JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 6, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2015.11.018

Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients

The RIDDLE-NSTEMI Study

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ABSTRACT

OBJECTIVES This study aimed to assess the clinical impact of immediate versus delayed invasive intervention in patients with non-ST-segment myocardial infarction (NSTEMI).

BACKGROUND Previous studies found conflicting results on the effects of earlier invasive intervention in a heterogeneous population of acute coronary syndromes without ST-segment elevation.

METHODS We randomized 323 NSTEMI patients to an immediate-intervention group (<2 h after randomization, n = 162) and a delayed-intervention group (2 to 72 h, n = 161).The primary endpoint was the occurrence of death or new myocardial infarction (MI) at 30-day follow-up.

RESULTS Median time from randomization to angiography was 1.4 h and 61.0 h in the immediate-intervention group and the delayed-intervention group, respectively ($p < 0.001$). At 30 days, the primary endpoint was achieved less frequently in patients undergoing immediate intervention (4.3% vs. 13%, hazard ratio: 0.32, 95% confidence interval: 0.13 to 0.74; $p = 0.008$). At 1 year, this difference persisted (6.8% in the immediate-intervention group vs. 18.8% in delayed-intervention group; hazard ratio: 0.34, 95% confidence interval: 0.17 to 0.67; $p = 0.002$). The observed results were mainly attributable to the occurrence of new MI in the pre-catheterization period (0 deaths + 0 MIs in the immediate-intervention group vs. 1 death + 10 MIs in the delayed-intervention group). The rate of deaths, new MI, or recurrent ischemia was lower in the immediate-intervention group at both 30 days (6.8% vs. 26.7%; $p < 0.001$) and 1 year (15.4% vs. 33.1%; $p < 0.001$).

CONCLUSIONS Immediate invasive strategy in NSTEMI patients is associated with lower rates of death or new MI compared with the delayed invasive strategy at early and midterm follow-up, mainly due to a decrease in the risk of new MI in the pre-catheterization period. (Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients [RIDDLE-NSTEMI]; NCT02419833) (J Am Coll Cardiol Intv 2016;9:541–9) © 2016 by the American College of Cardiology Foundation.

In patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS), an invasive strategy is favored over conservative management (1–7), but the issue of optimal timing remains unresolved, with the need to balance the risks of intervention for unstable plaque and the risk of new ischemic events while waiting to perform an invasive procedure. Pooled analyses of randomized, controlled trials indicate that the occurrence of death and myocardial infarction (MI) was similar, whereas

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Manuscript received August 31, 2015; revised manuscript received October 22, 2015, accepted November 5, 2015.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

ECG = electrocardiographic

IQR = interquartile range

MI = myocardial infarction

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

NSTEMI = non-ST segment myocardial infarction

PCI = percutaneous coronary intervention

ULN = upper limit of normal

recurrent ischemia was less frequent in patients undergoing earlier versus delayed invasive intervention (8–15). However, although some trials associated early intervention with reduced rates of ischemic events (16,17), others reported higher levels of cardiac injury biomarkers in patients undergoing early invasive treatment (18,19). Adding to the nonuniformity of previous studies, most included a heterogeneous group of NSTE-ACS patients with only 2 enrolling specifically non-ST-segment elevation MI (NSTEMI) patients, albeit both with a nonclinical primary endpoint (9,20).

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Our aim was therefore to compare the effects of immediate invasive intervention with a delayed invasive strategy in a more homogeneous population of initially stabilized NSTEMI patients only, with a robust clinical primary endpoint of death or reinfarction at 30 days.

METHODS

The RIDDLE-NSTEMI (Randomized study of Immediate versus Delayed Invasive Intervention in patients with Non ST-segment Elevation Myocardial Infarction), an investigator-initiated, randomized, parallel-group, open-label, single-center trial, tested the hypothesis that immediate invasive coronary angiography within 2 h of admission is superior to a delayed invasive strategy, within 72 h of admission.

The trial was conducted at a high-volume university hospital with 24-h on-site primary percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) availability and in compliance with the principles of the Declaration of Helsinki. The local ethics committee had previously approved the study protocol, and all patients provided written consent before being enrolled into the trial.

PATIENTS. Patients were eligible for inclusion if they had had an episode of chest pain occurring no more than 24 h before admission and if the following 2 findings were present on admission to the hospital: 1) elevation of cardiac troponin I greater than the upper limit of normal (ULN) and 2) new ST-segment depression at least 1 mV and/or T-wave inversion in ≥2 contiguous leads. Exclusion criteria were persistent ST-segment elevation, posterior MI, hemodynamic instability, cardiogenic shock, life-threatening ventricular arrhythmias, and/or refractory angina on admission, active bleeding, any contraindication for the use of dual antiplatelet therapy, and the presence of comorbidities with a life expectancy <6 months.

RANDOMIZATION AND INTERVENTIONS. Eligible patients were randomly assigned to either an immediate- or delayed-intervention group with 1:1 allocation ratio, per a computer-generated sequence of random numbers and using the envelope method. Patients in the immediate-intervention group were transferred for angiography as soon as possible but no later than 2 h after randomization. In the delayed-intervention group, patients underwent invasive intervention within 72 h of randomization, with the exception of patients in whom chest pain developed, who had recurrent ischemia, and/or who became clinically unstable while waiting to undergo the intervention. Coronary angiography was performed in accordance with standard local practice and existing clinical practice guidelines; in patients eligible for percutaneous revascularization, PCI was performed in the same setting. If CABG was recommended as means of revascularization, it was performed as soon as possible, regardless of the treatment group.

All patients received loading dose of dual antiplatelet therapy (aspirin 300 mg + clopidogrel 600 mg in case of immediate transfer to the cath lab and 300 + 300 mg if invasive intervention was delayed), followed by aspirin 100 mg and clopidogrel 75 mg daily. In cases in which patients had already been on dual antiplatelet therapy, standard maintenance doses were administered. Patients were treated with low molecular weight heparin, nitrates, beta-blockers, and angiotensin-converting enzyme inhibitors following the current clinical practice guidelines. Glycoprotein IIb/IIIa inhibitors were used at the operator's discretion.

PRIMARY AND SECONDARY OUTCOMES. The study's primary endpoint was the composite of death or new MI at 30-day follow-up. Death was defined as death from any cause. The definition of new MI was dependent on the time period after randomization. Early new MI, occurring within 24 h of randomization, was defined as new onset of symptoms of myocardial ischemia persisting >20 min and new or recurrent ST-segment elevation or depression >0.1 mV in ≥2 contiguous leads (10). Late new MI, occurring from 24 h to 7 days after randomization, was defined as new onset of ischemic symptoms lasting >20 min and an increase in troponin >20% if the initially elevated values were stable or decreasing and/or new or recurrent ST-segment elevation or depression >0.1 mV or new Q waves in ≥2 contiguous leads different from the index event (10,21).

After PCI, new MI was defined as new ST-segment elevation or Q waves in ≥2 contiguous leads and/or an increase in troponin >20% if the initially elevated values were stable or decreasing (10,21).

In patients whose troponin levels had returned to normal, new MI was defined as at least 1 value of troponin greater than the ULN in the presence of ischemic symptoms, electrocardiographic (ECG) changes suggestive of ischemia, imaging evidence of regional wall motion abnormality, and/or angiographic/autopsy confirmation of intracoronary thrombus.

The secondary endpoint was a combined incidence of death, new MI, and/or recurrent ischemia at 30 days and 1 year, as well as death or new MI at 1 year. Recurrent ischemia was defined as repeated episodes of ischemic symptoms lasting >5 min if all of the following applied: 1) the patient was on optimal medical therapy; 2) ECG changes indicative of ongoing myocardial ischemia; and 3) invasive intervention was required (10). Other endpoints included rates of individual components of the primary and secondary endpoints and major bleeding at 30 days and 1 year. Major bleeding was defined according to the Thrombolysis In Myocardial Infarction bleeding classification.

STATISTICAL ANALYSIS. Data were analyzed according to the intention-to-treat principle. Continuous variables were expressed as the median and interquartile range (IQR) and were compared between the 2 intervention groups using the Mann-Whitney *U* test, and, in case of normal distribution as confirmed by the Kolmogorov-Smirnov test, mean values were compared with the Student *t* test. Categorical data were expressed as counts and proportions and compared with the chi-square or Fisher exact test. Unadjusted and adjusted Cox regression models were constructed to assess the association of being assigned to 1 of the 2 intervention groups with the occurrence of clinical endpoints. Pre-specified subgroup analyses were based on sex, age younger than 65 years or 65 years or older, the presence of diabetes, GRACE (Global Registry of Acute Coronary Events) risk score >140 and ≤140, and Thrombolysis In Myocardial Infarction risk score <5 and ≥5. Cox regression models were constructed to test for a possible interaction of assignment to immediate or delayed invasive intervention with any of the pre-specified subgroup variables. Kaplan-Meier curves were plotted to depict time to event rates for both groups of patients and compared with the log-rank test. All tests were 2-sided with an alpha error of 5% being used. The statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, Illinois).

SAMPLE SIZE CALCULATION. Sample size calculation was performed to allow comparison of immediate and delayed invasive intervention with respect to the study's primary endpoint of the cumulative incidence of death or new MI at 30 days. In patients with delayed intervention, the primary endpoint rate of 16% was assumed, based on previously published studies in NSTE-ACS patients (17). The assumed absolute risk reduction with the immediate approach to invasive intervention was 11%, whereby the postulated rate for the primary endpoint was 5% in patients undergoing immediate invasive intervention. Assuming an alpha of 0.05 and a power of 80%, we calculated that the number sufficient to detect the postulated effect size difference was 139 patients per group. With a presumed 10% of patients being lost to follow-up, we aimed to recruit at least 154 patients in each treatment group.

RESULTS

PATIENTS. From September 2009 through February 2013, we enrolled 323 patients, of whom 162 were randomized to the immediate-intervention group and 161 to the delayed-intervention group. The study flow chart is shown in **Figure 1**. Complete 30-day follow-up was performed in all enrolled patients. Overall, baseline characteristics were similar between the 2 study groups, with more patients having diabetes in the delayed-intervention group, whereas current smoking was more frequent in the immediate-intervention group (**Table 1**). There were no significant differences in the use of in-hospital medication, except for nitrates and low molecular weight or unfractionated heparin before catheterization being used more frequently in patients undergoing delayed revascularization. Time from onset of pain to randomization was 5 h (IQR: 3 to 10 h) in the immediate-intervention group and 6.5 h (IQR: 3.5 to 10 h) in the delayed-intervention group. The median time from randomization to coronary angiography was 1.4 h in patients assigned to undergo immediate intervention and 61 h in the delayed-intervention arm (**Table 2**).

Angiographic baseline characteristics were similar with even distribution of single- and multivessel disease between the 2 groups. Procedural characteristics were similar except for the more frequent use of glycoprotein IIb/IIIa inhibitors in the immediate-intervention group (11.1% vs. 2.5%; p = 0.002). Manual thrombectomy was used in 3.9% and 1.0% in immediate- and delayed-intervention groups, respectively (p = 0.16). The PCI rate was higher in the group of patients randomized to immediate intervention compared with delayed intervention (78.4% vs. 65.0%), whereas CABG was more common in the delayed-intervention group (23.8% vs. 12.3%) (**Table 2**).

PRIMARY AND SECONDARY OUTCOMES. At 30-day follow-up, the occurrence of the primary endpoint (death or new myocardial infarction) was 4.3%

FIGURE 1 Study Flow Chart

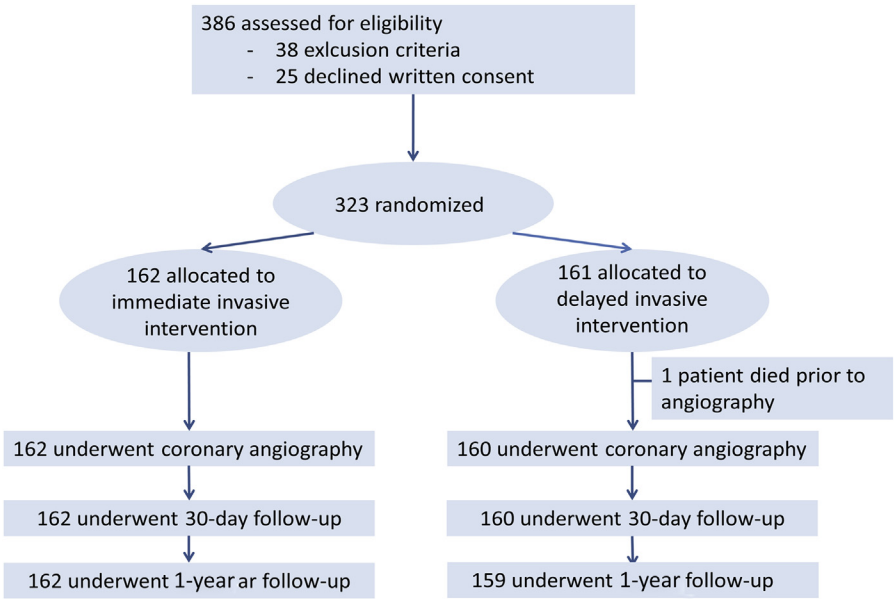


Diagram showing the flow of patients through each phase of the study. All randomized patients (n = 323) underwent 30-day follow-up for the primary endpoint.

(5 deaths, 2 nonfatal MIs) in immediate-intervention patients compared with 13.0% (5 deaths, 16 nonfatal MIs) in patients undergoing delayed invasive intervention (hazard ratio: 0.32, 95% confidence interval: 0.13 to 0.74; p = 0.008) (Table 3, Figure 2). At 30 days, mortality rates were the same for both groups of patients (3.1%; p = 0.97), whereas new MI was more frequent in patients undergoing delayed invasive intervention (9.9% vs. 2.5%; p = 0.01). The 30-day rates of combined secondary endpoints (death, new MI, or recurrent ischemia) were 6.8% in patients with immediate and 26.7% in patients with delayed intervention (p < 0.001) (Table 3).

A multivariable regression model constructed to include information about demographic characteristics, medical history, previous coronary procedures, and ECG changes from Table 1 yielded an adjusted hazard ratio of 0.42 (95% confidence interval: 0.17 to 1.01; p = 0.052) for the primary endpoint for immediate versus delayed intervention. There was no difference between median peak troponin levels in the immediate- versus delayed-intervention group (5.3 ng/ml, IQR: 1.88 to 3.64 vs. 3.60 ng/ml, IQR: 1.70 to 12.04, respectively; p = 0.18).

The largest difference in the rates of death or new MI in immediate- compared with delayed-intervention patients was documented in the pre-catheterization period (0 deaths + 0 MIs in the immediate-intervention group vs. 1 death + 10 MIs in the delayed-intervention group) (Figure 2).

At 1 year, the cumulative rates of death or new MI were lower in the immediate- intervention group versus delayed-intervention group (6.8% vs. 18.8%, respectively; p = 0.002) (Table 3), with no significant difference in the time period from 31 days to 1 year (Figure 3).

The secondary endpoint, cumulative occurrence of death, new MI, or recurrent ischemia at 1 year, was also lower in the immediate-intervention group (15.4% vs. 33.1%; p < 0.001) (Table 3).

The effect of immediate intervention on the primary endpoint was consistent across the pre-defined subgroups. There was no significant interaction between any of the variables denoting pre-specified subgroups and the assignment to immediate versus delayed invasive strategy on the primary endpoint (Figure 4).

BLEEDING. The occurrence of major bleeding was low and did not differ between the groups at 30 days and up to 1 year (Table 3). One patient in the immediate- and in 2 patients in the delayed-intervention group received a blood transfusion. Intracranial bleeding occurred in 1 patient randomized to the immediate invasive strategy. Four patients in the delayed-intervention group were treated for gastrointestinal bleeding.

TABLE 1 Baseline Characteristics and In-Hospital Medication

	Immediate (n = 162)	Delayed (n = 161)	p Value
Demographics			
Age, yrs	60.5 (52-69)	63.0 (55-71)	0.11
Female	48 (29.6)	55 (34.2)	0.38
Medical history			
Hypertension	106 (65.4)	116 (72.0)	0.20
Diabetes mellitus	35 (21.6)	52 (32.3)	0.03
Current smoker	84 (51.9)	62 (38.5)	0.02
Hyperlipidemia	121 (74.7)	119 (73.9)	0.87
MI	31 (19.1)	34 (21.1)	0.66
CVI	9 (5.6)	16 (9.9)	0.14
Previous coronary procedure			
Previous PCI	17 (10.5)	15 (9.3)	0.72
Previous CABG	8 (4.9)	12 (7.5)	0.35
Ischemic ECG changes			
ST-segment depression	125 (77.2)	130 (80.7)	0.43
T-wave inversion	34 (21.1)	30 (18.6)	0.58
Concomitant medication			
Nitrates	78 (48.1)	142 (88.2)	<0.001
Beta-blocker	146 (90.1)	148 (91.9)	0.57
Statin	160 (98.8)	158 (98.1)	0.65
ACE inhibitor	152 (93.8)	146 (90.7)	0.29
Oral anticoagulants	3 (1.9)	8 (5.0)	0.12
LMWH or UFH*	5 (3.1)	161 (100.0)	<0.001
Risk scores			
GRACE	131 (115-144)	129 (115-150)	0.52
GRACE >140	56 (34.6)	67 (41.6)	0.19
TIMI	3.5 (3-4)	4 (3-4.5)	0.22
TIMI ≥5	37 (22.8)	40 (24.8)	0.67

Values are median (interquartile range) or n (%). *Use of LMWH or UFH before catheterization.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CVI = cerebrovascular insult; ECG = electrocardiographic; GRACE = Global Registry of Acute Coronary Events; IQR = interquartile range; LMWH = low molecular weight heparin; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; UFH = unfractionated heparin.

TABLE 2 Angiographic and Procedural Characteristics

	Immediate (n = 162)	Delayed (n = 160*)	p Value
Number of coronary arteries with a stenosis ≥50%			0.56
None	3.1	2.5	
1	29.6	23.1	
2	32.1	33.8	
3	35.2	40.6	
Infarct-related artery			0.72
LM	5.6	5.6	
LAD	42.0	36.9	
LCx	32.1	30.6	
RCA	14.2	18.8	
Graft	3.1	5.6	
Interventions after randomization			
Coronary angiography	100.0	99.3*	0.50
Median time to coronary angiography, h	1.40 (1.00-2.24)	61.0 (35.8-85.0)	<0.001
PCI	78.4	65.0	0.01
			0.18
Drug-eluting stent	22.8	33.6	
Bare-metal stent	68.5	57.7	
POBA	8.7	8.6	
CABG	12.3	23.8	0.01

Values are % or median (interquartile range). *1 patient in the delayed-intervention group died before coronary angiography.

LAD = left anterior descending artery; LCx = left circumflex artery; LM = left main artery; POBA = plain old balloon angioplasty; RCA = right coronary artery; other abbreviations as in Table 1.

DISCUSSION

The main finding of our study is that in initially stabilized NSTEMI patients, immediate invasive intervention is associated with lower rates of death or MI compared with delayed invasive treatment. This difference was mainly attributable to lower rates of new MI in patients undergoing an immediate invasive procedure, mainly during the pre-catheterization period. Recurrent ischemia was also less frequent in patients undergoing immediate intervention. In the follow-up period after hospitalization and up to 1 year, the rates of death, new MI, and recurrent ischemia were similar. The rates of major bleeding were similar in both groups, at both 30 days and up to 1 year.

Due to considerable variation in study protocols with respect to the proportion of NSTEMI patients, the difference in the time between early and delayed invasive procedure and the definition of new MI, previously conducted randomized trials, including our study, are difficult to compare (22,23).

Regarding the studied population of NSTEMI patients only, our study is comparable to the LIPSIA-NSTEMI (Leipzig Immediate Versus Early and Late PercutaneouS Coronary Intervention triAl in NSTEMI) (9). The definition of early new MI in our study was clinically oriented and similar to that used in the TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial (10), whereas the large difference in median time to procedure between early and delayed treatment arms was comparable to that in the ISAR-COOL (Intracoronary Stenting With Antithrombotic Regimen Cooling-Off) trial (17).

STUDY POPULATION. Our trial included only patients with elevated biomarkers of myocardial injury at baseline, whereas other studies of optimal timing of invasive intervention in NSTE-ACS included different proportions of biomarker-positive patients, from 45% (18) to 78% (10,19). In addition, 79% of patients in our study had ST-segment depression on admission, which is higher compared with previous trials (9,17,18), and 89% underwent percutaneous or surgical revascularization, which is also a higher rate of invasive treatment compared with previous studies (10,17).

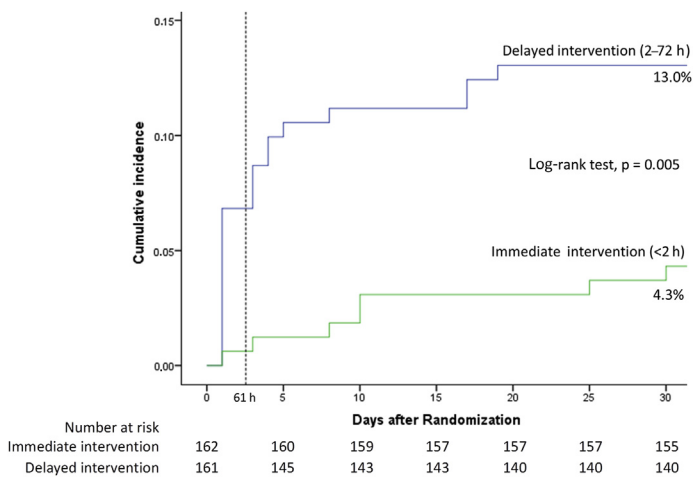
TABLE 3 Clinical Outcomes Up to 1 Year

	Immediate Intervention (n = 162)	Delayed Intervention (n = 161)*	HR (95% CI)†	p Value
30 days				
Death or MI	4.3	13.0	0.32 (0.13–0.74)	0.008
Death, MI, or recurrent ischemia	6.8	26.7	0.23 (0.12–0.45)‡	<0.001
Death§	3.1	3.1	0.98 (0.28–3.37)	0.97
MI	2.5	9.9	0.24 (0.08–0.70)	0.01
Recurrent ischemia	3.7	15.5	0.24 (0.10–0.57)‡	0.001
Major bleeding	0.6	0.6	0.99 (0.06–15.89)	0.99
31 days to 1 yr				
Death or MI	2.6	6.5	0.39 (0.12–1.27)	0.12
Death, MI, or recurrent ischemia	9.3	9.3	0.99 (0.45–2.19)‡	0.71
Death§	1.9	2.6	0.74 (0.17–3.31)	0.69
MI	0.6	4.3	0.15 (0.02–1.22)	0.07
Recurrent ischemia	6.5	2.2	2.99 (0.82–10.85)‡	0.06
Major bleeding	0.0	2.6	0.01 (0.01–46.38)	0.30
1 yr				
Death or MI	6.8	18.8	0.34 (0.17–0.67)	0.002
Death, MI, or recurrent ischemia	15.4	33.1	0.28 (0.15–0.51)‡	<0.001
Death§	4.9	5.6	0.87 (0.34–2.26)	0.78
MI	3.1	13.8	0.21 (0.08–0.55)	0.002
Recurrent ischemia	9.9	16.9	0.28 (0.12–0.63)‡	0.002
Major bleeding	0.6	3.1	0.20 (0.02–1.68)	0.14

Values are % unless other indicated. *In the delayed intervention group, 1 patient was not available for 1-year follow-up. †From unadjusted Cox regression models. ‡From an extended Cox regression model with assignment to immediate versus delayed invasive treatment as time-dependent variable. §All deaths were due to a cardiovascular cause.

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

FIGURE 2 Cumulative Incidence of the Primary Endpoint



Cumulative incidence of the combined primary endpoint of death or myocardial infarction at 30 days for immediate **(green line)** compared with delayed intervention **(blue line)**. **Dashed black line** intersecting the x-axis denotes the median time to angiography (61 h) in patients undergoing delayed invasive intervention.

To the best of our knowledge, this is the first randomized trial to include only NSTEMI patients while having a clinical primary endpoint. The LIPSIA-NSTEMI recruited a similar population of NSTEMI patients only but had a nonclinical primary outcome of peak creatine kinase-myocardial band activity and found no significant difference among immediate, delayed, and selective invasive approaches (9). Another large randomized study with an estimated enrollment of 4,500 NSTEMI patients, the NONSTEMI (Acute Versus Subacute Angioplasty in Patients With NON-ST-Elevation Myocardial Infarction) trial, is ongoing and is expected to be completed in 2017 (NCT01638806).

ENDPOINT DEFINITION AND TIMING OF INVASIVE INTERVENTION. The principal results of our study are similar to the results of the ISAR-COOL trial that showed a decrease in the rates of death or MI from 11.6% to 5.9% at 30 days in the delayed versus early intervention group, respectively (17). Similar to our findings, the observed difference in events in the ISAR-COOL trial was mainly attributable to lower rates of new MI in patients with immediate intervention, in the pre-catheterization period. However, most of other trials on optimal timing of invasive intervention in NSTE-ACS showed similar or even higher rates of new MI in patients with earlier versus delayed intervention (8–11,18,19). The observed discrepancy may have resulted from the inconsistency in defining new MI across different trials (23). In patients with elevated biomarkers of myocardial injury on admission who undergo early intervention, it is difficult to discriminate among the enzyme release due to the index ischemic event, periprocedural myocardial damage, or new MI. Thus, in trials that allowed for new MI to be adjudicated based on the post-procedural biomarker release alone, the frequency of new MI in patients with early intervention may have been overestimated (8,9,18,19). In our study, we noted a weak tendency toward higher peak biomarker values in patients undergoing early intervention. As the hitherto largest randomized trial on optimal timing of invasive intervention in NSTE-ACS patients, the TIMACS trial included ECG and clinical signs of ischemia as a mandatory part of the definition of early new MI (10). Our study also required the presence of symptoms and ECG signs of new or prolonged ischemia. In the TIMACS trial, the MI rate at 30 days was comparable to our findings for the early and notably lower for the delayed treatment group (3.6% in the TIMACS trial and 2.5% in our study and 4.1% in the TIMACS trial and 9.9% in our study, respectively) (10). The higher rate of new MI in our trial,

particularly in the delayed-intervention group, may in part be explained by the larger intrastudy time delay to invasive intervention (in our study, 1.4 h vs. 61.0 h, and in the TIMACS trial, 14 h vs. 50 h) and the fact that our study included only patients with NSTEMI, a higher risk subgroup of NSTE-ACS. As in our study, the intrastudy time delay to invasive procedure was large in the ISAR-COOL trial (2.4 h vs. 86.0 h in early vs. delayed, respectively), and the rate of new MI at 30 days was similar in the early- versus delayed-intervention group (5.9% vs. 10.1% in ISAR-COOL and 2.5% vs. 9.9% in our study).

Overall, the combined impact of a robust, clinically oriented definition of new MI and the large difference in median time to early versus delayed intervention may be the key determinants of the outcomes of our study.

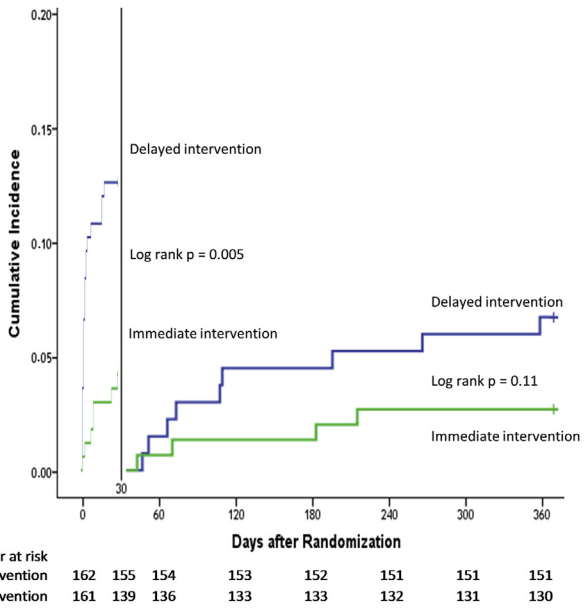
Unlike the discrepant findings on the rate of new MI, our finding that earlier intervention is associated with reduced rates of recurrent ischemia appears to be in accord with most of the previous studies and meta-analyses (12–14).

STUDY LIMITATIONS. One possible limitation of the present study is the relatively small sample size, as reflected by the small absolute number of events. The wide confidence intervals around the effect of immediate intervention on the primary endpoint may suggest a higher degree of uncertainty of its true magnitude.

Tests for interaction of immediate versus delayed intervention with the pre-specified subgroups are likely underpowered due to sample size calculation being based only on the difference between the effects of the 2 treatment groups on the primary endpoint.

Although our study provided scientific evidence of positive clinical effects of immediate invasive

FIGURE 3 Landmark Survival Analysis



Cumulative incidence of the combined primary endpoint of death or new myocardial infarction at 30 days and thereafter for patients undergoing immediate versus delayed invasive intervention. *1 patient was unavailable for follow-up in the period from 31 days to 1 year.

FIGURE 4 Forest Plot of HR for the Primary Endpoint of Death or Myocardial Infarction at 30 Days in Pre-Specified Groups of Patients

Subgroup	No. of patients	Immediate *percent*	Delayed	HR (95%CI)	p value for interaction
Overall	323	4.3	13.0	0.32 (0.13-0.74)	
Male	221	2.6	12.3	0.20 (0.06-0.72)	0.26
Female	102	8.5	14.5	0.55 (0.17-1.83)	
Age ≥ 65	126	12.5	21.4	0.54 (0.22-1.33)	0.24
Age < 65*	197	0.0	6.6	0.14 (0.02 -1.16)	
Diabetes	87	2.9	17.3	0.16 (0.02-1.25)	0.40
No diabetes	236	4.7	11.0	0.41 (0.15-1.09)	
GRACE ≤ 140	200	0.9	9.6	0.09 (0.01-0.75)	0.12
GRACE > 140	123	10.7	17.9	0.56 (0.21-1.51)	
TIMI < 5	246	3.2	7.4	0.42 (0.13-1.36)	0.53
TIMI ≥ 5	77	8.1	30.0	0.24 (0.07-0.85)	

Squares and **horizontal bars** represent within-subgroup hazard ratio (HR) and 95% confidence interval (CI), on a log scale. **Solid black vertical line** intersects the x-axis at the value of the overall HR, whereas the **dotted gray line** marks the HR of 1. *Yates correction. GRACE = Global Registry of Acute Coronary Events; TIMI = Thrombolysis In Myocardial Infarction.

strategy in patients presenting with NSTEMI, the timing of PCI in the delayed-intervention group (median of 61 h) may have potentiated such an outcome.

Furthermore, because the assessment of new MI in NSTE-ACS patients undergoing early PCI is challenging, our definition, which relied mainly on clinical and ECG signs of ischemia (10) within 24 h of admission but allowed for biomarker-based periprocedural myocardial infarction after 24 h, may have led to differential MI detection in the immediate- versus delayed-intervention groups. However, the 4 patients in the delayed-intervention group with a biomarker increase after PCI also had new-onset chest pain lasting >20 min and corresponding new ECG signs of ischemia. The prognostic significance of periprocedural MI in the setting of early intervention in NSTE-ACS patients, as defined across the previously conducted trials within the range of creatine kinase muscle-brain fraction of >1 to >5 ULN, remains controversial (24). Recent data estimated that for periprocedural MI to assume clinical relevance, it would have to be defined as an increase in creatine kinase muscle-brain fraction >10 or cardiac troponin >70 ULN (25,26).

Another potential limitation is the higher rate of surgical revascularization in patients assigned to delayed invasive strategy, which may have affected the outcomes due to longer delays associated with deferral to CABG and potential complications of surgical revascularization. However, the overall study results remained unaltered when patients treated with CABG were excluded from the analysis.

CONCLUSIONS

Our study showed that in initially stabilized patients with NSTEMI, immediate invasive intervention reduces the combined rate of mortality and new MI compared with delayed intervention at 30-day follow-up and persisting at 1 year. Immediate intervention had the largest effect on the reduction of new MI rate in the pre-catheterization period. Future studies with standardized protocols that include a clinically oriented definition of periprocedural MI, larger sample size, and longer term follow-up are needed to assess the true effect of immediate intervention in NSTEMI patients.

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PERSPECTIVES

WHAT IS KNOWN? Previous randomized studies indicated the potential of earlier invasive intervention to reduce rates of recurrent ischemia in NSTE-ACS patients but showed no mortality benefit and high between-study heterogeneity in the reported occurrence of new MI. However, clinical evidence regarding the effects of immediate invasive intervention in a high-risk population of NSTEMI patients is lacking.

WHAT IS NEW? An immediate invasive strategy in NSTEMI patients is associated with lower rates of death or MI at 30 days compared with a delayed invasive strategy with a median time delay to intervention of 61 h. The observed difference is mainly due to more frequent occurrence of new MI in the period before catheterization of patients referred to delayed invasive intervention.

WHAT IS NEXT? Further large randomized studies with longer term follow-up are needed to confirm these findings and to investigate whether the observed positive short-term effects of immediate invasive strategy in NSTEMI patients persist in the long term.

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KEY WORDS delayed intervention, immediate intervention, NSTEMI, randomized controlled trial