Comparison of Acute Versus Subacute Coronary Angiography in Patients With NON-ST-Elevation Myocardial Infarction (from the NONSTEMI Trial)

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The optimal timing of coronary angiography (CAG) in high-risk patients with acute coronary syndrome without persisting ST-segment elevation (NST-ACS) remains undetermined. The NON-ST-Elevation Myocardial Infarction trial aimed to compare outcomes in NSTE-ACS patients randomized to acute CAG (STEMI-like approach) with patients randomized to medical therapy and subacute CAG. We randomized 496 patients with suspected NST-ACS based on symptoms and significant regional ST depressions and/or elevated point-of-care troponin T (POC-cTnT) (≥50 ng/l) to either acute CAG (<2 hours, n = 245) or subacute CAG (<72 hours, n = 251). The primary end point was a composite of all-cause death, reinfarction, and readmission with congestive heart failure within 1 year from randomization. A final acute coronary syndrome (ACS) diagnosis was assigned to 429 (86.5%) patients. The median time from randomization to revascularization was 1.3 hours in the acute CAG group versus 51.1 hours in the subacute CAG group (p <0.001). The composite end point occurred in 25 patients (10.2%) in the acute CAG group and 29 (11.6%) in the subacute CAG group, p = 0.62. The acute CAG group had a 1-year all-cause mortality of 5.7% compared with 5.6% in the subacute CAG group, p = 0.96. In conclusion, neither the composite end point of all-cause death, reinfarction, and readmission with congestive heart failure nor mortality differed between an acute and subacute CAG approach in NSTE-ACS patients. However, identification of NSTE-ACS patients in the prehospital phase and direct triage to an invasive center is feasible, safe and may facilitate early diagnosis and revascularization. **(Am J Cardiol 2019;124:825−832)**

Current guidelines from the European Society of Cardiology (ESC) 2015[1] and the American Heart Association/American College of Cardiology 2014[2] on the management of patients with acute coronary syndrome without ST-elevations (NSTE-ACS) recommend coronary angiography (CAG) within 24 hours in high-risk patients. It remains unknown whether high-risk patients with NSTE-ACS benefit from an ST-elevation myocardial infarction (STEMI)-like management pathway that includes prehospital diagnosis, triage directly to an invasive center, and acute CAG followed by primary percutaneous coronary intervention, if indicated. The acute versus subacute angioplasty in patients with NON-ST-Elevation Myocardial Infarction (NONSTEMI) trial (clinicaltrials.gov: NCT01638806) was a randomized, open-labeled, 2-center study that compared a STEMI-like management pathway with the routine standard of care according to current guidelines for NSTE-ACS patients.[1,2] We analyzed phase 1 of the trial after inclusion of 250 patients and found that it was feasible to diagnose patients with NSTE-ACS in the prehospital phase or immediately upon hospital arrival.[3] The aim of the present phase 2 and 3 of the trial was to investigate whether a STEMI-like pathway with acute CAG improved the outcome with regard to a composite

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end point comprising death of all-cause, reinfarction, and readmission with congestive heart failure (CHF) within 1 year from randomization.

Methods

The design of the NONSTEMI trial and the primary results from phase 1 describing the first 250 patients have been reported previously.[3] In short, patients were eligible for enrolment when they presented with ongoing chest pain and either significant ST-segment depressions in the electrocardiogram (ECG) or elevated point-of-care cardiac troponin T (POC-cTnT) (≥50 ng/l) in the prehospital phase or immediately upon hospital admission. Patients were randomized to either acute CAG within 2 hours (subsequently referred to as "acute CAG group") or medical treatment and subacute CAG within 72 hours (<24 hours if their Global Registry of Acute Coronary Events score >140) according to ESC guidelines (subsequently referred to as the "subacute CAG group").[1] Although inclusion was ongoing, a software upgrade of the Cobas h232 instrument of 1 December 2015 lowered the detection limit to 40 ng/l which from that point onward was considered elevated. An independent event committee (see acknowledgments) had full access to the individual patient files and adjudicated the end points at 3 months and at the 12-month follow-up.

The primary end point was all-cause mortality and a composite end point of all-cause mortality, reinfarction or readmission with CHF within 1 year from randomization. The secondary end point comprised several elements: readmission with angina pectoris, readmission with stroke, nonscheduled reintervention, and bleeding within 1 year from randomization. Furthermore, the secondary end point included the rate and choice of revascularization, time from randomization to CAG and intervention, time to intervention, and total admission time during the index admission.

We estimated the 1-year all-cause mortality in NSTEMI patients to 10%. Assuming an absolute reduction in all-cause mortality of 2.5% with an alpha of 0.05 and a power of 80%, we calculated that 2,000 patients were needed in each group to compare mortality. Given an estimated risk of the composite end point (all-cause mortality, reinfarction or readmission with CHF) of 15% within 1 year, we calculated the number of patients required to document a 4% reduction in the composite end point to be 1,109 patients in each group. To document a 1.5-day reduction in length of stay (LOS), we calculated the number of patients required in each group to be 63.

Each of the 3 phases was dimensioned as follows: Phase 1 was based on the first 250 patients and aimed to determine if a sufficient number of enrolled patients had a final diagnosis of ACS, which would qualify for continuation of the study. The results from phase 1 were published in 2016.[3] Phase 2 was based on the first 2,500 patients and aimed to compare the composite endpoint (all-cause mortality, reinfarction or readmission with CHF) at 12 months from randomization. Phase 3 was based on 4,500 patients and aimed to compare mortality. The study was initiated in June 2012. Because the recruitment rate was lower than expected, the trial was terminated prematurely by the study steering committee, due to futility, in March 2016 after inclusion of 500 patients. The present paper reports the end points planned for phases 2 and 3.

The trial was performed in accordance with the Helsinki Declaration. The protocol was approved by the local ethics committee (Central Denmark Regional Ethical Committee) and the Danish Data Protection Agency. The trial is registered with ClinicalTrials.gov: NCT01638806. Data were analyzed by the intention-to-treat principle. Categorical data are presented as absolute numbers (percentages) and continuous variables are presented as medians with interquartile ranges. Differences between the groups were compared using the chi-squared test, the Wilcoxon rank-sum test, and the Kruskal-Wallis test as appropriate. We computed unadjusted Kaplan-Meier curves based on time-to-event (all-cause death and the composite event). The comparison was made using log-rank statistics. Tests were considered statistically significant if p values were below 0.05 (2-sided test). The statistical analyses were performed by MBR, CJT, and CS using Stata 13.1 (Stata Corporation, College Station, Texas).

Results

Of the 500 patients enrolled in the NONSTEMI trial, 247 were assigned to the acute CAG group and 253 to the subacute CAG group. The patient flow is shown in Figure 1. Baseline characteristics and medical treatment preadmission and during hospitalization did not differ between the 2 groups (Table 1). The majority of patients had an elevated POC-cTnT value at the time of enrolment as shown in Table 2. The final diagnosis confirmed by the Endpoint Committee is listed in Table 2. ACS was confirmed in 429 (87%) cases and a total of 332 (67%) patients had Non-ST-Elevation Myocardial Infarction (NSTEMI). Among the subacute CAG group, 42 (17%) had their CAG performed earlier than initially scheduled due to an unstable cardiovascular condition (Figure 1).

The angiography details and treatment of culprit lesion are listed in Table 3. A larger proportion of patients in the acute CAG group than in the subacute CAG group had a CAG performed. A culprit lesion was identified in 348 (70%) cases with a nonsignificant difference between the 2 groups, but a larger proportion of patients with a culprit lesion in the acute CAG group had TIMI flow 0. We found no significant difference in choice of treatment of culprit lesions between the 2 groups (Table 3). The median time from randomization to the first revascularization was 1.3 hours in the acute CAG group and 51.1 hours in the subacute CAG group (Table 4). Patients in the acute CAG group had a median time from randomization to discharge of 3.8 days compared with 4.2 days for patients in the subacute CAG group.

The primary and secondary end points after 12 months follow-up are shown in Table 5. All differences were nonsignificant. We found no difference in all-cause mortality and cumulative incidence of the composite end point as shown in Figure 2.

Discussion

The NONSTEMI trial is the first randomized controlled trial to compare a STEMI-like management pathway with conventional therapy in NSTE-ACS patients. It is also the first trial with prehospital or immediate hospital arrival

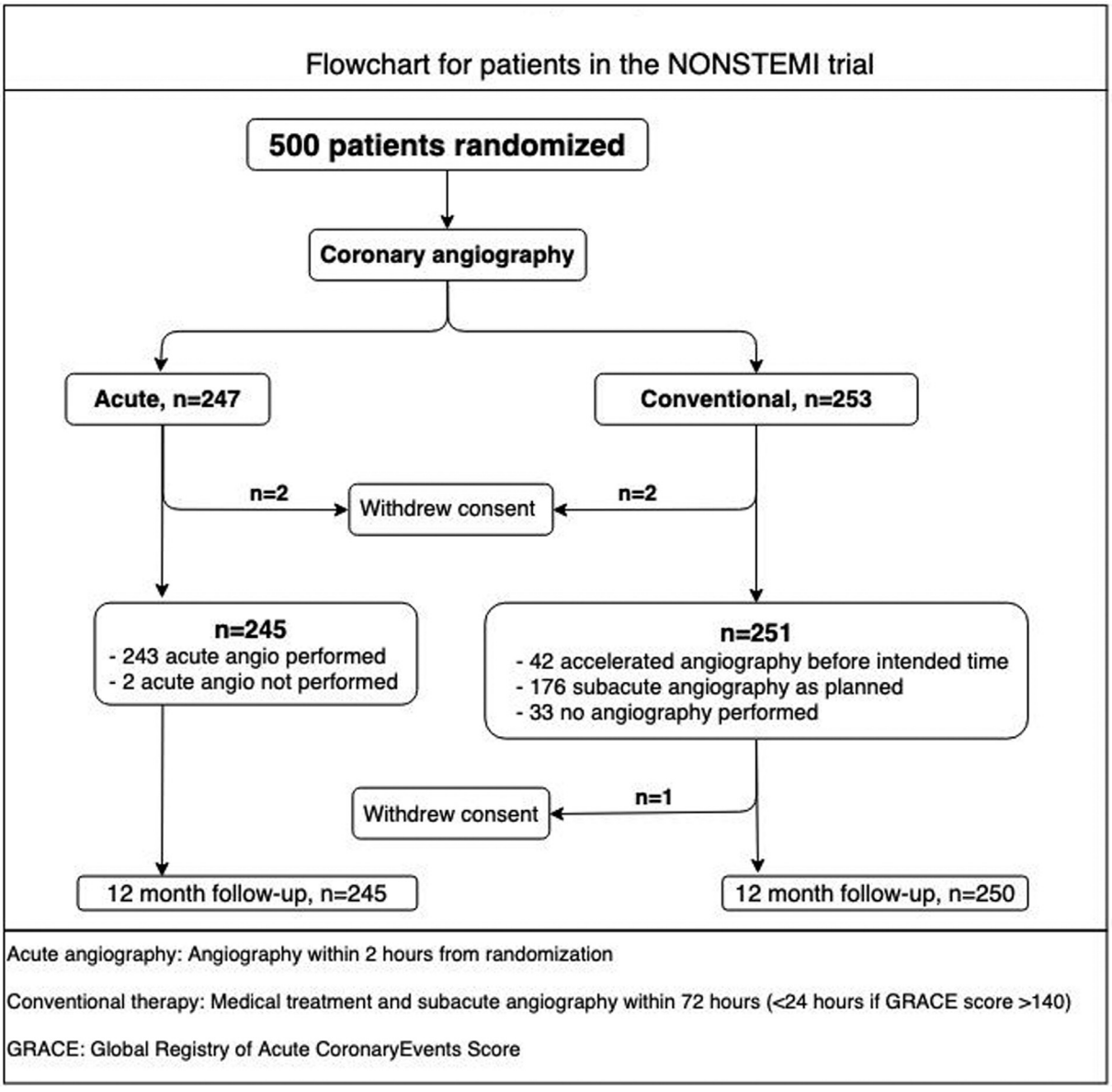

Figure 1. Flowchart for patients in the NONSTEMI trial.
Acute angiography: Angiography within 2 hours from randomization.
Conventional therapy: Medical treatment and subacute angiography within 72 hours (<24 hours if GRACE score >140). GRACE = Global Registry of Acute Coronary Events Score.

enrolment utilizing a combination of ECG and/or POC-cTn measurement. The ESC and American Heart Association/American College of Cardiology guidelines on the management of NSTE-ACS patients[1,2] recommend an immediate invasive strategy (<2 hours) in very high-risk NSTE-ACS patients, an early invasive strategy (<24 hours) in high-risk NSTE-ACS patients, and a selective invasive strategy (24 to 72 hours) for all other NSTE-ACS patients. The present study compared a STEMI-like management pathway with the guideline-recommended strategy, that is, with patients in the conventional group scheduled for CAG within 48 to 72 hours in general, but within 24 hours if their Global Registry of Acute Coronary Events score was >140.

We found no difference in overall 1-year mortality between the 2 groups (Figure 2). However, because the termination of the study was premature, it was not powered to detect a difference in mortality. In addition, the overall mortality in both groups was lower than expected, likely because our cohort comprised younger patients compared with all-comers with NSTE-ACS (Table 1). However, the median age and observed mortality are comparable to those of patients with NSTE-ACS having PCI performed in Denmark, and comparable to levels reported in previous randomized trials.[4–6]

The STEMI-like management of NSTE-ACS patients increased the rate of CAG. Some of the enrolled NSTE-ACS patients would have avoided the CAG if they had been admitted to the nearest hospital for further examination. However, even though the STEMI-like approach implied pretreatment with anticoagulants, the STEMI-like

Table 1
Baseline characteristics and medication

Variable	Valid cases 496	Coronary angiography	
		Acute (n = 245)	Conventional (n = 251)
Age (years)	496	65.4 (57.3-71.9)	65.9 (58.3-73.0)
Men	496	166 (67.8%)	165 (65.7%)
Body mass index (Kg/m^2)	492	26.2 (24.2-29.5)	26.9 (24.2-30.0)
Risk factors			
Diabetes mellitus	490	36 (14.7%)	41 (16.7%)
Smokers	495	174 (71.0%)	192 (76.8%)
Hypertension	495	105 (42.9%)	123 (49.2%)
Previous acute myocardial infarction	496	30 (12.2%)	30 (12.0%)
Previous revascularization	496	35 (14.3%)	34 (13.4%)
Previous heart failure	495	15 (6.2%)	16 (6.4%)
At admission:			
Symptom duration (hours)	420	3.5 (1.9-6.3)	3.8 (1.6-7.6)
Heart rate (beats/min)	496	82 (70-96)	84 (72-97)
Systolic blood pressure (mm Hg)	496	148 (130-167)	154 (130-171)
Medical treatment preadmission or during hospitalization			
Aspirin	490	219 (89.4%)	239 (94.4%)
ADP receptor blocker	490	208 (84.9%)	224 (89.2%)
Clopidogrel	490	28 (11.4%)	31 (12.4%)
Ticagrelor	490	181 (73.9%)	197 (78.5%)
Fondaparinux/LMWH	490	7 (2.9%)	192 (76.5%)
Unfractionated heparin	489	210 (85.7%)	124 (49.4%)
Abciximab	490	4 (1.6%)	2 (0.8%)
Bivalirudin	492	104 (42.5%)	33 (13.2%)

Values are median (interquartile range) or n (%).

Table 2
Inclusion details, biochemical details, and final diagnosis

Variable	Valid cases	Coronary angiography		Total	p Value
		Acute (n = 245)	Conventional (n = 251)		
Inclusion criteria	496				0.83
Only ST-segment depression		72 (29.4%)	70 (27.9%)	142 (28.6%)	
Only POC-cTnT ≥50 ng/L*		131 (53.5%)	133 (53.0%)	264 (53.2%)	
ST-segment depression + POC-cTnT ≥50 ng/L*		42 (17.1%)	48 (19.1%)	90 (18.1%)	
In-hospital biochemical values on admission					
Creatinine (μmol/L)	496	74 (62-88)	81 (64-96)		0.002
Troponin I (ng/L)	87	627 (169-2,292)	379 (47-2,010)		0.44
Troponin T (ng/L)	409	119 (45-314)	128 (55-337)		0.64
Prehospital biochemical data					
POC-cTnT measured	496	194 (79.2%)	203 (80.9%)		0.64
Above detection limit (≥40 ng/L/≥50 ng/L)*	496	171 (69.8%)	179 (71.3%)		0.99
Final diagnosis	496				0.27
Acute coronary syndrome		213 (86.9%)	216 (86.1%)	429 (86.5%)	
NSTEMI		171 (69.8%)	161 (64.1%)	332 (66.9%)	
STEMI		22 (9.0%)	25 (10.0%)	47 (9.5%)	
STEMI, visible at inclusion		20 (8.2%)	18 (7.2%)	38 (7.7%)	
STEMI after inclusion		2 (0.8%)	7 (2.8%)	9 (1.8%)	
Bundle branch block myocardial infarction		2 (0.8%)	3 (1.2%)	5 (1.0%)	
Unstable angina pectoris		18 (7.4%)	27 (10.8%)	45 (9.1%)	
Myocardial injury		20 (8.2%)	21 (8.4%)	41 (8.3%)	
Other		12 (4.9%)	14 (5.6%)	26 (5.2%)	

POC-cTnT: Point-of-care cardiac troponin T.
NSTEMI = Non-ST-segment elevation myocardial infarction; STD = ST-segment depression; STEMI = ST-segment elevation myocardial infarction.
* The detection limit in the Cobas h232 instrument was 50 ng/L in the period from June 2012 to November 2015. A software upgrade in the Cobas h232 instrument, performed 01.12.15, subsequently lowered the detection limit to 40 ng/L.

management approach did not seem to increase the risk of major adverse cardiovascular (Figure 2) or bleeding events within the first year (Table 5). Conversely, we observed a trend toward a lower rate of major adverse cardiovascular events within the first 30 days (Figure 2). However, the results from the NONSTEMI trial do not differ from those reported by other studies comparing acute CAG (<2 hours) with delayed CAG (8 to 72 hours).[4,7,8] Two exclusion

Table 3
Angiography, coronary lesions, and revascularization

Variable	Acute (n = 245)	Coronary angiography		p Value
		Conventional (n = 251)	Total (n = 496)	
Angiography performed	243/245 (99.2%)	218/251 (86.9%)	461/496 (92.9%)	<0.001
Coronary artery narrowed:				
Left main	15/243 (6.2%)	14/218 (6.4%)	29/461 (6.3%)	0.91
Left anterior descending	125/243 (51.4%)	129/218 (59.2%)	254/461 (55.4%)	0.096
Ramus	94/243 (38.7%)	102/218 (46.8%)	196/461 (42.5%)	0.079
Right	88/243 (36.2%)	99/218 (45.4%)	187/461 (40.6%)	0.045
Number of narrowed coronary arteries:				0.0098
None	61/243 (25.1%)	34/218 (15.6%)	95/461 (20.6%)	
1	81/243 (33.3%)	80/218 (36.7%)	161/461 (34.9%)	
2	67/243 (27.6%)	52/218 (23.9%)	119/461 (25.8%)	
3	34/243 (14.0%)	52/218 (23.9%)	85/461 (18.7%)	
Culprit lesion identified	169/245 (69.0%)	179/251 (71.3%)	348/461 (70.2%)	0.57
Location of culprit lesion				0.74
Left main	7/169 (4.1%)	7/179 (3.9%)	14/348 (4.0%)	
Left anterior descending	65/169 (38.5%)	74/179 (41.3%)	139/348 (39.9%)	
Ramus	56/169 (33.1%)	55/179 (30.7%)	111/348 (31.9%)	
Right	41/169 (24.3%)	43/179 (24.0%)	84/348 (24.1%)	
TIMI flow in culprit lesion before revascularization				0.009
0	53/169 (31.4%)	33/179 (18.4%)	86/348 (24.7%)	
1	11/169 (6.5%)	13/179 (7.3%)	24/348 (6.9%)	
2	14/169 (8.3%)	15/179 (8.4%)	29/348 (8.3%)	
3	91/169 (53.9%)	118/179 (65.9%)	209/348 (60.1%)	
Treatment of culprit lesion				0.23
PCI	124/169 (73.4%)	122/179 (68.2%)	246/348 (70.7%)	
CABG	21/169 (12.4%)	36/179 (20.1%)	57/348 (16.4%)	
Hybrid (CABG+PCI)	10/169 (5.9%)	8/179 (4.5%)	18/348 (5.2%)	
Medical treatment recommended	14/169 (8.3%)	13/179 (7.3%)	27/348 (7.8%)	

Values are n/N (%).
CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.

Table 4
Timing data

	Valid cases	Coronary angiography		p Value
		Acute (n = 245)	Conventional (n = 251)	
EMS call to randomization, h	464	0.9 (0.6-1.1)	0.8 (0.7-1.1)	0.6
Ambulance arrival to randomization, h	451	0.7 (0.5-1.0)	0.7 (0.5-0.9)	0.4
Randomization to angiography, h	460	1.0 (0.8-1.4)	47.8 (25.8-67.1)	<0.001
Randomization to first revascularization, h	320	1.3 (0.9-2.1)	51.1 (25.5-86.4)	<0.001
Randomization to discharge, days	477	3.8 (2.7-5.0)	4.2 (3.2-5.3)	<0.001
Patients with ACS	411	3.8 (2.8-4.9)	4.4 (3.63-5.4)	<0.001
Patients with AMI	369	3.9 (2.9-5.0)	4.4 (3.70-5.4)	<0.001
Revascularized patients	311	4.0 (3.0-5.0)	4.6 (3.8-6.0)	<0.001
Revascularized with PCI only	244	3.8 (3.0-4.3)	4.3 (3.7-5.1)	<0.001
Symptom onset to revascularization	270	6.5 (3.6-13.9)	58.3 (29.6-94.5)	<0.001
		Place of inclusion		
		Ambulance (n = 292)	Hospital (n = 204)	
EMS call to randomization, h	464	0.8 (0.6-1.0)	1.2 (0.7-1.5)	<0.001
Ambulance arrival to randomization, h	451	0.7 (0.5-0.8)	1.0 (0.6-1.3)	<0.001
Randomization to angiography, acute angiography group, h	243	1.0 (0.8-1.2)	1.3 (0.8-1.8)	<0.001
Randomization to angiography, conventional therapy group, h	217	49.1 (28.7-67.7)	45.7 (22.2-65.3)	0.1

Values are median (interquartile range).
ACS = acute coronary syndrome; AMI = acute myocardial infarction; EMS = emergency medical system; PCI = percutaneous coronary intervention.

Table 5
Clinical events up to 12 months

Variable	Coronary angiography		Total	p Value
	Acute (n = 245)	Conventional (n = 250)		
Events within 12 months				
Composite endpoint	25 (10.2%)	29 (11.6%)	54 (10.9%)	0.62
Death (all-cause)	14 (5.7%)	14 (5.6%)	28 (5.6%)	0.96
Reinfarction or recurrent MI	7 (2.9%)	10 (4.0%)	17 (3.4%)	0.49
Readmission with CHF	7 (2.9%)	12 (4.8%)	19 (3.8%)	0.26
Readmission with stable AP	12 (4.8%)	11 (4.5%)	23 (4.6%)	0.87
Readmission with unstable AP	7 (2.9%)	9 (3.6%)	16 (3.2%)	0.64
Readmission with stroke	4 (1.6%)	5 (2.0%)	9 (1.8%)	0.76
Nonscheduled reintervention				
PCI	1 (0.4%)	8 (3.2%)	9 (1.8%)	0.02
CABG	2 (0.8%)	2 (0.8%)	4 (0.8%)	0.98
Bleeding				
Major bleeding (BARC 3a/3b)	8 (3.3%)	8 (3.2%)	16 (3.2%)	0.97
Life-threatening (BARC 5)	4 (1.6%)	4 (1.6%)	8 (1.6%)	0.98

BARC = The Bleeding Academic Research Consortium; CABG = coronary artery bypass grafting; CHF = congestive heart failure; MACE: Death, AMI, CHF; MI = myocardial infarction; PCI = percutaneous coronary intervention.

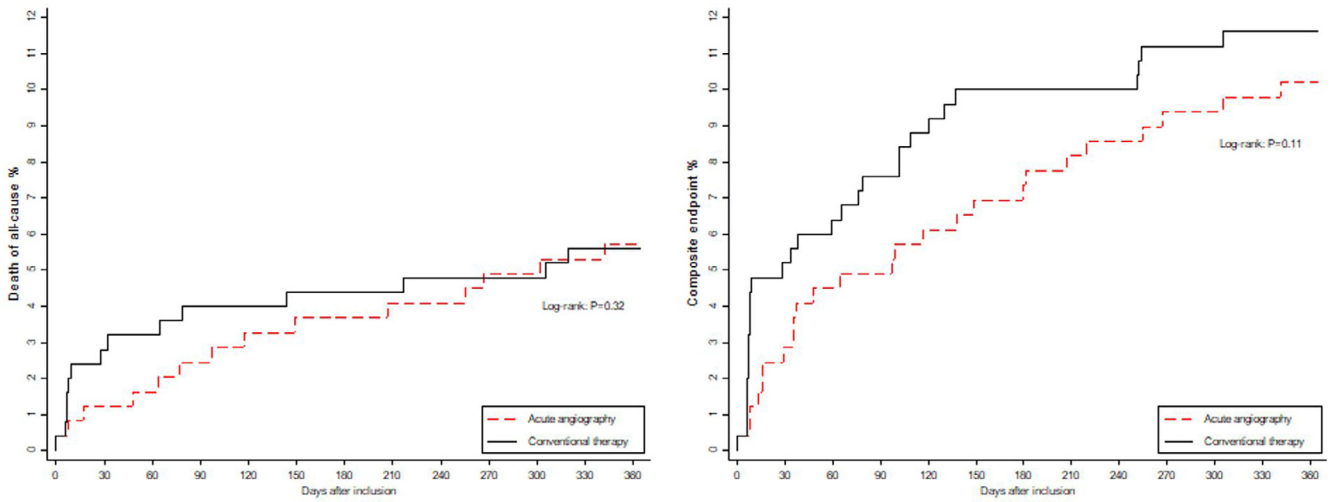

Figure 2. All-cause mortality and cumulative incidence of the composite endpoint; death, reinfarction and readmission with congestive heart failure.
Acute angiography: Angiography within 2 hours from randomization.
Conventional therapy: Medical treatment and subacute angiography within 72 hours (<24 hours if GRACE score >140). GRACE = Global Registry of Acute Coronary Events Score

criteria in our study were previous CABG and age >80 years. This is important because data suggest that NSTE-ACS patients aged 80 years or older gain more from an invasive than from a conservative strategy.[4,7–10] In a recently published meta-analysis,[11] Jobs et al compared 8 randomized controlled trials which all investigated an early versus a delayed invasive strategy in patients presenting with NSTE-ACS. They found no significant reduction in mortality with the early (1 to 14 hours) compared with the delayed invasive strategy (18 to 87 hours). In subgroup analyses, however, they found that subacute CAG as associated with a lower mortality in patients with elevated cardiac biomarker and high-risk NSTE-ACS patients overall.

One intriguing observation from the NONSTEMI trial is that 42 (16.7%) patients in the subacute CAG group developed an unstable cardiovascular condition and had an accelerated CAG performed earlier than scheduled, thus crossing over. This is in line with the Comparison of Two Treatment Strategies in Patients With an Acute Coronary Syndrome Without ST Elevation trial[5] that compared an early invasive strategy (<6 hours) with a delayed strategy (6 to 48 hours) and found that 21 patients (24%) in the delayed group had their CAG accelerated due to an unstable condition. The Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients study even included reinfarction in the period before catheterization as a component in the primary end point and found that a total of 10 (6.7%) patients had a reinfarction and 1 patient died within 72 hours while awaiting CAG.[7]

It is frequently argued that POC-cTn is irrelevant in the high-sensitivity era due to the limitations in detecting the subtle changes at levels near the 99th percentile upper reference limit. Although this is true for the final diagnosis, it

may be different when it comes to risk prediction and, thus, rule-in for an accelerated invasive strategy. The higher detection limit of POC-cTn compared with high-sensitivity troponin (hs-cTn) may be used confidently in prehospital risk-stratification of NSTEMI patients. It allows for identification of patients with the highest risk already in the prehospital phase or immediately after admission.[3,12,13] Moreover, an elevated POC-cTn falls in the same category as the 52 ng/l rule-in cut point applied in the ESC 0 h/1 h algorithm, implicating that an elevated prehospital or immediate POC-cTn should prompt rerouting either directly to the coronary care unit or even straight to an invasive center for accelerated CAG, as advocated by the ESC and the American Heart Association/American College of Cardiology.[1,2] This correlates well with a more aggressive invasive examination strategy in patients with the highest risk.

One additional property of a STEMI-like management pathway in patients with NSTEMI is its potential to substantially reduce the patient's LOS in hospital. The average time from randomization to discharge in the acute CAG group was 3.8 days compared with 4.2 days ($p < 0.001$) in the subacute CAG group (Table 5). This time reduction may appear very small, but with an observed difference in time from randomization to revascularization in our 2 groups of 49.8 hours, there is potential for further reduction in LOS in the acute CAG group if all patients were discharged within 24 hours after CAG as supported by the latest guidelines.[1]

Even though it was an exclusion criterion that percutaneous coronary intervention was already indicated at the time of assessing eligibility for the NONSTEMI trial, our cohort consisted of 47 patients (9.5%) with a STEMI diagnosis adjudicated by the Endpoint Committee. This could be interpreted as a limitation and an uncertainty in the setup. However, 9 (1.8%) developed STEMI after inclusion, and ECG changes in ACS can be equivocal. It can be challenging to establish a STEMI diagnosis in patients with borderline ST-segment elevations or bundle branch block. The physician on call assessed all patients in our cohort for signs of STEMI utilizing the prehospital ECG and the patient's history recorded over the phone. Cases with suspected STEMI were triaged directly to an invasive center without considering enrolment in the NONSTEMI trial. Thus, the 38 patients who, according to the Endpoint Committee, showed signs of STEMI at inclusion were not considered to have ST elevations by the attending physician. Had it not been for the POC-cTn, these patients would have been missed. POC-cTn can undoubtedly serve as a valuable aid in these situations by detecting high-risk patients with ECGs without significant ST changes or an equivocal ECG.

The NONSTEMI trial does not document a mortality benefit by performing acute CAG in patients with NSTE-ACS and documents no increase in major adverse cardiovascular events. The study does confirm the feasibility of prehospital diagnosis in NSTE-ACS patients, which may be used to triage these patients directly to an invasive center to facilitate earlier revascularization and earlier discharge.

Disclaimer

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Disclosures

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1. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol C, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J, Management of Acute Coronary Syndromes in Patients Presenting without Persistent STSEotESoC. 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, Casey DE Jr., Ganiats TG, Holmes DR Jr., Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ. 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–e228.
3. Stengaard C, Sorensen JT, Rasmussen MB, Sondergaard HM, Dodt KK, Niemann T, Frost L, Jensen T, Hansen TM, Riddervold IS, Rasmussen CH, Giebner M, Aaroe J, Maeng M, Christiansen EH, Kristensen SD, Botker HE, Terkelsen CJ. Editor's Choice-Acute versus subacute angiography in patients with non-ST-elevation myocardial infarction - the NONSTEMI trial phase I. *Eur Heart J Acute Cardiovasc Care* 2017;6:490–499.
4. Thiele H, Rach J, Klein N, Pfeiffer D, Hartmann A, Hambrecht R, Sick P, Eitel I, Desch S, Schuler G, Group L-NT. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI Trial). *Eur Heart J* 2012;33:2035–2043.

5. Reuter PG, Rouchy C, Cattan S, Benamer H, Jullien T, Beruben A, Montely JM, Assez N, Raphael V, Hennequin B, Boccara A, Javaud N, Soulat L, Adnet F, Lapostolle F. Early invasive strategy in high-risk acute coronary syndrome without ST-segment elevation. The Sisca randomized trial. *Int J Cardiol* 2015;182:414–418.
6. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, Afzal R, Chrolavicius S, Jolly SS, Widimsky P, Avezum A, Rupprecht HJ, Zhu J, Col J, Natarajan MK, Horsman C, Fox KA, Yusuf S, Investigators T. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009;360:2165–2175.
7. Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, Marinkovic J, Vukcevic V, Stefanovic B, Asanin M, Dikic M, Stankovic S, Stankovic G. Immediate versus delayed invasive intervention for Non-STEMI Patients: the RIDDLE-NSTEMI Study. *JACC Cardiovasc Interv* 2016;9:541–549.
8. Montalescot G, Cayla G, Collet JP, Elhadad S, Beygui F, Le Breton H, Choussat R, Leclercq F, Silvain J, Duclos F, Aout M, Dubois-Rande JL, Barthelemy O, Ducrocq G, Bellemain-Appaix A, Payot L, Steg PG, Henry P, Spaulding C, Vicaut E, Investigators A. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. *JAMA* 2009;302:947–954.
9. Tegn N, Abdelnoor M, Aaberge L, Endresen K, Smith P, Aakhus S, Gjertsen E, Dahl-Hofseth O, Ranhoff AH, Gullestad L, Bendz B, After Eighty study i. 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 (London, England)* 2016;387:1057–1065.
10. Gierlotka M, Gasior M, Tajstra M, Hawranek M, Osadnik T, Wilczek K, Kalarus Z, Lekston A, Zembala M, Polonski L. Outcomes of invasive treatment in very elderly Polish patients with non-ST-segment-elevation myocardial infarction from 2003-2009 (from the PL-ACS registry). *Cardiol J* 2013;20:34–43.
11. Jobs A, Mehta SR, Montalescot G, Vicaut E, Van't Hof AWJ, Badings EA, Neumann FJ, Kastrati A, Sciahbasi A, Reuter PG, Lapostolle F, Milosevic A, Stankovic G, Milasinovic D, Vonthein R, Desch S, Thiele H. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. *Lancet (London, England)* 2017;390:737–746.
12. Stengaard C, Sorensen JT, Ladefoged SA, Christensen EF, Lassen JF, Botker HE, Terkelsen CJ, Thygesen K. Quantitative point-of-care troponin T measurement for diagnosis and prognosis in patients with a suspected acute myocardial infarction. *Am J Cardiol* 2013;112:1361–1366.
13. Rasmussen MB, Stengaard C, Sorensen JT, Riddervold IS, Hansen TM, Giebner M, Rasmussen CH, Botker HE, Terkelsen CJ. Predictive value of routine point-of-care cardiac troponin T measurement for prehospital diagnosis and risk-stratification in patients with suspected acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2017;8:299–308.