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Early Invasive vs Conservative Treatment Strategies in Women and Men With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction

A Meta-analysis

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ALTHOUGH AN INVASIVE STRATEGY is frequently used in patients with unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI), data from some trials suggest that this strategy may not benefit women. Despite an overall benefit for patients randomized to an invasive strategy in the FRISC II (Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease) and the RITA 3 (Randomized Intervention Trial of Unstable Angina) trials,¹⁻³ subgroup analyses from these studies showed that an invasive strategy may be associated with a higher risk of death or MI in wom-

See also Patient Page.

Context Although an invasive strategy is frequently used in patients with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS), data from some trials suggest that this strategy may not benefit women.

Objective To conduct a meta-analysis of randomized trials to compare the effects of an invasive vs conservative strategy in women and men with NSTEMI ACS.

Data Sources Trials were identified through a computerized literature search of the MEDLINE and Cochrane databases (1970-April 2008) using the search terms *invasive strategy, conservative strategy, selective invasive strategy, acute coronary syndromes, non-ST-elevation myocardial infarction, and unstable angina*.

Study Selection Randomized clinical trials comparing an invasive vs conservative treatment strategy in patients with NSTEMI ACS.

Data Extraction The principal investigators for each trial provided the sex-specific incidences of death, myocardial infarction (MI), and rehospitalization with ACS through 12 months of follow-up.

Data Synthesis Data were combined across 8 trials (3075 women and 7075 men). The odds ratio (OR) for the composite of death, MI, or ACS for invasive vs conservative strategy in women was 0.81 (95% confidence interval [CI], 0.65-1.01; 21.1% vs 25.0%) and in men was 0.73 (95% CI, 0.55-0.98; 21.2% vs 26.3%) without significant heterogeneity between sexes (P for interaction = .26). Among biomarker-positive women, an invasive strategy was associated with a 33% lower odds of death, MI, or ACS (OR, 0.67; 95% CI, 0.50-0.88) and a nonsignificant 23% lower odds of death or MI (OR, 0.77; 95% CI, 0.47-1.25). In contrast, an invasive strategy was not associated with a significant reduction in the triple composite end point in biomarker-negative women (OR, 0.94; 95% CI, 0.61-1.44; P for interaction = .36) and was associated with a nonsignificant 35% higher odds of death or MI (OR, 1.35; 95% CI, 0.78-2.35; P for interaction = .08). Among men, the OR for death, MI, or ACS was 0.56 (95% CI, 0.46-0.67) if biomarker-positive and 0.72 (95% CI, 0.51-1.01) if biomarker-negative (P for interaction = .09).

Conclusions In NSTEMI ACS, an invasive strategy has a comparable benefit in men and high-risk women for reducing the composite end point of death, MI, or rehospitalization with ACS. In contrast, our data provide evidence supporting the new guideline recommendation for a conservative strategy in low-risk women.

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en.^{4,5} In contrast, an early invasive strategy was associated with improved outcomes in both men and women in the TACTICS-TIMI 18 (Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18) trial,⁶ with particular benefit observed in high-risk women identified by an elevated serum troponin. Thus, the benefit of an invasive strategy in women remains unclear. However, individual trials have not been large enough to explore outcomes reliably within subgroups. For this reason, we conducted a collaborative meta-analysis of randomized trials to examine the benefits and risks of an invasive strategy in women vs in men with non-ST-segment elevation acute coronary syndromes (NSTEMI ACS).

METHODS

Data Sources

A computerized literature search was conducted from 1970 through April 2008 of the MEDLINE and Cochrane databases by using search terms that included *invasive strategy*, *conservative strategy*, *selective invasive strategy*, *acute coronary syndromes*, *non-ST-elevation myocardial infarction*, and *unstable angina*. No other search restrictions were applied. In addition, we contacted experts in the field and hand-reviewed abstracts from major cardiology meetings.

Study Selection Criteria

Trials considered for inclusion were those that enrolled individuals with a diagnosis of NSTEMI ACS (unstable angina or NSTEMI) and randomized patients to either an invasive or conservative treatment strategy. An invasive strategy was defined as the referral of all patients with NSTEMI ACS for coronary angiography followed by revascularization if deemed appropriate. A conservative treatment strategy was defined as a primary strategy of pharmacological management and subsequent coronary angiography reserved only for those patients with recurrent symptoms of unprovoked ischemia or ob-

jective evidence of inducible ischemia on noninvasive testing.

Trials were excluded from participation if they primarily enrolled patients with stable angina or acute ST-segment elevation myocardial infarction (STEMI). Trials were excluded if data were not previously peer-reviewed, fibrinolytic therapy was to be administered in all patients, inadequate randomization was performed, coronary angiography was required before patient enrollment, or reliable sex-specific outcome data were unavailable.

End Points and Data Extraction

The principal investigators (W.E.B., E.B., C.P.C., R.J.W., K.A.A.F., P.A.M., R.S., L.W.) for each participating trial provided the sex-specific incidence of death, nonfatal MI, and rehospitalization with ACS, and the composites of these end points. Outcomes were collected from (1) randomization to hospital discharge, (2) hospital discharge to the end of 12 months of follow-up, and (3) randomization to the end of 12 months of follow-up. For the TACTICS-TIMI 18 trial,⁷ follow-up data were available through 6 months of follow-up. Outcomes were also substratified by the presence or absence of cardiac biomarker elevation (creatinine kinase MB or troponin) and ST-segment deviation on electrocardiogram. Patients without available biomarker or ST-segment deviation data were excluded from the respective high-risk subgroup analyses. Outcomes were collected for patients in each treatment group who ultimately underwent percutaneous coronary intervention or coronary artery bypass graft (CABG) surgery.

For the purpose of the current meta-analysis, nonfatal MI (both procedure-related and non-procedure-related) and rehospitalization with ACS were defined as reported in each of the individual trials. In addition, as per their original manuscript, the investigators from the ICTUS (Invasive vs Conservative Treatment in Unstable Coronary Syndromes) trial⁸ provided inci-

dence rates for nonfatal MI by applying the definitions of MI as used in the TACTICS-TIMI 18 and FRISC II trials.^{1,7}

For patients randomized to an invasive strategy, data were collected on the extent of coronary artery disease (CAD) at the time of coronary angiography. A diseased vessel was defined as a major epicardial vessel or CABG with at least 50% stenosis. In the ICTUS trial,⁸ data were provided for at least 70% stenosis in a major epicardial vessel or CABG.

All of the collected data were verified by each of the participating investigators (W.E.B., E.B., C.P.C., R.J.W., K.A.A.F., P.A.M., R.S., L.W.). When required, participating investigators performed new analyses to generate tabular data from the original trials.

Statistical Analyses

A meta-analysis was performed of the relative odds for each trial, both overall and stratified by sex, and based on random-effects models using the method by Der Simonian and Laird.⁹ Results are presented as odds ratios (ORs), with their 95% confidence intervals (CIs). Event rates for each trial individually and the pooled data are presented as frequencies. Heterogeneity between sex and between high-risk subgroups was assessed by calculating the OR for the interaction term between treatment strategy and subgroup for each individual trial, combining these ORs in random-effects models, and calculating *P* values for the combined interaction effect. For the biomarker analyses, the meta-analysis was restricted to those 5 trials that enrolled patients both with and without biomarker elevation (TIMI IIIB [Thrombolysis in Myocardial Infarction],¹⁰ MATE [Medicine vs Angiography in Thrombolytic Exclusion],¹¹ FRISC II,¹ TACTICS-TIMI 18,⁷ RITA 3²) to enable us to examine the relative benefit of each strategy across these subgroups.

With the available sample size and event rates, our meta-analysis had 80% power to detect a 33% difference in the relative odds of death, MI, or rehospitalization with ACS in the

invasive vs conservative groups between men and women. Corrections were not made for multiple hypothesis testing given the exploratory nature of the analyses. All statistical analyses were performed by using Stata/SE version 9.0 (StataCorp, College Station, Texas). All tests were 2-sided, with $P < .05$ considered significant.

RESULTS

A total of 18 randomized clinical trials were identified through literature review (FIGURE 1).^{1,2,7,8,10-23} Of these trials, 10 trials were subsequently excluded from participation because fibrinolytic therapy was to be administered in all patients in 2 trials,^{15,17} coronary angiography was required before enrollment in 4 trials,^{12-14,16} patients were enrolled with stable angina in 1 trial,²¹ patients were randomized based on the day of the week in 1 trial,¹⁹ patients were referred in both treatment groups to undergo coronary angiography within 5 days of randomization in 1 trial,²² and 1 trial had not yet been peer-reviewed and published.²³ A total of 8 remaining trials were determined to be eligible and were invited to collaborate (TABLE 1).^{1,2,7,8,10,11,18,20} Of the 8 invited trials, all the principal investigators agreed to participate in a collaborative meta-analysis and contributed sex-specific outcome data in tabular format.

Glycoprotein IIb/IIIa inhibitors were available for use in 4 of the 8 trials^{1,2,7,8} and were required per-protocol in the TACTICS-TIMI 18 trial.⁷ In the ICTUS trial,⁸ all patients who underwent an interventional procedure during the index hospitalization were to be administered a glycoprotein IIb/IIIa inhibitor. All patients in the VANQWISH (Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital),¹⁸ VINO (Value of First Day Angiography/Angioplasty In Evolving Non-ST Segment Elevation Myocardial Infarction),²⁰ and ICTUS⁸ trials required cardiac biomarker elevation to be eligible for trial enrollment. In the FRISC II trial,¹ data

on rehospitalization with ACS were available in patients enrolled in Denmark and Sweden, representing 97% of the study population.

Baseline Characteristics

These trials enrolled a total of 10 412 patients; sex-specific baseline characteristics are displayed in TABLE 2. Across all trials, the weighted mean age of patients was 64.1 years in women and 61.3 years in men. Women were significantly more likely to have baseline comorbidities, including diabetes mellitus, hypertension, and hyperlipidemia. Men were significantly more

likely to be active smokers and have a prior history of MI. The incidence of ST-segment depression was similar in both men and women; however, women were significantly more likely to have evidence of T-wave inversions on electrocardiogram. Men were significantly more likely than women to have elevated cardiac biomarkers (creatine kinase MB or troponin) at the time of randomization.

The extent of CAD was compared in men and women randomized to an invasive strategy and who underwent coronary angiography. Women were more frequently found to have no sig-

Figure 1. Selection of Randomized Clinical Trials for Inclusion in Meta-analysis

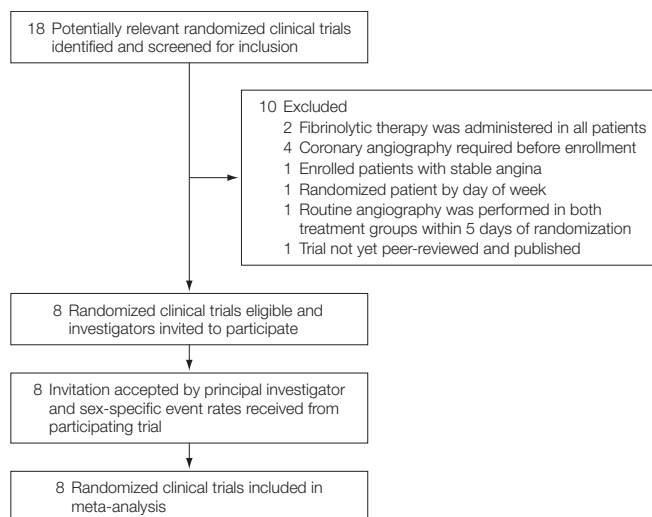


Table 1. Characteristics of Trials Included in the Collaborative Meta-analysis

Source	No. of Patients		Median Time to Angiography in Invasive Groups, h	Rate of Angiography in Conservative Groups by Hospital Discharge, %
	Men	Women		
TIMI IIIB, ¹⁰ 1994	976	497	36	57
MATE, ¹¹ 1998	129	72	16	60
VANQWISH, ¹⁸ 1998	896	24	48	23
FRISC II, ¹ 1999	1708	749	96	10
TACTICS-TIMI 18, ⁷ 2001	1463	757	22	51
VINO, ²⁰ 2002	80	51	6.2	12
RITA 3, ² 2002	1128	682	48	16
ICTUS, ⁸ 2005	880	320	23	53

Abbreviations: FRISC, Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease; ICTUS, Invasive vs Conservative Treatment in Unstable Coronary Syndromes; MATE, Medicine vs Angiography in Thrombolytic Exclusion; RITA, Randomized Intervention Trial of Unstable Angina; TACTICS-TIMI, Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction; TIMI, Thrombolysis in Myocardial Infarction; VANQWISH, Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital; VINO, Value of First Day Angiography/Angioplasty In Evolving Non-ST Segment Elevation Myocardial Infarction.

nificant CAD (<50% stenosis) at angiography than were men (24% vs 8%, $P < .001$) (Table 2), even if restricted to only those patients with ST-segment deviation on electrocardiogram (16% vs 6%, $P < .001$) or to those patients with elevated biomarkers (14% vs 6%, $P < .001$). Conversely, men were more frequently found to have 3-vessel or left main disease compared with women (35% vs 23%, $P < .001$).

Overall Clinical Outcomes

Data on the incidence of death, MI, or rehospitalization with ACS were available in 10 150 patients, including 3075 women and 7075 men. In the overall population and irrespective of sex, the composite end point of death, nonfatal MI, or rehospitalization with ACS occurred in 1075 of 5083 patients (21.1%) in the invasive group and 1313 of 5067 patients (25.9%) in the conservative group by

the end of 12 months of follow-up (OR, 0.78; 95% CI, 0.61-0.98) (FIGURE 2 and TABLE 3). Compared with the conservative strategy, the OR for death with an invasive strategy was 0.97 (95% CI, 0.71-1.32), the OR for recurrent nonfatal MI was 0.84 (95% CI, 0.63-1.12), the OR for death or MI was 0.92 (95% CI, 0.69-1.23), and the OR for rehospitalization with ACS was 0.68 (95% CI, 0.55-0.84) (Table 3).

Patient Sex and Clinical Outcomes

The end point of death, MI, or rehospitalization with ACS occurred in 709 of 3075 women (23%) and 1679 of 7075 men (24%) when pooled across treatment groups. The OR for the composite of death, MI, or rehospitalization with ACS with an invasive vs conservative strategy was 0.81 (95% CI, 0.65-1.01) in women and 0.73 (95% CI, 0.55-0.98) in men without statisti-

cally significant heterogeneity between sex (P for interaction = .26) (Figure 2 and Table 3).

Of the individual elements of the composite end point, a routine invasive strategy was associated with a substantial 32% to 34% significant decrease in the odds of rehospitalization with ACS in both women and men (Table 3). In contrast, in women, an invasive strategy had no significant effect on all-cause mortality (OR, 1.11; 95% CI, 0.72-1.70), nonfatal MI (OR, 0.93; 95% CI, 0.59-1.45), or the composite of death or MI (OR, 1.02; 95% CI, 0.67-1.55).

In men, an invasive strategy was associated with a nonsignificant 11% lower odds of death (OR, 0.89; 95% CI, 0.58-1.35), a nonsignificant 19% lower odds of nonfatal MI (OR, 0.81; 95% CI, 0.59-1.11), and a nonsignificant 13% lower odds of death or MI (OR, 0.87; 95% CI, 0.61-1.23).

Timing of Clinical Events

We examined clinical event rates both before and after hospital discharge to evaluate the possible existence of an early hazard in women or men randomized to an invasive strategy (FIGURE 3).

Before hospital discharge, an invasive strategy was associated with a nonsignificant higher incidence of death or recurrent MI in both women and men compared with those patients treated conservatively. Irrespective of sex, an invasive strategy was associated with a nonsignificant 37% increase in the odds of death or MI during index hospitalization compared with patients treated conservatively (OR, 1.37; 95% CI, 0.93-2.02). Death or recurrent MI during the index hospitalization occurred in 6.2% women in the invasive group vs 4.2% women in the conservative group (OR, 1.49; 95% CI, 0.72-3.09). In men, death or recurrent MI before first hospital discharge occurred in 6.5% men in the invasive group vs 4.8% men in the conservative group (OR, 1.33; 95% CI, 0.93-1.89, P for interaction (sex) = .45).

From the time of first hospital discharge through 12 months of follow-

Table 2. Pooled Baseline Characteristics in Women vs Men in the Invasive and Conservative Groups of Each Trial (N = 10 412)

	No./Total No. (%) of Patients			
	Women		Men	
	Invasive Groups (n = 1571)	Conservative Groups (n = 1581)	Invasive Groups (n = 3641)	Conservative Groups (n = 3619)
Weighted mean ^a				
Age, y	64.4	63.8	61.4	61.2
BMI	27.6	27.8	27.4	27.5
Current smoker	421/1569 (26.8)	503/1577 (31.9)	1308/3638 (36.0)	1285/3619 (35.5)
Diabetes mellitus	292/1451 (20.1)	273/1458 (18.7)	592/3419 (17.3)	586/3392 (17.3)
Hypertension	821/1567 (52.4)	816/1580 (51.6)	1475/3637 (40.6)	1487/3612 (41.2)
Prior MI	422/1571 (26.9)	366/1581 (23.1)	1266/3641 (34.8)	1224/3619 (33.8)
Hyperlipidemia	737/1538 (47.9)	725/1547 (46.9)	1427/3576 (39.9)	1377/3567 (38.6)
ST-segment depression	609/1561 (39.0)	608/1574 (38.6)	1352/3595 (37.6)	1336/3580 (37.3)
T-wave inversion	841/1561 (53.9)	849/1574 (53.9)	1561/3594 (43.4)	1550/3578 (43.3)
Creatine kinase MB or troponin elevation at randomization ^b	550/1293 (42.5)	550/1293 (42.5)	1392/2518 (55.3)	1353/2521 (53.7)
Extent of disease at angiography, % ^c				
None	24	NA	8	NA
1-vessel disease	32	NA	28	NA
2-vessel disease	21	NA	29	NA
3-vessel disease	23	NA	35	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MI, myocardial infarction; NA, not available.

^aStandard deviation not available.

^bBaseline biomarker status was restricted to those trials that enrolled patients both with and without baseline elevation of creatine kinase MB or troponin.

^cDiseased vessel defined as at least 50% stenosis in a major epicardial vessel or coronary artery bypass graft. Restricted to patients in the invasive groups.

up, an invasive strategy was associated with a significant 28% lower odds of death or MI (OR, 0.72; 95% CI, 0.52-0.99), irrespective of sex. The OR for the composite of death or MI from an invasive vs conservative strategy was 0.71 (95% CI, 0.48-1.07) in women and 0.70 (95% CI, 0.50-0.98) in men (*P* for interaction (sex) = .52).

High-Risk Subgroups

Because current guidelines recommend that high-risk features be used to help identify patients who might benefit most from an invasive strategy,^{24,25} we performed an exploratory analysis stratified by the presence or absence of cardiac biomarker elevation or ST-segment deviation on electrocardiogram (FIGURE 4). Cardiac biomarkers (creatinine kinase MB or troponin) were available at the time of enrollment in 97% of men and women. Because serum troponin was only available in 69% of women and 66% of men, analyses were not restricted to this parameter. The presence or absence of ST-segment deviation was available in 99.5% of women and 97% of men.

Irrespective of sex, the OR for death, MI, or rehospitalization with ACS with an invasive vs conservative strategy was 0.59 (95% CI, 0.51-0.69) for patients with elevated biomarkers (creatinine kinase MB or troponin) vs 0.79 (95% CI, 0.58-1.06) for those without (*P* for interaction = .18) (Figure 4). An invasive strategy was associated with a significant 32% reduction in the odds of death or MI in patients with elevated biomarkers (OR, 0.68; 95% CI, 0.56-0.82), whereas there was no reduction in death or MI in those patients who were biomarker-negative upon presentation (OR, 1.01; 95% CI, 0.79-1.28; *P* for interaction = .03).

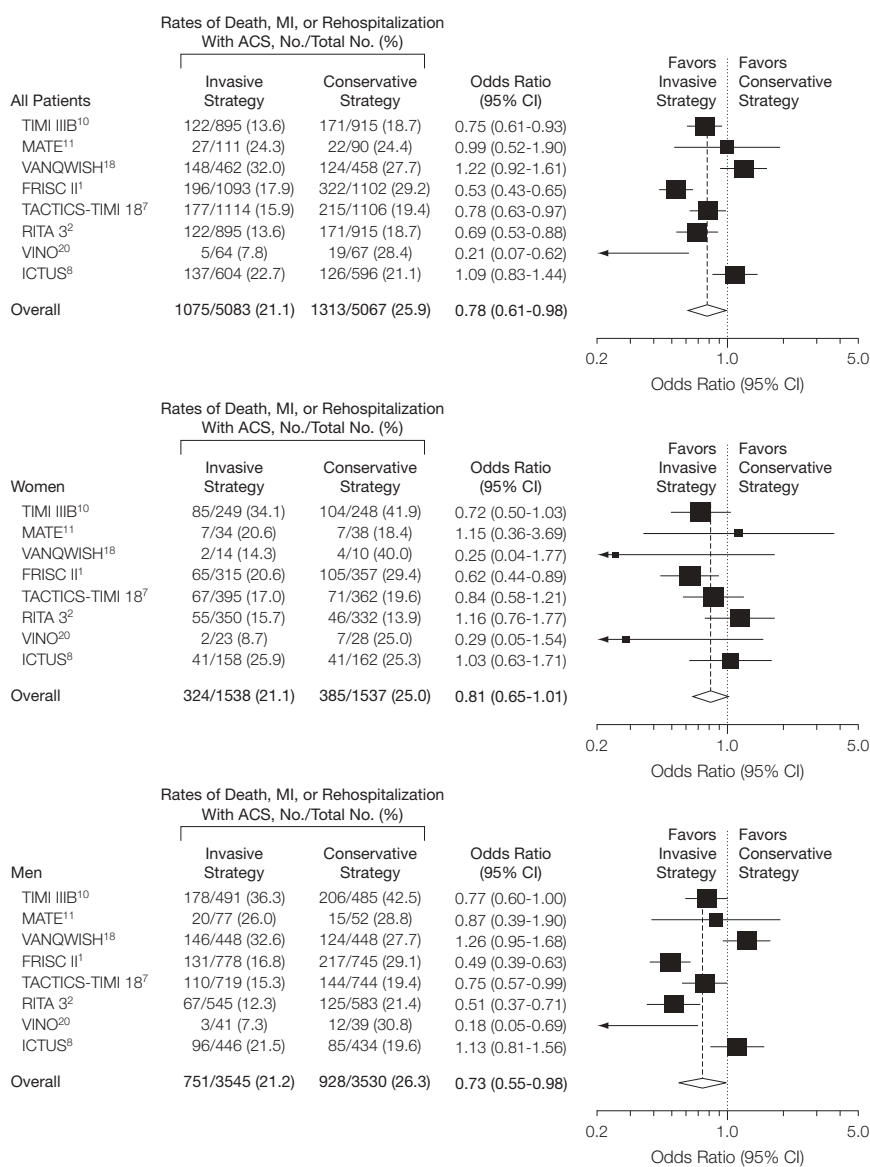
In men with an elevated cardiac biomarker, an invasive strategy compared with a conservative strategy was associated with a significant 44% lower odds of death, MI, or rehospitalization with ACS (OR, 0.56; 95% CI, 0.46-0.67) and a 36% lower odds of death or MI (OR, 0.64; 95% CI, 0.51-0.81). In men without biomarker elevation,

the quantitative benefit of an invasive strategy was numerically smaller for both the triple (OR, 0.72; 95% CI, 0.51-1.01) and double composite end points (OR, 0.87; 95% CI, 0.61-1.25), although the relative difference was not statistically significant (*P* = .09 and *P* = .28 for interaction, respectively).

Among women with an elevated cardiac biomarker, an invasive strategy sig-

nificantly decreased the odds of death, MI, or rehospitalization with ACS by 33% (OR, 0.67; 95% CI, 0.50-0.88), which was comparable with the benefit observed overall in men. In contrast, there was less apparent benefit with an invasive strategy in women in the absence of biomarker elevation (OR, 0.94; 95% CI, 0.61-1.44), although the test for heterogeneity did not meet sta-

Figure 2. Death, MI, or Rehospitalization With ACS in Trials of an Invasive vs Conservative Treatment Strategy in NSTEMI ACS



ACS indicates acute coronary syndromes; CI, confidence interval; MI, myocardial infarction; NSTEMI, non-ST-segment elevation. Size of data markers is weighted based on the inverse variance.

tistical significance (P for interaction = .36). An invasive strategy was associated with a nonsignificant 23% lower odds of death or MI in women with elevated biomarkers (OR, 0.77; 95% CI, 0.47-1.25), whereas an inva-

sive strategy was associated with a nonsignificant 35% higher odds of death or MI in biomarker-negative women (OR, 1.35; 95% CI, 0.78-2.35; P for interaction = .08).

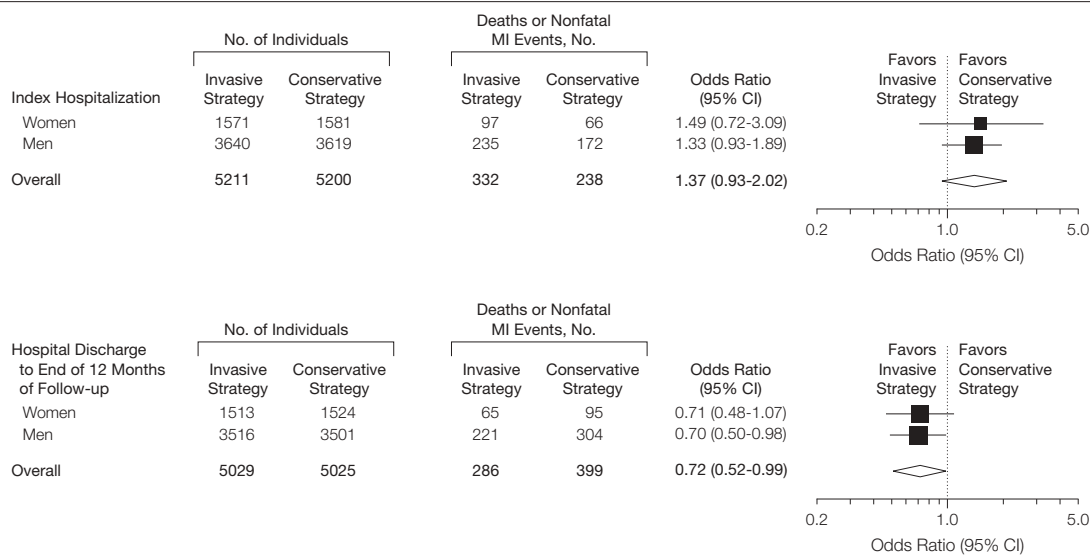
In addition, the presence of ST-segment deviation also identified those patients at higher risk and with modest but not statistically significant greater benefit from an invasive strategy (Figure 4).

Table 3. Summary of Odds Ratios and Pooled Event Numbers for Major Outcomes Both Overall and by Sex After 12 Months of Follow-up^a

	No./Total No. (%) of Patients		Odds Ratio (95% CI)
	Invasive Strategy	Conservative Strategy	
Overall			
Death, MI, or rehospitalization with ACS	1075/5083 (21.1)	1313/5067 (25.9)	0.78 (0.61-0.98)
Death or MI	595/5212 (11.4)	638/5200 (12.3)	0.92 (0.69-1.23)
Death	225/5212 (4.3)	227/5200 (4.4)	0.97 (0.71-1.32)
Nonfatal MI	382/5212 (7.3)	443/5200 (8.5)	0.84 (0.63-1.12)
Rehospitalization with ACS	652/5083 (12.8)	911/5067 (18.0)	0.68 (0.55-0.84)
Women			
Death, MI, or rehospitalization with ACS	324/1538 (21.1)	385/1537 (25.0)	0.81 (0.65-1.01)
Death or MI	162/1571 (10.3)	163/1581 (10.3)	1.02 (0.67-1.55)
Death	68/1571 (4.3)	62/1581 (3.9)	1.11 (0.72-1.70)
Nonfatal MI	98/1571 (6.2)	106/1581 (6.7)	0.93 (0.59-1.45)
Rehospitalization with ACS	208/1538 (13.5)	290/1537 (18.9)	0.68 (0.54-0.85)
Men			
Death, MI, or rehospitalization with ACS	751/3545 (21.2)	928/3530 (26.3)	0.73 (0.55-0.98)
Death or MI	433/3641 (11.9)	475/3619 (13.1)	0.87 (0.61-1.23)
Death	157/3641 (4.3)	165/3619 (4.6)	0.89 (0.58-1.35)
Nonfatal MI	284/3641 (7.8)	337/3619 (9.3)	0.81 (0.59-1.11)
Rehospitalization with ACS	444/3545 (12.5)	621/3530 (17.6)	0.66 (0.54-0.82)

Abbreviations: ACS, acute coronary syndromes; CI, confidence interval; MI, myocardial infarction.
^aThere was no evidence of statistical heterogeneity between men and women for any of the examined end points (P for interaction: death, MI, or rehospitalization with ACS, P = .26; death or MI, P = .17; death, P = .20; nonfatal MI, P = .41; and rehospitalization with ACS, P = .48).

Figure 3. Death or Nonfatal MI for Index Hospitalization and Hospital Discharge to End of 12 Months of Follow-up in Trials of an Invasive vs Conservative Treatment Strategy in NSTEMI ACS



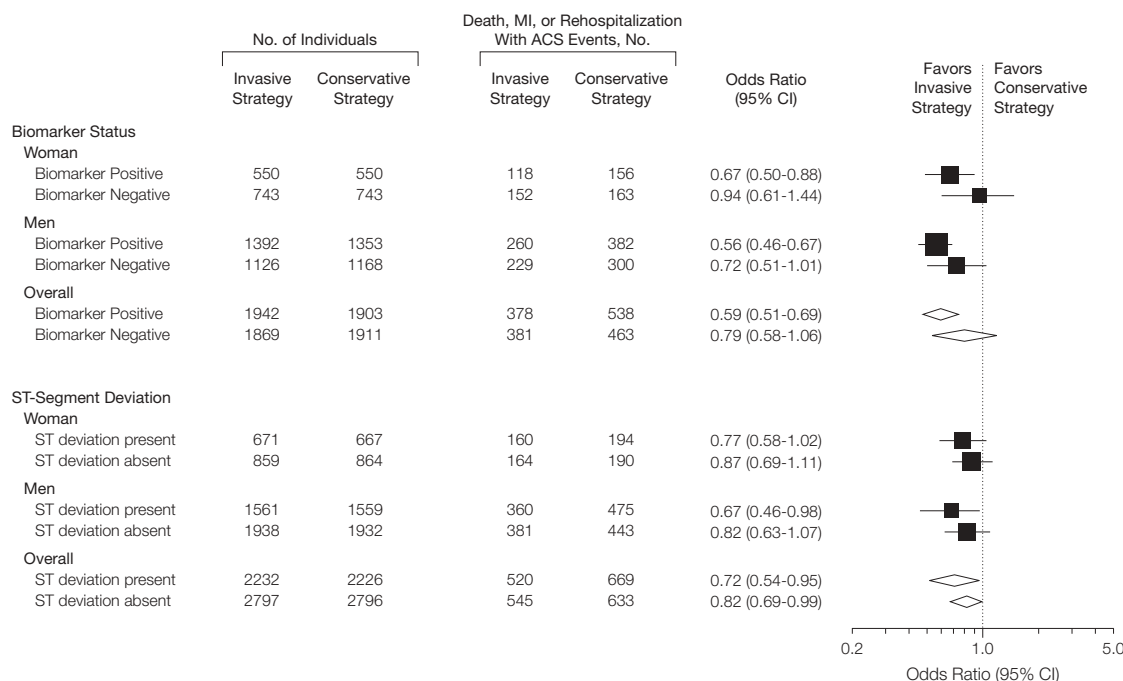
CI indicates confidence interval; MI, myocardial infarction; NSTEMI ACS, non-ST-segment elevation acute coronary syndromes. Odds ratios were generated from random-effects models. Size of data markers is weighted based on the inverse variance.

at 12 months of follow-up. Across treatment groups, there were no significant differences in the subsequent odds of death, MI, or rehospitalization with ACS in women vs men who underwent coronary revascularization

by percutaneous coronary intervention (pooled event rates, 31% vs 30%; random effects: OR, 1.14; 95% CI, 0.96-1.35). There were significantly higher odds of death, MI, or rehospitalization with ACS in women vs men

who required CABG surgery by the end of follow-up (33% vs 26%; OR, 1.44; 95% CI, 1.15-1.81). Conversely, there was a nonsignificantly lower event rate in women who were treated medically without coronary revascu-

Figure 4. Death, MI, or Rehospitalization With ACS for Biomarker Status and ST-Segment Deviation in Trials of an Invasive vs Conservative Treatment Strategy in NSTEMI ACS



ACS indicates acute coronary syndromes; CI, confidence interval; MI, myocardial infarction; NSTEMI, non-ST-segment elevation. Odds ratios were generated from random-effects models. Size of data markers is weighted based on the inverse variance. The odds ratios (ORs) and corresponding *P* values for the interaction terms for the efficacy of an invasive over a conservative strategy in biomarker-positive vs biomarker-negative patients were as follows: for all patients, OR for interaction, 0.79; *P* for interaction = .18; for women, OR for interaction, 0.75; *P* for interaction = .36; and for men, OR for interaction, 0.77; *P* for interaction = .09. The analogous data for patients with vs without ST-segment deviation were as follows: for all patients, OR for interaction, 0.83; *P* for interaction = .07; for women, OR for interaction, 0.87; *P* for interaction = .76; and for men, OR for interaction, 0.79; *P* for interaction = .07. VINO,²⁰ VANQWISH,¹⁸ and ICTUS⁸ trials were excluded from the primary biomarker analysis because they only enrolled patients with elevated biomarkers thus precluding the comparison of biomarker-positive and biomarker-negative subgroups. The meta-analysis OR and 95% CIs for the efficacy of an invasive strategy vs conservative strategy if those 3 trials were also included were as follows: for all patients biomarker-positive, OR, 0.72; 95% CI, 0.53-0.98; for all patients biomarker-negative, OR, 0.79; 95% CI, 0.60-1.03; for biomarker-positive men, OR, 0.71; 95% CI, 0.49-1.01; for biomarker-negative men, OR, 0.72; 95% CI, 0.54-0.98; for biomarker-positive women, OR, 0.71; 95% CI, 0.56-0.91; and for biomarker-negative women, OR, 0.94; 95% CI, 0.61-1.44.

Table 4. Rates of Coronary Revascularization Overall and by Sex After Randomization

	No. (%) of Patients					
	Overall		Women		Men	
	Invasive Groups (n = 5212)	Conservative Groups (n = 5200)	Invasive Groups (n = 1571)	Conservative Groups (n = 1581)	Invasive Groups (n = 3641)	Conservative Groups (n = 3619)
Revascularization during index hospitalization	3161 (60.6)	1298 (25.0)	870 (55.4)	361 (22.8)	2291 (62.9)	937 (25.9)
Revascularization by 12 months of follow-up	3425 (65.7)	2219 (42.7)	908 (57.8)	609 (38.5)	2517 (69.1)	1610 (44.5)
Percutaneous intervention by 12 months of follow-up	2196 (42.1)	1312 (25.2)	647 (41.2)	391 (24.7)	1549 (42.5)	921 (25.4)
CABG surgery by 12 months of follow-up	1369 (26.3)	991 (19.1)	313 (19.9)	242 (15.3)	1056 (29.0)	749 (20.7)

Abbreviation: CABG, coronary artery bypass graft.

larization compared with men (16% vs 20%; OR, 0.91; 95% CI, 0.66-1.22).

Heterogeneity Between Trials

There was evidence of heterogeneity between trials for the composite end points of death or MI (heterogeneity $\chi^2=34.5$, $P<.001$) and death, MI, or rehospitalization with ACS in men (heterogeneity $\chi^2=39.7$, $P<.001$), and death or MI in women (heterogeneity $\chi^2=17.0$, $P=.02$). Sensitivity analyses suggested that several trials contributed to this heterogeneity with the largest contribution provided by the ICTUS,⁸ VANQWISH,¹⁸ and VINO²⁰ trials. Importantly, heterogeneity did not appear to be explained by the year of publication or concomitant therapies alone. When the primary composite end point of death, MI, or rehospitalization with ACS was reanalyzed applying alternate definitions of MI for the ICTUS trial⁸ as defined in TACTICS-TIMI 18⁷ and FRISC II,¹ the heterogeneity between trials was not eliminated.

COMMENT

The findings of our meta-analysis suggest that both men and high-risk women, defined by elevated biomarkers of necrosis, have a comparable benefit from an invasive strategy in unstable angina and NSTEMI for reducing the odds of death, MI, or rehospitalization with ACS. In contrast, an invasive strategy does not appear to substantially benefit women in the absence of biomarker elevation and moreover may potentially increase the risk of death or MI. Our data provide evidence to support the updated American College of Cardiology/American Heart Association guidelines that now recommend that a conservative strategy be used in low-risk women with NSTEMI ACS.²⁴

Prior sex subgroup analyses within individual trials have yielded disparate findings.⁴⁻⁶ These conflicting data have led to controversy regarding the optimal treatment strategy in women with NSTEMI ACS. Despite an overall benefit for patients randomized to an in-

vasive strategy in RITA 3² and FRISC II¹ trials, subgroup analyses within these trials suggested that an invasive strategy may not benefit women and may potentially increase their risk of death or MI. In the FRISC II trial,¹ the higher event rate observed in women compared with men in the invasive group appeared to be largely due to a marked increase in death (9.9% vs 1.2%) and recurrent MI (12% vs 5%) in women who required CABG surgery.⁴ To that end, there is continuing debate as to whether women are inherently at increased risk of adverse outcomes after CABG surgery, or whether this apparent increase in risk is explained by body size and comorbidities.²⁶⁻³¹ Recent studies now suggest a more favorable prognosis than in the past for women with ACS undergoing CABG surgery.³²⁻³⁴

Methods of risk stratification, including cardiac biomarkers of necrosis, ST-segment changes, and risk scores, have been previously shown to help identify high-risk patients who might benefit most from an invasive strategy.^{8,24,35} In both the RITA 3² and FRISC II¹ trials, women overall had a more favorable prognosis compared with men. In addition, women in the RITA 3 trial² were at lower risk than women in the TACTICS-TIMI 18 trial.⁵ A larger proportion of lower-risk patients may help to explain the reduced benefit from an invasive strategy in women observed in some trials and may also highlight procedural risk. To that end, in the TACTICS-TIMI 18 trial,⁵ the benefit from an invasive strategy appeared to be restricted to women with an elevated troponin T (OR, 0.56; 95% CI, 0.32-0.97), whereas there was a trend toward harm from an invasive strategy in women who were troponin negative (OR, 1.46; 95% CI, 0.78-2.72).

In our meta-analysis, we found that women with elevated biomarkers at randomization had a significant 33% lower odds of death, MI, or rehospitalization with ACS (OR, 0.67; 95% CI, 0.50-0.88) and a directionally consistent but nonsignificant 23% lower odds of death or MI with an invasive strat-

egy (OR, 0.77; 95% CI, 0.47-1.25), benefits that were similar to the overall benefit observed in men. In contrast, women without biomarker elevation did not appear to have a significant benefit from an invasive strategy and had a nonsignificant higher odds of death or MI compared with those treated conservatively. Although the relative difference between biomarker-positive and biomarker-negative women was not statistically significant, tests for interaction are conservative and may miss a true difference when one does in fact exist. It may be challenging to detect a statistically significant difference between subgroups due to their inherently smaller sample size. Our findings emphasize the need for larger prospective trials to specifically examine the benefit of an invasive strategy in women both overall and within high-risk subgroups.

We found that regardless of sex, the benefit of an early invasive strategy was largely due to a significant reduction in rehospitalization with ACS, with more modest effects on death or MI. Consistent with prior analyses,³ we observed a signal toward an early hazard with an invasive strategy such that patients randomized to an invasive strategy had a higher rate of death or MI before first hospital discharge, but subsequently had a significant reduction in death or MI following hospital discharge compared with patients treated conservatively.

We also observed that women are significantly less likely than men to have obstructive CAD at the time of angiography despite a clinical presentation consistent with NSTEMI ACS. Overall, 24% of women randomized to an invasive strategy had no evidence of significant epicardial CAD at angiography vs only 8% of men. When restricted to only those patients with elevated biomarkers of necrosis, the incidence of obstructive CAD marginally increased in women and men; however, 14% of women still had no evidence of significant CAD. These findings may reflect a greater burden of microvascular disease or abnormal vasodilatory reserve

in women resulting in subendocardial ischemia, coronary vasospasm, or possibly other acute disease states that mimic ACS secondary to obstructive CAD.^{30,36,37} Because only a select subset of patients in the conservative group of each trial underwent coronary angiography, it is not possible to explore the relative benefit of an invasive or conservative strategy in patients who were found to have obstructive CAD due to the risk of selection bias.

The relative paucity of obstructive CAD in women may dilute the treatment benefit of an invasive strategy and may in part explain the signal toward harm observed in some trials from an invasive strategy in women, because patients without significant epicardial disease are unlikely to obtain benefit from coronary angiography. Although biomarkers of necrosis may be useful for helping to predict the presence of obstructive CAD, consideration should be given to identify additional high-risk features or novel biomarkers that may prove to be useful for predicting the benefit of an invasive strategy in women.³⁵

There are limitations to our analysis that warrant consideration. None of the trials were individually powered to examine outcomes within specific subgroups, and subgroup analyses inherently increase the risk that the findings might be explained by chance or uncontrolled confounding.^{38,39} In addition, because we did not find any effect modification by sex alone, further analysis within high-risk subgroups can only be performed on an exploratory basis and these results should be confirmed with prospective trials. Because directional consistency was not observed across the individual elements of the composite end points, the secondary end points should be interpreted as hypothesis generating. Finally, as with any meta-analysis, limitations to the methods include heterogeneity between trials and the possibility of publication bias. In particular, there are differences across the trials in terms of populations, adjunctive pharmacotherapy, invasive treat-

ment options, and outcome measures.⁴⁰ However, with regard to the latter, our findings did not qualitatively differ when alternate definitions for MI were applied to the ICTUS trial population.⁸

In our meta-analysis, we did not have access to patient-level data so it is not possible to assess whether differences in outcomes by sex can be explained by variations in baseline characteristics or presenting features. In addition, bleeding events were not collected in all trials, so we cannot ascertain whether women may be at increased risk of bleeding following angiography or revascularization. The meta-analysis spans trial publication dates of more than 10 years. Since the publication of the first trial, there have been several advances in the treatment of patients with ACS, including the routine use of glycoprotein IIb/IIIa inhibitors, thienopyridines, and evolutions with stent and surgical technologies. The use of these agents may differ both between trials and treatment groups. Moreover, the proportion of patients undergoing angiography and revascularization in the conservative groups varied widely across trials and may have contributed to the observed heterogeneity. More intensive background medical therapy may be present in more recent trials. However, importantly, heterogeneity between trials did not appear to be explained by publication date or concomitant therapies alone.

This is to our knowledge the first large-scale and collaborative meta-analysis that examines the association between sex and outcomes with an invasive or conservative treatment strategy in NSTEMI ACS across all of the major randomized trials. Combination of these data enabled us to explore the association of sex with outcomes both overall and within high-risk subgroups, whereas individual studies may be insufficiently powered in this regard. Future investigations should include novel methods for identifying women at high-risk of adverse outcomes after NSTEMI ACS and whose risk

could be modifiable with an invasive approach.

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Study concept and design: O'Donoghue, Braunwald, Cannon, de Winter, Fox, Spacek, Wallentin, Sabatine. **Acquisition of data:** O'Donoghue, Boden, Braunwald, Cannon, Clayton, de Winter, Fox, Lagerqvist, McCullough, Murphy, Spacek, Swahn, Wallentin, Windhausen, Sabatine.

Analysis and interpretation of data: O'Donoghue, Boden, Braunwald, Cannon, Clayton, de Winter, Fox, Lagerqvist, McCullough, Murphy, Spacek, Swahn, Wallentin, Windhausen, Sabatine.

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REFERENCES

1. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study: FRAGmin and Fast Revascularisation during Instability in Coronary artery disease Investigators. *Lancet*. 1999;354(9180):708-715.
2. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial: Randomized Intervention Trial of unstable Angina. *Lancet*. 2002;360(9335):743-751.
3. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA*. 2005;293(23):2908-2917.

4. Lagerqvist B, Safstrom K, Stahle E, Wallentin L, Swahn E. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators. *J Am Coll Cardiol*. 2001;38(1):41-48.
5. Clayton TC, Pocock SJ, Henderson RA, et al. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST-elevation myocardial infarction? the impact of gender in the RITA 3 trial. *Eur Heart J*. 2004;25(18):1641-1650.
6. Glaser R, Herrmann HC, Murphy SA, et al. Benefit of an early invasive management strategy in women with acute coronary syndromes. *JAMA*. 2002;288(24):3124-3129.
7. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344(25):1879-1887.
8. de Winter RJ, Windhausen F, Cornel JH, et al; Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) Investigators. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med*. 2005;353(11):1095-1104.
9. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
10. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB trial: Thrombolysis in Myocardial Ischemia. *Circulation*. 1994;89(4):1545-1556.
11. McCullough PA, O'Neill WW, Graham M, et al. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy: results of the Medicine versus Angiography in Thrombolytic Exclusion (MATE) trial. *J Am Coll Cardiol*. 1998;32(3):596-605.
12. Unstable angina pectoris: National Cooperative Study Group to Compare Surgical and Medical Therapy. *Am J Cardiol*. 1978;42(5):839-848.
13. Brown CA, Hutter AM Jr, DeSanctis RW, et al. Prospective study of medical and urgent surgical therapy in randomizable patients with unstable angina pectoris: results of in-hospital and chronic mortality and morbidity. *Am Heart J*. 1981;102(6 pt 1):959-964.
14. Luchi RJ, Scott SM, Deupree RH. Comparison of medical and surgical treatment for unstable angina pectoris: results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1987;316(16):977-984.
15. SWIFT trial of delayed elective intervention v conservative treatment after thrombolysis with anistreplase in acute myocardial infarction: SWIFT (Should We Intervene Following Thrombolysis?) Trial Study Group. *BMJ*. 1991;302(6776):555-560.
16. Scott SM, Deupree RH, Sharma GV, Luchi RJ; VA Study of Unstable Angina. 10-year results show duration of surgical advantage for patients with impaired ejection fraction. *Circulation*. 1994;90(5 pt 2):II120-II123.
17. Madsen JK, Grande P, Saunamaki K, et al. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI): DANish trial in Acute Myocardial Infarction. *Circulation*. 1997;96(3):748-755.
18. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy: Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med*. 1998;338(25):1785-1792.
19. Michalis LK, Stroumbis CS, Pappas K, et al. Treatment of refractory unstable angina in geographically isolated areas without cardiac surgery: invasive versus conservative strategy (TRUCS Study). *Eur Heart J*. 2000;21(23):1954-1959.
20. Spacek R, Widimsky P, Straka Z, et al. Value of first day angiography/angioplasty in evolving non-ST segment elevation myocardial infarction: an open multicenter randomized trial: the VINO study. *Eur Heart J*. 2002;23(3):230-238.
21. Pfisterer M, Buser P, Osswald S, et al. Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: one-year results of the randomized TIME trial. *JAMA*. 2003;289(9):1117-1123.
22. Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290(12):1593-1599.
23. Swahn E. *OASIS 5: Worse Outcome With an Invasive Strategy Among Women With Non ST-Elevation Acute Coronary Syndromes*. Vienna, Austria: ESC Congress; 2007.
24. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50(7):e1-e157.
25. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: the Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. *Eur Heart J*. 2007;28(13):1598-1660.
26. Bolooki H, Vargas A, Green R, Kaiser GA, Ghahramani A. Results of direct coronary artery surgery in women. *J Thorac Cardiovasc Surg*. 1975;69(2):271-277.
27. Khan SS, Nessim S, Gray R, Czer LS, Chaux A, Matloff J. Increased mortality of women in coronary artery bypass surgery: evidence for referral bias. *Ann Intern Med*. 1990;112(8):561-567.
28. Weintraub WS, Wenger NK, Jones EL, Craver JM, Guyton RA. Changing clinical characteristics of coronary surgery patients: differences between men and women. *Circulation*. 1993;88(5 pt 2):II79-II86.
29. O'Connor GT, Morton JR, Diehl MJ, et al. Differences between men and women in hospital mortality associated with coronary artery bypass graft surgery: the Northern New England Cardiovascular Disease Study Group. *Circulation*. 1993;88(5 pt 1):2104-2110.
30. Sullivan AK, Holdright DR, Wright CA, et al. Chest pain in women: clinical, investigative, and prognostic features. *BMJ*. 1994;308(6933):883-886.
31. Hochman JS, McCabe CH, Stone PH, et al. Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB: TIMI Investigators: Thrombolysis in Myocardial Infarction. *J Am Coll Cardiol*. 1997;30(1):141-148.
32. Jacobs AK, Kelsey SF, Brooks MM, et al. Better outcome for women compared with men undergoing coronary revascularization: a report from the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation*. 1998;98(13):1279-1285.
33. Lansky AJ. Outcomes of percutaneous and surgical revascularization in women. *Prog Cardiovasc Dis*. 2004;46(4):305-319.
34. Humphries KH, Gao M, Pu A, Lichtenstein S, Thompson CR. Significant improvement in short-term mortality in women undergoing coronary artery bypass surgery (1991 to 2004). *J Am Coll Cardiol*. 2007;49(14):1552-1558.
35. Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet*. 2005;366(9489):914-920.
36. Cannon RO III, Camici PG, Epstein SE. Pathophysiological dilemma of syndrome X. *Circulation*. 1992;85(3):883-892.
37. DeSanctis RW. *Clinical Manifestations of Coronary Artery Disease: Chest Pain in Women*. Greenwich, CT: Le Jacq Communications Inc; 1993.
38. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA*. 1991;266(1):93-98.
39. Rothwell PM. Treating individuals 2: subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet*. 2005;365(9454):176-186.
40. Naylor CD. Meta-analysis and the meta-epidemiology of clinical research. *BMJ*. 1997;315(7109):617-619.