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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

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Objectives We present the 5-year clinical outcomes according to treatment strategy with additional risk stratification of the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial.

Background Long-term outcomes may be relevant to decide treatment strategy for patients presenting with non–ST-segment elevation acute coronary syndromes (NSTE-ACS) and elevated troponin T.

Methods We randomly assigned 1,200 patients to an early invasive or selective invasive strategy. The outcomes were the composite of death or myocardial infarction (MI) and its individual components. Risk stratification was performed with the FRISC (Fast Revascularization in InStability in Coronary artery disease) risk score.

Results At 5-year follow-up, revascularization rates were 81% in the early invasive and 60% in the selective invasive group. Cumulative death or MI rates were 22.3% and 18.1%, respectively (hazard ratio [HR]: 1.29, 95% confidence interval [CI]: 1.00 to 1.66, p = 0.053). No difference was observed in mortality (HR: 1.13, 95% CI: 0.80 to 1.60, p = 0.49) or MI (HR: 1.24, 95% CI: 0.90 to 1.70, p = 0.20). After risk stratification, no benefit of an early invasive strategy was observed in reducing death or spontaneous MI in any of the risk groups.

Conclusions In patients presenting with NSTE-ACS and elevated troponin T, we could not demonstrate a long-term benefit of an early invasive strategy in reducing death or MI. (Invasive versus Conservative Treatment in Unstable coronary Syndromes [ICTUS]; ISRCTN82153174) (J Am Coll Cardiol 2010;55:858–64) © 2010 by the American College of Cardiology Foundation

The American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology guidelines recommend an early invasive strategy for patients presenting with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) without life-threatening symptoms but with high-risk features (1,2). An early invasive strategy consists of coronary angiography within 24 to 72 h, with subsequent revascularization when indicated. This recommendation is supported by meta-analyses showing evidence of an early hazard balanced by a late benefit, resulting in a significant reduction in death or myocardial infarction (MI) (3–5).

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The ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial compared an early invasive with a selective invasive strategy in patients with NSTE-ACS and positive troponin T (6). The ICTUS trial showed no benefit of the early invasive strategy for the composite of death, MI, or rehospitalization for anginal symptoms at 1- and 3-year follow-up (6,7). For patients stabilized on medical treatment, a Class IIb recommendation was included in the ACC/AHA guidelines for a selective invasive strategy (1).

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The 5-year results of the RITA-3 (Randomized Intervention Trial of unstable Angina 3) and FRISC II (Fast Revascularization in InStability in Coronary artery disease II) trials both emphasized the importance of long-term outcomes, showing differences in short-term and long-term mortality (8,9). Moreover, these studies showed a beneficial effect of the invasive strategy, most apparent in high-risk patients. To investigate the occurrence of late clinical events, we present the 5-year clinical outcomes of death and MI of the ICTUS trial, with additional subgroup analyses by categories of baseline risk.

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
HR = hazard ratio
MI = myocardial infarction
NSTE-ACS = non–ST-segment elevation acute coronary syndrome
PCI = percutaneous coronary intervention

Methods

Study design. The design of the Dutch multicenter ICTUS trial has been published previously (6). In short, 1,200 patients with NSTE-ACS and elevated cardiac troponin T were randomized to an early invasive or a selective invasive strategy.

Patients. Patients (age 18 to 80 years) were eligible if the following criteria were met: symptoms of ischemia that were increasing or occurring at rest, with the last episode occurring <24 h before randomization; elevated cardiac troponin T level (≥0.03 μg/l); and either ischemic changes as assessed by electrocardiography or a documented history of coronary artery disease. Exclusion criteria were: ST-segment elevation MI <48 h; an indication for reperfusion therapy; hemodynamic instability or overt congestive heart failure; and an increased risk of bleeding. The collection of long-term follow-up was planned in the protocol and approved by the authorized ethics committee. All patients provided written informed consent.

Randomization and study protocol. In the early invasive strategy, patients were scheduled to undergo coronary angiography within 24 to 48 h and revascularization when appropriate. Patients in the selective invasive strategy were medically stabilized, with angiography and revascularization in case of refractory angina, hemodynamic or rhythmic instability, or clinically significant ischemia on the pre-discharge exercise test. Pharmacological treatment consisted of aspirin, clopidogrel, enoxaparin, or abciximab during all percutaneous coronary interventions (PCI), and intensive lipid-lowering therapy (6).

Follow-up. Patients were contacted by telephone after 5 years from randomization. All potential outcome events were recorded; hospitalizations were reviewed for potential outcome events unless there was an unequivocally noncardiac reason for admission. If a patient could not be contacted, information was obtained from the patient's family, general practitioner, treating cardiologist, and hospital records. Follow-up was censored at the date of last telephone contact, or at 5 years, whichever came first. If the

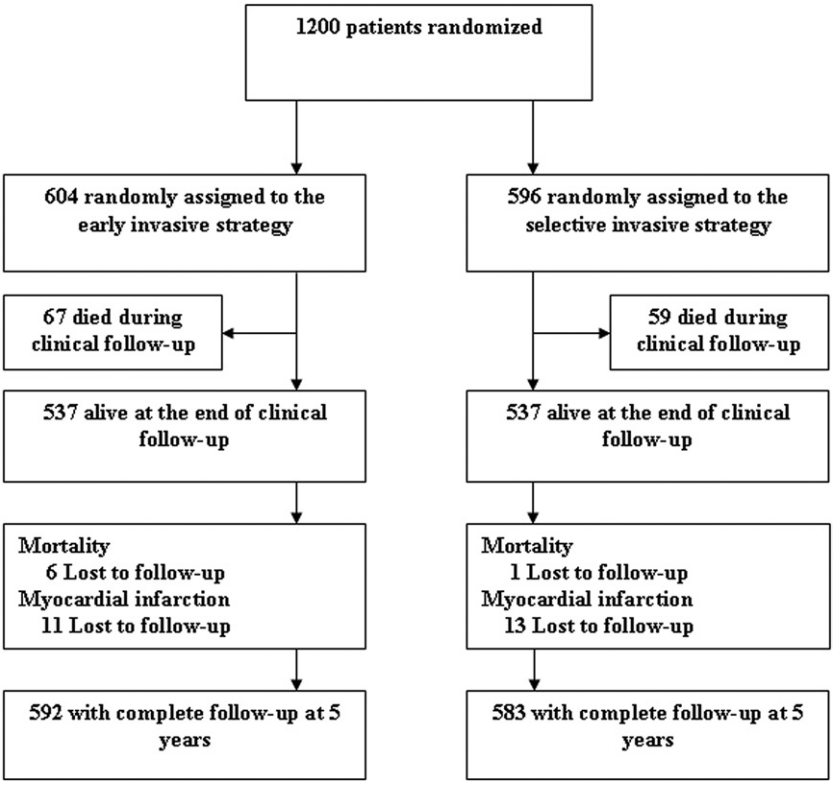

Figure 1 Trial Profile

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patient was lost to follow-up, censoring was done at the date of last clinical follow-up. Information on vital status was obtained from the Dutch national population registry and was verified until September 12, 2008. Cause of death was obtained from the general practitioner and hospital records. Follow-up for mortality was censored at 5 years. If a patient could not be identified in the national registry, censoring was done at the date of last clinical follow-up.

Outcomes. The main outcomes were the composite of death or recurrent MI, composite of death or spontaneous MI, and the individual components death, cardiovascular death, MI, first spontaneous MI, and first procedure-related MI. Cardiovascular death was defined as all-cause death, unless an unequivocal noncardiovascular cause could be established. Myocardial infarction was defined as documented myocardial necrosis either in the setting of myocardial ischemia (spontaneous MI) or in the setting of PCI or coronary artery bypass grafting (CABG) (procedure-related MI) following the recommendations of the Consensus Committee for the definition of MI (10). All new events occurring after previous reported data were adjudicated blinded to treatment allocation (R.J.d.W. and P.D.) (7).

Statistical analysis. Analysis was by intention-to-treat. Cumulative event rates were estimated using the Kaplan-Meier method. Hazard ratios (HRs) with 95% confidence intervals (CIs) were obtained with Cox proportional hazards models, including treatment strategy as the only covariate.

Pre-specified subgroup analyses included gender, and baseline risk according to the FRISC score. All patients were stratified by the FRISC score, being the sum of the following 7 factors present at admission: age ≥65 years, male sex, history of MI, diabetes mellitus, ST-segment depression, elevated troponin T concentration (≥0.03 μg/l), and elevated C-reactive protein concentration (≥10 mg/l) (7,11). ST-segment depression was considered present in case of left bundle branch block (12). Statistical analyses were done with the Statistical Package for Social Sciences (SPSS version 15.0 for Windows, Chicago, Illinois).

Results

Patients. A total of 604 patients were assigned to the early invasive and 596 patients to the selective invasive strategy (Fig. 1). Baseline characteristics were well balanced among the 2 groups (Table 1). The median duration of initial hospitalization was 6 days in the early invasive and 7 days in the selective invasive strategy, during which 76% and 40% of patients, respectively, had been revascularized. Five-year cumulative revascularization was 81% in the early invasive and 60% in the selective invasive strategy; CABG was the

Table 1 Baseline Characteristics

	Early Invasive Strategy (n = 604)	Selective Invasive Strategy (n = 596)
Demographics		
Age ≥65 yrs, n (%)	263 (44)	266 (45)
Body mass index, kg/m^2, mean ± SD	27 ± 4	27 ± 4
Male sex, n (%)	446 (74)	434 (73)
Clinical history, n (%)		
Myocardial infarction	153 (25)	125 (21)
Percutaneous coronary intervention	77 (13)	63 (11)
Coronary artery bypass grafting	62 (10)	43 (7)
Risk factors, n (%)		
Current cigarette smoking	244 (40)	248 (42)
Hypertension	226 (37)	240 (40)
Hypercholesterolemia	211 (35)	206 (35)
Diabetes	86 (14)	80 (13)
Family history of coronary artery disease	263 (44)	241 (40)
Electrocardiographic abnormalities, n (%)		
ST-segment deviation ≥0.1 mV	284 (49)	290 (51)
Left bundle branch block	8 (1)	6 (1)
Aspirin use at admission, n (%)	235 (39)	221 (37)
Laboratory assessments, median (IQR)		
Troponin T, μg/l	0.29 (0.12–0.78)	0.29 (0.13–0.69)
C-reactive protein, mg/l	3.5 (1.7–9.6)	4.3 (1.9–11.4)
Creatinine clearance, ml/min/1.73 m^2	85 (68–103)	85 (70–103)
FRISC score, n (%)		
Low risk, score 1–2	163 (27)	173 (29)
Intermediate risk, score 3–4	368 (61)	346 (58)
High risk, score 5–7	73 (12)	77 (13)

C-reactive protein measurements were available in 1,144 patients. Electrocardiography data were available in 1,149 patients.
FRISC = Fast Revascularization in InStability in Coronary artery disease; IQR = interquartile range.

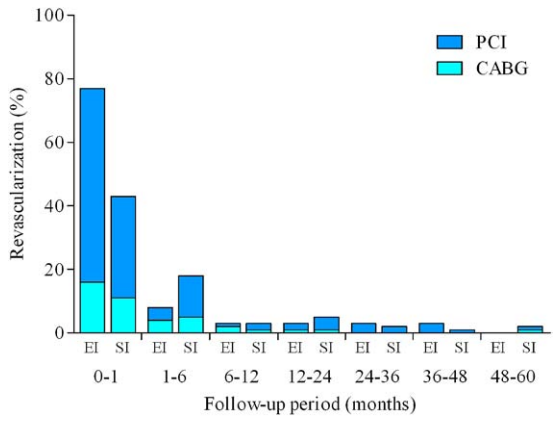

Figure 2 **Revascularization Procedures Over Time**

The Kaplan-Meier estimates for revascularization at 5 years were 81% in the early invasive group compared with 60% in the selective invasive group. CABG = coronary artery bypass grafting; EI = early invasive strategy; PCI = percutaneous coronary intervention; SI = selective invasive strategy.

first procedure in 23% and 25%, respectively. Figure 2 shows revascularization over time.

Outcomes. At 5-year follow-up, information on vital status was available for 1,193 patients (99.4%) and information on MI for 1,176 patients (98.0%). Five-year outcomes are shown in Table 2. A higher death or MI hazard was observed in the early invasive group (22.3% in the early invasive and 18.1% in the selective invasive group; HR: 1.29, 95% CI: 1.00 to 1.66, p = 0.053). No difference was observed in the composite of death or spontaneous MI (17.5% in the early invasive and 16.1% in the selective invasive group; HR: 1.10, 95% CI: 0.83 to 1.45, p = 0.52). Five-year mortality was 11.1% and 9.9%, respectively (HR: 1.13, 95% CI: 0.80 to 1.60, p = 0.49). No difference was observed in cardiovascular death (HR: 0.95, 95% CI: 0.61 to 1.47, p = 0.80). A slight trend towards an increased noncardiovascular mortality was observed in the early invasive group (HR: 1.52, 95% CI: 0.85 to 2.71, p = 0.16). MI rates were 13.9% and 11.7%, respectively (HR: 1.24, 95% CI: 0.90 to 1.70, p = 0.20). No sex-associated differences were observed in the composite of death or spontaneous MI (male: HR: 1.22, 95% CI: 0.87 to 1.71, p = 0.24; female: HR: 0.87, 95% CI: 0.53 to 1.43, p = 0.59). Kaplan-Meier curves are shown in Figures 3 and 4.

Patients who endured a major bleeding during initial hospitalization were at a higher risk for 5-year mortality compared with those who did not (17.2% vs. 10.4%, HR: 1.81, 95% CI: 0.74 to 4.43, p = 0.19).

Risk stratification. After stratification by the FRISC score, higher death or spontaneous MI rates were observed with increasing risk scores; 9.9% in the low-risk (scores 1 to 2), 16.8% in the intermediate-risk (scores 3 to 4), and 32.1% in the high-risk group (scores 5 to 7). No significant benefit from an early invasive treatment was observed in any of the risk groups; low-risk HR: 1.13 (95% CI: 0.57 to 2.24, p = 0.72), intermediate-risk HR: 1.06 (95% CI: 0.74 to 1.52, p = 0.74), and high-risk HR: 1.15 (95% CI: 0.66 to 2.03, p = 0.62) (Fig. 5A). For illustrative purposes, Figure 5B shows Kaplan-Meier curves after stratification using cutoff scores as defined in the long-term results of the FRISC II trial (9). The low-risk group (scores 0 to 1) is not shown, including only 3.7% of all patients. The intermediate-risk group includes 57.5% and the high-risk group 38.8% of all patients. Again, no benefit was observed with an early invasive strategy: low-risk HR: 0.52 (95% CI: 0.09 to 2.81, p = 0.44), intermediate-risk HR: 0.90 (95% CI: 0.57 to 1.42, p = 0.66), and high-risk HR: 1.27 (95% CI: 0.89 to 1.82, p = 0.20).

Discussion

The present analysis confirms and extends our previous reports, as we could not demonstrate that in patients presenting with NSTE-ACS and an elevated troponin T, an early invasive strategy was superior to a selective invasive strategy in reducing 5-year death or MI. In addition, there were no differences in the individual components of the composite outcome. No late effects were observed, with comparable increments in the outcomes death and MI in both treatment groups up to 5-year follow-up.

A slight trend towards an increase in noncardiovascular mortality was observed in the early invasive group, but this difference did not reach statistical significance (p = 0.16). In

Table 2 **Cumulative Event Rate and Hazard Ratios of the Composite Outcome and the Individual Outcomes at 5 Years**

	Early Invasive (n = 604)†	Selective Invasive (n = 596)†	Hazard Ratio (95% CI)	p Value*
Death or MI‡	134 (22.3)	107 (18.1)	1.29 (1.00–1.66)	0.053
Death or spontaneous MI	105 (17.5)	95 (16.1)	1.10 (0.83–1.45)	0.52
All-cause death	67 (11.1)	59 (9.9)	1.13 (0.80–1.60)	0.49
Cardiovascular death	38 (6.5)	40 (6.8)	0.95 (0.61–1.47)	0.80
MI	82 (13.9)	68 (11.7)	1.24 (0.90–1.70)	0.20
Spontaneous MI	50 (8.6)	54 (9.4)	0.92 (0.63–1.35)	0.66
Procedure-related MI	38 (6.4)	14 (2.4)	2.75 (1.49–5.08)	<0.01

Values are n (%). *p value derived from Cox proportional hazards model; †Kaplan-Meier estimate; ‡myocardial infarction (MI) definition based on the recommendations of the Consensus Committee for the Universal Definition of MI (10).

CI = confidence interval.

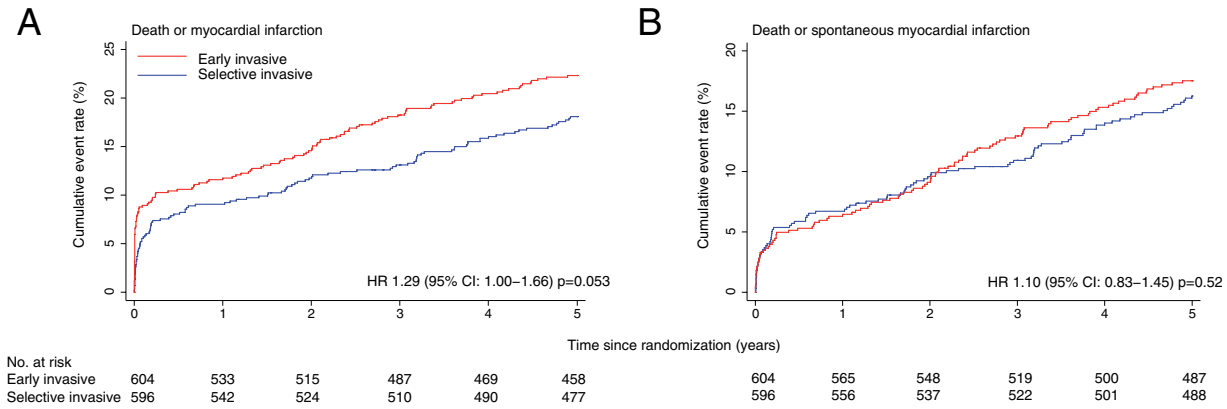

Figure 3 **Cumulative Risk According to Treatment Strategy of the Composite Outcomes**

Shown are Kaplan-Meier curves for the composite of death or recurrent myocardial infarction (MI) **(A)** and the composite of death or spontaneous MI **(B)**. Hazard ratios (HRs) and p values were obtained with Cox proportional hazards models. CI = confidence interval.

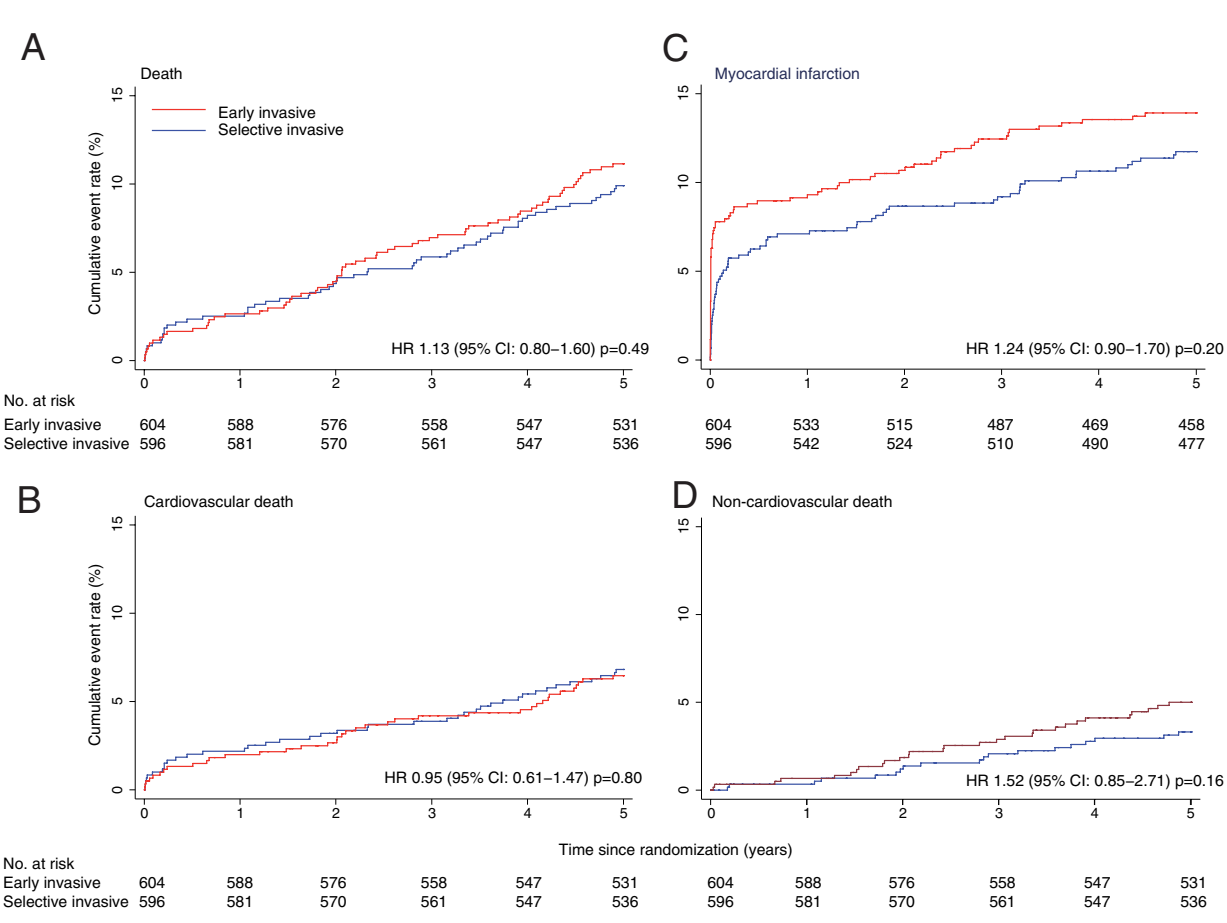

Figure 4 **Cumulative Risk According to Treatment Strategy of Individual Outcomes**

Outcomes shown are death **(A)**, cardiovascular death **(B)**, noncardiovascular death **(C)**, and myocardial infarction **(D)**. Hazard ratios and p values were derived from a Cox proportional hazards model. Abbreviations as in Figure 3.

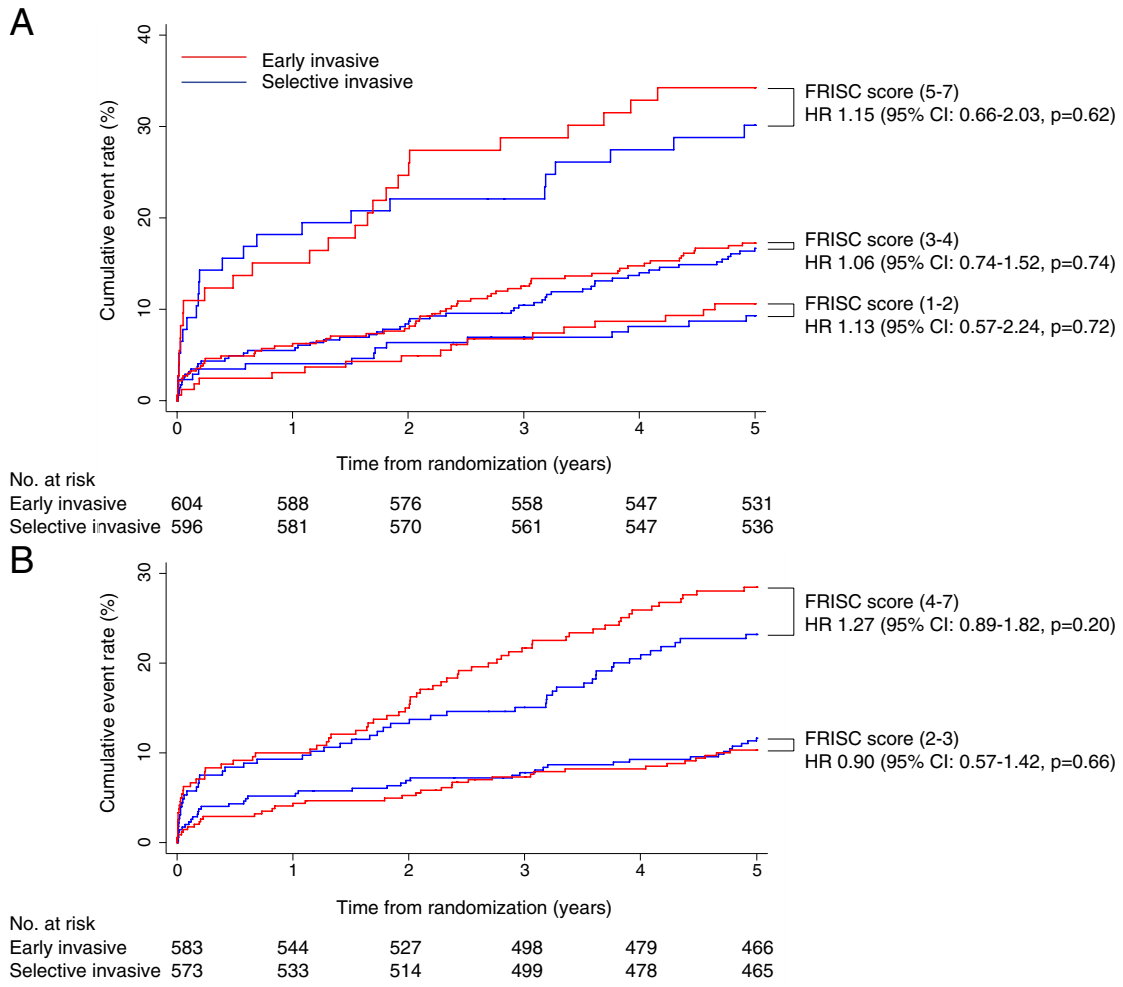

Figure 5 **Cumulative Risk of Death or Spontaneous MI by Treatment Strategy and FRISC Risk Score**

(A) Patients divided into 3 risk groups with cutoffs chosen to yield groups with comparable number of patients. **(B)** Patients divided into 3 risk groups as defined in the FRISC II long-term follow-up (9). FRISC score 0 to 1 not shown, HR: 0.52 (95% CI: 0.09 to 2.81, p = 0.44). Abbreviations as in Figure 3.

view of the lack of a biological rationale for this difference between the 2 treatment groups, this finding is likely the result of the play of chance.

Consequently, the slightly higher hazard for death or MI at 5 years associated with the early invasive strategy is primarily driven by an early increase in procedure-related MIs and this trend towards higher late noncardiovascular mortality.

Previous NSTE-ACS strategy trials with long-term follow-up. The results from our study show important differences when compared with the 5-year outcomes of the RITA-3 and FRISC II trials (8,9). In the FRISC II study, mortality was significantly different at 2-year, but not at 5-year, follow-up. In the RITA-3 study, no difference in mortality was observed at 2-year, but a difference was shown at 5-year follow-up. In the ICTUS trial, there was no difference in mortality, either at the 2- or 5-year follow up.

We observed no overall difference in MI between the 2 strategy groups at 5 years, although procedure-related MIs were slightly more frequent in the early invasive group.

In the RITA-3 and FRISC II trials, the greatest benefit of an invasive strategy was seen in high-risk patients. Remarkably, after risk stratification by the FRISC score, we found no interaction between treatment strategy and risk group. This is unlikely due to a predominance of low-risk patients being included in the ICTUS trial. Applying the FRISC II definition of risk groups, the percentage of patients in the intermediate- and high-risk groups in the ICTUS trial (58% and 39%, respectively) are higher compared with those of the FRISC II trial (53% and 30%, respectively) (9).

The explanation for diverging results between the 3 trials is likely multifactorial. The trials were done in different time periods, and there were differences in clinical practice such

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as the use of stents, glycoprotein IIb/IIIa inhibitors, and long-term antiplatelet agents and statin treatment. One other possible explanation may be the heterogeneity in the intensity of revascularization over time. In the ICTUS trial, the percentage of revascularized patients at 1-year follow-up was 79% in the early invasive and 54% in the selective invasive group, whereas in the RITA-3 and FRISC II trials, these percentages were 57% and 28%, and 78% and 44%, respectively. Therefore, the relatively high intensity of revascularization in the selective invasive arm in ICTUS may be important in explaining the differences in results.

Study limitations. Procedure-related MIs were analyzed mainly during initial hospitalization. Therefore, this could penalize the early invasive arm because other potential MIs as the result of new revascularizations—likely more common in the selective invasive arm—would have gone unnoticed. Procedure-related MIs as documented by hospital records were available up to 5-year follow-up, but routine serial sampling of cardiac biomarkers after PCI in patients without procedure-related complications or clinical symptoms was not available. For our current analysis, we included procedure-related MIs according to the universal definition of MI (10). Second, in accordance with the FRISC II and RITA-3 long-term follow-up, we limited our 5-year follow-up to death or MI. We observed no differences in rehospitalization for anginal complaints and pharmacological treatment at 2.7 years (7).

Conclusions

In patients presenting with NSTE-ACS and an elevated troponin T, we could not demonstrate a benefit of an early invasive strategy in reducing death or MI at 5 years compared with a selective invasive strategy. After risk stratification by the FRISC score, again no benefit from an early invasive strategy was observed. Although many may prefer an early invasive strategy in patients with NSTE-ACS and high-risk features, a selective invasive strategy may be an attractive alternative in medically stabilized patients.

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Key Words: NSTE-ACS ■ treatment strategy ■ long-term outcomes.