

Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study



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Summary

Background The ICTUS trial was a study that compared an early invasive with a selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome (nSTE-ACS). The study reported no difference between the strategies for frequency of death, myocardial infarction, or rehospitalisation after 1 year. We did a follow-up study to assess the effects of these treatment strategies after 4 years.

Methods 1200 patients with nSTE-ACS and an elevated cardiac troponin were enrolled from 42 hospitals in the Netherlands. Patients were randomly assigned either to an early invasive strategy, including early routine catheterisation and revascularisation where appropriate, or to a more selective invasive strategy, where catheterisation was done if the patient had refractory angina or recurrent ischaemia. The main endpoints for the current follow-up study were death, recurrent myocardial infarction, or rehospitalisation for anginal symptoms within 3 years after randomisation, and cardiovascular mortality and all-cause mortality within 4 years. Analysis was by intention-to-treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN82153174.

Findings The in-hospital revascularisation rate was 76% in the early invasive group and 40% in the selective invasive group. After 3 years, the cumulative rate for the combined endpoint was 30·0% in the early invasive group compared with 26·0% in the selective invasive group (hazard ratio 1·21; 95% CI 0·97–1·50; $p=0\cdot09$). Myocardial infarction was more frequent in the early invasive strategy group (106 [18·3%] vs 69 [12·3%]; HR 1·61; 1·19–2·18; $p=0\cdot002$). Rates of death or spontaneous myocardial infarction were not different (76 [14·3%] patients in the early invasive and 63 [11·2%] patients in the selective invasive strategy [HR 1·19; 0·86–1·67; $p=0\cdot30$]). No difference in all-cause mortality (7·9% vs 7·7%; $p=0\cdot62$) or cardiovascular mortality (4·5% vs 5·0%; $p=0\cdot97$) was seen within 4 years.

Interpretation Long-term follow-up of the ICTUS trial suggests that an early invasive strategy might not be better than a more selective invasive strategy in patients with nSTE-ACS and an elevated cardiac troponin, and implementation of either strategy might be acceptable in these patients.

Introduction

The optimum treatment of patients with a non-ST-elevation acute coronary syndrome (nSTE-ACS) has been debated during the past 10 years. A meta-analysis that compared a routine invasive strategy with a more conservative strategy in patients with nSTE-ACS showed superiority of an early invasive strategy in reducing major cardiovascular events as well as severe angina and rehospitalisation.¹ The early risk associated with a routine early invasive strategy was balanced by a reduction in adverse events during follow-up.

When the results of all strategy trials are taken into account as a whole, a mortality benefit at 6–12 months of an early invasive strategy could not be shown.^{1,2} Whether the early risk of an invasive strategy is outweighed by a long-term benefit is unclear. The 5-year mortality rates in the FRISC-II and RITA 3 trials have shown divergent results.^{3–5} In the FRISC-II trial, there was a significant reduction in mortality at 2 years associated with early invasive management

(3·7% vs 5·4%; $p=0\cdot04$) that was not sustained at 5 years (9·7% vs 10·1%; $p=0\cdot69$). By contrast, survival curves in the RITA 3 study started to diverge only after 2 years in favour of the early invasive strategy, resulting in a mortality of 12·1% in the early invasive strategy and 15·1% in the conservative strategy at 5 years ($p=0\cdot054$).^{3–5} In the RITA 3 study, cardiovascular mortality was significantly reduced at 5 years (7·3% vs 10·6%; $p=0\cdot026$) and both studies recorded a significant reduction in the combined endpoint of death or non-fatal myocardial infarction in patients randomised to an early invasive strategy, particularly in high risk patients.

The ICTUS trial did not show superiority of an early invasive strategy in patients with nSTE-ACS and an elevated troponin at 1-year follow-up.⁶ We report the 3-year clinical follow-up of these patients with regard to death, recurrent myocardial infarction, and rehospitalisation for anginal symptoms and the 4-year follow-up with regard to cardiovascular and all-cause mortality.

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Methods

Patients

The ICTUS trial was a randomised multicentre trial and the details of the design and main results at 1 year have been published previously.⁶ Between July, 2001, and August, 2003, 1200 patients were enrolled from 42 hospitals in the Netherlands, 12 of which were high-volume centres with facilities for percutaneous coronary intervention and on-site cardiac surgery. Eligible patients had to meet three criteria: (1) symptoms of ischaemia that were increasing or occurring at rest, with the last episode taking place no longer than 24 h before randomisation; (2) a raised serum cardiac troponin T (≥ 0.03 $\mu\text{g/L}$); and (3) either ischaemic changes on the electrocardiogram or a documented history of coronary artery disease. Main exclusion criteria were: age younger than 18 years or older than 80 years, ST-elevation myocardial infarction in the last 48 h, an indication for reperfusion therapy, haemodynamic instability or overt congestive heart failure, and increased risk of bleeding.

This study complied with the principles set out in the Declaration of Helsinki. All patients gave written informed consent before randomisation and the collection of long-term follow-up information was approved by the authorised ethics committee.

Procedures

Patients were randomly assigned with the use of a central telephone system.⁶ Patients assigned to the early invasive strategy were scheduled to undergo angiography within 24–48 h after randomisation and percutaneous revascularisation when appropriate based on the coronary anatomy. Cardiac surgery was recommended in the event of extensive 3-vessel disease or severe left main stem disease, and was to be done as soon as possible. Patients assigned to the selective invasive strategy were initially managed medically. These patients were to undergo angiography and subsequent revascularisation only in the event of refractory angina despite optimum medical treatment, haemodynamical or rhythmical instability, or substantial ischemia on the pre-discharge exercise test. Coronary angiography and revascularisation after the index hospital phase was done if severe anginal symptoms were present despite optimum anti-anginal medication or when documented ischemia on an ischemia detection test was present.

The protocol specified that patients receive daily aspirin, enoxaparin (1 mg/kg twice a day) subcutaneously for at least 48 h, and abciximab during all percutaneous coronary intervention (PCI) procedures. Abciximab was made available to the investigators during the first year of follow-up and after 1 year the use of abciximab was at the operator's discretion. The early use of clopidogrel (300 mg followed by 75 mg a day) in combination with aspirin was recommended to the investigators when the drug became available in the Netherlands in 2002 for the ACS indication.⁷ The protocol recommended intensive

lipid-lowering therapy, preferably with 80 mg of atorvastatin daily or equivalent, started as soon as possible after randomisation and continued indefinitely. Analysis was by intention to treat.

Follow-up and outcome

Patients were seen at the outpatient clinic at 1, 6, and 12 months. For the long-term clinical outcome, patients were contacted by telephone between 2 years and 4 years after randomisation. All potential outcome events were recorded and the patients' medical drug regimen was carefully assessed. In the event of a repeat hospital admission, follow-up information was obtained from hospital records. All hospitalisations were checked unless the patient had indicated that there was an unequivocally non-cardiac reason for admission. If the patient could not be contacted, information was obtained from the patients' family, family doctor, treating cardiologist, and hospital records. Follow-up for clinical events was censored at the actual date of the last telephone contact or at 3 years, whichever came first. If the patient was lost to follow-up, censoring was done at the date of last clinical follow-up. Information for vital status and cause of death when applicable was obtained by identifying the patients in the national population registry (Dutch Central Bureau of Statistics) and was verified by the registry until May 1, 2006. Follow-up for mortality was censored at May 1, 2006, or at 4 years. If a patient could not be identified in the national registry, censoring was at the date of the last contact.

The primary outcome was the composite endpoint death, recurrent myocardial infarction, or rehospitalisation for anginal symptoms. Secondary outcomes of the study were death, cardiovascular death, myocardial infarction, first spontaneous myocardial infarction, first procedural related myocardial infarction, rehospitalisation for anginal symptoms, the composite endpoint death or myocardial infarction, and the endpoint death or spontaneous myocardial infarction. Deaths were classified as cardiovascular or non-cardiovascular on the basis of hospital records, information from the patients' family doctor, and death certificates. Myocardial infarction was defined as documented myocardial necrosis either in the setting of myocardial ischaemia (spontaneous myocardial infarction) or in the setting of PCI following the recommendations of the Consensus Committee for the definition of myocardial infarction.⁸ Myocardial necrosis during the first year of follow-up was defined by an elevation in the CK myocardial band (CK-MB) concentration above the upper limit of normal (ULN). In the event of a raised CK-MB concentration at randomisation, recurrent myocardial infarction during the first 48 h was diagnosed when there was a 50% decrease from a previous peak value, followed by a subsequent rise to a level exceeding the ULN. Because the concentrations of CK-MB were not routinely measured in all hospitals after 1 year, an elevation of

troponin above the ULN was also regarded as a marker for myocardial necrosis in the setting of a spontaneous myocardial infarction after 1 year. A myocardial infarction in the setting of coronary artery bypass graft surgery (CABG) needed the appearance of new Q-waves on the electrocardiogram. All events were adjudicated by a blinded events committee.

Statistical analysis

Cumulative event rates for each cardiovascular outcome were calculated according to the Kaplan-Meier method, and the timing of the events illustrated by Kaplan-Meier plots. Treatment groups were compared with log-rank tests without adjustments for covariates. Hazard ratios with 95% CIs were obtained with Cox proportional-hazards models, with treatment allocation as the only covariate. Proportional hazards assumptions were verified by graphical examination of the partial residuals and by testing the significance of the interaction between treatment and time. In a separate analysis, the cumulative event rates were calculated from hospital discharge to end of follow-up. Patients who had a non-fatal event during initial hospitalisation were again at risk for new events between hospital discharge and end of follow-up.

The FRISC scoring system was used for risk stratification, and patients were stratified according to the FRISC score.^{5,9} The FRISC score was developed with data for the endpoint death or myocardial infarction from the FRISC-II trial, and is the sum of the following factors present at admission: age older than 65 years, male sex, diabetes mellitus, previous myocardial infarction, ST segment depression on admission, raised troponin concentration ($\geq 0.03 \mu\text{g/L}$), and raised concentration of C-reactive protein ($\geq 10 \text{ mg/L}$). In the ICTUS trial, the association between the treatment effect and the patients' risk on the outcome of death or spontaneous myocardial infarction was assessed by an interaction test in a Cox model.

All statistical tests were two-tailed, and a p value less than 0.05 was deemed significant. Statistical analysis was done with the Statistical Package for Social Sciences software (SPSS 12.0 for Windows), and for the meta-analysis Review Manager (RevMan 4.2 for Windows) was used. The study has been assigned the International Standard Randomised Control Trial Number ISRCTN82153174.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 1200 patients with nSTE-ACS and an elevated cardiac troponin level were randomly assigned to an early invasive strategy (604) or to a selective invasive strategy (596;

figure 1). In both treatment groups, the median follow-up was 2.7 years for clinical events. Five patients (four randomised to selective invasive and one to early invasive) were lost to follow-up. In both treatment groups, 97% of patients were identified in the national population registry with a median follow-up duration for death of 3.4 years.

The baseline characteristics of the study population were well matched between strategy groups (table 1). The median age was 62 years; 73% were men; 14% had diabetes; 38% used aspirin before admission; and 23% were known to have a clinical history of myocardial infarction. The median length of initial hospitalisation was 1 day shorter in the early invasive group than in the

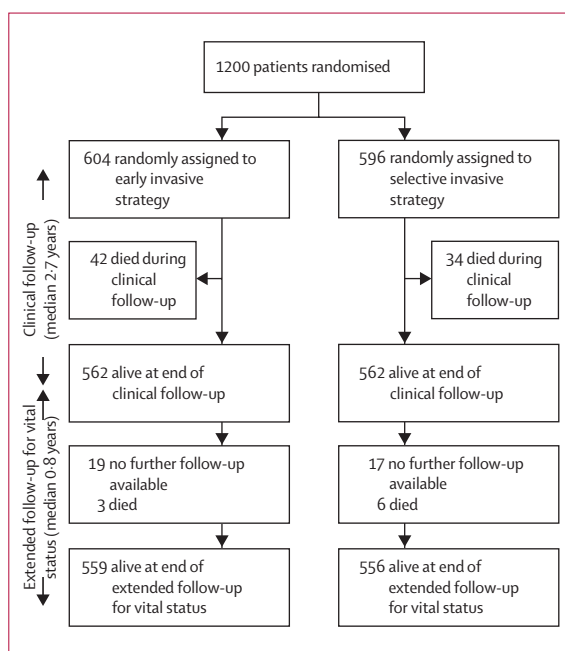


Figure 1: Trial profile

	Early invasive (n=604)	Selective invasive (n=596)
Age (years)	62 (55–71)	62 (54–71)
Men	446 (74%)	434 (73%)
Diabetes mellitus	86 (14%)	80 (13%)
History of myocardial infarction	153 (25%)	125 (21%)
Previous aspirin use	235 (39%)	221 (37%)
ST-segment deviation $\geq 0.1\text{mV}^*$	284 (49%)	290 (51%)
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)
Troponin T ($\mu\text{g/L}$)	0.29 (0.12–0.78)	0.29 (0.13–0.69)
Low risk (FRISC score 1–2)	163 (27%)	173 (29%)
Medium risk (FRISC score 3–4)	368 (61%)	346 (58%)
High risk (FRISC score 5–7)	73 (12%)	77 (13%)

Data are number (%) or median (25th–75th percentile). *Measured on electrocardiogram at admission in 578 patients in the early invasive group and 571 in the selective invasive group; [†]Samples for C-reactive protein were available in 579 patients in the early invasive group and 565 patients in the selective invasive group.

Table 1: Baseline characteristics

	At discharge		At 1 year follow-up		At long-term follow-up*	
	Early invasive (n=598)	Selective invasive (n=591)	Early invasive (n=571)	Selective invasive (n=558)	Early invasive (n=528)	Selective invasive (n=510)
Aspirin	92%	95%	92%	93%	91%	91%
ACE inhibitors	30%	34%	34%	33%	30%	28%
β blockers	87%	89%	79%	80%	71%	74%
Clopidogrel†	62%	49%	17%	14%	7%	5%
Calcium-channel antagonists	16%	28%	18%	24%	19%	19%
Nitrates	18%	32%	13%	19%	14%	19%
Statins	91%	94%	93%	95%	92%	94%

*Median follow-up of 2.7 years. †Treatment with clopidogrel in addition to aspirin for a duration of 9 months was recommended to the investigators when clopidogrel became available in the Netherlands in 2002 for the ACS indication.

Table 2: Medication therapy at discharge and during follow-up

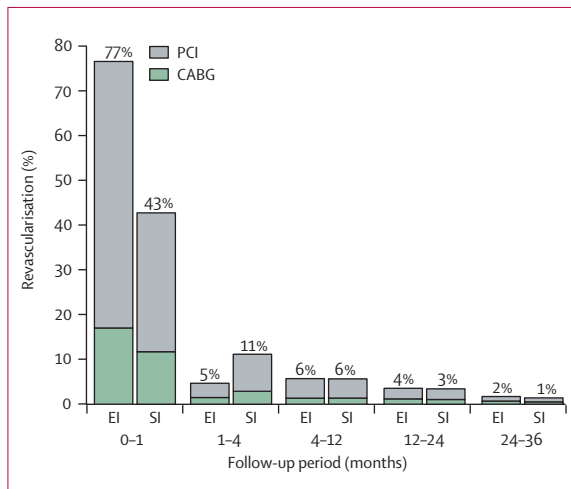


Figure 2: Revascularisation procedures over time
 The Kaplan-Meier estimates for revascularisation at 3 years were 81% in the early invasive strategy group compared to 58% in the selective invasive strategy group. PCI=percutaneous coronary intervention. CABG=coronary-artery bypass grafting. EI=early invasive strategy. SI=selective invasive strategy.

selective invasive group (6 days vs 7 days). Medical therapy at discharge and during follow-up is described in table 2. Pharmacological therapy for secondary prevention at end of clinical follow-up was high, with 91% of the patients using aspirin, 93% statins, and 72% β blockers. No differences in medical therapy were seen between the two treatment strategies at end of follow-up.

In the early invasive strategy group, coronary angiography was done in 97% of the patients within 2 days and in 98% of the patients during initial hospitalisation, compared with 11% and 53%, respectively, in the selective invasive strategy group. The Kaplan-Meier estimates for coronary angiography at 3 years were 99% in the early invasive group versus 70% in the selective invasive group. The reason for cardiac catheterisation during initial hospitalisation in the patients randomly assigned to the selective invasive strategy was refractory angina in 51%, significant ischaemia on exercise test in 41%, and other reasons in 8%.

PCI or CABG was done during initial hospitalisation in 76% and 40% of the patients in the early invasive and

	Early invasive (n=604)			Selective invasive (n=596)			Hazard ratio (95% CI)	Log-rank p value
	2 years	3 years	4 years	2 years	3 years	4 years		
Follow-up for vital status								
Death from any cause	27 (4.5%)	42 (7.1%)	45 (7.9%)	26 (4.4%)	35 (6.0%)	40 (7.7%)	1.11 (0.73-1.70)	0.62
Death from cardiovascular causes	16 (2.7%)	25 (4.2%)	26 (4.5%)	19 (3.2%)	23 (3.9%)	26 (5.0%)	0.99 (0.57-1.70)	0.97
Clinical follow-up								
Spontaneous myocardial infarction	31 (5.2%)	40 (7.4%)	-	37 (6.3%)	39 (7.2%)	-	1.02 (0.65-1.58)	0.94
Procedural related myocardial infarction	72 (12.0%)	72 (12.0%)	-	36 (6.1%)	36 (6.1%)	-	2.07 (1.39-3.10)	0.0002
Myocardial infarction	98 (16.3%)	106 (18.3%)	-	67 (11.4%)	69 (12.3%)	-	1.61 (1.19-2.18)	0.002
Rehospitalisation for anginal symptoms	55 (9.3%)	58 (10.1%)	-	70 (12.0%)	71 (12.4%)	-	0.79 (0.56-1.12)	0.18
Death or myocardial infarction	120 (19.9%)	139 (24.7%)	-	86 (14.4%)	91 (15.9%)	-	1.60 (1.23-2.09)	0.0004
Death or spontaneous myocardial infarction	55 (9.1%)	76 (14.3%)	-	57 (9.6%)	63 (11.2%)	-	1.19 (0.86-1.67)	0.30
Death, myocardial infarction, or rehospitalisation for anginal symptoms	160 (26.5%)	175 (30.0%)	-	145 (24.3%)	150 (26.0%)	-	1.21 (0.97-1.50)	0.09

Data are number of patients with percentages from the Kaplan-Meier curves.

Table 3: Event rates and hazard ratios for cardiovascular events

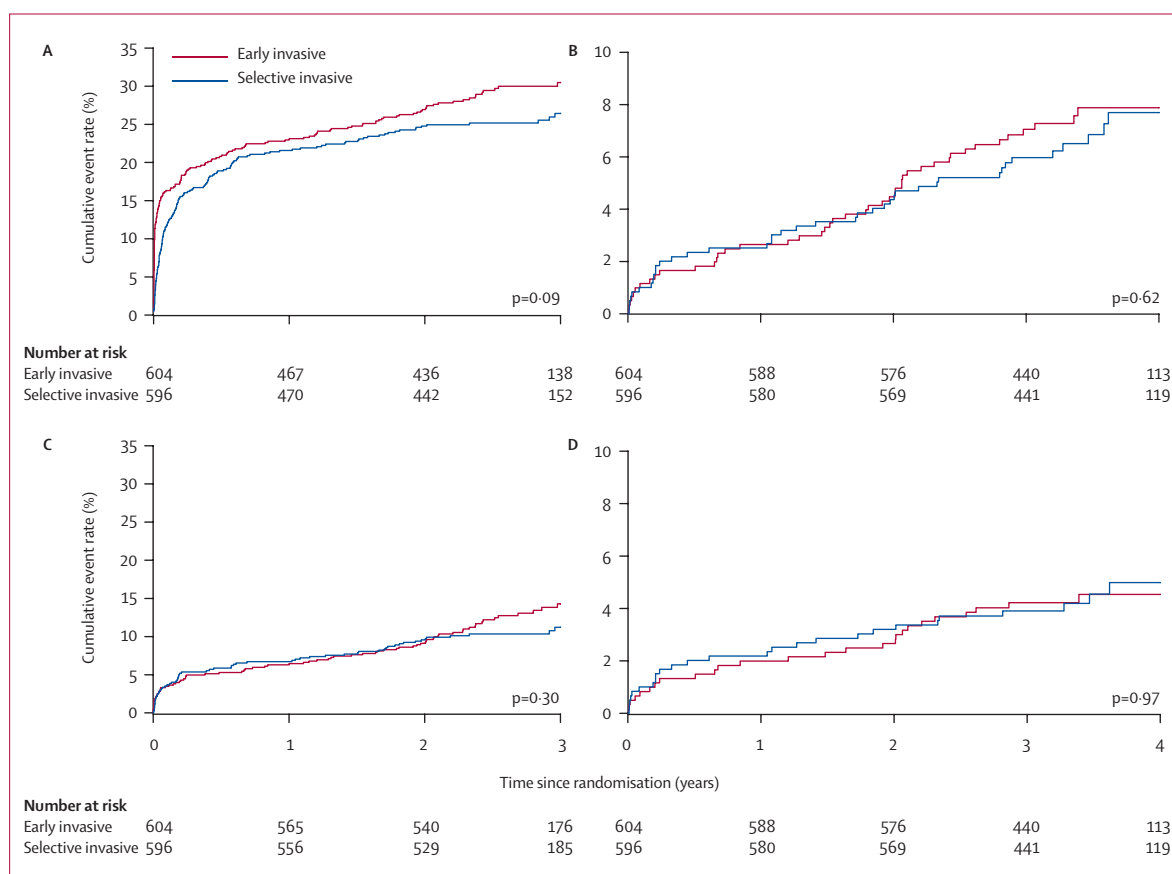


Figure 3: Cumulative risk according to treatment strategy of (A) the combined endpoint death, myocardial infarction, or rehospitalisation for anginal symptoms, (B) death, (C) death or spontaneous myocardial infarction, and (D) death from cardiovascular causes

selective invasive group, and the Kaplan-Meier estimates at 3 years were 81% and 58%, respectively. In the early invasive strategy group, 88% of the patients treated with PCI during the initial hospitalisation received one or more stents, and 4% of the PCI patients received at least one drug-eluting stent compared with 89% and 5% in the selective invasive strategy group. Glycoprotein IIb/IIIa inhibitors were used during 94% and 75% of the in-hospital PCI procedures in the early invasive and selective invasive strategy group, respectively. Within a year after randomisation, 93% and 69% of the patients who underwent a PCI were treated with glycoprotein IIb/IIIa inhibitors at the time of PCI. Of the patients who were revascularised within 3 years, CABG was the first procedure in 23% (110 of 486) of those in the early invasive group and 26% (88 of 342) in the selective invasive group. Figure 2 shows the revascularisation rates in different time frames. Of the patients who underwent PCI or CABG within 3 years, 14% (67 of 486) of those in the early invasive group and 12% (42 of 342) of those in the selective invasive group had more than one procedure.

Table 3 shows the cumulative event rates and hazard ratios for all specified cardiovascular outcomes. The estimated 3-year cumulative event rate for the composite endpoint death, myocardial infarction, or rehospitalisation for anginal symptoms was similar in the two

treatment groups (30.0% in the early invasive vs 26.0% in the selective invasive group; $p=0.09$). There were more rehospitalisations for anginal symptoms in the selective invasive group. However, unlike the results at 1-year follow-up, the difference is not significant (10.1% vs 12.4%, $p=0.18$). The 3-year event rate of myocardial infarction was higher in the early invasive group than in the selective invasive group with a hazard ratio (HR) of 1.61 ($p=0.002$). This difference was entirely due to the occurrence of more procedural related myocardial infarctions in the early invasive strategy group with a HR of 2.07 (95% CI 1.39–3.10; $p=0.0002$). Of the patients who underwent at least one PCI or CABG within 3 years, a procedural related myocardial infarction occurred in 72 (14.8%) of 486 patients in the early invasive and 36 (10.5%) of 342 patients in the selective invasive group. The cumulative event rate for spontaneous myocardial infarction was similar, with 7.4% in the early invasive group and 7.2% in the selective invasive group ($p=0.94$). No significant difference was seen in the occurrence of the composite endpoint of death or spontaneous myocardial infarction at the end of clinical follow-up

	At 1 year after discharge			Long-term follow-up*		
	Early invasive (n=598)	Selective invasive (n=591)	Log-rank p value	Early invasive (n=598)	Selective invasive (n=591)	Log-rank p value
Follow-up for vital status (until 4 years)						
Death from any cause	10 (1.7%)	10 (1.7%)	0.97	39 (7.0%)	35 (6.9%)	0.68
Death from cardiovascular causes	8 (1.3%)	8 (1.4%)	0.98	22 (3.9%)	21 (4.2%)	0.91
Clinical follow-up (until 3 years)						
Revascularisation (PCI/CABG)	58 (9.8%)	110 (18.7%)	<0.0001	80 (14.1%)	130 (23.2%)	<0.0001
Myocardial infarction	20 (3.4%)	26 (4.4%)	0.34	39 (7.3%)	37 (6.9%)	0.87
Rehospitalisation for anginal symptoms	44 (7.4%)	64 (10.9%)	0.04	58 (10.1%)	71 (12.4%)	0.18
Death, myocardial infarction, or rehospitalisation for anginal symptoms	68 (11.4%)	92 (15.6%)	0.03	115 (20.8%)	119 (21.0%)	0.57

Data are number of patients with percentages from the Kaplan-Meier curves at 1 year and long-term follow-up. Patients who had a non-fatal event during initial hospitalisation were again at risk for new events between hospital discharge and end of long-term follow-up. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. *4 years for vital status and 3 years for clinical follow-up.

Table 4: Event rates from hospital discharge until end of follow-up

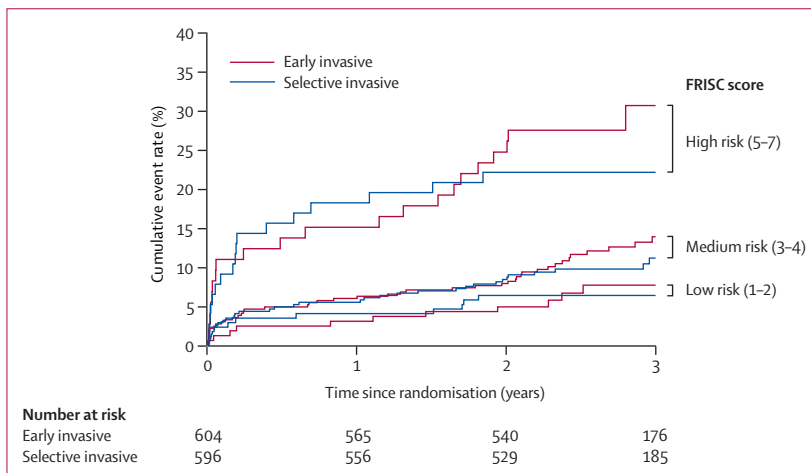


Figure 4: Cumulative risk of death or spontaneous myocardial infarction by treatment strategy and FRISC score p=0.64 for interaction between FRISC score (three groups) and treatment strategy.

between the early invasive and selective invasive group (76 [14.3%] vs 63 [11.2%]; HR 1.19 [95% CI 0.86–1.67], p=0.30). Of the 108 patients with an in-hospital myocardial infarction, the 4-year mortality was 6.6% compared with 7.9% in the 1092 patients without an in-hospital myocardial infarction (HR 0.88; 95% CI 0.41–1.92; p=0.75).

Figure 3 shows the Kaplan-Meier curves for the combined endpoint death, myocardial infarction, or rehospitalisation for anginal symptoms, the combined endpoint of death or spontaneous myocardial infarction, and the endpoint of death and death from cardiovascular causes. In total, 85 of 1200 patients died during follow-up. After 4 years, no difference in all-cause mortality (7.9% vs 7.7%, p=0.62) or in death from cardiovascular causes (4.5% vs 5.0%, p=0.97) was seen between the patients randomly assigned to an early invasive strategy or a selective invasive strategy. The Kaplan-Meier curves showed no significant difference

in all-cause mortality or in cardiovascular death at any time during follow-up.

Major bleeding during the initial hospitalisation was seen in 19 patients (3.1%) in the early invasive strategy group and in ten patients (1.7%) in the selective invasive strategy group.⁶ Of the 29 patients with an in-hospital major bleeding, the 4-year mortality was 18.6%, compared with 7.5% in the 1171 patients without in-hospital major bleeding (HR 2.68; 95% CI 1.08–6.61; p=0.03).

The cumulative event rates from hospital discharge until the end of follow-up are shown in table 4. The rate of the composite endpoint death, myocardial infarction, or rehospitalisation at 1 year after discharge was significantly lower with an early invasive strategy than with a selective invasive strategy (68 events [11.4%] vs 92 events [15.6%]; p=0.03). However, no significant difference was seen at 3-year follow-up (115 events [20.8%] vs 119 events [21.0%]; p=0.57). At 1 year and at the end of long-term follow-up, the rates of death and myocardial infarction were similar for both strategies. At 3 years, the rate of revascularisation was significantly lower in the early invasive group than in the selective invasive group (14.1% vs 23.2%; p<0.0001).

When the cumulative event rate of death or spontaneous myocardial infarction in relation to the FRISC score was assessed in all patients, an increasing event rate was seen with increasing FRISC score (7.0% in patients with a FRISC score of 1–2, 12.5% in patients with a FRISC score of 3–4, and 26.2% in patients with a score of 5–7). These results confirm the prognostic value of this scoring system in the patients with nSTE-ACS included in the ICTUS trial. However, none of these different risk groups showed a benefit of an early invasive strategy, compared with a selective invasive strategy: low risk 7.7% vs 6.4%; HR 1.06 (95% CI 0.46–2.44); p=0.90, medium risk 13.8% vs 11.1%; 1.19 (0.76–1.85); p=0.45, high risk 30.6% vs 22.1%; HR 1.30 (0.69–2.47); p=0.42 (figure 4).

Discussion

In our study, an early invasive strategy was not better than a selective invasive strategy in patients with nSTE-ACS and a raised cardiac troponin concentration. At 4-year follow-up no difference in death from all causes or cardiovascular death was seen between the two strategies. These results confirm the meta-analysis of Mehta and colleagues,¹ including seven strategy trials that did not show a mortality benefit in the short term.

When combining only strategy trials that routinely used stents in PCI procedures, no difference in 6-month to 12-month mortality was recorded (122 of 3899 [3.1%] vs 147 of 3919 [3.8%]; relative risk 0.82, 95% CI 0.57–1.19).² The Kaplan-Meier curves of the long-term follow-up of the FRISC-II and RITA 3 trials showed strikingly different patterns. In the RITA 3 trial the survival curves diverged only after 2 years in favour of the early invasive strategy group, and continued to diverge until the 5-year follow-up, resulting in a mortality of 12.1% for the early invasive strategy compared with 15.1% for the conservative strategy ($p=0.054$).⁴ By contrast, the curves in the FRISC-II trial separated early after randomisation and showed a significant mortality benefit of an early invasive strategy compared with the non-invasive group at 2 years, although this benefit was not sustained at 5 years (9.7% vs 10.1%; $p=0.69$).⁵ In our present analysis of the ICTUS trial, the Kaplan-Meier curves of the two strategies are identical during the entire follow-up. The explanation for these differences between the Kaplan-Meier curves in the three studies remains to be established, and might be partly explained by differences in study design, revascularisation rates, medical therapy during hospitalisation and for secondary prevention, and changes in practice of invasive therapy (choice of revascularisation method, use of stents, and adjunctive therapy).

From the data derived from a meta-analysis of 4–5-year mortality in FRISC-II, RITA 3, and ICTUS, the evidence could reasonably be compatible with a modest mortality benefit associated with an early invasive strategy compared with a more selective invasive strategy, although the CI around the point estimate for relative risk corresponds to a possible reduction in mortality of 23% or an increase of 6% (figure 5). This meta-analysis has several limitations. First, each individual trial was not powered to assess a difference in mortality, and the meta-analysis could be underpowered as well. Second, the shorter duration of follow-up in the ICTUS trial (4 years compared with 5 years in the FRISC-II and RITA 3) might underestimate potential differences between strategies that could become apparent during an additional year of follow-up. Third, the three trials show heterogeneity of the intensity of revascularisation in the early invasive and selective invasive treatment groups.

The 3-year clinical follow-up of the ICTUS trial showed similar rates of the combined endpoint death, recurrent myocardial infarction, or rehospitalisation for anginal

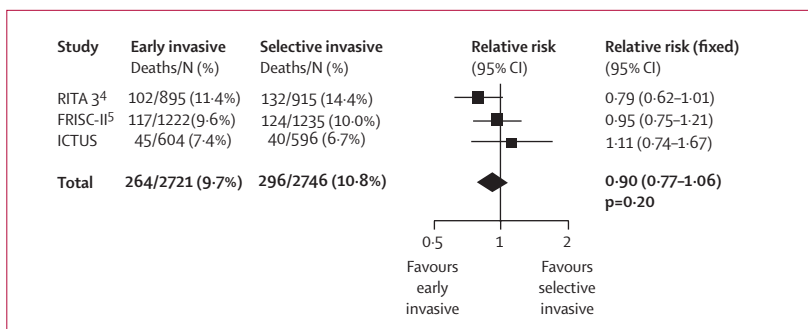


Figure 5: Meta-analysis

Relative risk for all-cause mortality in the three strategy trials with long-term follow-up (5 years in the RITA 3 and FRISC-II trial, and 4 years in the ICTUS trial). Test for heterogeneity $p=0.31$. Percentages shown for early invasive and selective invasive groups differ from reported Kaplan-Meier estimates.

symptoms. We should note that the current analysis has ample power ($\geq 80\%$) to detect relevant changes (relative risk reduction of 25%) in the frequency of the long-term combined endpoint. However, there were differences between the two strategy groups in the individual components of the combined endpoint. The rate of rehospitalisation for anginal symptoms was lower in the early invasive strategy group than in the selective invasive group, although this difference was not significant. Conversely, the rate of recurrent myocardial infarction was significantly higher in the patients randomised to an early invasive strategy. The absolute difference of 6.0% was due to twice the number of procedural related myocardial infarctions in the early invasive strategy compared with the selective invasive strategy, whereas no reduction in the number of spontaneous myocardial infarctions was noted during 3-year follow-up with an early invasive strategy.

Our results and those from the FRISC-II and RITA 3 trials differ in the number of myocardial infarctions in the early invasive strategy. The higher rate in the ICTUS trial was due to (1) no increased risk of spontaneous myocardial infarctions with a selective invasive strategy, and (2) a higher incidence of procedural related myocardial infarctions in both the early and selective invasive strategy in the ICTUS trial than the other trials.

The rates for spontaneous myocardial infarction after 3 years were not higher than expected in the early invasive group but were low in the selective invasive group. In the FRISC-II trial, the rate of spontaneous myocardial infarctions at 2 years was almost 4% in the early invasive group and 11% in the non-invasive group compared with 5% and 6% in the ICTUS trial, respectively.¹⁰ The low rate of spontaneous myocardial infarctions could be due to the compliance to early and long-term medical treatment in our study. Patients were treated with aspirin, enoxaparin, and glycoprotein IIb/IIIa inhibitors at the time of PCI.

A large difference in duration of enoxaparin treatment between the two strategy groups could be important. The protocol specified that all patients receive enoxaparin for

at least 48 h. Data for the exact duration of treatment with enoxaparin was not recorded in the case report form. Clinical practice in the Netherlands routinely included cessation of heparin after 48 h in medically treated patients. In patients managed invasively, the continuation of heparin after revascularisation was at the discretion of the operator. Clopidogrel was given after stent placement, and the early use of clopidogrel was recommended to the investigators when the drug became available in the Netherlands in 2002 for the ACS indication. Importantly, long-term pharmacological therapy for secondary prevention was high in the ICTUS study, with 91% of the patients using aspirin, 93% statins, and 72% β blockers at a median follow-up of 2.7 years.

A second reason that could explain our results is the high percentage of patients that were revascularised in the selective invasive group compared with the other trials. In the FRISC-II study, the revascularisation rate during initial hospitalisation was 13% in the non-invasive group and 76% in the invasive treatment group; in the TIMI IIIB 40% versus 60%; TACTICS-TIMI 18 36% and 60%; RITA 3 10% and 44%; and in the ICTUS study 40% and 76%.^{5,11-13} Therefore, the revascularisation rate in the invasive treatment group of the RITA 3 study is nearly identical to the revascularisation rate in the non-invasive treatment group in the ICTUS study (44% versus 40%). Moreover, revascularisation at follow-up was very similar (61% at 5 years in the RITA 3 versus 58% at 3 years in the ICTUS). Instead of comparing an invasive strategy to a non-invasive strategy, the ICTUS trial compared routine, early revascularisation to less aggressive, delayed intervention.

An early invasive strategy was associated with a 2–4 fold increased risk of procedural related myocardial infarctions in the ICTUS trial and in the FRISC-II and RITA 3 trials. However, the absolute percentage of patients with a procedural related myocardial infarction differed between the studies. In the RITA 3 trial, only 2–3% of all the patients who underwent a revascularisation procedure had a procedural related myocardial infarction compared with 6% in the FRISC-II trial and 13% in the ICTUS trial.^{10,13} First, we should note that rate comparison for peri-interventional myocardial infarction is difficult because the definition of myocardial infarction is different between the trials (ICTUS CK-MB >1 times ULN, FRISC-II >1.5 times the ULN, RITA 3 >2 times the ULN, and TACTICS-TIMI 18 trial ≥ 3 times the ULN). The prognostic implications of small PCI related myocardial infarctions are controversial.^{14,15} Some reports suggest that the prognosis of patients with small PCI-related myocardial infarctions should be regarded as similar to that of patients with spontaneous myocardial infarction, whereas other reports disagree and suggest a higher cut-off rate for myocardial infarctions related to PCI.¹⁶⁻¹⁹ Secondly, all patients in the ICTUS trial were troponin positive (troponin T ≥ 0.03 $\mu\text{g/L}$), which might partly explain the prevalence of procedural related myocardial infarction.¹⁸

Third, the median time to PCI in the early invasive strategy of the ICTUS trial was 23 h compared with 4 days in that of the FRISC-II trial. The combined effect of protracted antiplatelet, antithrombin, and anti ischaemic therapy before PCI or CABG might have lowered the rate of procedure-related myocardial infarction in the FRISC-II trial.²⁰ Fourth, CK-MB concentrations in the ICTUS trial were carefully and routinely measured after all PCIs (every 6 h after PCI for 24 h).

In our analysis of outcome after hospital discharge, an early invasive strategy had no advantage over a selective invasive strategy for death or myocardial infarction. Fewer rehospitalisations and fewer revascularisation procedures occurred in the early invasive group, which in turn might add to the patients' quality of life. This benefit must be balanced against the twofold increase in risk of procedural related myocardial infarction associated with an early invasive strategy (although in the present trial long-term mortality was not increased in patients in whom myocardial infarction took place before hospital discharge).

Both the FRISC-II and RITA 3 trial showed a benefit of an early invasive strategy for the combined endpoint death or myocardial infarction at 5-year follow-up. In both studies, this benefit was apparent in patients with an high risk profile. However, our data do not indicate that an early invasive strategy would prevent death or spontaneous myocardial infarctions in patients with a high FRISC score.

This study has some limitations. The difference in revascularisation rates during initial hospitalisation between the two treatment groups is 36% with a high revascularisation rate of 40% in the selective invasive group, and this difference is reduced to 23% at 3 years, which might have diminished the differences in outcome. A low percentage of patients in both treatment groups were taking clopidogrel at discharge. The event rates in both groups would probably have been lower if clopidogrel was more routinely used according to present guidelines. The study had a power of 80% to detect a relative risk reduction of 25% in the composite endpoint death, myocardial infarction, and rehospitalisation for anginal symptoms between the two strategy groups. The study is underpowered to compare the two strategies with regard to the components of the composite endpoint, to assess whether the effects of treatment are dependent on baseline risk, and to assess the effects of in-hospital myocardial infarction and major bleeding on mortality. The analysis with regard to the composite endpoint death or spontaneous myocardial infarction is a post-hoc analysis. In our data, no relation was seen between the FRISC score and the occurrence of procedural related myocardial infarctions or rehospitalisation for anginal symptoms, and therefore the association between the treatment effect and the patients' risk was investigated on the outcome death or spontaneous myocardial infarction. Finally, the duration of follow-up in our study is shorter than RITA 3 and

FRISC-II. Therefore, we cannot exclude the possibility of late accrual of treatment benefit.

In conclusion, the long-term follow-up of the ICTUS trial did not show that an early invasive strategy is better than a more selective invasive strategy in patients with nSTE-ACS and an elevated cardiac troponin. An early invasive strategy prevents rehospitalisation but no reduction in death or myocardial infarction was recorded. A possible explanation for these findings is the relatively high revascularisation rate of 40% in-hospital and 58% during long-term follow-up in the selective invasive group, together with optimised medical treatment including low-molecular-weight heparin, glycoprotein IIb/IIIa inhibition at the time of PCI, clopidogrel, and intensive medical therapy for secondary prevention during follow-up.

Contributors

R J de Winter was main investigator of the study, participated in the design, wrote the protocol and supervised collection and analysis of the data. F W A Verheugt participated in the design, wrote the protocol, contributed to data acquisition and statistical analysis. J G P Tijssen contributed to the design, wrote the protocol and supervised collection and analysis of the data. F W A Verheugt and J H Cornel contributed to the design and data acquisition. A Hirsch contributed to data acquisition and statistical analysis, and was responsible for writing the manuscript, which was commented and amended by all co-authors.

Conflict of interest statement

We declare that we have no conflict of interest with respect to the ICTUS trial. F W A Verheugt has received educational and research grants from Bayer AG, Roche, Eli Lilly, and Boehringer Ingelheim, and received honoraria for consultancies from Pharmacia Upjohn, Eli Lilly, Merck, and Bayer (Netherlands).

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