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Relationship Between Time to Invasive Assessment and Clinical Outcomes of Patients Undergoing an Early Invasive Strategy After Fibrinolysis for ST-Segment Elevation Myocardial Infarction

A Patient-Level Analysis of the Randomized Early Routine Invasive Clinical Trials

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ABSTRACT

OBJECTIVES This study investigated the relationship between time to invasive assessment and outcomes among ST-segment elevation myocardial infarction patients randomized to early angiography after fibrinolysis.

BACKGROUND The optimal timing of coronary angiography after fibrinolysis and the association with clinical outcomes is uncertain.

METHODS Patient-level data from 6 randomized trials, with a median time to angiography <12 h after fibrinolysis, were pooled. The primary endpoint was 30-day death or reinfarction. The key secondary endpoint was in-hospital major bleeding. The relationship between fibrinolysis to angiography time and symptom onset to angiography time with outcomes was studied using 2- and 4-h intervals, respectively, and in multivariable models.

RESULTS Among 1,238 patients, the median fibrinolysis to angiography time was 165 min, and the median symptom onset to angiography time was 5.33 h. The primary and key secondary endpoints occurred in 5.7% and 4.7%, respectively. These main endpoints did not vary significantly with increasing fibrinolysis to angiography time. Early angiography (<2 h) after fibrinolysis was not associated with increased bleeding. Recurrent ischemia increased with increasing fibrinolysis to angiography time (3.7% to 7.9%, p for trend = 0.02). Thirty-day and 1-year death/reinfarction and 30-day recurrent ischemia increased significantly with increasing symptom onset to angiography time. Neither fibrinolysis to angiography time nor symptom onset to angiography time was an independent predictor of the primary endpoint. Only symptom onset to angiography time was an independent predictor of 1-year death/reinfarction (hazard ratio: 1.07, 95% confidence interval: 1.02 to 1.12, p = 0.01).

CONCLUSIONS Very early angiography (<2 h) after fibrinolysis was not associated with an increased risk of 30-day death/reinfarction or in-hospital major bleeding, and angiography within 4 h after fibrinolysis was associated with reduced 30-day recurrent ischemia. A shorter symptom onset to angiography time (<4 h) was associated with reduced 30-day and 1-year death/reinfarction and 30-day recurrent ischemia. In the current environment of regional networks of 24/7 primary percutaneous coronary intervention (PCI) centers, the clinical implication of these findings is that patients initially treated with fibrinolysis should also be promptly transferred to the nearest PCI center for immediate angiography and PCI. (Early Percutaneous Coronary Intervention [PCI] After Fibrinolysis Versus Standard Therapy in ST Segment Elevation Myocardial Infarction [STEMI] Patients; NCT01014182) (J Am Coll Cardiol Intv 2015;8:166–74) © 2015 by the American College of Cardiology Foundation.

In ST-segment elevation myocardial infarction (STEMI), early routine percutaneous coronary intervention (PCI) after fibrinolysis results in a reduction in the incidence of reinfarction, recurrent ischemia, and death or reinfarction (1–8). This early invasive strategy achieves these benefits without an increase in the incidence of stroke or major bleeding complications, and these benefits have been sustained in long-term follow-up (1–8). Recent updates to the American College of Cardiology, American Heart Association, and European Society of Cardiology STEMI guidelines reflect these findings (9,10).

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Fibrinolysis followed by the early invasive strategy is the treatment of choice for STEMI patients arriving at hospitals unable to offer timely primary PCI. However, the optimal timing of coronary angiography after fibrinolysis and its relationship with clinical outcome is uncertain. In our previous cumulative meta-analysis (8), data on optimal timing of coronary angiography after fibrinolysis or on selected subgroups were not used. Thus, a patient-level analysis of these trials was planned to explore further the relationship between time to early angiography and clinical outcomes among STEMI patients randomized to a routine early invasive strategy after fibrinolysis.

METHODS

Patient-level data from 7 randomized trials evaluating early invasive versus standard management were included in a collaborative patient-pooled database: CAPITAL AMI (Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction) study (N = 170) (1), SIAM III (Southwest German Interventional Study in Acute Myocardial Infarction) (N = 197) (2), WEST (Which Early ST-Elevation Myocardial Infarction Therapy) study (N = 221) (3), NORDISTEMI (NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction) (N = 266) (4), GRACIA-1 (Grupo de Análisis de la Cardiopatía Isquémica Aguda-1) (N = 500) (5), CARESS-in-AMI (Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction) study (N = 597) (6), and the TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) (N = 1,059) (7).

STUDY POPULATION. The study population was the early invasive cohort from the above-mentioned studies (i.e., STEMI patients undergoing fibrinolysis and randomized to early angiography). Furthermore, the patients included in this analysis were those STEMI patients from trials in which the median time from fibrinolysis to angiography was <12 h. The

ABBREVIATIONS AND ACRONYMS

GPI = glycoprotein IIb/IIIa inhibitor

MI = myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

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GRACIA-1 study was not included in the present analysis because the invasive approach was undertaken up to 24 h post-fibrinolysis (median time from fibrinolysis to angiography of 17 h) (5).

DEFINITIONS. Door to needle time was defined as the time from hospital arrival to the administration of fibrinolysis (minutes). The fibrinolysis to angiography time was defined as the time from fibrinolysis administration to coronary angiography (minutes). Symptom onset to angiography time was defined as the time from symptom onset to angiography (hours). The primary endpoint for this analysis was the 30-day incidence of death or reinfarction. Key secondary endpoints were the 30-day incidences of death, reinfarction, recurrent ischemia, stroke, in-hospital Thrombolysis In Myocardial Infarction (TIMI) major bleeding, and the 1-year incidence of death, reinfarction, and the combined incidence of death or reinfarction.

STATISTICAL ANALYSIS. Categorical variables are presented as frequency (percentage) of nonmissing cases, whereas continuous variables are described as median with interquartile range. Differences between groups were compared using the Pearson chi-square, Cochran-Armitage trend, and Kruskal-Wallis tests as appropriate. Clinical outcomes were studied for the overall study cohort as well as according to time from fibrinolysis to angiography (2-h intervals) and time from symptom onset to angiography (4-h intervals). The analysis of outcomes over time intervals was exploratory in nature, and the time intervals were chosen based on what may be considered clinically relevant.

Multivariable models using Cox proportional hazards regression and stratified by trial were used to assess the relationship of fibrinolysis to angiography time and symptom onset to angiography time, as continuous variables, with 30-day and 1-year death or reinfarction. Baseline patient characteristics considered in the adjustment included age, sex, weight, heart rate, systolic blood pressure, Killip class, current smoker, history of hypertension, diabetes, previous MI, and infarct location (11,12). Linearity and proportional hazard assumptions were verified graphically by checking the log-log survival curves and residual plots. Approximately 8% of presenting heart rate and systolic blood pressure values were missing in the study population. Assuming data were missing at random, we used multiple imputation to impute the missing data. A single Markov chain Monte Carlo method, which assumes multivariate normality, was used. Results of the full models were obtained after combining 5 complete datasets to generate the inferences. The WEST study did not collect data regarding the incidence of reinfarction at 1 year and was therefore not included in the model created to study 1-year death or reinfarction. We tested for interstudy heterogeneity, and no significant heterogeneity was found. All statistical comparisons were 2 tailed with statistical significance defined at a p value <0.05. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS AND PROCEDURAL VARIABLES. In the 6 clinical trials, there were 1,261 patients randomized to an early invasive strategy. Of these patients, 20 did not undergo angiography (6 patients experienced early death), and 3 patients were outliers (1 patient without the time or date of thrombolysis recorded, and 2 patients with the time to angiography >65 h), leaving 1,238 patients in this analysis. There were 1 and 14 patients lost to follow-up at 30 days and 1 year, respectively.

The median age was 59 years, and most patients were Killip class I at presentation (**Table 1**, Online Tables 1 and 2). The prevalence of previous MI or previous revascularization procedures was low. The median door to needle time was 35 min, and the median time from fibrinolysis to angiography was 165 min (range, 21 to 2,850 min). The median symptom onset to angiography time was 5.3 h. Of 1,238 patients undergoing angiography, 87% underwent PCI (**Table 2**, Online Tables 3 and 4). The majority of patients undergoing angiography had a femoral vascular access site. Coronary stenting was performed in 84.3% of patients, and the use of drug-eluting stents was low (14.8%). The incidence of initial TIMI grade 3 flow after fibrinolysis was 55.4%. After PCI, 90.8% achieved TIMI flow grade 3. Glycoprotein IIb/IIIa inhibitors (GPIs) were used in 63.2% of cases and thienopyridine therapy, with either clopidogrel or ticlopidine, in 92.5% of cases.

CLINICAL OUTCOMES. The primary endpoint of 30-day death or reinfarction occurred in 5.7% of patients, and the incidence of in-hospital TIMI major bleeding was 4.7% (**Table 3**). When the patients were divided into groups according to the time from fibrinolysis to angiography (0 to 2 h, 2.1 to 4 h, >4 h), the outcomes appeared similar across time intervals except for recurrent ischemia, which increased significantly with time to angiography beyond 4 h (p [trend] = 0.02) (**Table 3**).

The relationship between symptom onset to angiography time (4-h time intervals) is shown in **Table 4**.

TABLE 1 Baseline Characteristics (N = 1,238)

Age, yrs	59 (51-68)
Male	980 (79.2)
Hypertension	460/1,217 (37.8)
Diabetes	180/1,230 (14.6)
Dyslipidemia	307/995 (30.9)
Current or former smoker	780/1,229 (63.5)
Current smoker	610/1,229 (49.6)
Previous myocardial infarction	125/1,227 (10.2)
Previous angioplasty	67/1,237 (5.4)
Previous coronary bypass surgery	7/1,130 (0.6)
Weight, kg	80 (70-90) [n = 1,217]
Systolic blood pressure, mm Hg	140 (125-160) [n = 1,144]
Diastolic blood pressure, mm Hg	82 (73-93) [n = 1,144]
Heart rate, beats/min	72 (61-85) [n = 1,144]
Killip class	
I	999/1,223 (81.7)
II	195/1,223 (15.9)
III	18/1,223 (1.5)
IV	11/1,223 (0.9)
Infarct location	
Anterior	609/1,236 (49.3)
Inferior	591/1,236 (47.8)
Others	36/1,236 (2.9)
Fibrinolysis	
Tenecteplase	855/1,238 (69.1)
Reteplase	380/1,238 (30.7)
Other	3/1,238 (0.2)
Time from symptom onset to administration of fibrinolysis, min	130 (83-202)
Door to needle time, min	35 (21-55) [n = 949]
Fibrinolysis to angiography time, min	165 (115-228)
Symptom onset to angiography time, h	5.33 (3.95-7.37)

Values are median (interquartile range), n (%), or n/N (%).

The 30-day combined incidence of death or reinfarction increased from 4.0% to 8.0% with increasing symptom onset to angiography time (p [trend] = 0.04). The incidence of recurrent ischemia increased from 3.4% to 8.8% with increasing symptom onset to angiography time (p [trend] = 0.004). In-hospital TIMI major bleeding was not significantly affected by increasing time from fibrinolysis to angiography or symptom onset to angiography time ($p > 0.05$ for both parameters). Patients having the shortest time interval from fibrinolysis to angiography (0 to 2 h) did not experience an increase in TIMI major bleeding events during their hospitalization.

Patients having initial TIMI flow grade 3 in the culprit vessel at angiography had lower rates of 30 day and 1-year death or reinfarction compared with patients having initial TIMI flow grade 0 to 2 in the culprit vessel (30-day: 3.6% vs. 8.4%, p = 0.0004; 1-year: 6.1% vs. 11.3%, p = 0.002).

After adjusting for other characteristics, neither time from fibrinolysis to angiography nor symptom onset to angiography time was a significant independent predictor of 30-day death or reinfarction (Table 5, Figures 1 and 2). At 1-year follow-up, symptom onset to angiography time was a significant independent predictor of death or reinfarction. For every hour increase in symptom onset to angiography time, there was a 7% relative increase in the hazard of death or reinfarction within 1 year. To evaluate whether the frequent use of GPIs in our study cohort (63% of patients) explained the low incidence of events, particularly at early time points (0 to 2 h and 2.1 to 4 h), we introduced the use of GPIs as a covariate in the multivariable models for 30-day death or reinfarction. The use of GPIs was not a significant predictor of 30-day death or reinfarction in the model including time from fibrinolysis to angiography (p = 0.42) nor in the model containing symptom onset to angiography time (p = 0.31); the

TABLE 2 Procedural Characteristics (N = 1,238)

PCI performed	1,080 (87.2)
Access site (if PCI performed)	
Femoral	806/991 (81.3)
Radial	185/991 (18.7)
Infarct-related artery	
Left main	6 (0.5)
Left circumflex	121 (9.8)
Left anterior descending	592 (47.8)
Right coronary artery	478 (38.6)
Unknown/none	41 (3.3)
Stent use	911/1,080 (84.3)
Bare metal	658/911 (72.2)
Drug eluting	135/911 (14.8)
Baseline TIMI flow	
0/1	305/1,205 (25.3)
2	232/1,205 (19.3)
3	668/1,205 (55.4)
Final TIMI flow grade	
0/1	37/1,087 (3.4)
2	63/1,087 (5.8)
3	987/1,087 (90.8)
Medications during hospitalization	
GPIs	776/1,227 (63.2)
Heparin or low molecular weight heparin use	1,231 (99.4)
Aspirin	1,149/1,229 (93.5)
Clopidogrel/ticlopidine	1,137/1,229 (92.5)
Medications at discharge	
Aspirin	1,013/1,113 (91.0)
Clopidogrel/ticlopidine	985/1,113 (88.5)
Beta-blocker	989/1,113 (88.9)
ACE/ARB inhibitor	895/1,113 (80.4)
Statin	1,017/1,113 (91.4)

Values are n (%) or n/N (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; GPIs = glycoprotein IIb/IIIa inhibitors; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

TABLE 3 Clinical Outcomes According to Time From Fibrinolysis to Angiography

	Overall (N = 1,238)	0–2 h (n = 349)	2.1–4 h (n = 622)	>4 h (n = 267)	p Value*
In-hospital					
TIMI major bleeding	58 (4.7)	16 (4.6)	32 (5.1)	10 (3.8)	0.68
30 days†					
Death or ReMI	70 (5.7)	17 (4.9)	36 (5.8)	17 (6.4)	0.41
Death	36 (2.9)	9 (2.6)	20 (3.2)	7 (2.6)	0.92
ReMI	37 (3.0)	8 (2.3)	18 (2.9)	11 (4.1)	0.19
Recurrent ischemia	57 (4.6)	13 (3.7)	23 (3.7)	21 (7.9)	0.02
Stroke	12 (1.0)	3 (0.9)	6 (1.0)	3 (1.1)	0.74
1 yr†					
Death or ReMI‡	93/1,117 (8.3)	25/341 (7.3)	55/574 (9.6)	13/202 (6.4)	0.95
Death	56/1,224 (4.6)	14/349 (4.0)	34/614 (5.5)	8/261 (3.1)	0.70
ReMI‡	42/1,116 (3.8)	11/341 (3.2)	24/574 (4.2)	7/201 (3.5)	0.77

Values are n (%) or n/N (%). *p value for trend. †Lost to follow-up: 1 patient at 30 days and 14 patients at 1 year. ‡WEST (Which Early ST-Elevation Myocardial Infarction Therapy) study not included for 1-year death/reinfarction or reinfarction.

ReMI = reinfarction; TIMI = Thrombolysis In Myocardial Infarction.

interaction terms for the use of GPIs with these time variables were also not significant (p = 0.67 and p = 0.92, respectively).

DISCUSSION

The question of optimal timing for invasive assessment after fibrinolysis in STEMI patients managed using the pharmacoinvasive approach is highly relevant to clinicians and interventional cardiologists at receiving PCI centers. The present study uses the largest available pooled clinical trial database using individual patient-level data to address this question. The main findings of this analysis were that time from fibrinolysis to angiography was not independently predictive of 30-day or 1-year death or reinfarction among fibrinolysis-treated STEMI patients undergoing early angiography. The time from symptom onset to angiography, however, was a significant predictor of 1-year death or reinfarction. Very early angiography (<2 h) after fibrinolysis and a shorter symptom onset to angiography time (<4 h) was not associated with an increased risk of 30-day death or reinfarction or in-hospital major bleeding. Early angiography (<4 h after fibrinolysis) was associated with a lower frequency of recurrent ischemia.

Time from fibrinolysis to angiography is influenced by clinical factors (hemodynamic stability, reperfusion status after fibrinolysis, risk of bleeding), transportation factors (ability to arrange timely transfer to receiving institution), and factors at the receiving institution (ability to assemble an interventional team in a timely manner). The time from symptom onset to angiography includes time to angiography after contact with the medical system, but is also heavily dependent on the patient's decision to seek medical attention for his or her symptoms, and the manner of transportation to the initial institution (self-transportation vs. ambulance call). Because this analysis did not definitively identify a direct relationship between time from fibrinolysis to angiography and the incidence of 30-day or 1-year death or reinfarction, one could question the merits of the early invasive strategy in this population and consider deferral of angiography to the following day for the stabilized STEMI patient arriving outside working hours. However, we did find indirect evidence of the importance of early invasive treatment on late outcomes based on the significant relationship of symptom onset to angiography time with the combined incidence of death or reinfarction at 1 year. Furthermore, when we compared the incidence of 30-day and 1-year death or reinfarction in our study cohort with the conservatively managed cohort of the pooled database, the pharmacoinvasive approach remained a dominant strategy over conservatively managed patients (30-day death/reinfarction, 11.8% vs. 5.7%, p < 0.001 and 1-year death/reinfarction, 13.6% vs. 8.3%, p = 0.0005).

Dimopoulos et al. (13) demonstrated in the CARESS-in-AMI trial that a mortality benefit was realized if revascularization took place within 3.35 h after hospitalization and fibrinolysis. This was likely achieved due to a reduction in the time to reperfusion among those patients with failed fibrinolysis (13). Furthermore, Danchin et al. (14) demonstrated that when used early after the onset of symptoms

TABLE 4 Clinical Outcomes According to Symptom Onset to Angiography Time

	Overall (N = 1,238)	0–4 h (n = 328)	4.1–8 h (n = 661)	>8 h (n = 249)	p Value*
In-hospital					
TIMI major bleeding	58 (4.7)	14 (4.3)	31 (4.7)	13 (5.2)	0.59
30 days†					
Death or ReMI	70 (5.7)	13 (4.0)	37 (5.6)	20 (8.0)	0.04
Death	36 (2.9)	6 (1.8)	20 (3.0)	10 (4.0)	0.12
ReMI	37 (3.0)	7 (2.1)	19 (2.9)	11 (4.4)	0.12
Recurrent ischemia	57 (4.6)	11 (3.4)	24 (3.6)	22 (8.8)	0.004
Stroke	12 (1.0)	2 (0.6)	5 (0.8)	5 (2.0)	0.11
1 yr†					
Death or ReMI‡	93/1,117 (8.3)	22/312 (7.1)	46/614 (7.5)	25/191 (13.1)	0.03
Death	56/1,224 (4.6)	11/326 (3.4)	30/653 (4.6)	15/245 (6.1)	0.12
ReMI‡	42/1,116 (3.8)	11/312 (3.5)	19/614 (3.1)	12/190 (6.3)	0.18

Values are n (%) or n/N (%). *p value for trend. †Lost to follow-up: 1 patient at 30 days and 14 patients at 1 year. ‡WEST study not included for 1-year death/reinfarction or reinfarction.

Abbreviations as in Table 3.

(<220 min), a pharmacoinvasive strategy yielded in-hospital, 30-day, and 1-year survival rates that were comparable to those of primary PCI. Recently, the STREAM (Strategic Reperfusion Early After Myocardial Infarction) investigators demonstrated comparable 30-day clinical outcomes when STEMI patients within 3 h of symptom onset received pre-hospital fibrinolysis a median of 100 min after the onset of symptoms was compared with primary PCI. More intracranial hemorrhage was observed in the fibrinolysis group, however (15). In contrast to the Danchin et al. study, we did not observe an increase in mortality when time from fibrinolysis to angiography and PCI was <2 h. The difference may be explained by the mandatory immediate transfer of all patients according to trial design in our pooled analysis versus the clustering of rescue angioplasty in patients with failed reperfusion in the Danchin et al. study. Our analysis would suggest that seeking medical attention as soon as possible, for a shorter symptom onset to fibrinolysis time (median of 130 min in our cohort) is an important driver of improved clinical outcomes in the long term and perhaps relatively more so than achieving a shorter time from fibrinolysis to angiography.

Although GPIs were used frequently in our study cohort (63% of patients), GPI use was not a significant predictor of 30-day death or MI in our multivariable models. Of the 6 pooled studies examined in our analysis, 1 study (CARESS-in-AMI [6]) mandated the use of half-dose reteplase and abciximab in all patients, whereas in the other trials, the use of GPIs was discretionary and not randomized. It is difficult to know whether patients experiencing reinfarction preferentially received GPIs because they were having a recurrent event or it was simply operator preference to use the agent routinely during STEMI PCI (more likely). The use of GPIs is less frequent nowadays; they have been replaced by potent antiplatelet drugs such as ticagrelor and prasugrel, which give GPI-like levels of platelet inhibition. Whether the combination of ticagrelor or prasugrel with thrombolysis mitigates early events or poses an early hazard is currently unknown.

Over the past 5 to 7 years, the predominant mode of reperfusion therapy has shifted from fibrinolysis to primary PCI (16,17) with the development of regional STEMI programs. For example, in the United Kingdom, among revascularized STEMI patients, the proportion of patients undergoing fibrinolysis decreased from 60% in 2008 to 6% in 2011, and the incidence of primary PCI increased from 46% to 94% over the same time period ($p < 0.001$) (18). Similar trends have been observed in North America (19).

TABLE 5 Clinical Predictors of Death or Reinfarction*

Variable	HR	95% CI	p Value
Time from fibrinolysis to angiography model: 30 days			
Age per 1-yr increase	1.07	(1.05–1.10)	<0.0001
Presenting heart rate (per 1-U increase)	1.03	(1.02–1.04)	<0.0001
Killip class ≥II	2.22	(1.24–3.97)	0.0072
Fibrinolysis to angiography time*	1.01	(0.95–1.08)	0.78
Time from symptom onset to angiography model: 30 days			
Age (per 1-yr increase)	1.07	(1.05–1.10)	<0.0001
Presenting heart rate (per 1-U increase)	1.03	(1.02–1.04)	<0.0001
Killip class ≥II	2.20	(1.24–3.93)	0.0074
Systolic blood pressure >140 mm Hg	0.59	(0.33–1.04)	0.068
Symptom onset to angiography time*	1.03	(0.98–1.08)	0.30
Time from fibrinolysis to angiography model: 1 yr			
Age (per 1-yr increase)	1.07	(1.05–1.10)	<0.0001
Presenting heart rate (per 1-U increase)	1.03	(1.02–1.04)	<0.0001
Killip class ≥II	1.75	(1.07–2.84)	0.025
Systolic blood pressure >140 mm Hg	0.42	(0.25–0.69)	0.0007
Diabetes	1.84	(1.11–2.93)	0.017
Fibrinolysis to angiography time*	1.04	(0.96–1.13)	0.32
Time from symptom onset to angiography model: 1 yr			
Age per 1-yr increase	1.07	(1.04–1.09)	<0.0001
Presenting heart rate per 1-U increase	1.03	(1.02–1.04)	<0.0001
Killip class ≥II	1.79	(1.10–2.91)	0.018
Systolic blood pressure >140 mm Hg	0.40	(0.25–0.67)	0.0004
Diabetes	1.78	(1.10–2.87)	0.019
Symptom onset to angiography time*	1.07	(1.02–1.13)	0.0054

*Per 1-h increase in this variable.
CI = confidence interval; HR = hazard ratio.

Although primary PCI is the preferred reperfusion strategy for STEMI patients, this approach is not feasible for many patients residing in rural locations with long transfer distances to PCI facilities (20). For

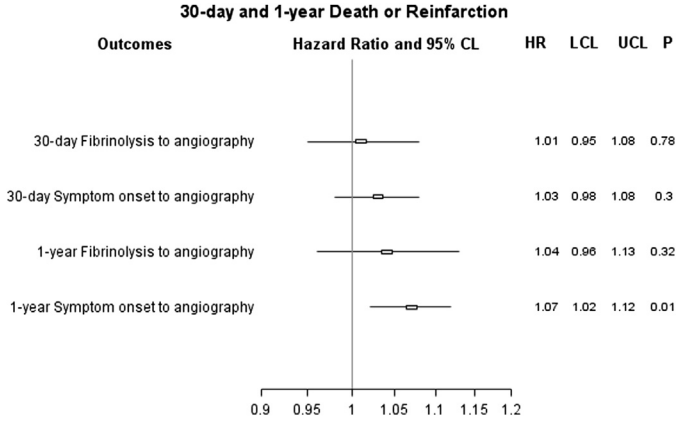

FIGURE 1 Association Between Time to Invasive Assessment and Clinical Outcomes

Adjusted associations between time from fibrinolysis to angiography and time from symptom onset to angiography with 30-day and 1-year outcomes. The hazard ratios are per hour of delay to angiography.

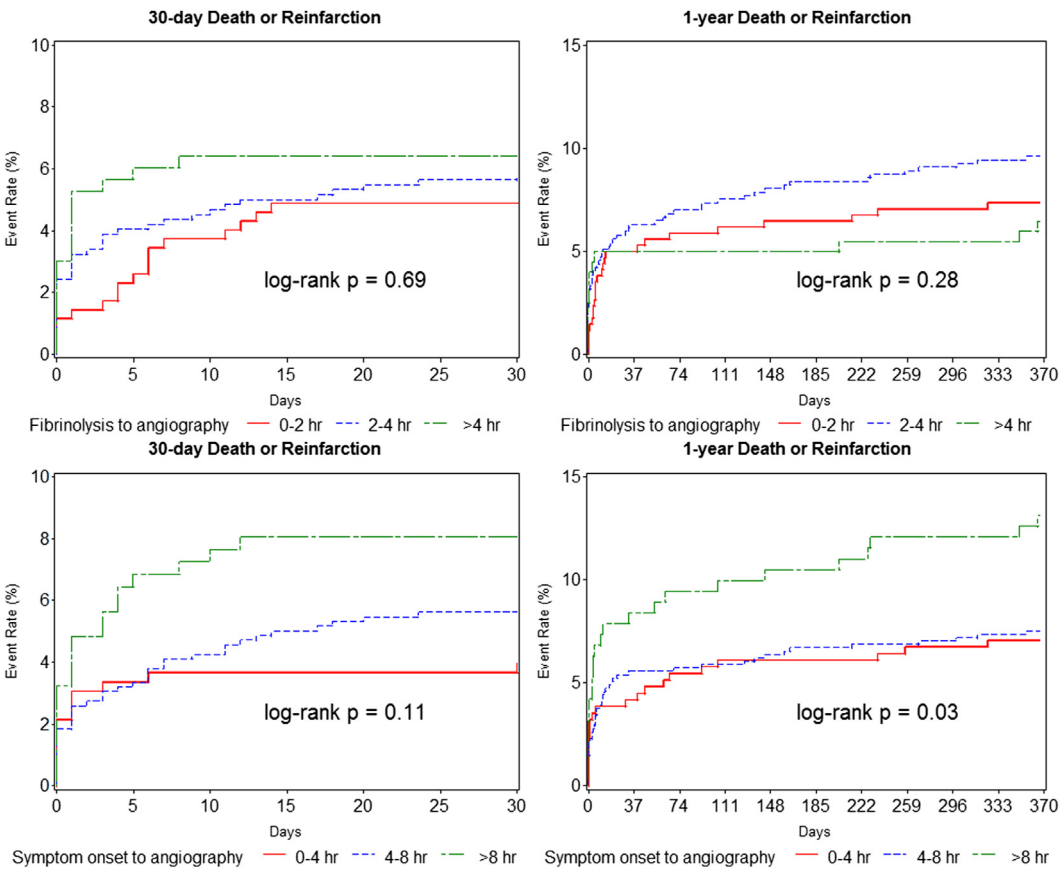

FIGURE 2 Kaplan-Meier Curve for 30-Day and 1-Year Death or Reinfarction

Kaplan-Meier curve for 30-day and 1-year death or reinfarction, according to time from fibrinolysis to angiography **(top)** and symptom onset to angiography time **(bottom)**.

these patients, fibrinolysis followed by the early invasive approach has been incorporated as part of most modern-day regional systems of STEMI care (16,17,20).

Patients undergoing very early angiography (<2 h) after fibrinolysis had clinical outcomes comparable to those of patients undergoing angiography at later time points. Trials of facilitated primary PCI have cautioned against performing PCI very early after fibrinolysis due to excess hazard observed among the patients treated in this manner (21,22). The early invasive approach evaluated in our trials should be distinguished from a facilitated PCI strategy. Facilitated PCI was formally investigated in the large ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy With Percutaneous Coronary Intervention-4), the FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) study, and several smaller studies (21–23). In this strategy, fibrinolysis was investigated as a form of adjunctive therapy, along with aspirin and anticoagulant therapy, before primary PCI. The time interval between fibrinolysis and balloon inflation was typically shorter than noted in early invasive studies (median of 104 min in the ASSENT-4 PCI and 90 min in the FINESSE) (21,22). In these studies, facilitation of primary PCI with fibrinolysis was associated with higher mortality, stroke, and bleeding complications compared with primary PCI alone and cannot be recommended as a viable STEMI strategy (21–23). Because the facilitated PCI strategy differed from the early invasive approach with respect to time from fibrinolysis to angiography, intent of primary PCI, and use of adjunctive antiplatelet therapies, such studies were not considered for inclusion in the present analysis.

In addition to improved infarct-related artery patency, and long-term survival, primary PCI results in decreased neurological complications, and a reduction in recurrent ischemia and reinfarction compared with fibrinolytic therapy (24). In our study, we confirmed the salutary effects of an early invasive approach for those STEMI patients unable to access primary PCI. The early invasive approach did not result in excessive rates of bleeding or stroke despite patients arriving at the cath lab a median of 165 min (2 h and 45 min) after fibrinolysis. In fact, even for patients with a time from fibrinolysis to angiography <2 h (n = 349), major bleeding events were not increased compared with patients having angiography performed at later time points. Furthermore, we confirmed a reduction in recurrent ischemia for those patients undergoing revascularization at earlier time points. Patients undergoing revascularization early likely had early infarct-related artery stabilization without subsequent ischemic events.

STUDY LIMITATIONS. This was a retrospective analysis of a pooled patient database from 6 previous randomized trials. These trials had varying definitions for certain variables, limiting our ability to combine all variables across studies (e.g., definition of recurrent ischemia, bleeding). The trials had variable use of certain drugs (e.g., GPIs) and angiography techniques (radial vs. femoral approach). Missing data for certain variables and outcomes limited our power to detect differences where they may exist. We could not comment on the effects of pre-hospital versus in-hospital fibrinolysis using this dataset nor did we examine the outcomes of patients undergoing rescue PCI after failed thrombolysis. Furthermore, if the dataset had been larger and with higher event rates, we may have been able to demonstrate a relationship for time from fibrinolysis to angiography and outcomes in higher risk subgroups where time is traditionally thought to be important in determining outcomes, such as anterior MI or higher Killip class. Finally, the comparison of clinical outcomes by time intervals was nonrandomized, and we had limited power to detect potential differences in outcomes based on time trends. A post-hoc power calculation for 30-day death or reinfarction revealed power of only 3.3%, and 9.4% for in-hospital major bleeding, respectively.

CONCLUSIONS

Very early angiography (<2 h) after fibrinolysis was not associated with an increased risk of 30-day death or reinfarction or in-hospital major bleeding, and angiography within 4 h after fibrinolysis was associated with a reduced rate of 30-day recurrent ischemia. A shorter symptom onset to angiography time (<4 h) was associated with reduced 30-day and 1-year death or reinfarction, and a reduction in 30-day recurrent ischemia. In the current environment characterized by the development of regional networks of 24/7 primary PCI centers, the clinical implication of these findings is that patients initially treated with fibrinolysis should also be promptly transferred to the nearest PCI center for immediate angiography and PCI.

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KEY WORDS fibrinolysis, myocardial infarction, percutaneous coronary intervention, timing of angiography

APPENDIX For supplemental tables, please see the online version of this article.