Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 22, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.03.007

Long-Term Outcome of a Routine Versus Selective Invasive Strategy in Patients With Non–ST-Segment Elevation Acute Coronary Syndrome

A Meta-Analysis of Individual Patient Data

Keith A. A. Fox, BSc, MB, ChB,* Tim C. Clayton, BSc, MSc,† Peter Damman, MD,‡ Stuart J. Pocock, BSc, MSc, PhD,† Robbert J. de Winter, MD, PhD,‡ Jan G. P. Tijssen, PhD,‡ Bo Lagerqvist, MD, PhD,§ Lars Wallentin, MD, PhD,§ for the FIR Collaboration

Edinburgh and London, United Kingdom; Amsterdam, the Netherlands; and Uppsala, Sweden

Objectives This study was designed to determine: 1) whether a routine invasive (RI) strategy reduces the long-term frequency of cardiovascular death or nonfatal myocardial infarction (MI) using a meta-analysis of individual patient data from all randomized studies with 5-year outcomes; and 2) whether the results are influenced by baseline risk.

Background Pooled analyses of randomized trials show early benefit of routine intervention, but long-term results are inconsistent. The differences may reflect differing trial design, adjunctive therapies, and/or limited power. This meta-analysis (n = 5,467 patients) is designed to determine whether outcomes are improved despite trial differences.

Methods Individual patient data, with 5-year outcomes, were obtained from FRISC-II (Fragmin and Fast Revascularization during Instability in Coronary Artery Disease), ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes), and RITA-3 (Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina) trials for a collaborative meta-analysis. A Cox regression analysis was used for a multivariable risk model, and a simplified integer model was derived.

Results Over 5 years, 14.7% (389 of 2,721) of patients randomized to an RI strategy experienced cardiovascular death or nonfatal MI versus 17.9% (475 of 2,746) in the selective invasive (SI) strategy (hazard ratio [HR]: 0.81, 95% confidence interval [CI]: 0.71 to 0.93; p = 0.002). The most marked treatment effect was on MI (10.0% RI strategy vs. 12.9% SI strategy), and there were consistent trends for cardiovascular deaths (HR: 0.83, 95% CI: 0.68 to 1.01; p = 0.068) and all deaths (HR: 0.90, 95% CI: 0.77 to 1.05). There were 2.0% to 3.8% absolute reductions in cardiovascular death or MI in the low- and intermediate-risk groups and an 11.1% absolute risk reduction in highest-risk patients.

Conclusions An RI strategy reduces long-term rates of cardiovascular death or MI and the largest absolute effect in seen in higher-risk patients. (J Am Coll Cardiol 2010;55:2435–45) © 2010 by the American College of Cardiology Foundation

Individual randomized trials of interventional strategies in non–ST-segment elevation acute coronary syndrome (ACS) have reported short- (1–7) or longer-term outcomes (8–10), but with differing conclusions. Uncertainty remains regarding the long-term benefits versus hazards of a routine early invasive strategy (angiography followed by revascularization where clinically indicated), and whether the outcomes are dependent on the baseline risk of patients (11–15). Whereas early results of some trials (FRISC-II [Fragmin and Fast Revascularization during Instability in Coronary Artery Disease], RITA-3 [Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina], TACTICS–TIMI 18 [Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18]) showed benefits (4–6), especially in reduced rates of myocardial infarction (MI) and refractory angina, there was no evidence of benefit in the ICTUS [Invasive Versus Conservative Treat-

*From the British Heart Foundation Professor of Cardiology, Centre for Cardiovascular Science, University and Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; †London School of Hygiene and Tropical Medicine, Keppel Street, London, United Kingdom; ‡Academic Medical Center–University of Amsterdam, Amsterdam, the Netherlands; and the §Uppsala Clinical Research Centre, University and Department of Medical Sciences Cardiology, Uppsala University, Uppsala, Sweden. The collaboration and the meta-analysis were conducted using resources from the host institutions for the respective studies (Dr. Fox is supported by the British Heart Foundation; Dr. Wallentin is supported by the Swedish Heart Foundation) and from the London School of Hygiene and Tropical Medicine. The original studies were supported as stated in the original reports. Dr. Fox has received grants and honoraria from Sanofi-Aventis/Bristol-Myers Squibb, GlaxoSmithKline, Lilly, and AstraZeneca. Dr. Pocock has consulted for The Medicines Company, and has served on a Boston Scientific-sponsored Data Monitoring Committee.

Manuscript received February 10, 2010; revised manuscript received March 4, 2010, accepted March 11, 2010.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CV = cardiovascular
MI = myocardial infarction
RI = routine invasive
SI = selective invasive

ment in Unstable Coronary Syndromes] trial (7). Moreover, longer-term mortality and cardiovascular (CV) mortality results of the individual trials appear inconsistent and showed either no benefit or trends at the margins of statistical significance (8–10), illustrating a lack of statistical power for any 1 trial to reach definitive conclusions. Previous pooled analyses have not been conducted using individual patient data, and outcome data beyond 1 year were not included (14–16).

Differences in outcomes in the respective trials may be the result of differences in inclusion criteria, differences in baseline characteristics of the patients, differences in the timing and threshold for revascularization, differences in adjunctive therapies, and other factors including the play of chance. An overall long-term meta-analysis is therefore required to define more reliably the relative risks and benefits of routine invasive (RI) and conservative strategies, particularly for CV mortality and nonfatal MI. Such an analysis would have substantially greater power to determine the impact on mortality and to explore how the effects depend on patients' baseline risk.

The FIR (FRISC-II, ICTUS, RITA-3) collaboration involves the 3 randomized trials with long-term outcome data (5-year outcome) with the hypothesis is that the meta-analysis will provide evidence of a reduced rate of CV death or MI associated with an RI strategy compared with a selective invasive (SI) strategy. The secondary hypothesis was that relative and absolute differences between the treatment strategies were influenced by the baseline risk of the patients. Resolving these issues has the potential to influence triage decisions for the spectrum of patients presenting with non–ST-segment elevation ACS and guidelines suggest the importance of risk stratification (11–13).

Methods

Study population and procedures. A computerized literature search was conducted from 1970 to 2009 of the MEDLINE and Cochrane databases by using terms that included: "invasive strategy," "conservative strategy," "selective invasive strategy," "intervention," "acute coronary syndromes," "non–ST-segment elevation myocardial infarction," and "unstable angina." Three randomized trials with long-term outcomes were identified that met these criteria (FRISC-II, RITA-3, and ICTUS) (8–10). The TACTICS–TIMI 18 trial has only 6-month outcome data (5), and none of the smaller trials has 5-year outcomes published or presented (1–3,14–16).

Individual outcomes and the design of the FRISC-II, RITA-3, and ICTUS trials have been reported previously (8–10). The previous publication of RITA-3 reported outcomes at a median of 5 years, and for consistency across the trials, the results are now extended with complete 5-year follow-up for all patients.

These trials compared an RI strategy with an SI strategy in patients with non–ST-segment elevation ACS but with differing criteria for the eligible population. The RI strategy consisted of "early" coronary angiography and the timing of this reflected contemporary clinical practice (within 24 to 48 h of randomization in ICTUS, within 72 h in RITA-3, and within 7 days in FRISC-II). The decision to proceed to percutaneous or surgical revascularization was based on the angiographic findings, but the threshold for proceeding to intervention differed in the 3 trials. In each trial, the SI "conservative" strategy consisted of initial medical treatment with coronary angiography and revascularization only for refractory or an accelerating pattern of angina despite optimal medical treatment (or in the case of hemodynamic or rhythmic instability in ICTUS). In the FRISC-II and ICTUS trials, a pre-discharge ischemia detection test was systematically performed, with criteria for "crossing over" to intervention from the SI strategy (4,7,9,10). By design, in RITA-3 the indication for coronary arteriography in the SI strategy was symptom-driven (6,8).

Setting and data collection. The principal investigators of FRISC-II, RITA-3, and ICTUS (L. W., K. A. A. F., R. J. d.W.) initiated this collaborative analysis, and a protocol was written summarizing the main pre-specified analyses and a common set of baseline and outcome variables. Investigators from the 3 trials provided individual patient data to form a pooled patient database in accordance with previously published methodologies (1–3,5,13–16). The database included core variables on demographics, clinical history, risk factors for coronary artery disease, baseline electrocardiographic characteristics, biomarkers of myocardial necrosis, and 5-year clinical outcomes. Data sets from each trial were sent for merging to the coordinating Academic Medical Center in Amsterdam, the Netherlands. The merged database was checked for completeness and consistency by all 3 participating sites.

Outcomes. The primary outcome was the composite of CV death or nonfatal MI. Other secondary outcomes included all-cause death and nonfatal MI alone. Myocardial infarction was defined as pre-specified in each trial (4,6,7).

Statistical analysis. The main outcomes were tabulated by treatment group for each study, and overall, with 5-year cumulative event rates estimated with the Kaplan-Meier method. The impact of the intervention was assessed using Cox regression models, stratified by trial. For the primary outcome of CV death or nonfatal MI, heterogeneity between treatment strategy and study was assessed using an interaction test in the Cox model. Univariable associations of the candidate baseline variables with the primary outcome were determined from the combined data. A forward stepwise Cox regression model was used to develop a multivariable model of key predictors of CV death or nonfatal MI with $p < 0.01$ by the Wald test used as the criterion for inclusion in the model. No adjustment for trial

was made to this model in order to develop a generalizable risk score based only on patient baseline factors. However, a model with trial entered as dummy variables was performed to assess whether this materially altered the hazard ratios for each predictor included.

The coefficients in the final Cox model were rounded to produce an integer risk score to predict a patient's 5-year probability of CV death or MI. For each risk factor a score of 0 is assigned to the lowest risk category and an individual's score increases by an integer amount for each level above the lowest category (with 1 unit increase in the integer score equating to approximately each 0.2 increase in the coefficient). In order to assess the effect of intervention according to risk, the integer score was calculated assuming the patient received the SI strategy. Patients were then categorized into 3 risk groups (each of the 3 groups contained approximately one-third of the primary outcome events). The percentage of patients with the primary outcome was tabulated by treatment group and risk category, along with hazard ratios and absolute risk differences, to consider whether the impact of intervention depended on underlying risk.

Risk categories were also defined based on the exact coefficients from the model to compare the results with those using the simple integer score. Finally, risk categorizations were used to assess the impact of intervention on CV mortality and for all-cause mortality. All analyses were carried out using Stata version 10.1 (StataCorp, College Station, Texas).

Results

Characteristics of the patients. Three randomized trials had outcome information with a minimum of 5 years of follow-up and the data were censored at 5 years. Overall, 2,746 patients were assigned an SI ("conservative") strategy and 2,721 patients an RI strategy.

The mean age was 63.3 years, body mass index was 27.2 kg/m^2 and 68.0% of the population were men (baseline variables in the respective studies: Table 1).

Comparing the baseline characteristics across the 3 trials, the majority of the patient demographics, the key risk factors, and the extent of prior coronary artery disease were similar (Table 1). Almost one-half of the patients (47.3%) had ST-segment deviation at presentation. There were differences in baseline characteristics in respective trials including a higher proportion of patients presented with ST-segment depression on the admission electrocardiogram in FRISC-II (47.1%) and ICTUS (44.6%) than in RITA-3 (36.5%) (Table 1). Troponin values were not available at baseline in all patients in RITA-3.

Revascularization rates over time. Among those randomized to an RI strategy, approximately two-thirds (64.1%) underwent revascularization during the index hospitalization; this figure rising to 71.8% at the end of 1 year and 73.3% at the end of 3 years. In comparison, the rate of revascularization in hospital in those randomized to an SI strategy was 17.6% but this rose to 41.6% at the end of 1 year and 47.8% at the end of 3 years (Kaplan-Meier plot) (Fig. 1). By design, the individual trials allowed for angiography and revascularization on the basis of symptoms and objective signs of ischemia (4,6,7) and routine pre-discharge stress testing led to higher crossover rates to intervention in the SI strategy patients, particularly in ICTUS (7,10). The Kaplan-Meier plot of revascularization over time shows that most of those crossing to intervention from the SI strategy had revascularization performed within 3 months of presentation (Fig. 1). Considering all revascularizations, there were 0.71 per patient in the RI group compared with 0.44 per patient in the SI group (RITA-3) (Fig. 1).

Impact of the randomized treatment: overall clinical outcomes. Over the course of 5 years, 14.7% (389 of 2,721) of patients randomized to an RI strategy experienced CV death or nonfatal MI compared with 17.9% (475 of 2,746) randomized to the SI strategy (hazard ratio [HR]: 0.81, 95% confidence interval [CI]: 0.71 to 0.93; p = 0.002)

Table 1 Baseline Characteristics by Study*

	FRISC-II (n = 2,457)	RITA-3 (n = 1,810)	ICTUS (n = 1,200)
Age, yrs	64.6 (9.1)	62.4 (10.3)	61.9 (10.6)
<55	470 (19.1%)	433 (23.9%)	298 (24.8%)
55–<60	179 (7.3%)	263 (14.5%)	210 (17.5%)
60–<65	475 (19.3%)	316 (17.5%)	163 (13.6%)
65–<70	567 (23.1%)	295 (16.3%)	176 (14.7%)
70–<75	305 (12.4%)	277 (15.3%)	201 (16.8%)
75+	461 (18.8%)	226 (12.5%)	152 (12.7%)
Weight, kg	79.6 (13.5)	78.6 (14.6)	81.5 (12.9)
BMI, kg/m^2	26.8 (3.8)	27.7 (4.7)	27.1 (3.7)
Sex			
Women	749 (30.5%)	682 (37.7%)	320 (26.7%)
Men	1,708 (69.5%)	1,128 (62.3%)	880 (73.3%)
Smoking			
Current	745 (30.3%)	586 (32.4%)	492 (41.0%)
Hypertension	743 (30.2%)	632 (34.9%)	466 (38.8%)
Hyperlipidemia	262 (10.7%)	579 (32.0%)	417 (34.8%)
Diabetes	299 (12.2%)	244 (13.5%)	166 (13.8%)
Previous MI	546 (22.2%)	501 (27.7%)	278 (23.2%)
Previous PCI	80 (3.3%)	93 (5.1%)	140 (11.7%)
Previous CABG	9 (0.4%)	0 (0.0%)	105 (8.8%)
ST-segment depression	1,152 (47.1%)	660 (36.5%)	513 (44.6%)
ST-segment elevation	202 (8.3%)	139 (7.7%)	137 (11.9%)
ST-segment deviation	1,240 (50.7%)	742 (41.0%)	574 (50.0%)

Values are mean (SD) or n (%). In total, of those discharged alive, 62.0% were discharged on a statin (RI: 61.9%, SI: 62.1%), 93.2% on aspirin (RI: 92.4%, SI: 94.0%), 80.6% on a beta-blocker (RI: 78.6%, SI: 82.6%), and 22.7% on an angiotensin-converting enzyme inhibitor (RI: 22.4%, SI: 22.9%). *For assessing differences in baseline characteristics across the 3 studies, $p < 0.001$ for each variable except diabetic status ($p = 0.27$).

BMI = body mass index; CABG = coronary artery bypass graft; FRISC-II = Fragmin and Fast Revascularization during Instability in Coronary Artery Disease; ICTUS = Invasive Versus Conservative Treatment in Unstable Coronary Syndromes; MI = myocardial infarction; PCI = percutaneous coronary intervention; RI = routine invasive; RITA-3 = Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina; SI = selective invasive.

JACC Vol. 55, No. 22, 2010
June 1, 2010:2435–45

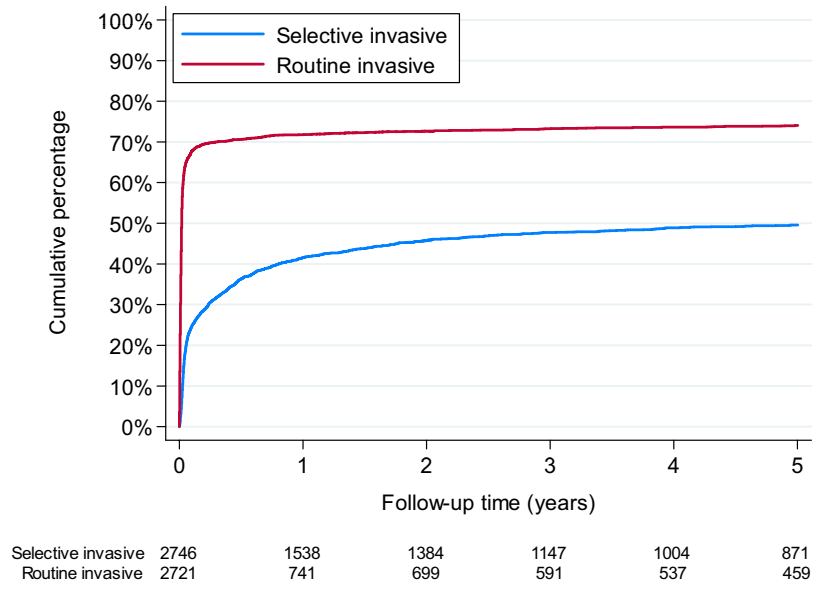


Figure 1 Timing of First Coronary Revascularization

All revascularizations: For routine invasive (RI) strategy, the total number of revascularizations was 633 in RITA-3 (Randomized Trial of a Conservative Treatment Strategy Versus an Interventional Treatment Strategy in Patients with Unstable Angina) trial (in 546 patients). In the selective invasive (SI) strategy, the respective figures are 406 (in 347 patients) for RITA-3. The data on total revascularizations are not available from FRISC-II (Fragmin and Fast Revascularization during Instability in Coronary Artery Disease) or ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes) trials. In the RI group, 1,248 had percutaneous coronary intervention (PCI) and 750 had coronary artery bypass graft (CABG) as their first procedure (1,998 patients total). In the SI group, 748 had PCI and 569 had CABG as their first procedure (1,317 patients total).

(Table 2, Fig. 2). The confidence bounds were unaffected by adjustment for study (Fig. 2). Including all periprocedure infarctions (Table 2), the data for FRISC-II and RITA-3 are unchanged and for ICTUS there were 14 additional patients with MIs with SI but 32 additional patients with MIs for the RI strategy. In consequence, combined, there were 487 (18.3%) CV deaths or MIs with SI and 420 (15.9%) with an RI strategy: HR: 0.86, 95% CI: 0.76 to 0.98; p = 0.028. Considering deaths from any cause or nonfatal MIs, the findings were similar with a 15% hazard reduction for the RI strategy (HR: 0.85, 95% CI: 0.75 to 0.96; p = 0.008) (Table 2). The most marked treatment effect was seen for nonfatal MIs that occurred in 10.0% of the population randomized to a RI strategy versus 12.9% to an SI strategy (HR: 0.77, 95% CI: 0.65 to 0.90; p = 0.001).

There were numerically fewer CV deaths among those randomized to a RI strategy (6.8%) versus those randomized to a SI strategy (8.1%) (HR: 0.83, 95% CI: 0.68 to 1.01; p = 0.068) (Table 2). Deaths from any cause were also numerically fewer among those randomized to a RI strategy (10.6% vs. 11.7% in the SI strategy, p = 0.19) although this difference is not statistically significant (Table 2).

Comparing the outcomes across the trials, the hazard ratios for the composite of CV death or nonfatal MI demonstrated similar findings in FRISC-II (HR: 0.79, 95% CI: 0.66 to 0.95) and RITA-3 (HR: 0.75, 95% CI: 0.58 to 0.96), and in both studies the confidence bounds did not overlap unity (Fig. 2). In ICTUS, the confidence bounds overlapped with those of the other 2 studies and with unity (HR: 0.99, 95% CI: 0.72 to 1.35) (Fig. 2). There is no evidence of heterogeneity between trials (interaction p = 0.37).

The Kaplan-Meier plots for CV death or nonfatal MI demonstrate early separation of the curves in favor of the RI strategy with sustained separation and slight divergence over the course of the 5 years of follow-up (Fig. 3).

Multivariable predictors for CV death or MI at 5 years of follow-up. The univariable and multivariable predictors of CV death or nonfatal MI were derived (Tables 3 and 4). The independent multivariable predictors for CV death or MI in the entire dataset were randomized treatment (HR: 0.76, 95% CI: 0.67 to 0.87; p < 0.0001), age per 5-year interval, diabetes, prior MI, presentation with ST-segment depression, hypertension, and low (<25 kg/m^2) or elevated body mass index (≥35 kg/m^2) (Table 4).

The relation between baseline risk and outcome at 5 years of follow-up. In the high-risk RI group there were 130 of 423 CV deaths or nonfatal MIs (32.1%) versus 159 of 379 (43.8%) in the SI group (HR: 0.66, 95% CI: 0.52 to 0.83, risk difference: −11.7%). In the moderate-risk patients (29% of the cohort), the respective figures for the RI group were 134 of 791 (17.4%) versus 152 of 774 for the SI group (20.3%) (HR: 0.86, 95% CI: 0.68 to 1.08, risk difference: −2.9%). In the low-risk patients (56% of the cohort), the respective figures for the RI group were 125 of 1,507 (8.5%) versus 164 of 1,593 for the SI group (10.6%) (HR: 0.80,

Table 2 Outcomes by Study and Treatment

Outcomes*	FRISC-II		RITA-3		ICTUS		Combined			
	SI (n = 1,235)	RI (n = 1,222)	SI (n = 915)	RI (n = 895)	SI (n = 596)	RI (n = 604)	SI (n = 2,746)	RI (n = 2,721)	HR (95% CI)	p Value
All-cause death	124 (10.1%)	117 (9.6%)	138 (15.1%)	104 (11.6%)	59 (9.9%)	67 (11.1%)	321 (11.7%)	288 (10.6%)	0.90 (0.77–1.05)	0.19
CV death	86 (7.1%)	79 (6.6%)	92 (10.3%)	64 (7.3%)	40 (6.8%)	38 (6.5%)	218 (8.1%)	181 (6.8%)	0.83 (0.68–1.01)	0.068
MI	206 (17.6%)	150 (12.9%)	78 (8.9%)	60 (6.9%)	54 (9.4%)	50 (8.6%)	338 (12.9%)	260 (10.0%)	0.77 (0.65–0.90)	0.001
All-cause death/MI	283 (23.8%)	231 (19.7%)	182 (20.2%)	144 (16.3%)	95 (16.1%)	105 (17.5%)	560 (20.9%)	480 (18.1%)	0.85 (0.75–0.96)	0.008
CV death/MI	254 (21.4%)	204 (17.4%)	143 (16.1%)	107 (12.2%)	78 (13.4%)	78 (13.2%)	475 (17.9%)	389 (14.7%)	0.81 (0.71–0.93)	0.002

*Percentages are Kaplan-Meier percentages at 5 years. Including all periprocedure infarctions, the data for FRISC-II and RITA-3 are unchanged, and for ICTUS, there were 14 additional MIs in the SI strategy and 32 additional MIs in the RI strategy. In consequence, combined, there were 487 (18.3%) CV death/MIs in the SI and 420 (15.9%) in the RI groups: hazard ratio (HR): 0.86, 95% confidence interval (CI): 0.76 to 0.98, p = 0.028.
CV = cardiovascular; other abbreviations as in Table 1.

95% CI: 0.63 to 1.01, risk difference: −2.1%). These risk differences are based on the exact coefficients. These agree closely with the simplified integer score.

In order to make the multivariable risk prediction more accessible to clinicians, it was converted into an integer score (Table 5, Fig. 4). The simple integer scoring system is based on the multivariable predictors: age: <60 years = 0 score, 60 to 64 years = +1, 65 to 69 years = +2, 70 to 74 years = +3, ≥75 years +5; diabetes: no = 0, yes = +4; hypertension: no = 0, yes = +1; ST-segment depression: no = 0, yes = +2; body mass index: <25 kg/m^2 = +1, 25 to <35 kg/m^2 = 0, ≥35 kg/m^2 = +2 (Fig. 6). We formed 3 risk groups: low, moderate, and high risk for integer scores of 0 to 4, 5 to 8, and ≥9, respectively. The aim was to have roughly equal numbers of primary outcomes in each risk group. As a consequence there are substantially more patients in the low-risk group and fewer in the high-risk group, compared with the moderate-risk group (Table 5). The risk stratification demonstrated separation of outcome according to the categories of risk. For both strategies, the combined rate of CV death or nonfatal MI was 9.3% in the low-risk group (263 of 2,926), 19.2% in the moderate-risk group (341 of 1,832), and 38.2% in the high-risk group (260 of 709). As there was no significant heterogeneity in the relative effect on outcome over the risk groups, the absolute impact of intervention differed in relation to the category of baseline risk (Table 5, Fig. 5). The largest absolute reduction in CV death or MI was seen in the 13% of patients in the highest risk group (HR: 0.68, 95% CI: 0.53 to 0.86; risk difference −11.1%, 95% CI: −18.4% to −3.8%). The lower rates of outcome events in the moderate- and lower-risk groups were associated with more modest reductions in absolute event rates of −3.8% (95% CI: −7.4% to −0.1%) in the moderate-risk group and −2.0% (95% CI: −4.1% to 0.1%) in the low-risk group.

Cardiovascular and all-cause mortality and risk group. There was a lower rate of CV mortality in the high-risk RI group (82 of 378 versus 84 of 331 for the SI group [HR: 0.83, 95% CI: 0.61 to 1.12; risk difference: −3.8%, 95% CI: −10.3% to 2.7%]). The high-risk RI group also showed a lower rate of all-cause mortality (107 of 378 vs. 107 of 331 for the SI group [HR: 0.84, 95% CI: 0.65 to 1.10; risk difference: −4.0%, 95% CI: −10.9% to 2.8%]). There were smaller but consistent absolute reductions even in the low-risk group for both CV mortality (−1.1%, 95% CI: −2.3% to 0.1%) and all-cause mortality (−0.9%, 95% CI: −2.5% to 0.7%).

Thus the largest absolute difference in CV death or MI, and in all-cause and CV mortality, was seen in the highest risk group. The test for interaction between treatment and risk score for CV death or MI was nonsignificant on the hazard ratio scale (p = 0.10), whereas it was highly significant on the risk difference scale (p < 0.0001); hence, the results are consistent with more modest treatment effects (in terms of absolute differences) in lower risk groups.

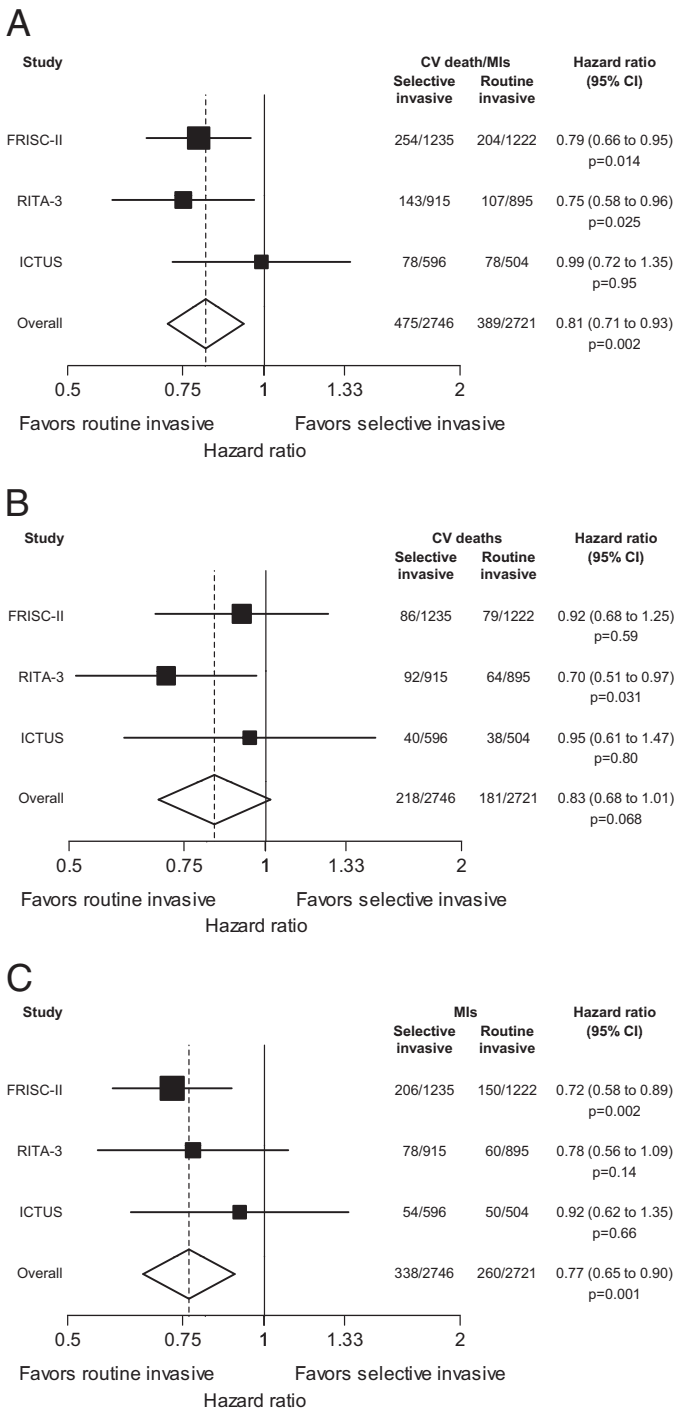


Figure 2 **Meta-Analyses for CV Death or MI (FRISC-II, RITA-3, ICTUS Studies)**

Meta-analyses for **(A)** cardiovascular (CV) death or myocardial infarction (MI), **(B)** CV death only, and **(C)** MI only combined across FRISC-II, RITA-3, and ICTUS trials. Abbreviations as in Figure 1.

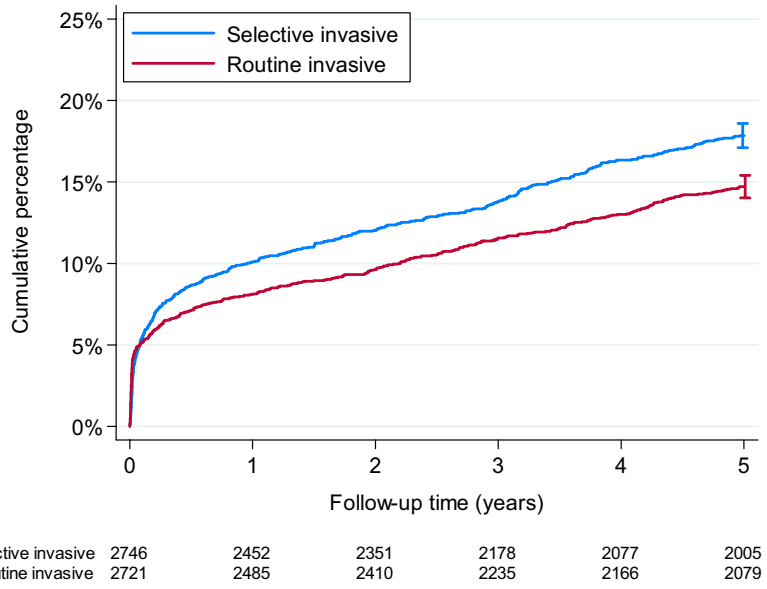


Figure 3 **Cumulative Risk of CV Death or MI**

Patients (n = 5,467) and follow-up: There were 4,084 patients without a primary event (CV death or MI) who were followed for 5 years. There were 864 primary end points and 194 other deaths. A further 38 patients were lost to follow-up and 287 censored because follow-up time differed from 5 years. Abbreviations as in Figure 2.

Discussion

This meta-analysis of the 3 trials that assessed the long-term impact of a RI strategy demonstrated a sustained advantage for the RI strategy in reducing subsequent CV death or nonfatal MI. The 19% relative risk reduction (HR: 0.81, 95% CI: 0.71 to 0.93) reflected a 3.2% absolute reduction in the combined end point. The difference was mainly driven by the 23% relative 2.9% absolute reduction in MI. However, there was also a consistent strong trend to a reduction in cardiovascular and total mortality. The randomized treatment was applied on top of the contemporary standard of secondary prevention therapy and the treatment effect was seen despite the fact that adjunctive therapy and instrumentation evolved over the course of the successive trials (e.g., use of thienopyridines, glycoprotein IIb/IIIa antagonists, stent and catheter technology). Furthermore, the benefit was seen despite a substantial crossover to invasive treatment event in the noninvasive treatment arm in several of the trials.

The hypothesis has been proposed that the timing of revascularization influences outcome but the most recent and largest of the studies (17) of timing did not demonstrate overall benefit of an early routine intervention compared with a delayed routine intervention (17–20).

Resolving the differences in outcome compared with individual studies. Previous combined analyses have not been conducted using individual patient data, and they lacked outcomes beyond a year (14–16). Why are the findings more clear-cut in this meta-analysis compared with individual trials? First, the substantially greater sample size, and second, the greater number of outcome events over 5 years. Individual trials had limited statistical power for cardiovascular death or MI. They either had composite end points (RITA-3, ICTUS), or they were powered for a large anticipated (33%) reduction in death or MI (FRISC-II) (14–16).

What accounts for the trial-to-trial differences in outcomes? First, there were different inclusion criteria in the trials with more unselected populations included in the first performed trials—FRISC-II and RITA-3. In the ICTUS study, patients included were all troponin-positive and had either ischemic chest pain or documented coronary artery disease. This may in part explain the high revascularization rate in the SI arm of ICTUS.

In FRISC-II and RITA-3, there was a wide separation in the frequency of early and late revascularization rates between the 2 arms of the respective trials. In FRISC-II, the revascularization rates were 71% within 10 days and 78% within 12 months in the RI group. This compares with 9% and 43%, respectively, in the SI group. In RITA-3, for the RI group, the revascularization rates were 44% within index hospitalization and 57% within 12 months compared with 10% and 28%, respectively, in the SI group. In ICTUS, for the RI group, 76% within index hospitalization and 79% within 12 months compared with 40% and 54%, respectively, in the SI group. Thus, especially the early rate of revascularization in the SI strategy was substantially higher in ICTUS than in FRISC-II or RITA-3, and the rate remained higher thereafter. In RITA-3, the rates of both early and late intervention, in the SI and RI strategies were lower than in FRISC-II and ICTUS. In fact, the rate of intervention in the SI arm of ICTUS resembled the rate in the RI arm of RITA-3.

JACC Vol. 55, No. 22, 2010
June 1, 2010:2435–45

Table 3 Univariable Associations With CV Death or MI

Risk Factor	Categories	Outcomes/Denominator	HR	95% CI	p Value
Randomized treatment	SI	475/2,746	1.00	—	
	RI	389/2,721	0.81	0.71–0.93	0.002
Study	FRISC-II	458/2,457	1.00	—	
	RITA-3	250/1,810	0.70	0.60–0.82	<0.001
	ICTUS	156/1,200	0.65	0.54–0.78	<0.001
Age	Per 5-yr increase	—	1.25	1.20–1.29	<0.001
	<55	115/1,201	1.00	—	<0.001
	55–<60	60/652	0.96	0.70–1.31	
	60–<65	127/954	1.42	1.10–1.83	
	65–<70	169/1,038	1.77	1.40–2.25	
	70–<75	156/783	2.20	1.73–2.79	
	75+	237/839	3.28	2.63–4.10	
Weight	Per 10-kg increase	—	0.98	0.93–1.03	0.44
BMI	Per kg/m^2 increase	—	0.96	0.89–1.05	0.39
	<25	283/1,633	1.00	—	0.005
	25–<30	383/2,625	0.82	0.70–0.95	
	30–<35	126/870	0.82	0.66–1.01	
	35+	55/260	1.24	0.93–1.66	
Sex	Women	261/1,751	1.00	—	
	Men	603/3,716	1.10	0.95–1.27	0.20
Smoking	No	626/3643	1.00	—	
	Yes	238/1,823	0.75	0.65–0.87	<0.001
Hypertension	No	494/3,626	1.00	—	
	Yes	370/1,841	1.52	1.33–1.74	<0.001
Hyperlipidemia	No	646/4,208	1.00	—	
	Yes	218/1,258	1.13	0.97–1.31	0.13
Diabetes	No	653/4,758	1.00	—	
	Yes	211/709	2.37	2.03–2.77	<0.001
Previous MI	No	533/4,142	1.00	—	
	Yes	331/1,325	2.07	1.80–2.37	<0.001
Previous PCI	No	803/5,154	1.00	—	
	Yes	61/313	1.25	0.96–1.62	0.097
Previous CABG	No	836/5,353	1.00	—	
	Yes	28/114	1.60	1.10–2.33	0.014
ST-segment depression	No	400/3,080	1.00	—	
	Yes	451/2,325	1.58	1.38–1.81	<0.001
ST-segment elevation	No	758/4,925	1.00	—	
	Yes	92/478	1.27	1.02–1.58	0.030
ST-segment deviation	No	367/2,849	1.00	—	
	Yes	484/2,556	1.55	1.36–1.78	<0.001

Abbreviations as in Tables 1 and 2.

Do the outcomes differ according to the extent of baseline CV risk? To resolve this issue, univariable (Table 3) and multivariable predictors (Table 4) of CV death or MI were derived and the entire population was separated into 3 groups based on an integer score so that each risk group contained approximately one-third of the outcome events. The identified risk characteristics and the results in the different risk groups correspond well to previous reports from the FRISC-II trial (9,21). The most pronounced treatment effect was seen in the high-risk group. However, although the treatment effect was less pronounced in the majority of patients at lower risk, the absolute number of events prevented was greater (20 events in the high-risk group, 31 events in the intermediate-risk, and 35 events in the low-risk patients (Table 5). Interestingly, the Kaplan-Meier plot suggests that the early invasive strategy is associated with a progressive benefit over time that may reflect a long-term reduced rate of MI because of avoidance of risk of episodes of ischemia and avoidance of the consequences of earlier myocardial injury on subsequent arrhythmic events and heart failure (increasing risk of CV mortality).

The relative and absolute benefits in the moderate and lower risk groups are of similar magnitude to those aimed for and seen in the overall results of recent trials of pharmaceutical treatments for non–ST-segment elevation ACS: TRITON–

Table 4 Multivariable Predictors of CV Death or MI (Cox Regression)

Risk Factor	HR	95% CI	Coefficient	*z*-Score*
Age, per 5 yrs above 60 yrs	1.29	1.23–1.36	0.256	9.89
Diabetes	2.06	1.75–2.41	0.72	8.83
Previous MI	1.83	1.59–2.10	0.60	8.50
ST-segment depression	1.42	1.24–1.63	0.35	5.03
Hypertension	1.26	1.10–1.45	0.23	3.33
BMI, kg/m^2†				
<25	1.25	1.08–1.45	0.22	2.98
25–<35	1.00	—	—	—
35+	1.52	1.15–2.01	0.42	2.91
Randomized treatment				
SI	1.00	—	—	—
RI	0.76	0.67–0.87	–0.27	–3.91

*Absolute value of z >1.96, 2.58, 3.29, 3.89, 4.42 corresponds to p value <0.05, 0.01, 0.001, 0.0001, 0.00001, respectively. †p = 0.0008 for inclusion of BMI group.
Abbreviations as in Tables 1 and 2.

TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) (22) and PLATO (Platelet Inhibition and Patient Outcomes) (23). However, the health economic considerations of the smaller number needed to treat per patient saved in the higher risk subgroup but greater number of patients saved by treating also lower risk populations need greater attention when interpreting how trial findings are best applied to future patients (24). In contrast to these findings from randomized trials, studies of clinical practice in multiple countries demonstrate a "treatment-risk paradox," whereby most interventions are performed in lower risk patients (25,26).

Can this risk model be converted into a readily usable integer risk predictor? The simplified integer score demonstrates very similar separation of the risk groups and similar risk differences compared with the exact coefficients from the model used to determine risk. This integer score has the potential to be applied at the bedside, and without the need for a nomogram or calculator. The receiver operator characteristic for the integer score was 0.69, which is almost identical to the score for the full multivariable model. The FRISC-II, RITA 3, and ICTUS studies lacked the variables necessary to apply other well-validated risk scores (e.g. TIMI, GRACE) (11–13).

Strengths and limitations. This is the first meta-analysis of the long-term impact of a RI strategy, on top of the current standard of adjunctive therapy. It is based on individual patient data.

Rates of adjunctive therapy increased in each successive study and rates were highest in ICTUS. Rates of intervention were also highest in ICTUS. There were differences in the definition of MI by study and differences in the sensitivity for detection of MI. Detection of the early occurrence of re-MI presents diagnostic challenges in all studies of non–ST-segment elevation ACS. However, such differences in definition and diagnostic threshold of biomarkers would tend to add "noise" to the meta-analysis and diminish the probability of showing any real impact on CV death or MI. The sensitivity for detection of infarction, including periprocedure infarction increased with successive studies and ICTUS routinely measured serial blood samples in patients for post-PCI elevations of creatine kinase-myocardial band (CK-MB) mass. However, in ICTUS, there was acknowledgment that periprocedure infarctions were more readily detected during the initial in-hospital phase in the RI group than in the SI group (undertaken later) (10). Specifically, of the 82 patients with MI in the RI group, 35 (42.7%) had procedure-related MIs alone compared with 14 of 68 (20.5%) in the SI group. Nevertheless, even including all of these procedure-related MIs in the meta-analysis, the RI strategy has a reduced rate of CV death or nonfatal MI (HR: 0.86, 95% CI: 0.76 to 0.98; p = 0.028).

The use and sensitivity of biomarkers of necrosis evolved over the successive studies. As differing troponin assays were used and not all patients had troponin values, this variable was not included in the multivariable risk calculation. Nevertheless, based on the other independent predictors, patients could be separated clearly into the 3 categories of risk (Fig. 5).

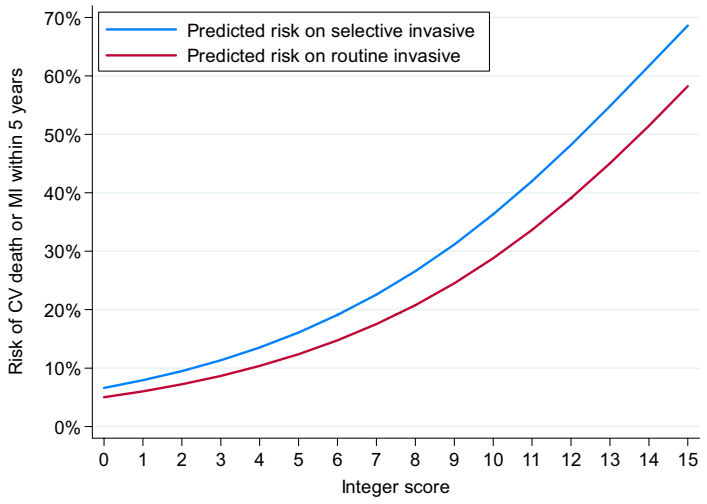
Finally, the differences may be influenced by sample size and the play of chance (ICTUS was the smallest study and had limited power to resolve differences in death or MI). Nevertheless, as illustrated in Figure 2, the confidence intervals for outcomes overlap and despite the differences in design, the meta-analysis strongly suggests a benefit for the RI strategy, even 5 years after randomization. This is despite subsequent late revascularizations in the selective strategy in each study, on account of symptoms and signs of ischemia.

Implications. Despite differences in trial design and in the evolution of adjunctive therapies and technologies, and indi-

Table 5 Treatment Effect by Integer Risk Category of CV Death or MI

		Treatment Group			
Risk Group*	Risk Score	SI	RI	HR† (95% CI)	Risk Difference‡ (95% CI)
1st (low)	0–4	149/1,503 (10.2%)	114/1,423 (8.2%)	0.80 (0.63 to 1.02)	–2.0% (–4.1% to 0.1%)
2nd (moderate)	5–8	186/912 (21.1%)	155/920 (17.3%)	0.81 (0.66 to 1.01)	–3.8% (–7.4% to –0.1%)
3rd (high)	≥9	140/331 (44.1%)	120/378 (33.0%)	0.68 (0.53 to 0.86)	–11.1% (–18.4% to –3.8%)
Total		475/2,746 (17.9%)	389/2,721 (14.7%)		

*Risk group determined assuming patient in the SI group and calculated according to approximate thirds of risk among those experiencing CV death or MI. Percentages and risk differences are calculated from 5-year Kaplan-Meier estimates. †Interaction of treatment by integer risk score on the HR scale, p = 0.10. ‡Interaction of treatment by integer risk score on the risk difference scale, p < 0.0001.
Abbreviations as in Tables 1 and 2.



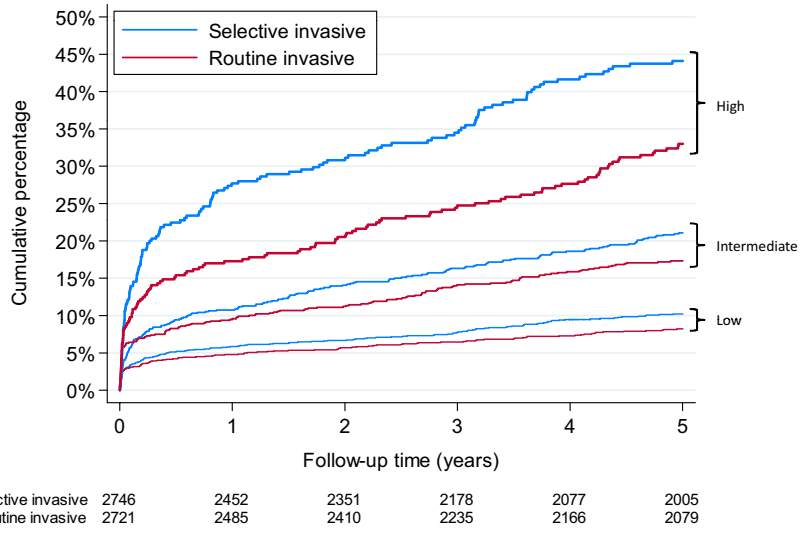
Distribution of patients in FIR database

Integer score	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15+	Total
Number of patients	431	525	615	761	594	596	490	415	331	245	174	139	82	31	15	23	5467

Figure 4 **Distribution of the Integer Risk Score and Probability of CV Death or MI at 5 Years**

Integer score components and values: age: <60 years = 0, 60 to 64 years = +1, 65 to 69 years = +2, 70 to 74 years = +3, and ≥75 years = +5; diabetes: no = 0, yes = +4; hypertension: no = 0, yes = +1; ST-segment depression: no = 0, yes = +2; body mass index (BMI): <25 kg/m^2 = +1, 25 to <35 kg/m^2 = 0, ≥35 kg/m^2 = +2. The receiver-operator characteristic (ROC) for the integer score was 0.69, which is almost identical to the score for the full multivariable model.

vidual differences from trial to trial in outcomes, the overall meta-analysis at 5 years shows a sustained reduction in the rate of CV death or MI by using a RI strategy in patients with non–ST-segment elevation ACS. The largest absolute benefit is observed in patients with higher baseline risk and such patients can be identified using simple clinical risk characteristics. However, even in intermediate- and lower risk populations, the benefits of an early invasive strategy are of similar magnitude as those aimed for and seen with current pharmacological interventions. It is remarkable that despite the systemic and diffuse nature of atheromatous disease, and disease progression elsewhere in the vascular system, an early routine revascularization strategy has a treatment benefit that is clearly evident after 5 years.



Selective invasive	2746	2452	2351	2178	2077	2005
Routine invasive	2721	2485	2410	2235	2166	2079

Figure 5 **Cumulative Risk of CV Death or MI by Risk Group**

The low-, intermediate-, and high-risk groups were divided according to the distribution of outcome events. Abbreviations as in Figure 2.

						Add to score
Age (years)	**<60**	**60-64**	**65-69**	**70-74**	**≥75**	
	0	+1	+2	+3	+5	
Diabetes	**No**			**Yes**		
	0			+4		
Previous MI	**No**			**Yes**		
	0			+3		
ST-depression	**No**			**Yes**		
	0			+2		
Hypertension	**No**			**Yes**		
	0			+1		
BMI	**<25**		**25-<35**		**≥35**	
	+1		0		+2	
		Total Score				

Figure 6 **Nomogram for Integer-Based Risk Score for CV Death or MI at 5 Years**

Integer risk score is the summation of integer values for each risk component. Abbreviations as in Figure 2.

Reprint requests and correspondence: Prof. Keith A. A. Fox, Centre for Cardiovascular Science, The University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, United Kingdom. E-mail: k.a.a.fox@ed.ac.uk.

REFERENCES

1. The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non–Q-wave myocardial infarction: results of the TIMI IIIB trial. Thrombolysis In Myocardial Ischemia. Circulation 1994;89:1545–56.
2. McCullough PA, O'Neill WW, Graham M, et al. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy: results of the Medicine versus Angiography in Thrombolytic Exclusion (MATE) trial. J Am Coll Cardiol 1998;32:596–605.
3. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non–Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy (erratum in N Engl J Med 1998;339:1091). N Engl J Med 1998;338:1785–92.
4. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC-II invasive randomised trial. FRISC-II Investigators. Fast Revascularisation during Instability in Coronary artery disease. Lancet 2000;356:9–16.
5. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 2001;344:1879–87.
6. Fox KA, Poole-Wilson PA, Henderson RA, et al., on behalf of Randomized Intervention Trial of unstable Angina Investigators. Interventional versus conservative treatment for patients with unstable angina or non–ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. Lancet 2002;360:743–51.
7. de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med 2005;353:1095–104.
8. Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non–ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. Lancet 2005;366:914–20.
9. Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non–ST-elevation acute coronary syndrome: a follow-up study. Lancet 2006;368:998–1004.
10. Damman P, Hirsch A, Windhausen F, Tijssen JG, de Winter RJ, ICTUS Investigators. 5-year clinical outcomes in the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial: a randomized comparison of an early invasive versus selective invasive management in patients with non–ST-segment elevation acute coronary syndrome. J Am Coll Cardiol 2010;55:865–6.
11. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non–ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598–660.
12. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2007;50:157
13. National Institute for Clinical Excellence. NICE guideline: unstable angina and NSTEMI: the early management of unstable angina and non–ST-segment-elevation myocardial infarction. 2010. Available at: http://guidance.nice.org.uk/CG/Wave14/24#keydocs. Accessed February 2, 2010.
14. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. J Am Coll Cardiol 2006;48:1319–25.
15. Qayyum R, Khalid MR, Adomaityte J, Papadakos SP, Messineo FC. Systematic review: comparing routine and selective invasive strategies for the acute coronary syndrome. Ann Intern Med 2008;148:186–96.
16. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. JAMA 2005;293:2908–17.
17. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165–75.
18. Prasad A, Gersh BJ, Bertrand ME, et al. Prognostic significance of periprocedural versus spontaneously occurring myocardial infarction after percutaneous coronary intervention in patients with acute coronary syndromes: an analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. J Am Coll Cardiol 2009;54:477–86.
19. Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. JAMA 2003;290:1593–9.
20. Riezebos RK, Ronner E, Ter BE, et al. Immediate versus deferred coronary angioplasty in non–ST-segment elevation acute coronary syndromes. Heart 2009;95:807–12.
21. Lagerqvist B, Diderholm E, Lindahl B, et al. FRISC score for selection of patients for an early invasive treatment strategy in unstable coronary artery disease. Heart 2005;91:1047–52.
22. Wiviott SD, Braunwald E, McCabe CH, on behalf of the TRITON Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
23. Wallentin L, Becker RC, Budaj A, et al., on behalf of the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.
24. Pocock SJ, Lubsen J. More on subgroup analyses in clinical trials. New Engl J Med 2008;358:2076.
25. Bhatt DL, Roe MT, Peterson ED, et al., on behalf of the CRUSADE Investigators. Utilization of early invasive management strategies for high-risk patients with non–ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA 2004;292:2096–104.
26. Fox KAA, Anderson FA, Dabbous OH, et al., on behalf of the GRACE Investigators. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). Heart 2007;93:177–82.

Key Words: acute coronary syndrome ■ percutaneous coronary intervention ■ interventional strategy.