Original Investigation

Fibrinolysis Use Among Patients Requiring Interhospital Transfer for ST-Segment Elevation Myocardial Infarction Care
A Report From the US National Cardiovascular Data Registry

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IMPORTANCE Guidelines for patients with ST-segment elevation myocardial infarction (STEMI) recommend timely reperfusion with primary percutaneous coronary intervention (pPCI) or fibrinolysis. Among patients with STEMI who require interhospital transfer, it is unclear how reperfusion strategy selection and outcomes vary with interhospital drive times.

OBJECTIVE To assess the association of estimated interhospital drive times with reperfusion strategy selection among transferred patients with STEMI in the United States.

DESIGN, SETTING, AND PARTICIPANTS We identified 22 481 patients eligible for pPCI or fibrinolysis who were transferred from 1771 STEMI referring centers to 366 STEMI receiving centers in the Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines database between July 1, 2008, and March 31, 2012.

MAIN OUTCOMES AND MEASURES In-hospital mortality and major bleeding.

RESULTS The median estimated interhospital drive time was 57 minutes (interquartile range [IQR], 36-88 minutes). When the estimated drive time exceeded 30 minutes, only 42.6% of transfer patients treated with pPCI achieved the first door-to-balloon time within 120 minutes. Only 52.7% of eligible patients with a drive time exceeding 60 minutes received fibrinolysis. Among 15 437 patients with estimated drive times of 30 to 120 minutes who were eligible for fibrinolysis or pPCI, 5296 (34.3%) received pretransfer fibrinolysis, with a median door-to-needle time of 34 minutes (IQR, 23-53 minutes). After fibrinolysis, the median time to transfer to the STEMI receiving center was 49 minutes (IQR, 34-69 minutes), and 97.1% underwent follow-up angiography. Patients treated with fibrinolysis vs pPCI had no significant mortality difference (3.7% vs 3.9%; adjusted odds ratio, 1.13; 95% CI, 0.94-1.36) but had higher bleeding risk (10.7% vs 9.5%; adjusted odds ratio, 1.17; 95% CI, 1.02-1.33).

CONCLUSIONS AND RELEVANCE In the United States, neither fibrinolysis nor pPCI is being optimally used to achieve guideline-recommended reperfusion targets. For patients who are unlikely to receive timely pPCI, pretransfer fibrinolysis, followed by early transfer for angiography, may be a reperfusion option when potential benefits of timely reperfusion outweigh bleeding risk.

Invited Commentary

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The benefit of timely reperfusion in patients with acute ST-segment elevation myocardial infarction (STEMI) has been well documented.[1] Primary percutaneous coronary intervention (pPCI), which has proven mortality benefit over fibrinolysis in clinical trials, is the preferred reperfusion strategy, provided that it can be delivered in an expedient manner.[1,2] Nevertheless, only one-third of acute care hospitals in the United States have around-the-clock PCI capability.[3,4] Although several regional STEMI systems have been successful in reducing reperfusion delays,[5,6] on a national level a substantial proportion of patients with STEMI who are transferred for pPCI still fail to achieve the recommended goal of first medical contact to reperfusion within 120 minutes.[3,7] Current American College of Cardiology Foundation/American Heart Association[1] guidelines recommend consideration of fibrinolytic therapy for eligible patients who are first treated at a hospital without PCI capability and cannot receive timely pPCI (class I; level of evidence, A). Although we have some knowledge of practice patterns internationally[8-11] and within a few regional STEMI networks in the United States,[5,6,12-14] little information exists to date on nationwide patterns of reperfusion strategy selection and associated outcomes among patients with STEMI who require interhospital transfer in the United States. In particular, it is unclear how reperfusion selection varies based on the predicted travel time needed for patients who are first triaged at a hospital without pPCI capability (a STEMI referring center) and then transferred to a STEMI receiving center.

Our study of the National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines (ACTION Registry-GWTG) included 2478 unique pairs of STEMI referring and receiving centers across the United States, offering the first description to date of nationwide reperfusion practices for patients with STEMI who are initially seen at a hospital without PCI capability. The first objective of our study was to describe how fibrinolysis vs pPCI strategy selection varies with the estimated drive time between STEMI referring and receiving centers among all transferred patients. The second objective was to focus on the cohort of patients for whom fibrinolytic therapy or pPCI could be a reasonable option based on estimated interhospital drive times and to compare timeliness of care and outcomes associated with each reperfusion strategy.

Methods

Data Sources

The ACTION Registry-GWTG is the largest ongoing quality improvement registry of acute myocardial infarction in the United States, capturing detailed clinical information on consecutive patients treated at participating centers. The registry serves as the hospital data collection and evaluation mechanism for the American Heart Association's Mission: Lifeline program. Each study hospital's institutional review board approved participation in the registry, and the requirement for informed consent was waived because data were collected without individual patient identifiers. Institutions participating in the ACTION Registry-GWTG reported detailed information on baseline demographic and clinical characteristics, care processes, and in-hospital outcomes for all patients initially seen with acute myocardial infarction. Data were screened for completeness and accuracy during web-based entry, and data quality and integrity are maintained through the use of standardized data definitions, uniform data transmission protocols, and routine data quality checks and audits.[15]

For all patients transferred to an ACTION Registry-GWTG hospital, the name and/or American Hospital Association identification number of the transferring hospital was collected as free-text elements on the ACTION Registry-GWTG data collection form. We manually linked each transferring hospital name to its record in the American Hospital Association survey database to access hospital information such as address, bed size, and available inpatient facilities and services.[16]

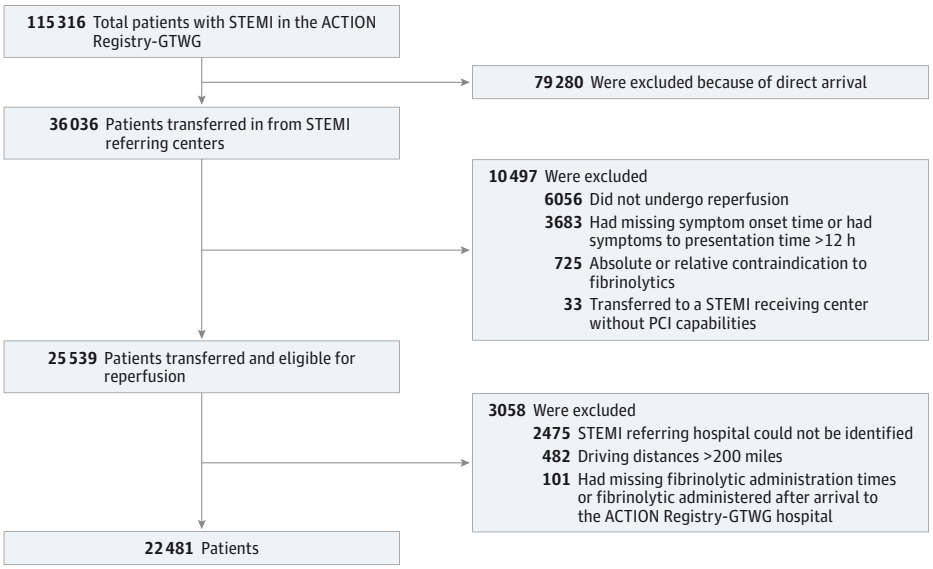
Study Population

Among 115 316 patients with STEMI captured in the ACTION Registry-GWTG between July 1, 2008, and March 31, 2012, we focused on 36 036 patients (31.2%) who were initially seen at a STEMI referring center and were subsequently transferred to a STEMI receiving center (**Figure 1**). We first excluded patients who did not receive reperfusion (n = 6056), patients with symptom onset to first presentation exceeding 12 hours or missing symptom onset time (n = 3683), patients who were transferred to a hospital without PCI capabilities (n = 33), and patients with absolute or relative contraindications to fibrinolytic therapy (n = 725). Finally, among 25 539 remaining patients who were transferred and eligible for reperfusion, we excluded transfer patients from STEMI referring centers that could not be linked to a valid address survey data set (n = 2475), patients with missing fibrinolytic administration times or with receipt of fibrinolytics after arrival to the STEMI receiving center (n = 101), and patients with a drive distance exceeding 200 miles who would almost certainly require nonground transportation (n = 482). Similar patient characteristics were observed between patients who were included in vs removed from the analysis population after this last series of exclusions (eTable 1 in the Supplement). Our final study population included 2478 unique pairs among 1771 STEMI referring and receiving centers that transferred 22 481 patients with STEMI to 366 STEMI receiving centers in the ACTION Registry-GWTG.

Outcomes

Descriptive outcomes include the use of fibrinolysis or pPCI and the first door-to-balloon (DTB) time for patients treated with pPCI, defined as the interval from the STEMI referring center presentation to the first device activation time, regardless of the type of device used. The clinical outcomes of interest were in-hospital mortality and major bleeding. In-hospital major bleeding, as defined by the ACTION Registry-GWTG,[17] included any of the following: an absolute hemoglobin level decrease of 4 g/dL or more, intracranial hemorrhage, any red blood cell transfusion with a baseline hemoglobin level of 9 g/dL or higher, or a red blood cell transfusion with a baseline

Figure 1. Study Population Characteristics



Shown are the included and excluded patients. ACTION Registry-GWTG indicates Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction.

hemoglobin level of less than 9 g/dL and a suspected bleeding event (to convert hemoglobin level to grams per liter, multiply by 10.0).

Statistical Analysis

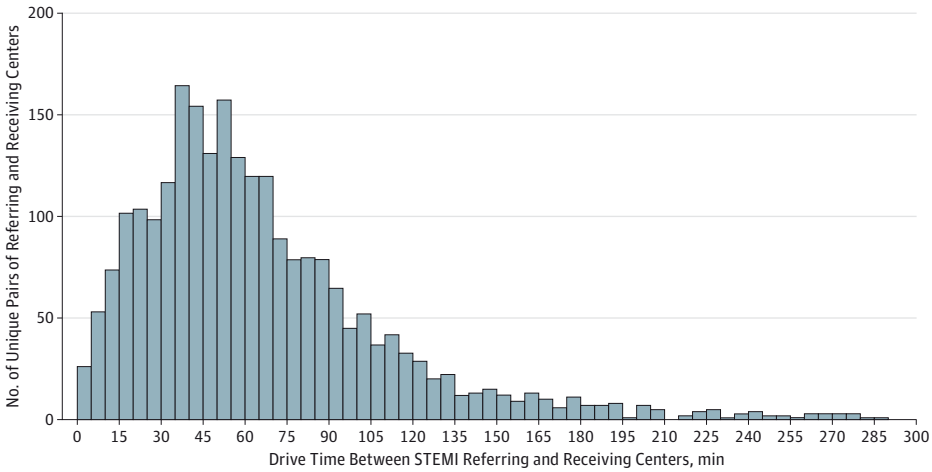
For each unique STEMI referring and receiving center pair, we used Google Maps (https://www.google.com/maps) to calculate the drive distance and time between hospitals, providing drive time estimates similar to what hospitals would use during reperfusion decision making. The median difference between estimated drive times and documented transfer times (departure from the STEMI referring center to arrival at the STEMI receiving center) was 9 minutes (interquartile range [IQR], 6-31 minutes).

We first assessed the distribution in distance and estimated drive times between STEMI referring and receiving centers and then compared these between patients treated with fibrinolytics vs pPCI among all transferred patients. The proportions of patients achieving a first DTB time within 120 minutes and receiving fibrinolysis were reported after stratification by the estimated drive time between STEMI referring and receiving centers.

In the analyses comparing patients receiving pPCI and fibrinolysis, we focused on a secondary cohort of transferred patients with STEMI with an estimated drive time between 30 and 120 minutes. These times were selected to identify a cohort for whom fibrinolysis or pPCI would be a reasonable reperfusion strategy because fibrinolytics would not be indicated if a first DTB time within 120 minutes could be easily achieved (95% of patients with an estimated drive time ≤30 minutes underwent pPCI), and pPCI would not be recommended if a first DTB time within 120 minutes was impossible (95% of patients with an estimated drive time >120 minutes received fibrinolysis). In this secondary cohort of 15 437 patients eligible for fibrinolysis or pPCI, we examined reperfusion strategy selection and timeliness. We then compared baseline patient and hospital characteristics, as well as in-hospital treatment between reperfusion strategies, using Pearson χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. The following patient characteristics at the time of presentation were abstracted into the data collection form based on medical records transferred to the STEMI receiving center: electrocardiographic changes on the initial electrocardiogram, admission heart rate, admission systolic blood pressure, and the presence of heart failure plus shock on admission. Data are presented as frequencies and percentages for categorical variables and as medians (IQRs) for continuous variables. Finally, we used logistic regression with generalized estimating equations to compare risk-adjusted outcomes between patients receiving pretransfer fibrinolytics and those receiving pPCI. This method accounts for within-hospital clustering because patients treated at the same hospital tend to have more similar responses relative to patients treated at other hospitals.[18] Each outcome was adjusted for a comprehensive list of variables adapted from the previously validated ACTION Registry-GWTG mortality[19] and bleeding risk[17] models (eTable 2 in the Supplement), including the estimated drive time between STEMI referring and receiving centers, whether travel occurred during peak hours (defined as 8 AM to 6 PM) or nonpeak hours, and other significant variables in univariate comparisons. We performed a sensitivity analysis using mixed-effects models that include random effects for hospitals to estimate site-specific comparisons.

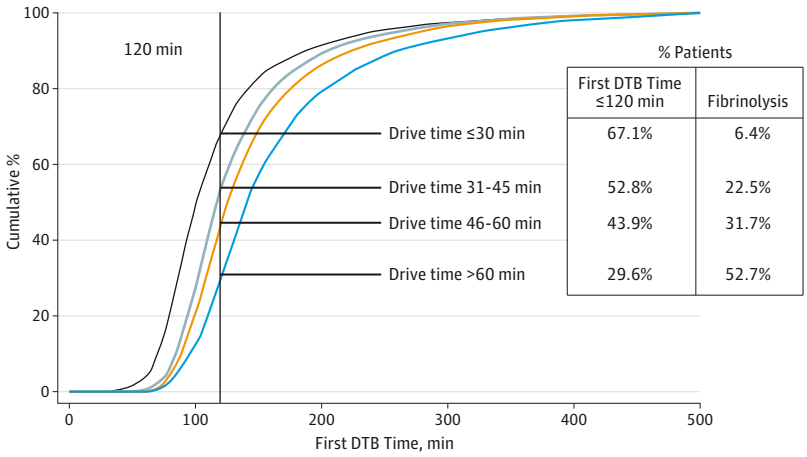
In addition, we examined bleeding outcomes among fibrinolysis-treated patients who (1) required rescue PCI after failed fibrinolysis, (2) did not require rescue PCI and underwent cardiac catheterization within 6 hours of fibrinolysis (pharmacoinvasive strategy as exemplified by the Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction[20]), and (3) did not

Figure 2. Distribution of the ST-Segment Elevation Myocardial Infarction (STEMI) Referring and Receiving Center Pairs Based on the Estimated Interhospital Drive Time



Each bar represents the number of unique pairs of STEMI receiving and referring centers (2478 total) that had an estimated drive time within the specified time frame.

Figure 3. Cumulative Proportion of Patients Who Received Primary Percutaneous Coronary Intervention Stratified by the Estimated Interhospital Drive Time



Each line represents a group of patients stratified by the estimated interhospital drive time. The x-axis represents the first door-to-balloon (DTB) time to primary percutaneous coronary intervention. The intersection of each line with the 120-minute mark represents the observed percentage of patients who achieved a first DTB time within 120 minutes in each estimated interhospital drive time group.

require rescue PCI and had no catheterization or delayed catheterization beyond 6 hours after fibrinolytic administration. Using the methods described above, we compared unadjusted and adjusted bleeding outcomes for each of these groups with those of patients who received pPCI.

Statistical significance was defined as $P < .05$. All analyses were performed by the NCDR data analysis center at the Duke Clinical Research Institute using statistical software (SAS, version 9.3; SAS Institute Inc).

Results

Association of Estimated Interhospital Drive Times With Reperfusion Strategy Selection and Timeliness

Among 22 481 fibrinolysis-eligible patients with STEMI transferred between 2478 STEMI referring and receiving center pairs in the ACTION Registry-GWTG, 6642 patients (29.5%) received pretransfer fibrinolytic therapy, whereas 15 839 patients (70.5%) were directly transferred for pPCI. **Figure 2** shows the distribution of estimated interhospital drive times for these centers. The median estimated interhospital drive time was 57 minutes (IQR, 36-88 minutes), with a median drive distance of 48 miles (IQR, 28-81 miles). The median estimated drive times and distances were 39 minutes (IQR, 25-57 minutes) and 32 miles (IQR, 18-49 miles) among patients who received pPCI and were 66 minutes (IQR, 48-97 minutes) and 58 miles (IQR, 41-89 miles) among patients who received pretransfer fibrinolysis.

Overall, 8132 of 15 839 patients with STEMI (51.3%) who were transferred for pPCI achieved guideline-recommended first DTB time within 120 minutes. As the estimated drive time increased, the proportion of patients achieving a first DTB time within 120 minutes was lower and the proportion of patients receiving fibrinolysis was higher (**Figure 3**). When the estimated drive time between hospitals exceeded 30 minutes, only

Table 1. Baseline Characteristics of Patients According to Reperfusion Strategy

Variable	Fibrinolysis (n = 5296)	Primary PCI (n = 10 141)	*P* Value
Demographics			
Age			
Median (IQR), y	59 (51-67)	59 (51-69)	.03
≥75 y, No. (%)	631 (11.9)	1477 (14.6)	<.001
Female sex, No. (%)	1430 (27.0)	2762 (27.2)	.76
Insurance status, No. (%)			.19
Private or health maintenance organization	2813 (53.1)	5511 (54.3)	
Medicare, Medicaid, or Veterans Affairs	1485 (28.0)	2745 (27.1)	
Self or none	925 (17.5)	1784 (17.6)	
Other or missing	73 (1.4)	101 (1.0)	
Clinical Characteristics			
Prior myocardial infarction, No. (%)	965 (18.2)	1746 (17.2)	.12
Prior heart failure, No. (%)	196 (3.7)	391 (3.9)	.64
Prior PCI, No. (%)	1010 (19.1)	1905 (18.8)	.63
Prior coronary artery bypass graft surgery, No. (%)	287 (5.4)	531 (5.2)	.62
Prior stroke, No. (%)	182 (3.4)	433 (4.3)	.01
Peripheral arterial disease, No. (%)	247 (4.7)	478 (4.7)	.89
Weight, median (IQR), kg	86.2 (75-100)	86.2 (75-100)	.51
Hypertension, No. (%)	3280 (61.9)	6276 (61.9)	.93
Diabetes mellitus, No. (%)	1103 (20.8)	2311 (22.8)	.006
Dyslipidemia, No. (%)	2627 (49.6)	5179 (51.1)	.08
Home warfarin sodium, No. (%)	90 (1.7)	269 (2.7)	<.001
Presentation Features			
Time from symptom onset to arrival at the referring center, median (IQR), min	84 (50-151)	80 (47-165)	.55
Electrocardiogram findings, No. (%)			.07
ST-segment elevation	5230 (98.8)	9967 (98.3)	
New left bundle branch block	34 (0.6)	93 (0.9)	
Isolated posterior myocardial infarction	27 (0.5)	72 (0.7)	
Hypotension, systolic blood pressure ≤90 mm Hg, No. (%)	286 (5.4)	570 (5.6)	.58
Signs of heart failure, No. (%)	343 (6.5)	675 (6.7)	.69
Cardiogenic shock, No. (%)	328 (6.2)	770 (7.6)	.002
Creatinine clearance <60 mL/min/1.73 m^2, No. (%)[a]	886 (16.8)	1801 (17.9)	.07
Baseline hemoglobin level, median (IQR), g/dL	14.8 (13.5-15.9)	14.6 (13.4-15.7)	<.001
Troponin I level, times the institutional upper limit of normal, median (IQR)	1.09 (0.28-14.25)	1.40 (0.26-25.20)	<.001
ACTION Registry-GWTG, %			
In-hospital mortality risk	1.9	2.1	.002
Major bleeding risk	8.6	8.6	<.001

Abbreviations: ACTION Registry-GWTG, Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines; IQR, interquartile range; PCI, percutaneous coronary intervention.

SI conversion factors: To convert hemoglobin level to grams per liter, multiply by 10.0; to convert creatinine clearance to milliliters per second per meter squared, multiply by 0.0167.

[a] Creatinine clearance was calculated using the Cockroft-Gault formula among patients not receiving dialysis.

42.6% of transfer patients received pPCI within 120 minutes, and when the estimated drive time exceeded 60 minutes, only 29.6% of patients received pPCI within 120 minutes. Only 52.7% of eligible patients with an estimated drive time exceeding 60 minutes received fibrinolysis.

Characteristics of Patients Treated With Fibrinolysis vs Primary PCI

Because 95% of patients with estimated interhospital drive times of 30 minutes or less underwent pPCI and 95% of patients with estimated drive times exceeding 120 minutes received fibrinolysis, we examined reperfusion strategy selection and timeliness in a secondary cohort of 15 437 fibrinolysis-eligible patients transferred to a STEMI receiving center 30 to 120 minutes away for whom either may have been a possible reperfusion strategy. In this cohort, 5296 patients (34.3%) received pretransfer fibrinolysis, and 10 141 patients (65.7%) were directly transferred for pPCI. Among the latter group transferred for pPCI, only 43.7% achieved a first DTB time within 120 minutes.

In our study cohort, patients who received fibrinolysis were less likely to be 75 years or older and had modestly lower rates of prior stroke and diabetes mellitus than patients who received pPCI (**Table 1**). Fibrinolysis-treated patients were less likely to exhibit signs of cardiogenic shock on admission, and the predicted in-hospital mortality risk (using the ACTION Registry-GWTG mortality risk score) was slightly lower in the fibrinolysis group. Compared with patients who were trans-

Table 2. Hospital Characteristics and In-Hospital Treatment of Patients According to Reperfusion Strategy

Variable	Fibrinolysis (n = 5296)	Primary PCI (n = 10 141)	*P* Value
STEMI Referring Centers			
Teaching hospital, No. (%)	1 (0.02)	22 (0.2)	.003
Total hospital beds, median (IQR)	89 (49-142)	95 (50-148)	.03
PCI capability, No. (%)[a]	332 (6.3)	970 (9.6)	<.001
Cardiac surgery capability, No. (%)	149 (2.8)	410 (4.0)	<.001
STEMI Receiving Centers			
Teaching hospital, No. (%)	1819 (34.3)	3445 (34.0)	.70
Total hospital beds, median (IQR)	523 (338-739)	493 (320-730)	<.001
Cardiac surgery capability, No. (%)	5150 (97.2)	9922 (97.8)	.02
Reperfusion Timeliness, Median (IQR), min			
First door-to-balloon time	NA	126 (104-165)	NA
Door-to-needle time	34 (23-53)	NA	NA
Door-in-door-out time	85 (63-118)	58 (40-85)	<.001
Needle-to-door-out time	49 (34-69)	NA	NA
Estimated interhospital drive time	63 (48-82)	48 (39-63)	<.001
Second-door-to-balloon time	NA	28 (21-40)	NA
Medications Used Within 24 h of Presentation, No. (%)[b]			
Aspirin	5200 (99.2)	9914 (99.0)	.09
$P2Y_{12}$ receptor inhibitor	4503 (85.8)	9688 (95.9)	<.001
Glycoprotein IIb/IIIa inhibitor	1653 (32.1)	6967 (69.1)	<.001
Anticoagulant, No. (%)			<.001
Unfractionated heparin	4176 (79.0)	8247 (81.4)	
Low-molecular-weight heparin	901 (17.0)	941 (9.3)	
Bivalirudin	131 (2.5)	800 (7.9)	
None	0	2 (0.02)	

Abbreviations: IQR, interquartile range; NA, not applicable; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

[a] STEMI referring centers with PCI capability may not have 24-hour coverage for primary PCI.

[b] Medications used within 24 hours of presentation include those that were administered at the STEMI referring center before transfer. Patients who are contraindicated or blinded for the medication are excluded from the denominator.

ferred for pPCI, patients who received fibrinolytic therapy before transfer were more likely to originate from a hospital without PCI or cardiac surgery capability and to transfer into a larger STEMI receiving center (**Table 2**).

The median door-to-needle time was 34 minutes (IQR, 23-53 minutes); only 43.8% of patients achieved a door-to-needle time within 30 minutes. The most commonly used fibrinolytic agent was tenecteplase (74.6%), followed by reteplase (21.6%); 95.8% of fibrinolysis-treated patients received a full dose of the fibrinolytic agent. The median time from fibrinolytic administration to departure from the STEMI referring center was 46 minutes (IQR, 28-70 minutes). After transfer, 97.1% of fibrinolysis-treated patients underwent cardiac catheterization. Rescue PCI, defined by the NCDR as PCI performed after failed full-dose fibrinolysis, was performed in 2200 of 5296 patients (41.5%) treated with fibrinolytics, with a median time from fibrinolytic administration to PCI of 148 minutes (IQR, 117-204 minutes). Among patients not requiring rescue PCI, the median time from fibrinolytic administration to PCI was 19.5 hours (IQR, 7.7-34.0 hours), and a pharmacoinvasive strategy, defined as cardiac catheterization within 6 hours of fibrinolytic administration,[20] was used in 1195 patients (38.9%). $P2Y_{12}$ receptor inhibitors and glycoprotein IIb/IIIa inhibitors were used within the first 24 hours of presentation in 85.8% and 32.1%, respectively, of patients who received fibrinolysis (Table 2).

In-Hospital Mortality and Major Bleeding

Among patients transferred to a STEMI receiving center between 30 and 120 minutes away, we observed no difference in unadjusted and adjusted in-hospital mortality between patients treated with fibrinolysis vs pPCI (3.7% vs 3.9%; adjusted odds ratio [aOR], 1.13; 95% CI, 0.94-1.36). The risk of in-hospital major bleeding was higher in patients receiving pretransfer fibrinolytic therapy vs pPCI (10.7% vs 9.5%; aOR, 1.17; 95% CI, 1.02-1.33). This increase in bleeding risk with fibrinolysis was primarily observed in patients who required rescue PCI (12.9% vs 9.5%; aOR, 1.44; 95% CI, 1.22-1.70 [compared with pPCI]). After excluding patients who required rescue PCI, no significant difference was observed in bleeding risk between fibrinolysis and pPCI when cardiac catheterization was performed within 6 hours after fibrinolytic administration (9.1% vs 9.5%; aOR, 0.93; 95% CI, 0.72-1.19). Also, no difference was observed in bleeding risk between fibrinolysis and pPCI if catheterization was performed more than 6 hours after fibrinolytic administration or no catheterization was performed (9.2% vs 9.5%; aOR, 0.97; 95% CI, 0.81-1.16). Sensitivity analyses using hierarchical models to estimate a site-specific comparison yielded similar results. Intracranial hemorrhages were rare, occurring in 32 of 5296 patients treated with fibrinolysis (0.6%) and in 6 of 10 141 patients treated with pPCI (0.06%). These event rates were too low to permit multivariable adjustment.

Discussion

This study represents the first evaluation of reperfusion strategy selection, timeliness, and outcomes on a national scale for patients with STEMI initially seen at a STEMI referring center and subsequently transferred to a STEMI receiving center. We found that less than half of patients with STEMI achieved pPCI within the guideline-recommended time frame if they required transfer to a STEMI receiving center more than 30 minutes away. Yet, fibrinolytic therapy use was infrequent among eligible patients who had a low likelihood of achieving timely pPCI, and its administration was often delayed. Among eligible patients transferred 30 to 120 minutes away, no significant difference was observed in mortality between pPCI and a contemporary, guideline-recommended pretransfer fibrinolytic strategy involving early transport to a STEMI receiving center. Although intracranial hemorrhages were rare, the risk of overall major bleeding was higher among patients receiving pretransfer fibrinolytic therapy vs pPCI.

Guidelines recommend pPCI within 120 minutes for patients requiring interhospital transfer for STEMI care, and regional STEMI initiatives have led to improvements in DTB times for these patients.[6,9,11,14,21] For example, the Minneapolis Network demonstrated the ability to achieve a first DTB time within 120 minutes for patients as far as 60 miles away from the pPCI center.[5] In our study, 51.3% of transferred patients nationally achieved a first DTB time within 120 minutes, which is improved from 30% in a 2005 to 2007 NCDR survey.[7] Nonetheless, room for improvement remains in reperfusion performance in the United States because our study shows that neither fibrinolysis nor pPCI is being optimally used to achieve guideline-recommended treatment targets. A previous editorial[22] echoes this point, advocating for reconsideration of fibrinolysis among eligible patients who are unable to achieve timely primary PCI, and we have observed limited reductions in interhospital transfer times for patients with STEMI despite significant investment of effort and resources. When estimated drive times exceeded 30 minutes (as is the case with most transferred patients with STEMI in the United States) in our study, more than half of these patients failed to achieve a first DTB time within 120 minutes. In this setting, current guidelines would recommend consideration of pretransfer fibrinolysis, yet fibrinolysis is infrequently used and often delayed among eligible patients, even among those who have little expectation of attaining a first DTB time within 120 minutes.[1] Although our data do not capture causes for these care gaps, potential explanations may include indecision regarding reperfusion strategy, complex care coordination between STEMI referring and receiving centers, and reluctance to consider fibrinolysis.[23]

Previous studies[2,24] of fibrinolytic therapy showed increased mortality and bleeding risks compared with pPCI. However, a 2011 observational study[25] of 5295 patients with STEMI in Belgium found a narrowing mortality gap among patients treated with pPCI vs fibrinolysis (with 84% undergoing subsequent invasive evaluation). More recently, the Strategic Reperfusion Early After Myocardial Infarction (STREAM) study[26] found no mortality difference between prehospital fibrinolysis and pPCI. A significantly higher risk of intracranial hemorrhage in the fibrinolysis group, detected in the early phase of this trial, led to fibrinolytic dose reduction among older patients, after which the intracranial hemorrhage rate no longer differed from that of the PCI group. While not designed to directly compare outcomes between pPCI and fibrinolysis, the results of our observational study suggest that the estimated interhospital drive time should be factored into the decision between fibrinolysis and pPCI. For patients with an estimated drive time between 30 and 120 minutes (a population for whom fibrinolysis or transfer for pPCI would be a reasonable option), we observed no significant mortality difference between reperfusion strategies. These data are in line with the results of other recent fibrinolysis investigations. A next phase of the Mission: Lifeline geospatial information systems project will prospectively designate statewide preferred reperfusion strategies to best meet current guideline benchmarks based on interhospital distance and transportation options.[27]

The incidence of intracranial hemorrhage was low (32 patients [0.6%]) among 5296 fibrinolysis-treated patients, but the overall odds of major bleeding associated with fibrinolysis was 16.5% higher than that among pPCI-treated patients. The 2013 American College of Cardiology Foundation/American Heart Association[1] STEMI guidelines provide a class IIA recommendation for routine transfer of all patients after administration of fibrinolytic therapy for early coronary angiography and potential revascularization; this recommendation is based on several randomized clinical trials[20,28] and on a meta-analysis.[29] As such, most patients in our study were transferred to a pPCI center within 1 hour of fibrinolytic administration. The excess bleeding risk associated with fibrinolytic therapy was largely observed in patients who required rescue PCI. In these patients, bleeding risk may be compounded by periprocedural anticoagulant and antiplatelet therapy use. A pharmacoinvasive strategy involving cardiac catheterization within 6 hours of fibrinolytic administration was associated with no significant difference in bleeding compared with pPCI. Fibrinolysis with delayed catheterization beyond 6 hours or without catheterization, as was the case with most of the participants in the STREAM study,[26] also appeared to be as safe as pPCI. Given its higher associated bleeding risk, the potential benefit of pretransfer fibrinolysis should be weighed against bleeding risk and may be a reperfusion option for only a subset of patients deemed unlikely to receive timely pPCI.

Our study has some limitations that warrant consideration. First, we cannot account for the influence of regionally established STEMI care networks on reperfusion strategy selection and timeliness because this information was not captured in the ACTION Registry-GWTG. Care protocols established by such networks may be uniquely tailored to the geographic needs and capabilities of its component centers such that timely pPCI is achieved, even for patients with long transportation distances.[5,21,30] Second, heterogeneity among the STEMI receiving centers that did not participate in the ACTION Registry-GWTG may affect the generalizability of our results. Third, we had no information on actual drive times and routes for each transferred patient, and our study could not

take into account specific travel considerations, including traffic congestion or weather-related delays; however, our Google Maps estimates are similar to estimates that hospitals use during reperfusion decision making. The estimated patient-level drive times correlated well with documented transfer times (door-out time from the STEMI referring center to arrival at the STEMI receiving center). Fourth, the rate of rescue PCI in our observational study was higher than that previously reported.[31] Rescue PCI was not centrally adjudicated but was reported by the site using a standardized NCDR definition. The time from fibrinolytic administration to PCI was substantially shorter among patients coded as receiving rescue PCI vs those not requiring rescue PCI. Fifth, we have no data regarding the anatomic location of the STEMI and the consequent culprit lesion. Sixth, given the few intracranial hemorrhages, we were unable to perform multivariable-adjusted analyses. Seventh, patients in this observational study treated with pPCI had higher estimated mortality risk than those treated with fibrinolysis based on comparisons of measured clinical characteristics. We cannot exclude the possibility that physicians may be selecting pPCI as a treatment strategy for higher-risk patients, even in the face of longer DTB times. Despite robust multivariable adjustment, the presence of unmeasured confounding could mask a potential benefit from PCI. Finally, post-discharge outcomes were not collected by the NCDR because of US privacy laws, precluding comparisons of longer-term outcomes.

Conclusions

In summary, this is the first description to date of nationwide reperfusion practices in the United States. We observed that neither fibrinolysis nor pPCI is being used optimally to achieve guideline-recommended reperfusion targets for patients with STEMI who are first evaluated at a hospital without PCI capability. Our study findings suggest consideration of estimated interhospital drive times when making reperfusion decisions because less than half of patients transferred for pPCI achieved a first DTB time within 120 minutes when estimated drive times exceeded 30 minutes. Among eligible patients who required 30-minute to 120-minute transfers, fibrinolysis was associated with no significant mortality difference but with increased bleeding risk compared with pPCI. Therefore, for such patients who are unlikely to receive timely pPCI, pretransfer fibrinolytics, followed by early transfer for angiography, may be a contemporary reperfusion option when potential benefits of timely reperfusion outweigh bleeding risk.

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REFERENCES

1. O'Gara PT, Kushner FG, Ascheim DD, et al; American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61(4):e78-e140.

2. 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(9351):13-20.

3. Jacobs AK, Antman EM, Faxon DP, Gregory T, Solis P. Development of systems of care for ST-elevation myocardial infarction patients: executive summary. *Circulation*. 2007;116(2):217-230.

4. Concannon TW, Nelson J, Goetz J, Griffith JL. A percutaneous coronary intervention lab in every hospital? *Circ Cardiovasc Qual Outcomes*. 2012;5(1):14-20.

5. Henry TD, Sharkey SW, Burke MN, et al. A regional system to provide timely access to

percutaneous coronary intervention for ST-elevation myocardial infarction. *Circulation*. 2007;116(7):721-728.

6. Jollis JG, Roettig ML, Aluko AO, et al; Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Departments (RACE) Investigators. Implementation of a statewide system for coronary reperfusion for ST-segment elevation myocardial infarction. *JAMA*. 2007;298 (20):2371-2380.

7. Wang TY, Peterson ED, Ou FS, Nallamothu BK, Rumsfeld JS, Roe MT. Door-to-balloon times for patients with ST-segment elevation myocardial infarction requiring interhospital transfer for primary percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. *Am Heart J*. 2011;161(1):76-83.e1.

8. Danchin N, Coste P, Ferrières J, et al; FAST-MI Investigators. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment–elevation acute myocardial infarction: data from the French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI). *Circulation*. 2008;118(3): 268-276.

9. Kalla K, Christ G, Karnik R, et al; Vienna STEMI Registry Group. Implementation of guidelines improves the standard of care: the Viennese Registry on Reperfusion Strategies in ST-Elevation Myocardial Infarction (Vienna STEMI Registry). *Circulation*. 2006;113(20):2398-2405.

10. Le May MR, So DY, Dionne R, et al. A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2008;358(3): 231-240.

11. McLean S, Egan G, Connor P, Flapan AD. Collaborative decision-making between paramedics and CCU nurses based on 12-lead ECG telemetry expedites the delivery of thrombolysis in ST elevation myocardial infarction. *Emerg Med J*. 2008;25(6):370-374.

12. Eagle KA, Nallamothu BK, Mehta RH, et al; Global Registry of Acute Coronary Events (GRACE) Investigators. Trends in acute reperfusion therapy for ST-segment elevation myocardial infarction from 1999 to 2006: we are getting better but we have got a long way to go. *Eur Heart J*. 2008;29(5): 609-617.

13. Gibson CM, Pride YB, Frederick PD, et al. Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. *Am Heart J*. 2008;156(6):1035-1044.

14. Ting HH, Rihal CS, Gersh BJ, et al. Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction: the Mayo Clinic STEMI protocol. *Circulation*. 2007;116(7):729-736.

15. Messenger JC, Ho KK, Young CH, et al; NCDR Science and Quality Oversight Committee Data Quality Workgroup. The National Cardiovascular Data Registry (NCDR) data quality brief: the NCDR Data Quality Program in 2012. *J Am Coll Cardiol*. 2012;60(16):1484-1488.

16. Health Forum. *AHA Guide 2013 (American Hospital Association Guide to the Health Care Field)*. Chicago, IL: American Hospital Association; 2012. http://www.ahadataviewer.com/book-cd-products/AHA-Guide. Accessed October 30, 2014.

17. Mathews R, Peterson ED, Chen AY, et al. In-hospital major bleeding during ST-elevation and non–ST-elevation myocardial infarction care: derivation and validation of a model from the ACTION Registry-GWTG. *Am J Cardiol*. 2011;107(8): 1136-1143.

18. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42(1):121-130.

19. Chin CT, Chen AY, Wang TY, et al. Risk adjustment for in-hospital mortality of contemporary patients with acute myocardial infarction: the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry-Get With the Guidelines (GWTG) acute myocardial infarction mortality model and risk score. *Am Heart J*. 2011;161(1):113-122.e2.

20. Cantor WJ, Fitchett D, Borgundvaag B, et al; TRANSFER-AMI Trial Investigators. Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med*. 2009;360(26):2705-2718.

21. Huber K, Goldstein P, Danchin N, et al. Enhancing the efficacy of delivering reperfusion therapy: a European and North American experience with ST-segment elevation myocardial infarction networks. *Am Heart J*. 2013;165(2):123-132.

22. Redberg RF. Reconsidering transfer for percutaneous coronary intervention strategy: time is of the essence. *Arch Intern Med*. 2012;172(2):98-99.

23. Miedema MD, Newell MC, Duval S, et al. Causes of delay and associated mortality in patients transferred with ST-segment–elevation myocardial infarction. *Circulation*. 2011;124(15):1636-1644.

24. Morrow DA, Antman EM, Parsons L, et al. Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. *JAMA*. 2001;286(11):1356-1359.

25. Claeys MJ, de Meester A, Convens C, et al. Contemporary mortality differences between primary percutaneous coronary intervention and thrombolysis in ST-segment elevation myocardial infarction. *Arch Intern Med*. 2011;171(6):544-549.

26. Armstrong PW, Gershlick AH, Goldstein P, et al; STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;368(15):1379-1387.

27. Rokos IC, Henry TD, Weittenhiller B, Bjerke CM, Bates ER, French WJ. Mission: Lifeline STEMI networks geospatial information systems (GIS) maps. *Crit Pathw Cardiol*. 2013;12(2):43-44.

28. Bøhmer E, Hoffmann P, Abdelnoor M, Arnesen H, Halvorsen S. 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). *J Am Coll Cardiol*. 2010;55(2):102-110.

29. Borgia F, Goodman SG, Halvorsen S, et al. Early routine percutaneous coronary intervention after fibrinolysis vs standard therapy in ST-segment elevation myocardial infarction: a meta-analysis. *Eur Heart J*. 2010;31(17):2156-2169.

30. Larson DM, Duval S, Sharkey SW, et al. Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. *Eur Heart J*. 2012;33(10):1232-1240.

31. Burjonroppa SC, Varosy PD, Rao SV, et al. Survival of patients undergoing rescue percutaneous coronary intervention: development and validation of a predictive tool. *JACC Cardiovasc Interv*. 2011;4(1):42-50.