syndromes and revascularization procedures

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Abstract

A growing body of gender-related research in coronary artery disease is beginning to gradually elucidate differences between women and men. In patients presenting with acute coronary syndromes (ACS), these sex differences include varying risk factor profiles, accuracy of diagnostic testing, clinical presentations, treatment practices and outcomes. There is also a differential expression of cardiac biomarkers by sex, which remains unexplained. This paper reviews all the available information on the effect of gender on cardiac biomarkers by search of MEDLINE using the terms gender differences, biomarkers, ACS and revascularization procedures. A better understanding of the sex disparities in biomarkers along with all other clinical information is essential to optimal management and patient care in the future.

Keywords: Gender, biomarkers, acute coronary syndromes, revascularization

Introduction

Gender differences have been identified in nearly all areas of coronary artery disease (Elsaesser & Hamm 2004; Jacobs 2006; Jacobs 2009). Although women have a proportionally lower prevalence of disease and tend to develop it later in life than men do, it remains unclear why the cardiovascular death rates are declining in men, whereas they remain constant in women (Jacobs 2009). Women are generally older with more comorbidities and present more frequently with atypical symptoms and with equivocal diagnostic tests, when diagnosed with acute coronary syndromes (ACS), (Table 1). Women with ACS are less likely to receive invasive evaluation and treatment and have higher rates of drug side effects, complications and risk of death after ACS and revascularization procedures, than men do (James et al. 2009), (Table 1). However, contemporary management strategies incorporating platelet glycoprotein IIb/IIIa inhibitors and novel intracoronary stents seem to favor early invasive therapy in women with increased troponins (Table 1).

A great number of biomarkers has been under investigation as potential indicators of each aspect of pathophysiological process within ACS spectrum, but only few have been qualified for clinical use (Table 2, Figure 1), (Morrow et al. 2007; Eggers et al. 2009). It is also well known that cardiac biomarkers play a central role in establishing or ruling out the correct diagnosis, in assessing the risk and in initiating the optimal treatment in patients with ACS (Ohman et al. 1996; Wu and Feng 1998). Up-to-date, limited data exist regarding gender-related differences in cardiac biomarkers profiles and their release patterns. Potential limitations include the under-representation of women in clinical studies and the subsequent low rates of sex-specific analyses in conjunction with the variability of the used cut-off values and the absence of a reference "gold standard" for clinical application (Apple et al. 2005; Stramba-Badiale 2010).

We performed a literature search by using MEDLINE and combinations of the following words: sex or gender differences and biomarkers and ACS or revascularization procedures (percutaneous coronary intervention and coronary artery bypass graft surgery).

Established biomarkers

Cardiac troponin

Troponins are the most important markers in risk stratification of patients with ACS and in guiding optimal treatment (Wu and Feng 1998). Elevated troponin levels

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Table 1. Important studies and their significant findings with special interest to women.

Author	Study	Study design and sample size	Findings
Merz et al. (2001)	Women's Ischemia Syndrome Evaluation	Interventional diagnostic study (women over 18 years who have suspected ischemic heart disease)	—Ischemia due to vascular dysfunction plays an important role in women —Stress echocardiography and nuclear imaging techniques have a high degree of accuracy 2- to 5-year event-free survival in women with chest pain
Blomkalns et al. (2005)	Can Rapid Risk Stratification of UA Patients Suppress Adverse Outcomes (CRUSADE)	Large-scale observational study of 35,875 patients with NSTEMI (41% women)	—Women were older and more often had diabetes and hypertension —Women with NSTEMI are treated less aggressively than men
Hochman et al. (1999)	Global Use of Strategies to Open Occluded Coronary Arteries in ACS IIb Investigators (GUSTO IIb)	12,142 patients with ACS (3662 women)	—Women were older and more often had diabetes and hypertension but were less frequently smokers —Women had more in-hospital complications and a higher mortality rate at 30 days
Heer et al. (2006)	Gender differences in acute NSTEMI	6358 with NSTEMI (34.1% women)	—Women were older and more often had concomitant diseases —They less often received acute PCI and less often were treated with clopidogrel —There was no difference in age-adjusted mortality in women
Milcent et al. (2007)	Gender differences in hospital mortality and use of PCI in AMI: Microsimulation analysis of the 1999 nationwide French hospitals database	74,389 patients with AMI (30% women)	—Age-adjusted hospital mortality was higher for women and was associated with a lower rate of PCI
Hvelplund et al. (2010)	Women with ACS are less invasively examined and subsequently less treated than men	9561 women and 16,406 men admitted to Danish hospitals with ACS in 2005-2007	—Less women received coronary angiography, even after adjustment for age and comorbidity —Revascularization was less likely in women —More women had no significant stenosis
Gan et al. (2000)	Treatment of AMI and 30-day mortality among women and men	138,956 Medicare beneficiaries (49% women) who had an AMI in 1994–1995	—Women were less likely to receive thrombolytic therapy within 60 minutes or to receive aspirin within 24 hours after arrival at the hospital —After adjustment, women and men had similar 30-day mortality rates
Clayton et al. (2004)	Do men benefit more than women from an interventional strategy in patients with UA or NSTEMI? The impact of gender in the RITA 3 trial	1810 patients (682 women) with NSTEMI or UA randomized to early intervention or conservative care	—Women benefited less from an early intervention for death or non-fatal MI at 1 year
Glaser et al. (2002)	Benefit of an early invasive management strategy in women with ACS (TACTICS-TIMI 18 trial)	Prospective analysis of 757 women and 1463 men with ACS	—The benefit of an early invasive strategy incorporating tirofiban and intracoronary stents was enhanced in women presenting with markers of increased risk

UA, unstable angina; NSTEMI, non-ST elevation myocardial infarction; ACS, acute coronary syndromes; PCI, percutaneous coronary intervention; AMI, acute myocardial infarction.

are more sensitive for detecting myocardial cell damage resulting from distal embolization, due to its higher myocardial tissue content and specificity than the creatine kinase-MB isoenzyme and myoglobin (Wu and Feng 1998; Apple et al. 2005). Over the last few years, there has been a great improvement in clinical and analytical performance of troponin I and T assays and a constant evolution of diagnostic cut-off concentrations used (Wu 2009).

The findings of large randomized, controlled trials highlight elevated troponin levels as useful tool in risk-stratifying women with ACS prior to angiography (Säfström et al. 2000; Lagerqvist et al. 2001; Glaser et al. 2002; Fox et al. 2002). However, in a TACTICS-TIMI 18 substudy, a different pattern of presenting biomarkers was revealed between sexes (Wiviott et al. 2004) (Figure 2). Women were more likely to have lower and less frequent elevations of troponins than men. Should these findings be given a serious consideration? First, female patients are generally lower-risk population—accounting for lower troponins—with smaller and frequently normal coronary arteries (Lagerqvist et al. 2001; De Bruyne et al. 2001; Elsaesser & Hamm 2004). Secondly, these gender

variations in troponins may mirror the pathophysiological differences in ACS between the sexes. Endothelial dysfunction, microvascular disease, and diffuse atherosclerosis are commonly identified causes of ischemia in women (Jacobs 2009). Moreover, coronary plaque erosions are more frequently found in women presenting with ACS while in men, complete plaque ruptures are usually responsible for repetitive thrombus embolization and for subsequent troponins elevation (Farb et al. 1996). Thirdly, it should be taken into account that advanced technology of troponins assays may detect such low levels which do not necessarily reflect myocardial necrosis but small leaks from the free cytosolic pool of troponins, particularly in men (Elsaesser & Hamm 2004). However, this was not evident either after correcting for body weight or after examining the heart tissue content of troponin T in an autopsy study (Swaanenburg et al. 2001).

Table 2. Biomarkers in Acute Coronary Syndromes and Revascularization Procedures.

Established Biomarkers	Novel Biomarkers
Cardiac Troponin I and T	Myeloperoxidase
B-type natriuretic peptide (BNP) and	CD40 ligand
N-terminal-proBNP	Pregnancy-associated plasma protein A
C-reactive protein	Heart-type fatty acid binding protein
	Ischemia modified albumin
	D-dimer
	Metalloproteinases
	Neopterin
	Cystatin C

Minor differences in the cut-off concentrations of troponin have minimal clinical significance after ST-segment elevation myocardial infarction since it can increase multifold from the baseline, whereas the achievable levels of troponin are considerably lower after ACS. Thus, troponin values should be interpreted as a continuum in sex-related analysis, because prognostic information can be obtained with lower threshold levels and even within the normal range (Wu 2009). Controversy still exists as to whether elevated troponin levels can identify a high-risk group of females who may have an enhanced benefit with early invasive management. A favorable finding is the stronger predictive value of the serum cardiac troponins for benefit than ST-segment changes and the TIMI risk scores (Glaser et al. 2002). In a more recent epidemiologic study, cases diagnosed with myocardial infarction and meeting only troponin-based criteria were more likely to women (Roger et al. 2006).

Natriuretic peptides

B-type natriuretic peptide (BNP) and its prohormone, N-terminal pro-BNP (NT-proBNP), reflect cardiac neurohormonal activity and increase after permanent or transient myocardial dysfunction (de Lemos et al. 2001). Elevation of BNP levels in ACS is predictive of increased mortality, postinfarction heart failure, or reinfarction (Jernberg et al. 2002). BNP measurements reflect the infarct size, progressive remodeling, and the degree of myocardial dysfunction (Nilsson et al. 2002; Steen et al. 2007). Even transient episodes of myocardial ischemia lead to increased production of BNP, by increasing LV wall stress, even in the absence of necrosis or preexisting LV dysfunction (Sabatine et al. 2004).

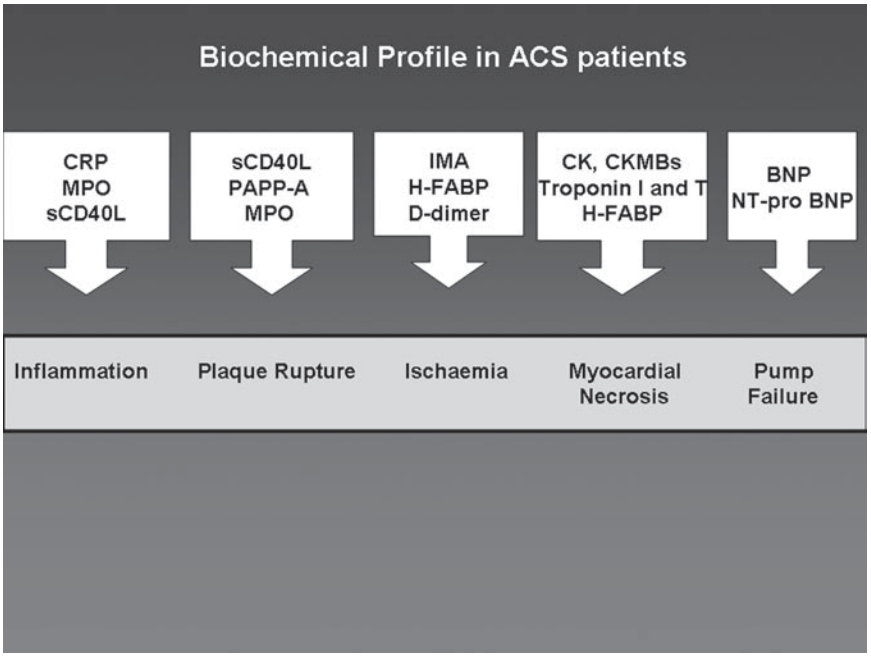

Figure 1. Biochemical profile in patients with acute coronary syndromes. ACS, acute coronary syndromes; CRP, C-reactive protein; MPO, myeloperoxidase; sCD40L, soluble CD40 ligand; PAPP-A, pregnancy-associated plasma protein A; H-FABP, heart-type fatty acid binding protein; CK, creatine kinase; CK-MB, the MB isoenzyme of creatine kinase; BNP, B-type natriuretic peptide; NT-pro BNP, N-terminal pro-BNP.

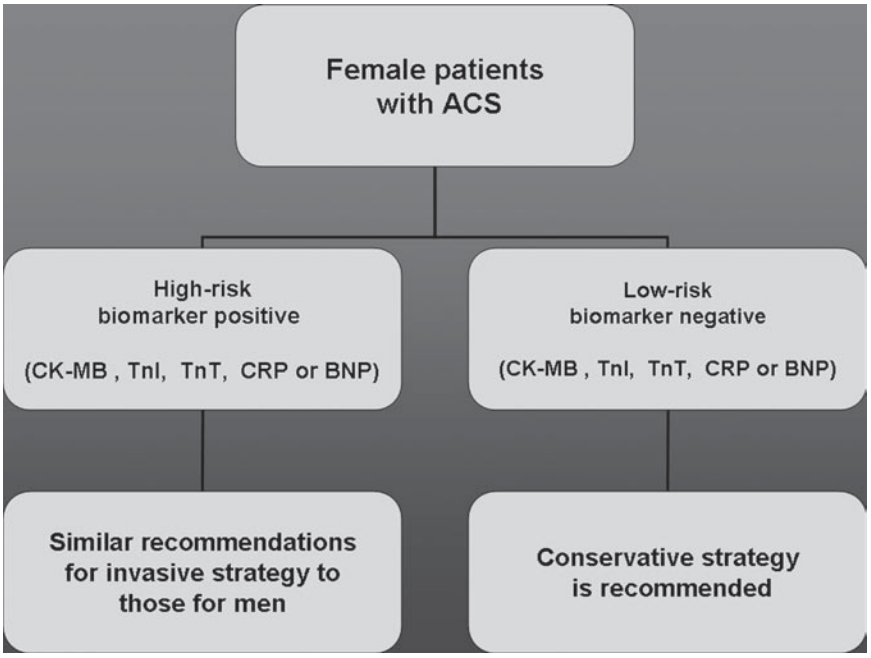

Figure 2. Flow diagram illustrating the differences in treatment strategy according to biomarkers status in women with acute coronary syndromes. ACS, acute coronary syndromes; CK-MB, the MB isoenzyme of creatine kinase; Tn, troponin; CRP, C-reactive protein; BNP, B-type natriuretic peptide.

Although there are data suggesting a benefit from an invasive management of patients with elevated BNP/NT-proBNP levels, the link to therapeutic measures could not yet be established as convincingly as for troponins (James et al. 2006; Weber & Hamm 2008). The prognostic value of these peptides is over and above the other conventional risk factors, whereas serial measurements provide more prognostic information than those of a single measurement (Eggers et al. 2009). Previous studies have reported age- and gender-dependent differences in BNP (Wang et al. 2002). BNP levels increase with age and are higher in healthy women than in men, independently of other baseline variables such as hypertension or renal dysfunction. However, the distribution of concentrations varies considerably among studies, making retrospective determination of optimal thresholds problematic and the clinical relevance of their findings unclear. In stable coronary artery disease, the reported values for NT-proBNP vary between 302 pg/mL (both genders), 169 pg/mL (both genders) and 127 pg/mL in men and 196 pg/mL in women (Ndrepepa et al. 2005; Kragelund et al. 2005; Omland et al. 2007). In patients with ACS, women are more likely to have elevated BNP indicating gender differences in the pathophysiologic mechanisms and particularly the higher prevalence of congestive heart failure (Wiviott et al. 2004).

C-reactive protein

C-reactive protein (CRP) is an acute phase protein that rises as a consequence of the inflammatory response to myocardial ischemia or necrosis (Heeschen et al. 2000; Blake & Ridker 2003). Interleukin (IL)-6 is primarily the responsible cytokine for the induction of acute phase protein production by the liver. Elevated levels of CRP, measured with high-sensitive assays, are associated with an increased risk of first and recurrent events in the whole spectrum of ACS (Heeschen et al. 2000; Blake & Ridker 2003). IL-6 levels also mirror cardiovascular risk factors in a fashion similar to CRP (Elsaesser & Hamm 2004). Average concentrations of high-sensitive CRP appear to be higher in healthy women than in men and to increase modestly with age through middle age in men but not in women (Koenig et al. 1999; McConnell et al. 2002; Rogowski et al. 2004). However, the amplitude of seasonal fluctuations in high-sensitive CRP is significant only in women, reflecting their greater variability in physiologic variables and an overall dynamic physiology that may be more adaptable to changing circumstances (Chiriboga et al. 2009). CRP levels are higher in women taking oral hormonal replacement therapy though this therapy is not associated with higher IL-6 levels (Ridker et al. 1999; Kritchevsky et al. 2005). Thus, gender-specific cut points for CRP are currently not advocated. The predictive value of CRP in women with ACS has been shown in a dose-response relationship, which is independent of other major risk factors (Roeters van Lennep et al. 2002; Arant et al. 2009). Higher levels of CRP in women with ACS may be related to different degrees of inflammation as compared with men, highlighting a more generalized systemic inflammatory status in women (Kip et al. 2005).

Revascularization procedures

Despite the improvements in stents (smaller and more flexible) and operative surgical techniques (minimal access approaches), marked sex disparities have been

consistently reported in patients undergoing revascularization, which can partially be explained by certain female-related biological characteristics (O'Donoghue et al. 2008; Presbitero 2009; Jacobs 2009). Smaller and stiffer vasculature size along with reduced creatinine clearance in women predisposes to excess dosing of anticoagulant therapies and contrast agents resulting in bleeding complications and contrast-induced renal injury (Sederholm et al. 2011). Cystatin C, as a marker of acute renal injury, is less influenced by age, gender, and muscle mass than serum creatinine and thus may be a better indicator of cardiovascular risk, especially in elderly women (Jernberg et al. 2004). Lower hemoglobin levels are associated with a higher risk for adverse outcomes in women undergoing evaluation and revascularization for coronary artery disease (Arant et al. 2004; Blake et al. 2004; Arant et al. 2009).

For patients undergoing surgical revascularization, the impact of gender on periprocedural troponin levels is controversial (Schwarzenberger et al. 2003; Stearns et al. 2009). Since previous studies were conducted primarily in men, there is no available troponin reference standard. Further, troponin cut-off concentrations can be influenced by many surgical confounding variables. After surgery, lower cut-off values of troponin I (>7.6 ng/mL) were suggested as optimum for predicting risk for adverse cardiac events compared to previously reported risk stratification studies conducted primarily in males (>9–15 ng/mL), (Stearns et al. 2009). It has been suggested that there may be differences in postsurgical risks for women versus men regarding the extent of myocardial damage (Matyal 2008; Stearns et al. 2009).

Emerging biomarkers

Some of the new emerging biomarkers have been recognized for decades though they have been subject to debate and controversy and consensus has not been reached on their inclusion in ACS evaluation.

Myeloperoxidase

Myeloperoxidase (MPO) is a marker of inflammation and oxidative stress, which has been consistently demonstrated to be elevated in patients with ACS (Weber & Hamm 2008). MPO may induce plaque rupture not only secondary to recruitment and activation of neutrophils but also by activating metalloproteinases, triggering endothelial cell apoptosis, and increasing the thrombogenicity of the plaque structure (Hazen 2004). MPO levels are elevated in persons with angiographically documented cardiovascular disease and within eroded or ruptured plaques (Naruko et al. 2010). The reported predictive value of MPO was independent of other biomarkers and in particular of troponins (Baldus et al. 2003; Brennan et al. 2003). Evidence suggests that there is a female gender-preference for superficial coronary artery erosions, possessing a subendothelium enriched with MPO (Sugiyama et al. 2001; Zhang et al. 2002). Remarkably, endogenous estrogen has recently been reported as a potential substrate for MPO in plasma that is capable of initiating lipid peroxidation (Farb et al. 1996). Previous studies have demonstrated that although plasma levels of MPO tend to be lower or equal in females, they have similar or even stronger prognostic power of risk in females than in males (Baldus et al. 2003; Brennan et al. 2003). No gender differences have been reported in other macrophage activation markers associated with MPO, such as matrix metalloproteinases and neopterin (Kai et al. 1998; Garcia-Moll et al. 2000; Adachi et al. 2007).

CD40 ligand

Soluble CD40 ligand is mainly released from stimulated platelets and activated lymphocytes and reflects the combined activation of inflammatory and procoagulant pathways identified as central to plaque destabilization and the pathogenesis of ACS (Varo et al. 2003). In patients with ACS, elevation of soluble CD40 ligand levels indicates an increased risk of cardiovascular events beyond the evidence provided by other established markers (Heeschen et al. 2003; Morrow et al. 2008). Increased plasma levels of soluble CD40 ligand have also been shown to be associated with increased risk for cardiovascular events in apparently healthy women, but the relevant diagnostic levels remain undetermined (Schönbeck et al. 2001). So far, studies have flagged doubts on the gender influence on CD40 ligands concentrations given pre-analytical and analytical issues on measurement of this marker and the demographic limitations of the studied populations, like the preponderance of male patients (Weber et al. 2006; Olenchock et al. 2008).

Pregnancy-associated plasma protein A (PAPP-A)

PAPP-A, a zinc-binding metalloproteinase, is highly expressed in eroded and ruptured plaques probably being involved in the processing of the plaque's extracellular matrix and weakening of the fibrous cap (Bayes-Genis et al. 2001; Futterman & Lemberg 2002). Previous reports have showed higher levels of PAPP-A in healthy men than in women, but the reason for this difference remains speculative (Khosravi et al. 2002). PAPP-A levels and its ratio with a proform of eosinophil major basic protein—an endogenous inhibitor of the proteolytic activity of PAPP-A—were significantly higher in men than in women with chronic stable angina (Hájek et al. 2008). Serum PAPP-A circulating levels are significantly elevated in patients with ACS than in patients with stable coronary artery disease or in healthy subjects, but levels are not influenced by sex (Cosin-Sales et al. 2005). PAPP-A has also been shown to be a strong independent predictor of event risk in troponin-negative or CRP-normal ACS patients (Lund et al. 2003). Further research is needed to determine whether PAPP-A, as a marker of plaque vulnerability, could be useful as an early indicator of the high risk coronary eroded plaques, which mainly characterizes women presenting with ACS.

Heart-type fatty acid binding protein (H-FABP)

H-FABP is one of the most abundant cytosolic proteins in both skeletal and cardiac muscle (Azzazy et al. 2006). H-FABP is the principal transporter of long-chain fatty acids in the cardiomyocyte and is released rapidly into the circulation in response to myocardial injury (Azzazy et al. 2006). As such, there are data regarding the diagnostic utility and the prognostic value of H-FABP in patients presenting across the spectrum of ACS (Okamoto et al. 2000; Haltern et al. 2010). Although, men were shown to have higher plasma H-FABP concentrations than women, because of their relatively larger muscle mass, this finding was not confirmed by later studies (Bathia et al. 2009). However, H-FABP was equally useful for risk stratification in both older men and women who present with ACS (McCann et al. 2009). It seems that as women age and their renal function decreases—the predominant site of circulating H-FABP clearance—they catch up with men in terms of plasma H-FABP levels (Pelsers et al. 1999).

Ischemia-modified albumin

Ischemia-modified albumin (IMA) is a new sensitive marker of ischemia that increases following percutaneous or surgical revascularization procedures and in relation to ACS (Sbarouni et al. 2008; Sbarouni et al. 2009; Dominguez-Rodriguez & Abreu-Gonzalez 2010). Gender does not seem to influence the biochemical transformation of albumin to IMA, and subsequently, differences in IMA among individuals do not seem to occur (Govender et al. 2008).

D-dimer

There are mixed data on the predictive value of plasma D-dimer level for the occurrence of acute coronary events among middle-age and older healthy postmenopausal women (Folsom et al. 2001; Pradhan et al. 2004; May et al. 2007). However, D-dimer was found to be a stronger predictor for cardiac events (nonfatal reinfarction or cardiac death) in postinfarction men than women, indicating possible gender-related differences in the pathophysiologic mechanisms of recurrent cardiac events (Kalaria et al. 2000; Gorog 2010).

Conclusion

To conclude, although the incidence of ACS is high in women, only sparse data pertain to female-group. Extrapolating from male to female may be potentially misleading, and it is important to specifically examine the evidence relating markers of ACS in female populations. Gender differences in assay's performance may not be important in promulgating the use of biomarkers clinically. What is apparent is that a multimarker approach would help in better characterizing and tailoring therapy for women with ACS as an adjunct to clinical data. What is warranted is further research to provide a clear understanding of the gender differences in novel biomarkers.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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