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Risk Stratification in Unstable Coronary Artery Disease

Exercise Test and Troponin T from a Gender Perspective

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OBJECTIVES The study was done to determine the prognostic yield of an early symptom-limited exercise test (ET) and measurement of troponin T (TnT) in men and women with unstable coronary artery disease (CAD), with special reference to gender differences.

BACKGROUND Early risk assessment is essential for the application of appropriate treatment and further management in patients with unstable CAD. The early symptom-limited ET together with specific biochemical marker determination is an inexpensive, widely applicable method for early risk stratification. In women, however, the ET is considered less reliable, and there are few data on biochemical markers for risk stratification in women.

METHODS In a substudy of the Fragmin during InStability in Coronary artery disease (FRISC I) trial, 395 women and 778 men with unstable CAD who performed an early ET were followed for six months. Blood samples for TnT determination were taken in 342 women and 621 men at inclusion.

RESULTS Based on the ET results, low-, intermediate-, and high-risk response groups were identified with event rates of cardiac death or myocardial infarction (MI) of 1%, 9%, and 19%, respectively, among women and 8%, 14%, and 20%, respectively, among men. Patients who could not perform the ET had an event rate similar to the high-risk group. The TnT levels were divided into three groups: <0.06, $0.06-0.19$, and ≥ 0.20 μg/liter with event rates of 1%, 10%, and 18%, respectively, among women and 9%, 14%, and 18%, respectively, among men. Combining the ET results with TnT levels identified a low-risk group with an event rate of 3% in the male population and no events in the female population.

CONCLUSIONS Direct comparison between men and women from the same population with a high pretest likelihood of disease suggests that both TnT and the early symptom-limited ET are at least as useful as prognostic risk indicators in women as they are in men. (J Am Coll Cardiol 2000; 35:1791–800) © 2000 by the American College of Cardiology

Unstable coronary artery disease (CAD) is still associated with high mortality and morbidity despite considerable progress in therapy. A nonocclusive thrombus is usually the pathophysiologic mechanism behind the rapid deterioration from stable angina to unstable angina or the development of a non-Q-wave myocardial infarction (MI). To save myocardium it is of utmost importance to prevent the vessel from permanently occluding. In recent decades efforts have been made to find feasible instruments for early risk stratification, with the aim of intervening and eliminating or at least postponing the risk for MI or sudden death in patients with unstable CAD. Several studies have shown that it is possible to reveal high-, medium-, and low-risk patients using an early exercise test (ET), at least in men (1–4). The diagnostic and prognostic information gained from an ET is considered less reliable in women than in men, mostly due to the high percentage of false-positive tests (5,6). This may, at least partly, be due to a lower pretest likelihood among those women studied. In a population with a lower prevalence of a certain parameter any test for this tends to have more false-positive results and thus a lower specificity. For these reasons, electrocardiogram (ECG) changes in exercise tests in the absence of CAD are more frequently observed in women due to a lower prevalence of CAD in most populations (i.e., when comparing age-matched populations).

During recent years the cardiac-specific troponins have been shown to have not only diagnostic but also prognostic significance (7–14). However, studies have consisted of mixed male and female, or male-dominated populations. Thus, the aim of this study was to compare, between men and women, the use of early symptom-limited ET and early

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
ECG = electrocardiogram
ET = exercise test
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
TnT = troponin T

troponin T (TnT) release as tools for risk stratification in a population with a presumed high prevalence of significant ischemic heart disease.

METHODS

Study population. The study was part of a prospective randomized trial of low molecular weight heparin (dalteparin sodium, Fragmin Pharmacia Upjohn, Sweden) in patients with unstable CAD including 1,506 patients at 23 hospitals throughout Sweden between May 1992 and October 1994 (15). The inclusion criteria were a history of unstable angina or chest pain suggestive of acute MI, with onset of the last episode of chest pain within 72 h in conjunction with signs of ischemia in the form of transient or persistent ST-depression of ≥0.1 mV in at least two adjacent leads and/or transient or persistent T-wave inversion of ≥0.1 mV in at least two adjacent leads. Exclusion criteria consisted mainly of conditions with an increased risk for bleeding and difficulties in interpreting the ECG—for example, pacemaker rhythm or left bundle branch block (15).

Pharmacological treatment included aspirin and beta-blockade if not contraindicated and, as required, organic nitrates and calcium antagonists. The patients were randomly assigned to dalteparin sodium (Fragmin: 120 IU per kg body weight) or placebo given subcutaneously twice daily for five to seven days and then 7,500 IU or placebo once daily for another five weeks. Other medications were given at the discretion of the physician. All drugs were continued during the ET. Coronary angiography and revascularization were recommended in cases of refractory or incapacitating angina despite optimal pharmacological treatment or signs of severe ischemia at the ET. All therapeutic decisions were made without knowledge of the patient's TnT levels. Each patient stayed in hospital during the acute phase for at least five days. After six weeks the patients attended the outpatient department. The final visit took place five to seven months after trial inclusion. The study was approved by the ethics committees of all participating university hospitals. All patients provided informed consent.

The ECG and exercise test. A resting ECG (12 lead) was taken at admission, at inclusion in the study, after 5 to 8, 40 to 50, and 150 to 210 days. Extra ECGs were obtained at recurrence of chest pain during hospitalization, at readmission, or at unscheduled visits to the outpatient department. All patients who were considered stable (i.e., no ECG changes or chest pain at rest during the previous 48 h) were to perform an ET prior to discharge at the earliest five days and at the latest eight days after admission. The ET was performed with the patient sitting on an electrically braked bicycle ergometer starting at 10 to 30 W with repeated load increases of 10 W/min. The test was terminated when limiting symptoms occurred, such as chest pain of a degree 5/10, dyspnea of 5/10, or at exertion degree of 17/20 using the Borg scales (16). The test was also terminated if any of the following occurred: ST depression ≥0.3 mV, fall in systolic blood pressure >15 mm Hg measured once or 10 mm Hg measured twice with a 1-min interval, or serious arrhythmia—that is, ventricular tachycardia with three or more ventricular beats, >5 beats of bigeminal type, or the appearance of second- or third-degree atrioventricular block.

A 12-lead ECG was obtained before, continuously during, and for 10 min after the ET. Heart rate was measured every minute and systolic blood pressure and respiratory rate every third minute. Perceived exertion, chest pain, and dyspnea were rated by the patient every third minute during the test using the Borg scales; ST depression during the ET was measured 60 ms after the J-point.

The ECG and ETs were first interpreted by the local investigator, who also made all decisions regarding further treatment, although the final analysis used in this report was made centrally (Departments of Clinical Physiology, Uppsala and Jönköping) and without knowledge of patients' diagnosis and outcome. Computer-aided systems and, thus, averaged ECG complexes were used (Marquette Electronics, Milwaukee, Wisconsin; Schiller, Switzerland; FMAB, Partille, Sweden; Siemens Elema AB, Stockholm, Sweden). The raw data were manually examined to confirm the accuracy of the computer averages. An abnormal ST reaction was defined as a ≥0.1-mV downsloping or horizontal depression of the ST segment compared to resting ECG.

Previous studies from our group on male patients or male-dominated populations have shown that a low maximal workload and/or the number of leads with ST-depression ≥0.1 mV and/or maximal rate pressure product are independent factors of future cardiac events (4,17) and severity of coronary lesions (2). In accordance with previous results (2,4,17), a combination of these factors was used to define three risk groups: a "high-risk group" where patients had at least two out of three criteria; an "intermediate-risk group" with one criteria, and a "low-risk group" where patients lacked all three criteria. The criteria were a low maximal workload defined as a workload below the 33rd percentile of the distribution for men (90 W) and women (70 W), respectively; ST-depression ≥0.1 mV in ≥3 leads; and a small increase in rate-pressure product during exercise (heart rate × systolic blood pressure at peak load − heart rate × systolic blood pressure at rest) defined as a value

below the 33rd percentile of the distribution for men (8,750) and women (8,000), respectively.

Blood samples and laboratory methods. Venous blood samples for analysis of plasma TnT were obtained at inclusion and then after 12, 24, 48, and 120 h. Blood was collected in EDTA-containing tubes and was then centrifuged. The plasma was frozen in aliquots and stored for subsequent analysis. Troponin T (TnT) was determined using the Enzymun-Test system (Boeringer-Mannheim) (18). The lower detection limit is 0.04 μg/liter according to the manufacturer, and the upper reference level in healthy blood donors is 0.06 μg/liter (19). All analyses were performed at one laboratory (Department of Clinical Chemistry, Uppsala). The between-day coefficient of variation over four months (n = 99) at the laboratory was 10.2% and 5.1% at a level of 0.28 and 6.10 μg/liter, respectively.

According to a previous report from the present study (20), the maximal TnT level obtained during the first 24 h was an independent predictor of future cardiac events (cardiac death or MI) in patients with unstable CAD. The addition of samples at 48 and 120 h did not improve the prognostic value of the test. A maximal TnT value of <0.06, 0.06 to 0.19, and ≥0.2 μg/liter during the first 24 h enabled stratification of the subjects into low-, intermediate-, and high-risk groups, respectively (20). The same cutoff values were used in the present analysis.

Evaluation of index event and end point definition. All primary end points (i.e., death and nonfatal MI) were classified by an independent end point committee. Great care was taken to differentiate new events from the initial event. At admission and at recurrence of severe chest pain, serial blood samples for measurement of biochemical markers of MI were obtained. The episode that qualified a patient for enrollment in the study (index event) was classified retrospectively as acute MI or unstable angina, based on the maximal levels of available cardiac enzymes obtained and analyzed at the local hospital immediately after that episode, as described in a previous report (20). Myocardial infarction was defined by conventional WHO criteria (21). Cause of death was based on hospital records and, if available, necropsy reports. Sudden death was considered cardiac. If the patient had more than one event (i.e., MI and death) during follow-up, only the first-occurring event was taken into consideration in the combined end points. Readmission because of refractory angina or MI was especially recorded.

Statistical analysis. Differences in proportions were judged by chi-square analysis with the Yates continuity correction. For nonparametric unrelated data, the Mann-Whitney *U* test was used. Comparison of continuous variables was performed using unpaired *t*-test. The cumulative hazard curves were constructed using the Kaplan-Meier method. End points were cardiac death or nonfatal MI. Noncardiac death was treated as a censored observation. Statistical assessment was performed using the log-rank test. To identify variables of independent prognostic importance, forward stepwise multiple logistic regression analysis was performed regarding the predefined end points MI or cardiac death. The cutoff value for entry into the model was 0.05. Evaluated independent variables were clinical (age; diabetes mellitus; smoking habits; congestive heart failure; hypertension; previous MI; enzyme release above decision limits for MI at the initial event), number of antianginal drugs at ET, maximum TnT during first 24 h: <0.06; 0.06 to 0.19; ≥0.2 μg/liter, and ET; "low-risk"; "intermediate-risk"; "high-risk/no ET." As the event rate in the non-ET group was similar to the "high-risk response group" these two groups were considered together in the multiple regression analysis. In all tests a p value of <0.05 was considered statistically significant. All statistical analyses were performed by a computer using the SPSS system (Statistical Package for the Social Sciences, Chicago, Illinois).

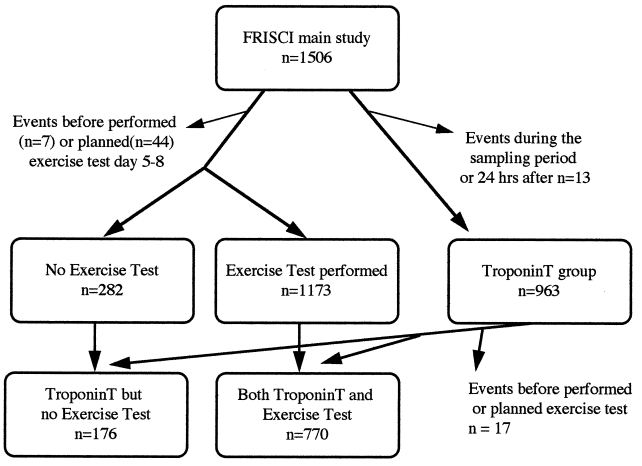

Figure 1. Recruitment of the study population.

RESULTS

An ET was performed in 1,180 patients. Seven patients already had a new event before the test, leaving 1,173 patients for evaluation of the ET. A total of 326 patients did not perform the ET. Forty-four of these patients were excluded from the analysis due to an event before day 8—that is, the last day upon which the ET could be performed. Blood samples for TnT analysis were drawn in 976 patients. Patients with events during the sampling period and one day beyond were excluded, leaving 963 patients for TnT analyses (Fig. 1).

General findings. Women were older than men in both the ET and non-ET groups. Previous congestive heart failure and use of diuretics were more common among women in each ET group (Table 1). Women had a lower median TnT maximum than did men (0.17 vs. 0.51 μg/liter $p < 0.0001$). During six months of follow-up from the ET (or day 8 in the non-ET group) there were 22 (4.2%) and 44

Table 1. Clinical Characteristics of the Study Group (n = 1,455)

	Exercise Test Group		Nonexercise Test Group	
	Men (n = 778)	**Women (n = 395)**	**Men (n = 150)**	**Women (n = 132)**
Background factors				
Age	69 (60–74)	71 (64–76)***	72 (64–77)†††	74 (68–80)**†††
Diabetes	88 (11)	56 (14)	22 (15)	30 (23)†
Current smoking	180 (23)	62 (15)**	28 (19)	21 (16)
Previous CHF	51 (7)	43 (11)*	16 (11)	30 (23)*††
Previous stroke	23 (3)	17 (4)	14 (9)†††	14 (11)†
Hypertension	226 (29)	137 (35)	48 (32)	58 (44)
History of CAD				
Previous MI	213 (27)	99 (25)	58 (39)††	55 (42)†††
Occurrence of angina at rest the preceding week	378 (49)	181 (46)	71 (47)	69 (52)
Ongoing angina at admission	418 (54)	242 (61)*	110 (73)†††	84 (64)
Inclusion diagnosis				
Non-Q-wave MI	313 (40)	131 (33)*	70 (47)	46 (35)
Medication at inclusion				
Aspirin	265 (34)	130 (33)	69 (46)††	60 (46)†
Beta-blocker	267 (34)	163 (41)*	61 (41)	46 (35)
Calcium inhibitor	149 (19)	85 (22)	43 (29)†	39 (30)
Nitroglycerin prophylactic	199 (26)	112 (28)	48 (32)	55 (42)††
Diuretics	129 (17)	114 (29)***	39 (26)††	63 (48)***†††
Digoxin	42 (5)	29 (7)	10 (7)	19 (14)†
ACE inhibitor	62 (8)	33 (8)	20 (13)†	11 (8)
ECG at rest at inclusion				
Q wave	202 (21)	71 (13)***	37 (25)	23 (17)
ST depression	602 (63)	318 (59)	104 (69)	84 (64)
T-wave inversion	637 (81)	337 (85)*	111 (74)†	112 (85)*

CHF = congestive heart failure; CAD = coronary artery disease; MI = myocardial infarction. Values are median (25th to 75th percentile) or n (%).
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ men vs. women within exercise test or nonexercise test groups. †$p < 0.05$; ††$p < 0.01$; †††$p < 0.001$ men vs. men and women vs. women comparing the exercise test group to the nonexercise test group.

(4.7%) deaths, 59 (11%) and 106 (11%) MIs, 167 (32%) and 339 (37%) PTCA/CABG (percutaneous transluminal coronary angioplasty/coronary artery bypass graft surgery) in women and men, respectively.

Nonexercise test group. Both men and women in the non-ET group were older and had more often experienced a previous stroke or MI than did patients of respective gender in the ET group. The median TnT maximum did not differ between the ET and non-ET group (0.32 vs. 0.34 μg/liter, p = NS). In the nonexercise test group, women had significantly lower median TnT values than did men (0.20 vs. 0.62 μg/liter, $p < 0.01$).

Patients who did not perform the ET (n = 282) had significantly more cardiac deaths in both men and women. Women in the non-ET group had a higher incidence of the combined end point cardiac death/MI ($p < 0.001$) compared to women in the ET group, whereas the same did not apply to men (Table 2).

The exercise test group. An ET was performed a median of five days after inclusion (95% of the patients from day 4 to day 7); results are shown in Table 3. Women were older, had less ST-depression, and reported less pain at the ET than did men. Female subjects had lower maximum workload but reached the same expected maximum workload as did men in relation to gender, body weight, and age.

The number of patients in the three prespecified risk

Table 2. End Points After Six-Month Follow-Up

	Exercise Test Group		Nonexercise Test Group	
	Men (n = 778)	**Women (n = 395)**	**Men (n = 150)**	**Women (n = 132)**
Cardiac death	30 (4)	12 (3)	14 (9)††	10 (8)†
Myocardial infarction	87 (11)	29 (7)*	19 (13)	17 (13)
Cardiac death/MI	104 (13)	35 (9)*	26 (17)	23 (17)††
CABG/PTCA	277 (36)	126 (32)	68 (45)†	41 (31)*

MI = myocardial infarction; CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty. Values are n (%).
*$p < 0.05$ men vs. women within the same group. †$p < 0.05$; ††$p < 0.01$ men vs. men and women vs. women comparing the exercise test group to the nonexercise test group.

Table 3. Findings at the Predischarge Symptom-Limited Exercise Test (n = 1,173)

	Men (n = 778)	Women (n = 395)
Median (33rd to 67th percentile)		
Maximum workload (W)	105 (90–120)	80 (70–90)***
% of Expected maximum workload	79 (69–89)	80 (71–90)
Maximum heart rate (beats·min^{-1})	111 (104–122)	113 (104–124)
Maximum blood pressure (mm Hg)	175 (160–190)	175 (160–190)
Maximum perceived effort (Borg)	16 (15–19)	17 (15–17)**
Raise in rate pressure product	10,560 (8,750–12,870)	10,500 (8,000–13,140)
% of Patients		
Chest pain during exercise	42	32***
No ST-depression ≥1 mV	38	53***
1–2 leads with ST depression	22	16*
≥3 leads with ST depression	40	31**
% of Patients receiving treatment at ET		
Beta-blockers	80	82
Calcium inhibitors	32	39*
Nitrates	61	63
Digitalis	5	7

Raise in rate pressure product = heart rate × systolic blood pressure at peak load − heart rate × systolic blood pressure at rest. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

response groups (low-, intermediate-, and high-) were evenly distributed, except for women, where there were fewer in the high-risk response group (Table 4). The TnT values were lower for women than for men in the ET group (0.15 vs. 0.48 μg/liter, $p < 0.00001$).

We found a definite low-risk response group among women, where only 1% had a serious cardiac event (cardiac death/MI) compared to men, where 8% had an event during the follow-up period. In the high-risk response group, women and men had a similar event rate of 19% and 20%, respectively (Fig. 2A). The rate of revascularization at six months was 36% in women and 49% in men (Table 4). When combining all end points (cardiac death/MI/PTCA/CABG) at six months the event rates in the high-risk response group were 49% and 59% for women and men, respectively, compared to 18% and 27% in the low-risk group ($p < 0.0001$ for women vs. women and $p < 0.001$ for men vs. men).

Troponin T. Troponin T was sampled and measured in 963 patients. During the first 24 h three samples were obtained in 884 patients; 62 patients left two samples and in 17 patients only one sample was measured. Forty-nine percent of the women and 64% of the men had TnT values above the decision limit for MI (≥0.20 μg/liter), which was regarded as the high-risk group. In this group 18% of both women and men had a serious cardiac event (cardiac death/MI) during the follow-up compared to 1% and 9%, respectively, in the group with TnT values <0.06 μg/liter (Table 4, Fig. 2B).

Exercise test and troponin T in combination. A population of 770 patients (255 women and 515 men) performed an ET as well as had TnT measured. Combining ET risk response and TnT values we found that male and female patients with low TnT values and a low risk response at the ET had very few cardiac events during follow-up (no women and one man). In the high-risk group (combined ET and TnT values) the event rate was 31% and 26% in women and men, respectively (Fig. 3).

Multivariate logistic regression analysis. Univariate and multivariate stepwise logistic regression analyses were performed to assess the value of a number of clinical variables, findings at the predischarge ET, and maximum TnT value in predicting cardiac events. In the multivariate analysis, the ET was the best variable to predict cardiac death/nonfatal MI during follow-up (Table 5).

DISCUSSION

In this population of patients admitted to hospital because of an episode of unstable CAD we had the opportunity to compare 928 men with 527 women regarding clinical parameters and indices of risk. We studied a population at high risk, as the combined end point of cardiac death/MI was high in both men and women during the six-month follow-up period (13.2% and 16.6% in women and men, respectively) in the entire FRISC I (Fragmin during InStability in Coronary artery disease) population.

The women were, in general, older, had more previous congestive heart failure, and used more diuretics than did men. Both women and men in the non-ET group were older, and more patients had suffered from previous cardiovascular disease, such as MI and stroke, than did patients in the ET group. These patients thus constituted a group who, in accordance with previous studies (17,22), were sicker. Consequently, this group had a worse prognosis than the others, regarding cardiac death in both women and men, whereas only women had a higher incidence of the combined end point cardiac death/MI ($p < 0.001$). Male and female patients with unstable CAD who are not able to

Table 4. Comparison of Troponin T and the Predischarge Exercise Test Regarding Different Endpoints After Six-Month Follow-up

	Troponin T					
	<0.06 μg/liter		0.06–0.19 μg/liter		≥0.20 μg/liter	
n (%)	Men (n = 94)	Women (n = 88)	Men (n = 132)	Women (n = 88)	Men (n = 395)	Women (n = 166)
Cardiac death	1 (1)	0 (0)	4 (3)	4 (5)	26 (7)	13 (8)‡
Cardiac death/MI	8 (9)	1 (1)	18 (14)	9 (10)†	70 (18)‡	30 (18)‡‡‡
CABG/PTCA	43 (46)	19 (22)**	53 (40)	33 (38)†	143 (36)	64 (39)‡‡
	Exercise Test					
	Low-risk response (no risk criteria)*		Intermediate-risk response (one criteria)*		High-risk response (at least two criteria)*	
	Men (n = 267)	Women (n = 142)	Men (n = 281)	Women (n = 155)	Men (n = 230)	Women (n = 98)
Cardiac death	3 (1)	0 (0)	11 (4)	5 (3)	16 (7)‡‡	7 (7)‡‡
Cardiac death/MI	21 (8)	2 (1)*	38 (14)†	14 (9)††	45 (20)‡‡‡	19 (19)†‡‡‡
CABG/PTCA	56 (21)	24 (17)	108 (38)†††	67 (43)†††	113 (49)†‡‡‡	35 (36)*‡‡

*The criteria were a low maximal workload defined as a workload below the 33rd percentile of the distribution for men (90 W) and women (70 W), respectively; ST-depression ≥0.1 mV in ≥3 leads; and a low increase in rate-pressure product during exercise (heart rate × systolic blood pressure at peak load − heart rate × systolic blood pressure at rest) defined as a value below the 33rd percentile of the distribution for men (8,750) and women (8,000), respectively. Women compared to men in the same "risk group": *$p < 0.05$; **$p < 0.01$. Each gender compared to the same gender in the "risk group" on its left: †$p < 0.05$; ††$p < 0.01$; †††$p < 0.001$. Each gender compared to the same gender in the second "risk group" on its left: ‡$p < 0.05$; ‡‡$p < 0.01$; ‡‡‡$p < 0.001$. MI = myocardial infarction; CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty.

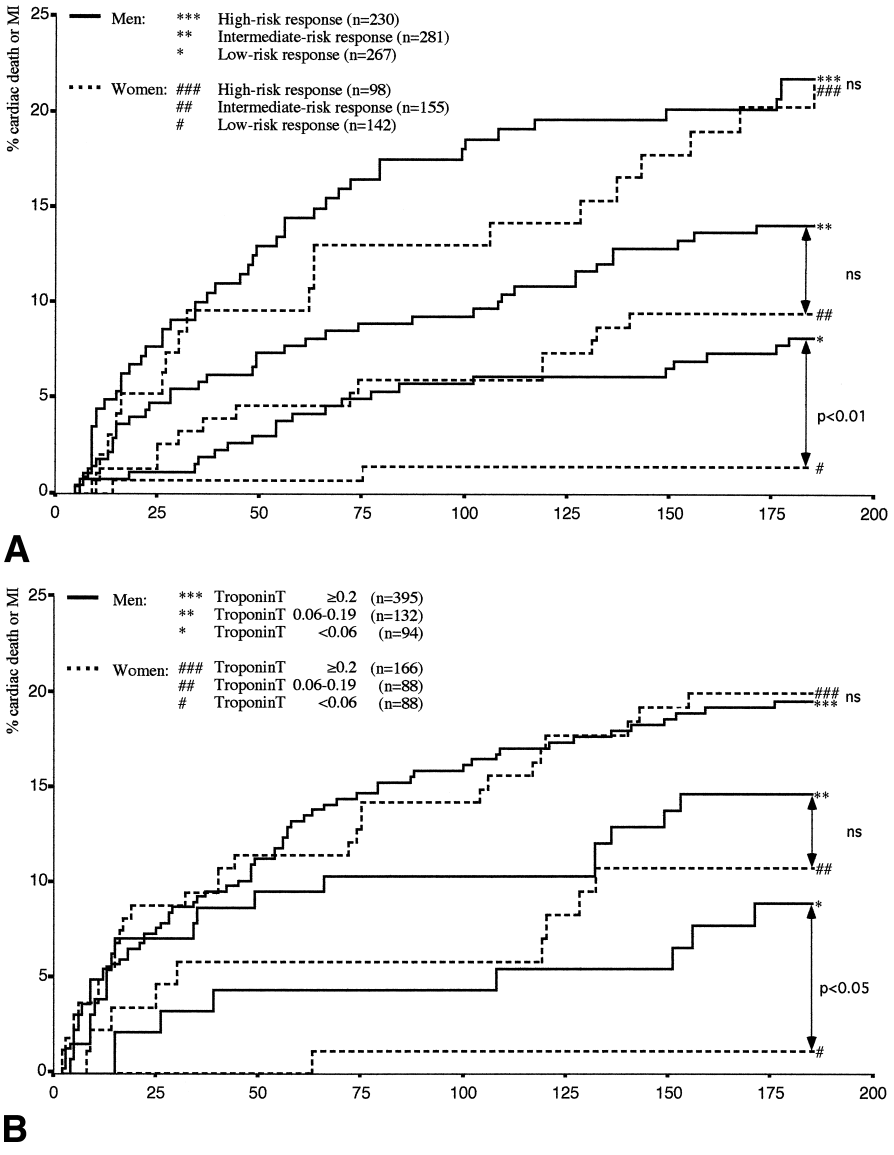

Figure 2. **(A)** Cumulative risk and time of occurrence of cardiac death or myocardial infarction (MI) in groups based on exercise test findings. **(B)** Cumulative risk and time of occurrence of cardiac death or myocardial infarction (MI) in groups based on maximal troponin T levels during the first 24 h (μg/liter).

perform an early ET thus belong to a high-risk group and should be treated accordingly.

Exercise test. Among patients who performed the ET, women reached the expected maximum workload with the same increase in rate-pressure product but with a higher perceived effort, with less ST-depression and less chest pain, compared to men. Thus, it seems that women, despite being older, performed an adequate ET but with fewer signs of ischemia. These findings indicate a female population more healthy than the male population.

As with TnT, the ET was able to identify a low-risk group among women, but not among men (1% vs. 8% cardiac death/MI during six months). In the high-risk response group, women and men had an event rate of 19% and 20%, respectively, which is high despite optimal medication with beta-blockers and aspirin. Very few, however, used statins as the study was completed before the publication of the 4S-study (23). The rate of revascularization at six months was also quite high, partly because the ET in some cases influenced the decision to catheterize the patient. In this direct comparison between women and men with unstable CAD, performed during the same time period with the same inclusion/exclusion criteria and medication, we found that the ET tended to be of even higher prognostic value in women than in men, which to our knowledge has not been described previously.

Myocardial marker troponin T. The median TnT maximum did not differ between the ET and non-ET groups, but women did have lower median TnT values than men. Even so, there were more patients with high TnT levels in

JACC Vol. 35, No. 7, 2000
June 2000:1791–800

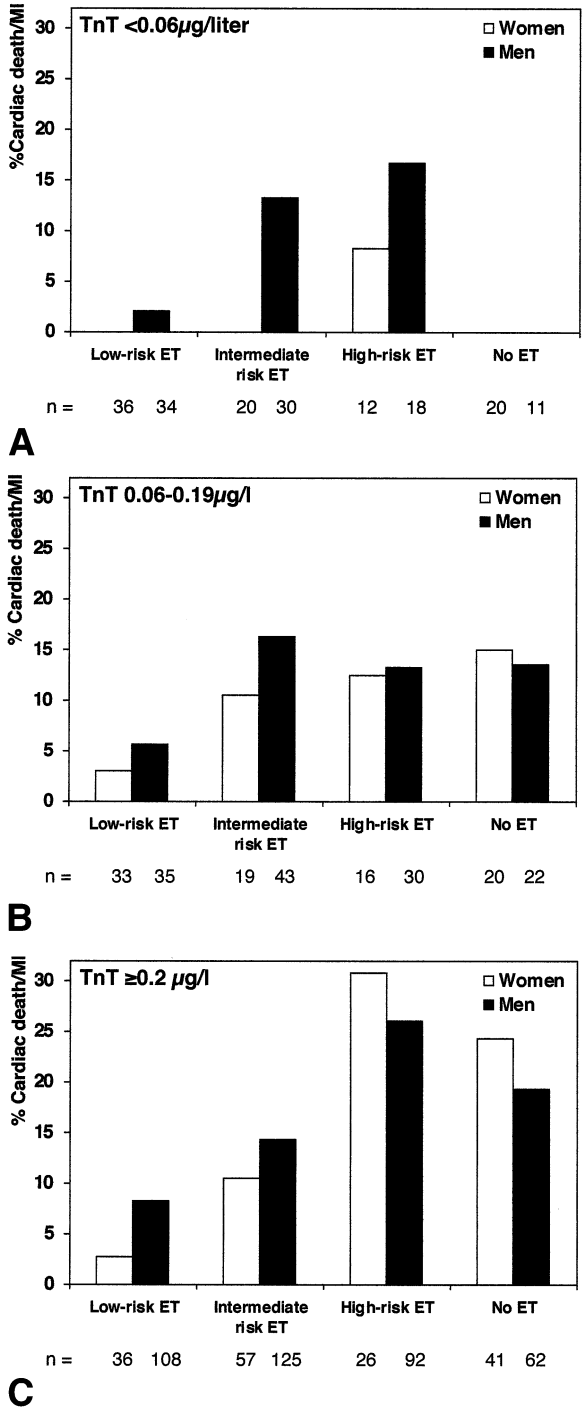

Figure 3. (A–C) Six-month risk for cardiac death or myocardial infarction (MI) in relation to maximal troponin T levels during the first 24 h and exercise test response. No ET = No exercise test group. Patients with events before performed or planned ET are excluded.

the non-ET group compared to the ET group (17% vs. 12% with TnT >3.0 μg/liter), this again indicating a sicker patient group. As the majority of the patients had TnT levels exceeding the decision level for MI, TnT seems to be a poor sole-selection criteria for high-risk patients in this type of population of unstable CAD patients admitted to hospital with ST-T-changes on the resting ECG. It was not possible to find a real low-risk group among men (event rate 9%), in contrast to women (1%), again reflecting the differences between the sexes even in such a seemingly homogeneous population as in our study.

Combination of exercise test and troponin T. Combining the results from the ET and the TnT values we found it possible to find a small low-risk group even among men, with an event rate of 3% (n = 1) during follow-up. The combination also revealed a small population with a high risk (31% and 26% events in women and men, respectively). The major part of the population, however, consisted of patients with an intermediate risk where we do not, as yet, have a satisfactory risk indicator.

Gender differences. Both tests enabled identification of low-, intermediate-, and high-risk groups regarding cardiac death in both women and men. Both intermediate-risk and high-risk groups identified by ET or TnT regarding cardiac death or MI also had similar female and male event rates. Among men, however, there were difficulties in identifying a true low-risk group regarding the combined end point cardiac death or MI. Only when combining the ET and TnT values was it possible to identify a group with a relatively low risk (3%). This group, however, was small (n = 34), indicating that the men constituted a relatively homogeneous high-risk population. Among the women it was possible to identify a low-risk group with either ET or TnT. When combining the two methods we were able to identify a group with no death or MI during follow-up. These results indicate a healthier female population.

In contrast, the women were older, more often had previous congestive heart disease, and used more diuretics, three well-known indicators of a worse prognosis. Furthermore, the intermediate- and high-risk groups identified by either TnT or the ET had similar event rates among women and men. The female population therefore seems to be more heterogeneous than the male population, most probably due to a higher proportion of female patients with no or less serious atherosclerosis in their coronary arteries, as is usually the case when comparing female populations with CAD to similar male populations (24,25).

Thus, it seems that the criteria used to identify unstable CAD patients in this study (history of angina and ST-T changes on the ECG taken while at rest) correctly identify a high-risk population among men, while the specificity among women is somewhat lower. In men it can be discussed whether or not further risk stratification is justified. In the female population, however, risk stratification with TnT and an early symptom-limited ET can identify a low-risk group, and these women can be assured of a good prognosis. With the development of more sensitive TnT tests with better discrimination of the very low values it might be possible to improve the value of this test for risk stratification among both men and women.

Table 5. Univariate and Multivariate Logistic Regression Analysis of Clinical, ECG, and Laboratory Parameters in Relation to Myocardial Infarction and Cardiac Death During a Six-Month Follow-up Period

	Men (n = 610)		Women (n = 336)	
	Univariate p	Multivariate p	Univariate p	Multivariate p
Clinical				
Age	<0.02	NS	<0.04	NS
Diabetes	NS	NS	NS	NS
Current smoking	NS	NS	NS	NS
Previous CHF	NS	NS	NS	NS
Hypertension	NS	<0.04	<0.04	NS
Previous MI	NS	NS	NS	NS
Non-Q-wave MI at inclusion	NS	NS	<0.04	NS
Number of antianginal drugs* at ET	NS	NS	<0.002	<0.006
Exercise test (low-; intermediate-; high-risk/no ET)	<0.0003	<0.0003	<0.0002	<0.002
Troponin T (<0.06; 0.06–0.19; >0.2 μg/liter)	<0.05	<0.05	<0.001	<0.002

Patients that left blood samples for troponin T measurements are included in the analysis. Seventeen patients that had an event before performed or planned exercise test were excluded. CHF = congestive heart failure; ET = exercise test; MI = myocardial infarction. *Beta-blocker, calcium inhibitor, and/or prophylactic nitrates.

Study limitations. The study population consisted of men and women with a high probability of CAD. The results may not be applicable to patient populations with low pretest probability such as patients with chest pain syndromes at large and no changes on the ECG taken while at rest.

Conclusions. We found that male and female patients who were not able to perform the early ET constituted a high-risk group. In the intermediate- and high-risk groups defined by ET results or TnT, both women and men had the same high event rate of death or MI. We found women on the whole to be older, with more previous cardiovascular disease but paradoxically with less ischemia and fewer coronary events. This paradox was easier to understand as we found it possible to identify women with very little risk for a coronary event. This was possible with both the ET and TnT levels and especially a combination of these indicating that the female population was more heterogeneous, with a higher proportion of patients with no or mild CAD. Among the men, only the combination of ET and TnT could identify a group with a low risk for subsequent death or MI, possibly because of a higher likelihood of disease. By this direct comparison between men and women from the same population with a high pretest likelihood of disease, it is possible to conclude that both TnT and the early ET are at least as useful as prognostic risk indicators in women as they are in men.

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