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Early Versus Standard Care Invasive Examination and Treatment of Patients with Non-ST-Segment Elevation Acute Coronary Syndrome: The VERDICT (Very EaRly vs Deferred Invasive evaluation using Computerized Tomography) – Randomized Controlled Trial

Running Title: *Kofoed et al.; Early Invasive Strategy in Acute Coronary Syndrome*

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Abstract

Background: The optimal timing of invasive coronary angiography (ICA) and revascularization in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is not well defined. We tested the hypothesis, that a strategy of very early invasive coronary angiography (ICA) and possible revascularization within 12 hours of diagnosis, is superior to an invasive strategy performed within 48-72 hours in terms of clinical outcomes.
Methods: Patients admitted with clinical suspicion of NSTE-ACS in the Capital Region of Copenhagen, Denmark were screened for inclusion in the VERDICT trial (ClinicalTrials.gov NCT02061891). Patients with ECG changes indicating new ischemia and/or elevated troponin, in whom ICA was clinically indicated and deemed logistically feasible within 12 hours, were randomized 1:1 to ICA within 12 hours or standard invasive care within 48-72 hours. The primary endpoint was a combination of all-cause death, non-fatal recurrent myocardial infarction, hospital admission for refractory myocardial ischemia or hospital admission for heart failure.
Results: A total of 2147 patients were randomized; 1075 patients allocated to very early invasive evaluation had ICA performed at a median of 4.7 hours after randomization, whereas 1072 patients assigned to standard invasive care had ICA performed 61.6 hours after randomization. Among patients with significant coronary artery disease identified by ICA, coronary revascularization was performed in 88.4% (very early ICA) and 83.1% (standard invasive care) of the patients. Within a median follow-up time of 4.3 (IQR 4.1-4.4) years the primary endpoint occurred in 296 (27.5%) of participants in the very early ICA group and 316 (29.5%) in the standard care group (HR 0.92 [CI95 0.78-1.08]). Among patients with a GRACE risk score >140, a very early invasive treatment strategy improved the primary outcome compared with the standard invasive treatment (HR 0.81 95% CI 0.67-1.01, p-value for interaction = 0.023).
Conclusions: A strategy of very early invasive coronary evaluation does not improve overall long-term clinical outcome compared with an invasive strategy conducted within 2-3 days in patients with NSTE-ACS. However, in patients with the highest risk, very early invasive therapy improves long-term outcomes.
Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT02061891

Key Words: acute coronary syndrome, coronary revascularization, PCI, time factors, clinical outcome

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Clinical Perspective

What is new?

- VERDICT is a large scale randomized controlled trial evaluating the value of a very early invasive strategy conducted within 12 hours of diagnosis on long-term clinical outcome in patients with NSTE-ACS.
- An invasive strategy performed within 4.7 hours after diagnosis was not associated with improved outcome compared to an invasive strategy conducted within 2-3 days.
- However, in the prespecified subgroup of patients with a GRACE risk score >140, a very early invasive treatment strategy improved outcome compared to a standard invasive treatment strategy.

What are the clinical implications

- Very early coronary evaluation, and intervention can safely be performed in NSTEMI patients with high-risk clinical features including dynamic ECG changes and/or cardiac troponin elevation.
- The findings of the VERDICT trial do not support an advantage of routine invasive strategy performed within less than 12 hours in all-comer patients compared with a more delayed invasive approach.
- In highest risk patients with a GRACE risk score >140 a very early invasive strategy improved clinical outcomes, a finding consistent with results from the TIMACS trial.

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Introduction

Clinical outcomes in patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS) have progressively improved within the last two decades with a trend towards a smaller improvement in recent years.[1] An important contemporary challenge in the management of patients with NSTE-ACS is to define the optimal timing of invasive coronary angiography (ICA) and revascularization. Several large-scale trials have explored the impact of timing on mainly short-term clinical outcomes to further improve clinical outcome.[2-8] The coronary pathology found in patients with acute coronary syndrome varies substantially ranging from structurally normal vessels, non-obstructive atherosclerotic disease to severe multi-vessel obstructive including occlusive coronary artery disease (CAD). The relative importance between antithrombotic and/or anti-inflammatory medical therapy and coronary revascularization, specifically in terms of timing to achieve the highest clinical benefit of treatment, is not clearly defined.[9] An early invasive strategy conducted within 12 hours of diagnosis could be helpful to identify patients with imminent or established vessel closure, in whom prompt revascularization might result in salvage of ischemic myocardium.[10] On the other hand, a prolonged antithrombotic and lipid-lowering pre-treatment could stabilize the coronary plaques and thus optimize conditions for a subsequent revascularization.

Current guidelines from the American Heart Association and the European Society of Cardiology for the treatment of patients with NSTE-ACS recommend an early invasive strategy within 24 hours of hospital admission, specifically in patients with at least one high-risk criterion (abnormal cardiac troponin compatible with myocardial infarction, dynamic ECG changes, or a GRACE risk score>140).[11, 12] The recommendation to conduct ICA within 24 hours of hospital admission is logistically demanding for many health care systems, requiring

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either an onsite catheterization laboratory or a fast-responding inter-hospital patient transportation service. The scientific evidence base specifically supporting the <24 hours invasive recommendation is primarily provided by "The Timing of Intervention in Acute Coronary Syndromes" (TIMACS) trial, that investigated 3031 patients with an acute coronary syndrome older than 60 years of age.[5] In this trial, invasive examination conducted within 14 hours was not advantageous in terms of the primary endpoint of short-term (6 months) clinical outcome (death, myocardial infarction or stroke), except for patients with a Global Registry of Acute Coronary Events (GRACE) risk Score >140. On the other hand, a significant beneficial effect on the secondary endpoint of refractory myocardial ischemia was observed. It is unknown to what extent patient might benefit from an invasive strategy conducted even earlier than 14 hours.

We therefore conducted the VERDICT trial in all-comer patients presenting with acute coronary syndrome and at least one high-risk criterion (troponin rise and/or ischemia in ECG). We tested the hypothesis, that a strategy of very early ICA and revascularization if needed conducted within 12 hours from the time point of the diagnosis is superior to a standard care invasive strategy that implies ICA within 48-72 hours in terms of long term clinical outcome.

Methods

Study Design

The VERDICT trial was a prospective, multicenter, open label, parallel group, randomized controlled trial assessing the optimal timing of coronary invasive management strategy in terms of long-term clinical outcome in patients with NSTE-ACS. Patients were randomized 1:1 to either an early invasive coronary angiography and possible revascularization within 12 hours

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from time of diagnosis or a standard care invasive strategy performed within 48-72 hours. The trial was conducted as a pragmatic clinical study embedded in routine clinical practice at the participating hospitals. Clinical outcomes were assessed when all patients had been followed for at least 18 months after randomization. The VERDICT trial also included a post-randomization, observational study, in which participants underwent coronary computerized tomography angiography (CCTA) before invasive examination when logistically possible. CCTA findings remained blinded throughout the entire study period and the results are not included in this report. The study was approved by the Danish National Committee on Health Research Ethics (Journal number H-4-2010-039) and the Danish Data Protection Agency and registered at ClinicalTrials.gov NCT02061891. Written informed consent was obtained from all participants. None of the funders have taken any part in designing the study, study conduct, data analysis, data interpretation or writing of this report. The corresponding author has had full access to all data of the study and has the final responsibility for the decision to submit the report for publication. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Participants

Patients from 9 hospitals in the Capital Region of Copenhagen, Denmark, admitted with chest pain and clinical suspicion of acute coronary syndrome were screened for inclusion. Patients in whom ICA was deemed clinically indicated and logistically possible within 12 hours from time of diagnosis were offered participation in the study according to inclusion and exclusion criteria. Inclusion criteria were age $\geq$ 18 years, clinical suspicion of acute coronary syndrome and at least one of the following high-risk criteria: 1) ECG changes indicating new ischemia (new ST segment depression, horizontal or down sloping $\geq$ 0.05 mV in two consecutive leads and/or T-

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wave inversion > 0.01 mV in two leads with prominent R wave or R/S ratio>1 2) An increased in coronary markers of ischemia (troponin). Exclusion criteria were pregnancy, patient inability to understand trial information, an indication for acute ICA (very high-risk NSTE-ACS,[12] including ongoing ischemia in spite of intravenous nitroglycerin infusion, hemodynamic or electrical instability, acute heart failure, mechanical complication or cardiac arrest), expected survival <1 year and known intolerance to platelet inhibitors, heparin or X-ray contrast, which could not be remedied medically. All included patients provided written informed consent.

Randomization and clinical management strategy

Patients accepting participation were prospectively randomized 1:1 to a very early or a standard invasive treatment strategy. Randomization was performed centrally by study personnel at the two invasive centers at Rigshopitalet and Gentofte University Hospitals using an electronic case report form by means of permuted-block randomization and stratified by including site. All patients randomized to the very early invasive strategy were transferred immediately from the referring hospital to the invasive center for ICA and possible revascularization, except during night-time, where patient transfer was postponed to the early morning for logistic reasons. Patients randomized to a deferred invasive strategy were transferred within 48-72 hours to the invasive center.

Procedures

Medical treatment

At time of hospitalization and prior to randomization, all patients received oral beta blockers, statins, a loading dose of either clopidogrel 600 mg or ticagrelor 180 mg according to local practice, aspirin 300 mg, and fondaparinux 2.5 mg administered subcutaneously daily unless contraindicated.

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Coronary Angiography and revascularization

ICA was performed according to guidelines and clinical practice at the individual invasive center.

Procedural diagnostic methods, procedural medication and coronary revascularization, was performed at the discretion of the interventional cardiologist, which in some patients included staged invasive procedures. Patients undergoing percutaneous coronary intervention (PCI) received unfractionated heparin to obtain an activated clotting time between 250-300 seconds. Any addition of bivalirudin or glycoprotein IIB/IIIA inhibitors was at the discretion of the operator. Complete revascularization was encouraged, but not mandatory. Patients with a coronary anatomy not suited for partial or complete revascularization by PCI were presented at the heart team conference intending to perform revascularization by coronary bypass graft surgery (CABG) within 1-2 weeks.

Study outcomes

The primary endpoint was a combination of all-cause death, non-fatal recurrent myocardial infarction, hospital admission for refractory myocardial ischemia or hospital admission for heart failure. Secondary endpoints were invasive procedure complications during index hospitalization (procedure related death, bleeding by The Bleeding Academic Research Consortium (BARC) criteria,[13] procedure related non-fatal acute myocardial infarction, stroke or transient ischemic attack) in addition to the occurrence of each of the following events at any time after randomization: death, non-fatal acute myocardial infarction, admission for refractory myocardial ischemia, repeat coronary revascularization, or hospital admission for heart failure. For endpoint definitions, see supplement 1. All endpoints were recorded by review of patients' electronic and

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hardcopy medical files and adjudicated by an event committee blinded to management strategy allocation.

Statistical analyses

The primary hypothesis of the study was that very early invasive evaluation and possible coronary revascularization would reduce the primary outcome by at least 25%. Power calculations were conducted based on previous studies in patients with NSTE-ACS, in whom the expected event rate of the primary endpoint was 15% within 1 year and 50% at 4 years of the primary combined endpoint. The trial was event-driven. To demonstrate a relative risk reduction of 25% with a power of 80%, we estimated that 711 patients in each group would need to be included within a 6-year period, with a minimum follow-up of 1 year, to accrue at least 375 primary events. Inclusion was stopped June 2016 (at which time point more than 2100 patients were included) and more than 400 events had occurred.

Descriptive statistics were summarized using median and quartiles for continuous variables and number/percentages for discrete variables. Time to event outcomes were presented as cumulative events (1 - Kaplan Meier estimates for endpoints including death, and the Aalen-Johansen method for other endpoints). Comparison was with the log-rank test for events including death and Gray's test for endpoints with a competing risk.[14] For all time-to-event outcomes, univariable Cox regression was used to derive a hazard ratio (HR) and confidence interval (CI). Presence or absence of hospital complications were presented as percentages and compared with the chi-square test. Analysis of prespecified subgroups used univariable Cox regression and comparisons were tests for interaction. The prespecified subgroups were: previous myocardial infarction, previous PCI, previous CABG, known heart failure, known valvular heart disease), GRACE risk score ≤140 vs. >140,[15] troponin (normal vs increased

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(>URL)), pathological ST-depression and/or T-wave inversion on ECG, Killip class (>1), estimated glomerular filtration rate (>45, 45-30, <30 ml/min/1.73m[16]), anemia (Hgb <8.3 mmol/L men, <7.3 mmol/L women at hospitalization), and atrial fibrillation. The subgroups by Killip Class and glomerular filtration were omitted from presentation because of very few patients with poor renal function and with Killip class > 1. Statistical analyses were conducted with R version 3.5.1.[16]

Results

From November 2010 to June 2016, 2147 patients met inclusion criteria and consented to be randomized in the VERDICT trial. Patients in allocated treatment strategy groups were similar regarding age, gender, medical history, previous coronary revascularization procedures and NSTE-ACS risk criteria (Table 1). Among patients allocated to a very early invasive strategy, 33 patients (3.1%) did not undergo ICA compared to 66 patients (6.2%) in the standard invasive strategy group (P<0.001), Table 2. The reason was that more patients in the standard invasive strategy group had ICA cancelled by the treating physician at the referring hospital (Figure 1). In the very early invasive strategy group, 1042 patients had ICA performed a median of 4.7 (interquartile range [IQR] 3.0 – 12.2) hours after randomization, whereas 1006 patients assigned to standard care invasive strategy had ICA performed after 61.6 (IQR 39.4 – 87.8) hours. Procedural and angiographic findings are reported in Table 2. Procedural times were slightly longer, and radiation doses were slightly higher in the standard strategy group compared to corresponding values of the very early invasive group. Slightly more patients in the early strategy group underwent PCI compared to the standard strategy group (Table 3).

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The median follow-up time after randomization of the patients was 4.3 (IQR 4.1-4.4) years. There was no significant difference in the primary composite endpoint of all-cause death, non-fatal recurrent myocardial infarction, hospital admission for refractory myocardial ischemia or hospital admission for heart failure between the very early invasive and standard invasive groups (27.5% vs. 29.5%, HR 0.92, 95% CI 0.78 – 1.08; p=0.29) (Table 4, Figure 2). Analysis of the primary endpoint in prespecified patient subgroups is given in figure 3. No significant difference was noted between the two treatment strategies for the primary endpoint across subgroups, except among patients with a GRACE risk score >140. In this subgroup, a very early invasive treatment strategy improved the primary outcome compared to a standard invasive treatment strategy (HR 0.81, 95% CI 0.67-1.01, p for interaction=0.023.

Secondary endpoints are reported in table 4 and figure 4. Procedural complications during the index hospitalization were similar in the two treatment strategy groups. Except for non-fatal acute myocardial infarction, all long-term secondary endpoints were not significantly different between the two treatment strategy groups. At 15 days after randomization, no difference in non-fatal acute myocardial infarction was observed between treatment strategy groups. However, over the duration of follow-up, a very early invasive evaluation was associated with a significantly reduced risk of non-fatal acute myocardial infarction compared to standard care invasive strategy (8.4% vs. 11.2%. HR 0.73, 95% CI 0.56-0.96, p=0.025) (figure 4).

Discussion

In the VERDICT trial, we found that a strategy of routine very early invasive coronary evaluation and revascularization performed a median of 4.7 hours after time of diagnosis did not improve overall long-term clinical outcomes compared with an invasive strategy conducted

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within 2-3 days (median 61.6 hours) among patients presenting with NSTE-ACS. The rate of periprocedural complications was low and similar in the two treatment strategy groups. Our trial included patients presenting with either dynamic ECG changes and/or cardiac troponin elevation, corresponding to clinical high-risk criteria as defined by current guidelines.[11, 12] Evidently, very early coronary evaluation and intervention may safely be performed, but appears to offer no advantage in terms of overall long-term morbidity and mortality in patients with clinical features. However, among the highest risk patients, defined by a GRACE score > 140, outcomes were improved with very early invasive therapy.

Early invasive coronary evaluation was conducted much earlier in our trial than in the TIMACS trial[5] (median 4.6 hours in VERDICT vs. 14 hours in TIMACS), and the standard invasive strategy was conducted somewhat later (median 61.6 hours in VERDICT vs. 50 hours in TIMACS). If an early invasive strategy is truly better than a standard invasive strategy, it is reasonable to hypothesize that a beneficial effect on outcomes would be more likely to be detected in the current trial than in TIMACS, as the time difference between the two strategy groups was considerably larger in the current trial. Moreover, even though the follow-up duration was longer in the current trial, we did not observe a difference between the two strategy groups for the primary composite endpoint.

The primary composite endpoint of the VERDICT trial was defined to detect potential clinical benefits of early myocardial salvage, including death, non-fatal myocardial infarction, refractory ischemia and heart failure. Thus, our study does not support the hypothesis that prompt coronary revascularization to salvage ischemic jeopardized myocardium is a major determinant of clinical outcomes in unselected patients with NSTE-ACS. Overall, although the VERDICT and the TIMACS trials have differences in sample size, timing of invasive strategies,

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components of the primary composite endpoint and duration of clinical follow-up, the overall conclusions of the two trials appear rather similar. As in the TIMACS trial, we did not observe any difference in all-cause mortality in the VERDICT trial with a very early invasive strategy. This finding is consistent with a recent meta-analysis that included 5324 patients from 8 previous trials,[17] and with current guidelines.[11, 12] Nevertheless, it is noteworthy that both the TIMACS and the VERDICT trial found that the subgroup of patients with a GRACE risk score >140 had improved outcome when treated with a very early invasive strategy.[2-8, 17] These consistent observations support an individualized approach to timing of invasive therapy in NSTE-ACS, in which the highest risk patients are considered for very early intervention in the absence of contraindications

Routine ICA in the treatment of patients with NSTE-ACS has been reported to be associated with a significant reduction in recurrent acute myocardial infarction, refractory angina pectoris, rehospitalization and a trend towards a reduction in cardiovascular death compared to an individualized, selective invasive strategy.[18, 19] Still, an important caveat of a routine invasive strategy is an increased risk of bleeding as a consequence of concurrent antithrombotic medical therapy.[19] The primary mechanism by which routine ICA is thought to improve clinical outcome in patients with NSTE-ACS is the identification of hemodynamically significant stenosis. Revascularization of these lesions relieves ischemia in addition to avoiding vessel closure at the location of unstable plaques. Furthermore, by ruling out epicardial coronary disease, an invasive investigation can lead to cessation of unnecessary antithrombotic medications, and thus prevent potential side-effects/complications such as bleeding. The proportion of patients with non-significant CAD presenting with NSTE-ACS in previous trials have been reported to vary considerably from 0% up to 30% (the VERDICT and TIMACS cohorts).[17] This broad range

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most likely reflect differences of inclusion criteria and local clinical practice. In the VERDICT cohort, we found that approximately two thirds of the patients had significant CAD, one quarter of the patients had at least one occluded coronary artery and more than 70% of patients with CAD underwent complete coronary revascularization with either PCI or CABG. Additionally, the procedural risk of bleeding was low in both strategy groups. *A priori*, it appears conceivable that any suggested benefit of an invasive strategy in terms of improved clinical outcomes would be more prominently related to the extent, severity and timing of revascularization. In patients with an elevated GRACE risk score above 140, we found that a very early invasive treatment strategy resulted in improved clinical outcomes compared to a standard invasive treatment strategy. Recently it was reported that a GRACE risk score >140 is a significant predictor of high-risk CAD defined as left main stenosis>50%, proximal LAD lesion>70%, and/or 2- to 3-vessel disease involving the LAD.[20] It could therefore be speculated that the improved outcome observed in VERDICT patients with a high GRACE risk score allocated to a very early invasive strategy is explained by a more timely revascularization of severe CAD. This concept is a matter of future analyses of our data, and will include the recorded CCTA data. As defined in the VERDICT trial, research protocol CCTA conducted prior to ICA might offer a means for very early identification of high-risk CAD in need of revascularization. Interestingly, a similar concept is currently being evaluated in the randomized controlled trial RAPID-CTCA currently being conducted in the UK.[21]

A very early invasive strategy was associated with a small (2.8%) yet significant reduction in non-fatal AMI compared to a standard invasive strategy. This finding is hypothesis-generating and must be viewed within the context of an overall neutral trial for the primary endpoint. This finding is also discordant from a recent meta-analysis on the optimal timing of a

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coronary invasive strategy that included more than 5000 patients, where no impact on recurrent, non-fatal AMI was detected with a very early invasive strategy.[22]

Some limitations of the VERDICT trial should be considered. First, the trial was conducted as a pragmatic clinical study embedded in routine clinical practice at the participating hospitals, and it was therefore not logistically possibly to record all patients assessed for eligibility during the enrolment of patients in the trial. However, clinical characteristics and coronary angiography findings in the study cohort enrolled are comparable to patients included in earlier studies on timing of invasive treatment strategy in NSTE-ACS.[17] We therefore believe that the results of the VERDICT trial can be extrapolated to the general population of patients with NSTE-ACS. Secondly, slightly more patients in the standard invasive strategy group had ICA cancelled compared to the very early invasive strategy group, and thus a potential clinical advantage of a standard invasive strategy compared to the very early strategy might be missed. However, this would further bias the results towards the null. Thirdly, approximately 12% of patients were referred for CABG performed about 2 weeks after randomization. These patients could thus have limited our ability to show a beneficial effect in the very early invasive group. However, the proportion of patients referred for CABG was similar in the two groups. Lastly, although we prespecified several subgroups to be analyzed with regards to the primary endpoint, the study was not powered to assess the potential differential impact of a very early invasive strategy in these subgroups.

In conclusion, a strategy of invasive coronary evaluation within 4.7 hours after time of diagnosis does not improve overall long-term clinical outcomes compared to an invasive strategy conducted within 2-3 days in patients with NSTE-ACS.

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Table 1. Clinical Characteristics

Variable	Very Early (n=1075)	Standard (n=1072)	P value
Male gender, n (%)	716 (66.6)	696 (64.9)	0.43
Age in years, mean (SD)	63.6 (12.1)	63.6 (12.5)	0.89
BMI, kg/m2, mean (SD)	26.9 (4.7)	27.2 (4.8)	0.19
Prior smoker, n (%)	403 (37.5)	407 (38.0)	0.67
Current smoker, n (%)	342 (31.8)	323 (30.1)	0.88
Diabetes, n (%)	158 (14.7)	173 (16.1)	0.38
Hypertension, n (%)	543 (50.5)	578 (53.9)	0.12
Obstructive lung disease, n (%)	175 (16.3)	164 (15.3)	0.57
Renal disease, n (%)	95 (8.8)	103 (9.6)	0.58
eGFR, ml/min (SD)	90.5 (23.7)	91.2 (23.7)	0.49
Previous stroke, n (%)	94 (8.7)	82 (7.6)	0.39
History of CV disease	302 (28.1)	305 (28.5)	0.89
Known valve disease, n (%)	35 (3.3)	53 (4.9)	0.06
Previous AMI, n (%)	186 (17.3)	186 (17.4)	1.00
Previous PCI, n (%)	151 (14.0)	163 (15.2)	0.48
Previous CABG, n (%)	57 (5.3)	57 (5.3)	1.00
GRACE score, mean (SD)	141.3 (29.8)	140.8 (31.4)	0.72
GRACE score >140, n (%)	520 (49.3)	505 (48.7)	0.78
ECG with new ischaemia, n (%)	648 (61.1)	640 (60.8)	0.94
Elevated Troponin, n (%)	871 (81.2)	847 (79.2)	0.26

SD: standard deviation BMI: body mass index eGFR: estimated glomerular filtration rate CV: cardiovascular AMI: acute myocardial infarction PCI: percutaneous coronary intervention CABG: coronary artery bypass grafting GRACE score: Global Registry of Acute Coronary Events risk score ECG: electrocardiography

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Table 2. Procedural and angiographic characteristics

Variable	Very Early (n=1075)	Standard (n=1072)	P value
Procedural details			
Coronary angiography, n (%)	1042 (96.9)	1006 (93.8)	0.0009
Femoral access, n (%)	898 (83.5)	857 (79.9)	0.15
Median procedural time, min (IQR)	10.0 (7.0 -18.0)	13.0 (9.0- 20.0)	0.0005
Radiation (mSv), median (IQR)	2.3 (1.6-4.1)	2.7 (1.8-5.4)	0.008
Angiographic characteristics			
No coronary stenosis, n (%)	311 (29.8)	302 (30.0)	0.97
LM, 1,2,3-VD			0.66
LM stenosis, n (%)	70 (6.7)	58 (5.8)	
1-VD, n (%)	351 (33.7)	342 (34.0)	
2-VD, n (%)	174 (16.7)	159 (15.8)	
3-VD, n (%)	117 (11.2)	131 (13.0)	0
≥ 1 occluded coronary artery, n (%)	277 (26.6)	249 (24.8)	0.36
LAD stenosis, n (%)	480 (46.1)	456 (45.3)	0.77
LCx stenosis, n (%)	345 (33.1)	333 (33.1)	1.00
RCA stenosis, n (%)	376 (36.1)	378 (37.6)	0.51

LM: Left main coronary artery LAD: left anterior descending artery LCx: left circumflex artery RCA: right coronary artery VD: vessel disease PCI: percutaneous coronary intervention CABG: coronary artery bypass grafting

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Table 3. Details of Coronary Revascularization

Variable	Very Early (n=1075)	Standard (n=1072)	P value
PCI performed, n (%)	498 (46.3)	442 (41.2)	0.019
≥ 1 drug eluting stent	425 (85.3)	383 (86.7)	0.62
≥ 1 bare metal stent	28 (5.6)	19 (4.3)	0.43
Balloon angioplasty alone	35 (7.0)	28 (6.3)	0.76
Staged PCI, n (%)	8 (0.7)	8 (0.7)	1.00
Complete revascularization by PCI, n (%)	379 (76.1)	347 (78.5)	0.05
Number of treated lesions, n (%)			0.65
1	385 (77.3)	354 (80.1)	
2	85 (17.1)	71 (16.1)	
3	21 (4.2)	13 (2.9)	
4≥	5 (1.0)	2 (0.5)	
Number of stents, n (%)			0.48
0	46 (9.2)	37 (8.4)	
1	298 (59.8)	286 (64.7)	
2	111 (22.3)	94 (21.3)	
3≥	42 (16.0)	25 (5.7)	
CABG, n (%)	132 (12.2)	132 (12.3)	1.00
Antiplatelet & Antithrombotic medication at time of discharge			
Aspirin, n (%)	878 (81.7)	891(83.1)	0.99
Ticagrelor, n (%)	500 (46.5)	500 (46.6)	1.00
Clopidogrel n (%)	228 (21.2)	236 (22.0)	0.97
Prasugrel n (%)	22 (2.0)	17 (1.6)	0.42
Warfarin/NOAC n (%)	78 (7.2)	70 (6.5)	0.90

PCI: percutaneous coronary intervention POBA: plain old balloon angioplasty CABG: coronary artery by-pass grafting NOAC: Direct Oral Anti Coagulant.

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Table 4. Trial endpoints

Variable	Very Early (n=1075)	Standard (n=1072)	Hazard ratio (95% CI)	P value
Primary endpoint				
All-cause death				
Non-fatal AMI				
Refractory ischemia				
Heart failure				
	296 (27.5)	316 (29.5)	0.92 (0.78-1.08)	0.29
Secondary endpoints				
Non-fatal AMI	90 (8.4)	120 (11.2)	0.73 (0.56-0.96)	0.025
Refractory ischemia	64 (6.0)	49 (4.6)	1.32 (0.91-1.91)	0.14
Heart failure	99 (9.2)	126 (11.8)	0.78 (0.60-1.01)	0.06
Death	131 (12.2)	135 (12.6)	0.97 (0.76-1.23)	0.96
Repeat coronary revascularisation	86 (8.0)	70 (6.5)	1.24 (0.91-1.70)	0.18
*Invasive procedural complications**				
Cardiac arrest	3 (0.3)	4 (0.4)	-	0.99
Bleeding	19 (1.8)	19 (1.8)	-	1.0
Stroke/TIA	6 (0.6)	4 (0.4)	-	0.75
Non-fatal AMI	1 (0.1)	5 (0.5)	-	0.21

AMI: acute mycoardial myocardial infarction *Refractory ischemia:* hospital admission for refractory myocardial ischemia *Heart failure*: hospital admission for heart failure. TIA: transient ischemia attack * Procedural complications were recorded as binary data and p values are for differences assessed with Chi-square test.

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Figure Legends

Figure 1. Study flow chart

ICA: invasive coronary angiography

Figure 2. Event rates of the combined primary endpoint

The combined primary endpoint: all-cause death, non-fatal recurrent myocardial infarction, hospital admission for refractory myocardial ischemia or hospital admission for heart failure. Differences in cumulative incidence including 95% confidence limits are given *Early Invasive:* invasive coronary angiography and possible revascularization within 12 hours from time of diagnosis. *Standard*: invasive coronary angiography and possible revascularization within 48-72 hours from time of diagnosis

Figure 3. Hazard ratio in subgroups for the combined primary endpoint

Early Invasive: invasive coronary angiography and possible revascularization within 12 hours from time of diagnosis. *Standard*: invasive coronary angiography and possible revascularization within 48-72 hours from time of diagnosis. P-interaction: P value for interaction in each subgroup

Troponin: missing values n=4 *GRACE:* Global Registry of Acute Coronary Events risk score, missing values n=55 *ST/T changes:* electrocardiographic changes indicating new ischemia, missing value n=34 *Heart rate*: missing values n=45 Prior *CV dis.:* Prior cardiovascular disease *Anemia*: missing value n=19 *Atrial fib*: atrial fibrillation, missing value n=19

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Figure 4. Event rates of the secondary endpoints

Differences in cumulative incidence including 95% confidence limits *Revascularization:* repeated coronary revascularization *AMI:* hospital admission for non-fatal acute myocardial infarction *Refractory angina:* hospital admission for refractory myocardial ischemia *Heart failure admission*: hospital admission for heart failure *Early Invasive:* invasive coronary angiography and possible revascularization within 12 hours from time of diagnosis. *Standard*: invasive coronary angiography and possible revascularization within 48-72 hours from time of diagnosis