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Efficacy and Safety of Immediate Angioplasty Versus Ischemia-Guided Management After Thrombolysis in Acute Myocardial Infarction in Areas With Very Long Transfer Distances

Results of the NORDISTEMI (NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction)

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Objectives The goal of this study was to compare a strategy of immediate transfer for percutaneous coronary intervention (PCI) with an ischemia-guided approach after thrombolysis in patients with very long transfer distances to PCI.

Background Thrombolysis remains the treatment of choice in ST-segment elevation myocardial infarction (STEMI) when primary PCI cannot be performed within 90 to 120 min. The optimal treatment after thrombolysis is still unclear.

Methods A total of 266 patients with acute STEMI living in rural areas with more than 90-min transfer delays to PCI were treated with tenecteplase, aspirin, enoxaparin, and clopidogrel and randomized to immediate transfer for PCI or to standard management in the local hospitals with early transfer, only if indicated for rescue or clinical deterioration. The primary outcome was a composite of death, reinfarction, stroke, or new ischemia at 12 months, and analysis was by intention to treat.

Results The primary end point was reached in 28 patients (21%) in the early invasive group compared with 36 (27%) in the conservative group (hazard ratio: 0.72, 95% confidence interval: 0.44 to 1.18, p = 0.19). The composite of death, reinfarction, or stroke at 12 months was significantly reduced in the early invasive compared with the conservative group (6% vs. 16%, hazard ratio: 0.36, 95% confidence interval: 0.16 to 0.81, p = 0.01). No significant differences in bleeding or infarct size were observed.

Conclusions Immediate transfer for PCI did not improve the primary outcome significantly, but reduced the rate of death, reinfarction, or stroke at 12 months in patients with STEMI, treated with thrombolysis and clopidogrel in areas with long transfer distances. (Norwegian Study on District Treatment of ST-Elevation Myocardial Infarction; NCT00161005).
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Primary percutaneous coronary intervention (PCI) is the preferred treatment for patients with ST-segment elevation myocardial infarction (STEMI), if it can be delivered in a timely manner by an experienced team (1,2). However, in rural areas with long transfer distances to PCI centers, primary PCI cannot be performed within the recommended time limits and thrombolysis remains the treatment of choice (2). The optimal treatment after thrombolysis is still unclear. Several studies have shown a beneficial effect of early transfer for coronary angiography and PCI if indicated, but the exact timing of angiography, the adjunctive antithrombotic medication, and the strategy for the conservative group in these studies have differed (3–7). Furthermore, few

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of the studies have included patients with very long transfer distances. Long transfer distances to PCI might increase the need for early transfer in case of rescue indication, but also might increase the risk of complications.

Because more data are needed on the effects of early PCI after thrombolytic treatment for STEMI, we designed NORDISTEMI (NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction) (8). The goal of this trial was to compare the effects of 2 reperfusion strategies both applied after full-dose thrombolysis: to transfer all patients immediately for PCI or to manage the patients more conservatively with an ischemia-guided strategy. The study was performed in a rural area with long transfer distances to PCI and widespread use of pre-hospital thrombolysis.

Methods

The design features of NORDISTEMI have been published previously (8).

Patient selection. The study was conducted in 5 community hospitals in the southeastern part of Norway, with the interventional facility located at Oslo University Hospital, Ulleval. Enrollment was performed between February 2005 and April 2008 in a pre-defined area with 100- to 400-km transfer distances to PCI and a well-established system for pre-hospital thrombolysis. Table 1 shows the inclusion and exclusion criteria. The protocol was approved by the Regional Committee for Medical Research Ethics, and all patients provided written, informed consent in accordance with the revised Declaration of Helsinki.

Study design. All patients received standard weight-adjusted dose tenecteplase, aspirin 300 mg orally, and enoxaparin 30 mg intravenously followed by a subcutaneous dose of 1 mg/kg repeated every 12 h up to hospital discharge or revascularization for a maximum of 7 days. All patients also received clopidogrel 300 mg on the first day (9).

Table 1 Study Inclusion and Exclusion Criteria

Inclusion criteria
1. Age 18–75 yrs
2. Symptoms of myocardial infarction present for <6 h
3. ECG indicative of an acute STEMI: ≥2 mm ST-segment elevation in 2 contiguous precordial leads or ≥1 mm ST-segment elevation in 2 contiguous extremity leads or new left bundle branch block
4. Expected time delay from first medical contact to PCI >90 min
5. Receiving thrombolytic treatment with tenecteplase
6. Informed consent for participation
Exclusion criteria
1. Standard exclusion criteria for tenecteplase
2. Cardiogenic shock or serious arrhythmias at randomization
3. Pregnancy
4. Known serious renal failure (serum creatinine >250 mmol/l)
5. Other diseases with life expectancy <12 months
6. Psychiatric disease, mental retardation, dementia, drug abuse, alcoholism, or conditions that can severely reduce compliance

ECG = electrocardiogram; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Abbreviations and Acronyms

CI = confidence interval
ECG = electrocardiogram
HR = hazard ratio
IQR = interquartile range
PCI = percutaneous coronary intervention
SPECT = single-photon emission computed tomography
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

Eligible patients were asked for participation at the same time as thrombolysis was given, and randomized in a 1:1 way to an early invasive or a conservative strategy. Permuted block randomization stratified by site, and sealed envelopes containing treatment modality according to random numbers were used. The random allocation sequence was generated at the Center for Clinical Research, Oslo University Hospital, Ulleval.

Patients assigned to the early invasive strategy were transferred to the PCI center as soon as possible after thrombolysis, for immediate coronary angiography and angioplasty of the infarct-related artery if indicated (≥50% diameter stenosis). The choice of stent type and use of glycoprotein IIb/IIIa inhibitor were at the operator's discretion. Likewise, referral for surgery in case of left main coronary artery disease or serious 3-vessel disease was left to the judgment of the operator.

Patients assigned to conservative treatment were admitted to (in case of pre-hospital thrombolysis) or kept in the community hospitals for continued care, with referral for urgent angiography if persistent chest pain and <50% reduction of ST-segment elevation 60 min after initiation of thrombolysis (rescue indication) or hemodynamic instability. Referral for early coronary angiography was recommended if the patient had spontaneous recurrent ischemia with or without electrocardiogram (ECG) changes, or if signs of ischemia (chest pain, significant ST-segment changes, hypotension, or ventricular tachycardia) occurred in the exercise ECG recommended before hospital discharge. In all other patients, coronary angiography as a routine assessment after successful thrombolysis was encouraged within 2 to 4 weeks after discharge.

Beta-blockers and statins were administered to all patients unless contraindicated, angiotensin-converting enzyme inhibitors when indicated. Patients receiving stents were recommended clopidogrel 75 mg daily for 9 months. The other patients were recommended clopidogrel until angiography was performed or for 9 months, at the discretion of the treating physician. Complete clinical follow-up was performed at 3 and 12 months, and telephone follow-up was performed at 1 and 7 months. Troponin-T levels were measured in all patients the third morning after onset of STEMI, and myocardial perfusion single-photon emission computed tomography (SPECT) was scheduled after 3 months.

End points and definitions. The primary end point was a composite of death, reinfarction, stroke, or new myocardial ischemia at 12 months. Reinfarction in the first 18 h was defined as recurrent symptoms of ischemia at rest accompanied by new ST-segment elevation of ≥0.1 mV in at least 2 contiguous leads, lasting ≥30 min. After 18 h, the definition was: new Q waves in 2 or more leads, or new increase in concentrations of creatine kinase-MB or troponins above the upper limit of normal (>3× upper limit of normal after PCI and >5× upper limit of normal after coronary artery bypass graft), and >50% higher than the previous value. Stroke was defined as a new focal, neurological deficit of vascular origin lasting more than 24 h. New myocardial ischemia was defined as unstable angina (chest pain at rest suspicious for coronary disease with or without ECG changes), recurrent angina grade II to IV (Canadian Cardiovascular Society classification) or serious arrhythmias (ventricular tachycardia/ventricular fibrillation) that appeared more than 12 h after randomization.

The secondary end points included a composite of death, stroke, or reinfarction at 12 months, transport-related complications, bleeding at 30 days, and infarct size. Bleeding complications were classified according to the GUSTO (Global Use of Strategies To Open coronary arteries) severity scale (10). Infarct size was assessed by SPECT (11,12), and by troponin T levels (13,14).

A blinded, independent Clinical Event Committee adjudicated all possible events related to the primary outcome. The SPECT analysis and processing of recordings and the evaluation of all angiograms were performed by people unaware of the clinical data and treatment allocation. An independent monitor verified a random sample of 20% of the patient data entry into the case-report forms against the patient's medical records.

Statistical analysis. On the basis of previous reports (3–5), we anticipated that the occurrence of the primary end point would be 30% in the conservative group and 15% in the early invasive group. With a 2-sided alpha of 5% and a power of 80%, a total of 266 patients were required. Statistical analyses were performed according to the intention-to-treat principle. Continuous variables were expressed as median with interquartile range (IQR) or mean ± SD, and compared between groups using the Mann-Whitney *U* test or 2-sample *t* tests, respectively. Categorical variables were expressed as frequency (percentage) and compared using the chi-square test with Yates correction or Fisher exact test, as appropriate. Estimation of the cumulative primary event rate was performed with the Kaplan-Meier method, and events over time were compared using the log rank test. The Cox proportional hazards model was used to estimate the treatment effect as unadjusted hazard ratio (HR) with 95% confidence intervals (CIs). A 2-sided value of $p < 0.05$ was considered significant. Patient data and analysis results were managed in a database/analysis program (Epi Data/Epi Info version 3.4.3, 2007, Centers for Disease Control and Prevention, Atlanta, Georgia).

Results

Baseline characteristics. During the enrollment period, 524 patients were treated with thrombolysis for STEMI and screened for participation in the study, and 276 patients (53%) were subsequently included (Fig. 1). Ten patients were secondarily excluded because of violation of inclusion or exclusion criteria. Thus, 134 patients were left to follow-up in the early invasive and 132 in the conservative group. With the exception of 2 patients with very short time to treatment, all included patients had their STEMI diagnosis supported by increase of troponin concentrations above the upper limit of normal. In the conservative group, there was a higher prevalence of hypertension and a higher heart rate at randomization. Otherwise, the baseline characteristics were well balanced between the groups (Table 2).

Treatment received. Among all, 57% received thrombolysis in the pre-hospital setting, and time delay from symptom onset to thrombolysis was 123 min (IQR 80 to 195 min). Invasive procedures performed in the 2 groups are described in Table 3. Most patients in both groups were referred to coronary angiography, but the procedure was delayed by a median time of 5.5 days in the conservative compared with the early invasive group. The total number of PCI procedures was significantly higher in the early invasive group. In contrast, the number of coronary bypass grafts was higher in the conservative group (p = NS).

In the conservative group, 36 patients (27%) were transferred for rescue coronary intervention, and 32 patients underwent rescue PCI. Distances, delays, and Thrombolysis In Myocardial Infarction (TIMI) flow grade in this rescue group, compared with the early invasive group, are presented in Table 4. The rescue group had their PCI performed significantly later than the early invasive group, but no differences in the rate of TIMI flow grade 3 were observed, neither before nor after PCI (Table 4). Of the remaining 96 patients, 89 underwent angiography at a median time of 11 days (IQR 3 to 23 days) after randomization, and PCI was performed in 62 patients (65%); TIMI flow grade 3 was found in 77 of these patients (87%) before intervention.

At discharge, 98% of patients were prescribed aspirin, 92% clopidogrel, 90% beta-blockers, and 99% statins, with no difference between groups. The use of agents acting on the renin-angiotensin system was higher in the conservative (60%) compared with the invasive (42%) group. At 1 year, medication was unchanged except for clopidogrel, which was used in only 21% of patients (no difference between groups). At 7 months, 83% of patients were still taking clopidogrel.

Clinical outcome. The clinical outcomes at 30 days and 12 months are listed in Table 5. The primary end point at 12

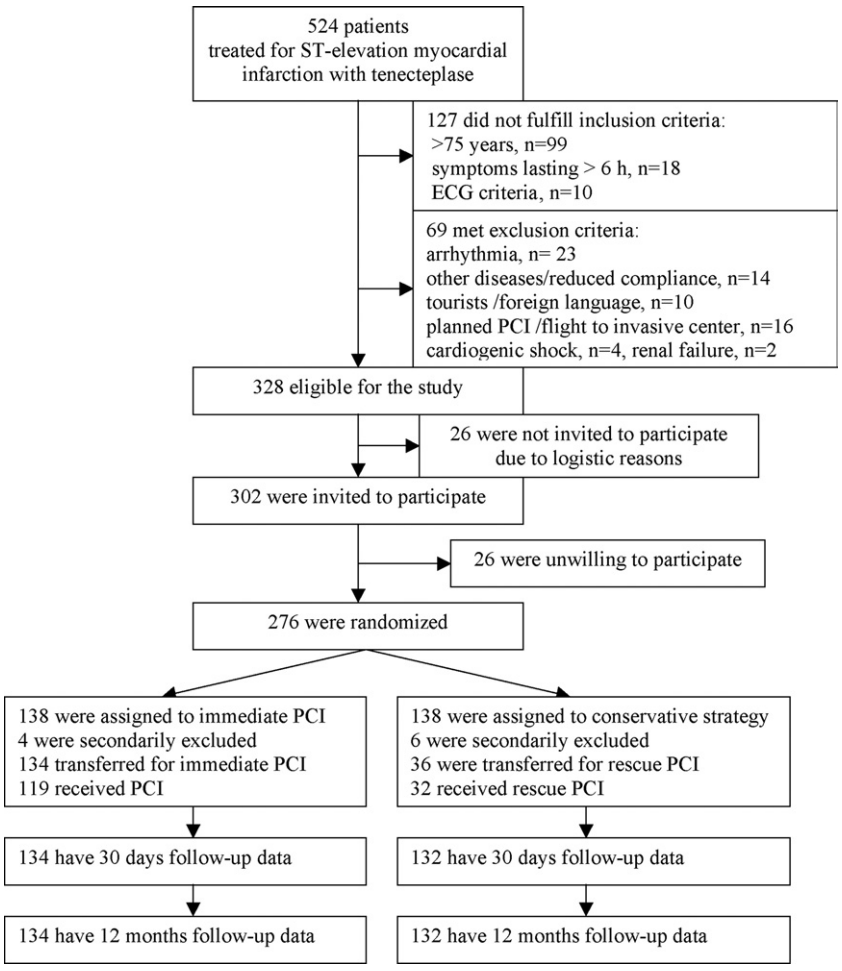

Figure 1 **Study Flow Chart**

ECG = electrocardiogram; PCI = percutaneous coronary intervention.

months occurred in 28 patients (21%) in the early invasive group and in 36 patients (27%) in the conservative group (HR: 0.72, 95% CI: 0.44 to 1.18, p = 0.19) (Fig. 2A). The secondary composite end point of death, stroke, or reinfarction at 12 months occurred in 8 patients (6%) in the early invasive group and in 21 patients (16%) in the conservative group (HR: 0.36, 95% CI: 0.16 to 0.81, p = 0.01) (Fig. 2B). The overall mortality was 2.6%. The causes of death were cardiogenic shock (n = 3), intracranial hemorrhage (n = 2), cerebral infarction (n = 1), and cancer (n = 1).

At 30 days, the combined incidence of death, reinfarction, stroke, or new ischemia was significantly reduced in the early invasive compared with the conservative group (10% vs. 21%, relative risk: 0.49, 95% CI: 0.27 to 0.89, p = 0.03). The incidence of the secondary composite end point at 30 days was also lower in the invasive group (4.5% vs. 9.8%, relative risk: 0.45, 95% CI: 0.18 to 1.16, p = 0.14).

No significant difference was observed in risk of bleeding between the 2 groups (Table 6). Only 2 patients (0.8%) received blood transfusion. All severe bleedings were caused by intracranial hemorrhages. In these 5 patients (1.9%), onset of symptoms was <12 h after thrombolysis.

The transfer distances from first medical contact to the PCI center were long, with a median distance of 158 km (IQR 129 to 200 km) in the early invasive group (Table 4). One patient (0.7%) died during transfer, and 4 (3%) were successfully defibrillated in the early invasive group. In the conservative group, 2 patients had ventricular tachycardia treated with intravenous drugs.

Infarct size. After 3 months, SPECT with determination of infarct size was performed in 125 (93%) patients in the early invasive and 120 patients (91%) in the conservative group. Eighty-two patients (34%) had no signs of infarction. Median infarct size, estimated as percent of the left ventricle, was 7% (IQR 0% to 24%) in the early invasive group compared with 6% (IQR 0% to 19%) in the conservative group (p = 0.29). Furthermore, no significant differ-

Table 2 Baseline Characteristics at Randomization

	Early Invasive Group (n = 134)	Conservative Group (n = 132)	p Value
Age (yrs)	60 (55, 67)	61 (53, 68)	0.98
Men	107 (80%)	94 (71%)	0.13
Body mass index (kg/m^2)	26.5 (24.7, 30.0)	26.4 (24.1, 30.0)	0.21
Total cholesterol (mmol/l)	5.2 (1.1)	5.4 (1.1)	0.11
Treated hypertension	33 (25%)	50 (38%)	0.03
Diabetes mellitus	8 (6%)	10 (8%)	0.78
Current or previous smoker	106 (79%)	104 (79%)	0.93
Family history of coronary heart disease	77 (58%)	78 (59%)	0.88
Previous angina	17 (13%)	17 (13%)	0.89
Previous myocardial infarction	15 (11%)	14 (11%)	0.97
Previous coronary bypass graft	4 (3%)	3 (2%)	1.0
Previous angioplasty	9 (7%)	12 (9%)	0.62
Infarct location on ECG			
Anterior	59 (44%)	51 (39%)	0.44
New left bundle branch block	4 (3%)	0 (0%)	0.12
Nonanterior	71 (53%)	81 (61%)	0.21
Blood pressure before thrombolysis (mm Hg)			
Systolic	133.4 (22.9)	134.2 (22.4)	0.74
Diastolic	80.7 (15.2)	82.0 (15.9)	0.48
Heart rate (beats/min)	65.3 (14.6)	70.7 (17.6)	0.02
Time intervals (min)			
Symptom onset to first medical contact	67 (34, 122)	65 (40, 135)	0.68
Symptom onset to tenecteplase	117 (80, 195)	126 (80, 195)	0.72
Pre-hospital tenecteplase	80 (60%)	71 (54%)	0.40

Data are median (25th, 75th percentiles), mean (SD), or n (%).
ECG = electrocardiogram; RAS = renin-angiotensin system.

ence in third-day troponin-T concentration was found between the early invasive (n = 126) and the conservative group (n = 130) (1.75 μg/l [IQR 0.86 to 2.92 μg/l] vs. 2.08 μg/l [IQR 0.78 to 3.97 μg/l], p = 0.38).

Discussion

Even the best-organized networks between ambulance service, community hospitals, and PCI centers cannot make

Table 3 Invasive Procedures in the 2 Randomization Groups

	Early Invasive Group (n = 134)	Conservative Group (n = 132)	p Value
Coronary angiography performed	133 (99%)	125 (95%)	0.04
Time from TNK to arrival at catheterization laboratory	130 (105, 155) min	5.5 (0, 17.5) days	<0.001
Angiography within 3 h of TNK	111 (83%)	16 (12%)	<0.001
Angiography within 12 h of TNK	133 (99%)	43 (33%)	<0.001
Angiography within 30 days	133 (99%)	114 (86%)	<0.001
PCI performed	119 (89%)	94 (71%)	0.001
Time from TNK to first balloon	163 (137, 191) min	3.0 (0, 13) days	<0.001
Radial access	111 (83%)	118 (89%)	0.17
Stents implanted	115 (86%)	90 (68%)	0.001
Bare-metal stents	111 (83%)	80 (61%)	<0.001
Drug-eluting stents	4 (3%)	10 (8%)	0.16
Abciximab	16 (14%)	8 (6%)	0.14
Thrombectomy	0 (0%)	1 (0.8%)	0.5
Intra-aortic balloon pump	2 (1.5%)	2 (1.5%)	1.0
CABG performed	9 (7%)	16 (12%)	0.19
CABG within 7 days	2 (1.5%)	0 (0%)	0.50
Repeat angiography during follow-up	23 (17%)	17 (13%)	0.42
Repeat PCI during follow-up	15 (11%)	9 (7%)	0.30

Data are n (%) or median (25th, 75th percentiles).
CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; TNK = tenecteplase.

Table 4 Transfer Distances, Time Intervals, and Angiographic Characteristics of the Early Invasive Group and the Rescue Population of the Conservative Group

	Early Invasive Group (n = 134)	Conservative/Rescue Group (n = 36)	p Value
Transport distance from first medical contact to PCI center (km)	158 (129, 200)	180 (132, 234)	0.39
Time from tenecteplase to arrival at catheterization laboratory (min)	130 (105, 155)	187 (149, 240)	<0.001
Immediate/rescue PCI performed	118 (88%)	32 (89%)	1.0
Time from tenecteplase to first balloon (min)	162 (137, 189)	209 (193, 247)	<0.001
Symptom onset to first balloon (min)	302 (236, 380)	340 (279, 400)	0.04
Infarct-related artery			
Left anterior descending artery	62 (47%)	19 (53%)	0.61
Left circumflex artery	12 (9%)	0 (0%)	0.07
Right coronary artery	55 (41%)	15 (42%)	0.90
Graft	3 (2%)	1 (3%)	1.0
Not identified	1 (1%)	1 (3%)	0.38
TIMI flow grade pre-PCI	(n = 133)	(n = 36)	
0	17 (13%)	9 (25%)	0.12
1	10 (8%)	2 (6%)	1.0
2	39 (29%)	8 (22%)	0.54
3	67 (50%)	17 (47%)	0.91
TIMI flow grade post-PCI	(n = 118)	(n = 32)	
0	2 (2%)	1 (3%)	0.52
1	2 (2%)	0 (0%)	1.0
2	11 (9%)	3 (9%)	1.0
3	103 (87%)	28 (88%)	1.0

Data are median (25th, 75th percentiles) or n (%).
PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

primary PCI available in a timely manner to all patients with STEMI. The NORDISTEMI study was designed to assess the optimal treatment for patients with STEMI living in rural areas where thrombolysis is the primary revascularization therapy. The effect of early invasive treatment after thrombolysis in areas with very long transfer distances have not been evaluated previously.

In the NORDISTEMI study, the median transfer distance to PCI was 158 km, and the median transfer time was 130 min. The early invasive strategy was associated with a reduction in the primary end point at 12 months compared with a conservative strategy, but the reduction did not reach statistical significance. Recent trials evaluating the effect of early angioplasty after thrombolysis, including the recent TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) study (15), have reported a significantly improved outcome with an early invasive strategy (3–7,15,16). Timing of PCI after thrombolysis, control-group interventions, and definitions of end points have varied considerably among these trials and might contribute to this discrepancy. Furthermore, it should be noted that at 30 days, the composite of death, reinfarction, stroke, and new ischemia was significantly reduced in the invasive group, in accordance with previous trials (relative risk: 0.49, p = 0.03).

Table 5 Clinical Outcomes at 30 Days and 12 Months

	Early Invasive Group (n = 134)	Conservative Group (n = 132)
At 30 days		
Death, reinfarction, stroke, or new ischemia	14 (10.0%)	28 (21.2%)
Death, reinfarction, or stroke	6 (4.5%)	13 (9.8%)
Death	3 (2.2%)	3 (2.3%)
Reinfarction	2 (1.5%)	7 (5.3%)
Stroke	3 (2.2%)	5 (3.8%)
Recurrent ischemia	8 (6.0%)	16 (12.1%)
At 12 months		
Death, reinfarction, stroke, or new ischemia	28 (20.9%)	36 (27.3%)
Death, reinfarction, or stroke	8 (6.0%)	21 (15.9%)
Death	3 (2.2%)	4 (3.0%)
Reinfarction	4 (3.0%)	12 (9.1%)
Stroke	3 (2.2%)	7 (5.3%)
Recurrent ischemia	20 (15.0%)	20 (15.2%)

Data are n (%).

Both in our study and in the TRANSFER-AMI trial (15), an antithrombotic regimen including enoxaparin and clopidogrel was given in addition to full-dose tenecteplase. The early addition of clopidogrel to aspirin and fibrinolytic treatment has been shown to reduce the risk of cardiac events (9,17), but has not been used in previous trials investigating the effect of early PCI after thrombolysis.

Compared with most previous studies (3,4,7), a more liberal referral for angiography in the conservative group was allowed, and 95% of patients underwent angiography at a medium time of 5.5 days after thrombolysis. This more aggressive treatment of the conservative group in our study, with liberal referral to coronary angiography

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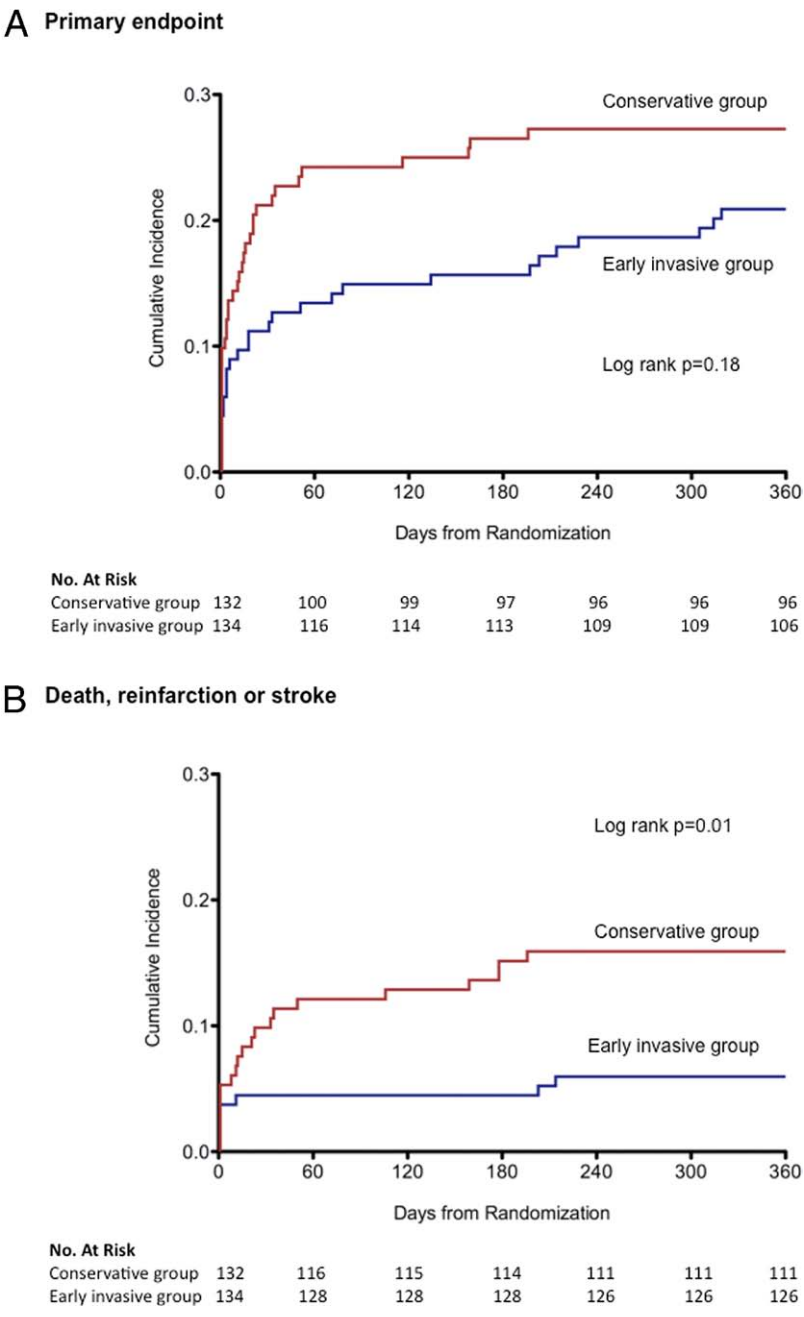

Figure 2 Kaplan-Meier Curves

Kaplan-Meier curves for **(A)** the primary outcome (composite of death, reinfarction, stroke, or new ischemia) and **(B)** the composite of death, stroke, or reinfarction.

and early addition of clopidogrel, has probably reduced the difference between groups at 12 months. Furthermore, no high-risk characteristics were demanded for inclusion in our study. This benign risk profile of the cohort may have prevented the demonstration of a more significant benefit.

The risk reduction associated with an early invasive strategy in previous studies has mainly been attributed to reductions in reinfarction or recurrent ischemia. Our study was not powered to look at individual end points. However, the rate of new ischemia was numerically similar in both groups. New ischemia was approved as an end point without ECG changes, and this soft definition might have resulted in misclassification of some events. Therefore, the secondary composite end point of death, reinfarction, and stroke at 12 months should be noted, being significantly reduced in the early invasive group compared with the conservative group (HR: 0.36, $p = 0.01$).

Table 6 30-Day Bleeding Events (GUSTO Classification)

	Early Invasive Group (n = 134)	Conservative Group (n = 132)	p Value
Severe bleeding, including ICH	2	3	
Moderate bleeding	0	3	
Minor bleeding	14	13	
All	16 (12%)	19 (14%)	0.68

Data are n or n (%).
GUSTO = Global Use of Strategies To Open coronary arteries; ICH = intracranial hemorrhage.

The rate of bleeding was low and did not differ between groups. Use of radial approach in 86% of patients together with limited use of glycoprotein IIb/IIIa inhibitors (9%) were probably the main reasons for the low number of GUSTO minor and moderate bleedings (18). The rate of GUSTO severe bleeding was as reported in other trials (1.9%); however, the rate of intracranial hemorrhage was higher than expected (19). The heavy loading of patients with antithrombotic drugs might be of concern, but recent analysis has not shown any increase in intracranial hemorrhages when adding enoxaparin and clopidogrel to fibrinolytic treatment (20).

Trials such as the NORDISTEMI study, in which PCI is performed a few hours after fibrinolysis, are different from the approach of performing PCI immediately after fibrinolysis (facilitated PCI), which has been associated with no clinical benefit compared with primary PCI (21,22). The time between fibrinolysis and PCI might have been too short in these studies (90 to 104 min).

The optimal time window for early PCI after fibrinolysis is unsettled. Five recent studies investigating the effect of early PCI after fibrinolysis had intervals from fibrinolysis to PCI ranging from 2 to 17 h (3–5,7,15). In our study, the median time from fibrinolysis to PCI was 163 min (2.7 h) in the early invasive group. Although short delays, the incidence of death, reinfarction, or stroke at 30 days was low (4.5%). We might speculate that the antithrombotic cotherapy used in our study has mitigated the early thrombotic complications observed in the ASSENT-4 (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) trial (21), and that this antithrombotic regimen together with use of a radial approach, might allow a shorter time between fibrinolysis and PCI.

Information about the risk of adverse events during transfer of STEMI patients has mostly come from studies comparing transfer for primary PCI to local thrombolysis (1). Although considerably longer transfer distances in the NORDISTEMI study, the occurrence of transfer complications in the early invasive group was consistent with previous results.

The median infarct sizes determined by SPECT at 3 months were small and did not differ significantly between groups. One-third of patients had no visible infarctions at SPECT. The very short median time of 123 min from symptom onset to fibrinolysis, with 25% of patients treated within 80 min, might contribute to this high percentage of invisible infarctions (23). A previous trial has reported smaller infarct sizes with early angioplasty compared with conventional care after thrombolysis (24). Because of the long transfer distances in the NORDISTEMI study, median time from symptom onset to first balloon was 5 h in the early invasive group, being beyond the time limit for major myocardial salvage (25).

Both the small infarct sizes and the low 1-year mortality (2.6%) might reflect the short time to treatment obtained by means of a well-organized system for pre-hospital thrombolysis (26,27). Our study indicates a potential for improving reperfusion strategies for patients living in rural areas with long transfer distances to PCI. This may be achieved by applying a well-organized pharmacoinvasive approach including pre-hospital thrombolysis and rapid transfer to an invasive center.

Study limitations. This study was powered only to detect differences in the primary composite end point, but not for the individual components of the end point or for safety. Because of the design of the trial, infarct size was not assessed in the acute phase. The open-label design might have introduced some bias. However, the clinical end points were adjudicated by an event committee blinded to the allocated treatment, and infarct size was assessed without knowledge of treatment assignment.

Unfortunately, randomization was not entirely successful in producing balanced groups. It cannot be ruled out that the small imbalance might have had some confounding effect on the outcome.

The study did not question the superiority of timely primary PCI over thrombolysis. At the time when the NORDISTEMI study was initiated, transfer for primary PCI in areas with more than 2-h delays was not an option because of ethical reasons.

According to the inclusion and exclusion criteria, the conclusions of the study are applicable only to STEMI patients age <76 years with symptom onset <6 h, without cardiogenic shock at randomization and with long transfer delays to primary PCI.

Conclusions

Although the study did not show any significant reduction in the primary outcome at 12 months, the significant reduction in the composite of death, reinfarction, or stroke suggests that an early invasive strategy may be the preferred option in patients receiving thrombolytic therapy, also in areas with long transfer distances. These findings might be taken into consideration when making algorithms for treatment of STEMI in rural areas.

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REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.
2. Van de Werf F, Bax J, Betriu A, et al., for the Task Force on the Management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. Eur Heart J 2008;29:2909–45.
3. Fernandez-Avilés F, Alonso JJ, Castro-Beiras A, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. Lancet 2004;364:1045–53.
4. Le May MR, Wells GA, Labinaz M, et al. Combined angioplasty and pharmalogical intervention versus thrombolysis alone in acute myocardial infarction. J Am Coll Cardiol 2005;46:417–24.
5. Scheller B, Hennen B, Hammer B, et al. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. J Am Coll Cardiol 2003;42:634–41.
6. Armstrong PW. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction: the WEST (Which Early ST-elevation myocardial infarction Therapy) study. Eur Heart J 2006;27:1530–8.
7. Mario CD, Dudek D, Piscione F, et al. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): an open, prospective, randomised multicenter trial. Lancet 2008;371:559–68.
8. Bohmer E, Arnesen H, Abdelnoor M, Mangschau A, Hoffmann P, Halvorsen S. The Norwegian study on district treatment of ST-elevation myocardial infarction (NORDISTEMI). Scand Cardiovasc J 2007;41:32–8.
9. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179–89.
10. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–82.
11. Benoit T, Vivegnis D, Foulon J, Rigo P. Quantitative evaluation of myocardial single-photon emission tomographic imaging: application to the measurement of perfusion defect size and severity. Eur J Nucl Med 1996;23:1603–12.
12. Halvorsen S, Muller C, Bendz B, Eritsland J, Brekke M, Mangschau A. Left ventricular function and infarct size 20 months after primary angioplasty for acute myocardial infarction. Scand Cardiovasc J 2001;35:379–84.
13. Giannitsis E, Steen H, Kurz K, et al. Cardiac magnetic resonance imaging study for quantification of infarct size comparing directly serial versus single time-point measurements of cardiac troponin T. J Am Coll Cardiol 2008;51:307–14.
14. Bohmer E, Hoffmann P, Abdelnoor M, Seljeflot I, Halvorsen S. Troponin T concentration 3 days after acute ST-elevation myocardial infarction predicts infarct size and cardiac function at 3 months. Cardiology 2009;13:207–12.
15. Cantor WJ, Fitchett D, Borgundvaag B, et al. Routine early angioplasty after fibrinolysis for acute myocardial infarction. N Engl J Med 2009;360:2705–18.
16. Wijeysundera HC, You JJ, Nallamathou BK, Krumholz HM, Cantor WJ, Ko DT. An early invasive strategy versus ischemia-guided management after fibrinolytic therapy for ST-segment elevation myocardial infarction: a meta-analysis of contemporary randomized controlled trials. Am Heart J 2008;156:564–72.
17. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: a randomised placebo-controlled trial. Lancet 2005;366:1607–21.
18. De Carlo M, Borelli G, Gistri R, et al. Effectiveness of the transradial approach to reduce bleedings in patients undergoing urgent coronary angioplasty with GPIIb/IIIa inhibitors for acute coronary syndromes. Catheter Cardiovasc Interv 2009;74:408–15.
19. Van De Werf F, Adgey J, Ardissino D, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet. 1999;354:716–22.
20. Sabatine MS, Morrow DA, Dalby A, et al. Efficacy and safety of enoxaparin versus unfractionated heparin in patients with ST-segment elevation myocardial infarction also treated with clopidogrel. J Am Coll Cardiol 2007;49:2256–63.
21. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. Lancet 2006;367:569–78.
22. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205–17.
23. Verheugt FWA, Gersh BJ, Armstrong PW. Aborted myocardial infarction: a new target for reperfusion therapy. Eur Heart J 2006;27:901–4.
24. Thiele H, Engelmann L, Elsner K, et al. Comparison of pre-hospital combination-fibrinolysis plus conventional care with pre-hospital combination-fibrinolyse plus facilitated percutaneous coronary intervention in acute myocardial infarction. Eur Heart J 2005;26:1956–63.
25. Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of future? JAMA 2005;293:979–86.
26. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. JAMA 2000;283:2686–92.
27. Danchin N, Durand E, Blanchard D. Pre-hospital thrombolysis in perspective. Eur Heart J 2008;29:2835–42.

Key Words: acute myocardial infarction ■ ST-segment elevation ■ pre-hospital thrombolysis ■ percutaneous coronary intervention.

APPENDIX

For SPECT details and a complete list of contributors, committees, and sites, please see the online version of this article.