



REVIEW

# How should patients with unstable angina and non-ST-segment elevation myocardial infarction be managed? A meta-analysis of randomized trials

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## KEYWORDS:

Meta-analysis;  
Meta-regression;  
Acute coronary  
syndromes;  
Unstable angina;  
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Coronary  
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Myocardial  
revascularization

## ABSTRACT

**PURPOSE:** Patients with unstable angina or non-ST-segment elevation myocardial infarction (MI) may be managed with either an “invasive” or “conservative” strategy. It is unclear which of these strategies is superior.

**METHODS:** We identified studies with MEDLINE and EMBASE searches (1966–September 2003) and by reviewing reference lists. Studies were included if they were randomized controlled trials comparing management strategies for patients in the early post-unstable angina/non-ST-segment elevation MI period and had follow-up data for at least 3 months.

**RESULTS:** Seven trials that randomized a total of 9212 patients were included. The pooled odds ratio (OR) for all-cause mortality was 0.96 (95% confidence interval [CI]: 0.72 to 1.27). The occurrence of fatal or nonfatal re-infarction was reduced with an invasive strategy (OR 0.73; 95% CI: 0.61 to 0.88) as was readmission to hospital (OR 0.67; 95% CI: 0.48 to 0.94). The endpoints of nonfatal MI and the composite of death or nonfatal MI showed nonsignificant trends favoring an invasive strategy. Trials that included a higher proportion of patients with ST-segment depression on admission and trials in which a larger proportion of patients underwent revascularization showed a greater magnitude of benefit for an invasive strategy.

**CONCLUSION:** For patients with unstable angina/non-ST-segment elevation MI, an invasive strategy reduces rates of fatal or nonfatal re-infarction and hospital readmission, but not all-cause mortality, when compared with a noninvasive strategy. These results suggest that an invasive management strategy should be considered for all patients with unstable angina/non-ST-segment elevation MI and perhaps in particular those with ST-segment depression.

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There are two approaches to managing patients with unstable angina or non-ST-segment elevation myocardial infarction (MI). In an "early invasive" strategy, coronary angiography is routinely performed in all patients. In an early "conservative" or "noninvasive" strategy, angiography is conducted only on patients who are at high risk of cardiovascular morbidity and mortality. In both cases, subsequent revascularization is guided by angiographic findings.

The American College of Cardiology/American Heart Association and the European Society of Cardiology recommend that an invasive strategy be used selectively for patients with certain features based on history (ie, percutaneous coronary intervention within the preceding 6 months, prior bypass surgery), admission characteristics (ie, elevated levels of cardiac enzymes, new ST-segment depression), hospital course (ie, hemodynamic instability, sustained ventricular tachycardia, recurrent angina or ischemia at rest or with low-level activities despite intensive anti-ischemic therapy, recurrent ischemia-induced heart failure or mitral regurgitation), or diagnostic testing (ie, high-risk findings on noninvasive stress testing, depressed left ventricular systolic function).<sup>1-3</sup> For lower risk patients, the European Society of Cardiology recommends that a noninvasive strategy be used, and the American College of Cardiology/American Heart Association recommends that either risk stratification strategy would be appropriate.<sup>1,3</sup> Making more definitive recommendations has been challenging because the randomized controlled trials that have attempted to address this issue provide conflicting results.<sup>4-10</sup>

We performed a systematic review and meta-analysis of these trials to clarify the advantage of one strategy over another, if such an advantage exists. This is of particular importance because the trials enrolled all unstable angina/non-ST-segment elevation MI patients and not just those at high risk. Thus, a finding of superiority of an invasive strategy would mean that low and intermediate risk unstable angina/non-ST-segment elevation MI patients should undergo routine angiography as well.

## Methods

We searched the MEDLINE and EMBASE databases (Ovid Technologies, 1966–September 2003; English language) for keywords related to acute coronary syndromes (eg, coronary artery disease, myocardial infarction, unstable angina), medical therapy (eg, platelet aggregation inhibitor, antithrombotic, thrombolysis), interventional therapy (eg, angioplasty, percutaneous transluminal coronary angioplasty, coronary angiography), and risk stratification. Two investigators independently reviewed the search results to select articles. After retrieval, the reference lists of all identified articles were reviewed to identify other studies that may have been missed. Studies were included if they were randomized controlled trials whose objective was to com-

pare noninvasive and invasive management strategies for patients in the early post-unstable angina/non-ST-segment elevation MI period; measured mortality, re-infarction or re-hospitalization as outcomes; and had follow-up data for at least 3 months. Trials were excluded if they dealt with patients with ST-segment elevation MI, stable angina or cardiogenic shock, or if all patients underwent angiography.

Two investigators independently extracted data on patient characteristics, outcomes, and study quality from each trial. Disagreements were resolved by consensus. The quality of each trial was assessed with respect to blinding, treatment allocation, withdrawals, and standardization of assessment using an instrument based on the Cochrane Collaboration Handbook to Systematic Reviews.<sup>11</sup>

## Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI) were calculated for the outcomes in each study, based on intention-to-treat principles. After visually inspecting the plot of odds ratios, the two strategies were compared by combining the results from different trials with both a fixed effect and a DerSimonian and Laird random effects model.<sup>12</sup> Given the relatively small number of trials included, conclusions were drawn based on the results of the random effects calculations, as these provide the most conservative estimates of effect size. For trials that reported data at multiple time-points, those endpoints with the longest length of follow-up that still had a less than 15% rate of loss to follow-up were used. The length of follow-up ranged from 3 months to 2 years.

Sensitivity analysis was conducted by sequentially eliminating low quality studies and those with atypical inclusion criteria to determine whether this had any effect on our pooled results.

For each analysis, heterogeneity was explored in 3 ways. First, a plot of the odds ratios was visually inspected. Second, the heterogeneity Q statistic was calculated and compared with a chi-squared distribution with  $k - 1$  degrees of freedom, where  $k$  is the number of trials in the analysis; heterogeneity was considered to be present when  $Q > k - 1$ .<sup>13</sup>

Third, sources of systematic heterogeneity were assessed by performing univariate meta-regression analyses.<sup>14</sup> Meta-regression attempts to identify significant relations between treatment effects and covariates of interest and, as such, to assess whether subsets of patients demonstrate a particular benefit of treatment. We conducted our meta-regression analysis using Bayesian hierarchical models with the software hblm in S-Plus (Mathsoft, Inc., Seattle, WA).<sup>15</sup> Among the advantages of the Bayesian approach are the more realistic incorporation of between-study variability and the ability to directly report the probability that, for example, an odds ratio is less than 1.<sup>16</sup> Diffuse normal priors were used for all regression parameters and the Pareto prior distribution was used for the variances.<sup>14</sup> We assessed the relationship between study outcomes and the following study characteristics: the proportion of patients in the non-

invasive group of each trial who received angiography; the proportion of patients with multi-vessel coronary artery disease; mortality in the noninvasive group (ie, baseline mortality); the proportion of patients in either group who underwent revascularization; the proportion of patients who had ST-segment depression or positive cardiac enzymes on admission; the mean time to angiography in the invasive strategy; and the length of follow-up. Insufficient data were available in the trial reports to assess the impact of depressed left ventricular systolic function, recent percutaneous intervention, or prior bypass surgery on study outcomes. The small number of studies included in the analyses meant that it was feasible to perform meta-regression with only one predictor at a time.

We report an association between a study characteristic and an outcome if in the Bayesian model there is a low posterior probability (at most 10%) that the slope relating the log odds ratio to the study characteristic is in the direction opposite to that expected or, equivalently, there is a high likelihood that the association between the study characteristic and outcome is in the expected direction.

The presence of publication bias was assessed using the Begg<sup>17</sup> and the Egger<sup>18</sup> techniques with a funnel plot.

## Results

### Trial characteristics and methodological quality

Our initial search yielded 382 citations, of which 328 articles were excluded on the basis of an abstract review. Of the remaining 54 references, 42 were excluded because they reported trials that enrolled patients with ST-segment elevation MI, did not report the results of a clinical trial, were duplicate publications, described studies that only randomized patients with cardiogenic shock or high risk post-MI patients, were not published in English, or did not fulfill inclusion criteria for other reasons. The 12 reports of 7 clinical trials that were left formed the basis of our results. These trials are described in Table 1.

The trials randomized a total of 9212 patients (4608 to invasive and 4604 to noninvasive management) and ranged in size from 131 to 2457 patients. The mean age of the study participants was 62 years. The proportion of patients with ST-segment depression associated with their unstable angina/non-ST-segment elevation MI admissions ranged from 21% to 47%. The proportion of patients with cardiac enzyme elevation associated with their unstable angina/non-ST-segment elevation MI admissions ranged from 18% to 100%. There were a total of 498 deaths by the end of follow-up time (247 deaths in the invasive groups and 251 in the noninvasive group). Average baseline rates of the endpoints (ie, rates in the noninvasive group) were: 28% for hospital re-admission, 10% for fatal or nonfatal re-infarction, 10% for nonfatal

re-infarction, and 16% for the combined endpoint of death or nonfatal re-infarction.

Six of the 7 trials were of high methodological quality. The Value of First Day Coronary Angiography/Angioplasty In Evolving Non ST-Segment Elevation Myocardial Infarction: An Open Multicenter Randomized (VINO) trial did not report the type of analysis (ie, intention-to-treat) or the degree of follow-up but was otherwise of adequate quality.<sup>10</sup> Begg's and Egger's tests did not demonstrate any evidence of publication bias, although statistical power for these tests is limited with a small number of studies.

### Effect of treatment strategy on outcomes

Study-specific and pooled results are presented in Table 2. All 7 trials measured all-cause mortality as an outcome and when combined showed no difference between strategies with respect to this outcome (OR 0.96; 95% CI: 0.72 to 1.27; Figure 1).

Four trials reported rates of nonfatal re-infarction, and when pooled these trials demonstrate a nonsignificant trend towards reduction in this outcome with an invasive strategy (OR 0.79, 95% CI: 0.53 to 1.16). The composite endpoint of nonfatal and fatal MI was significantly reduced with an invasive strategy (OR = 0.73; 95% CI: 0.61 to 0.88;  $P < 0.001$ ) in the 3 trials that reported this outcome.

Five trials reported the impact of treatment strategy on hospital re-admission. The pooled estimate from these studies demonstrates a significant reduction in the rate of readmission with an invasive strategy (OR = 0.67; 95% CI: 0.48 to 0.94;  $P = 0.02$ ).

The combined endpoint of re-infarction or death was reported in all 7 trials. Overall, the OR for this outcome was 0.84 (95% CI: 0.68 to 1.02;  $P = 0.08$ ), demonstrating a nonsignificant trend in favor of the invasive strategy (Figure 2).

### Sensitivity analysis

As noted above, the VINO trial was of lower methodological quality than the other included studies. In addition, the Medicine versus Angiography in Thrombolytic Exclusion (MATE) trial was qualitatively different because its primary objective was to assess the impact of risk-stratification strategy for patients who were ineligible to undergo thrombolysis. Seventy-nine percent of these patients were deemed ineligible because they had non-ST segment elevation events. All of our results were similar when these trials were excluded individually and simultaneously.

### Meta-regression analysis

Significant heterogeneity was present in the trials reporting results for all-cause mortality, re-hospitalization, and the composite endpoint of re-infarction or death (Table 2).

**Table 1** Study design and quality assessment of included trials

	VINO <sup>10</sup>	RITA-3 <sup>9</sup>	TACTICS-TIMI 18 <sup>6</sup>	FRISC II <sup>4</sup>	VANQWISH <sup>8</sup>	MATE <sup>5</sup>	TIMI IIIB <sup>7</sup>
Type of ACS included	Non-ST-elevation acute myocardial infarction	UA	Unstable angina/non-ST-segment elevation acute myocardial infarction	Unstable angina/non-ST-segment elevation acute myocardial infarction	Non-Q-wave myocardial infarction*	Acute coronary syndromes ineligible for thrombolysis†	Unstable angina/non-ST-segment elevation acute myocardial infarction
Publication year	2002	2002	2001	2000	1998	1998	1995
Number of patients	131	1810	2220	2457	920	201	1473
Duration of follow-up (months)	6	12	6	12	23	21	12
Patient characteristics						59 (NA)	
Mean ( $\pm$ SD) age (years)	66 ( $\pm$ 11)	62 ( $\pm$ 10)	62 ( $\pm$ 12)	66‡	62 ( $\pm$ 10)		59 ( $\pm$ 10)
Male sex (%)	74	62	66	70	97	75	66
Diabetes mellitus (%)	25	13	28	13	26	18	NA
Previous myocardial infarction (%)	26	28	29	23	43	21	41
Cardiac enzyme elevation (%)	100	18	54	58	100	53	NA
ST-depression (%)	47	37	39	46	38	21	33
Multivessel or left main coronary disease (%)§	70	46	43	57	74	40	45
Baseline mortality (%)	13.4	3.9	3.5	3.9	10	10	4.4
Interventions							
Thrombolysis	No	No	No	No	Some**	No	Randomized to thrombolysis
Gp IIb/IIIa inhibitors	No	If appropriate with percutaneous intervention	Yes	With angioplasty	No	No	No
Anticoagulants	Unfractionated heparin	Low molecular weight heparin	Unfractionated heparin	Randomized to low molecular weight heparin	Unfractionated heparin	Unfractionated heparin	Unfractionated heparin
Angiography in non-invasive arm (% of patients)	55	48	61	52	48	60	73

**Table 1** Study design and quality assessment of included trials Continued.

	VINO <sup>10</sup>	RITA-3 <sup>9</sup>	TACTICS-TIMI 18 <sup>6</sup>	FRISC II <sup>4</sup>	VANQWISH <sup>8</sup>	MATE <sup>5</sup>	TIMI IIIB <sup>7</sup>
Median (interquartile range) time to angiography in invasive arm (hours)	6.2 (0.5–22)	48 (NA)	22 (18–39)	96(24–144)††	NA	16 (+14)‡‡	36 (NA)‡‡
PTCA in invasive arm (%)§§	52	36	42	44	21	43	39
PTCA in non-invasive arm (%)§§	13	16	29	21	12	30	32
CABG in invasive arm (%)§§	35	22	22	38	21	16	30
CABG in non-invasive arm (%)§§	30	12	16	23	19	8	30
Quality assessment							
Analysis by intention to treat principle?	Not described	Yes	Yes	Yes	Yes	Yes	Yes
Loss to follow-up	Not described	<5%	None	None	<1%	None	<5%
Outcome assessors blinded?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

FRISCII = Fast Revascularization During Instability in Coronary Artery Disease II Trial; MATE = Medicine versus Angiography in Thrombolytic Exclusion Trial; RITA 3 = Randomized Intervention Trial of Unstable Angina 3 Trial; TACTICS-TIMI 18 = Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction 18 Trial; TIMI IIIB = Thrombolysis in Myocardial Infarction IIIB Trial; VANQWISH = Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital Trial; VINO = Value of First Day Coronary Angiography/Angioplasty In Evolving Non ST-Segment Elevation Myocardial Infarction. An Open Multicenter Randomized Trial; NA = data not available; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting.

\*30% of patients had ST-segment elevation at admission.

†79% of the patients were felt to be ineligible for thrombolysis by ECG criteria; 11% of the patients had persistent ST-elevation but were ineligible for other reasons (eg, timing, age, bleeding risk).

‡Median age. Interquartile ranges for entire cohort not presented in the trial report.

§Multivessel defined as 2 or 3 vessel disease; data presented for patients randomized to invasive strategy.

||Mortality rate in non-invasive group by end of follow-up.

\*\*97 of 272 (36%) patients with ST-elevation in addition to 18 subjects without ST-elevation.

††Range presented is for the 10th to 90th percentile.

‡‡Mean (SD) time to catheterization.

§§By end of follow-up time.

**Table 2** Summary of treatment effects of invasive vs. noninvasive management of patients with unstable angina/non-ST elevation MI

Trial name	Odds ratio (95% confidence intervals)*				
	All-cause mortality	Non-fatal MI	Fatal and non-fatal MI	Death or MI	Readmission
TIMI IIIB	0.93 (0.56–1.54)	NA	0.88 (0.61 to 1.26)	0.88 (0.64–1.21)	0.72 (0.58–0.91)
VANQWISH	1.42 (0.98–2.04)	0.87 (0.62–1.24)	NA	1.13 (0.85–1.49)	NA
MATE	1.09 (0.44–2.72)	1.64 (0.29–9.19)	NA	1.12 (0.49–2.58)	1.02 (0.52–1.98)
FRISC II	0.67 (0.45–0.98)	NA	0.69 (0.53–0.89)	0.70 (0.56–0.88)	0.45 (0.38–0.53)
TACTICS-TIMI 18	0.94 (0.59–1.49)	NA	0.68 (0.47–0.97)	0.75 (0.55–1.01)	0.78 (0.60–1.00)
VINO	0.21 (0.04–1.00)	0.18 (0.04–0.88)	NA	0.23 (0.07–0.74)	0.69 (0.19–2.56)
RITA 3	1.17 (0.74–1.85)	0.78 (0.49–1.23)	NA	0.91 (0.65–1.28)	NA
Combined or all trials (random effects)	0.96 (0.72–1.27)	0.79 (0.53–1.16)	0.73 (0.61–0.88)	0.84 (0.68–1.02)	0.67 (0.48–0.94)
P value for heterogeneity	0.06	0.23	0.51	0.05	0.0002

FRISC II = Fast Revascularization During Instability in Coronary Artery Disease II Trial; MATE = Medicine versus Angiography in Thrombolytic Exclusion Trial; RITA 3 = Randomized Intervention Trial of Unstable Angina 3 Trial; TACTICS-TIMI 18 = Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction 18 Trial; TIMI IIIB = Thrombolysis in Myocardial Infarction IIIB Trial; VANQWISH = Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital Trial; VINO=Value of First Day Coronary Angiography/Angioplasty In Evolving Non ST-Segment Elevation Myocardial Infarction. An Open Multicenter Randomized Trial; MI = myocardial infarction; NA = data not available.

\*Data presented as a ratio of the odds of the outcome in the invasive group as compared with the odds of the outcome in the noninvasive group such that an odds ratio (OR) of <1 indicates that the invasive strategy was superior and an OR of >1 indicates that the conservative strategy was superior.

Sources of the observed heterogeneity were identified in our meta-regression analysis. Trials that included a higher proportion of patients with ST-segment depression on admission demonstrated a greater magnitude of benefit for an invasive strategy with respect to all 3 outcomes (posterior probabilities 0.075 for all-cause mortality, 0.025 for re-hospitalization, and 0.010 for the composite endpoint of death or nonfatal myocardial infarction). As an example, Figure 3 provides a graphical representation of this relationship for the combined endpoint of death or nonfatal myocardial infarction.

Trials in which a greater proportion of patients were revascularized after being randomized to an invasive strategy also showed a greater magnitude of benefit for an invasive strategy (posterior probabilities 0.005 for all-cause mortality, 0.007 for re-hospitalization, and 0.03 for the composite endpoint or death or nonfatal re-infarction; Figure 4).

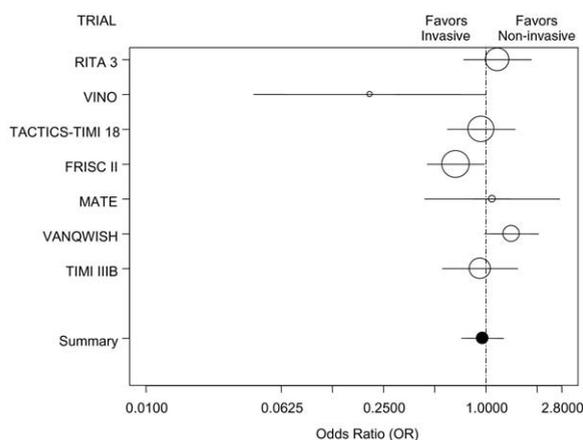
Trials with a longer average time to cardiac catheterization in the patients randomized to an invasive strategy showed greater reductions from an invasive strategy on the odds of re-hospitalization (posterior probability 0.007) but not the other two outcomes (posterior probabilities 0.24 for all-cause mortality and 0.35 for re-hospitalization). Trials with longer follow-up times also showed greater reductions from an invasive strategy on the odds of re-hospitalization (posterior probability 0.06) but not the other two outcomes (posterior probabilities 0.65 for all-cause mortality and 0.79 for re-hospitalization).

There were no associations between any outcomes and study level differences in the proportion of patients with cardiac enzyme elevation on admission (posterior probabilities

0.50 for all-cause mortality, 0.40 for re-hospitalization, and 0.57 for the composite endpoint or death or nonfatal re-infarction), baseline mortality rates (posterior probabilities 0.78 for all-cause mortality, 0.68 for re-hospitalization, and 0.84 for the composite endpoint or death or nonfatal re-infarction), the percentage of patients in the noninvasive group who underwent angiography (posterior probabilities 0.28 for all-cause mortality, 0.88 for re-hospitalization, and 0.37 for the composite endpoint or death or nonfatal re-infarction), the portion of patients in the noninvasive group who were re-vascularized (posterior probabilities 0.16 for all-cause mortality, 0.55 for re-hospitalization, and 0.27 for the composite endpoint or death or nonfatal re-infarction), or the proportion of patients with multi-vessel disease (posterior probabilities 0.63 for all-cause mortality, 0.13 for re-hospitalization, and 0.67 for the composite endpoint or death or nonfatal re-infarction).

## Discussion

This meta-analysis demonstrates that when compared with a conservative strategy, an invasive management strategy reduces rates of re-hospitalization and the combined endpoint of fatal and nonfatal re-infarction for patients with unstable angina and non-ST-elevation MI. A nonsignificant trend favoring an invasive strategy for reducing the composite endpoint of death or nonfatal re-infarction was also observed, but there was no advantage of either strategy with respect to all-cause mortality or nonfatal re-infarction. The confidence intervals for our



**Figure 1** Comparison of invasive and noninvasive strategies with respect to the likelihood of all-cause mortality. Data are presented as a ratio of the odds of all-cause mortality in the invasive group as compared with the odds of the outcome in the non-invasive group such that an odds ratio (OR) of  $<1$  indicates that the invasive strategy was superior and an OR of  $>1$  indicates that the conservative strategy was superior. The hollow circles represent the ORs from the individual trials, with the size of the circles reflecting the sample sizes of the trials. The solid circle represents the summary odds ratio. The horizontal bars extending from the circles represent the 95% confidence intervals for the OR. FRISC II = Fast Revascularization During Instability in Coronary Artery Disease II Trial; MATE = Medicine versus Angiography in Thrombolytic Exclusion Trial; RITA 3 = Randomized Intervention Trial of Unstable Angina 3 Trial; TACTICS-TIMI 18 = Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18 Trial; TIMI IIIB = Thrombolysis in Myocardial Infarction IIIB Trial; VANQWISH = Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital Trial; VINO=Value of First Day Coronary Angiography/Angioplasty In Evolving Non ST-Segment Elevation Myocardial Infarction. An Open Multi-center Randomized Trial; MI = myocardial infarction.

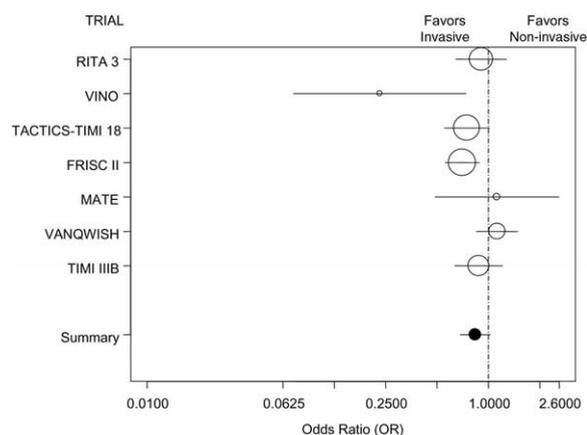
nonsignificant results indicate that although we are unable to exclude small but clinically meaningful differences between treatment strategies, large differences are unlikely.

The magnitude of benefit from an invasive strategy was greater for trials in which a higher proportion of patients underwent subsequent revascularization. Therefore, it appears that the advantage of an invasive management strategy results from the ability to intervene appropriately using prognostic information arising from a direct assessment of coronary anatomy.

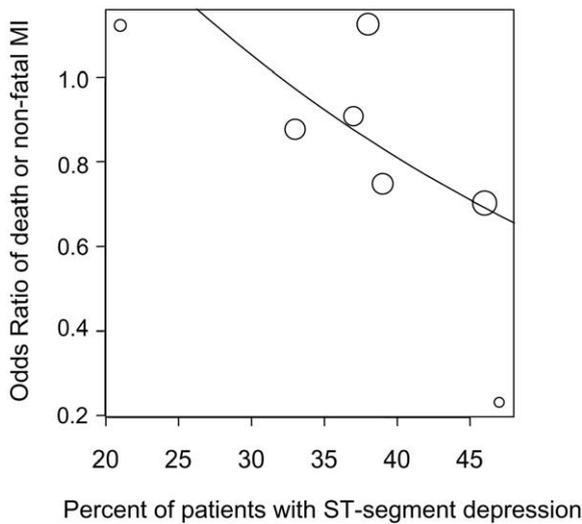
Our results suggest that unstable angina/non-ST-segment elevation MI patients of all risk levels, not only those who are considered to be at high risk, may benefit from early angiography with subsequent revascularization, if appropriate. Although the presence of high-risk features may be useful for prognostication and to institute specific therapy (eg, ACE inhibitors), our analysis indicates that these characteristics should not necessarily influence whether or when angiography should be performed.

Trials that enrolled a higher proportion of patients with ST-segment depression demonstrated a greater benefit for an invasive strategy. This finding supports the current European Society of Cardiology<sup>1</sup> and American College of Cardiology/American Heart Association<sup>2,3</sup> guidelines. However, our results showing no association between the proportion of patients with cardiac enzyme elevation on admission and the magnitude of benefit with an invasive strategy are in contrast with these guidelines and results from the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) trial.<sup>19</sup> Many of the trials reported in our analysis relied on creatinine kinase levels for biochemical evidence of myocardial injury. Troponin is a better prognostic marker,<sup>20</sup> but there were, unfortunately, too few studies to perform additional analysis that may have added further insight into this issue.

Our meta-regression analysis also demonstrates that an invasive strategy leads to greater reductions in rates of



**Figure 2** Comparison of invasive and noninvasive strategies with respect to the likelihood of the composite endpoint of death or nonfatal myocardial infarction. Data are presented as a ratio of the odds of the composite endpoint in the invasive group as compared with the odds of the outcome in the noninvasive group such that an odds ratio (OR) of  $<1$  indicates that the invasive strategy was superior and an OR of  $>1$  indicates that the conservative strategy was superior. The hollow circles represent the ORs from the individual trials, with the size of the circles reflecting the sample sizes of the trials. The solid circle represents the summary odds ratio. The horizontal bars extending from the circles represent the 95% confidence intervals for the OR. FRISC II = Fast Revascularization During Instability in Coronary Artery Disease II Trial; MATE = Medicine versus Angiography in Thrombolytic Exclusion Trial; RITA 3 = Randomized Intervention Trial of Unstable Angina 3 Trial; TACTICS-TIMI 18 = Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis in Myocardial Infarction 18 Trial; TIMI IIIB = Thrombolysis in Myocardial Infarction IIIB Trial; VANQWISH = Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital Trial; VINO=Value of First Day Coronary Angiography/Angioplasty In Evolving Non ST-Segment Elevation Myocardial Infarction. An Open Multicenter Randomized Trial; MI = myocardial infarction.



**Figure 3** The effect of management strategy on the odds of the composite endpoint of death or nonfatal infarction as a function of the percentage of patients in each of the trials with ST-segment depression. Data are presented as a ratio of the odds of the composite endpoint in the invasive group as compared with the odds of the outcome in the noninvasive group such that an odds ratio (OR) of  $<1$  indicates that the invasive strategy was superior and an OR of  $>1$  indicates that the conservative strategy was superior. Each circle represents the OR from the individual trials, with the area of the circles being proportional to the inverse of the variance of the log OR. The curve is the best-fit line from the meta-regression analysis and suggests that trials with a higher proportion of patients with ST-segment depression demonstrate a greater benefit of an invasive strategy. MI = myocardial infarction.

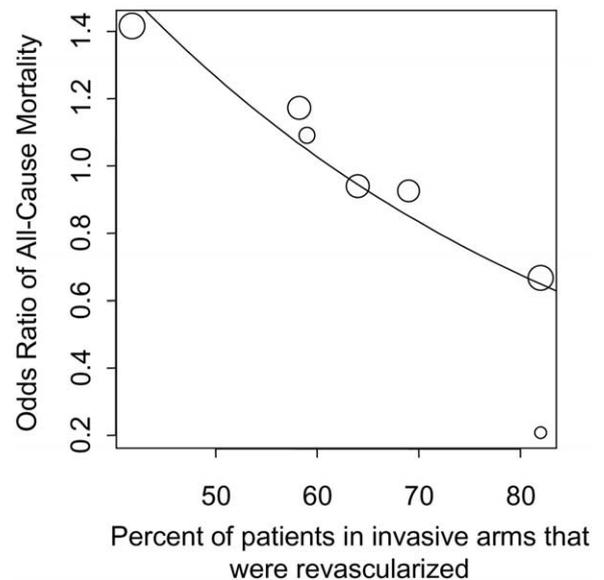
re-hospitalization for trials that had longer follow-up times. This may reflect the observation within the clinical trials that although the risk of re-infarction and death from acute non-ST-segment elevation MI is greatest in the early postinfarct period and the value of early intervention is maximal when intervention is carried out by 48–72 hours postinfarct,<sup>21,22</sup> the benefit from intervention with regard to clinical events increases over time.

The results of the TACTICS-TIMI 18 and FRISC II trials have been criticized because of their use of a higher threshold for diagnosing re-infarction in those patients undergoing angioplasty or coronary-artery bypass.<sup>9,23,24</sup> This may have falsely lowered the reported rates of re-infarction in the invasive arms of these trials and may have biased our re-infarction analyses in favor of an invasive strategy. Others suggest that this use of different definitions for patients postintervention is prognostically appropriate.<sup>24</sup> In a post hoc analysis, we excluded the TACTICS-TIMI 18 and FRISC II trials and found that the OR for the composite endpoint of death or re-infarction was 0.92 (95% CI: 0.70 to 1.20). The loss of statistical significance reflects the fact that these two trials were the most heavily and third most heavily weighted trials in our analysis and demonstrated the second and third largest magnitude of benefit from an invasive strategy. Our findings regarding rates of nonfatal re-infarction

are not subject to this potential bias, as neither TACTICS-TIMI 18 nor FRISC II reported this outcome and were thus not included in our analysis.

The nonsignificant results for all-cause mortality and the combined endpoint of death or re-infarction for unstable angina/non-ST-segment elevation MI (UN/NSTEMI) patients may have been due, in part, to the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial. In this trial, patients who underwent revascularization had a 30-day mortality rate of 4.8%, as compared with 1.3% in conservatively managed patients. This early hazard was not observed in any of the other included trials and may have masked the benefit of an invasive strategy. In addition, approximately 30% of patients in both the VANQWISH and MATE trials had ST-segment elevation on admission. These patients may represent “completed” infarction and accordingly may not have benefited from angiography (in particular because it was performed on average at 16 hours after admission and thus was not used as a primary reperfusion strategy).

The management of UA/NSTEMI has changed substantially with the advent of interventions that were not used in some of the trials included in our analysis. Coronary stents



**Figure 4** The effect of management strategy on the odds of all-cause mortality as a function of the percentage of patients in the invasive arms of the trials that were revascularized. Data are presented as a ratio of the odds of death in the invasive group as compared with the odds of the outcome in the noninvasive group such that an odds ratio (OR) of  $<1$  indicates that the invasive strategy was superior and an OR of  $>1$  indicates that the conservative strategy was superior. Each circle represents the OR from the individual trials, with the area of the circles being proportional to the inverse of the variance of the log OR. The curve is the best-fit line from the meta-regression analysis and suggests that trials with a higher proportion of patients that were revascularized demonstrate a greater benefit of an invasive strategy. MI = myocardial infarction.

reduce rates of re-stenosis following angioplasty<sup>25</sup> but were only routinely used in the 3 most recent trials.<sup>6,9,10</sup> Our meta-regression analysis demonstrated a greater magnitude of benefit in those trials in which a greater proportion of patients underwent revascularization. Therefore, the routine use of stents would be expected to lead to greater benefits from invasive management. Drug-eluting stents, which were not used by any of the included trials, may further reduce the rate of re-stenosis.<sup>26</sup> Glycoprotein IIb/IIIa therapy, in particular during percutaneous coronary intervention, reduces rates of death, myocardial infarction, and urgent revascularization<sup>27</sup> but were used by only 3 of the trials in this analysis.<sup>4,6,9</sup> All of these trials had treatment effects favoring an invasive strategy, and therefore, the routine use of these agents during percutaneous intervention should lead to an even greater benefit of an invasive strategy. In contrast, glycoprotein IIb/IIIa are also of modest benefit for patients not scheduled to undergo percutaneous intervention, in particular those at high risk of thrombotic complications.<sup>28</sup> Consequently, greater use of these agents for such patients may reduce the relative benefit of an invasive strategy. That said, superiority of an invasive management strategy was still observed in the TACTICS-TIMI 18 trial even though all patients received tirofiban.

Economic analyses based on the VANQWISH and Thrombolysis in Myocardial Infarction (TIMI IIB) trials<sup>29,30</sup> suggest that the routine performance of coronary angiography in all UA/STEMI patients may not be economically justifiable. However, the trials on which these analyses were based did not find reductions in rates of either re-hospitalization or re-infarction. In contrast, when these outcomes are included, as was done in cost-effectiveness analyses from the TACTICS-TIMI 18<sup>31</sup> and FRISC II<sup>32</sup> trials, it appears that the benefits of an invasive strategy are achieved without substantial increases in cost. Moreover, any incremental cost associated with routine early angiography would have to be weighed against incremental improvements in quality of life. This tradeoff has not been adequately assessed.

In summary, our analysis demonstrates reductions in rates of fatal or nonfatal re-infarction and hospital readmission but not all-cause mortality with the use of an invasive management strategy for patients with unstable angina/non-ST-segment elevation MI. Although patients with ST-segment depression may particularly benefit from the use of an early invasive strategy, our results suggest that routine angiography and subsequent revascularization, if appropriate, should be considered for all patients with unstable angina/non-ST-segment elevation acute MI and not only those at high risk.

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