REVIEW

Routine vs Selective Invasive Strategies in Patients With Acute Coronary Syndromes

A Collaborative Meta-analysis of Randomized Trials

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Context Patients with unstable angina or non–ST-segment elevation myocardial infarction (NSTEMI) can be cared for with a routine invasive strategy involving coronary angiography and revascularization or more conservatively with a selective invasive strategy in which only those with recurrent or inducible ischemia are referred for acute intervention.

Objective To conduct a meta-analysis that compares benefits and risks of routine invasive vs selective invasive strategies.

Data Sources Randomized controlled trials identified through search of MEDLINE and the Cochrane databases (1970 through June 2004) and hand searching of cross-references from original articles and reviews.

Study Selection Trials were included that involved patients with unstable angina or NSTEMI who received a routine invasive or a selective invasive strategy.

Data Extraction Major outcomes of death and myocardial infarction (MI) occurring from initial hospitalization to the end of follow-up were extracted from published results of eligible trials.

Data Synthesis A total of 7 trials (N=9212 patients) were eligible. Overall, death or MI was reduced from 663 (14.4%) of 4604 patients in the selective invasive group to 561 (12.2%) of 4608 patients in the routine invasive group (odds ratio [OR], 0.82; 95% confidence interval [CI], 0.72-0.93; $P=.001$). There was a nonsignificant trend toward fewer deaths (6.0% vs 5.5%; OR, 0.92; 95% CI, 0.77-1.09; $P=.33$) and a significant reduction in MI alone (9.4% vs 7.3%; OR, 0.75; 95% CI, 0.65-0.88; $P<.001$). Higher-risk patients with elevated cardiac biomarker levels at baseline benefited more from routine intervention, with no significant benefit observed in lower-risk patients with negative baseline marker levels. During the initial hospitalization, a routine invasive strategy was associated with a significantly higher early mortality (1.1% vs 1.8% for selective vs routine, respectively; OR, 1.60; 95% CI, 1.14-2.25; $P=.007$) and the composite of death or MI (3.8% vs 5.2%; OR, 1.36; 95% CI, 1.12-1.66; $P=.002$). But after discharge, the routine invasive strategy was associated with fewer subsequent deaths (4.9% vs 3.8%; OR, 0.76; 95% CI, 0.62-0.94; $P=.01$) and the composite of death or MI (11.0% vs 7.4%; OR, 0.64; 95% CI, 0.56-0.75; $P<.001$). At the end of follow-up, there was a 33% reduction in severe angina (14.0% vs 11.2%; OR, 0.77; 95% CI, 0.68-0.87; $P<.001$) and a 34% reduction in rehospitalization (41.3% vs 32.5%; OR, 0.66; 95% CI, 0.60-0.72; $P<.001$) with a routine invasive strategy.

Conclusions A routine invasive strategy exceeded a selective invasive strategy in reducing MI, severe angina, and rehospitalization over a mean follow-up of 17 months. But routine intervention was associated with a higher early mortality hazard and a trend toward a mortality reduction at follow-up. Future strategies should explore ways to minimize the early hazard and enhance later benefits by focusing on higher-risk patients and optimizing timing of intervention and use of proven therapies.

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DESPITE ADVANCES IN INVASIVE coronary procedures over the past decade, their optimal role and timing in patients with unstable angina and non–ST-segment myocardial infarction (NSTEMI) remains a challenge.[1] The question of whether to routinely refer patients with unstable angina or NSTEMI for invasive procedures, or whether to treat such patients aggressively with pharmacological interventions followed by selective referral of those with refractory or inducible ischemia, is a decision clinicians commonly face. Uncertainty about the value of a routine invasive strategy is reflected by widespread variations in procedure use among individual clinicians, institutions, and countries.[2-4] Over the past decade, randomized trials and large-scale registries addressing this question have spawned debate, partly because they pit different management philosophies

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against each other and partly because they have challenged clinical practice in some settings.

We sought to evaluate the early and late effects of a routine invasive strategy compared with a selective invasive strategy on major cardiovascular outcomes in patients with unstable angina and NSTEMI, based on the totality of data from randomized trials. If benefits of a routine intervention emerge early, then it could be argued that strategies for the care of such patients should be geared toward rapid catheterization and early revascularization. If, on the other hand, benefits are delayed, a more selective approach might be clinically preferable. To accomplish this task, we performed a collaborative meta-analysis of the randomized trials, focusing on key outcomes during the initial hospitalization and over the longer term.

METHODS

Search Strategy

Studies were identified through a computerized literature search of the MEDLINE and Cochrane databases from 1970 through June 2004 and screening of abstracts from major cardiology meetings. In addition, extensive hand searching was performed using cross-references from original articles and reviews.

Definitions

A routine invasive strategy was defined as the referral of all patients with unstable angina or NSTEMI for coronary angiography followed by revascularization in those with suitable coronary anatomy. A selective invasive strategy (also referred to as a conservative or noninvasive strategy) was defined as an approach whereby patients were initially treated with pharmacological therapy, after which cardiac catheterization and revascularization was performed only for those with recurrent symptoms or objective evidence of inducible ischemia on noninvasive testing.

Study Selection Criteria

Trials were included if they enrolled patients with unstable angina or NSTEMI and randomly allocated patients to receive a routine invasive strategy or a selective invasive strategy. Trials were excluded if the majority of patients randomized in the trial had stable angina pectoris or acute ST-segment elevation myocardial infarction (MI). Trials with inadequate concealment of the randomized treatment allocation (eg, allocation by day of the week) were excluded, as were trials in which inclusion was determined after the performance of coronary angiography.

Data Extraction and Statistical Analyses

Data on in-hospital and longer-term death, nonfatal MI, the composite of death or nonfatal MI, Canadian Cardiovascular Society class III or IV angina, and rehospitalization were extracted from each of the published studies independently by 2 investigators. The extracted data were then sent to the principal investigators of the selected studies, who were invited to participate in this collaborative meta-analysis. They were asked to verify the accuracy of the data and, when necessary, to provide additional data. Data were checked and verified by the principal investigators in all of the included trials. Procedure-related and non–procedure-related MI was defined in this analysis according to how it was reported in each of the individual trials.

The statistical methods used to combine the data have been described in detail and used extensively.[5] The underlying principle is the comparison of patients allocated to intervention in a given trial only with those allocated to control treatment in the same trial, avoiding direct comparisons of patients across different trials. These are basically the standard methods for the combination of information from multiple 2×2 tables, as reviewed by Mantel and Haenszel[6] and modified by Yusuf et al.[7] This method entailed calculating the observed events (O, number of events in the treatment group) minus the expected events (E, average number of events for treatment and control groups) and determining the variance (V) for each trial. Grand totals were calculated for each and the ratio of the 2 was used to estimate the odds ratio (OR) and its 95% confidence interval (CI) for each trial. The χ^2 tests for heterogeneity were approximated by summing the N separate χ^2 test statistics ($O-E^2/V$) for each trial and subtracting the overall χ^2 value (GT^2/SIV, where GT indicates grand total and SIV, the sum of the individual variances) from this, using $N-1$ degrees of freedom.[7] The data were also analyzed using a random-effects model,[8] and the relative risks and 95% CIs for each outcome are presented; however, in no case did the results qualitatively differ from those of the primary analysis. Comprehensive Meta-analysis version 1.0.25 (Biostat Inc, Englewood, NJ) was used for the analysis. $P<.05$ was set as the level of significance.

RESULTS

We identified 84 articles, of which 14 were reports of the main findings of randomized controlled trials. Of these 14 eligible trials, 7 were excluded[9-22] because patient eligibility was based on results of coronary angiography (n=4),[9-12] because they were limited mainly to patients with ST-segment elevation MI who were receiving thrombolytic therapy (n=2),[13,14] or because randomization was based on day of the week (n=1).[15]

Seven trials involving 9208 patients (4608 routine invasive and 4604 selective invasive) met the inclusion criteria and were included in the analysis (TABLE 1).[16-22] Verification of data by the trials' principal investigators was achieved in 100% of the trials.

Baseline Characteristics

Baseline characteristics are shown in TABLE 2. The weighted mean duration of follow-up of all patients was 17.3 (range, 6-24) months. The mean age of patients was 62.4 (range, 59-66) years. The mean proportion of patients with diabetes was 18.9% (range,

12%-28%), and 32.5% (range, 21%-43%) had a history of MI. A total of 59.0% of patients presented with NSTEMI and 41.0% with unstable angina. Electrocardiographic ST-segment depression was present at baseline in 37.0% of patients, ST-segment elevation (mostly transient) in 9.6%, and T-wave inversion in 49.4%.

Table 1. Entry Criteria, Use of Antithrombotic Medications, Timing of Interventions, and Definitions of Non–Procedure-Related and PCI-Related Myocardial Infarction in Trials of Routine vs Selective Invasive Management of Acute Coronary Syndromes

	Antithrombotic Treatment		Time to Cardiac Catheterization		Enzyme/Marker Criteria	
Source	Background	GpIIb/IIIa Inhibitor, %	Routine Invasive Group, h	Selective Invasive Group, d	Non–Procedure-Related MI	PCI-Related MI
TIMI IIIB,[16] 1994	Aspirin, UFH	0	36	7.1	CK >ULN or CK-MB >2× ULN	CK >2× ULN or CK-MB >ULN
MATE,[17] 1998	Aspirin, UFH	0	16	3.5	CK >230 U/L (males) or >150 U/L (females) CK-MB index >3%	Re-elevation of CK >230 U/L (males) or >150 U/L (females) CK-MB index >3%
VANQWISH,[18] 1998	Aspirin, UFH	0	48	14	CK >2× ULN or CK-MB >ULN	CK >2× ULN or CK-MB >ULN
FRISC II,[19] 1999	Aspirin, dalteparin	10	96	17	CK-MB mass >ULN in 1 sample or CK, CK-B, or CK-MB activity >2× ULN in 1 sample or CK-MB activity >ULN in 2 samples	CK-MB mass >1.5× ULN in 1 sample OR CK, CK-B, or CK-MB activity >3× ULN in 1 sample OR >1.5× ULN in 2 samples
TACTICS-TIMI 18,[20] 2001	Aspirin, UFH, tirofiban	94	22	3.3	CK-MB >ULN and >50% over previous	CK-MB >3× ULN and >50% over previous
VINO,[21] 2002	Aspirin, UFH	0	6.2	61	CK-MB >1.5× ULN	Not diagnosed first 72 h
RITA 3,[22] 2002	Aspirin, enoxaparin	25	48	42.5	CK-MB and troponin >2× ULN	CK-MB and troponin >2× ULN

Abbreviations: CK, creatine kinase; CK-MB, creatine kinase–MB fraction; FRISC, Fragmin and Fast Revascularization During Instability in Coronary Artery Disease; Gp, glycoprotein; MATE, Medicine vs Angioplasty for Thrombolytic Exclusions; MI, myocardial infarction; PCI, percutaneous coronary intervention; RITA, Randomized Intervention Trial of Unstable Angina; TACTICS, Treat Angina With Aggrastat and Determine Cost of Therapy With Invasive or Conservative Strategy; TIMI, Thrombolysis in Myocardial Infarction; UFH, unfractionated heparin; ULN, upper limit of normal; VANQWISH, Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital; VINO, Value of First Day Angiography/Angioplasty in Evolving ST-Segment Elevation Myocardial Infarction.

Table 2. Baseline Characteristics of Included Studies

Characteristic	TIMI IIIB (n = 1473)	MATE (n = 201)	VANQWISH (n = 920)	FRISC II (n = 2457)	TACTICS-TIMI 18 (n = 2220)	VINO (n = 131)	RITA 3 (n = 1810)	Total (N = 9208)
Age, mean, y	59	59	61	65	62	66	63	62.4*
Men, No. (%)	972 (66)	129 (64)	896 (98)	1708 (70)	1463 (66)	80 (61)	1128 (62)	6376/9208 (69.2)
Diabetes, No. (%)	NA	36 (18)	240 (26)	299 (12)	613 (28)	33 (25)	244 (13)	1465/7735 (18.9)
Previous MI, No. (%)	604 (41)	43 (21)	396 (43)	546 (22)	866 (39)	34 (26)	701 (39)	2990/9208 (32.5)
Suspected MI at randomization, No. (%)	471 (32)	201 (100)	916 (100)	1348 (58)	826 (37)	131 (100)	1358 (75)	5251/9208 (57.0)
ST-segment elevation, No. (%)	147 (10)	61 (30)	272 (32)	0	266 (12)	0	139 (8)	885/9208 (9.6)
ST-segment depression, No. (%)	486 (33)	47 (23)	356 (41)	1114 (46)	688 (31)	60 (46)	660 (37)	3411/9208 (37.0)
T-wave inversion, No. (%)	678 (46)	66 (43)	448 (49)	NA	777 (35)	NA	1298 (72)	3267/6620 (49.4)
Thrombolytic therapy, No. (%)	722 (49)	0	115 (13)	0	0	0	0	837/9208 (9.1)
Duration of follow-up, mean, mo	12	21	23	24†	6	6	24	17.3*
Revascularization rates, routine group/selective group, %								
Revascularization during initial hospitalization	60/40	58/37	44/33	71/9	60/36	78/39	44/10	58.4/24.0
Revascularization at end of follow-up	64/58	58/37	44/33	78/43	61/44	78/39	57/28	63.6/41.5
PCI at follow-up	39/32	43/30	19/7	44/21	42/29	52/13	36/16	25.3/9.9
CABG surgery at end of follow-up	24/30	16/8	15/7	38/23	22/16	35/30	22/12	17.3/8.8

Abbreviations: CABG, coronary artery bypass graft; MI, myocardial infarction; NA, data not available; PCI, percutaneous coronary intervention. See Table 1 footnote for trial dates, references, and expansions of trial names.
*Mean was weighted according to the sample size of each trial.
†Twelve-month FRISC II data were used for all analyses.

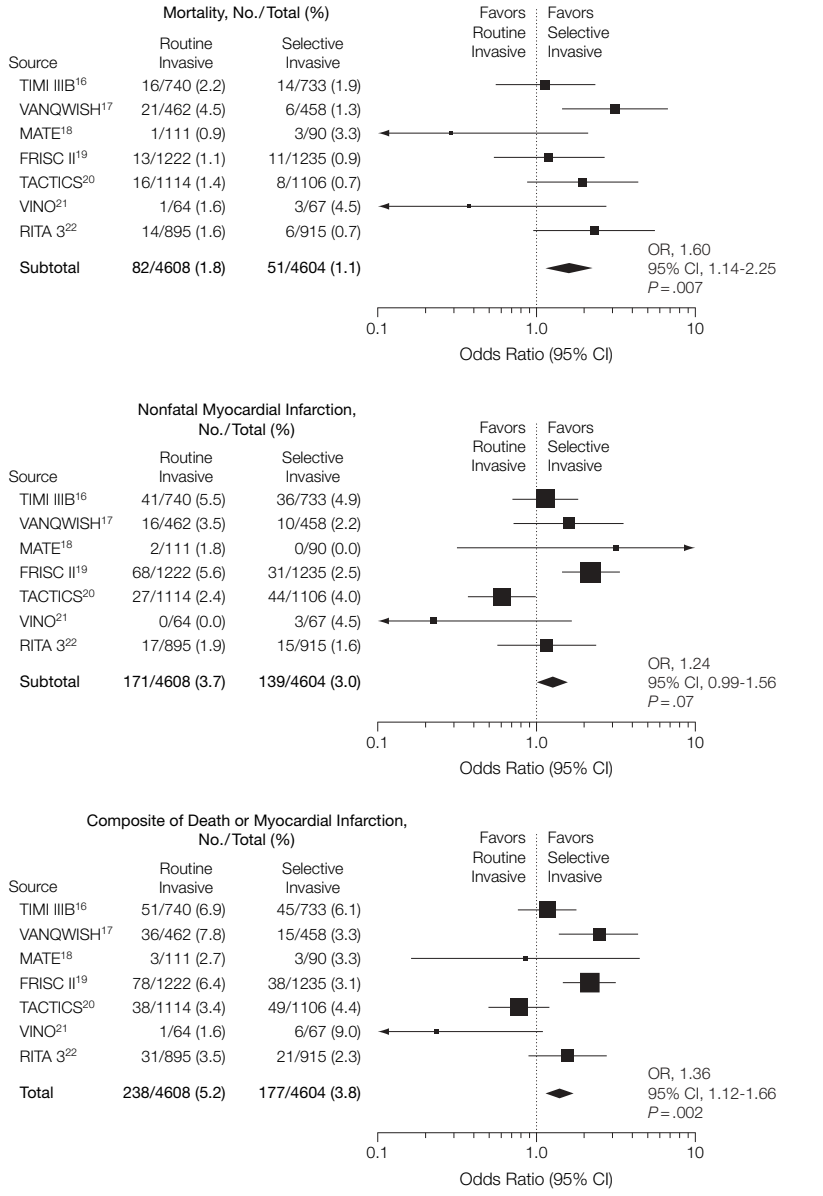
In-hospital and follow-up revascularization rates among the studies are shown in Table 1. During the initial hospitalization, 2691 (58.4%) of 4608 patients underwent revascularization in the routine intervention group and 1104 (24.0%) of 4604 patients underwent revascularization in the selective intervention group, for a 34.4% in-hospital contrast in revascularization between the groups. At the end of follow-up, 2934 (63.6%) of 4608 underwent revascularization in the routine invasive group compared with 1909 (41.5%) of 4604 in the selective invasive group, for a 22.1% overall contrast in revascularization between the groups. Percutaneous coronary intervention (PCI) was performed in 1167 (25.3%) of 4608 in the routine invasive group and 454 (9.9%) of 4604 in the selective invasive group. Coronary artery bypass graft surgery was performed in 796 (17.3%) of 4608 in the routine invasive group and in 404 (8.8%) of 4604 in the selective invasive group.

Main Outcomes

Randomization to Hospital Discharge. Main outcomes for this period are shown in FIGURE 1. During the initial hospitalization, 82 (1.8%) of 4608 patients in the routine invasive group died compared with 51 (1.1%) of 4604 in the selective invasive group (OR, 1.60; 95% CI, 1.14-2.25; $P=.007$). Myocardial infarction was also increased, with 171 (3.7%) of 4608 having had an MI during the initial hospitalization in the routine invasive group, compared with 139 (3.0%) of 4604 in the selective invasive group (OR, 1.24; 95% CI, 0.99-1.56; $P=.07$). Overall, 238 (5.2%) of 4608 patients in the routine invasive group had a death or MI during the initial hospitalization compared with 177 (3.8%) of 4607 in the selective invasive group (OR, 1.36; 95% CI, 1.12-1.66; $P=.002$).

Hospital Discharge to End of Follow-up. Main outcomes for this period are shown in FIGURE 2. After hospital discharge the number of events were fewer in the routine intervention group. Overall, 172 (3.8%) of 4526 patients died during this period in the routine invasive group compared with 223 (4.9%) of 4552 in the selective invasive group (OR, 0.76; 95% CI, 0.62-0.94; $P=.01$). Similarly, there was a 44% relative odds reduction in MI during this period (164/4370 [3.8%] vs 294/4430 [6.6%]; OR, 0.56; 95% CI, 0.46-0.67; $P<.001$) and a 36% relative odds reduction in the composite of death or MI (323/4370 [7.4%] vs 486/4430 [11.0%]; OR, 0.64; 95% CI, 0.56-0.75; $P<.001$).

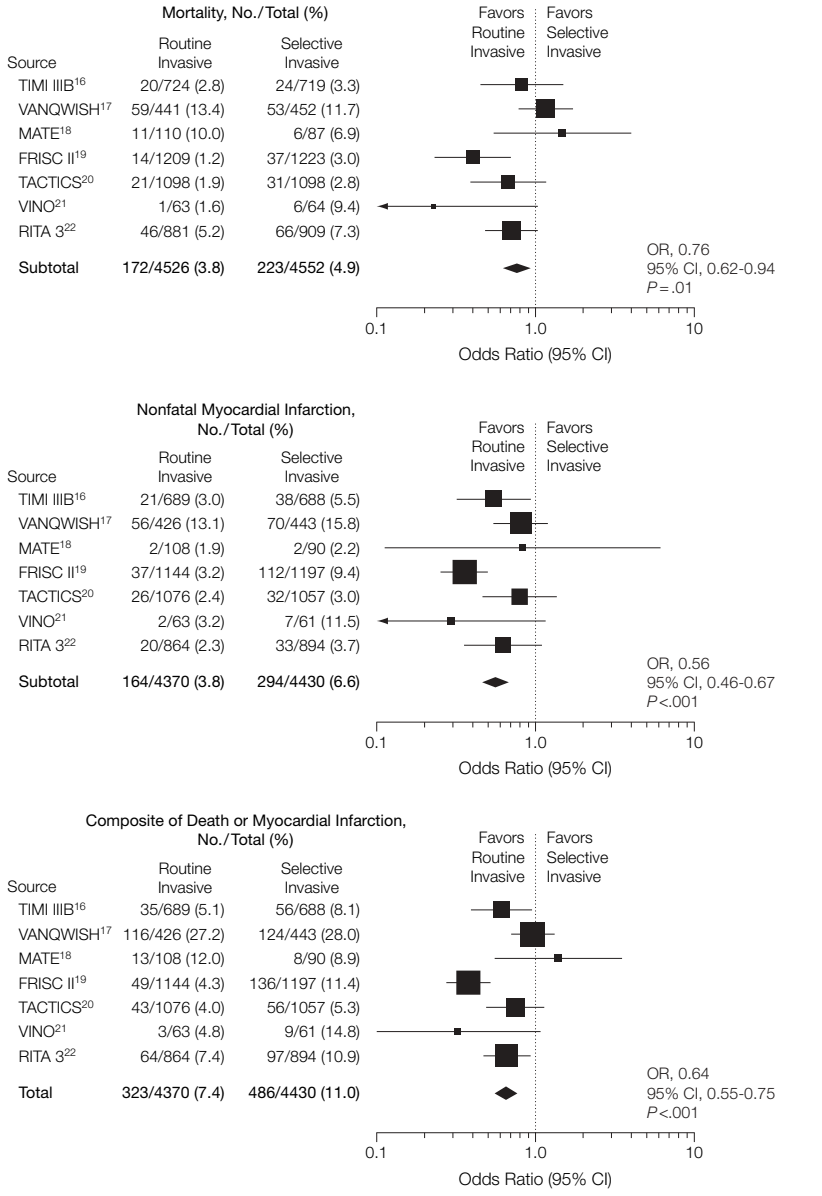
Figure 1. Main Outcomes From Randomization to Hospital Discharge in Trials of Routine vs Selective Invasive Management of Acute Coronary Syndromes



Sizes of data markers are proportional to the amount of data contributed by each trial. Tests for heterogeneity: mortality, $P=.15$; nonfatal myocardial infarction (MI), $P=.001$; composite of death or MI, $P=.001$. Relative risks and 95% confidence intervals (CIs) from random-effects model: mortality, 1.56 (0.96-2.53); nonfatal MI, 1.20 (0.73-1.97); death or MI, 1.31 (0.85-2.01). OR indicates odds ratio. See Table 1 footnote for trial dates and expansions of trial names.

Randomization to End of Follow-up. Main outcomes for this period are shown in FIGURE 3. Overall, death occurred in 254 (5.5%) of 4608 patients in the routine invasive group compared with 274 (6.0%) of 4604 in the selective invasive group, a nonsignificant 8% relative odds reduction in mortality (OR, 0.92; 95% CI, 0.77-1.09; $P=.33$). Myocardial infarction occurred in 335 (7.3%) of 4608 patients in the routine invasive group and 433 (9.4%) of 4604 in the selective invasive group (OR, 0.75; 95% CI, 0.65-0.88; $P<.001$). The composite of death or MI was also significantly reduced in the routine invasive group: 561 (12.2%) of 4608 compared with 663 (14.4%) of 4604 in the selective invasive group (OR, 0.82; 95% CI, 0.72-0.93; $P=.001$).

Figure 2. Main Outcomes From Hospital Discharge to End of Follow-up in Trials of Routine vs Selective Invasive Management of Acute Coronary Syndromes



Sizes of data markers are proportional to the amount of data contributed by each trial. Tests for heterogeneity: mortality, $P=.04$; nonfatal myocardial infarction (MI), $P=.02$; composite of death or MI, $P=.001$. Relative risks and 95% confidence intervals (CIs) from random-effects model: mortality, 0.74 (0.52-1.05); nonfatal MI, 0.57 (0.40-0.80); death or MI, 0.65 (0.46-0.91). See Table 1 footnote for trial dates and expansions of trial names. OR indicates odds ratio.

Rehospitalization and Angina

There was a significant reduction in rehospitalizations with a routine invasive strategy (1889/4571 [41.3%] vs 1487/4576 [32.5%] for selective vs routine, respectively; OR, 0.66; 95% CI, 0.60-0.72; $P<.001$) (FIGURE 4). There was also a significant reduction in the proportion of patients with Canadian Cardiovascular Society class III or IV angina in the routine invasive strategy group compared with the selective invasive strategy group (633/4507 [14.0%] vs 507/4525 [11.2%]; OR, 0.77; 95% CI, 0.68-0.87; $P<.001$). A summary of ORs for all major outcomes is shown in TABLE 3.

Exploring Heterogeneity

There was evidence of heterogeneity in the outcome of in-hospital MI ($P=.001$ for heterogeneity) and the composite of death or MI ($P=.001$ for heterogeneity). Sensitivity analysis revealed that the source of this heterogeneity was almost entirely due to the TACTICS-TIMI 18 (Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Therapy–Thrombolysis in Myocardial Infarction 18) trial[20] (and to a lesser extent, the much smaller VINO [Value of First Day Angiography/Angioplasty in Evolving ST-Segment Elevation Myocardial Infarction] trial[21]) relative to the other studies ($P=.14$ for heterogeneity with TACTICS-TIMI 18 excluded). The possible reasons for the heterogeneity in early MI may have been related to the routine use of a glycoprotein IIb/IIIa antagonist in TACTICS but not in the other trials. Alternatively, it may have been related to the TACTICS differential cardiac marker threshold for an MI outcome after PCI (3 times the upper limit of normal), compared with a non–procedure-related MI (defined as cardiac marker levels above the upper limit

of normal) (Table 1). Since procedures were more commonly performed in the routine invasive group, this differential may have biased the results in favor of this group. Although some of the other trials also had a higher threshold for PCI-related MI, the differentials between PCI-related and spontaneous MIs were smaller than in TACTICS (Table 1).

Stratified Analyses

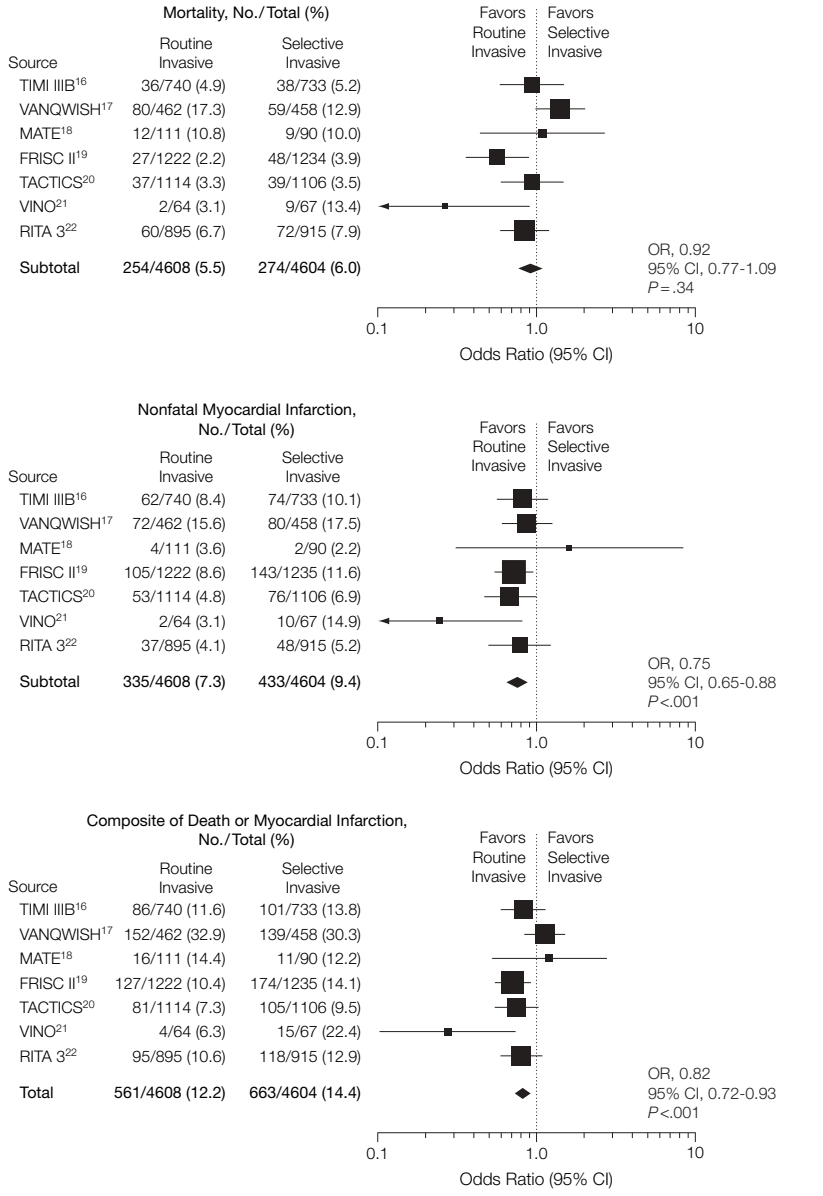
A stratified analysis according to year of publication was performed to assess the impact of advances in overall care, including medical and interventional therapies over the years (FIGURE 5). Trials published prior to 1999 demonstrated neutral results for death or MI at end of follow-up, whereas trials published after 1999 demonstrated a clear reduction in death or MI with a routine invasive strategy. Troponin data were available in the 3 most recently performed trials. In patients who were troponin-positive at baseline, there was a clear reduction in the composite of death or MI in favor of a routine invasive strategy. However, in those who were troponin-negative, there was no advantage of a routine invasive strategy. Similar results are observed when any biomarker (including creatine kinase, creatine kinase–MB, or troponin) was used. All the trials were included in this latter analysis.

COMMENT

Our meta-analysis has demonstrated that, in patients with unstable angina and NSTEMI, a routine invasive strategy is superior to a selective invasive (ie, conservative) strategy in reducing long-term major cardiovascular events, as well as severe angina and rehospitalizations. The benefits of a routine invasive strategy emerged mainly after hospital discharge; during the initial hospitalization, this strategy was associated with an increased early hazard. This early hazard, followed by later benefit, suggests that further strategies to favorably enhance the overall benefit-risk ratio associated with a routine invasive strategy need to be considered.

First, appropriate risk stratification of patients with unstable angina and NSTEMI can maximize the benefits of a routine invasive strategy by focusing on those patients who are at higher risk, in whom the absolute benefits of a routine invasive approach are greatest.[1] The main benefits of routine intervention over the long term were observed in higher-risk patients with positive baseline cardiac marker levels, with no such benefit observed in patients with negative marker levels (Figure 5), a finding also observed in subgroup analyses from 2 of the

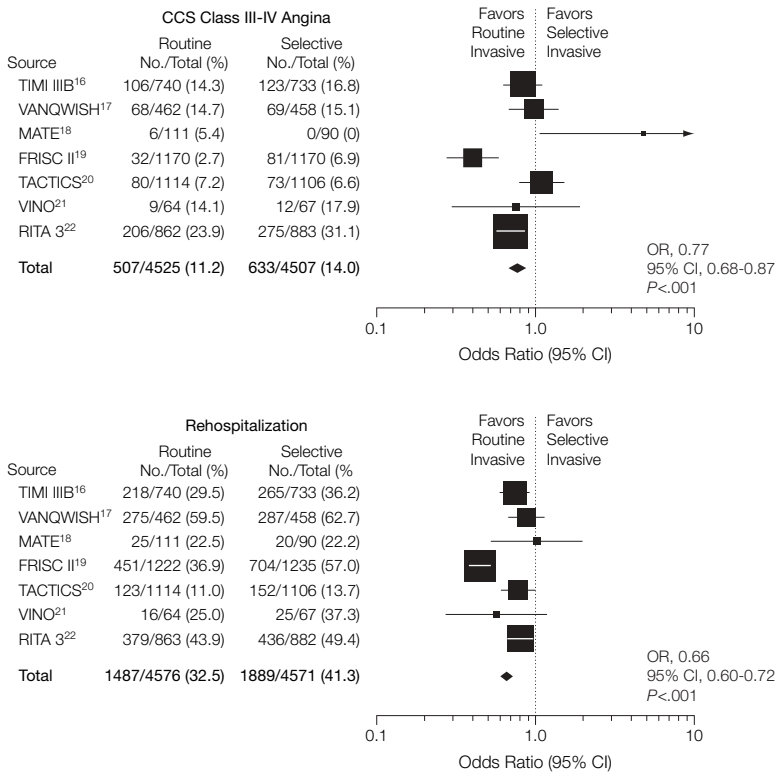
Figure 3. Main Outcomes From Randomization to End of Follow-up in Trials of Routine vs Selective Invasive Management of Acute Coronary Syndromes



Sizes of data markers are proportional to the amount of data contributed by each trial. Tests for heterogeneity: mortality, $P=.04$; nonfatal myocardial infarction (MI), $P=.51$; composite of death or MI, $P=.06$. Relative risks and 95% confidence intervals (CIs) from random-effects model: mortality, 0.88 (0.66-1.18); nonfatal MI, 0.76 (0.65-0.88); death or MI, 0.82 (0.68-0.99). See Table 1 footnote for trial dates and expansions of trial names. OR indicates odds ratio.

trials.[23,24] The early hazard associated with routine intervention might be deemed acceptable in the higher-risk patients but unacceptable in most lower-risk patients, in whom there is no evidence of long-term benefit.

Figure 4. Rates of Canadian Cardiovascular Society (CCS) Class III-IV Angina and Rehospitalization at End of Follow-up in Trials of Routine vs Selective Invasive Management of Acute Coronary Syndromes



Sizes of data markers are proportional to the amount of data contributed by each trial. Tests for heterogeneity: CCS class III-IV angina, $P<.001$; rehospitalization, $P<.001$. Relative risks and 95% confidence intervals (CIs) from random-effects model: CCS class III-IV angina, 0.78 (0.58-1.04); rehospitalizations, 0.71 (0.55-0.92). See Table 1 footnote for trial dates and expansions of trial names. OR indicates odds ratio.

Table 3. Summary of Odds Ratios for All Major Outcomes

Outcome	No./Total (%) Routine	No./Total (%) Selective	Odds Ratio (95% CI)	*P* Value
Randomization to Hospital Discharge				
Death	82/4608 (1.8)	51/4604 (1.1)	1.60 (1.14-2.25)	.007
Nonfatal MI	171/4608 (3.7)	139/4604 (3.0)	1.24 (0.99-1.56)	.07
Death or MI	238/4608 (5.2)	177/4604 (3.8)	1.36 (1.12-1.66)	.002
After Hospital Discharge to End of Follow-up				
Death	172/4526 (3.8)	223/4552 (4.9)	0.76 (0.62-0.94)	.01
Nonfatal MI	164/4370 (3.8)	294/4430 (6.6)	0.56 (0.46-0.67)	<.001
Death or MI	323/4370 (7.4)	486/4430 (11.0)	0.64 (0.56-0.75)	<.001
Randomization to End of Follow-up				
Death	254/4608 (5.5)	274/4604 (6.0)	0.92 (0.77-1.09)	.33
Nonfatal MI	335/4608 (7.3)	433/4604 (9.4)	0.75 (0.65-0.88)	<.001
Death or MI	561/4608 (12.2)	663/4604 (14.4)	0.82 (0.72-0.93)	.001

Abbreviations: CI, confidence interval; MI, myocardial infarction.

Despite these data and the recommendations of expert guideline committees,[1] contemporary registry data suggest that higher-risk patients are paradoxically being treated more conservatively, while lower-risk patients are more likely to undergo an invasive strategy.[3] The data from our meta-analysis further support the wider adoption of a routine invasive strategy in higher-risk patients and suggest that lower-risk patients, in whom the hazards have a greater likelihood of outweighing the benefits, might be better managed with a more selective approach. In addition to patients with positive baseline cardiac marker levels, the American College of Cardiology/American Heart Association guidelines recommend an invasive strategy in other high-risk groups, such as those with cardiogenic shock or significant heart failure and those with refractory symptoms who are already receiving maximal medical therapies.[1]

Second, the timing of angiography and revascularization in the routine invasive group may also influence both early and late outcomes. The timing of intervention in patients receiving a routine invasive strategy can involve either very early angiography (for example, within the first 24 hours), or it may involve a more delayed approach (after a period of a few days). Although the TACTICS trial (mean time to angiography, 22 hours) and FRISC II (Fragmin and Fast Revascularization During Instability in Coronary Artery Disease 2) trial (mean time to angiography, 4 days) both demonstrated benefit of a routine invasive strategy on a composite of events, the trial in which intervention was delayed (the FRISC II trial) additionally demonstrated a reduction in mortality. Because the benefits of a routine invasive strategy emerge mainly over the long term (with evidence of early hazard), very early timing of intervention may not enhance the benefits of routine intervention. On the other hand, it may be that there is an immediate hazard with any invasive or surgical procedure that cannot be mitigated by delaying the timing of the procedure. Thus,

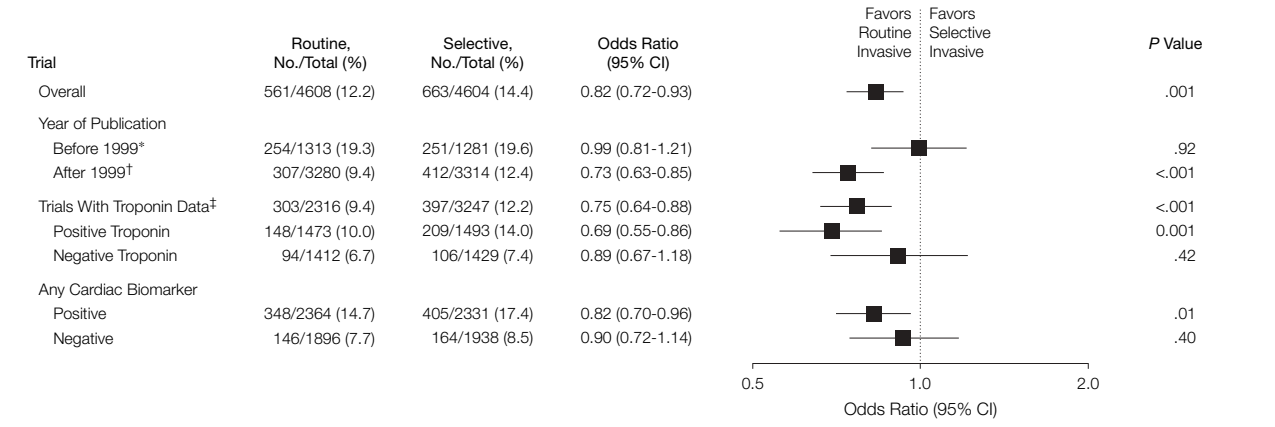
although a policy of very early intervention has been adopted in some regions, the benefits of this approach on major cardiovascular outcomes remain unclear compared with those of interventions performed after a few days. Clarifying this issue has considerable importance for optimum patient care as well as for the organization of health care services, especially access to rapid cardiac catheterization for all high-risk patients with acute coronary syndromes.

Two randomized studies have addressed the potential benefits of early intervention, with contrasting results. First, a very small, single-center trial demonstrated apparent benefit of an early invasive strategy vs a delayed invasive strategy (12/203 vs 24/207; relative risk, 0.51; 95% CI, 0.26-0.99); however, the CIs of this study were very wide, in keeping with its modest sample size and small number of outcome events.[25] Given these important limitations, a much larger number of patients is needed to reliably assess the effects of early vs delayed intervention. Second, a recent Dutch randomized trial of 1201 patients reported no benefit of a routine early invasive strategy, with an overall increase in MI.[26] As opposed to most of the trials in this meta-analysis, this trial used the same definition of spontaneous events and MI after PCI. In addition, newer therapies such as clopidogrel and high-dose statins were used in a greater proportion of patients in both groups compared with the older studies. These factors may have narrowed the difference between the 2 groups. Two additional large-registry studies have shown that patients who present to hospitals with catheterization laboratories undergo invasive procedures earlier, yet in these studies mortality was not improved in such centers and there were increases in bleeding and stroke.[2,27] Therefore, to reliably address the question of timing of intervention (ie, whether earlier is superior to delayed intervention) among patients undergoing a routine invasive strategy, much larger randomized trials than those currently reported are needed.

Third, greater use of adjunctive pharmacological therapies prior to and after PCI have the potential to reduce periprocedural events and could improve the outcomes associated with the routine invasive approach. Trials of clopidogrel in addition to aspirin have shown that pretreatment with these agents reduces the risk of events that occur prior to, during, and after the revascularization procedure.[28-31] However, the benefit of clopidogrel is apparent not only in patients treated prior to PCI (at least 6 hours) but also in those treated medically.[28] In both these groups, benefit emerges as early as 24 hours, with incremental reductions in death, MI, and stroke with continued long-term therapy.[31] Because the trials included in this meta-analysis were designed before the benefits of thienopyridines in patients with unstable angina and NSTEMI were known, these agents were mainly given to patients for 30 days following stent placement, thus creating an imbalance in their use between the groups, which may have impacted on the results of the trials.

Early use of glycoprotein IIb/IIIa inhibitors has also been proven to reduce cardiovascular events, mainly in patients with unstable angina and NSTEMI who are undergoing PCI.[32,33] Greater use of these agents in eligible patients would therefore be expected to enhance the benefits of a routine invasive strategy. The TACTICS-TIMI 18 trial used these agents as background

Figure 5. Stratified Analyses of Trials Published Before and After 1999 and According to Baseline Troponin and Cardiac Biomarker Status: Death or Myocardial Infarction From Randomization to Follow-up



Sizes of data markers are proportional to the amount of data contributed by each trial. Cardiac biomarkers are creatine kinase, creatine kinase–MB fraction, and troponin. In 3 of the 7 trials included in this analysis (VANQWISH, MATE, and VINO), all patients had elevated marker levels at baseline. See Table 1 footnote for trial dates and expansions of trial names.
*TIMI 3B, VANQWISH, and MATE.
†FRISC II, TACTICS, VINO, and RITA 3.
‡FRISC II, TACTICS, and RITA 3.

therapy in both groups for 48 hours, which may have contributed to the better outcomes in the routine invasive group in that study.

Although antithrombin agents such as enoxaparin are as effective as standard unfractionated heparin in patients with unstable angina and NSTEMI who are undergoing an invasive strategy,[34,35] newer agents such as the synthetic penta-saccharide fondaparinux or the direct thrombin inhibitor bivalirudin may potentially provide incremental benefit over unfractionated heparin in this setting and are currently being studied in large-scale randomized trials. Meanwhile, increased long-term use of statins, β-blockers, and angiotensin-converting enzyme inhibitors would improve outcomes in patients with unstable angina and NSTEMI, regardless of management approach.

Combining the data from these trials comparing selective vs routine invasive strategies has several advantages. First, it improves statistical power to detect important differences between the groups. Because these trials involved a pragmatic clinical approach comparing 2 management strategies, revascularization procedures were allowed in both groups. Thus, contrast in revascularization rates between the routine and selective invasive strategies was modest (34% during the initial hospitalization and 22.1% at follow-up), which reduces statistical power in the individual trials. By combining the data in the form of a meta-analysis, as we have done, the power to detect even moderate but clinically important differences between the 2 strategies substantially increases. Second, there has been controversy about the interpretation of individual trial results when they may not intuitively support specific practice philosophies. It is possible that an unexpected result for a single outcome in a particular randomized trial may be real or due to the play of chance. For example, there has been discussion regarding the higher mortality associated with routine intervention in the VANQWISH (Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital) study[18] vs the others. However, sensitivity analysis demonstrates that when VANQWISH is removed from the analysis, there is still a consistent early risk in mortality among the other trials (OR, 1.35; 95% CI, 0.92-2.00), with no statistical heterogeneity. The advantage of combining the results of all trials addressing the same broad question is that the results reflect a wider range of practices and technical skills,[36] and a more robust estimate of risk is likely to be obtained.[35] This also minimizes the play of chance affecting a particular end point in any one trial. Consequently, if a real difference (or lack of a difference) exists, it is likely to be detected.

The largest benefits of a routine invasive strategy in our meta-analysis were in preventing severe angina and rehospitalization, followed by MI prevention and a trend toward a reduction in death. Given the 25% reduction in nonfatal MIs, most of which occurred after hospital discharge, it is plausible that the benefits of a routine invasive strategy on mortality could widen during even longer-term follow-up, as observed in at least 1 trial in this meta-analysis.[37,38] In the trials of coronary artery bypass graft surgery vs medical therapy, for example, reductions in mortality became evident only after 1 year, with maximum benefit not observed until 5 to 7 years.[39] Thus, longer-term follow-up of the patients included in the current trials would be important to further assess the relative value of the 2 strategies, particularly with respect to mortality.

In patients with unstable angina and NSTEMI, a routine early invasive strategy is superior to a selective invasive strategy in reducing major cardiovascular events as well as severe angina and rehospitalization. However, the main benefit of a routine invasive strategy was in preventing events over the longer term with evidence of early hazard. Therefore, future strategies should explore means of minimizing the early hazard and enhancing the later benefits by focusing on higher-risk patients, optimizing the timing of intervention, and maximizing the use of adjunctive evidence-based therapies.

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