

# No Gender Difference in the Clinical Management and Outcome of Unstable Angina

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**Key words:** gender, unstable angina, management, prognosis

## Abstract

**Background:** Women with myocardial infarction have a less favorable prognosis than men. Many studies have indicated gender bias in the evaluation and treatment of myocardial infarction, but few data exist concerning these aspects in the management of unstable angina.

**Objective:** To investigate gender differences in the baseline characteristics, clinical presentation, treatment and prognosis of women with unstable angina.

**Method:** Data were collected prospectively as part of the Acute Coronary Syndromes Israeli Survey in 2000 at Soroka University Medical Center. In-hospital management and 2 year follow-up were monitored for 226 consecutive patients with unstable angina admitted to our medical center during February and March 2000.

**Results:** Women were older ( $71 \pm 12$  vs.  $66 \pm 12$ ,  $P = 0.006$ ), more diabetic (41.3% vs. 34.5%, not significant) and hypertensive (76.3% vs. 64.6%,  $P = 0.07$ ). Women presented more often with atypical chest pain (18.8% vs. 7.5%,  $P = 0.038$ ). Heparin, aspirin and angiotensin-converting enzyme inhibitor were delivered equally, but more beta-blockers were administered to women (88.5% vs. 75.7%,  $P = 0.02$ ) and more statins to men (48.1% vs. 35.4%,  $P = 0.07$ ). Angiography rates were similar (17.7% vs. 19.6%). Similar management was documented during the 2 year follow-up. Re-hospitalization rates were similar (53.3% of women and 63.7% of men, NS). Men had a tendency to develop acute myocardial infarction more often (9.6% vs. 2.7%,  $P = 0.06$ ) and to develop peripheral vascular disease (3.7% vs. 0%,  $P = 0.09$ ), and they had a non-significant higher rate of coronary artery bypass graft (6.7% vs. 1.3%,  $P = 0.08$ ). No gender difference was found in angiography (14.7% of women vs. 16.3% of men) or percutaneous intervention (13% vs. 16.7%). At 2 years there was no gender-related difference in mortality (13.3% of women vs. 16.3% of men, NS). Kaplan-Meier analysis for event-free survival after 2 years showed no gender difference in survival. Multi-regression analysis showed that gender was not a prognostic factor for survival.

**Conclusions.** We found no major difference in the management of men and women with unstable angina. Although men showed a tendency to suffer more major cardiac events, their 2 year prognosis was the same as for women.

*IMAJ 2005;7:228–232*

Cardiovascular disease has traditionally been considered a disease of men. However, recent studies show that coronary artery disease is a major cause of morbidity and the leading cause of death in men and women in Israel as well as in the western world [1,2]. Women with coronary heart disease tend to be older and have higher rates of diabetes, hypertension, dyslipidemia and other co-morbidities compared to men [3–7].

A worse prognosis for women after acute myocardial infarction has been clearly demonstrated in numerous trials [5,6,8,9]. Studies

have shown that in-hospital, as well as post-infarction, mortality is higher in women compared with men [4,9]. However, the impact of gender on unstable angina is not well defined, and there are only limited data on gender differences in the presentation, management and outcome of patients with this disorder. Diagnosing women with UA can be misleading because women tend to present with atypical complaints and symptoms [8,10,11]. Previous studies indicate some bias against women in the evaluation process, management and treatment of UA [3,12–14]. Women and men with UA tend to have equal outcomes [7,8,15,16], although some studies report a worse prognosis for men [5,6,12].

## Patients and Methods

This is a prospective study of all patients hospitalized in the Soroka University Medical Center in Beer Sheva during February and March 2000 with a discharge diagnosis of unstable angina (as defined by ICD-9 code 411), and a sub-study of the “Acute Coronary Syndromes Israel 2000” (ACSIS 2000) study reported previously [17]. ACSIS 2000 was a prospective study of all patients with a discharge diagnosis of acute coronary syndromes hospitalized in different hospitals in Israel during February and March 2000. At the Soroka University Medical Center in Beer Sheva, data were collected for patients with a discharge diagnosis of unstable angina who were hospitalized either in the cardiology department (10 of 80 women, 14.3%, and 18 of 146 men, 14.1%) or in the medical wards (85.8% of patients). During the index hospitalization, demographic and clinical data, as well as data on diagnostic procedures and treatment, were collected from medical files. A 2 year follow-up of these patients was performed using computerized medical records. Of 226 patients, 16 were excluded from follow-up only because computerized data were unavailable. Data concerning major cardiac events (death, MI, stroke, percutaneous transluminal coronary angioplasty, UA or cardiac hospitalization) and the results of invasive and non-invasive studies were collected.

## Statistical analysis

Chi-square test and analysis of variance were used to compare the clinical characteristics of patients. Kaplan-Meier and Cox regression analysis formulas were used to analyze the clinical outcomes after 2 years of follow-up.

UA = unstable angina  
MI = myocardial infarction

## Results

### Clinical background

The study population comprised 226 consecutive patients, 80 (35%) of whom were women. Women were 5 years older than men ( $71 \pm 12$  vs.  $66 \pm 12$ ,  $P = 0.006$ ). Men had a higher prevalence of history of past MI, CABG, PVD, renal failure, and active smoking as compared to women [Table 1].

### Clinical presentation

A higher percentage of men arrived at the emergency department by mobile coronary care unit (18.5% vs. 4.5%,  $P = 0.02$ ). Over two-thirds of the patients had typical chest pain at presentation. However, more women than men presented with atypical complaints of chest discomfort [Table 2]. No gender differences were seen in the admission electrocardiogram and Killip score.

### In-hospital management

Men and women were admitted equally to the medical and cardiology wards. There were no significant differences in the referral of men and women to angiography (19.6% of men, 17.7% of women) and ECG (24% of men, 33.8% of women). Both groups received similar in-hospital medication: aspirin (94.4% of men, 94.9% of women), heparin (31.2% of men, 36.7% of women), and low molecular weight heparin (67.4% of men, 68.4% of women). There was no gender difference in the number of patients who underwent angioplasty during hospitalization (2.1% of men, 3.8% of women). The mean (SD) length of the index hospitalization was  $5.5 \pm 3.1$  days for men and  $6.3 \pm 4.1$  for women (NS).

At discharge, 88.5% of the women and 75.7% of the men ( $P = 0.02$ ) received beta-blockers. There was a slight preference for statin use in men (48.1% vs. 35.4%, NS), although women and men had the same rates of dyslipidemia [Table 1]. There was no significant gender difference in other medications used for secondary prevention: aspirin (89.9% of women, 91.2% of men) or ACE inhibitors (49.4% of women, 43.8% of men).

### Follow-up

We conducted a 2 year follow-up of major cardiovascular events as well as a cardiovascular workup [Table 3]. Follow-up was performed in 210 patients. Sixteen patients were excluded from follow-up because computerized information was unavailable. The percent of patients admitted at least once during the 2 years was 63.7% for men and 53.3% for women (NS); the time elapsed between discharge to the first re-hospitalization tended to be shorter for men ( $141 \pm 97$  days) than for women ( $180 \pm 111$  days) ( $P = 0.06$ ). Men were hospitalized for  $5.8 \pm 7.1$  days in subsequent hospitalizations and women for  $6.1 \pm 7.9$  days (NS).

During the follow-up period men had a tendency to be hospitalized more frequently with chest pain or PVD and had a tendency to suffer more myocardial infarctions ( $P = 0.06$ ). We found no statistical differences in the rates of stroke, congestive heart

**Table 1.** Medical history and risk factors

	Women % (n=80)	Men % (n=146)	P
Myocardial infarction	22.8	42.0	0.04
Unstable angina	51.3	59.3	0.24
Coronary artery bypass graft	7.5	20.1	0.009
Percutaneous intervention	17.5	26.6	0.12
Heart failure	8.8	12.6	0.38
Stroke	11.3	12.6	0.78
Peripheral vascular disease	2.5	10.5	0.02
Renal failure	8.9	23.6	0.004
Dyslipidemia	60.8	60.8	0.99
Hypertension	76.3	64.6	0.07
Diabetes	41.3	34.5	0.31
Active smoking	7.8	28.4	0.001

**Table 2.** Presentation on admission

	Women % (n=80)	Men % (n=146)	P
<b>Pain</b>			
Typical chest pain	63.8	74.7	
Atypical chest pain	18.8	7.5	0.038
Other symptoms	17.6	17.8	
<b>ECG findings</b>			
ST segment changes	22.5	17.8	
No ST segment changes	17.5	23.3	0.7
T-wave inversion	42.5	42.5	
Non-specific	17.5	16.4	

**Table 3.** New cardiovascular events within 2 years

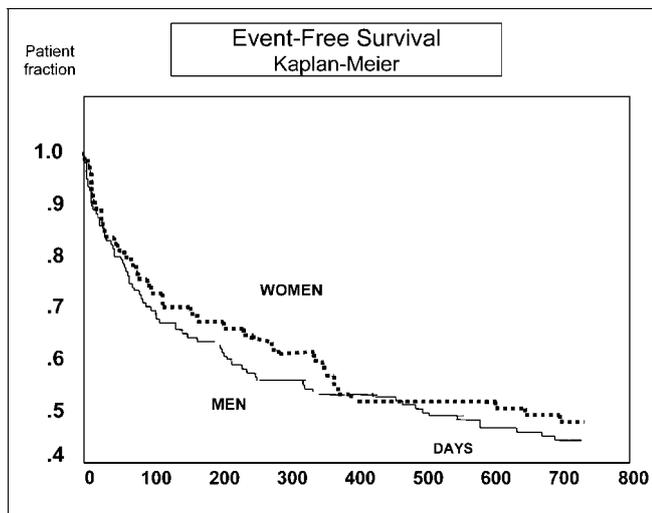
	Women % (n=75)*	Men % (n=135)*	P
Myocardial infarction	2.7	9.6	0.06
Unstable angina	33.3	37.8	0.52
Angiography	14.7	16.3	0.76
Coronary artery bypass graft	1.3	6.7	0.08
Percutaneous intervention	13.0	16.7	0.60
Heart failure	6.7	9.6	0.46
Chest pains	21.3	32.6	0.12
Arrhythmias	12.0	8.2	0.36
Stroke	2.7	3.7	0.70
Peripheral vascular disease	0	3.7	0.09

\* 16 patients were excluded from follow-up due to unavailability of data.

failure, arrhythmias or other cardiac hospitalizations between the two groups. During this period there was no difference between the two groups in cardiac catheterization rates, although men tended to have higher CABG rates ( $P = 0.08$ ). At 2 years there was no gender-related difference in mortality (13.3% of women vs. 16.3% of men, NS). Cardiac functions assessed by echocardiogram at the end of the first year of follow-up showed that women had higher rates of normal or mild left ventricular dysfunction than men (89.5% vs. 71%,  $P = 0.01$ ).

No significant differences were found in event-free survival for men and women at the end of 2 years (using the Kaplan-Meier

CABG = coronary artery bypass graft  
PVD = peripheral vascular disease  
ACE = angiotensin-converting enzyme



**Figure 1.** Event-free survival from major cardiac events (cardiac death, MI, stroke, CABG, angioplasty, angiography, UA). There was no significant gender-related difference in event-free survival during the follow-up period.

formula [Figure 1]. Cox regression analysis showed that gender was not a predictor for new cardiac events (death, MI, stroke, PTCA, UA, or cardiac hospitalization) in the 2 years following the index hospitalization ( $P = 0.7$ ). Factors found to be positive predictors for such events were diabetes ( $P < 0.01$ ), renal insufficiency ( $P < 0.01$ ), and past angina pectoris ( $P < 0.01$ ).

## Discussion

The process of diagnosing UA in women is paved with potential obstacles. Atypical presentation of UA can cause much confusion among physicians and caregivers. The presentation of chest pain is the point where studies have shown extensive differences in cardiac care for women and men [10–12,18]. This raises the question of whether the presenting symptoms in women are “atypical” or an example of our lack of knowledge with regard to the presentation of heart disease in women. The presenting symptoms will, to a great extent, determine the course and urgency of the diagnostic evaluation procedures to which he or she would be referred.

According to the literature, even women who present with typical anginal complaints have a lower probability of significant coronary disease compared to men [8,10]. For example, a 60 year old woman with typical anginal symptoms has the same chance of having significant coronary disease as a 40 year old man presenting with the same symptoms [8]. Thus, the physician must consider not only the symptoms that the patient presents but also the pretest probability of coronary disease in different age groups in both genders. The presenting ECG abnormalities were a major support for coronary disease cases where patients presented with atypical pains, thus closing the gap between the two genders.

## Diagnostic evaluation

This study found no gender bias in the diagnostic evaluation (echocardiogram, nuclear studies and angiography) of men and

women, despite lower rates of co-morbidities and prior cardiac events, and higher rates of atypical presentation in women. The competence of the physician to diagnose UA, despite atypical pain, led to the same diagnostic processes and equal treatment for men and women during and after the index hospitalization.

The use of diagnostic procedures to assess the existence and extent of coronary disease is another example of potential confusion among physicians. Studies have shown that the wide usage of stress testing in women is less sensitive because of the low pretest probability of coronary artery disease in this group [8,10]. Although this is the cornerstone for non-invasive evaluation of myocardial ischemia, it tends to give more false positive results for women [10]. Nuclear studies and stress echocardiography were found to be more accurate for the validation of ischemia in women [10,19]. The gold standard of the evaluation process is coronary angiography. Schulman and colleagues [18] used actors to present anginal symptoms to 720 primary physicians. They found that women were 40% less likely to be referred for angiography than men, although they had the same risk for coronary disease. The same group of physicians, however, did not show such differences in the referral for stress testing [18]. It is not clear whether these differences show gender bias against women or simply reflect confusion among clinicians concerning the best diagnostic strategy for women. It does, however, emphasize the need for better risk stratification for women with UA in order to improve the evaluation process and treatment of women. Since the introduction of troponin as a routine diagnostic tool, the diagnosis of UA in patients referred to the intensive care coronary unit decreased by 40% and the diagnosis of non ST-elevation MI increased by 53% [20], raising the resolution of risk stratification.

## Treatment

No major gender-related differences were found in the cardiac care of men and women with UA during the index hospitalization and 2 years of follow-up. Men and women were admitted equally to the cardiology ward and they received similar medical care, except for more use of beta-blockers in women, probably because they had more hypertension. There were similar rates of referral for revascularization (CABG, PCI) during the index hospitalization, although men tended to undergo more CABG during the subsequent 2 years ( $P = 0.08$ ), which could be attributed to their higher rates of cardiac risk factors, evidence of systemic atherosclerosis (PVD, stroke), worse cardiac functions by echocardiogram, and higher rates of MI during follow-up.

## Applicability of guidelines to women

The treatment of UA is based on data derived mainly from studies on men [1,10]; whether these recommendations also apply to women is unclear. Few studies have evaluated gender differences in the treatment of UA patients. The GUARANTEE study (1995-1996) [3] showed that women with UA were admitted less frequently to the cardiology wards, received less aspirin and

PTCA = percutaneous transluminal coronary angioplasty

PCI = percutaneous intervention

heparin during hospitalization, and were referred less often to procedures (angiography) and CABG. Another study showed a 24% higher use of cardiac procedures in men compared to women [12], and the MITI study, when adjusted for age and medical history, showed that women underwent fewer CABG procedures [7], while other studies showed none of these gender differences [14].

Guidelines currently in use [21,22] are based mainly on data from men. The alleged differences between the two genders raise the question of whether the current guidelines for treatment of UA are as beneficial to women as they are to men. This study shows that a competent physician is capable of correctly applying the guidelines to women.

### Prognosis

In the 2 years following their hospitalization, men and women had similar rates of re-hospitalization. Men tended to suffer more major cardiovascular events. Overall mortality was similar between the two groups. There were no statistical differences in the rate of UA, congestive heart failure or other cardiac events. There were no gender differences in event-free survival. Thus, although the two groups were treated equally, men presented with more cardiac risk factors and more history of cardiac events, and tended to have a slightly worse outcome. The relatively high rates of re-hospitalization and CABG among men are not surprising considering their clinical background, the course of their hospitalization, and their cardiac functions.

Our results are comparable with other studies that found no gender differences with regard to prognosis [3,7,15] and even found a better outcome for women with unstable angina compared to men [5,6,12]. Even though endpoints differ greatly among studies, it is clear that women are less subject to myocardial infarctions or death after being hospitalized with UA compared to men. A worse prognosis was reported for women after MI. How, indeed can we explain the better prognosis for UA women? Many studies demonstrated that women with acute coronary syndrome have a less severe angiographic disease than men [3,5,13,16]. Some argue that this might explain the better outcome seen in women, although women are more subject to the vasospastic effect of coronary arteries (syndrome X) and therefore suffer ischemia in spite of normal coronary arteries at angiography [10]. This again emphasizes the lack of sufficient data on cardiovascular disease in women, particularly UA, and the need for extensive research in that group. As long as such data are deficient, women are still subject to the possibility of treatment bias.

### Limitations

This study was a single center study. At the time of this survey, troponin level was not tested in our center. Thus, some of the patients diagnosed with UA may have been diagnosed as having non-ST elevation MI. Importantly, we do not have the data of patients who were discharged from the emergency department after presenting with chest pain, where some gender bias may have been found.

### Conclusions

The possible impact of gender on clinical evaluation, treatment and outcome has not been fully elucidated. Only a small number of studies compared the different aspects of gender in UA. This is a prospective study, conducted for the first time in Israel, that included all patients admitted to both the medical and cardiology wards with a discharge diagnosis of unstable angina. This enabled a comprehensive examination of the medical approach to women with UA as compared to men. Unstable angina pectoris represents a significant potential for morbidity and mortality among men and women. We found no differences in the clinical presentation, diagnostic workup and treatment of the two groups. Men, however, tended to have a less favorable prognosis. The issue of risk stratification in women and innovating specific guidelines is still an issue to be addressed.

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