Long-term Outcome of Primary Percutaneous Coronary Intervention vs Prehospital and In-Hospital Thrombolysis for Patients With ST-Elevation Myocardial Infarction

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Context Whether the superior results of percutaneous coronary intervention (PCI) reported in clinical trials in which patients with ST-segment elevation myocardial infarction (STEMI) received reperfusion treatment can be replicated in daily practice has been questioned, especially whether it is superior to prehospital thrombolysis (PHT).

Objective To evaluate the outcome of different reperfusion strategies in consecutive STEMI patients.

Design, Setting, and Patients A prospective observational cohort study of 26 205 consecutive STEMI patients in the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) who received reperfusion therapy within 15 hours of symptom onset. The registry includes more than 95% of all Swedish patients, of all ages, who were treated in a coronary intensive care unit between 1999 and 2004.

Interventions Seven thousand eighty-four patients underwent primary PCI; 3078, PHT; and 16 043, in-hospital thrombolysis (IHT).

Main Outcome Measures Mortality, reinfarction, and readmissions as reported in the National Health Registries through December 31, 2005.

Results After adjusting for younger age and less comorbidity, primary PCI was associated with lower mortality than IHT at 30 days (344 [4.9%] vs 1834 [11.4%]; hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.53-0.71) and at 1 year (541 [7.6%] vs 2555 [15.9%]; HR, 0.68; 95% CI, 0.60-0.76). Also primary PCI correlated with lower mortality than PHT at 30 days (344 [4.9%] vs 234 [7.6%]; HR, 0.70; 95% CI, 0.58-0.85) and 1 year (541 [7.6%] vs 317 [10.3%]; HR, 0.81; 95% CI, 0.69-0.94). Prehospital thrombolysis predicted a lower mortality than IHT at 30 days (HR, 0.87; 95% CI, 0.76-1.01) and at 1 year (HR, 0.84; CI 0.74-0.95). Beyond 2 hours' treatment delay, the observed mortality reductions with PHT tended to decrease while the benefits with primary PCI seemed to remain regardless of time delay. Primary PCI was also associated with shorter hospital stay and less reinfarction than either PHT or IHT.

Conclusions In unselected patients with STEMI, primary PCI, which compared favorably with IHT and PHT, was associated with reduced duration of hospital stay, readmission, reinfarction, and mortality.

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Since the late 1980s acute reperfusion with fibrinolytic drugs has been the primary treatment in ST-segment elevation myocardial infarction (STEMI). However, primary percutaneous coronary intervention (PCI) is associated with higher rates of reperfusion and lower risks of reocclusion and reinfarction.[1-3] The initial series of randomized trials comparing primary PCI with in-hospital thrombolytic therapy showed no consistent differences in long-term mortality.[4] However, after additional trials[5,6] several recent meta-analyses[3,7] now provide evidence of improved survival. Still it has been questioned whether similar results are achieved in the real-life setting[8] or if prehospital thrombolysis (PHT) given within the first hours after onset of symptoms provides similar results as primary PCI.[9] Therefore we compared the outcomes of primary PCI with PHT and in-hospital thrombolysis (IHT) in STEMI patients admitted between 1999 and 2004 in the Swedish national prospective registry.

METHODS

The Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) registers all patients admitted to 75 of 78 hospitals with coronary care units. The full protocol has been published.[10] (Detailed information is available at http://www.riks-hia.se.) Survival status of all patients was obtained by merging the

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RIKS-HIA database with the National Cause of Death Register. Hospital admissions for cardiovascular disease were obtained by merging with the National Patient Register. Reinfarction after discharge was defined as a rehospitalization with a discharge diagnosis including MI. A new MI causing immediate death and no hospitalization was not included in the reinfarction category but was included in the mortality statistics. All patients for whom data were entered into RIKS-HIA were informed of their participation in the registry and the long-term follow-up. According to Swedish law written consent is not necessary. On admission patients receive written information about RIKS-HIA and other quality registries. They have the right to deny participation immediately or have it removed later. Data used for research purposes have had all personal identifiers removed. The study was approved by the ethics committee and the Epidemiological Centre of the Swedish National Board of Health and Welfare.

All patients fulfilling both criteria of ST-segment elevation on the electrocardiogram (ECG) at entry and with acute MI as the final diagnosis were included. *ST-elevation* was defined as significant ST-segment elevation in at least 2 adjacent leads[12] but was not considered in cases of left-bundle branch block or pacemaker ECG. The criteria for the diagnosis of acute MI were standardized and identical for all participating hospitals using the World Health Organization and Joint European Society of Cardiology/American College of Cardiology Committee criteria.[11,12] Delay times were calculated from onset of symptoms to initiation of reperfusion therapy, ie, start of intravenous administration of fibrinolytic therapy or when local anesthetics was given to access artery for primary PCI procedure. Data verification was performed by comparing entered data in RIKS-HIA database with the hospital records of 1972 randomly chosen patients at 38 different hospitals with 97% concordance among the 24 covariates included in the Cox regression models.

Prehospital thrombolysis was available at about half of the hospitals in Sweden, and required ECG telemetry by radio-wave to the hospital where the cardiologist on call made the decision whether to start thrombolysis in the ambulance or not. There were never physicians in the ambulances, but at least one of the ambulance staff had to be a fully qualified nurse; protocols have been published elsewhere.[13]

Statistical Analysis

Cox proportinal hazard regression analyses were performed to estimate the hazard of mortality in the 3 groups of reperfusion treatment. To compensate for the nonrandomized study design a propensity score for the likelihood of receiving primary PCI was calculated. This score was calculated using 25 variables including: age, sex, history of important diseases (including diabetes mellitus, previous MI, coronary artery revascularization, congestive heart failure, hypertension, peripheral artery disease, stroke, dementia, renal failure, chronic pulmonary disease, cancer within 3 years), medications before study entry (including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, anticoagulants, aspirin and/or thienopyridines, β-blockers, digitalis, diuretics, lipid-lowering drugs, and long-acting nitrates), circulatory arrest on arrival, admission year, in-house catheterization laboratory, age as second-degree polynomial, and access to 24-hour in-house PCI services. All Cox regression analyses were performed with the same first 23 variables as in the propensity score model, the type of hospital (primary, secondary, or tertiary), and the propensity score itself. Killip class was registered on arrival to hospital, and when included in the models, it disfavored PHT where successful therapy in the ambulance could improve or prevent worse Killip class as previously shown.[14] Including Killip class in the models made no difference to the results of primary PCI, so it was excluded.

A sensitivity analysis was performed for patients who survived to hospital discharge in which adjustments were made for propensity to receive primary PCI and for which discharge medications were prescribed.

Analysis of mortality in relation to delay time was performed for the 21 227 patients for whom both the time for onset of symptoms and start of reperfusion were available and whose delay time did not exceed 15 hours. Adjustment for age was performed by the method of direct standardization based on a division of age into tertiles. Mortality rates within each of the 3 treatment strata were thus standardized to reflect an age distribution similar to the one for the 3 groups combined. The same analysis was also performed using the propensity score. A smooth estimate of the relation between the standardized rates and delay times was calculated by the loess method. Furthermore, separate Cox regression models were fitted for the subpopulations: reperfusion treatment before and after 2 hours from symptom onset, respectively. To evaluate if the effects of the treatments were different when initiated before and after 2 hours,an interaction term between treatment and time interval was included in the model. The reason for evaluation of outcome in relation to a dichotomization at 2 hours' delay time was based on the results in the Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction (CAPTIM) trial[9] and other studies.[15,16]

Lengths of hospital stay for the 3 reperfusion treatment groups were compared by fitting a Cox regression model including the propensity score. Comparison of in-hospital reinfarction was evaluated by logistic regression analysis including the same variables as that in the mortality model.

Statistical analyses were performed with R version 2.3.1 with survival package 2.28 (R foundation for Statistical Computing; available at http://www.R-project.org) and SPSS software version 14.0 (SPSS Inc, Chicago, Ill). All *P* values were 2-sided, and a value of

<.05 was considered statistically significant. The proportional hazards assumption was confirmed by studying the mortality curves.

RESULTS

Hospital and Baseline Characteristics

Out of 39 192 STEMI patients of all ages included between 1999 and 2004 in the RIKS-HIA registry 26 205 (66.9%) received reperfusion therapy with a range between centers of 50.5% to 84.0%. Primary PCI was used for 7084 (18.2%; range, 0%-54.5%), PHT was used for 3078 (8.3%; range, 0%-28.6%), and IHT was used for 16 043 (41.3%; range, 13.4%-84.0%). Compared with IHT, patients receiving PHT and primary PCI were younger, were more often men and current smokers, had less often experienced heart failure, were slightly less often taking diuretics, and had a better Killip class (TABLE 1). Because patients receiving primary PCI were the youngest with more previous coronary intervention, they more often took aspirin, β-blocker, and statin on admission than those who received thrombolysis.

Treatments and Development Over the Years

In 1999, 8.3% of STEMI patients underwent primary PCI because, at the time, it was mainly used for patients with cardiogenic shock and large anterior wall infarctions. Use of primary PCI gradually increased to 37.2% in 2004. FIGURE 1 illustrates that as PCI use gradually increased from the years 1999 through 2004, it has been associated with comparative reduction in 1-year mortality, as evaluated by propensity score–adjusted hazard ratios (HRs).

Median delay times from onset of symptom to the start of IHT treatment was 167 minutes, median delay was 47 minutes shorter for PHT and 43 minutes longer for primary PCI (TABLE 2). Rescue PCI, indicated in cases for whom thrombolysis had not resulted in ST-resolution and who experienced persistent pain after 60 to 90 minutes after initiation of thrombolytics, was performed 2.5 times more often among those who received PHT. Revascularization within 2 weeks was performed in nearly half of the PHT group and a third of the IHT group. Clopidogrel at discharge was 2.5 to 4 times more commonly used in the primary PCI group than in the 2 thrombolysis groups.

In-Hospital Outcomes

The median hospital stay was 2 days shorter with primary PCI than with IHT and 1 day shorter than with PHT, and these differences remained statistically significant even after adjusting for differences in baseline characteristics (TABLE 3). Both in-hospital reinfarction and readmission for acute MI within the first year occurred less often among those who underwent primary PCI than those who received IHT. When comparing primary PCI with PHT, the adjusted odds ratio (OR) for in-hospital reinfarction was 0.64 (95% confidence interval [CI], 0.46-0.89) and also readmission for acute MI within the first year was reduced after adjustment: HR, 0.60 (95% CI, 0.50-0.71). There was no significant difference in reinfarctions between the PHT and the IHT groups (Table 3).

Mortality

The differences in unadjusted mortality during the first year in the 3 treat-

Table 1. Baseline Characteristics in ST-Elevation Myocardial Infarction Patients Admitted Between 1999-2004 (N = 26 205)*

	In-Hospital Thrombolysis (n = 16 043)	Prehospital Thrombolysis (n = 3078)	Primary PCI (n = 7084)
Age, mean (SD), y	68.6 (12.2)	66.3 (11.4)	64.2 (11.9)
Women	5507 (34.3)	871 (28.3)	1934 (27.3)
Current smoker	4232 (28.2)	930 (31.8)	2253 (34.2)
Hypertension	5153 (32.5)	931 (30.6)	2255 (32.3)
Diabetes mellitus	2769 (17.3)	437 (14.2)	1136 (16.0)
Previous myocardial infarction	3189 (19.9)	517 (16.8)	1381 (19.5)
Previous heart failure	949 (6.1)	102 (3.5)	261 (3.9)
Previous PCI or CABG	618 (3.9)	135 (4.5)	663 (9.5)
Previous stroke	1054 (6.8)	97 (3.3)	411 (6.2)
Peripheral artery disease	502 (3.3)	65 (2.2)	203 (3.1)
Chronic obstructive pulmonary disease	613 (4.0)	85 (2.9)	209 (3.2)
Cancer within 3 y	390 (2.5)	70 (2.4)	193 (2.9)
Renal insufficiency	90 (0.6)	10 (0.3)	55 (0.8)
Dementia	33 (0.2)	9 (0.3)	2 (0.0)
Medication prior to admission			
ASA and/or platelet inhibitors	4949 (31.0)	889 (29.1)	2473 (35.3)
Oral anticoagulants	245 (1.5)	30 (1.0)	246 (3.5)
β-Blockers	4797 (30.1)	889 (29.2)	2292 (32.8)
Calcium channel inhibitors	2140 (13.5)	373 (12.3)	790 (11.3)
ACE inhibitors or AR blockers	2248 (14.1)	432 (14.2)	1088 (15.6)
Diuretics	2942 (18.5)	451 (14.8)	929 (13.3)
Digitalis	582 (3.7)	67 (2.2)	129 (1.8)
Nitroglycerin long acting	1738 (10.9)	242 (7.9)	627 (9.0)
Lipid-lowering drugs	1975 (12.4)	408 (13.4)	1241 (17.8)
Hospital arrival status			
Killip class			
I	10531 (69.0)	2305 (77.2)	5411 (81.0)
II	2472 (16.2)	398 (13.3)	563 (8.4)
III	418 (2.7)	41 (1.4)	118 (1.8)
IV	1836 (12.0)	242 (8.1)	586 (8.8)
Circulatory arrest	113 (0.7)	7 (0.2)	65 (0.9)

Abbreviations: ACE, angiotensin-converting enzyme; AR, angiotensin II receptor; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.
*All variables presented as absolute numbers (percentage) unless otherwise stated.

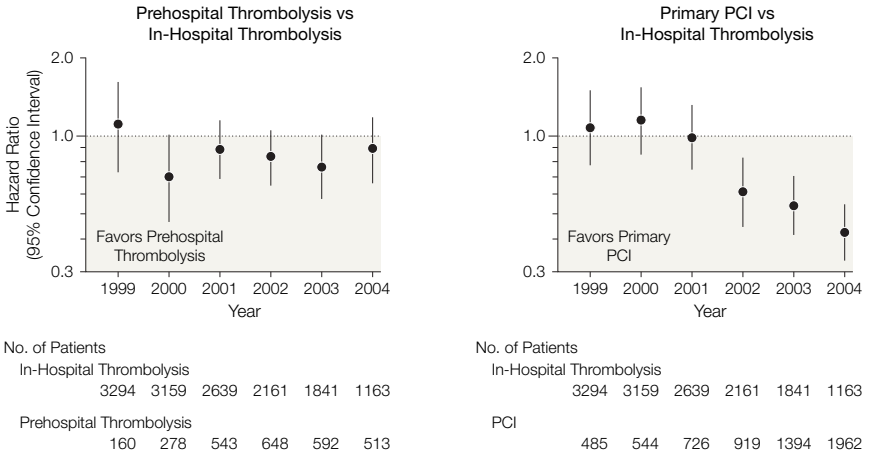
ment groups are presented in FIGURE 2. After adjustment for propensity score and 24 covariates, primary PCI was associated with lower mortality than IHT at 7 days, 30 days, and 1 year (Table 3). Also PHT predicted a lower adjusted mortality than IHT at 30 days and 1 year. Finally, primary PCI predicted lower mortality than PHT at 30 days: 344 (4.9%) vs 234 (7.6%); (HR, 0.70; 95% CI, 0.58-0.85) and 1 year: 541 (7.6%) vs 317 (10.3%) (HR, 0.81; 95% CI, 0.69-0.94). There was no significant interaction between treatment delay and the effects of the different treatments on 1-year mortality (interaction $P=.17$) but a trend concerning 30-day mortality (interaction $P=.052$). Thus, the observed lack of difference in the HR for mortality between PHT and IHT after 2 hours' delay tended to be supported by the interaction analysis (FIGURE 3, Table 3).

The continuous relation between delay time and the effects of the different reperfusion treatments on the age standardized 1-year mortality indicated that thrombolysis was associated with a steeper rise in mortality during the first 6 hours after symptom onset compared with primary PCI (FIGURE 4). During the first 2 hours, there was an approximate 2% absolute difference in mortality, which rose to about 6% to 7% after 6 to 7 hours. Not until after 7 hours' delay did the age-adjusted 1-year mortality for primary PCI reach the same mortality as thrombolysis given within 2 hours (Figure 4).

There was a higher proportion of deaths because of ischemic heart disease, 85% vs 82%, and stroke 4.3% vs 1.4% in the thrombolysis groups than the primary PCI group, respectively. There was no difference in deaths caused by noncerebral bleedings, while cancer, 2 % vs 7%, was a more common cause of death among primary PCI patients within 1 year.

In a sensitivity analysis among hospital survivors (n=24 246), primary PCI was associated with a lower risk of death at 1 year than IHT (adjusted HR, 0.82; 95% CI, 0.69-0.97) or PHT (adjusted HR, 0.98; 95% CI, 0.78-1.23) even after accounting for the propensity score for primary PCI and which discharge medications were prescribed.

Figure 1. Comparision of Mortality Among ST-Elevation Myocardial Infarction Patients Receiving Prehospital Thrombolysis or Primary Percutaneous Coronary Intervention (PCI) With In-Hospital Thrombolysis, 1999-2004



Error bars indicate 95% confidence intervals.

Table 2. Delay Times and Interventions for ST-Elevation Myocardial Infarction Patients Admitted Between 1999-2004 (N = 26 205)

	In-Hospital Thrombolysis (n = 16 043)	Prehospital Thrombolysis (n = 3078)	Primary PCI (n = 7084)
Delay symptom to reperfusion start, median (IQR), h:min			
All	2:47 (1:47-4:37)	2:00 (1:12-3:40)	3:30 (2:15-5:34)
≤2 h	1:30 (1:10-1:45)	1:13 (0:55-1:35)	1:35 (1:15-1:50)
>2 h	3:45 (2:45-5:45)	3:40 (2:40-5:42)	4:14 (2:57-6:15)
Coronary angiography or intervention, No. (%)			
Coronary angiography before discharge	4757 (29.7)	1514 (49.2)	7084 (100.0)
Rescue PCI (on admission day)	1765 (11.0)	846 (27.5)	0 (0.0)
All PCI or CABG within 14 d	4544 (28.3)	1457 (47.3)	7084 (100.0)
Medication at discharge, No. (%)*			
ASA	13 113 (85.1)	2611 (86.9)	6247 (90.1)
Clopidogrel	2587 (16.8)	976 (32.5)	5684 (81.9)
Warfarin	11 884 (7.8)	173 (5.8)	401 (5.8)
β-Blocker	13 037 (84.7)	2668 (88.9)	6029 (87.0)
Calcium antagonists	1272 (8.3)	227 (7.6)	492 (7.2)
ACE inhibitors or AR blockers	7323 (47.8)	1479 (49.4)	3592 (52.2)
Diuretics	4897 (32.0)	687 (23.0)	1509 (22.0)
Digitalis	696 (4.6)	90 (3.0)	231 (3.4)
Nitroglycerin long acting	3581 (23.4)	481 (16.2)	691 (10.1)
Lipid-lowering drugs	8616 (56.2)	1980 (66.1)	4909 (71.3)

Abbreviations: ACE, angiotensin-converting enzyme; AR, angiotensin II receptor; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.
*Absolute numbers and percentage of medications at discharge presented in patients for whom data were available. Discharge medications were missing in between 3.2% and 4.4% of the cases (most often when the patient had died before discharge).

COMMENT

Strengths and Limitations of a Registry Study

The relative efficacies of different treatments, such as reperfusion treatment with primary PCI compared with thrombolysis, is most reliably

estimated in prospective randomized trials in a selected target population in highly qualified centers.[3,7] However, the outcome of the disease and the effectiveness of the treatment need to be verified in unselected patient cohorts in real-life health care settings as when all consecutive patients from a whole country are included in current and other RIKS-HIA cohorts.[17,18] Registry data can also provide estimates on treatment effectiveness when there is a lack of information from randomized trials[10,19,20]—in the current study, for example, by comparing PHT and primary PCI. This RIKS-HIA study has the advantages of providing a large unselected population of consecutive patients with STEMI of all ages and managed with all kinds or reperfusion strategies from all hospitals in a single country with a high validity in data and a complete long-term follow-up concerning mortality and morbidity. Therefore, in contrast to most randomized trials and meta-analyses, these registry data can provide information on long-term outcome concerning not only survival and reinfarction but readmission for all types of cardiovascular disease and causes of death.

An observational cohort study cannot provide the same degree of evidence of superiority of a certain treatment as a randomized trial or a meta-analysis of randomized trials[3,7] because variables not included in the analyses might influence both the selection of treatment and the outcome. Thus, despite thorough multivariable propensity analyses, it cannot be excluded that our results from a nonrandomized large cohort were influenced by differences between the groups that could not be adequately adjusted for. It is noteworthy that the present material contained twice as many patients in the primary PCI group (n=7084) and 4 times as many in the IHT group (n=16 043) compared with the most recent meta-analysis of randomized trials comparing these 2 treatments.[7] Furthermore, to our knowledge, our study for the first time was able to properly compare the outcome of primary PCI with PHT because the database contained 7 times as many of these patients as in the only reported randomized trial,[21] and 17 times more than the French registry study.[14] The reliability of the present study was further increased because the choice of reperfusion strategy in many centers mainly was influenced by the available treatment facilities rather than on patient characteristics.[22]

Differences in Materials Between the Registry and Randomized Trials

When comparing the present registry material with randomized trials of primary PCI vs thrombolysis,[7] the patients treated with primary PCI and PHT were 1 to 2 years older and the IHT patients were about 5 years older. There were also more comorbidities and comedications, which may influence both benefits and risks of the tested treatments and their outcomes.[23] Interventional treatments as evaluated among selected centers and experienced operators in randomized trials might not have the same outcome when applied to the full spectrum of health care facilities and performed by less experienced physicians.[24,25] However, it is noteworthy that the standards of care seemed rather similar in the real-life situation with almost identical treatment delays in this registry material as in the randomized trials.[7]

Table 3. Outcome In-Hospital, at 7 Days, 30 Days, and 1 Year in ST-Elevation Myocardial Infarction Patients Admitted Between 1999-2004 (N = 26 205) Adjusted for 24 Covariates Described in the Methods Section Including the Propensity Score

	In-Hospital Thrombolysis (n = 16 043)	Prehospital Thrombolysis (n = 3078)	Primary PCI (n = 7084)
Hospital stay			
Index event all patients, median (IQR), d	6 (4-8)	5 (4-7)	4 (3-6)
Adjusted HR (95% CI)	1.00	0.83 (0.80-0.87)	0.68 (0.65-0.70)
Reinfarction, No. (%)			
In-hospital	642 (4.0)	105 (3.4)	141 (2.0)
Adjusted HR (95% CI)	1.00	0.88 (0.68-1.14)*	0.79 (0.70-0.88)*
Readmission AMI in first year	1548 (9.6)	276 (9.0)	340 (4.8)
Adjusted HR (95% CI)	1.00	1.02 (0.90-1.17)	0.61 (0.53-0.71)
Mortality in all patients, No. (%)			
7 d	1411 (8.8)	181 (5.9)	250 (3.5)
Adjusted HR (95% CI)	1.00	0.90 (0.76-1.06)	0.61 (0.51-0.73)
30 d	1834 (11.4)	234 (7.6)	344 (4.9)
Adjusted HR (95% CI)	1.00	0.87 (0.76-1.01)	0.61 (0.53-0.71)
1 y	2555 (15.9)	317 (10.3)	541 (7.6)
Adjusted HR (95% CI)	1.00	0.84 (0.74-0.95)	0.68 (0.60-0.76)
1 y, No./total (%)†	1026/9135 (11.2)	309/3001 (10.3)	541/7084 (7.6)
Adjusted HR (95% CI)	1.00	0.89 (0.77-1.03)	0.70 (0.61-0.80)
Mortality by reperfusion delay, No. (%)‡			
30-d Mortality			
Time to reperfusion ≤2 h	375 (8.6)	70 (5.6)	39 (3.8)
Adjusted HR (95% CI)	1.00	0.74 (0.56-0.97)	0.52 (0.35-0.78)
Time to reperfusion >2 h	1073 (11.4)	110 (8.9)	180 (4.5)
Adjusted HR (95% CI)	1.00	1.03 (0.84-1.26)	0.62 (0.51-0.76)
1-y Mortality			
Time to reperfusion ≤2 h	522 (11.9)	100 (8.0)	68 (6.7)
Adjusted HR (95% CI)	1.00	0.78 (0.62-0.98)	0.63 (0.47-0.84)
Time to reperfusion >2 h	1528 (16.3)	146 (11.8)	289 (7.3)
Adjusted HR (95% CI)	1.00	0.94 (0.79-1.13)	0.66 (0.56-0.78)

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Odds ratios by logistic regression analysis.
†Streptokinase patients excluded.
‡Times for symptom onset and start of reperfusion available for 21 227 cases.

Hospital Stay

In the present study, primary PCI was associated with considerably shorter length of stay than thrombolysis, which is consistent with previous randomized trials.[26,27] Prehospital thrombolysis had shorter hospitalization time than IHT, which might be explained by the more frequent use of early revascularization that seems to shorten hospital stay.[26,27] However, the present study clearly demonstrated that primary PCI reduced hospital stay compared with PHT.

Reinfarction

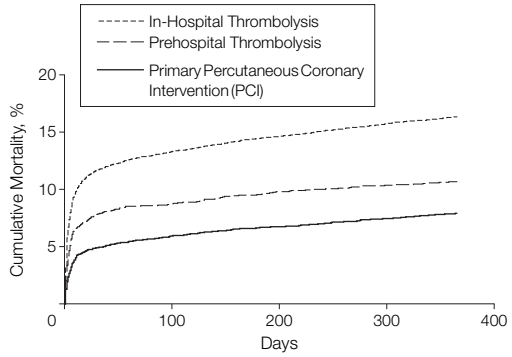
The rate of both early and late reinfarction was reduced by primary PCI compared with both types of thrombolysis in close accordance with the results of the randomized trials[2,3,27] and meta-analysis.[7] Primary PCI with stenting combined with intense acute-phase antithrombotic treatment and proper long-term platelet inhibition not only restores blood-flow but also maintains long-term patency with full diameter of the vessel and thereby decreases the risk of future reocclusion.[28,29] This reduction in the rate of reinfarctions will contribute to reduced utilization of health care resources, avoid readmissions, and shorten the period of rehabilitation.

Mortality

The present registry study showed in a real-life setting a 39% relative reduction in 30-day mortality and a 33% reduction in 1-year mortality by primary PCI compared with IHT which is in close accordance with the meta-analysis of the randomized trials.[3,7] Similar result has also been seen in some[30] although not all registry studies.[8,31,32] These results also corroborated the results of other studies[27,30,33,34] and of Danish Trial in Acute Myocardial Infarction 2[5] that primary PCI is associated with a better outcome than thrombolysis at delay times of up to at least 3 to 4 hours.

In accordance with many previous reports, our study showed that the benefits of all types of reperfusion treatment depend on the treatment delay but that the loss in benefit by longer delay is less pronounced and appears later with primary PCI than with thrombolysis. Therefore the relative mortality benefits with primary PCI might amount to approximately 20% during the first hours but increase to 35% after 4 to 7 hours. These time-related finding in this registry trial are very similar to the observations in the meta-analysis of ran-

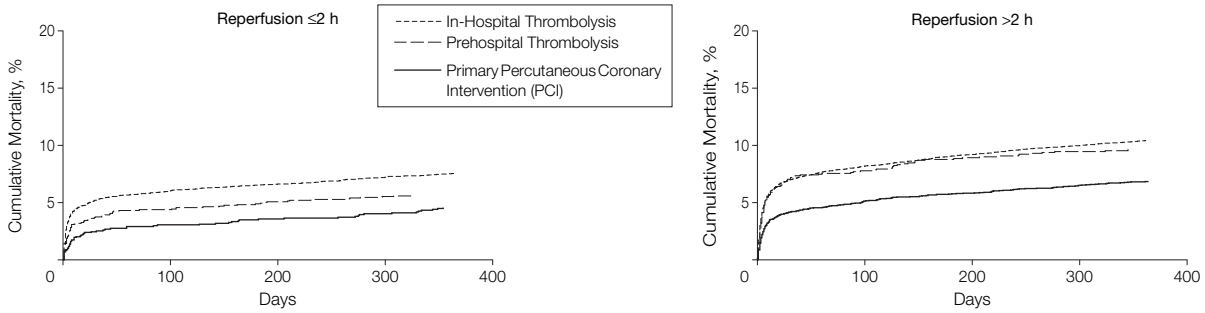
Figure 2. Unadjusted Cumulative Mortality During the First Year After the Index Event Admission



No. at Risk				
Thrombolysis				
In-Hospital	14260	12322	12100	11931
Prehospital	2736	2491	2460	2442
Primary PCI	6030	5661	5607	5555

Unadjusted mortality (Kaplan-Meier) first year after index admission for the 26 205 patients with ST-segment elevation myocardial infarction receiving reperfusion therapy between 1999-2004.

Figure 3. Estimated Cumulative Mortality for Patients Receiving Reperfusion Treatment Within or After 2 Hours of Symptom Onset



No. at Risk								
Thrombolysis								
Prehospital	3993	3571	3530	3490	8892	7675	7519	7417
Post-Hospital	1155	1077	1066	1060	1155	1020	1004	997
Primary PCI	979	936	928	916	3592	3375	3344	3318

Mortality curves calculated using Cox regression analysis including propensity score for primary PCI.

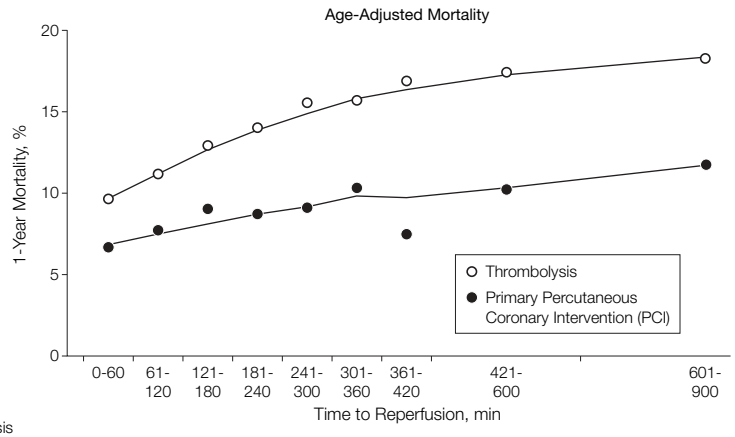
domized trials.[7] Thus, primary PCI consistently has a lower mortality at comparable delay times and not until after a delay of 6 to 7 hours, the mortality of primary PCI becomes comparable with thrombolysis within the first hours. Also in patients with very short treatment delay, primary PCI was associated with a better survival than the pooled material of PHT- and IHT-treated patients and a similar trend was seen at the direct comparison between subgroups with less than 2 hours' treatment delay.

Our results as well as the meta-analysis[7] is at variance with the French studies, the CAPTIM trial[9] and the USIC 2000 Registry[14] that reperfusion initiated within 2 hours of symptom onset might yield lower mortality with PHT than would primary PCI. However, both results from the French studies might have been influenced by the too low statistical power and the very high rates of rescue and early PCI in the PHT group.[9,14] Second, the CAPTIM and USIC trials were performed 1997-2000 when the results with primary PCI were less successful as illustrated by the significantly improved outcome with primary PCI over the years (Figure 1). Because studies of "facilitated PCI" have shown no advantages,[35] there is currently very little rationale to use fibrinolytic treatment even within the first 2 hours if primary PCI is available within 4 hours of symptom onset. The mortality benefit by primary PCI was also corroborated by the causes of deaths indicating reductions in fatalities because of ischemic heart disease and stroke, whereas there was no difference in causes of death between the groups treated with PHT and IHT. The somewhat higher rate of cancer deaths in the primary PCI group might be explained either by contraindications to thrombolysis in cancer patients because of a raised bleeding risk or by competing causes of death in elderly patients.

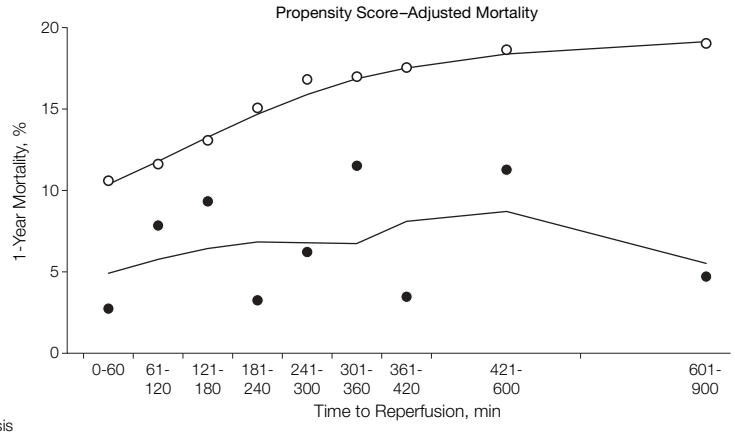
CONCLUSIONS

This large registry study with complete long-term follow-up of all unselected consecutive patients from almost all coronary care units in an entire country clearly indicates a superiority of primary PCI for the treatment of STEMI in the real-life setting. Compared with thrombolytic treatment primary PCI reduces short- and long-term mortality and reinfarction rate by 30% to 40%, shortens hospital stay and reduces later need for hospital care. Only at delay times of less than 2 hours, PHT might accomplish a similar mortality as primary PCI, and only at delay times beyond 7 hours

Figure 4. Age-Adjusted and Propensity Score–Adjusted Mortality According to Time to Reperfusion and Type of Therapy



	0-60	61-120	121-180	181-240	241-300	301-360	361-420	421-600	601-900
Thrombolysis									
No. of Deaths	122	503	503	332	239	159	121	196	139
Total No. of Patients	1248	4375	3659	2199	1438	946	658	1061	703
Primary PCI									
No. of Deaths	7	61	81	50	43	37	17	41	31
Total No. of Patients	125	895	1126	776	567	453	282	458	332



	0-60	61-120	121-180	181-240	241-300	301-360	361-420	421-600	601-900
Thrombolysis									
No. of Deaths	116	459	448	301	218	146	110	188	131
Total No. of Patients	1075	3856	3272	1984	1298	853	586	976	645
Primary PCI									
No. of Deaths	7	51	71	42	37	35	16	36	25
Total No. of Patients	115	795	987	660	474	383	238	384	281

By applying propensity score adjustment the decreased number of events in the primary PCI group causes the line to be uneven and less reliable than the age-adjusted. However, the pattern is the same in both figures, indicating improved survival for primary PCI compared with thrombolysis at least with delay times up to 4 hours. The thrombolysis group includes data from both prehospital and in-hospital patients. One-year mortality was plotted at the mid value of each time interval and smooth curves for each therapy calculated by loess method. Outcome of prehospital and in-hospital thrombosis is combined in a single group named "Thrombolysis."

primary PCI is associated with higher mortality than any delay with thrombolysis. Therefore, if available, primary PCI today is the treatment of choice for STEMI. Only if delivered within 2 hours of onset of symptoms in areas with more than 4 hours' transportation time to a PCI procedure, PHT might offer a comparable alternative.

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Study concept and design: Stenestrand, Wallentin.
Acquisition of data: Stenestrand, Wallentin.
Analysis and interpretation of data: Stenestrand, Lindback, Wallentin.
Drafting of the manuscript: Stenestrand.
Critical revision of the manuscript for important intellectual content: Stenestrand, Lindback, Wallentin.
Statistical analysis: Stenestrand, Lindback.
Obtained funding: Stenestrand, Wallentin.
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