Annals of Internal Medicine | REVIEW

Optimal Timing of Coronary Invasive Strategy in Non–ST-Segment Elevation Acute Coronary Syndromes

A Systematic Review and Meta-analysis

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Background: The optimal timing of coronary intervention in patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACSs) is a matter of debate. Conflicting results among published studies partly relate to different risk profiles of the studied populations.

Purpose: To do the most comprehensive meta-analysis of current evidence on early versus delayed invasive treatment in NSTE-ACS.

Data Sources: MEDLINE, PubMed Central, and Google Scholar databases; conference proceedings; ClinicalTrials.gov registry; and Current Controlled Trials registry through May 2012.

Study Selection: Available randomized, controlled trials (RCTs) and observational studies comparing early versus delayed intervention in the NSTE-ACS population.

Data Extraction: Data were extracted for populations, interventions, outcomes, and risk of bias. All-cause mortality was the prespecified primary end point. The longest follow-up available in each study was chosen. The odds ratio with 95% CI was the effect measure.

Data Synthesis: Seven RCTs (5370 patients) and 4 observational studies (77 499 patients) were included. Early intervention was less than 20 hours after hospitalization or randomization for RCTs and 24 hours or less for observational studies. Meta-analysis of the RCTs was inconclusive for a survival benefit associated with the early invasive strategy (odds ratio, 0.83 [95% CI, 0.64 to 1.09]; $P = 0.180$); a similar result emerged from the observational studies. With early versus late intervention, the odds ratios in the RCTs were 1.15 (CI, 0.65 to 2.01; $P = 0.63$) and 0.76 (CI, 0.56 to 1.04; $P = 0.090$) for myocardial infarction and major bleeding during follow-up, respectively.

Limitation: Current evidence from RCTs is limited by the small overall sample size, low numbers of events in some trials, and heterogeneity in the timing of intervention and in patient risk profiles.

Conclusion: At present, there is insufficient evidence either in favor of or against an early invasive approach in the NSTE-ACS population. A more definitive RCT is warranted to guide clinical practice.

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Invasive coronary revascularization has been shown to be superior to conservative medical treatment in patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACSs) and is recommended by international guidelines (1–3), but the optimal timing of intervention remains unclear; for example, data conflict about whether catheterization needs to be done early (within <20 to 24 hours) or whether it can safely be delayed while the patient receives medical therapy. In a recent meta-analysis of clinical trials published through 2009, we reported that, in patients with NSTE-ACS, a routine early invasive intervention strategy did not significantly improve outcomes compared with a delayed approach (4), but the CIs around our estimates were wide and we could not exclude a clinically relevant benefit of early invasive intervention. We updated our literature review into 2012 and reviewed observational studies in an attempt to more thoroughly summarize the literature comparing early versus delayed invasive revascularization in patients with NSTE-ACS.

Methods

The previous meta-analysis (4) and this update were done according to established methods (5, 6) and in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting systematic reviews and meta-analyses in health care interventions (7). Neither the original review nor the update was based on a written protocol or registered in a review registry.

Literature Search

An updated PRISMA flow chart providing detailed descriptions of publication screening and reasons for exclusion is shown in **Appendix Figure 1** (available at www.annals.org). We repeated our search of MEDLINE (**Appendix Table 1**, available at www.annals.org), PubMed Central, and Google Scholar and conference proceedings from the American College of Cardiology, American Heart Association, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and European Association

See also:

Web-Only
CME quiz (preview on page I-30)

of Percutaneous Cardiovascular Interventions scientific sessions to identify observational studies published between November 1994 and May 2012 and randomized, controlled trials (RCTs) published since our last search ended (24 September 2010) (4). We also searched clinical trial registries (www.clinicaltrials.gov and www.controlled-trials.com) for unpublished studies.

Selection Criteria and Internal Validity

Inclusion criteria for RCTs included a diagnosis of NSTE-ACS and allocation to early or delayed coronary revascularization, where early intervention was defined as coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting based on angiographic characteristics and physicians' clinical judgment) less than 20 hours after hospitalization or randomization. Delayed intervention was defined as pretreatment using standard medical therapy and subsequent revascularization 20 hours or more after enrollment. The 20-hour threshold was chosen because it clearly distinguished early from delayed intervention groups in the trials. Studies comparing invasive (≥20 hours) versus conservative strategies or selective intervention done only in case of refractory angina were excluded from the analysis.

Inclusion criteria for observational studies included a diagnosis of NSTE-ACS and allocation to early or delayed coronary revascularization. We used a threshold of 24 hours to distinguish early from delayed intervention in observational studies because it best distinguished early from delayed intervention in the 4 studies with that design.

Data were abstracted on prespecified forms by 2 independent investigators not involved in any of the retrieved studies. Internal validity was independently appraised by 2 investigators, and divergences were resolved by discussion with a third investigator.

The potential risk of bias of RCTs was appraised by 2 unblinded investigators according to the Cochrane Collaboration guidelines (concealment of treatment allocation; blinding of participants, personnel, or outcome assessors; adequate assessment of incomplete outcome data; presence of selective outcome reporting; and other potential sources of bias). Nonrandomized studies were evaluated using the Newcastle–Ottawa Scale for cohort studies (representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and demonstration that outcomes were not present at study start), cohort comparability, and outcomes (means, duration, and adequacy of assessment) (5).

Study End Points

As in our original review (4), overall mortality was the primary end point and recurrent myocardial infarction (MI), major bleeding complications, refractory ischemia, and repeated revascularization were secondary end points. Recurrent MI was defined as new or recurrent ischemic symptoms lasting more than 20 minutes and an increase of the creatine kinase–MB (CK-MB) level to greater than 2 times the upper limit of normal or electrocardiographic changes (transient ST-segment depression or elevation >0.1 mV in >2 contiguous leads or development of new pathologic Q-waves in ≥2 contiguous leads); most studies used a CK-MB enzyme rather than troponin as the biomarker of necrosis. Major bleeding was defined using the Thrombolysis in Myocardial Infarction criteria (intracranial hemorrhage, a ≥5-g/dL decrease in the hemoglobin concentration, or a ≥15% absolute decrease in the hematocrit) or as defined by trial or study investigators. Refractory ischemia was defined in only 1 study (8) as recurrent ischemic symptoms lasting more than 5 minutes while the patient received optimal medical therapy (≥2 antiangina treatments) with documented characteristic electrocardiographic changes indicative of ischemia and requiring additional intervention.

For each end point, the longest follow-up available in each study was chosen.

Data Synthesis and Analysis

Data were analyzed according to the intention-to-treat principle. Odds ratios (ORs) and 95% CIs were used as summary statistics. Heterogeneity was assessed by the Cochran Q test. Statistical heterogeneity was summarized by the I^2 statistic, which quantifies the percentage of variation in study results that is due to heterogeneity rather than chance (9). Pooled ORs were calculated using the DerSimonian and Laird random-effects model. In case of 0 outcome events, the continuity correction approach was done by adding a correction factor of 0.5 to the number of events and nonevents in each intervention group (10).

We did 2 additional sets of analyses: one in which we assessed the influence of each study on estimates of effect by removing each and assessing the effect of the removal on the effect estimate, and another in which we included events from 2 groups (immediate [<2 hours] and early [10 to 48 hours]) from a 3-group trial (comparing immediate, early, and delayed intervention). Review Manager, version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark), and SPSS, version 15 (SPSS, Chicago, Illinois), were used for statistical computations.

Role of Funding Source

This study did not receive external funding.

RESULTS

Study and Patient Characteristics

We screened 8472 potentially relevant articles and identified 22 potentially relevant studies. After 11 exclusions we had 7 RCTs (8, 11–16) (2 new to this update [14, 16]) and 4 observational studies (17–20) (all new to this update) (**Appendix Figure 1**). None of the observational studies was primarily designed to assess timing of interventions.

The RCTs enrolled 5370 patients; 2799 were randomly assigned to early and 2571 to delayed invasive in-

Table 1. **Timing of the Invasive Approach, Definitive Treatment, and Clinical Outcomes at Follow-up for Randomized, Controlled Trials Comparing Early and Delayed Strategies**

Study, Year (Reference)	Trial Name	Median Time of Catheterization, *h*		Patients, *n*		Definitive Treatment, *n* (%)		Clinical Outcomes at Follow-up
		Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy	
Mehta et al, 2009 (8)	TIMACS	14	50	1593	1438	PCI: 954 (59.9) CABG: 255 (16.0) Medical: 384 (24.1)	PCI: 796 (55.4) CABG: 219 (15.2) Medical: 423 (29.4)	Death, MI, major bleeding, re-PCI, refractory ischemia at 6 mo
Montalescot et al, 2009 (11)	ABOARD	1.1	20.5	175	177	PCI: 117 (66.9) CABG: 16 (9.1) Medical: 42 (24.0)	PCI: 105 (59.3) CABG: 17 (9.6) Medical: 55 (31.1)	Death, MI, major bleeding, re-PCI, refractory ischemia at 1 mo
Neumann et al, 2003 (12)	ISAR-COOL	2.4	86	203	207	PCI: 143 (70.4) CABG: 16 (7.9) Medical: 44 (21.7)	PCI: 133 (64.3) CABG: 16 (7.7) Medical: 58 (28.0)	Death, MI, major bleeding, refractory ischemia at 1 mo
Riezebos et al, 2009 (13)	OPTIMA	0.5	25	73	69	PCI: 73 (100)	PCI: 69 (100)	Death, MI, major bleeding, re-PCI at 6 mo
Thiele et al, 2012 (14)	LIPSIA-NSTEMI	<2	>48	200	200	PCI: 151 (75.5) CABG: 16 (8.0) Medical: 33 (16.5)	PCI: 114 (57.0) CABG: 25 (12.5) Medical: 61 (30.5)	Death, MI, refractory ischemia at 6 mo, in-hospital major bleeding
van 't Hof et al, 2003 (15)	ELISA	6	50	109	111	PCI: 66 (60.5) CABG: 15 (13.8) Medical: 27 (24.7)	PCI: 64 (57.7) CABG: 21 (18.9) Medical: 25 (23.4)	Death, MI, major bleeding, refractory ischemia at 6 mo
Zhang et al, 2010 (16)	NA	9.3	49.9	446	369	PCI: 314 (70.4) CABG: 41 (9.2) Medical: 91 (20.4)	PCI: 252 (68.3) CABG: 37 (10.1) Medical: 80 (21.6)	Death, MI, major bleeding, re-PCI, refractory ischemia at 6 mo

ABOARD = Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention; CABG = coronary artery bypass graft; ELISA = Early or Late Intervention in Unstable Angina; ISAR-COOL = Intracoronary Stenting With Antithrombotic Regimen Cooling Off; LIPSIA-NSTEMI = Leipzig Immediate Versus Early and Late Percutaneous Coronary Intervention Trial in Non–ST-Segment Elevation Myocardial Infarction; MI = myocardial infarction; NA = not available; PCI = percutaneous coronary intervention; TIMACS = Timing of Intervention in Acute Coronary Syndromes.

tervention. For the 3-group trial (LIPSIA-NSTEMI [Leipzig Immediate Versus Early and Late Percutaneous Coronary Intervention Trial in Non–ST-Segment Elevation Myocardial Infarction]), which compared immediate, early, and delayed invasive interventions, the immediate and delayed intervention groups most closely matched the early and delayed interventions of other trials, and we included data from those in our primary analysis. Trial characteristics are summarized in **Table 1**; additional patient and trial characteristics are shown in **Appendix Table 2** (available at www.annals.org). The time of the invasive approach ranged in RCTs from 0.5 to 14 hours after randomization (early intervention) and from 20.5 to 86 hours (delayed intervention). Follow-up duration was the same for all end points in each study except LIPSIA-NSTEMI, which reported rates of major bleeding in the hospital phase but rates of death and MI up to 6 months. Most patients treated by coronary revascularization had PCI, and some had coronary artery bypass grafting. Patients randomly assigned to early versus delayed intervention were well-matched for demographic and clinical characteristics. Use of glycoprotein IIb/IIIa inhibitors was similar between study groups, except in the ELISA (Early or Late Intervention in Unstable Angina) trial, which did not prescribe the agents for the early intervention group.

Two of the 4 observational studies (ACUITY [Acute Catheterization and Urgent Intervention Triage Strategy] and SYNERGY [Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors]) were post hoc analyses of RCTs originally designed to compare antithrombotic strategies (17, 18) and the other 2 were analyses of large registry databases (CRUSADE [Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines] and GRACE [Global Registry of Acute Coronary Events]) (19, 20) (**Table 2**). The median timing of intervention reported in the observational studies was 24 hours or less in the early group versus more than 24 hours in the delayed group. Mortality was reported in all 4 observational studies involving 77 499 patients, whereas data on MI and major bleeding were available in 3 studies (**Table 2**). In the CRUSADE study, weekend versus weekday was used as an "instrumental variable" to objectively reflect early versus delayed timing of the invasive approach, which was in fact the real comparison, given the shorter interval during weekdays (median, 23.4 hours) versus weekends (median, 46.3 hours), thereby offering a quasi-randomization design. In the observational studies, adjusted estimates were not always available and the measures of effect were heterogeneous; therefore, unadjusted ORs, derived from the event rates and the total number of patients in each group, were used for the present analysis; on the other hand, as shown in **Appendix Table 3** (available at www.annals.org),

Table 2. **Timing of the Invasive Approach, Definitive Treatment, and Clinical Outcomes at Follow-up for Observational Studies Comparing Early and Delayed Strategies***

Study, Year (Reference)	Trial Name	Time of Catheterization, *h*		Patients, *n*		Definitive Treatment, *n* (%)		Clinical Outcomes at Follow-up
		Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy	
Sorajja et al, 2010 (17)	ACUITY	≤24	>24	4937	2812	PCI: 4937 (100)	PCI: 2812 (100)	Death, MI, major bleeding at 12 mo
Ryan et al, 2005 (20)	CRUSADE	23.4	46.3	45 548	10 804	PCI: 19 130 (42.0) CABG: 6103 (13.4) Medical: 20 315 (44.6)	PCI: 4354 (40.3) CABG: 1394 (12.9) Medical: 5056 (46.8)	Death and MI at hospital discharge
Montalescot et al, 2005 (19)	GRACE	<24	>48	2407	4639	PCI: 1539 (63.9) CABG: 269 (11.2) Medical: 599 (24.9)	PCI: 2073 (44.7) CABG: 394 (8.5) Medical: 2172 (46.8)	Death at 6 mo, major bleeding at hospital discharge
Tricoci et al, 2007 (18)	SYNERGY	≤24	>24	3326	3026	PCI: 1924 (57.8) CABG: 723 (21.7) Medical: 679 (20.4)	PCI: 1586 (52.4) CABG: 591 (19.5) Medical: 849 (28.1)	Death, MI, major bleeding at 30 d

ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; CABG = coronary artery bypass graft; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines; GRACE = Global Registry of Acute Coronary Events; MI = myocardial infarction; PCI = percutaneous coronary intervention; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors.
* Percentages may not sum to 100 due to rounding.

the clinical variables were well-balanced between the 2 strategies, thus mitigating this potential limitation.

Risk of Bias of Included Studies

The RCTs were similar in their risk of bias (**Appendix Table 4**, available at www.annals.org). All were done according to the intention-to-treat principle; losses to follow-up were infrequent and described in detail. Outcomes were adjudicated by blinded central committees. In the OPTIMA trial, the methods for random-sequence generation and allocation concealment were unclear. Except for ELISA, which was a single-center study, and the ISAR-COOL (Intracoronary Stenting With Antithrombotic Regimen Cooling Off) trial, which was conducted at 2 sites, the RCTs and observational studies were multicenter studies. Patients and providers were not blinded to the timing and identity of interventions, a feature common to trials of coronary angiography.

The patient populations of the observational studies seemed to be representative of a contemporary patient with NSTE-ACS having invasive management; the study participants allocated to early or delayed intervention seemed similar and were generally well-matched for clinical characteristics and concomitant therapies; the assessment of clinical outcomes was checked by an independent events committee or by using standardized case report forms; on the other hand, follow-up duration varied, ranging from the in-hospital phase up to 1 year. The ACUITY study was originally designed to compare the efficacy and safety of heparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, and bivalirudin alone in 13 819 patients with NSTE-ACS having angiography within 72 hours of hospitalization. The SYNERGY study was designed to compare enoxaparin or unfractionated heparin in 10 027 patients with NSTE-ACS having angiography. Both were large, multicenter studies with adequate methods, follow-up, and recording of patient characteristics; on the other hand, selection bias may have occurred with regard to PCI and its timing; indeed, precise reasons for delaying PCI were not prospectively collected. The GRACE and CRUSADE studies were prospective international multicenter registries conducted to improve the quality of care of patients with ACS, reflecting a high-risk population from the real world. They mainly assessed general items in the ACS setting and had fewer data available on timing of the invasive approach. The main characteristics and potential risk of bias of the 4 observational studies are reported in **Appendix Table 5** (available at www.annals.org).

Mortality

Individual and pooled ORs for mortality in the RCTs are shown in **Figure 1**. One-hundred-ten of 2799 patients (3.9%) in the early invasive groups died compared with 120 of 2571 patients (4.7%) in the delayed invasive groups (OR, 0.83 [95% CI, 0.64 to 1.09]; $P = 0.180$; heterogeneity $P = 0.58$; $I^2 = 0\%$). The pooled estimate from observational studies (**Figure 1**) confirmed the RCT findings (pooled OR, 0.80 [CI, 0.63 to 1.02]; $P = 0.070$), although there was substantial heterogeneity (heterogeneity $P = 0.004$; $I^2 = 78\%$).

Secondary End Points

Individual and pooled ORs for secondary outcomes are shown in **Figures 2** and **3** and **Appendix Figure 2** (available at www.annals.org). Two-hundred-eleven of 2799 patients (7.5%) in the early invasive groups had MI compared with 197 of 2541 patients (7.8%) in the delayed invasive groups (pooled OR, 1.15 [CI, 0.65 to 2.01]; $P = 0.63$; heterogeneity $P < 0.001$; $I^2 = 82\%$). Major bleed-

ing occurred in 78 of 2799 patients (2.8%) in the early invasive groups and 95 of 2571 patients (3.7%) in the delayed invasive groups (OR, 0.76 [CI, 0.56 to 1.04]; $P =$ 0.090; heterogeneity $P = 0.90$; $I^2 = 0\%$). Refractory ischemia occurred in 103 of 2726 patients (3.8%) in the early invasive groups and 182 of 2502 patients (7.3%) in the delayed invasive groups (OR, 0.55 [CI, 0.35 to 0.86]; $P =$ 0.008; heterogeneity $P = 0.030$; $I^2 = 60\%$), and repeated revascularizations were required by 154 of 2287 patients (6.7%) in the early invasive groups and 143 of 2053 patients (7%) in the delayed invasive groups (OR, 0.98 [CI, 0.77 to 1.24]; $P =$ 0.86; heterogeneity $P = 0.69$; $I^2 =$ 0%).

Observational findings for MI suggested greater benefit with early intervention than trial findings but were statistically heterogeneous (OR, 0.86 [CI, 0.69 to 1.08]; $P =$ 0.190; heterogeneity $P < 0.001$; $I^2 = 86\%$) (**Figure 2**). Observational findings for major bleeding suggested potential for harm with early intervention, unlike trial findings, but were also statistically heterogeneous (OR, 1.12 [CI, 0.69 to 1.82]; $P = 0.64$; heterogeneity $P < 0.001$; $I^2 =$ 92%) (**Figure 3**).

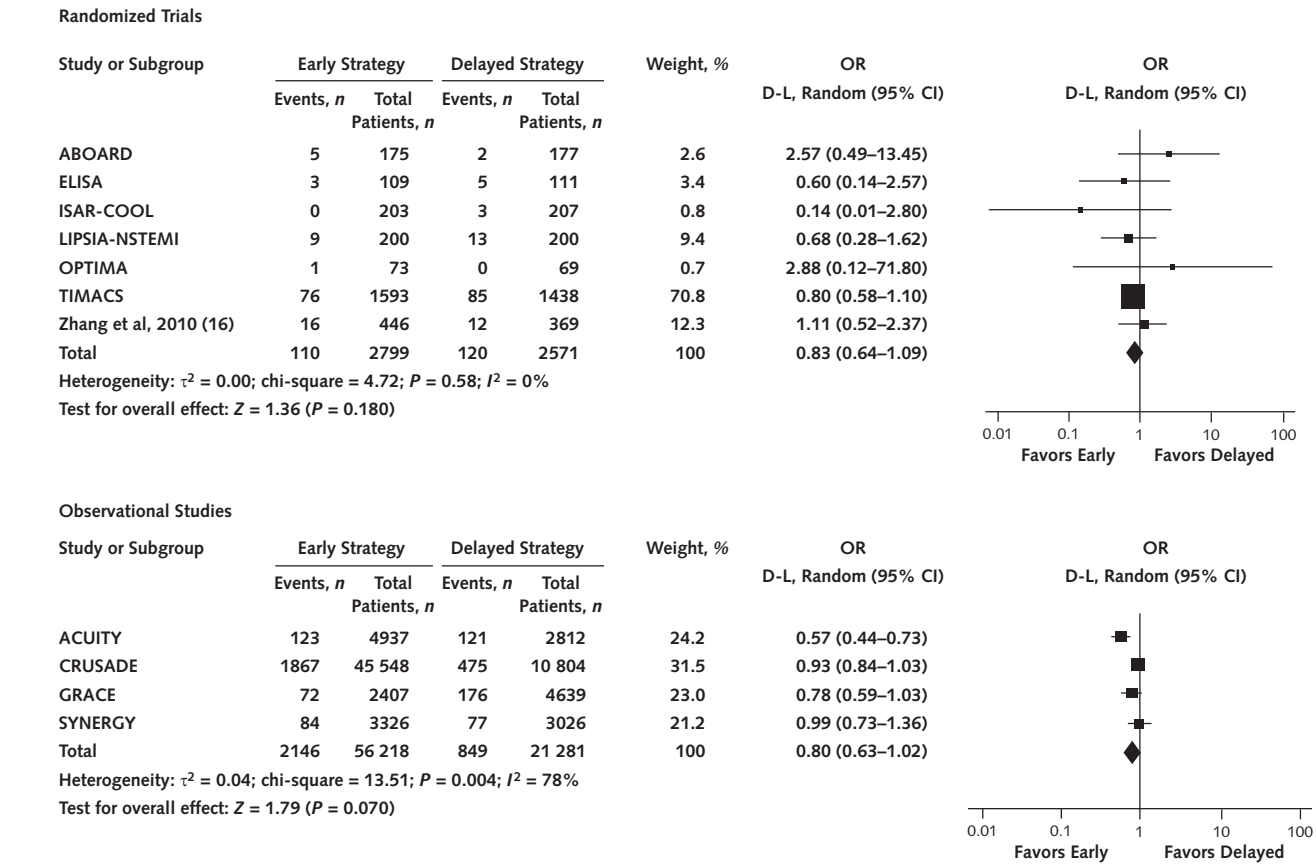
Sensitivity Analyses

Sensitivity analyses, done by removing each of the studies 1 at a time, demonstrated that no single study changed the statistical significance of the overall results. Adding events from the early group in the LIPSIA-NSTEMI trial to those of the immediate group did not change the estimates of effect for any outcome.

Discussion

In this update of our previous review and meta-analysis (4), we added evidence from 2 additional trials and

Figure 1. **Individual and summary ORs for mortality in randomized trials and observational studies comparing early versus delayed intervention.**



ABOARD = Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention; ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines; D-L = DerSimonian and Laird; ELISA = Early or Late Intervention in Unstable Angina; GRACE = Global Registry of Acute Coronary Events; ISAR-COOL = Intracoronary Stenting With Antithrombotic Regimen Cooling Off; LIPSIA-NSTEMI = Leipzig Immediate Versus Early and Late Percutaneous Coronary Intervention Trial in Non–ST-Segment Elevation Myocardial Infarction; OR = odds ratio; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; TIMACS = Timing of Intervention in Acute Coronary Syndromes.

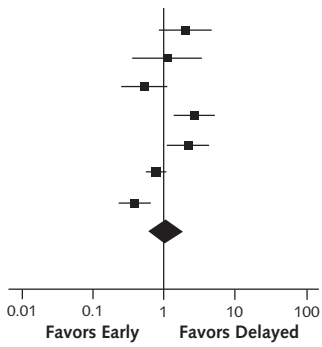
Figure 2. **Individual and summary ORs for myocardial infarction in randomized trials and observational studies comparing early versus delayed intervention.**

Randomized Trials

Study or Subgroup	Early Strategy Events, *n*	Early Strategy Total Patients, *n*	Delayed Strategy Events, *n*	Delayed Strategy Total Patients, *n*	Weight, %	OR D-L, Random (95% CI)
ABOARD	16	175	8	177	12.8	2.13 (0.89–5.10)
ELISA	7	109	6	111	10.6	1.20 (0.39–3.70)
ISAR-COOL	12	203	21	207	14.0	0.56 (0.27–1.16)
LIPSIA-NSTEMI	33	200	13	200	14.6	2.84 (1.45–5.58)
OPTIMA	44	73	27	69	14.6	2.36 (1.20–4.63)
TIMACS	76	1593	82	1438	17.5	0.83 (0.60–1.14)
Zhang et al, 2010 (16)	23	446	40	369	15.9	0.41 (0.24–0.69)
Total	211	2799	197	2541	100	1.15 (0.65–2.01)

Heterogeneity: $\tau^2 = 0.44$; chi-square = 32.98; $P < 0.001$; $I^2 = 82\%$

Test for overall effect: $Z = 0.48$ ($P = 0.63$)

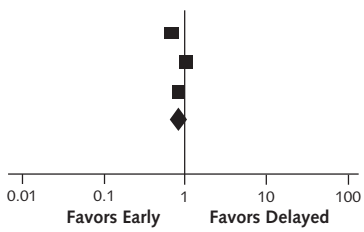


Observational Studies

Study or Subgroup	Early Strategy Events, *n*	Early Strategy Total Patients, *n*	Delayed Strategy Events, *n*	Delayed Strategy Total Patients, *n*	Weight, %	OR D-L, Random (95% CI)
ACUITY	382	4937	301	2812	32.4	0.70 (0.60–0.82)
CRUSADE	1366	45 548	313	10 804	34.5	1.04 (0.91–1.17)
SYNERGY	404	3326	416	3026	33.1	0.87 (0.75–1.00)
Total	2152	53 611	1030	16 642	100	0.86 (0.69–1.08)

Heterogeneity: $\tau^2 = 0.03$; chi-square = 14.66; $P < 0.001$; $I^2 = 86\%$

Test for overall effect: $Z = 1.32$ ($P = 0.190$)



ABOARD = Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention; ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines; D-L = DerSimonian and Laird; ELISA = Early or Late Intervention in Unstable Angina; ISAR-COOL = Intracoronary Stenting With Antithrombotic Regimen Cooling Off; LIPSIA-NSTEMI = Leipzig Immediate Versus Early and Late Percutaneous Coronary Intervention Trial in Non–ST-Segment Elevation Myocardial Infarction; OR = odds ratio; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; TIMACS = Timing of Intervention in Acute Coronary Syndromes.

4 observational studies to the estimates we previously reported for outcomes among patients with NSTE-ACS receiving early compared with delayed invasive intervention. With the additional evidence, we estimate that early intervention leads to a nonsignificant decrease in mortality rate compared with delayed intervention. Early intervention also seems to be associated with a nonsignificant increase in MI and decrease in major bleeding and statistically significant decrease in refractory ischemia during follow-up. Strictly interpreted, the current meta-analysis indicates that early intervention offers little or no statistically significant clinical benefit compared with a delayed invasive approach. However, the CIs around our estimates are wide and include values compatible with potentially important benefits and harms of early intervention. Thus, although limited trial evidence suggests decreases in refractory ischemia with early intervention, evidence is otherwise inconclusive about the relative effects of early and late intervention in patients with NSTE-ACS, and an appropriately powered RCT is warranted to definitively determine whether early intervention really benefits patients.

Several RCTs and meta-analyses have shown that an invasive strategy is superior to an initially conservative approach, in which angiography is done on the basis of clinical or noninvasive evidence of recurrent ischemia (1–3). With invasive management, an early approach may facilitate rapid diagnosis, earlier mechanical revascularization, and shorter hospital stays; there may also be potential for early hazard because of intervention on unstable plaques with fresh thrombus. Conversely, a delayed strategy may provide benefits through plaque passivation by optimal medical treatment followed by intervention on more stable plaques; this potential advantage, however, may be offset by a higher risk for events while waiting for angiography. Suggestions of benefit with an early strategy, using the combined end point of death and MI, mainly come from 2 trials. In ISAR-COOL, in which patients with ischemic symptoms and ST-segment depression or increased tro-

ponin levels were randomly assigned to a very early (median, 2.4 hours) versus delayed (median, 86 hours) invasive strategy (12), the primary combined end point of death or large, nonfatal MI at 30 days was increased in patients having a delayed invasive strategy (11.6% vs. 5.9%). In the TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial (8), the primary combined end point (death, new MI, or stroke at 6 months) did not differ significantly between the early and delayed groups, although a significant decrease in the rate of death and MI was seen in the prespecified subgroup with high GRACE risk scores (>140) having early intervention (14.1% vs. 21.6%). On the other hand, the OPTIMA trial (13), although underpowered, suggests an increased risk for MI with early intervention; this trial randomly assigned 142 patients with ACS eligible for PCI to immediate (0.5 hours) or delayed (25 hours) PCI; a broad MI definition was used that incorporated all MIs in its end point, including evolving MI at randomization; this was done because, with early PCI, periprocedural MIs are difficult to differentiate from spontaneously evolving MIs that started before PCI. The OPTIMA trial showed that MI rates were significantly higher in patients receiving early PCI; this difference was most likely due to an excess of periprocedural MIs in the immediately treated group. No published trial was powered to assess a significant difference in survival rate as a single end point; moreover, most patients included in the available RCTs were at lower risk, compared with the subgroup analyzed in the TIMACS trial.

Current international guidelines recommend an early invasive strategy within 12 to 24 hours for patients with NSTE-ACS with high-risk features, defined by a GRACE score greater than 140, and within 72 hours for those at lower risk, with GRACE scores less than 140 (21, 22); this recommendation, however, is mainly based on the subgroup analysis of the TIMACS trial, which was not powered to answer the question about survival. The IDEAL NSTEMI (Immediate Versus Early Invasive Approach in Non–ST-Elevation Myocardial Infarction) is another study that was planned to compare, in a large sample (2100 par-

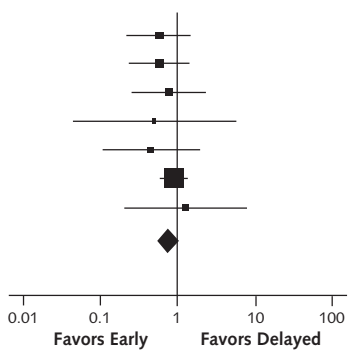
Figure 3. **Individual and summary ORs for major bleeding complications in randomized trials and observational studies comparing early versus delayed intervention.**

Randomized Trials

Study or Subgroup	Early Strategy		Delayed Strategy		Weight, %	OR	OR
	Events, *n*	Total Patients, *n*	Events, *n*	Total Patients, *n*		D-L, Random (95% CI)	D-L, Random (95% CI)
ABOARD	7	175	12	177	10.4	0.57 (0.22–1.49)	
ELISA	9	109	15	111	12.5	0.58 (0.24–1.38)	
ISAR-COOL	6	203	8	207	8.2	0.76 (0.26–2.22)	
LIPSIA-NSTEMI	1	200	2	200	1.6	0.50 (0.04–5.53)	
OPTIMA	3	73	6	69	4.7	0.45 (0.11–1.87)	
TIMACS	49	1593	50	1438	59.5	0.88 (0.59–1.32)	
Zhang et al, 2010 (16)	3	446	2	369	3.0	1.24 (0.21–7.48)	
Total	78	2799	95	2571	100	0.76 (0.56–1.04)	

Heterogeneity: $\tau^2 = 0.00$; chi-square = 2.17; $P = 0.90$; $I^2 = 0\%$

Test for overall effect: $Z = 1.70$ ($P = 0.090$)

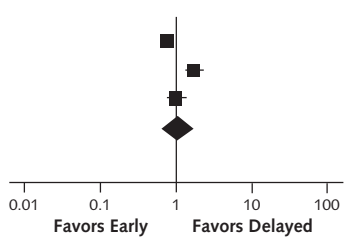


Observational Studies

Study or Subgroup	Early Strategy		Delayed Strategy		Weight, %	OR	OR
	Events, *n*	Total Patients, *n*	Events, *n*	Total Patients, *n*		D-L, Random (95% CI)	D-L, Random (95% CI)
ACUITY	267	4937	191	2812	34.4	0.78 (0.65–0.95)	
GRACE	116	2407	130	4639	33.0	1.76 (1.36–2.27)	
SYNERGY	113	3326	99	3026	32.6	1.04 (0.79–1.37)	
Total	496	10 670	420	10 477	100	1.12 (0.69–1.82)	

Heterogeneity: $\tau^2 = 0.17$; chi-square = 24.46; $P < 0.001$; $I^2 = 92\%$

Test for overall effect: $Z = 0.47$ ($P = 0.64$)



ABOARD = Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention; ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; D-L = DerSimonian and Laird; ELISA = Early or Late Intervention in Unstable Angina; GRACE = Global Registry of Acute Coronary Events; ISAR-COOL = Intracoronary Stenting With Antithrombotic Regimen Cooling Off; LIPSIA-NSTEMI = Leipzig Immediate Versus Early and Late Percutaneous Coronary Intervention Trial in Non–ST-Segment Elevation Myocardial Infarction; OR = odds ratio; SYNERGY= Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; TIMACS = Timing of Intervention in Acute Coronary Syndromes.

ticipants), an immediate versus early invasive approach but was withdrawn before enrollment for lack of funding (23). Two recent meta-analyses (4, 24) were consistent in suggesting no clear-cut survival benefit and fewer major bleeding complications with an early invasive compared with a delayed approach. These reports, however, did not include the findings on the high-risk population enrolled in the LIPSIA-NSTEMI trial (14), which was not yet available, or the results of an RCT that was not published in English (16). There was also no systematic analysis of the available observational studies. In LIPSIA-NSTEMI, 600 high-risk patients with NSTE-ACS were randomly assigned to an immediate (<2 hours) versus a moderate (<24 hours) versus a delayed (>48 hours) strategy; the immediate strategy was not found to offer an advantage in survival or decreased MI rates over the other 2 strategies. Thus, the available RCTs were powered to assess differences in composite rather than individual end points (mainly death, MI, or stroke); although these study designs enabled a decrease of sample size, treatment effects varied largely across end points and individual components.

Moreover, the wide CI around the pooled OR for mortality in our meta-analysis reflects the small overall sample size, the inclusion of several small RCTs, the low event rates, and the fact that a single trial contributed to most events. In addition, heterogeneity was found across studies in the timing of intervention, definitions of MI and major bleeding, and patients' risk profiles. Thus, the interpretation of the survival results has varied from positive (based on the subgroup analysis of the composite end point in TIMACS) to negative (based on the previous meta-analyses) to nonconclusive, as shown by the present comprehensive report. This uncertainty contrasts with the current guideline recommendations (21, 22).

To definitively answer the question of a potential survival benefit with early compared with later intervention, we estimate that an RCT would require approximately 7807 patients per group (a total of 15 614 patients) to have 80% statistical power and approximately 10 450 per group (a total of 20 900 patients) to have 90% statistical power to detect the 30-day mortality decrease estimated in this analysis (OR, 0.80, translating into a 1% absolute difference in favor of early intervention, assuming the absolute mortality rate of 4.7% seen in the late intervention groups) with a 2-sided α of 0.05. In the setting of ST-segment elevation MI, the GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial compared streptokinase plus intravenous heparin against recombinant tissue–type plasminogen activator plus intravenous heparin (25). The primary end point was 30-day mortality; with approximately 10 350 patients per group, 30-day death rates were 7.4% for streptokinase versus a significantly lower 6.3% rate for the recombinant tissue–type plasminogen activator, which led to the recommendation of a recombinant tissue–type plasminogen activator as preferred thrombolytic strategy (26). Similarly, detection of a 1% absolute difference in mortality with an early versus a delayed invasive strategy in the management of the large NSTE-ACS population (which is larger than that of patients with ST-segment elevation MI, numbering millions per year worldwide and increasing as a result of the growing and aging population) could have important clinical implications. It is conceivable that the absolute mortality difference between the 2 strategies may increase with longer follow-up; indeed, the post hoc timing analysis of the ACUITY trial suggests greater survival benefit at 1 year than at 30 days with early compared with delayed intervention (17). In the present meta-analysis of RCTs, the maximum length of follow-up for death was 6 months, and we believe that a future trial should extend its follow-up to 1 year. The population to be included in such a trial should reflect the real-world population, focusing on high-risk groups that may derive the greatest survival benefit with the early approach; the currently available studies (except for LIPSIA-NSTEMI, which was not powered to assess mortality differences) included a substantial portion of patients (ranging from 33% to 54%) without elevated plasma troponins, indicating a low-risk population. To date, all of the studies on timing of intervention in patients with NSTE-ACS were conducted using variable loading doses of 300 to 600 mg of clopidogrel; new, more potent, and rapidly acting antiplatelet agents (prasugrel or ticagrelor), as well as safer anticoagulants (such as bivalirudin), are now recommended by guidelines and may be crucial in modulating the relationship between timing of intervention and clinical outcome; ideally, a future RCT should plan appropriate concomitant adjunctive medical therapy. Secondary end points should include careful appraisal of MI, stratified by time of occurrence (during index hospitalization vs. follow-up) and major bleeding.

In conclusion, the current available evidence does not allow firm conclusions to be drawn in favor of or against an early invasive approach in the NSTE-ACS population. A more definitive RCT, properly powered for mortality as the single end point, and related cost-effective analyses are warranted to quantify the potential survival benefits and assess the feasibility of an early approach in patients with NSTE-ACS.

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Note: The authors take full responsibility for data collection, data interpretation, and writing of the manuscript. Drs. Navarese and Andreotti

had full access to all of the data and were finally responsible for submitting the manuscript for publication.

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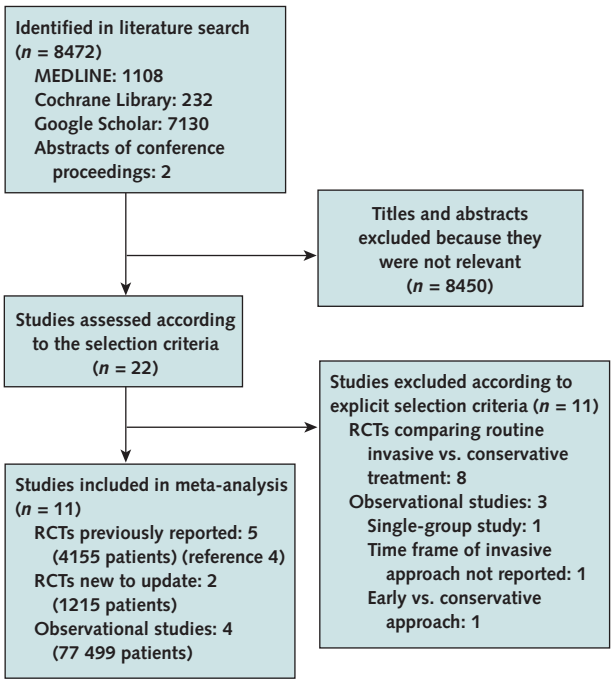
Appendix Figure 1. **Summary of evidence search and selection.**



RCT = randomized, controlled trial.

Appendix Table 1. **Full Electronic Search in MEDLINE Database Through May 2012**

Search	Query	Items Found, *n*
12	Search early coronary intervention AND delayed coronary intervention AND acute coronary syndrome	25
11	Search acute coronary syndrome AND timing	170
8	Search acute coronary syndrome AND early PCI	219
7	Search acute coronary syndrome AND early coronary angioplasty	399
6	Search acute coronary syndrome AND early coronary intervention	499
5	Search ACS AND coronary invasive	484
4	Search NSTE-ACS AND coronary invasive	123
3	Search NSTEMI AND coronary invasive	119
2	Search non-st-elevation myocardial infarction AND coronary invasive	208
1	Search acute coronary syndrome AND coronary invasive	859

Appendix Table 2. Clinical Characteristics of Randomized, Controlled Trials Included in the Meta-analysis

Study, Year (Reference)	Trial Name	Age, *y*		Female sex, *n* (%)		Patient Ethnicity	Positive Biomarkers, %		Diabetes, *n* (%)		ST-Segment Depression, *n* (%)		3-Vessel Disease, *n* (%)		Glycoprotein IIb/IIIa Inhibitors, *n* (%)	
		Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy		Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy
Mehta et al, 2009 (8)	TIMACS	65	65.7	554 (34.8)	498 (34.6)	American, Australian, European, East Asian	77.2	76.9	422 (26.5)	394 (27.4)	1282 (80.5)	1149 (79.9)	272 (17.1)	227 (15.8)	370 (23.2)	322 (22.4)
Montalescot et al, 2009 (11)	ABOARD	65	65	48 (27.4)	52 (29.4)	European	75.4	72.9	38 (21.7)	57 (32.2)	122 (69.7)	136 (76.8)	32 (18.3)	44 (24.9)	114 (65.1)	101 (57.1)
Neumann et al, 2003 (12)	ISAR-COOL	70	70	67 (33.0)	69 (33.3)	European	67.6	66.0	53 (26.1)	65 (31.4)	133 (65.5)	135 (65.2)	94 (46.3)	92 (44.4)	203 (100)	207 (100)
Riezebos et al, 2009 (13)	OPTIMA	63	62	22 (30.0)	18 (26.0)	European	47	45	14 (19.2)	14 (20.3)	38 (52.1)	36 (52.2)	10 (13.7)	9 (13.0)	71 (97.3)	64 (92.8)
Thiele et al, 2012 (14)	LIPSIA-NSTEMI	68	70	68 (34.0)	72 (36.0)	European	75	71	76 (38.0)	64 (32.0)	122 (61.0)	124 (62.0)	59 (39.5)	63 (31.5)	195 (97.5)	197 (98.5)
van 't Hof et al, 2003 (15)	ELISA	63	65	79 (72.4)	76 (68.4)	European	78	71	16 (14.6)	16 (14.4)	NA	NA	31 (28.4)	33 (29.7)	0 (0.0)	111 (100)
Zhang et al, 2010 (16)	NA	67	66	151 (33.9)	119 (32.2)	East Asian	79.1	77.8	105 (23.5)	83 (22.5)	425 (95.3)	349 (94.6)	195 (43.7)	148 (40.1)	82 (18.4)	79 (21.4)

ABOARD = Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention; ELISA = Early or Late Intervention in Unstable Angina; ISAR-COOL = Intracoronary Stenting With Antithrombotic Regimen Cooling Off; LIPSIA-NSTEMI = Leipzig Immediate Versus Early and Late Percutaneous Coronary Intervention Trial in Non–ST-Segment Elevation Myocardial Infarction; NA = not applicable; TIMACS = Timing of Intervention in Acute Coronary Syndromes.

Appendix Table 3. Clinical Characteristics of Observational Studies Included in the Meta-analysis

Study, Year (Reference)	Trial Name	Age, *y*		Female sex, *n* (%)		Patient Ethnicity	Positive Biomarkers, %		Diabetes, *n* (%)		ST-Segment Depression, *n* (%)		Glycoprotein IIb/IIIa Inhibitors, *n* (%)	
		Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy		Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy	Early Strategy	Delayed Strategy
Sorajja et al, 2010 (17)	ACUITY	62.5	63	580 (11.7)	759 (27.0)	American, Australian, European	64.4	66.2	1318 (26.7)	821 (29.2)	1742 (35.3)	1029 (36.6)	3290 (66.6)	1844 (65.6)
Ryan et al, 2005 (20)	CRUSADE	67	68	17 764 (39.0)	4300 (39.8)	American	88.3	90.5	14 621 (32.1)	3490 (32.3)	18 174 (39.9)	4278 (39.6)	17 445 (38.3)	1844 (17.1)
Montalescot et al, 2005 (19)	GRACE	62.7	64.7	640 (26.6)	1492 (32.2)	American, Australian, European, East Asian	55.0	48.5	587 (24.4)	1286 (27.7)	906 (37.6)	1651 (35.6)	788 (32.7)	349 (7.5)
Tricoci et al, 2007 (18)	SYNERGY	67	67.5	1085 (32.6)	1027 (33.9)	American, European, East Asian	79.8	83.7	913 (27.5)	849 (28.1)	477 (14.3)	386 (12.8)	2086 (62.7)	1889 (62.4)

ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines; GRACE = Global Registry of Acute Coronary Events; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors.

Appendix Table 4. **Risk of Bias of Included Randomized, Controlled Trials**

Study, Year (Reference)	Trial Name	Multicenter Trial	Adequate Sequence Generation	Allocation Concealment	Patient Blinding	Physician Blinding	Adjudication of Outcomes Blinding	Incomplete Data Outcome Addressed?	Selective Outcome Reporting	Free of Other Bias
Mehta et al, 2009 (8)	TIMACS	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
Montalescot et al, 2009 (11)	ABOARD	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
Neumann et al, 2003 (12)	ISAR-COOL	2 sites	Yes	Yes	No	No	Yes	Yes	No	Yes
Riezebos et al, 2009 (13)	OPTIMA	Yes	Unclear	Unclear	No	No	Unclear	Yes	No	Yes
Thiele et al, 2012 (14)	LIPSIA-NSTEMI	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes
van 't Hof et al, 2003 (15)	ELISA	No	Yes	Yes	No	No	Yes	Yes	No	Yes
Zhang et al, 2010 (16)	NA	Yes	Unclear	Unclear	No	No	Yes	Yes	No	Yes

ABOARD = Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention; ELISA = Early or Late Intervention in Unstable Angina; ISAR-COOL = Intracoronary Stenting With Antithrombotic Regimen Cooling Off; LIPSIA-NSTEMI = Leipzig Immediate Versus Early and Late Percutaneous Coronary Intervention Trial in Non–ST-Segment Elevation Myocardial Infarction; NA = not applicable; TIMACS = Timing of Intervention in Acute Coronary Syndromes.

Appendix Table 5. Study Design, Inclusion and Exclusion Criteria, and Risk of Bias of Included Observational Studies

Study, Year (Reference)	Study Design	Original Study Design	Inclusion Criteria	Exclusion Criteria	Stars for Selection, *n**	Stars for Comparability, *n**	Stars for Outcome, *n**	Score†
Ryan et al, 2005 (20)	Timing analysis of CRUSADE registry; quasi-randomized study comparing patients hospitalized on weekdays and weekends (median time to catheterization, 23.4 vs. 46.3 h) (56 352 participants)	CRUSADE, a multidisciplinary effort (including an ACS registry designed to characterize demographic patterns and risk stratification results and measure the use of treatment methods, including aspirin, heparin, β-blockers, and platelet inhibitors, as recommended in the ACC/AHA guidelines) (201 032 participants)	Unselected high-risk patients hospitalized with UA or NSTE-ACS within 24 h of onset of symptoms with at least 1 high-risk feature, including ST-segment depression, transient ST-segment elevation, or positive cardiac biomarkers	No exclusion criteria established	4	2	2	8
Montalescot et al, 2005 (19)	Timing analysis of the GRACE registry (7046 participants)	GRACE, a prospective multicenter registry aimed to improve the quality of care in patients with ACS (102 341 participants)	UA or NSTE-ACS patients aged ≥18 y and alive at the time of hospital presentation having at least 1 of the following: electrocardiographic changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, or documentation of CAD	Precipitated or accompanied by significant comorbid conditions (e.g., trauma or surgery); development of ACS during hospitalization for any reason	4	1	2	7
Sorajja et al, 2010 (17)	Post hoc analysis of the ACUITY trial (7749 participants)	ACUITY, an RCT in which participants were assigned to heparin plus a glycoprotein IIb/IIIa inhibitor, bivalirudin plus a glycoprotein IIb/IIIa inhibitor, or bivalirudin alone (13 819 participants)	UA or NSTE-ACS patients aged ≥18 y with ischemic symptoms within the preceding 24 h and at least 1 of the following: new ST-segment depression or transient elevation of ≥1 mm; elevations in troponin I, troponin T, or CK-MB levels; known CAD; or all 4 other variables for predicting TIMI risk scores for UA	ST-segment elevation MI or cardiogenic shock; bleeding diathesis or major bleeding episode within 2 wk; thrombocytopenia; a calculated creatinine clearance rate <30 mL/min per 1.73 m^2; recent administration of abciximab, warfarin, fondaparinux, fibrinolytic agents, bivalirudin, or 2 or more doses of low-molecular-weight heparin; and allergy to any of the study drugs or iodinated contrast medium that could not be controlled in advance with medication	4	2	3	9
Tricoci et al, 2007 (18)	Post hoc analysis of the SYNERGY trial selecting patients who had angiography within 48 h (6352 participants)	SYNERGY, an RCT in which enoxaparin was compared with unfractionated heparin (10 027 participants)	UA or NSTEMI patients with ischemic symptoms for ≥10 min within 24 h and ≥2 of the following characteristics: age ≥60 y, troponin or CK-MB elevation greater than the upper limit of normal, or ST-segment depression	Active bleeding; PCI or thrombolysis within the 24 h preceding enrollment and calculated creatinine clearance rate <30 mL/min per 1.73 m^2	4	2	3	9

ACC = American College of Cardiology; ACS = acute coronary syndrome; ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; AHA = American Heart Association; CAD = coronary artery disease; CK-MB = creatine kinase–MB; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; GRACE = Global Registry of Acute Coronary Events; MI = myocardial infarction; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; NSTEMI = non–ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized, controlled trial; SYNERGY = Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors; TIMI = Thrombolysis in Myocardial Infarction; UA = unstable angina.

* According to the Newcastle–Ottawa Scale, stars were assigned for the study quality items: selection, comparability, and outcome. Selection assesses 1) adequate definition and representativeness of case participants in the community, 2) adequate definition and representativeness of control participants in the community, 3) ascertainment of exposure with secure records or structured interviews, and 4) demonstration that the outcome of interest was not present at the start of the study. Comparability assesses whether cases and control participants are comparable in terms of 1) design or analysis, and 2) any additional control factors. Outcome addresses 1) analysis of outcome, 2) length, and 3) adequacy of the follow-up. The maximum number of stars awardable to selection, comparability, and outcome is 4, 2, and 3, respectively.

† Newcastle–Ottawa Scale summary score out of 9 possible points.

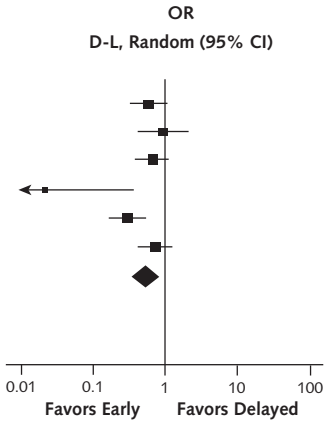
Appendix Figure 2. **Individual and summary ORs for refractory ischemia and repeated revascularization in patients treated with early versus delayed intervention.**

Refractory Ischemia

Study or Subgroup	Early Strategy		Delayed Strategy		Weight, %	OR D-L, Random (95% CI)
	Events, *n*	Total Patients, *n*	Events, *n*	Total Patients, *n*		
ABOARD	21	175	33	177	19.9	0.60 (0.33–1.08)
ELISA	13	109	14	111	15.3	0.94 (0.42–2.10)
ISAR-COOL	27	203	39	207	21.2	0.66 (0.39–1.13)
LIPSIA-NSTEMI	0	200	20	200	2.3	0.02 (0.00–0.37)
TIMACS	16	1593	47	1438	20.3	0.30 (0.17–0.53)
Zhang et al, 2010 (16)	26	446	29	369	20.9	0.73 (0.42–1.26)
Total	103	2726	182	2502	100	0.55 (0.35–0.86)

Heterogeneity: $\tau^2 = 0.17$; chi-square = 12.50; $P = 0.030$; $I^2 = 60\%$

Test for overall effect: $Z = 2.64$ ($P = 0.008$)

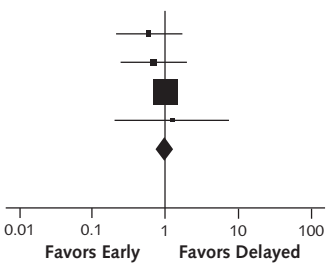


Repeated Revascularizations

Study or Subgroup	Early Strategy		Delayed Strategy		Weight, %	OR D-L, Random (95% CI)
	Events, *n*	Total Patients, *n*	Events, *n*	Total Patients, *n*		
ABOARD	6	175	10	177	5.3	0.59 (0.21–1.67)
OPTIMA	7	73	9	69	5.2	0.71 (0.25–2.02)
TIMACS	138	1593	122	1438	87.7	1.02 (0.79–1.32)
Zhang et al, 2010 (16)	3	446	2	369	1.8	1.24 (0.21–7.48)
Total	154	2287	143	2053	100	0.98 (0.77–1.24)

Heterogeneity: $\tau^2 = 0.00$; chi-square = 1.46; $P = 0.69$; $I^2 = 0\%$

Test for overall effect: $Z = 0.18$ ($P = 0.86$)



ABOARD = Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention; D-L = DerSimonian and Laird; ELISA = Early or Late Intervention in Unstable Angina; ISAR-COOL = Intracoronary Stenting With Antithrombotic Regimen Cooling Off; LIPSIA-NSTEMI = Leipzig Immediate Versus Early and Late Percutaneous Coronary Intervention Trial in Non–ST-Segment Elevation Myocardial Infarction; OR = odds ratio; TIMACS = Timing of Intervention in Acute Coronary Syndromes.