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Ten-year outcomes of an early invasive or a selective invasive strategy in non-ST-segment elevation acute coronary syndrome patients with and without diabetes mellitus: a subgroup analysis of the ICTUS trial

Niels P.G. Hoedemaker^a, Peter Damman^{a,b}, Pier Woudstra^a, Alexander Hirsch^{c,d}, Fons Windhausen^e, Jan G. Tijssen^a and Robbert J. de Winter^a; on behalf of the ICTUS investigators

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^aHeart Center, Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, ^bDepartment of Cardiology, Radboud University Medical Center, Nijmegen, Departments of ^cCardiology, ^dRadiology and Nuclear Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam and ^eDepartment of Cardiology, Rode Kruis Ziekenhuis, Beverwijk, The Netherlands

Correspondence to Robbert J. de Winter, MD, PhD, FESC, Department of Cardiology, B2-137, Academic Medical Center Amsterdam, Meibergdreef 9 1105, Amsterdam, The Netherlands
Tel: +0031205669111; fax: +0031206962609; e-mail: r.j.dewinter@amc.uva.nl

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Approximately 20%–25% of non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) patients have diabetes mellitus (DM) [1]. Patients with DM have worse outcomes due to higher rates of cardiovascular risk factors and coronary artery disease compared to non-diabetic patients [2]. The European and American guidelines recommend an invasive strategy with coronary angiography within 72 hours after presentation in patients with DM, whereas a selective invasive strategy remains reserved for lower risk NSTEMI-ACS patients [3,4]. These recommendations are based on meta-analysis with less than 9000 patients demonstrating a short- and medium-term reduction in MI and rehospitalisation at 1 year [5]. Long-term outcomes of an early or selective invasive strategy in NSTEMI-ACS patients with DM remain underreported. Therefore we assessed 10-year outcomes of an early or selective invasive strategy in NSTEMI-ACS patients with or without DM.

Between July 2001 and August 2003, 1200 NSTEMI-ACS patients enrolled in the Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial were randomly assigned to an early invasive (n = 604, angiography <24–48 hours after randomisation) or a selective invasive strategy [n = 596, optimal (antianginal) medical therapy, angiography in case of refractory angina or inducible signs of ischemia during a pre-discharge ischemia detection test]. The study design of the ICTUS trial has been previously reported [6]. We collected and adjudicated 10-year follow-up of death, myocardial infarction (MI), and revascularisation through the Dutch population registry, phone calls, and patient records. The main outcome was 10-year death or spontaneous MI.

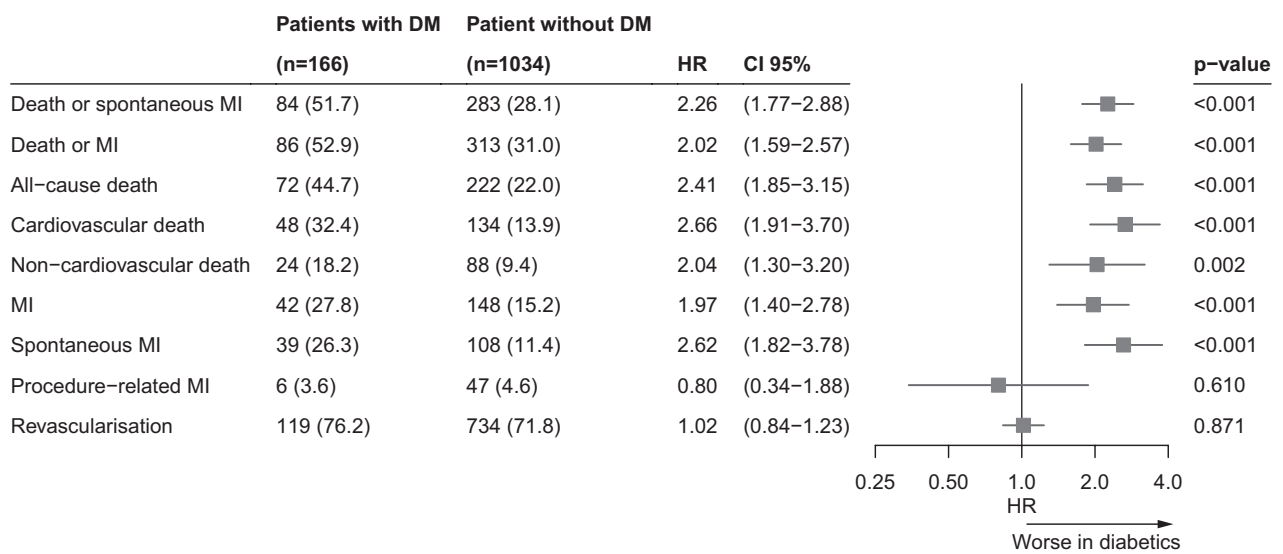
At baseline 166 patients (14%) were known with DM, of which 86 were randomised to an early invasive and 80 to a selective invasive strategy. Baseline characteristics were

evenly distributed between patients in the early or selective invasive groups, regardless of the presence of DM. However, diabetic patients in the early invasive group were older compared to the selective invasive group [69.0 years; interquartile range (IQR): 60.8–74.0 vs. 65.5 years; IQR: 55.3–72.0; $P = 0.025$]. Diabetic patients had higher rates prior MI (31% vs. 22%), hypertension (57% vs. 36%), ST-segment deviation (55% vs. 47%), and three-vessel and/or left main coronary artery disease (31% vs. 14%).

In-hospital angiography (75% vs. 77%, $P = 0.77$) and revascularisation (56% vs. 58%, $P = 0.60$) were similar in patients with and without DM. Among diabetic patients, in-hospital angiography was performed in 97.7% in the early invasive group and 53.8% in the selective invasive group ($P > 0.001$). In-hospital revascularisation among patients with DM was 70.9% and 40.0% in the early and selective invasive groups respectively ($P < 0.001$). Most diabetics patients were treated with percutaneous coronary intervention (early: 52.3% vs. selective: 30.0%; $P = 0.004$). In-hospital coronary artery bypass grafting performance in diabetic patients was not significantly different between the two groups (early: 18.6% vs. selective: 10.0%; 0.115).

Patients with DM had worse 10-year clinical outcomes compared to patients without DM, as is displayed in Fig. 1. Death or spontaneous MI at 10-year was significantly higher in diabetic patients (51.7%) vs. non-diabetic patients (28.1%) [hazard ratio (HR): 2.26; 95% confidence interval (CI): 1.77–2.88; $P < 0.001$]. All other events also were significantly higher among diabetic patients, with the exception of first revascularisation and procedure-related MI. Among patients with DM, 10-year death or spontaneous MI was 58.5% in the early invasive group and 44.4% in the selective invasive group (HR: 1.44; 95% CI: 0.93–2.22; $P = 0.101$) (Table 1). There were no significant differences

Fig. 1



Ten-year clinical outcomes of non-ST-segment elevation acute coronary syndrome patients with or without DM. CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction.

Table 1 Kaplan–Meier estimates of 10-year clinical outcomes in non-ST-segment elevation acute coronary syndrome patients with or without diabetes mellitus

	Patients with diabetes mellitus (n = 166)				Patients without diabetes mellitus (n = 1034)				Interaction P value
	EIS (n = 86)	SIS (n = 80)	Hazard ratio (95% CI)	P value	EIS (n = 518)	SIS (n = 516)	Hazard ratio (95% CI)	P value	
Death or spontaneous MI	49 (58.5)	35 (44.4)	1.44 (0.93–2.22)	0.101	150 (29.7)	133 (26.6)	1.12 (0.89–1.42)	0.328	0.316
Death or MI	50 (59.6)	36 (45.7)	1.46 (0.95–2.25)	0.081	172 (34.0)	141 (28.1)	1.26 (1.01–1.58)	0.041	0.561
All-cause death	42 (51.4)	30 (37.8)	1.50 (0.94–2.39)	0.093	114 (22.6)	108 (21.4)	1.06 (0.82–1.38)	0.664	0.202
Cardiovascular death	26 (36.9)	22 (28.8)	1.26 (0.71–2.22)	0.428	71 (14.8)	63 (13.0)	1.13 (0.81–1.59)	0.475	0.741
Non-cardiovascular death	16 (23.1)	8 (12.7)	2.15 (0.92–5.02)	0.078	43 (9.2)	45 (9.7)	0.96 (0.63–1.46)	0.849	0.093
MI	21 (27.0)	21 (28.1)	1.01 (0.55–1.84)	0.982	85 (17.6)	63 (12.9)	1.39 (1.00–1.93)	0.047	0.362
Spontaneous MI	19 (25.7)	20 (26.8)	0.94 (0.50–1.76)	0.839	56 (11.9)	52 (10.8)	1.07 (0.74–1.56)	0.716	0.747
Procedure-related MI	5 (5.8)	1 (1.3)	4.79 (0.56–41.03)	0.153	34 (6.6)	13 (2.5)	2.67 (1.41–5.07)	0.003	0.610
Revascularisation	68 (83.8)	51 (68.2)	2.12 (1.47–3.07)	<0.001	428 (83.2)	306 (60.4)	2.62 (2.26–3.04)	<0.001	0.261

CI, confidence interval; EIS = early invasive strategy; MI, myocardial infarction; SIS, selective invasive strategy.

in other outcome measures in diabetic patients treated with an early or selective invasive strategy, except for a higher rate of revascularisation in the early invasive group [83.8% vs. 68.2% (HR: 2.12; 95% CI: 1.47–3.07; $P < 0.001$)]. There was no significant interaction between the presence of DM and treatment strategy for any of the study outcomes.

In a Cox proportional hazards model that adjusted for age, there was no significant difference in death or spontaneous MI at 10 years between diabetic patients treated with an early or selective invasive strategy (HR: 1.13; 95% CI: 0.72–1.75; $P = 0.603$). Adjustment for age >65 years (HR: 1.24; 95% CI: 0.80–1.92; $P = 0.346$) or age >70 year demonstrated similar results (HR: 1.18; 95% CI: 0.76–1.84; $P = 0.463$).

In this analysis of high-risk NSTEMI-ACS patients with elevated cardiac troponin, patients with DM had worse

10-year outcomes compared to patients without DM. We could not demonstrate a statistically significant difference in 10-year death or spontaneous MI between the two strategies. This finding remained unchanged after adjustment for age. Our findings remain limited due to the small sample size, with only 166 diabetic patients. We did not record insulin-dependency of DM patients in our study and did not collect information on the development of DM during follow-up. Contemporary improvements such as drug-eluting stents, potent P2Y12 inhibitors, and radial access were not in use at the time of inclusion. Our findings illustrate the continuing long-term adverse effect of DM in NSTEMI-ACS. Although observed in other studies, non-cardiovascular death was also increased by two-fold in diabetics, suggesting unidentified confounding. Research to identify and improve treatment strategies for diabetic NSTEMI-ACS patients are warranted.

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Conflicts of interest

There are no conflicts of interest.

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