

FOCUS ISSUE: CARDIAC INTERVENTION**Intervention in Acute Coronary Syndromes**

Benefit of Early Invasive Therapy in Acute Coronary Syndromes

A Meta-Analysis of Contemporary Randomized Clinical Trials

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OBJECTIVES	This study sought to systematically determine whether early invasive therapy improves survival and reduces adverse cardiovascular events in the management of non-ST-segment elevation acute coronary syndromes.
BACKGROUND	Although early invasive therapy reduces recurrent unstable angina, the magnitude of benefit on other important adverse outcomes is unknown.
METHODS	Clinical trials that randomized non-ST-segment elevation acute coronary syndrome patients to early invasive therapy versus a more conservative approach were included for analysis.
RESULTS	In all there were 7 trials with 8,375 patients available for analysis. At a mean follow-up of 2 years, the incidence of all-cause mortality was 4.9% in the early invasive group, compared with 6.5% in the conservative group (risk ratio [RR] = 0.75, 95% confidence interval [CI] 0.63 to 0.90, $p = 0.001$), and at 1 month (RR = 0.82, 95% CI 0.50 to 1.34, $p = 0.43$). At 2 years of follow-up, the incidence of nonfatal myocardial infarction was 7.6% in the invasive group, versus 9.1% in the conservative group (RR = 0.83, 95% CI 0.72 to 0.96, $p = 0.012$), and at 1 month (RR = 0.93, 95% CI 0.73 to 1.19, $p = 0.57$). At a mean of 13 months of follow-up, there was a reduction in rehospitalization for unstable angina (RR = 0.69, 95% CI 0.65 to 0.74, $p < 0.0001$).
CONCLUSIONS	Managing non-ST-segment elevation acute coronary syndromes by early invasive therapy improves long-term survival and reduces late myocardial infarction and rehospitalization for unstable angina. (J Am Coll Cardiol 2006;48:1319–25) © 2006 by the American College of Cardiology Foundation

Although early invasive therapy is recommended for non-ST-segment elevation acute coronary syndromes (NSTE-ACS) (1), the use of this approach remains suboptimal among eligible patients (2). This strategy reduces composite cardiac outcomes, largely by decreasing recurrent unstable angina and the need for subsequent rehospitalization and revascularization (3). Meta-analyses have reported that early invasive therapy increases mortality and myocardial infarction during the index hospitalization (4), although a modest reduction in mortality may emerge later (4–6). Moreover, the most recent trial on this topic documented a 50% increased risk for myocardial infarction ($p = 0.005$), with similar mortality 1 year after hospitalization for the NSTE-ACS ($p = 0.97$) (7). Because additional studies and prolonged follow-up of earlier trials have now been reported, we sought to perform an updated meta-analysis to determine the magnitude of benefit of early invasive therapy on individual outcomes of mortality, myocardial infarction, and recurrent unstable angina.

METHODS

Literature review. We conducted a computerized literature search of the Medline and Google Scholar databases for randomized clinical trials in the English language from 1990 to 2006 using the search terms early invasive therapy, conservative therapy, unstable angina, non-ST-segment elevation myocardial infarction, and acute coronary syndrome. We also corresponded with experts in the field and used the Science Citation Index to cross-reference any studies that met our selection criteria.

Selection criteria. We selected studies that enrolled patients with a diagnosis of NSTE-ACS, and randomized individuals to early invasive therapy versus a more conservative approach. We required that glycoprotein IIb/IIIa inhibitors and/or thienopyridines, and coronary stents were available for use during percutaneous coronary intervention (PCI). We excluded studies that enrolled patients with chronic stable angina or with ST-segment elevation myocardial infarction, that used fibrinolytic agents, or that did not have reliable outcome data available.

End points/data extraction. The primary end point was all-cause mortality. Secondary end points were nonfatal myocardial infarction and recurrent unstable angina that

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CI	= confidence interval
FRISC-II	= Fragmin and Fast Revascularization During Instability in Coronary Disease
ICTUS	= Invasive Versus Conservative Treatment in Unstable Coronary Syndromes Investigators
ISAR-COOL	= Intracoronary Stenting With Antithrombotic Regimen Cooling Off
NSTE-ACS	= non-ST-segment elevation acute coronary syndrome
PCI	= percutaneous coronary intervention
RITA-3	= Randomized Intervention Trial of Unstable Angina
RR	= risk ratio
TACTICS TIMI-18	= Treat Angina With Aggrastat and Determine the Cost of Therapy With an Invasive or Conservative Strategy—Thrombolysis In Myocardial Infarction
TRUCS	= Treatment of Refractory Unstable Angina in Geographically Isolated Areas Without Cardiac Surgery
VINO	= Value of First Day Coronary Angiography/Angioplasty in Evolving Non-ST-Segment Elevation Myocardial Infarction

resulted in rehospitalization. We included all myocardial infarctions from each trial, rather than attempting to apply a uniform definition of myocardial infarction across all the studies. We tabulated overall rates of revascularization at the time of follow-up. Baseline information was tabulated, such as patient demographics, adjunctive medications, and the proportion of patients who received glycoprotein IIb/IIIa inhibitors and coronary stents. Three independent reviewers (D.J.K., A.N.R., and A.T.A.) tabulated each clinical outcome. Once an event occurred, that patient was censored from contributing to future similar outcomes. Discrepancies were resolved through a fourth reviewer (A.A.B.). The totality of data (i.e., cumulative events up to the extent of follow-up in each trial) was used to assess all outcomes, although restricted data (i.e., cumulative events up to a specific follow-up period) were used for subanalysis. Because some degree of invasive therapy and subsequent revascularization will invariably occur among conservatively treated patients both during the index hospitalization and after discharge, we performed a subanalysis on studies with a similar relative difference in use of revascularization between treatment arms at follow-up. We also performed subanalysis on studies based on the median time of angiography.

Statistical analysis. We used the intention-to-treat principle to calculate risks. The risk for an outcome was defined as the number of cardiac events that occurred during clinical follow-up divided by the number of individuals randomized to invasive therapy or to conservative therapy. Risk ratios were defined as the risk of an outcome among those who received invasive therapy compared with the risk of the outcome among those who received conservative therapy. A Mantel-Haenszel model was used to calculate a summary statistic for each outcome. We assessed for heterogeneity between studies by computing the *Q* statistic and for publication bias by constructing a Begg funnel plot. Mean follow-up was weighted according to each individual trial's sample size. All *p* values were 2-tailed, with statistical significance set at 0.05, and confidence intervals calculated at the 95% level. Analyses were performed using STATA software version 9.0. (Stata Corp., College Station, Texas).

RESULTS

Baseline characteristics. A total of 13 studies were initially identified; 3 studies were excluded for being noncontemporary (i.e., before the era of enhanced antiplatelet therapy and coronary stents) (8–10), 2 were excluded because fibrinolytic agents were used (11,12), and 1 study was excluded because patients had chronic stable angina (13). In all, there were 7 studies with 8,375 total patients that were included for analysis (Table 1) (3,7,14–21). Follow-up ranged from 1 month (ISAR-COOL [Intracoronary Stenting With Antithrombotic Regimen Cooling Off]) to 60 months (RITA-3 [Randomized Intervention Trial of Unstable Angina]), and 4 of the 7 studies have reported outcomes beyond 1 year. The weighted mean follow-up was 23.7 months. Completeness of follow-up ranged from 98.8% to 100%. All participants received aspirin and either unfractionated or low-molecular-weight heparin. Glycoprotein IIb/IIIa inhibitors were available during PCI in all trials except for VINO (Value of First Day Coronary Angiography/Angioplasty in Evolving Non-ST-Segment Elevation Myocardial Infarction), and during medical stabilization in TACTICS TIMI-18 (Treat Angina With Aggrastat and Determine the Cost of Therapy With an Invasive or Conservative Strategy—Thrombolysis In Myocardial Infarction) and ISAR-COOL. Thienopyridines were used as an adjunct to PCI in all trials.

Invasively treated patients were directed to catheterization laboratories, and depending on coronary anatomy, continued medical therapy or underwent revascularization (either by PCI or coronary artery bypass grafting [CABG]). Conservatively treated patients were generally managed with antiplatelet and antithrombin agents, and only directed to catheterization laboratories if there were persistent anginal symptoms despite maximal medical therapy, if there were hemodynamic or electrical instability, or if a large ischemic burden was shown on predischarge stress testing. A notable exception to this approach was the ISAR-COOL

Table 1. Baseline Characteristics and Rates of Revascularization of the Study Participants

Characteristic	FRISC-II	TRUCS	TIMI-18	VINO	RITA-3	ISAR-COOL	ICTUS
Enrollment period	1996–1998	1997–1998	1997–1999	1998–2000	1997–2001	2000–2002	2001–2003
Invasive/conservative patients, n	1222/1234	76/72	1114/1106	64/67	895/915	203/207	604/596
Age, yrs (mean)	66*	62	62	66	62	70*	62*
Women, %	30	27	34	39	38	33	27
Diabetes, %	12	29	28	25	13	29	14
Prior myocardial infarction, %	22	27†	39	26	28	23	23
Current smokers, %	30	31	NA	NA	32	21	41
Statin at randomization, %	10	21	52‡	43‡	45	NA	27
Statin at follow-up, %	55	NA	NA	NA	80	85	92
Thienopyridine with PCI, %	100§	NA	NA	100§	96	100¶	100
Elevated troponin at randomization, %	55	NA	54	100	75	67	100
Hours to angiography, median**	96/408	48/120††	22/79	6.2/1,464	48/1,020	2.4/86	23/283‡‡
Glycoprotein IIb/IIIa inhibitor, type	NA	NA	Tirofiban	NA	NA	Tirofiban	Abciximab
Invasive undergoing PCI, %	10	95	94	0	25	100¶	93
Conservative undergoing PCI, %	NA	96	59	0	25	100¶	69
Conservative not undergoing PCI, %	NA	NA	99	0	0	100¶	0
Coronary stent use with PCI, %**	62/69	85/85	83/86	44/50	88/90	87/92	88/88
Overall PCI or CABG, %**	78/45	100/61	64/45	73/39	61/38	78/72	79/54
Relative difference in revascularization between treatment arms, %	73	64	42	87	61	8	46

*Median age. †Defined by prior PCI or CABG. ‡Defined as lipid-lowering therapy. §By protocol, patients who received a stent were treated with a thienopyridine for 1 month. ¶By protocol, patients in both study arms received continuous tirofiban and daily clopidogrel (after a 600-mg loading dose) until PCI, followed by tirofiban for 24 h and clopidogrel for 4 weeks. These agents were discontinued if PCI was not indicated. ||Patients in both study arms initially received daily clopidogrel (after a 300-mg loading dose). At discharge, clopidogrel was used in 61% of invasively treated patients, and 49% of conservatively treated patients reflecting those who were not revascularized. **Data are formatted as invasive arm/conservative arm. ††Protocol required that patients undergo invasive therapy within these times. ‡‡Median time until PCI, in hours.

CABG = coronary artery bypass grafting; NA = not available; PCI = percutaneous coronary intervention.

trial, in which diagnostic catheterization was performed early (i.e., within 6 h) or delayed (i.e., within 3 to 5 days). Over the mean follow-up of 23.7 months, 71.1% of invasively treated patients eventually underwent revascularization by PCI or CABG, compared with 46.4% of conservatively treated patients.

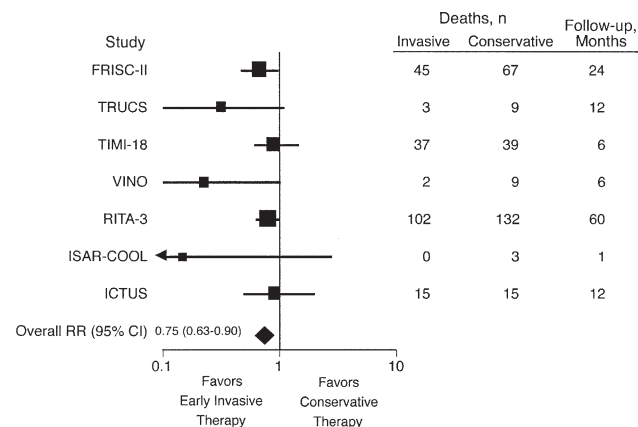


Figure 1. Relative risk of all-cause mortality for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. The results show a long-term survival benefit from early invasive therapy. CI = confidence interval; FRISC-II = Fragmin and Fast Revascularization During Instability in Coronary Disease; ICTUS = Invasive Versus Conservative Treatment in Unstable Coronary Syndromes Investigators; ISAR-COOL = Intracoronary Stenting With Antithrombotic Regimen Cooling Off; RITA-3 = Randomized Intervention Trial of Unstable Angina; RR = relative risk; TIMI-18 = Thrombolysis In Myocardial Infarction-18; TRUCS = Treatment of Refractory Unstable Angina in Geographically Isolated Areas Without Cardiac Surgery; VINO = Value of First Day Coronary Angiography/Angioplasty in Evolving Non-ST-Segment Elevation Myocardial Infarction.

All-cause mortality. For the primary outcome of all-cause mortality, the weighted mean follow-up was 23.7 months. Among patients randomized to early invasive therapy compared with a more conservative approach, the mortality incidence was 4.9% versus 6.5% (risk ratio [RR] = 0.75, 95% confidence interval [CI] 0.63 to 0.90, $p = 0.001$) (Fig. 1). The number needed to treat with early invasive therapy to save 1 life was 62 patients ($p = 0.001$). There was no evidence for heterogeneity among the studies (chi-square [6 degrees of freedom] 7.38, $p = 0.29$) or publication bias ($p = 0.26$). When the analysis was restricted to specific follow-up periods, the RR for mortality at 1 month was 0.82 (95% CI 0.50 to 1.34, $p = 0.43$); at 6 months 0.83 (95% CI 0.63 to 1.09, $p = 0.19$); at 12 months 0.80 (95% CI 0.61 to

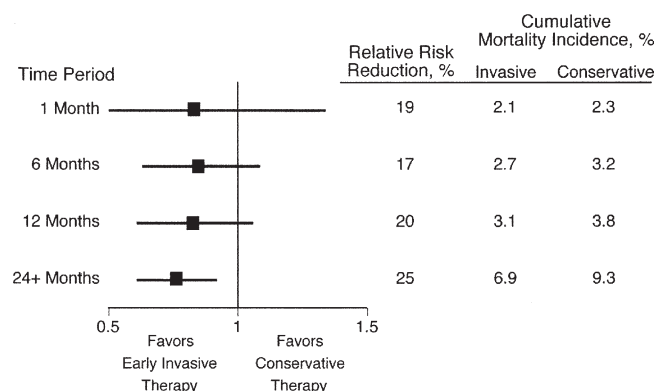


Figure 2. Relative risk of all-cause mortality for early invasive therapy compared with conservative therapy as a function of time. The results show a long-term survival benefit from early invasive therapy without an increase in early adverse events.

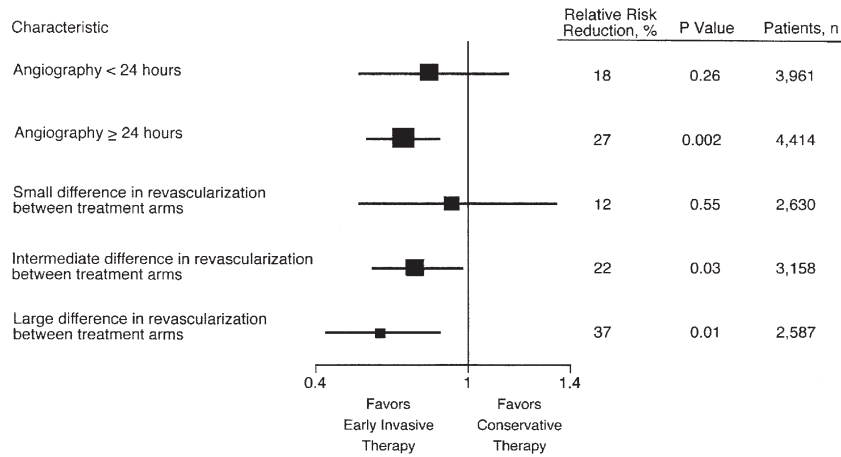


Figure 3. Relative risk of all-cause mortality based on time of angiography and the extent of revascularization. The results show that invasive therapy at a median of 9.3 h does not provide a greater survival advantage compared with angiography at a median of 39.4 h. In contrast, when a large proportion of invasively treated patients relative to conservatively treated patients undergo revascularization by follow-up, there is a strong improvement in late survival.

1.06, $p = 0.12$); and at more than 24 months 0.75 (95% CI 0.61 to 0.92, $p = 0.006$) (Fig. 2).

There were 4 studies (TIMI-18, VINO, ISAR-COOL, and ICTUS [Invasive Versus Conservative Treatment in Unstable Coronary Syndromes Investigators]) with 3,961 patients that performed early invasive therapy on average within 24 h (weighted median time to angiography of 9.3 h) and 3 studies (FRISC-II [Fragmin and Fast Revascularization During Instability in Coronary Disease], TRUCS [Treatment of Refractory Unstable Angina in Geographically Isolated Areas Without Cardiac Surgery], and RITA-3) with 4,414 patients that performed early invasive therapy more than 24 h after randomization (weighted median time to angiography of 39.4 h). When early invasive therapy was performed more than 24 h after randomization, there was a reduction in mortality (RR = 0.73, 95% CI 0.60 to 0.89, $p = 0.002$); however, when angiography was performed within 24 h there was no incremental improvement in this benefit (RR = 0.82, 95% CI 0.57 to 1.16, $p = 0.26$) (Fig. 3).

In 2 studies (TIMI-18 and ISAR-COOL, with 2,630 patients) there was a relatively small difference in the use of revascularization (PCI or CABG) at the extent of follow-up between the treatment arms (Table 1). Similarly, there were 3 studies (TRUCS, RITA-3, and ICTUS, with 3,158 patients) with an intermediate difference in the use of revascularization, and 2 studies (FRISC-II and VINO, with 2,587 patients) with a relatively large difference in the use of revascularization between treatment arms (Table 1). Among studies with a small difference in the use of revascularization between treatment arms, there was no obvious mortality benefit from early invasive therapy (RR = 0.88, 95% CI 0.57 to 1.35, $p = 0.55$); however, when there was a large difference in the use of revascularization, there was a significant reduction in all-cause mortality (RR = 0.63, 95% CI 0.44 to 0.89, $p = 0.01$) (Fig. 3).

Nonfatal myocardial infarction. All trials reported nonfatal myocardial infarction as separate events, except for TIMI-18, which reported fatal and nonfatal myocardial

infarction as a composite event. The cumulative incidence of nonfatal myocardial infarctions was 7.6% among recipients of early invasive therapy compared with 9.1% among conservatively treated patients over a weighted mean follow-up of 23.7 months (RR = 0.83, 95% CI 0.72 to 0.96, $p = 0.012$) (Fig. 4). The number needed to treat with early invasive therapy to prevent 1 myocardial infarction was 66 patients ($p = 0.011$). There was no evidence for publication bias ($p = 0.99$), although there was excess heterogeneity that was caused by increased postprocedural myocardial infarction in the ICTUS trial (chi-square [6 degrees of freedom] 21.30, $p = 0.002$). There was no longer heterogeneity when only spontaneous myocardial infarction in the ICTUS trial was analyzed (chi-square [6 degrees of freedom] 3.88, $p = 0.69$). When the analysis was restricted to specific follow-up periods, the risk for myocardial infarction was similar at 1 month (RR = 0.93, 95% CI 0.73 to 1.19, $p = 0.57$), at 6 months (RR = 0.90, 95% CI 0.76 to 1.06, $p = 0.20$), and at 12 months (RR = 0.95, 95% CI 0.80 to

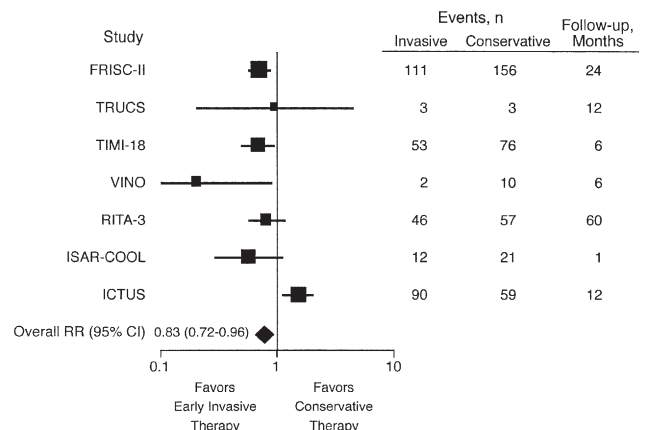


Figure 4. Relative risk of recurrent nonfatal myocardial infarction for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. The results show a long-term reduction in myocardial infarction from early invasive therapy. Abbreviations as in Figure 1.

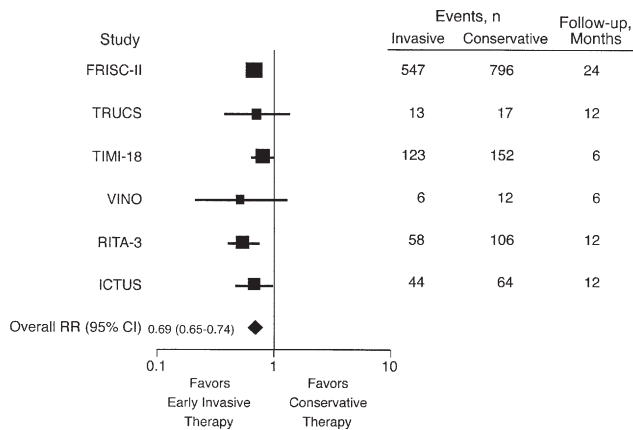


Figure 5. Relative risk of recurrent unstable angina resulting in rehospitalization for early invasive therapy compared with conservative therapy at a mean follow-up of 13 months. The results show a long-term reduction in recurrent unstable angina from early invasive therapy. Abbreviations as in Figure 1.

1.12, $p = 0.53$), and was reduced at more than 24 months of follow-up (RR = 0.77, 95% CI 0.63 to 0.92, $p = 0.007$). **Recurrent unstable angina requiring rehospitalization.** For the outcome of recurrent unstable angina requiring rehospitalization, the weighted mean follow-up was 13.2 months. This outcome occurred in 19.9% of individuals who received early invasive therapy, compared with 28.7% of conservatively treated patients (RR = 0.69, 95% CI 0.65 to 0.74, $p < 0.0001$) (Fig. 5). The number needed to treat with early invasive therapy to prevent 1 rehospitalization for unstable angina was 11 patients ($p < 0.0001$). There was no evidence for heterogeneity among the studies (chi-square [5 degrees of freedom] 3.95; $p = 0.56$) or publication bias ($p = 0.71$).

DISCUSSION

Our analysis of 7 contemporary randomized trials in over 8,000 NSTEMI-ACS patients treated in the era of potent antiplatelet therapy and coronary stents shows that early invasive therapy decreases mortality by 25% at a mean of 2 years of follow-up, compared with a more conservative approach. To save 1 life, 62 patients need to be treated with early invasive therapy. Early invasive therapy also decreases nonfatal myocardial infarction by 17% and recurrent unstable angina requiring rehospitalization by 31%. To prevent 1 myocardial infarction, 66 patients need to be treated, and to prevent 1 future episode of rehospitalization for unstable angina, 11 patients need to be treated with this approach.

Trials that performed very early invasive therapy (median of 9.3 h) did not show an improvement in long-term survival compared with trials that performed later angiography (median of 39.4 h). The ISAR-COOL trial was the only trial in which both study arms underwent invasive therapy, and this study found that very early angiography (median of 2.4 h) was superior to delayed angiography (median of 86 h); however, it is also possible that delaying invasive therapy for nearly 4 days with continuous glycoprotein IIb/IIIa inhibition could have been harmful (21).

Although later angiography in our analysis was associated with improved survival, we would caution against purposefully delaying invasive therapy because these trials were also those that revascularized a large proportion of early invasive patients relative to conservatively treated patients. These findings suggest that revascularization may be the key determinant and not the timeliness of invasive therapy in improving late clinical outcomes. The goal in the management of NSTEMI-ACS should be to perform early invasive therapy within 48 h. This view is also supported by recent insight from the CRUSADE registry, in which a delay of invasive therapy of 46 h was not associated with increased adverse events, compared with a delay of only 23 h (22).

The ICTUS trial documented a high incidence of postprocedural myocardial infarction, although this study used the lowest threshold for defining (creatinine kinase-MB fraction more than the upper limit of normal) and the highest frequency of sampling (every 6 h after PCI for 24 h) for these events (7). Although this definition is consistent with the current consensus document of the joint European Society of Cardiology/American College of Cardiology (23), it is in contradistinction to the other trials, which generally only sampled blood once after PCI and defined a postprocedural myocardial infarction as a creatine kinase-MB >1.5 to 5 times the upper limit of normal. It is possible that the other trials in this analysis would have also documented the same finding had they used a similar threshold and frequency for detecting such events. The significance of increased postprocedural events has been controversial (24,25), although an analysis of over 14,000 NSTEMI-ACS patients showed that spontaneous myocardial infarction is associated with a 6% to 8% higher absolute mortality compared with postprocedural myocardial infarction (26). The FRISC-II trial also showed that over the long term, the benefit of revascularization seems to outweigh any early harmful effects. In this trial, mortality and myocardial infarction were both significantly reduced at 1 year from early invasive therapy despite a small excess in early myocardial infarctions (14).

The results of the ICTUS trial may have moved some practitioners to a state of uncertainty in regard to the optimal treatment of NSTEMI-ACS (7). In fact, an accompanying editorial to this trial suggested that the current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines may need to be challenged (27). This position should be tempered by the current meta-analysis, which provides solid evidence that early invasive therapy results in a long-term survival advantage without early harm.

A strength of this study is that it reflects current practice. Analysis of noncontemporary trials performed before the era of potent antiplatelet therapies and coronary stents showed that early invasive therapy was associated with harm (5). Glycoprotein IIb/IIIa inhibitors and stents enhance the safety of PCI by decreasing major adverse cardiac events, including myocardial infarction and death (28–30). Addi-

tionally, a meta-regression identified glycoprotein IIb/IIIa inhibitors and stents to be the most significant predictors of event-free survival among invasively treated NSTEMI-ACS patients (31). Other concerns exist with noncontemporary trials such as VANQWISH (Veterans Affairs Non-Q-Wave Infarction Strategies In Hospital), in which the use of heparin, beta-blockers, angiotensin-converting-enzyme inhibitors, and lipid-lowering therapies were encouraged, but not required (10), and in TIMI IIIb, in which half of the participants received tissue plasminogen activator (8), although fibrinolytic agents are now contraindicated in this population (1). Accordingly, for a meta-analysis to be relevant and guide management decisions, the studies that are included for analysis should reflect current practice (32).

The optimized medical management that conservatively treated patients received in the ICTUS trial needs to be emphasized. By discharge, 94% of conservatively treated patients were taking a statin, and 49% were taking clopidogrel. Both of these therapies have been shown to reduce composite cardiac outcomes, including mortality, in the management of NSTEMI-ACS (33–36). Although the current body of evidence clearly supports early invasive therapy in the management of NSTEMI-ACS, future research is needed to more precisely determine the optimal timing of this approach, the appropriate concomitant adjuvant therapy that is required, and whether additional risk stratification is needed before angiography is performed.

In summary, early invasive therapy in the management of NSTEMI-ACS provides a durable survival advantage without increasing early adverse events. This approach also reduces nonfatal myocardial infarction and recurrent unstable angina requiring rehospitalization.

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