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Is Early Invasive Treatment of Unstable Coronary Artery Disease Equally Effective for Both Women and Men?

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BACKGROUND The Fragmin and fast Revascularization during InStability in Coronary artery disease (FRISC II) trial compared the effectiveness of an early invasive versus a noninvasive strategy in terms of the incidence of death and myocardial infarction (MI) in patients with unstable coronary artery disease (CAD).

OBJECTIVES In this subanalysis, we sought to evaluate gender differences in the effect of these different strategies.

METHODS The patients (749 women and 1,708 men) were randomized to early invasive or noninvasive strategies. Coronary angiography was performed within the first 7 days in 96% and 10% of the invasive and noninvasive groups, respectively, and revascularization was performed within the first 10 days in 71% and 9% of the invasive and noninvasive groups, respectively.

RESULTS Women presenting with unstable CAD were older, but fewer had previous infarctions, left ventricular dysfunction and elevated troponin T levels. Women had fewer angiographic changes. There was no difference in MI or death at 12 months among women in the invasive and noninvasive groups (12.4% vs. 10.5%, respectively), in contrast to the favorable effect in the invasively treated group of men (9.6% vs. 15.8%, $p < 0.001$). In an interaction analysis, there was a different effect of the early invasive strategy for the two genders ($p = 0.008$).

CONCLUSIONS Women with symptoms and/or signs of unstable CAD are older, but still have less severe CAD and a better prognosis compared with men. In contrast to its beneficial effect in men, an early invasive strategy did not reduce the risk of future events among women. Further research is warranted to identify the most appropriate treatment strategy in women with unstable CAD. (J Am Coll Cardiol 2001;38:41–8) © 2001 by the American College of Cardiology

The attitudes, treatment methods and rehabilitation goals of doctors differ with respect to men and women, and in recent years, several centers have reported gender differences in the diagnosis and medical treatment of cardiovascular disease, to the detriment of women (1–4). In part, the less aggressive treatment of women's disease can be explained by the results from early studies (5–9) of coronary artery bypass graft surgery (CABG), which showed a markedly increased risk of death among women. Later studies of CABG have shown a higher preoperative mortality among women (10), although the long-term results have been comparatively similar between the genders (8). Female gender is also a known risk factor for mortality and morbidity in relation to a percutaneous coronary intervention (PCI) (11–13). This has been partly explained by women's older age, cardiac failure, severe vascular disease, smaller coronary arteries, and so forth. The long-term results of PCI during this period, however, have been equal to those displayed by men (13–18). In the Fragmin and fast Revascularization during InStability in Coronary artery disease (FRISC II) invasive trial, an early invasive strategy was compared with a noninvasive strategy in patients with unstable coronary artery disease (CAD) treated with optimal antithrombotic medication. The trial showed the superiority of the invasive strategy over the more conservative approach. However, in predefined subgroups, there was a significant interaction between female gender and the invasive strategy (14).

The aim of the present analysis of the FRISC II is to compare men and women with unstable CAD in terms of their clinical variables at hospital admission, coronary anatomy, events during follow-up and outcome of the randomized invasive strategy compared with the noninvasive strategy.

METHODS

The FRISC II study was a prospective, randomized, multicenter trial with parallel groups. The invasive versus noninvasive comparison was carried out in a factorial design. Half of the patients within each group were randomized to receive continued treatment with subcutaneous dalteparin or

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Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
CK-MB = creatine kinase-MB isoenzyme
FRISC = Fragmin and fast Revascularization during InStability in Coronary artery disease study
LMCA = left main coronary artery
MI = myocardial infarction
PCI = percutaneous coronary intervention

placebo for three months. All patients received open-label dalteparin treatment for at least five days and always until the invasive procedure. The comparison of the invasive versus noninvasive strategies was open. Patients meeting the entry criteria were randomized, and stratified by center, to one of four treatment regimens as soon as possible after hospital admission, but at the latest within 72 h after the start of open-label dalteparin (or standard heparin) administration. The treatment groups included: 1) the invasive strategy and extended treatment with dalteparin; 2) the invasive strategy and long-term placebo; 3) the noninvasive strategy and extended treatment with dalteparin; and 4) the noninvasive strategy and long-term placebo. In the invasive strategy, the target was to perform all invasive procedures *within seven days* after starting open-label dalteparin.

Patients. Patients were eligible for inclusion if they had symptoms of ischemia that were increasing or occurring at rest or if they had symptoms warranting suspicion of acute myocardial infarction (MI), with the last episode preceding the first dose of dalteparin or standard heparin by <48 h. Furthermore, myocardial ischemia had to be verified by electrocardiography (ST segment depression ≥0.1 mV or T-wave inversion ≥0.1 mV) or by elevation of biochemical markers: creatine kinase-MB isoenzyme (CK-MB) >6 μg/l, troponin T >0.10 μg/l, qualitative test for troponin T as positive or catalytic activity of CK, CK-B or CK-MB above the local decision limit for the diagnosis of MI. The details of exclusion criteria, the follow-up procedure and concomitant therapies are described in previous reports (15,16).

The study complied with the Declaration of Helsinki, and all local ethics committees approved the protocol. Written, informed consent was received from all patients.

Interventional strategies. The invasive strategy required coronary angiography within a few days of enrollment, aiming for revascularization within seven days of starting open-label dalteparin (or standard heparin). Revascularization was recommended for all patients with ≥70% diameter obstruction in any artery supplying a significant proportion of the myocardium. If there were one or two target lesions, PCI was recommended, whereas CABG was preferred in patients with three-vessel or left main coronary artery (LMCA) disease.

The noninvasive strategy included coronary angiography in patients with refractory or recurrent symptoms, despite maximal medical treatment or severe ischemia on a predischarge symptom-limited exercise test (15). During long-term follow-up, invasive procedures were considered, regardless of randomized strategy, for all patients with incapacitating symptoms, recurrence of instability or MI.

In accordance with these guidelines, coronary angiography was performed within the first 7 days in 96% of the invasive group and in 10% of the noninvasive group, and revascularization was performed within the first 10 days in 71% and 9% of the invasive and noninvasive groups, respectively.

Statistical analysis. Statistical analysis was performed on an intention-to-treat basis. Comparison of continuous variables was performed using the unpaired *t* test. The Mantel-Haenszel chi-square test was used to test the significance between the two strategy groups. Efficacy analyses were based on point estimates of events occurring from the start of open-label dalteparin treatment until 12 months and included only patients with an adjudicated event or with recorded absence of the evaluated event until at least day 335 of follow-up. The probability curves were constructed using the Kaplan-Meier method. Multivariate logistic regression analysis was performed to evaluate the effect of gender as an independent prognostic factor relating to the predefined combined end points of MI and death. In our model, we adjusted for the following clinical variables: age, diabetes, medically treated hypertension, smoking, history of angina pectoris for at least three months, previous MI, ST segment depression at hospital admission, troponin T ≥0.10 μg/l at admission and randomized long-term (three months) treatment with either low-molecular weight heparin (dalteparin) or placebo. When the model was used on the entire data (i.e., both strategy groups), then the randomized strategy (invasive or noninvasive) and the interaction variable of gender-strategy were included in the statistical model. In the invasive strategy group, a second multivariate analysis was performed when the presence or absence of angiographically significant stenosis was adjusted for. In all tests, $p < 0.05$ was considered statistically significant. The coordinating investigators performed data processing and statistical analyses using the SPSS version 10.0.5 statistical program for personal computers (SPSS, Inc., Chicago, Illinois).

RESULTS

Baseline characteristics and gender. There were 749 women and 1,708 men in the study. The distribution of all patients in relation to strategy, gender and revascularization is presented in Figure 1. The women were older than the men, and there were also some gender differences in the risk factors and in the medications at admission (Table 1). More women had previous angina treated with anti-anginal medication, and more men had previous MI and pathologic Q-waves at admission. Fewer women had left ventricular dysfunction and elevated troponin T levels. At admission, there was no difference in the rate of ST segment depression

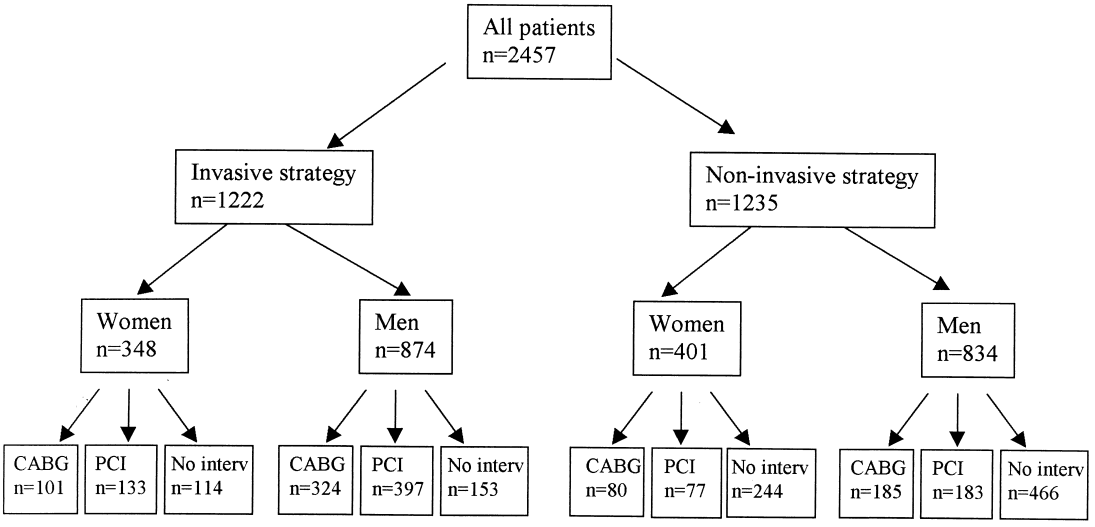

Figure 1. The number of patients in relation to randomized strategy, gender and first intervention. CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention.

between women and men; however, T-wave inversion was seen more often in women. There were only minor differences in baseline characteristics between the two strategy groups within the genders. Women in the invasive strategy group had more Canadian Cardiovascular Society (CCS) class III/IV angina (35%), compared with women in the noninvasive group (26%) ($p = 0.008$). There were no other gender-related differences in the baseline variables between the invasive and noninvasive groups.

There were more patients without significant coronary stenosis ($p < 0.001$) among the women. Men had more severe and extended coronary disease: LMCA disease and three- or two-vessel disease with proximal left anterior descending coronary artery stenosis was more prevalent in men ($p = 0.001$) (Table 2).

There were several specific differences in the clinical profile of patients recommended for CABG (Table 3). Female patients who underwent CABG in the invasive group had more previous MI and diabetes mellitus compared with women in the PCI and noninvasive groups; this was not the case with men (Table 3).

Noninvasive group: gender differences in outcome. In the noninvasive group, coronary angiography was performed in 52% of both women and men during the first 12 months (p = NS). There was no difference between the genders in terms of the overall frequency of the intervention or in selection of the type of intervention. In the noninvasive strategy group, the incidence of MI and of the combined end point of death or MI was significantly less in women than in men during 12 months of follow-up (Table 4). In

Table 1. Baseline Characteristics

Variable	Women (n = 749)	Men (n = 1,708)	Total (n = 2,457)	p Value
Age (mean ± SD, yrs)	68 ± 8	64 ± 10	65 ± 9	<0.001
Coronary risk factors (%)				
Hypertension	36	28	30	<0.001
Cholesterol >5.5 mmol/l	68	53	58	<0.001
Current smoker	29	31	30	NS
Diabetes mellitus	11	13	12	NS
Previous and current cardiac disease (%)				
Previous MI	18	24	22	0.001
Angina history >48 h	72	67	68	0.015
CCS angina class III/IV	31	30	30	NS
Chest pain at rest	83	80	81	NS
Troponin T ≥0.1 μg/l	47	62	58	<0.001
LVEF <45%	9	14	13	0.002
Medication at admission (%)				
Acetylsalicylic acid	35	36	35	NS
Beta-blocker	37	30	32	0.001
ACE inhibitor	13	12	12	NS
Calcium antagonist	19	17	18	NS
Long-acting nitrate	25	11	15	<0.001
Diuretic	22	18	19	0.017
Statin	10	10	10	NS
ECG at admission (%)				
ST segment depression at entry	49	45	46	NS
T-wave inversion	72	64	66	<0.001
Pathologic Q-waves	14	20	18	0.001

ACE = angiotensin-converting enzyme; CCS = Canadian Cardiovascular Society; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NS = not significant.

Table 2. Gender Distribution in Severity of Coronary Artery Disease in Patients Randomized to the Invasive Strategy

	Women	Men
None	85 (24.6%)	81 (9.5%)
One-vessel disease	110 (31.9%)	239 (28.0%)
Two-vessel disease	54 (15.7%)	240 (28.1%)
Three-vessel disease	72 (20.9%)	225 (26.3%)
LMCA disease	24 (7.0%)	70 (8.2%)
LMCA/three-vessel disease/ two-vessel disease with proximal LAD stenosis	111 (32.2%)	368 (43.0%)

LAD = left anterior descending coronary artery; LMCA = left main coronary artery.

Table 3. Some Background and Clinical Variables of the Different Strategy Groups

	Women					
	CABG			PCI		
	Invasive (n = 101)	Noninvasive (n = 80)	p Value	Invasive (n = 133)	Noninvasive (n = 77)	p Value
Age (yrs)	70	68	NS	66	65	NS
Days to angiography	4	30	<0.001	4	42	<0.001
Days to revascularization	8	50	<0.001	5	52	<0.001
Diabetes (%)	26	13	0.027	6	9	NS
Previous MI (%)	37	14	0.001	11	13	NS
Smoker (%)	21	38	0.013	37	33	NS
Three-vessel disease/LMCA disease (%)	78	76	NS	8	8	NS
	Men					
	CABG			PCI		
	Invasive (n = 324)	Noninvasive (n = 185)	p Value	Invasive (n = 397)	Noninvasive (n = 183)	p Value
Age (yrs)	67	65	NS	62	61	NS
Days to angiography	4	41	<0.001	4	40	<0.001
Days to revascularization	9	58	<0.001	4	50	<0.001
Diabetes (%)	12	16	NS	14	10	NS
Previous MI (%)	34	36	NS	18	18	NS
Smoker (%)	25	23	NS	35	39	NS
Three-vessel disease/LMCA disease (%)	77	75	NS	9	16	0.021

CABG = coronary artery by pass graft surgery; LMCA = left main coronary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention.

the multivariate analysis of the noninvasive group (Table 5), male gender was found to be an independent risk factor for death or MI at 12 months.

Invasive group: gender differences in outcome. In the invasive strategy group, 98% of men and 99% of women underwent coronary angiography. The median time from admission to coronary angiography was four days. The results of these coronary angiograms are presented in Table 2. There were fewer interventions in the female group (n = 234 [67%]) than in the male group (n = 721 [82%], p < 0.001), but among those who were revascularized, there were no significant differences in the choice of procedure

The outcomes are shown in Table 6. There was a trend toward a more severe outcome in the female group, but the difference was not statistically significant.

In the multivariate analysis (Table 5), gender was not found to be an independent risk factor when adjusting for the same clinical and baseline variables as in the noninvasive group. However, if the presence or absence of significant stenosis after angiography was also included in the statistical model, female gender was found to be an independent risk factor for death or MI.

Outcomes of different types of coronary intervention in relation to gender (invasive group). Percutaneous coronary intervention was the first and, in most cases, the only intervention in 530 patients (43%; 133 women and 397 men) during follow-up. The corresponding number of patients who had CABG was 425 (35%; 101 women and 324 men). In 267 patients (22%; 114 women and 153 men), no intervention was performed.

There was no difference in outcome between the two genders if the first procedure was a PCI or if no intervention was performed. After CABG, there was a significantly worse outcome at 12 months in women compared with men (Table 7).

All patients: outcomes and interaction. Four patients, at their request, were lost to follow-up. The total mortality rate

Table 4. First Revascularization Procedure and Outcome at 12 Months of Follow-Up in the Group Randomized to the Noninvasive Strategy According to Gender

	Women (n = 401)	Men (n = 834)	p Value
Intervention	157 (39%)	368 (44%)	NS
PCI	77 (19%)	183 (22%)	NS
CABG	80 (20%)	185 (22%)	NS
Death	13 (3.2%)	35 (4.2%)	NS
MI	34 (8.5%)	109 (13.1%)	0.019
Death/MI	42 (10.5%)	132 (15.8%)	0.005

Abbreviations as in Table 3.

Table 5. Effect of Female Gender on Death or Myocardial Infarction at 12 Months

Group Tested*	OR	95% CI	p Value
Noninvasive strategy group	0.64	0.43–0.97	0.034
Invasive strategy group	1.46	0.96–2.23	NS
Invasive strategy group, also adjusted for presence of coronary stenosis	1.72	1.11–2.65	0.014
All patients, also adjusted for strategy (invasive/noninvasive)	0.91	0.68–1.22	NS

*Multivariate analysis using a logistic regression model adjusting for age, diabetes, hypertensive medical treatment, smoking, history of angina pectoris (>3 months), previous myocardial infarction, ST segment depression at admission, troponin T >0.1 μg/liter and randomized long-term (3 months) dalteparin/placebo treatment.

CI = confidence interval; OR = odds ratio.

Table 6. Outcomes at 12 Months in the Group Randomized to the Early Invasive Strategy With Respect to Gender

	Women (n = 348)	Men (n = 874)	p Value
Death	14 (4.0%)	13 (1.5%)	NS
MI	32 (9.2%)	73 (8.4%)	NS
Death/MI	43 (12.4%)	84 (9.6%)	NS

MI = myocardial infarction.

at 12 months of follow-up was 3.1% (3.6% for women and 2.8% for men, p = NS). The procedure-related mortality rate was, according to the End Points Committee, 0.3% in men and 1.8% in women (p = 0.002).

The event rates for women and men according to strategy group are presented in Figure 2A and B.

In the multivariate analysis of all patients, adjustment for the randomized strategy and for the same variables as in the noninvasive strategy group was made. Gender was not found to be an independent risk factor for death or MI (Table 5). An interaction analysis was performed with introduction of the interaction variable of gender-strategy. In the model, this interaction variable was significant (p = 0.008), indicating a different response to the early invasive strategy in men and women.

DISCUSSION

In the FRISC II study, we found that women and men differed with respect to several clinical characteristics. The women were older and had more hypertension, hypercholesterolemia and a higher rate of previous angina, but fewer of them experienced a previous or index MI compared with men. Women had a higher frequency of angiographically normal coronary arteries and, among those with significant coronary lesions, a lower rate of two- or three-vessel disease compared with men, which is a common phenomenon in mixed-gender study groups of patients with ischemic heart disease (17–23). It could be expected that this difference should have been less in this group of patients, where all of the women were older and postmenopausal and all patients had ischemic electrocardiographic changes or raised biochemical markers of MI, or both. However, T-wave inversion, without elevation of biochemical markers, was more commonly seen in the female group. This is known to be less specific for CAD than ST segment changes or elevation of biochemical markers (24). Therefore, despite the same inclusion criteria, the female cohort represented a lower risk group with no or single-vessel disease in the majority of cases (56%); hence, they had little to gain from invasive procedures with the inherent risks of side effects.

Noninvasive strategy arm. Fewer interventions were made in women, because more women had normal coronary arteries or single-vessel disease. It is well known that patients without significant stenosis or single-vessel disease have a lower event rate compared with patients with significant two- or three-vessel disease or LMCA stenosis. In the present study, patients with no coronary stenosis had an excellent prognosis, with no deaths occurring during the 12-month follow-up period. Thus, the lower event rate seen in the noninvasive female group versus the noninvasive male group could be explained, to a large extent, by a greater proportion of patients with normal coronary angiograms among women. To illustrate this, the following calculation was performed. The rate of normal coronary angiograms and the prognosis in this group of patients were supposed to be the same in the noninvasive as in the invasive strategy group both for men and women. The presumed number of patients without coronary stenosis was excluded from the calculation. In the rest of the noninvasive group, the rate of death or MI within 12 months was calculated to 13.2% in women and 16.4% in men (p = 0.186, risk ratio 0.80, 95% confidence interval 0.58 to 1.11). Thus, after this calculated compensation for the lower prevalence of significant CAD among women, there was no actual gender difference in prognosis in the noninvasive strategy arm.

Table 7. Outcomes at 12 Months of Follow-Up in Women and Men Randomized to the Early Invasive Strategy in Relation to the Type of First Coronary Intervention

Event	Women/Men n	Women n (%)	Men n (%)	p Value	RR (95% CI)
Death					
Intervention					
CABG	101/324	10 (9.9%)	4 (1.2%)	<0.001	8.79 (2.69–28.7)
PCI	133/397	2 (1.5%)	4 (1.0%)	NS	1.50 (0.27–8.28)
No intervention	114/153	2 (1.8%)	5 (3.3%)	NS	0.53 (0.10–2.80)
MI					
Intervention					
CABG	100/322	12 (12.0%)	16 (5.0%)	<0.014	2.61 (1.19–5.72)
PCI	133/397	18 (13.5%)	54 (13.6%)	NS	0.99 (0.56–1.77)
No intervention	114/153	2 (1.8%)	3 (2.0%)	NS	0.89 (0.15–5.43)
Death/MI					
Intervention					
CABG	100/322	19 (19.0%)	19 (5.9%)	<0.001	3.74 (1.89–7.40)
PCI	133/397	20 (15.0%)	58 (14.6%)	NS	1.03 (0.60–1.80)
No intervention	114/153	4 (3.5%)	7 (4.6%)	NS	0.76 (0.22–2.66)

CI = confidence interval; RR = risk ratio; other abbreviations as in Table 3.

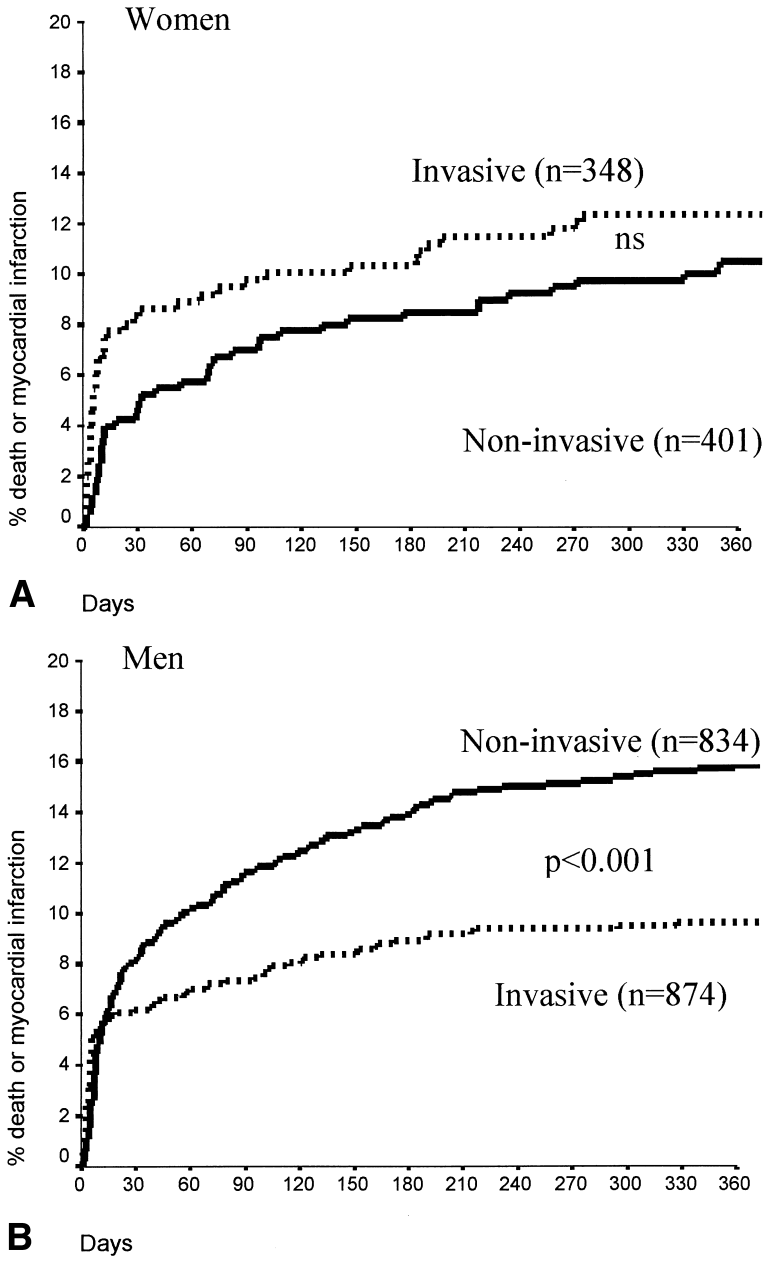

Figure 2. Cumulative probability of death or myocardial infarction during 12-month follow-up in **(A)** women and **(B)** men in relation to randomized strategy (**solid line** = noninvasive strategy; **dotted line** = early invasive strategy). ns = not significant.

Invasive strategy arm. In the invasive group, there was no gender difference. One reason for this finding could be the higher procedure-related mortality in association with CABG among women. These findings are in accordance with the earlier randomized studies in which CABG-related mortality was higher among women (9,21). This is also in accordance with the Thrombolysis In Myocardial Infarction (TIMI IIIB) substudy in which the 42-day mortality rate tended to be higher in operated-on women (8.5%) than in operated-on men (2.2%) ($p = 0.05$) (18). However, subsequent larger scale studies have, to some degree, rejected these findings and have shown that the gender difference can be explained, to a large extent, by differences in comorbidities and other confounding factors (10,25). This explanation might also be the main reason for the outcome of CABG in the present trial, where women who underwent CABG were older and more often diabetic than men.

Thus, it is possible to speculate that the higher procedure-related mortality in women was due to the fact that CABG-treated women formed an especially high-risk group at surgery because of age, diabetes and more frequent previous MIs. It should also be observed that mortality in the CABG-treated men in the invasive arm was surprisingly low and not different from that in the PCI-treated cohort,

despite considerable differences in risk factors between these groups. Thus, it cannot be excluded that the gender difference in CABG-related mortality in the invasive group was, to a large extent, a play of chance and that the overall mortality among the CABG-treated patients was the most representative procedure-related risk, regardless of gender.

Multivariate analysis. In the multivariate analysis, there was a clear gender-strategy interaction, even when taking into consideration confounding factors. The interaction analysis showed a different effect of the early invasive strategy for the two genders. Thus, in the present trial, women did not benefit from an early invasive strategy when they had unstable CAD, in contrast to men. This is partly attributable to a higher CABG-related mortality in women. However, subgroup analysis of the effect of the different types of intervention was not predefined in the FRISC II study. Furthermore, selection of the invasive procedure (PCI vs. CABG) was based on a "clinical decision" and not on randomization. This could have resulted in a concentration of high risk factors in women chosen for surgery. Consequently, it is important to be very cautious with the interpretation of these findings. The final evaluation of the efficacy of an early invasive strategy in women with unstable CAD will have to await the long-term follow-up of the present trial and the outcome of other ongoing trials on the same subject.

Study limitations. This study is based on a predefined substudy of the FRISC II invasive trial, analyzing gender differences. The numbers are too small and not powered enough to draw final conclusions, but they can be used to generate a hypothesis. As in the main study, all eligible patients were not included due to exclusion criteria, which is a limitation of all clinical trials. For definite knowledge, it is necessary to conduct a trial with enough power to detect differences in the early invasive treatment of women with unstable CAD.

Conclusions. We found that women in the FRISC II study had less advantage of an early invasive strategy, compared with men. The results emphasize that women with symptoms and/or signs of unstable CAD have less advanced atherosclerosis and a better prognosis, but often have important comorbidities associated with an increased invasive procedure-related risk. Therefore, despite demonstrating similar symptoms and signs of unstable CAD, women have less to gain from an early invasive strategy, at least in the short term. Thus, further research is warranted to identify women who are likely to benefit from or be harmed by an early invasive approach.

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