JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN
COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 69, NO. 15, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.02.021

EDITORIAL COMMENT

Non–ST-Segment Elevation Acute Coronary Syndromes

Lessons Learned Over the Last Decade*

Anthony A. Bavry, MD, MPH[a,b]

The cardiology community continues to debate the optimal management for patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS). Strategies include planned catheterization versus an ischemia-guided approach where the decision to perform catheterization is based on identification of high-risk characteristics ascertained from clinical observation and/or imaging studies. The argument to perform routine catheterization is to identify and revascularize the culprit lesion, which is usually a severe stenosis and not an occluded vessel. This strategy may prevent coronary artery occlusion and subsequent large myocardial infarction, as well as the deleterious effects of chronic myocardial ischemia, including left ventricular systolic/diastolic dysfunction, malignant arrhythmias, and unstable angina requiring hospitalization and revascularization. An ischemia-guided approach may be preferred to limit the risks of catheterization and revascularization including bleeding, periprocedural myocardial infarction, stent thrombosis, and in-stent restenosis (1).

SEE PAGE 1883

In this issue of the *Journal*, the ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes) investigators have reported their 10-year findings (2). They concluded that early invasive therapy was associated with a similar incidence of death or spontaneous myocardial infarction compared with selective invasive therapy (hazard ratio: 1.12; 95% confidence interval [CI]: 0.97 to 1.46; $p = 0.11$). However, there was increased incidence of long-term death or myocardial infarction among the early invasive group compared with the selective invasive group due to periprocedural myocardial infarction. This report provides an opportunity to review some of the key lessons learned in NSTE-ACS over the last decade.

The first lesson pertains to older trials that are now quite dissimilar to current practice. The VANQWISH (Veterans Affairs Non-Q-Wave Infarction Strategies In Hospital) trial was among the first trials to compare the effectiveness of invasive strategies (3). That trial concluded that invasive therapy was associated with excess deaths at hospital discharge, at 1 month, and at 1 year (3). Whereas this is an important historical trial, it does not represent current percutaneous coronary intervention practice, in that it largely predated the era of coronary stents and potent antiplatelet therapy. Moreover, approximately one-half of the patients assigned to invasive therapy underwent coronary artery bypass graft and subsequently experienced high operative mortality (12%) (3). A meta-analysis that included these early trials concluded that early invasive therapy was associated with increased deaths during the index hospitalization, with a decrease in deaths after hospital discharge (4). Later trials include FRISC II (Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease) (5), TACTICS-TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18) (6), RITA 3 (Randomized Intervention Trial of Unstable Angina) (7), and ICTUS (8). These trials are distinct from the earlier trials in

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the [a]Department of Medicine, University of Florida, Gainesville, Florida; and the [b]North Florida/South Georgia Veterans Health System, Gainesville, Florida. Dr. Bavry has received an honorarium from the American College of Cardiology.

that referral for coronary artery bypass graft was less frequent (16% to 35%) and operative mortality was much lower (1% to 3%) (5-8). Another difference is that percutaneous coronary intervention was conducted with stents and adenosine diphosphate receptor antagonists/glycoprotein IIb/IIIa inhibitors, which are known to prevent ischemic events including stent thrombosis (1). With the exception of the ICTUS trial, early invasive therapy was associated with a reduction in adverse cardiovascular events at 4 to 12 months (5-7). Meta-analysis of trials conducted in the era of stents and adenosine diphosphate receptor antagonists/glycoprotein IIb/IIIa inhibitors documented that early invasive therapy was associated with a reduction in mortality and myocardial infarction at 2 years compared with selective invasive therapy (9).

The second lesson pertains to the definition of the control group. In FRISC II, revascularization procedures (within 10 days) occurred in 9% of the control arm (5), whereas in ICTUS, revascularization procedures (during the initial hospitalization) occurred in 40% (8). Thus, the control arm in the former trial more closely resembled conservative therapy. The greater the difference in the incidence of revascularization between treatment arms, the greater the magnitude of benefit from invasive therapy (9). The After-Eighty trial is one of the more recent trials, and it compared invasive therapy versus conservative therapy (10). In the invasive group, catheterization was performed at a mean of 3 days, whereas catheterization was not performed in the conservative group. Invasive therapy was associated with a reduction in death, myocardial infarction, stroke, or urgent revascularization compared with conservative therapy. Benefit for invasive therapy diminished with increasing age; subjects ≤90 years were associated with fewer adverse events with invasive therapy, whereas those >90 years were associated with harm with invasive therapy (10). A meta-analysis that included these most recent trials documented that early invasive therapy was associated with a reduction in mortality or myocardial infarction at a mean of 39 months compared with selective invasive therapy. This was primarily due to a reduction in the risk of myocardial infarction (11).

The third lesson pertains to possible effect modification by sex. Women with NSTE-ACS tend to have less severe coronary artery disease than their male counterparts have; thus, they could have less to gain from invasive therapy (12,13). The OASIS 5 (Organization to Assess Strategies in Acute Ischemic Syndromes Investigators) substudy was conducted entirely in women (n = 184). This trial found that invasive therapy was associated with a markedly increased rate of major bleeding at 30 days and deaths at 1 year compared with selective invasive therapy (14). Meta-analysis found evidence of effect modification for increased death or myocardial infarction among invasively managed women (14). However, updated meta-analysis has failed to find any evidence for effect modification by sex (11). In fact, a contemporary observational analysis documented lower in-hospital mortality among women who underwent early invasive versus initial conservative therapy (15).

The fourth lesson pertains to the impact of long-term follow-up. Many patients initially selected for an ischemia-guided approach will ultimately have catheterization performed. This could be due to failure of antiangina therapy to prevent angina symptoms, but it could also represent progression of underlying coronary artery disease and development of unstable coronary syndromes. From randomized trial data, approximately one-third to one-half of patients in the control arm underwent revascularization after the index hospitalization (11). Taken to an extreme, mortality will be 100% in both treatment groups if follow-up is long enough. Thus although long-term follow-up is laudable, it is not surprising that earlier benefit from invasive therapy is not sustained to later time points (i.e., 5 to 10 years).

Invasive therapy remains an appropriate treatment strategy for patients with NSTE-ACS. Treatment guidelines recommend that NSTE-ACS patients undergo invasive therapy; urgent (<2 h), early (<24 h), or delayed (25 to 72 h) depending on clinical characteristics (16). Ischemia-guided therapy can be considered for the lowest risk patients (i.e., TIMI [Thrombolysis In Myocardial Infarction] score <2 or GRACE [Global Registry of Acute Coronary Events] score <109) (16). Current practice emphasizes bleeding avoidance and optimal stent implantation; thus maximizing benefit and minimizing harm from invasive therapy (17,18). In summary, the last decade taught us that invasive therapy reduces adverse ischemic events, including early and intermediate death, myocardial infarction, or urgent revascularization for unstable angina. The benefit from invasive therapy applies to both men and women. Future research will need to refine the lowest risk patients who are appropriate for conservative therapy.

ADDRESS FOR CORRESPONDENCE: Dr. Anthony A. Bavry, North Florida/South Georgia Veterans Health System, Malcom Randall Veterans Administration Medical Center, Medical Service, Cardiology Section (111D), 1601 SouthWest Archer Road, Gainesville, Florida 32608. E-mail: anthony.bavry@va.gov.

JACC VOL. 69, NO. 15, 2017
APRIL 18, 2017:1894–6

REFERENCES

1. Bavry AA, Bhatt DL. Appropriate use of drug-eluting stents: balancing the reduction in restenosis with the concern of late thrombosis. Lancet 2008;371:2134–43.

2. Hoedemaker NPG, Damman P, Woudstra P, et al., on behalf of the ICTUS Investigators. Early invasive versus selective strategy for non-ST-segment elevation acute coronary syndrome: the ICTUS trial. J Am Coll Cardiol 2017;69:1883–93.

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. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. N Engl J Med 1998;338:1785–92.

4. 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.

5. FRISC-II Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet 1999;354:708–15.

6. Cannon CP, Weintraub WS, Demopoulos LA, et al., for the TACTICS-TIMI 18 Investigators. 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.

7. Fox KA, Poole-Wilson PA, Henderson RA, et al., for the RITA-3 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.

8. 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.

9. 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.

10. Tegn N, Abdelnoor M, Aaberge L, et al., for the After Eighty Study Investigators. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet 2016;387:1057–65.

11. Elgendy IY, Kumbhani DJ, Mahmoud AN, Wen X, Bhatt DL, Bavry AA. Routine invasive versus selective invasive strategies for Non-ST-elevation acute coronary syndromes: an updated meta-analysis of randomized trials. Catheter Cardiovasc Interv 2016;88:765–74.

12. Lagerqvist B, Safstrom K, Stahle E, et al., for the FRISC II Study Group Investigators. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? J Am Coll Cardiol 2001;38:41–8.

13. Clayton TC, Pocock SJ, Henderson RA, et al. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST-elevation myocardial infarction? The impact of gender in the RITA 3 trial. Eur Heart J 2004;25:1641–50.

14. Swahn E, Alfredsson J, Afzal R, et al. Early invasive compared with a selective invasive strategy in women with non-ST-elevation acute coronary syndromes: a substudy of the OASIS 5 trial and a meta-analysis of previous randomized trials. Eur Heart J 2012;33:51–60.

15. Elgendy IY, Mahmoud AN, Mansoor H, Bavry AA. Early invasive versus initial conservative strategies for women with non-ST-elevation acute coronary syndromes: a nationwide analysis. Am J Med 2017 July [E-pub ahead of print].

16. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:e344–426.

17. Hamon M, Rasmussen LH, Manoukian SV, et al. Choice of arterial access site and outcomes in patients with acute coronary syndromes managed with an early invasive strategy: the ACUITY trial. EuroIntervention 2009;5:115–20.

18. Elgendy IY, Mahmoud AN, Elgendy AY, Bavry AA. Outcomes with intravascular ultrasound-guided stent implantation: a meta-analysis of randomized trials in the era of drug-eluting stents. Circ Cardiovasc Interv 2016;9:e003700.

KEY WORDS invasive treatment, long-term outcome, non-ST-segment elevation myocardial infarction

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 69, NO. 15, 2017
ISSN 0735-1097
http://dx.doi.org/10.1016/j.jacc.2017.02.023

ORIGINAL INVESTIGATIONS

Early Invasive Versus Selective Strategy for Non–ST-Segment Elevation Acute Coronary Syndrome

The ICTUS Trial

Niels P.G. Hoedemaker, MD, Peter Damman, MD, PhD, Pier Woudstra, MD, Alexander Hirsch, MD, PhD, Fons Windhausen, MD, PhD, Jan G.P. Tijssen, PhD, Robbert J. de Winter, MD, PhD, on behalf of the ICTUS Investigators

ABSTRACT

BACKGROUND The ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes) trial compared early invasive strategy with a selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and an elevated cardiac troponin T. No long-term benefit of an early invasive strategy was found at 1 and 5 years.

OBJECTIVES The aim of this study was to determine the 10-year clinical outcomes of an early invasive strategy versus a selective invasive strategy in patients with NSTE-ACS and an elevated cardiac troponin T.

METHODS The ICTUS trial was a multicenter, randomized controlled clinical trial that included 1,200 patients with NSTE-ACS and an elevated cardiac troponin T. Enrollment was from July 2001 to August 2003. We collected 10-year follow-up of death, myocardial infarction (MI), and revascularization through the Dutch population registry, patient phone calls, general practitioners, and hospital records. The primary outcome was the 10-year composite of death or spontaneous MI. Additional outcomes included the composite of death or MI, death, MI (spontaneous and procedure-related), and revascularization.

RESULTS Ten-year death or spontaneous MI was not statistically different between the 2 groups (33.8% vs. 29.0%, hazard ratio [HR]: 1.12; 95% confidence interval [CI]: 0.97 to 1.46; $p = 0.11$). Revascularization occurred in 82.6% of the early invasive group and 60.5% in the selective invasive group. There were no differences in additional outcomes, except for a higher rate of death or MI in the early invasive group compared with the rates for the selective invasive group (37.6% vs. 30.5%; HR: 1.30; 95% CI: 1.07 to 1.58; $p = 0.009$), driven by a higher rate of procedure-related MI in the early invasive group (6.5% vs. 2.4%; HR: 2.82; 95% CI: 1.53 to 5.20; $p = 0.001$).

CONCLUSIONS In patients with NSTE-ACS and elevated cardiac troponin T levels, an early invasive strategy has no benefit over a selective invasive strategy in reducing the 10-year composite outcome of death or spontaneous MI, and a selective invasive strategy may be a viable option in selected patients. (J Am Coll Cardiol 2017;69:1883–93)

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the Department of Cardiology, Heart Center, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. This work was supported by the Interuniversity Cardiology Institute of the Netherlands, the Working Group on Cardiovascular Research of the Netherlands, and educational grants from Eli Lilly, Sanofi/Synthelabo, Sanofi, Pfizer, and Medtronic. Roche Diagnostics, the Netherlands, provided the reagents for core laboratory cardiac troponin T measurements. Dr. Damman has received a research grant from AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Anthony A. Bavry, MD, served as Guest Editor for this paper.

Manuscript received January 19, 2017; accepted February 4, 2017.

JACC VOL. 69, NO. 15, 2017
APRIL 18, 2017:1883-93

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CI = confidence interval

FIR = FRISC II, ICTUS, and RITA-3 trials

HR = hazard ratio

hs-cTn = high-sensitivity troponin assay

MI = myocardial infarction

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

PCI = percutaneous coronary intervention

Different treatment strategies are available for patients presenting with non-ST-segment elevation acute coronary syndromes (NSTE-ACS). In the ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes) trial, an early invasive treatment strategy (also called routine invasive strategy) consisted of intensive antianginal and antithrombotic medical treatment aimed at stabilization and coronary angiography within 24 to 72 h, and angiography-guided subsequent appropriate treatment, either by revascularization or continued optimized pharmacological therapy. A selective invasive strategy (or ischemia-driven strategy) also consisted of antianginal and antithrombotic medical treatment, but with coronary angiography only in cases of refractory angina or inducible ischemia by pre-discharge noninvasive stress testing. The definitions used in the ICTUS trial predate the definitions that are currently used in the European and American guidelines. Current guidelines recommend an early invasive strategy (<24 h) for high-risk patients, whereas a delayed strategy (<25 to 72 h) is recommended for intermediate-risk patients. For low-risk patients either a delayed strategy or an ischemia-driven strategy can be used (1,2). Importantly, NSTE-ACS patients with an elevated cardiac troponin T are considered high risk.

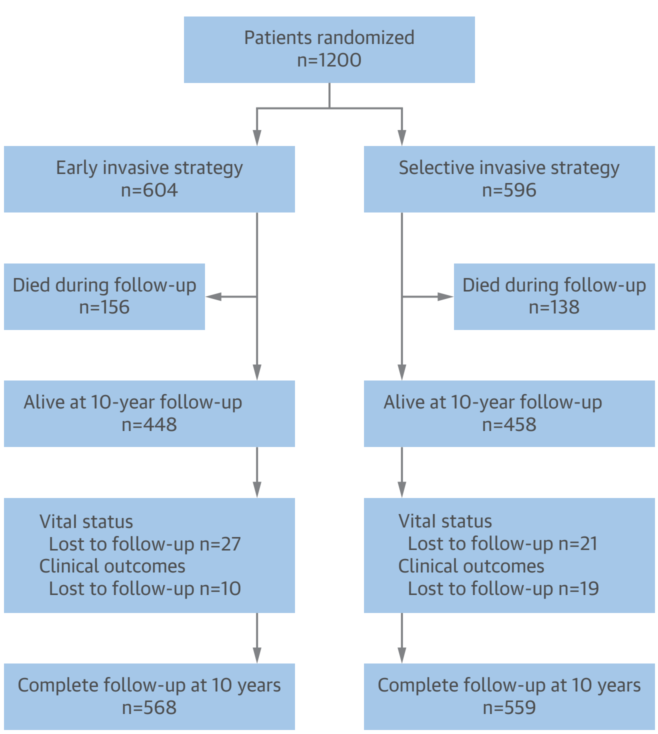
Those recommendations are largely based on multiple randomized clinical trials that have been included in several meta-analyses (3-6). A patient-pooled meta-analysis of the FRISC II (Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease), ICTUS, and RITA-3 (Third Randomised Intervention Treatment of Angina) trials (FIR) showed a reduction of long-term rates of cardiovascular death or myocardial infarction (MI) at 5 years, for patients who underwent an early invasive strategy (7). In the analysis, the largest risk reduction was observed in patients with the highest baseline risk. This reduction in clinical outcomes was mainly driven by a reduction in nonfatal MI, whereas a nonsignificant trend was observed in cardiovascular death.

SEE PAGE 1894

Long-term follow-up is important to appreciate the full clinical impact of such treatment strategies in NSTE-ACS patients. The ICTUS trial assigned 1,200 NSTE-ACS patients with an elevated cardiac troponin to either an early invasive or a selective invasive strategy. After 1 year of follow-up, an early invasive strategy was not associated with a benefit in death, MI, or rehospitalization for anginal symptoms despite an increase in early procedure-related myocardial infarction (8). At 5-year follow-up, there was no significant benefit of an early invasive strategy regardless of the patient baseline risk profile (9,10).

Recently, the RITA-3 study showed no difference between an early invasive or a noninvasive strategy for all-cause and cardiovascular mortality after 10 years of follow-up, in contrast to the 5-year outcome that showed a mortality benefit of an early invasive strategy (3,11). In addition, the 15-year follow-up of the FRISC-II study was recently published, showing a significant 18-month postponement of the occurrence of death or next MI and 37 months postponement of rehospitalization for ischemic heart disease, but similar mortality with either strategy (12). In this report we describe the 10-year clinical outcomes of the ICTUS trial. We report all-cause mortality, cardiovascular mortality, MI (spontaneous and procedure-related), and revascularization, and we assess the impact of baseline risk.

FIGURE 1 **Flow Diagram of the ICTUS Trial**



Of a total 1,200 patients, 10-year follow-up was complete for 568 patients in the early invasive group and 559 patients in the selective invasive group. ICTUS = Invasive Versus Conservative Treatment in Unstable Coronary Syndromes.

METHODS

STUDY DESIGN. The original design and methods of the ICTUS study have been published previously (8). Between July 2001 and August 2003, we enrolled 1,200 NSTE-ACS patients with an elevated cardiac troponin T in 42 Dutch hospitals (Online Appendix). Within 24 h after onset of symptoms, the patients were randomized to either an early invasive strategy or a selective invasive strategy.

PATIENTS. Patients ages 18 to 80 years were eligible if they had all 3 of the following: ongoing chest pain (>20 min); an elevated cardiac troponin T level (≥0.03 g/l); and either ischemic changes as assessed by electrocardiography (defined as ST-segment depression or transient ST-segment elevation exceeding 0.05 mV or T-wave inversion of ≥0.2 mV in 2 contiguous leads) or a documented history of coronary artery disease (clinical history of MI, percutaneous coronary intervention [PCI], and/or coronary artery bypass graft [CABG]). Patients were excluded in case of: an ST-segment elevation MI <48 h before randomization, an indication for reperfusion therapy, hemodynamic instability or overt congestive heart failure, and an increased bleeding risk.

TREATMENT STRATEGY. Patients randomized to an early invasive strategy underwent coronary angiography within 24 to 48 h after randomization and the requirement for revascularization by PCI or CABG was guided by the findings of the angiography. Patients assigned to a selective invasive strategy received optimal (antianginal) medical treatment. Coronary angiography was performed in cases of refractory angina or inducible signs of ischemia during a mandatory pre-discharge ischemia detection test.

OPTIMIZED MEDICAL THERAPY. All patients received optimal pharmacological treatment including aspirin, clopidogrel, enoxaparin, intravenous nitrates, beta-blockers, and intensive lipid-lowering therapy. The protocol recommended all PCI be performed with the use of abciximab, given as bolus of 0.25 mg/kg, followed by an infusion of 0.125 μg/kg/min for 12 h, and started 10 to 60 min before the first balloon inflation.

FOLLOW-UP. We collected the patients' vital status from the Dutch national population registry at least 10 years after randomization. We contacted all patients known to be alive at 10 years by telephone to collect information on rehospitalization for cardiac reasons. If patients were rehospitalized, we obtained the discharge letters from the hospitals the patients were admitted to. If necessary, hospitalization information was obtained from their general practitioners.

TABLE 1 Baseline Characteristics

	Early Invasive Strategy (n = 604)	Selective Invasive Strategy (n = 596)
Demographics		
Age ≥65, yrs	263 (44)	266 (45)
Body mass index, kg/m^2	27 ± 4	27 ± 4
Male	446 (74)	434 (73)
Clinical history		
Myocardial infarction	153 (25)	125 (21)
Percutaneous coronary intervention	77 (13)	63 (11)
Coronary artery bypass graft	62 (10)	43 (7)
Risk factors		
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 disease	263 (44)	241 (40)
Electrocardiographic abnormalities		
ST-segment deviation ≥0.1 mV	284 (49)	290 (51)
Left bundle branch block	8 (1)	6 (1)
Aspirin use at admission	235 (39)	221 (37)
Laboratory assessments		
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)
FIR score		
Low risk, score 0–4	329 (57)	333 (58)
Intermediate, score 5–8	181 (31)	175 (31)
High, score ≥9	68 (12)	63 (11)

Values are n (%), mean ± SD, or median (interquartile range). C-reactive protein was available in 1,444 patients. Electrocardiogram data were available in 1,149 patients. FIR score could be calculated for 1,149 patients.

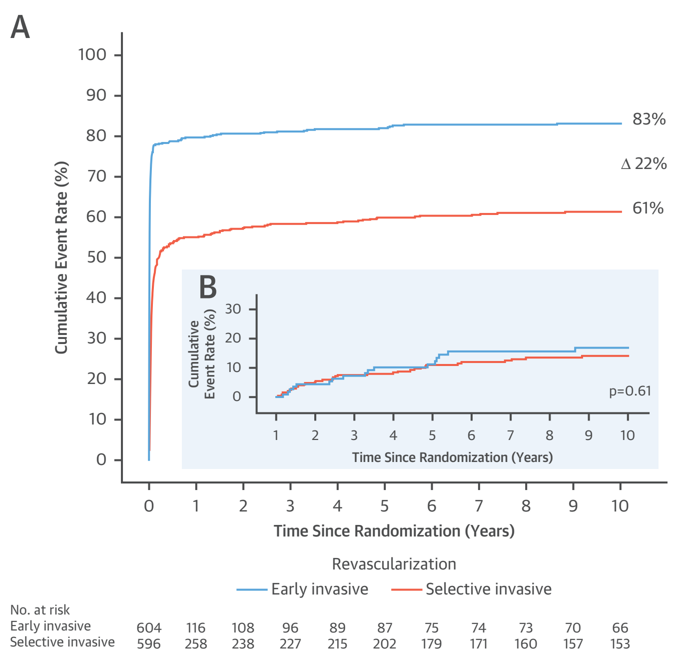
FIR = FRISC II (Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease)–ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes)–RITA-3 (Third Randomised Intervention Treatment of Angina).

For deceased patients, we collected clinical event information and cause of death from their general practitioners or from hospital records. Patients were considered lost to follow-up if no contact could be made with either the patient or the general practitioner. The Medical Ethics Committee of the Academic Medical Center-University of Amsterdam approved the long-term follow-up.

OUTCOMES. The main outcome of this study was the composite of all-cause death and spontaneous MI. Additional outcomes were the composite of all-cause death and MI, all-cause death, cardiovascular death, noncardiovascular death, MI, spontaneous MI, procedure-related MI, and revascularization by PCI or CABG. All deaths were considered cardiovascular unless an unequivocal noncardiovascular cause could be established. MI was defined as documented myocardial necrosis either in the setting of myocardial ischemia (spontaneous MI) or in the setting of PCI or CABG (procedure-related MI) following the

JACC VOL. 69, NO. 15, 2017
APRIL 18, 2017:1883–93

FIGURE 2 10-Year Cumulative Incidence of Revascularization Accounted for Competing Risk of Death and Landmark Analysis of Revascularization With a Landmark at 1 Year



(A) Revascularization at 10 years was 83% in the early invasive group and 61% in the selective invasive group. **(B)** In a landmark analysis with a landmark at 1 year, there was no significant difference in revascularization rates among the early invasive and selective invasive groups.

recommendations of the Consensus Committee for the definition of MI (13). All events were adjudicated, those within the first 5 years by a blinded adjudication committee and later ones by 2 co-authors (N.P.G.H. and P.D.).

STATISTICAL ANALYSIS. The analyses were by intention to treat. We calculated the nonparametric estimator of the cause-specific cumulative incidence of revascularization to account for competing risk of death. We performed a landmark analysis for revascularization with a landmark at 1 year. For all other outcomes, we used the Kaplan-Meier method to estimate cumulative incidence, and Cox proportional hazards model to obtain hazard ratios (HRs) with 95% confidence intervals (CIs). Follow-up was censored at 3,655 days or at the last date of known clinical outcome status for patients with incomplete follow-up. For endpoints not including all-cause death, cardiovascular death, or noncardiovascular death, follow-up was censored at the time of death if not preceded by the outcome. We performed a stratified analysis according to baseline risk using the FIR risk score (7). The FIR score is a sum of the following factors: age (<60 years [+0], 60 to 64 years [+1], 65 to 69 years [+2], 70 to 74 years [+3], ≥75 years [+5]); diabetes mellitus (+4); previous MI (+3); ST-segment depression (+2); hypertension (+1); and body mass index (<25 [+1], 25 to <35 [+0], ≥35 [+2]). A multivariate predictive model for death or spontaneous MI was developed with a Cox proportional hazards model. The model was developed by backward stepwise elimination from a larger predefined set of baseline variables including the following: age ≥65 years; sex; body mass index; diabetes mellitus; current smoker at time of enrollment; hypertension; hypercholesterolemia; family history of coronary artery disease; history of MI; history of PCI; history of CABG; aspirin use at admission; C-reactive protein ≥10 mg/l; ST-segment depression; ST-segment elevation; ST-segment deviation; creatinine clearance ≤60 ml/min/1.73 m^2. We used the Wald test with a p value of 0.1 for exclusion from the model. All statistical analyses were performed with SPSS version 23.0 (SPSS Inc., IBM, Armonk, New York), except for the calculation of nonparametric estimator of the cause-specific cumulative incidence of revascularization and the landmark analysis, for which we used R version 3.3.0 (R Foundation, Vienna, Austria).

TABLE 2 Cumulative Event Rate by Treatment Strategy

	Early Invasive (n = 604)	Selective Invasive (n = 596)	HR (95% CI)	p Value
Death or spontaneous MI	199 (33.8)	168 (29.0)	1.12 (0.97–1.46)	0.11
Death or MI	222 (37.6)	177 (30.4)	1.30 (1.07–1.58)	0.009
All-cause death	156 (26.7)	138 (23.7)	1.14 (0.92–1.44)	0.25
Cardiovascular death	97 (17.6)	85 (15.2)	1.15 (0.86–1.54)	0.34
Noncardiovascular death	59 (10.9)	53 (10.0)	1.13 (0.78–1.63)	0.53
MI	106 (18.9)	84 (14.9)	1.30 (0.98–1.73)	0.07
Spontaneous MI	75 (13.8)	72 (12.9)	1.04 (0.75–1.43)	0.82
Procedure-related MI	39 (6.5)	14 (2.4)	2.82 (1.53–5.20)	0.001

Values are number of event outcomes (Kaplan-Meier estimate). The p values are derived from Cox proportional hazards model.

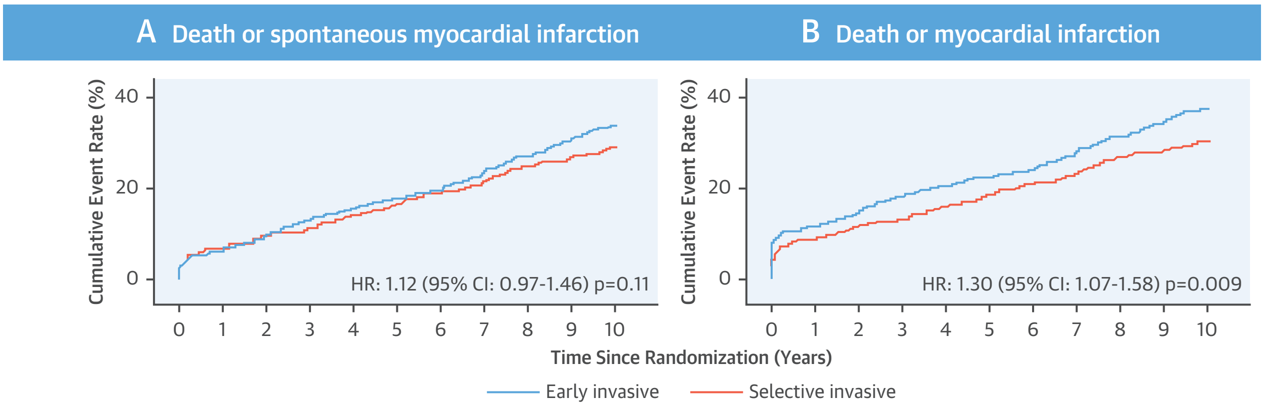
CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

RESULTS

PATIENTS. Of 1,200 patients, 604 patients were assigned to an early invasive strategy and 596 patients were assigned to a selective invasive strategy (**Figure 1**). The 2 groups showed well-matched baseline characteristics (**Table 1**).

The median age was 62 years; approximately 75% of the patients were male; and 14% had diabetes. Ischemic electrocardiographic changes were present in 50% of patients. All patients had elevated cardiac troponin T levels. The median troponin T level at

CENTRAL ILLUSTRATION Early Invasive Strategy Versus a Selective Invasive Strategy in High-Risk Patients: 10-Year Clinical Outcomes



No. at risk																						
Early invasive	604	566	549	523	505	492	462	440	419	398	380		604	534	516	491	474	463	435	413	394	374	357
Selective invasive	596	556	538	524	505	489	457	442	424	413	399		596	542	525	512	493	478	447	432	414	404	391

Hoedemaker, N.P.G. et al. J Am Coll Cardiol. 2017;69(15):1883–93.

Kaplan-Meier estimates of the cumulative rate of the composite outcomes of death or spontaneous myocardial infarction (MI) **(A)** and death or MI **(B).** In patients with non–ST-segment elevation acute coronary syndrome and an elevated troponin level, an early invasive strategy did not reduce the outcomes of death or spontaneous MI and death or MI at 10 years. Hazard ratios (HRs) and p values were obtained with Cox proportional hazards models. CI = confidence interval.

admission was 0.29 μg/l. Cardiac catheterization was performed during the initial hospitalization in 98% of patients in the early invasive group and 53% in the selective invasive group. Within 1 year, 79% of the patients in the early invasive group had undergone revascularization compared with 54% in the selective invasive group. When we accounted for competing risk of death, the 10-year revascularization rate was 83% in the early invasive group and 61% in the selective invasive group (Figure 2A). There was no difference in revascularization from 1 year to 10 years of follow-up (p = 0.61) (Figure 2B).

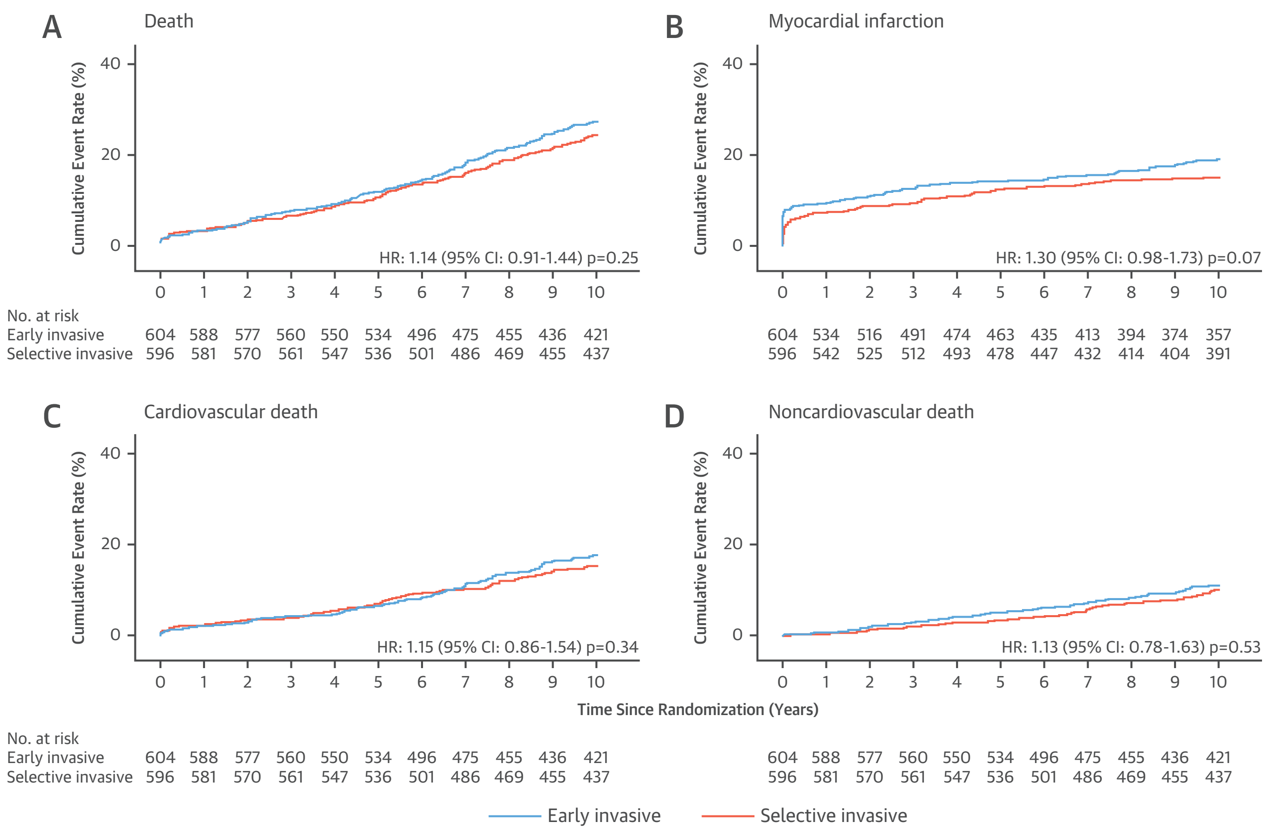
OUTCOMES. Vital status at 10 years was known for 1,152 patients (96.0%) and was equally distributed between both groups (Figure 1). Clinical outcome status (MI and revascularization) at 10 years was known for 1,171 patients (97.6%), 594 patients (98.3%) in the early invasive group and 577 patients (96.8%) in the selective invasive group. Table 2 displays the 10-year cumulative event rates and HR of the main composite and individual outcomes. The 10-year composite outcome of death or spontaneous MI was 33.8% for the early invasive group and 29.0% for the selective invasive group (Central Illustration) (HR: 1.12; 95% CI: 0.97 to 1.46; p = 0.11) and 37.6% versus 30.4% (HR: 1.30; 95% CI: 1.07 to 1.58; p = 0.009) for death or MI, respectively.

Figure 3 shows the Kaplan-Meier curves for the other additional outcomes. There was no difference in all-cause death for early invasive strategy (26.6%) versus selective invasive strategy (23.7%) (HR: 1.14; 95% CI: 0.91 to 1.44; p = 0.25) (Table 2, Figure 3A) or for cardiovascular death (17.6% vs. 15.2%, respectively; HR: 1.15; 95% CI: 0.86 to 1.54; p = 0.34) (Table 2, Figure 3C). Additionally, MI in the early invasive group was 18.9% versus 14.9% in the selective invasive group (HR: 1.30; 95% CI: 0.98 to 1.73; p = 0.07) (Table 2, Figure 3B). This nonsignificant difference in MI was mainly driven by a higher rate of procedure-related MI: 6.5% versus 2.4% for early invasive and selective invasive strategies, respectively (HR: 2.82; 95% CI: 1.53 to 5.20; p = 0.001), as the 10-year rate of spontaneous MI was similar in both groups (13.8% vs. 12.9% respectively; HR: 1.04; 95% CI: 0.75 to 1.43; p = 0.82).

RISK STRATIFICATION. Figure 4 displays the Kaplan-Meier estimate curves for death or spontaneous MI stratified by FIR score. There was no benefit for an early invasive strategy regardless of the baseline risk: 1) for low risk, HR = 0.95 (95% CI: 0.67 to 1.34; p = 0.76); 2) for intermediate risk, HR = 1.40 (95% CI: 0.99 to 1.97; p = 0.054); and 3) for high risk, HR = 1.07 (95% CI: 0.69 to 1.67; p = 0.76). Looking at both risk score (FIR) and treatment strategy, we could not demonstrate an interaction of sex with outcomes.

JACC VOL. 69, NO. 15, 2017
APRIL 18, 2017:1883-93

FIGURE 3 **Kaplan-Meier Estimates of the Cumulative Rate of Death, MI, Cardiovascular Death, and Noncardiovascular Death**



Kaplan-Meier estimates of the cumulative rate of death **(A)**, myocardial infarction (MI) **(B)**, cardiovascular death **(C)**, and noncardiovascular death **(D)**. Hazard ratios (HR) were derived from a Cox proportional hazards model. CI = confidence interval.

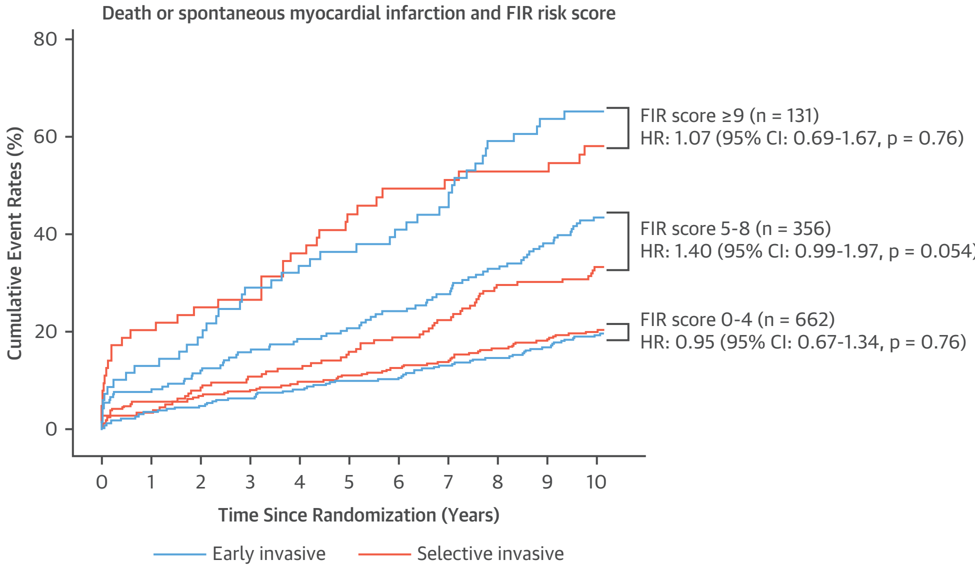
MULLTIVARIATE MODELS. Table 3 shows baseline characteristics independently associated with 10-year death or spontaneous MI. In the multivariate model, there was no difference between the early invasive and selective invasive strategy with regard to the 10-year risk of death or spontaneous MI (HR: 1.20; 95% CI: 0.97 to 1.48; p = 0.096).

DISCUSSION

In this study, we report the 10-year clinical outcomes of the ICTUS study. Our results show that, in patients with NSTE-ACS with elevated cardiac troponin T levels, there was no benefit associated with an early invasive strategy in reducing death or spontaneous MI after 10 years of follow-up. In addition, we did not observe differences in rates of death or spontaneous MI after risk stratification with the FIR score. No late effects were observed, with comparable increments for death or MI in both treatment groups up to 10-year follow-up. Although more procedure-related MI occurred in the early invasive group, there was no significant difference in mortality at 10 years. The current result confirms and extends the results of previous studies, with one-third of patients enduring death or spontaneous MI within 10 years despite treatment. These findings are in contrast to the results of the long-term outcome of the FRISC-II and RITA-3 studies, where a benefit of an early invasive strategy was shown.

CONTEXT AND INTERPRETATION OF THE CURRENT RESULTS. There may be many reasons for the differences observed in the ICTUS trials when compared with the FRISC-II and RITA-3 studies. The trials enrolled patients in different time periods, and there were differences in clinical practice. Compared with the RITA-3 and FRISC-II trials, the ICTUS trial was the most contemporary and included the use of stents, glycoprotein IIb/IIIa inhibitors during PCI, long-term

FIGURE 4 Kaplan-Meier Estimates of the Cumulative Rate of the Composite Outcome of Death or Spontaneous MI Stratified and Divided in 3 Groups



No. at risk											
Early invasive	604	566	549	523	505	492	462	440	419	398	380
Selective invasive	596	556	538	524	504	489	457	442	424	413	399

Risk stratification by baseline risk with the FRISC II (Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease)–ICTUS–RITA-3 (Third Randomised Intervention Treatment of Angina) (FIR) (7). HR and p values were derived from a Cox proportional hazards model. Abbreviations as in **Figures 1 and 3**.

(dual) antiplatelet agents, and high-dose statin treatment.

Perhaps the most important difference among the 3 trials was the timing and intensity of revascularization (**Figure 5**). In the ICTUS trial, in the early invasive strategy as per protocol, 97% of patients underwent coronary angiography within 48 h and 98% during hospitalization (8). Coronary angiography during hospitalization was 96% in both early invasive groups of RITA-3 and FRISC-II, and by design, was to be performed <72 h from randomization and <7 days from admission for the index event, respectively (14,15). More importantly, coronary angiography during hospitalization in the noninvasive groups of FRISC-II and RITA-3 was only 7% and 16%, respectively, compared with 53% of patients in the selective invasive group in ICTUS, which better reflects contemporary practice (8,14,15). All patients in ICTUS were troponin positive, making the presence of an ACS more likely. Furthermore, after diagnostic coronary angiography, subsequent revascularization was more frequent in the ICTUS trial. Revascularization during hospitalization was 76% in the early invasive group and 40% in selective invasive group compared with 76% in the early invasive group versus 14% in the noninvasive group of FRISC-II and 44% versus 10% in RITA-3 (8,14,15).

Meta-analyses have shown a mortality benefit with an early invasive strategy at 2 years when combining data from randomized trials (5,16). In ICTUS, an absolute 22% difference in revascularization between the early invasive and the selective invasive group was sustained until 10 years, with mortality showing no difference at 1-, 5-, and 10-year follow-up. In FRISC-II, a significant difference in mortality was observed at 2 years, which dissipated at 5-year and 15-year follow-ups (4,12). In the RITA-3 study, there was no difference in mortality at 2-year follow-up. A significant difference in mortality was observed at 5 years, which no longer existed at 10-year follow-up (3,11). We are unaware of a plausible pathophysiological mechanism or change in clinical practice over time that may explain these observations. Therefore, considering the long-term observations of all 3 strategy trials, one may assume that any observed difference in mortality is the result of a play of chance. In summary, although the 3 individual trials may not be statistically powered to detect a difference in

TABLE 3 Multivariate Predictors of Death or Spontaneous MI at 10-Year Follow-Up

	Number of Events	%	HR (95% CI)	p Value
Allocated treatment strategy				0.097
Selective invasive	168/596	28.2	1.00	
Early invasive	199/604	32.9	1.20 (0.97–1.48)	
Age ≥65 yrs				<0.001
No	132/671	19.7	1.00	
Yes	235/529	44.4	2.25 (1.77–2.86)	
Diabetes mellitus				<0.001
No	283/1,034	27.4	1.00	
Yes	84/166	50.6	1.62 (1.24–2.11)	
Current smoker				0.094
No	228/708	32.2	1.00	
Yes	139/492	28.3	1.21 (0.97–1.52)	
Hypercholesterolemia				0.009
No	205/783	26.2	1.00	
Yes	162/417	38.8	1.36 (1.08–1.72)	
History of MI				0.007
No	239/922	25.9	1.00	
Yes	128/278	46.0	1.43 (1.10–1.86)	
Aspirin use prior to admission				0.052
No	174/744	23.4	1.00	
Yes	193/456	42.2	1.29 (0.99–1.66)	
C-reactive protein ≥10 mg/l				0.001
No	252/906	27.8	1.00	
Yes	115/294	39.1	1.49 (1.20–1.87)	
Cumulative ST-segment deviation ≥0.1 mV				0.065
No	303/1,012	29.9	1.00	
Yes	42/137	30.7	1.22 (0.99–1.51)	
Creatinine clearance <60 μmol/l				<0.001
No	299/1,082	27.6	1.00	
Yes	68/117	58.1	1.78 (1.32–2.39)	

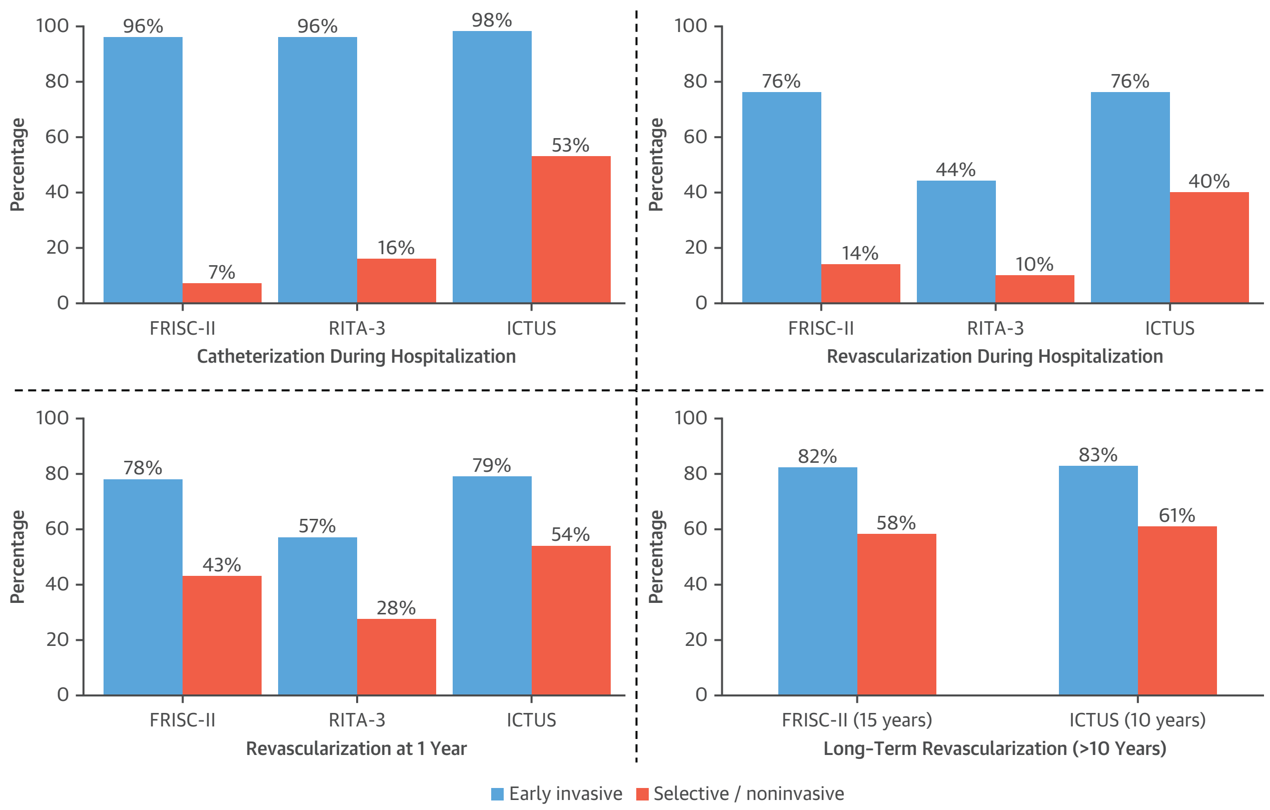
Abbreviations as in Table 2.

mortality, the long-term (≥10 years) results found in the 3 studies suggest that, compared with a selective invasive strategy, an early invasive strategy is not associated with a long-term mortality benefit, even in NSTE-ACS patients with an elevated cardiac troponin.

Concerning the incidence of MI, the long-term results varied among the 3 strategy trials. Our current results show there is no benefit associated with an early invasive strategy in reducing death or MI at 10 years, and our results are consistent with the earlier results from the ICTUS study (8–10). At 1 and 5 years, an early invasive strategy was not associated with a reduction in the composite of death or MI. Nor was there is difference in the 2 individual endpoints. In contrast to our results, the 5-year composite of death or MI in RITA-3 was higher in the noninvasive group (20.0%) compared with the early invasive group (16.6%; p = 0.044) (3). Yet, MI as an individual endpoint did not differ between the 2 groups at 5 years (early invasive: 6.8% vs. 8.3%; p = 0.22). In FRISC-II, death or MI at 5 years was significantly higher in the noninvasive group (24.5% vs. 19.9%; p = 0.009) and was mainly driven by a higher number of MI in the noninvasive group (17.7%) compared with the early invasive group (12.9%; p = 0.002) (4). Looking at all events, not just the first event, this result persisted at 15 years of follow-up in FRISC-II. In this study, an early invasive strategy was associated with a postponement of death or new MI by 18 months and death or next readmission for ischemic heart disease by 37 months. This was mainly driven by a higher rate of MI or readmission in the noninvasive group during the first 3 to 4 years of the study, with the event curves running parallel thereafter (12). Again, the difference in early revascularization between the early invasive and the noninvasive treatment arm in FRISC-II was profound, with unplanned revascularization occurring 30% more often in the noninvasive group during the first 3 to 4 years. Thus, the more frequent occurrence of spontaneous MI in the noninvasive group in the first 3 years in FRISC-II over time, parallels a low percentage of early revascularization followed by more frequent unplanned revascularization at a later time when compared with the early invasive group. Current European and American NSTE-ACS guidelines recommend an early invasive strategy for troponin-positive patients, with coronary angiography being done preferably within 24 h (1,2). Yet, in the long-term results of FIR there was no mortality benefit associated with an early invasive strategy. Moreover, we could not show a reduction in MI at 10-year follow-up, provided there was a revascularization rate of 61% in the selective invasive group at 10 years (with an absolute difference in revascularization of 22%). Taken together, when balancing the risks and benefits of angiography and revascularization, we conclude that a selective invasive strategy may be a viable option in selected patients.

FUTURE PERSPECTIVES. We acknowledge several important developments in diagnostic and therapeutic armamentarium for NSTE-ACS patients over the past years. First, the high-sensitivity troponin assay (hs-cTn) is now widely available. The introduction of hs-cTn has improved the rule-out process in NSTE-ACS patients with a normal hs-cTn (17). Since its introduction, hs-cTn also has markedly changed the troponin-positive NSTE-ACS population; a recent study demonstrated an increase of troponin-positive NSTE-ACS (or non-ST-segment elevation MI) and a decrease in unstable angina diagnoses at discharge

FIGURE 5 Catheterization and Revascularization Rates in FRISC-II, RITA-3, and ICTUS



In the early invasive groups of FIR (8,12,14,15), catheterization during hospitalization was similar. In the selective invasive group of ICTUS catheterization during hospitalization was markedly higher than in FRISC-II and RITA-3. Revascularization during hospitalization was similar in the early invasive groups of FRISC-II and ICTUS and was higher in the selective invasive group of ICTUS. Revascularization at 1 year showed similar results for FRISC-II and ICTUS for both groups; however, the early invasive group of RITA-3 and the selective invasive group of ICTUS are similar. Long-term revascularization in FRISC-II and ICTUS are similar. Abbreviations as in **Figures 1 and 4**.

(18). Subsequently, a rise or fall in cardiac troponin has been indicated as a high-risk feature, mandating an invasive strategy by the most recent treatment guidelines. Therefore, more patients who were previously diagnosed with unstable angina now have an indication for early coronary angiography. Patients with minor elevations measured with hs-cTn, who are at the lower end of the risk spectrum, have not been included in any the strategy trials.

Second, pharmacological and invasive treatment options, used at the time of enrollment of the study, have been developed further. For example, several trials with novel $P2Y_{12}$ inhibitors have shown benefit over clopidogrel in reducing death, MI, and stroke, including patients with an intended noninvasive management (19–21). The use of radial approach is more prevalent and has been shown to reduce major bleeding in NSTE-ACS patients, and stent technology has improved with the introduction of latest generation drug-eluting stents (22,23).

Finally, we emphasize the importance of secondary prevention by means of optimized medical treatment, lifestyle changes, and smoking cessation, as recommended by international guidelines (1,2). As all these new developments affect both an early invasive approach and a more selective invasive approach, a future study is warranted.

STUDY LIMITATIONS. First, we collected our follow-up information through patient phone calls, general practitioners, hospital records, and the national population registry. Unreported hospital admissions or patients who were lost-to-follow-up may lead to an underestimation of event rates. Second, routine serial measurement of cardiac biomarkers after PCI was not part of clinical practice during long-term follow-up and some procedure-related MI without clinical symptoms may have been missed. Third, the results of this study reflect clinical practice in the Dutch health care system. The Netherlands is a small, densely populated country with many heart centers, adequate capacity for PCI or CABG, and well-organized primary care. Fourth, mean age of the patients in our study was 62 years with relatively few patients older than 80 years, making a comparison with the recently published After Eighty study difficult (24). Finally, although the quality of secondary prevention including medical treatment was likely to be high, this was not prospectively recorded during the 10-year follow-up.

CONCLUSIONS

Our results show that, in patients with NSTE-ACS with elevated cardiac troponin T levels, an early invasive strategy has no benefit in reducing the 10-year composite and individual outcomes of death or spontaneous MI. Additionally, rates of the composite of death or spontaneous MI did not differ after risk stratification for baseline risk with the FIR score. When balancing the risks and benefits of angiography and revascularization, we believe that a selective invasive strategy may be a viable option in selected patients. Future randomized controlled trials reflecting present-day clinical practice for NSTE-ACS patients, are warranted.

ACKNOWLEDGMENTS The authors thank the investigators of the ICTUS trial and the medical and nursing staff in the participating centers (Online Appendix). The authors also thank all the patients who participated in this trial.

ADDRESS FOR CORRESPONDENCE: Prof. Robbert J. de Winter, Department of Cardiology, B2-137, Academic Medical Center, Meibergdreef 9, 1105 Amsterdam, the Netherlands. E-mail: r.j.dewinter@amc.uva.nl.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with NSTE-ACS with elevated cardiac troponin-T levels, an early invasive strategy does not reduce the 10-year composite outcome of death or spontaneous MI compared to a selective invasive strategy.

TRANSLATIONAL OUTLOOK: Further research is needed to determine the optimum basis on which to decide between early and selective invasive strategies for NSTE-ACS patients in the era of hs-cTn, novel $P2Y_{12}$ inhibitors, radial arterial access, and drug-eluting stents.

REFERENCES

1. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.

2. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-Elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139–228.

3. 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.

4. Lagerqvist B, Husted S, Kontny F, et al., for the FRISC-II Investigators. 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.

5. 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.

6. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. JAMA 2008;300:71–80.

7. Fox KA, Clayton TC, Damman P, et al., for the FIR Collaboration. 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. J Am Coll Cardiol 2010;55:2435–45.

8. de Winter RJ, Windhausen F, Cornel JH, et al., for the ICTUS Investigators. Early invasive versus selectively invasive management for acute coronary syndromes. N Engl J Med 2005;353:1095–104.

9. Hirsch A, Windhausen F, Tijssen JG, et al., for the ICTUS Investigators. 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. Lancet 2007;369:827–35.

10. Damman P, Hirsch A, Windhausen F, et al., for the 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;55:858–64.

11. Henderson RA, Jarvis C, Clayton T, Pocock SJ, Fox KA. 10-year mortality outcome of a routine invasive strategy versus a selective invasive strategy in non-ST-segment elevation acute coronary syndrome: the British Heart Foundation RITA-3 randomized trial. J Am Coll Cardiol 2015;66:511–20.

12. Wallentin L, Lindhagen L, Arnstrom E, et al., for the FRISC-II Study Group. Early invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. Lancet 2016;388:1903–11.

13. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173–95.

14. Fox KA, Poole-Wilson PA, Henderson RA, et al., for the 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.

15. 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.

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. James SK, Lindback J, Tilly J, et al. Troponin-T and N-terminal pro-B-type natriuretic peptide predict mortality benefit from coronary revascularization in acute coronary syndromes: a GUSTO-IV substudy. J Am Coll Cardiol 2006;48:1146–54.

18. Twerenbold R, Jaeger C, Rubini Gimenez M, et al. Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. Eur Heart J 2016;37:3324–32.

19. Wallentin L, Becker RC, Budaj A, et al., for the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.

20. Wiviott SD, Braunwald E, McCabe CH, et al., for the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

21. James SK, Roe MT, Cannon CP, et al., for the PLATO Study Group. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. BMJ 2011;342:d3527.

22. Valgimigli M, Gagnor A, Calabro P, et al., for the MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. Lancet 2015;385:2465–76.

23. Klutstein MW, Westerhout CM, Armstrong PW, et al. Radial versus femoral access, bleeding and ischemic events in patients with non-ST-segment elevation acute coronary syndrome managed with an invasive strategy. Am Heart J 2013;165:583–90.e1.

24. Tegn N, Abdelnoor M, Aaberge L, et al., for the After Eighty Study Investigators. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet 2016;387:1057–65.

KEY WORDS invasive treatment, long-term outcome, non-ST-segment elevation myocardial infarction

APPENDIX For the investigators and research coordinators that participated in the ICTUS trial, please see the online version of this article.