Benefit of Transferring ST-Segment–Elevation Myocardial Infarction Patients for Percutaneous Coronary Intervention Compared With Administration of Onsite Fibrinolytic Declines as Delays Increase

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Background**—**Although randomized trials suggest that transfer for primary percutaneous coronary intervention (X-PCI) in ST-segment–elevation myocardial infarction is superior to onsite fibrinolytic therapy (O-FT), the generalizability of these findings to routine clinical practice is unclear because door-to-balloon (XDB) times are rapid in randomized trials but are frequently prolonged in practice. We hypothesized that delays resulting from transfer would reduce the survival advantage of X-PCI compared with O-FT.

Methods and Results**—**ST-segment–elevation myocardial infarction patients enrolled in the National Registry of Myocardial Infarction (NRMI) within 12 hours of pain onset were identified. Propensity matching of patients treated with X-PCI and O-FT was performed, and the effect of PCI-related delay on in-hospital mortality was assessed. PCI-related delay was calculated by subtracting the XDB from the door-to-needle time in each matched pair. Conditional logistic regression adjusted for patient and hospital variables identified the XDB door-to-needle time at which no mortality advantage for X-PCI over O-FT was present. Eighty-one percent of X-PCI patients were matched (n=9506) to O-FT patients (n=9506). In the matched cohort, X-PCI was performed with delays >90 minutes in 68%. Multivariable analysis found no mortality advantage for X-PCI over O-FT when XDB door-to-needle time exceeded ≈120 minutes.

Conclusion**—**PCI-related delays are extensive among patients transferred for X-PCI and are associated with poorer outcomes. No differential excess in mortality was seen with X-PCI compared with O-FT even with long PCI-related delays, but as XDB door-to-needle time times increase, the mortality advantage for X-PCI over O-FT declines. (***Circulation*****. 2011;124:2512-2521.**)

Key Words: catheter ■ comparative effectiveness research ■ fibrinolysis ■ myocardial infarction ■ stents ■ thrombolysis ■ transfer

Many ST-segment–elevation myocardial infarction (STEMI) patients arrive at hospitals in the United States without primary percutaneous coronary intervention (PPCI) capability. More than 25% of hospitals do not have access to timely PPCI, so a large proportion of STEMI patients are transferred for PPCI (X-PCI) with resultant delays to reperfusion compared with administration of onsite fibrinolytic therapy (O-FT).[1–3] Randomized comparisons demonstrate the superiority of X-PCI over O-FT, and a meta-regression of 11 randomized trials involving 5741 patients comparing X-PCI with O-FT demonstrated that X-PCI was superior to O-FT in reducing mortality, recurrent MI, and stroke. This benefit was independent of the delay to PCI.[4] These observations, however, can be generalized only to the selected patients in these trials with short transfer door-to-balloon (XDB) times[5] and may not reflect the larger group of STEMI patients for whom XDB times are substantially longer owing to extensive transport times, variations in local expertise, and patient risk.[2,6,7]

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Although X-PCI is associated with favorable outcomes when performed rapidly, clinicians must account for both

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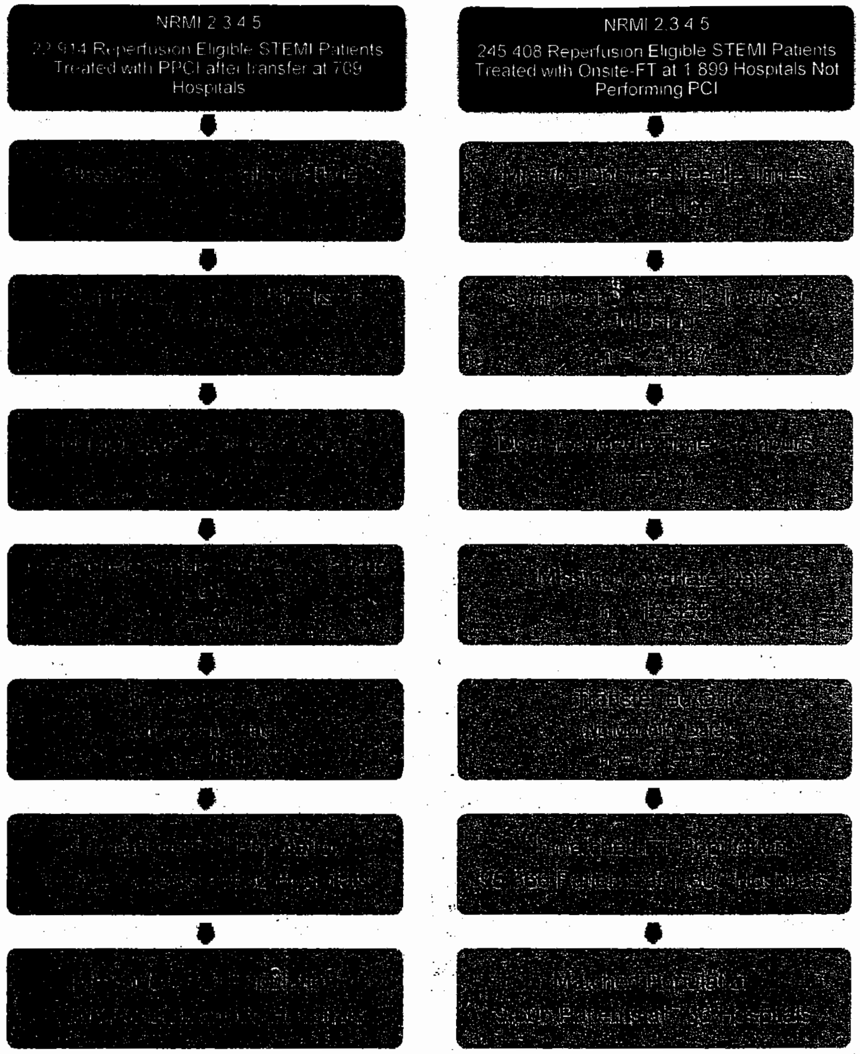

Figure 1. Study design. STEMI indicates ST-segment–elevation myocardial infarction; NRMI, National Registry of Myocardial Infarction; FT, fibrinolytic therapy; PCI, percutaneous coronary intervention; and PPCI, primary percutaneous coronary intervention.

patient-based risk factors and hospital-based factors such as the PCI-related delay when selecting a reperfusion strategy. Indeed, American College of Cardiology/American Heart Association (ACC/AHA) guidelines recognize that 1 reperfusion approach is not superior for all patients, in all clinical settings, at all times of day.[8] ACC/AHA guidelines suggest a time from first medical contact to balloon of 90 minutes[8] for X-PCI patients, whereas the European Society of Cardiology guidelines suggest 120 minutes.[9] Only 5% to 18% of transfer patients meet the ACC/AHA guidelines for timely reperfusion in the United States,[1,2,10] where the median XDB time is >150 minutes.[2]

It has been shown in a group of STEMI patients managed primarily without X-PCI that the mortality benefit of PPCI over fibrinolytic administration is time dependent.[11] Subtracting the door-to-needle time (DN) from the door-to-balloon DB time using comparative data allows the PCI-related delay (DB-DN) to be quantified and associated with outcomes. Analyses from randomized trial and registry data demonstrate that as the PCI-related delay increases, the mortality advantage of PPCI compared with FT is negated with substantial variance in the rate of erosion of the benefit based on patient risk.[7,11]

This analysis addresses a substantial gap in knowledge by evaluating the optimal reperfusion strategy for the large group of STEMI patients treated at hospitals that do not perform PCI routinely and where extensive delays resulting from X-PCI are common. The purpose of this study was to evaluate the effect of delays to reperfusion on the comparative efficacy of X-PCI and O-FT. The hypothesis tested was that the advantage of X-PCI compared with O-FT would decline as XDB-DN time increased in clinical practice, where XDB times are more prolonged than in randomized controlled trials.

Methods

NRMI 2, 3, 4, and 5 were voluntary, prospective registries that collected data from June 1994 to December 2006 on consecutive patients admitted to participating hospitals with documented acute MI. Characteristics of the NRMI data-gathering procedures, reliability, and hospital and patient variables (demographics, ECG findings, timelines, etc) have been described previously.[12,13]

Statistical Methods

Patients with STEMI (ST-segment elevation and/or left bundle-branch block on initial ECG and <12 hours after onset of pain) eligible for either reperfusion strategy who received O-FT or who underwent X-PCI as initial reperfusion therapy were identified

Table 1. Baseline Characteristics

	Study Population Before Matching			Matched Patients		
Covariate	X-PCI (n=11 662)	O-FT (n=95 366)	Standardized Difference*	X-PCI (n=9506)	O-FT (n=9506)	Standardized Difference*
Age (mean±SD, y	61.4±12.1	63.0±12.4	−12.94	61.5±12.1	61.8±12.0	−2.63
<50, %†	23.1	20.6	6.04	22.7	21.7	2.41
50–59, %†	28.3	24.6	8.44	28.4	28.2	0.37
60–69, %†	22.8	24.4	−3.67	22.9	23.6	−1.44
>70, %†	25.8	30.4	−10.40	26.0	26.6	−1.27
Female, %†‡	29.0	31.9	−6.30	27.4	27.4	0
Caucasian/white, %†	87.4	85.8	4.86	87.4	87.0	1.32
African American/black, %†	3.6	5.5	−9.11	3.4	3.4	−0.12
Hispanic, %†	2.2	3.7	−9.25	2.2	2.7	−2.98
Year after discharge†‡	8.2±3.5	4.6±2.5	119.4	7.5±3.4	7.5±3.4	0
Diabetes mellitus, %†	19.0	19.5	−1.31	18.5	18.9	−1.11
Hypertension, %†	49.3	46.5	5.60	48.1	48.1	−0.17
History of angina, %†	9.4	10.2	−2.85	9.0	8.9	0.33
Hypercholesterolemia, %†	37.8	31.5	13.24	36.4	36.3	0.24
History of smoking, %†	43.8	39.5	8.73	43.0	41.4	3.22
Family history of CAD, %†	28.7	33.1	−9.65	29.5	29.0	1.13
History of prior MI, %†	16.2	17.8	−4.15	16.3	15.1	3.09
Congestive heart failure, %†	3.1	4.8	−8.95	3.0	3.0	−0.18
Prior stroke, %†	5.8	3.8	9.13	5.5	5.3	0.65
Prior PCI, %†	13.6	7.9	18.64	13.2	12.8	1.35
Prior CABG, %†	5.0	6.7	−7.11	5.2	5.0	1.05
LBBB (old/new/unknown), %†	2.7	2.2	3.46	2.6	2.6	0.33
Prehospital delay, %						
<2 h	64.7	63.9	1.48	65.1	64.7	0.84
2–6†	25.8	29.4	−8.10	25.8	25.7	0.24
6–12†	9.5	6.6	10.7	9.1	9.6	−1.73
HR >100 bpm, %†	11.8	12.1	−0.92	11.5	11.0	1.30
SBP >100 mm Hg, %†	90.0	91.0	−3.55	90.2	90.3	−0.25
Anterior/septal, %†	38.7	34.8	8.03	38.5	38.6	−0.24
Ongoing chest pain, %						
Yes	94.7	93.8	3.85	94.8	94.5	1.40
No†	4.1	4.2	−0.66	4.1	4.2	−0.21
Missing†	1.2	2.0	−6.11	1.1	1.4	−2.47
Killip class 1, %	89.0	87.0	6.27	89.0	89.1	−0.20
Killip class 2 or 3, %†	7.7	11.7	−13.4	8.2	8.0	0.96
Killip class 4, %†	3.2	1.3	12.93	2.8	3.0	−1.20
On-hours arrival time, %†	34.8	27.5	15.86	33.3	34.1	−1.54
Teaching hospital, %†	23.2	11.2	31.98	18.2	17.5	1.84
Urban hospital, %†	95.7	89.0	25.56	95.5	96.2	−3.70
Public hospital, %	6.1	12.8	−23.2	6.6	6.2	1.72
Not-for-profit hospital, %†	89.7	81.1	24.67	89.0	89.8	−2.63
For-profit, %†	4.2	6.1	−8.64	4.5	4.1	1.93
Insurance, %						
Occupational health and safety†	98.1	60.6	104.5	97.9	97.6	1.56
Commercial/PPO/HMO only†	40.7	39.9	1.66	41.0	39.7	2.53
Medicare only	25.4	30.5	−11.30	25.9	23.6	5.14
Medicare and other	12.3	8.6	12.00	12.0	13.0	−2.89
Medicaid or self	12.8	11.7	3.32	12.0	13.5	−4.32
Other/unknown	8.8	9.3	−1.71	9.1	10.1	−3.61

X-PCI indicates primary percutaneous coronary intervention; O-FT, onsite fibrinolytic therapy; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft surgery; LBBB, left bundle-branch block; HR, heart rate; and SBP, systolic blood pressure. *P* values are for trend. A positive standardized difference reflects a higher value for X-PCI patients; a negative standardized difference indicates a higher value for O-FT patients.

*Standardized difference (d) in general, an absolute value of standardized difference >10%, represents meaningful imbalance between comparison groups.

†Covariates used in propensity score model.

‡Exact match enforced in sex and discharge year (for main study, numbered 1–13 for years 1994–2006) and sex and registry (for matching 127 sensitivity patients).

Table 2. Time Intervals

	PCI-Related Delay <60 min			PCI-Related Delay 60–90 min		
Interval	X-PCI (n=1478)	O-FT (n=1478)	Total (n=2956)	X-PCI (n=1604)	O-FT (n=1604)	Total (n=3208)
Symptom onset to door, h						
Mean±SD	2.1±2.1	2.5±2.5	2.3±2.3	2.1±2.2	2.4±2.3	2.2±2.3
Median (IQR)	1.3 (0.8–2.5)	1.5 (1.0–3.0)	1.4 (0.9–2.8)	1.3 (0.8–2.4)	1.5 (0.9–2.8)	1.5 (0.8–2.6)
Door to door, min						
Mean±SD	148.0±388.3	554.9±769.0	262.7±555.3	124.2±299.8	496.1±793.3	229.0±519.3
Median (IQR)	73.0 (56.0–100.0)			79.0 (64.0–97.5)		
Door to needle, min						
Mean±SD		86.0±58.6			43.8±27.4	
Median (IQR)	NA	70.0 (45.0–110.0)	NA	NA	38.0 (25.0–54.5)	NA
Door to balloon, min						
Mean±SD	107.8±38.0			120.2±27.8		
Median (IQR)	100.0 (84.0–124.0)	NA	NA	115.0 (102.0–131.0)	NA	NA
PCI-related delay (XDB-DN), min						
Mean±SD	21.8±42.8			76.4±8.4		
Median (IQR)	35.0 (10.0–50.0)			77.0 (69.5–84.0)		

PCI indicates percutaneous coronary intervention; X-PCI, transfer primary PCI; O-FT, onsite fibrinolytic therapy; IQR, interquartile range; XDB, door-to-balloon time in transfer; and DN, door-to-needle time.

(Figure 1). Patients who had missing time interval data were excluded. Patients transferred to an NRMI hospital for X-PCI were included, but because mortality data were not available for these patients, patients transferred out from a NRMI hospital were excluded. Because this analysis focused on patients at hospitals where PPCI was not used, O-FT patients were included only from hospitals treating <1% of their STEMI patients with PPCI. DB and DN times >6 hours were excluded because they were not deemed to be for patients receiving primary reperfusion therapy. Selection criteria yielded a total of 107 028 patients eligible for analysis (11 662 X-PCI patients at 595 hospitals and 95 366 O-FT patients from 1803 hospitals, a collective total of 1872 hospitals; Figure 1).

For X-PCI patients, the points of reference to calculate XDB times were the first hospital arrival date/time and the balloon time at the recipient PCI hospital. Subtraction of the hospital arrival time from the FT initiation time produced the DN time. The PCI-related delay for a matched pair, ie, the time delay in performing X-PCI over administering O-FT, was calculated by subtracting the DN from the XDB.

To account for differences in baseline characteristics and risk between O-FT and X-PCI patients, propensity score matching was performed. The propensity score was defined as the conditional probability of being an X-PCI patient given the covariates used in a nonparsimonious, noninteractive, multivariable logistic regression model. Using the logit of the propensity score and a caliper width of 0.03, we matched study patients undergoing X-PCI with replacement 1:1 with O-FT patients. X-PCI patients who could not be matched to O-FT patients and any nonmatched O-FT patients were excluded from the eligible population. The matched study population comprised 9506 X-PCI and 9506 FT patients from 580 and 733 hospitals, respectively (Figure 1).

The PCI-related advantage (difference in outcome for patients treated with X-PCI versus O-FT) was assessed. Given the paired nature of the data, conditional logistic regression modeled the effects of reperfusion method and delay on outcomes. Thus, an equation describing the clinical outcome for X-PCI patients and another for O-FT patients were created, allowing adjustment for patient- and hospital-level characteristics and treatment time (XDB or DN in minutes) and a variable for treatment assignment (O-FT). To determine the XDB-DN time that canceled out the advantage of X-PCI, the difference between the 2 equations for X-PCI and O-FT patients was set to 0 and solved for the XDB-DN (equipoise) time. The same factors used in the propensity model were used to construct adjusted versions of these models. To account for curvilinearity in the relationship of XDB-DN and outcome, the quadratic term of XDB-DN was added to the models.

Sensitivity analysis was performed to account for death occurring before PPCI could be performed. Reanalysis was performed including STEMI patients transferred to an NRMI hospital receiving no reperfusion and dying <3 hours after arriving from the referral hospital. These patients were matched to O-FT patients. Using an imputed XDB, the hospital's median XDB, we assigned an XDB-DN. A total of 120 patients assumed to have died before X-PCI were matched to 120 O-FT patients, and the resulting data set was appended to the original propensity-matched study population for sensitivity analyses. Sensitivity analyses were repeated with total ischemic times by including prehospital delay in the total time to reperfusion. Attempts to address the possibility of confounding were made with the unadjusted and adjusted analyses in the matched and unmatched cohorts, as well as an inverse-probability weighted cohort.

All statistical analyses were performed with SAS 9.1.3 Service Pack 4, (SAS Institute, Cary, NC). Continuous variables are reported as mean±SD or median and interquartile range (IQR). The standardized group mean difference (d), the Cohen d, was used to compare continuous and dichotomous variables in matched and unmatched data. The d is the difference between group means divided by the pooled SD and is expressed as a percent.[14] A positive d reflects a higher value for X-PCI patients; a negative d indicates a higher value for O-FT patients. An absolute value of d>10% is considered a meaningful imbalance between groups. PROC PHREG was used for conditional logistic regression.

The statisticians had full access to the data, and the authors take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Matching Procedure

In the unmatched X-PCI and O-FT comparison groups, the standardized mean difference of the propensity scores was 145%, and the c statistic for the propensity model was 0.87, indicating fair discriminatory ability in predicting X-PCI. For the propensity-matched comparison groups, the standardized difference was −0.0008%. Baseline characteristics for the matched and unmatched populations are reported in Table 1.

Table 2. Continued

PCI-Related Delay >90 min			All Matched			Unmatched		
X-PCI (n=6424)	O-FT (n=6424)	Total (n=12 848)	X-PCI (n=9506)	O-FT (n=9506)	Total (n=19 012)	X-PCI (n=11 662)	O-FT (n=95 366)	Total
2.4±2.5 1.5 (0.8–3.0)	2.3±2.3 1.5 (0.9–2.8)	2.4±2.4 1.5 (0.8–2.9)	2.3±2.4 1.4 (0.8–2.8)	2.3±2.3 1.5 (0.9–2.8)	2.3±2.3 1.5 (0.8–2.8)	2.3±2.4 1.4 (0.8–2.9)	2.2±2.1 1.5 (0.9–2.8)	2.2±2.1 1.5 (0.9–2.8)
154.0±185.9 132.0 (100.0–175.0)	586.3±891.4	268.5±521.7	148.1±248.5 112.0 (80.0–160.0)	565.1±856.2	260.8±526.8	144.6±238.4 110.0 (80.0–157.0)	847.9±1084.5	556.8±912.6
NA	36.8±23.6 31.0 (21.5–45.0)	NA	NA	45.6±36.7 35.0 (24.0–55.0)	NA	NA	48.2±38.6 38.0 (25.0–58.0)	NA
204.5±62.2 192.0 (153.0–247.0)	NA	NA	175.2±69.1 161.0 (122.0–220.0)	NA	NA	173.2±68.2 158.0 (121.0–216.0)	NA	158.0 (121.0–216.0)
167.7±59.8 154.0 (118.0–206.0)		154.0 (118.0–206.0)	129.6±77.3	119.0 (78.0–178.0)		129.6±77.3 119.0 (78.0–178.0)		

The absolute standardized differences between the matched groups were ≤5% for all covariates.

Time parameters for the matched and unmatched patients are reported in Table 2. Clinical outcomes for patients before matching are given in Table 3. Compared with O-FT, X-PCI was associated with fewer in-hospital ischemic complications and shorter length of stay. Length of stay >5 days was more frequent with O-FT (28.5% versus 57.5%; −61.22).

Procedural Characteristics and Clinical Outcomes in Matched Population

Among matched patients, the median prehospital delay was similar to that of the overall population (1.5 hours; IQR, 0.8–2.8 hours). Median DN time was 35 minutes (IQR, 24–55 minutes). Median XDB time was 161 minutes (IQR, 122–220 minutes; Table 2). Subsequently, 81.9% of O-FT patients underwent coronary angiography, 14% had coronary artery bypass graft surgery, and 55% had PCI (36% electively and 20% for rescue PCI). Coronary artery bypass graft surgery occurred in 5.0% of X-PCI patients. The timing of subsequent PCI after FT administration was not available.

Among matched patients, survival was similar with X-PCI and O-FT (4.8% versus 6.2%; d=−5.94%; Table 3). Rates of death/MI and death/MI/stroke were lower with X-PCI (Figure 2). Length of stay >5 days was less frequent among X-PCI patients (29.6% versus 45.9%; d=−34.02%). Stratifying by

Table 3. Unadjusted In-Hospital Outcomes Stratified By Transfer Delay

			In-Hospital Death			In-Hospital Death or Recurrent MI			In-Hospital Stroke			In-Hospital Death or Recurrent MI or Stroke		
Label	n	XDB-DN Median (IQR)	X-PCI, %	O-FT, %	d*	X-PCI, %	O-FT, %	d*	X-PCI, %	O-FT, %	d*	X-PCI, %	O-FT, %	d*
Unmatched	10 7028		4.9	8.1	−13.25	5.9	10.0	−15.39	0.6	2.2	−13.22	6.3	11.0	−16.89
Matched	19 012	119 (78–178)	4.8	6.2	−5.94	5.9	8.5	−10.12	0.7	1.9	−10.97	6.3	9.3	−11.43
XDB-DN <60 min	2956	35 (10–50)	2.7	7.4	−21.46	3.9	9.3	−21.99	0.6	2.7	−16.35	4.3	10.6	−24.10
XDB-DN 61–90 min	3208	77 (70–84)	3.6	5.5	−9.25	4.6	7.5	−12.05	0.6	1.5	−8.57	5.0	8.4	−13.75
XDB-DN >90 min	12 848	154 (118–206)	5.7	6.1	−1.92	6.7	8.6	−7.17	0.7	1.8	−10.2	7.1	9.3	−8.14
XDB-DN tertile 1	6288	63 (37–78)	3.1	6.4	−15.40	4.2	8.3	−17.20	0.6	2.0	−12.5	4.6	9.4	−19.03
XDB-DN tertile 2	6412	119 (105–136)	4.8	6.3	−6.52	5.6	8.6	−11.64	0.6	1.7	−10.01	6.0	9.4	−12.68
XDB-DN tertile 3	6312	208 (179–250)	6.6	5.9	2.88	7.8	8.5	−2.54	0.7	1.9	−10.4	8.3	9.3	−3.47

XDB indicates door-to-balloon time in transfer; DN, door-to-needle time; IQR, interquartile range; X-PCI, transfer primary percutaneous coronary intervention; O-FT, onsite fibrinolytic therapy; and MI, myocardial infarction.

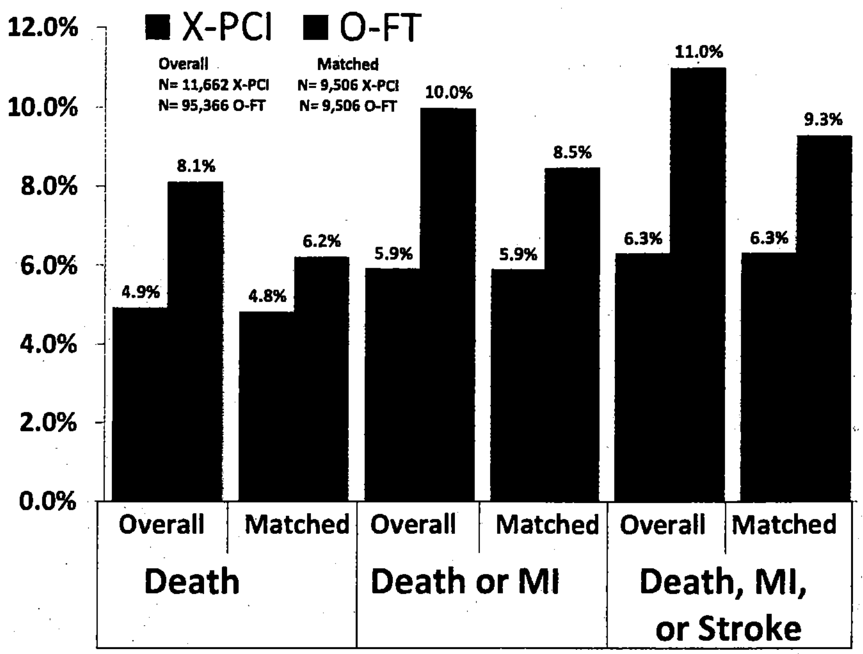

Figure 2. Clinical outcomes in all patients and matched patients. Standardized differences were >10% for all comparisons except death for matched patients (d=−5.94). X-PCI indicates transfer for percutaneous coronary intervention; O-FT, onsite fibrinolytic therapy; and MI, myocardial infarction.

PCI-related delay showed that the PCI-related benefit was time dependent (Figure 3). The mortality rate was lower with X-PCI with PCI-related delay of 0 to 60 minutes, diminished for those with PCI-related delays of 60 to 90 minutes, and absent with PCI-related delays >90 minutes (Figure 3). With PCI-related delays of <60 or 60 to 90 minutes, X-PCI was associated with lower rates of the combined end points of death/MI and death/MI/stroke compared with O-FT (Table 3).

For 68% of patients (n=12 848) with PCI-related delay >90 minutes (median, 154 minutes; IQR, 118–206 minutes), there was no meaningful imbalance in mortality (5.7% versus 6.1%; d=−1.92%), death/MI, and death/MI/stroke (Figure 3), but the rate of in-hospital stroke was lower with X-PCI (0.7% versus 1.8%; d=−10.2) versus O-FT. Across tertiles of PCI-related delay, X-PCI was associated with an advantage for all measured clinical end points among patients in the lowest tertile (median, 63 minutes; IQR, 37–78 minutes). Although no mortality benefit was found among the second tertile of delay (median, 119 minutes; IQR, 105–1360 minutes), an advantage for X-PCI was identified with respect to death/MI and death/MI/stroke. For the tertile with the longest delay (median, 208 minutes; IQR, 179–250 minutes), only a benefit for stroke was noted with X-PCI (Table 3).

Stratified Analyses in Matched Population

Clinical outcomes stratifying matched patients based on various factors are reported in Table 4. The magnitude of benefit was greater with X-PCI compared with O-FT for

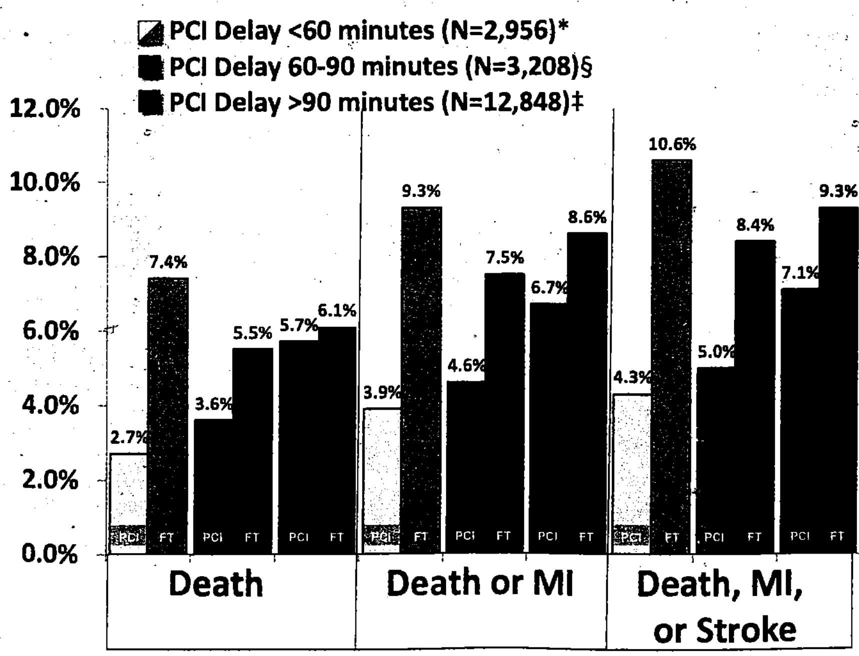

Figure 3. Clinical outcomes among matched patients stratified by percutaneous coronary intervention (PCI)–related delay. FT indicates fibrinolytic therapy; MI, myocardial infarction. *Standardized difference >10% for all outcomes. §Standardized difference >10% for only death or myocardial infarction and for death, MI, or stroke. ‡Standardized difference <10% for all outcomes.

Table 4. Unadjusted Stratified Analyses

			In-Hospital Death			Recurrent MI			In-Hospital Death or Recurrent MI			Stroke			In-Hospital Death or Recurrent MI or Stroke		
Label	n	XDB-DN Median (IQR)	X-PCI, %	O-FT, %	d*	X-PCI, %	O-FT, %	d*	X-PCI, %	O-FT, %	d*	X-PCI, %	O-FT, %	d*	X-PCI, %	O-FT, %	d*
Age <65 y	11 422	117 (79–177)	2.5	2.5	0.40	1.1	2.4	−9.73	3.5	4.7	−6.10	0.4	1.1	−7.82	3.8	5.1	−6.33
Age ≥65 y	7590	122 (78–179)	8.4	11.7	−10.98	1.8	3.4	−10.19	9.6	14.1	−14.03	1.0	3.0	−14.39	10.1	15.6	−16.46
Anterior MI	7325	120 (80–181)	6.9	8.0	−4.29	1.7	3.3	−10.2	8.0	10.5	−8.48	0.7	2.5	−14.7	8.3	11.8	−11.45
Nonanterior MI	11 687	118 (78–177)	3.6	5.1	−7.35	1.2	2.5	−9.78	4.5	7.2	−11.50	0.7	1.5	−8.24	5.0	7.8	−11.53
Delay <2 h	12 340	117 (78–174)	4.9	5.5	−2.7	1.4	2.7	−8.93	5.9	7.9	−7.60	0.7	1.9	−10.49	6.4	8.6	−8.43
Delay 2–6 h	4894	120 (79–182)	4.1	7.6	−14.8	1.3	2.1	−6.70	5.2	9.2	−15.52	0.5	1.8	−11.98	5.4	10.2	−17.72
Delay >6 h	1778	131 (81–192)	6.6	7.3	−2.94	1.5	5.5	−21.78	7.5	11.0	−11.90	0.6	1.9	−11.82	8.0	12.2	−13.93
TRS 0–2	10 451	114 (77–170)	1.4	2.1	−4.83	0.9	2.5	−12.05	2.3	4.4	−11.72	0.3	0.9	−7.49	2.5	4.6	−11.33
TRS 3–4	5513	121 (79–183)	5.3	6.4	−4.33	1.6	2.6	−6.65	6.4	8.5	−7.70	0.9	2.9	−15.32	7.0	10.1	−11.28
TRS ≥5	3048	135 (83–197)	15.0	21.1	−15.8	2.5	4.4	−10.90	16.5	23.6	−17.75	1.4	3.5	−13.80	17.3	25.3	−19.71
Urban	18 224	118 (78–177)	4.8	6.1	−5.87	1.4	2.8	−9.6	5.8	8.4	−9.89	0.6	1.9	−11.50	6.2	9.2	−11.40
Rural	788	136 (90–193)	6.5	8.9	−8.95	0.5	2.8	−18.4	7.0	11.7	−16.2	1.7	2.0	−2.42	8.2	12.3	−13.57
Killip class I	16 928	118 (78–177)	3.2	4.4	−6.11	1.2	2.6	−10.28	4.2	6.6	−10.79	0.5	1.7	−11.00	4.5	7.3	−11.87
Killip class II–IV	2084	132 (85–187)	18.1	21.1	−7.54	2.8	4.3	−8.41	19.8	24.0	−10.07	1.5	3.3	−11.65	20.6	25.9	−12.61

XDB indicates door-to-balloon time in transfer; DN, door-to-needle time; IQR, interquartile range; X-PCI, transfer primary percutaneous coronary intervention; O-FT, onsite fibrinolytic therapy; MI, myocardial infarction; and TRS, Thrombolysis In Myocardial Infarction risk score.

patients ≥65 years of age, those with longer symptom-onset-to-door time, and patients at higher risk for STEMI defined by the Thrombolysis in Myocardial Infarction risk score. X-PCI was not associated with worse outcomes compared with O-FT in any of the subgroups evaluated.

Regression Analyses

Conditional logistic regression demonstrated no mortality benefit of X-PCI over O-FT with XDB-DN times exceeding 121 minutes (Figure 4). This XDB-DN time was exceeded in 48% of patients. For the end point of death/MI/stroke, equipoise occurred at ≈158 minutes. When the subgroup of patients presenting with <2 hours of symptoms were evaluated, the equipoise for mortality was ≈132 minutes. Models with additional presentation and hospital factors led to overcorrection and unreliable estimates.

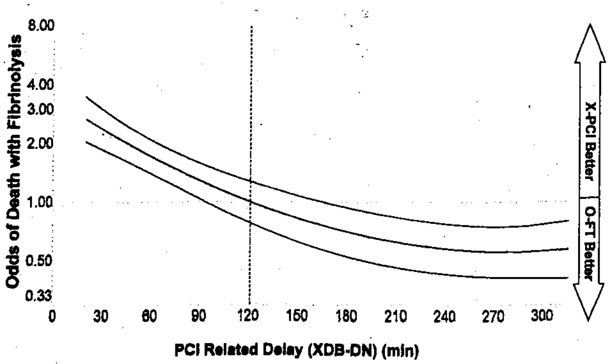

Figure 4. Relationship between percutaneous coronary intervention (PCI)–related delay (minutes) and in-hospital mortality. Dotted lines represent 95% confidence intervals. XDB-DN indicates transfer delay (transfer door-to-balloon–door-to-needle time).

Sensitivity Analyses

Sensitivity analysis including patients who may have died before X-PCI (Table 5) demonstrated a reduction in the magnitude of benefit associated with X-PCI. Results using total ischemic times were similar to the primary analysis. The analyses of adjusted and unadjusted models in unmatched, matched, and inverse-probability weighted cohorts supported the findings of the primary analysis. The odds ratios from the matched analysis (with or without adjustment) were similar to the adjusted odds ratios from the unmatched and inverse-probability weighted analyses. In addition, differences in the odds ratios between the unadjusted and adjusted analyses for the unweighted and unmatched data support the smaller differences in event rates that are detailed in this article.

Discussion

This analysis represents the largest observational comparison of O-FT and X-PCI. This study expands on randomized data and meta-regression analyses and differs in several important respects. Drawing from a significantly larger, less highly selected, and more heterogeneous cohort of ≈19 000 propensity score–matched STEMI patients, it demonstrates delays to X-PCI in transfer patients. For example, patients in a pooled analysis of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trials had shorter median DB times (107 minutes [IQR, 79–146 minutes] versus 161 minutes [IQR, 122.0–220.0 minutes]).[15] The present analysis demonstrates that outcomes are related to these delays and confirms that X-PCI is superior to O-FT in rapidly treated patients. These data define and quantify the

Table 5. Unadjusted Sensitivity Analysis

			In-Hospital Death			In-Hospital Death or Recurrent MI			Stroke			In-Hospital Death or Recurrent MI or Stroke		
Label	n	XDB-DN, Median (IQR)	X-PCI, %	O-FT, %	d*	X-PCI, %	O-FT, %	d*	X-PCI, %	O-FT, %	d*	X-PCI, %	O-FT, %	d*
Unmatched	107 208		4.9	8.1	−13.25	5.9	10.0	−15.40	0.6	2.2%	−13.22	6.3	11.0	−16.89
Matched	19 252	119 (79–178)	6.0	6.5	−1.76	7.1	8.7	−6.21	0.7	1.9	−11.1	7.4	9.6	−7.67
XDB-DN <60 min	2978	35 (10–50)	3.4	7.6	−18.33	4.6	9.5	−19.28	0.6	2.7	−16.29	5.0	10.8	−21.50
XDB-DN 60–90 min	3240	77 (70–84)	4.6	5.7	−5.31	5.6	7.7	−8.46	0.6	1.5	−8.53	5.9	8.6	−10.25
XDB-DN >90 min	13 034	154 (118–206)	7.0	6.4	2.46	8.0	8.8	−2.99	0.7	1.8	−10.34	8.4	9.6	−4.14
XDB-DN tertile 1	6368	63 (37–78)	4.3	6.6	−9.96	5.4	8.5	−12.27	0.6	2.0	−12.41	5.8	9.6	−14.31
XDB-DN tertile 2	6492	119 (105–136)	6.0	6.5	−2.04	6.8	8.8	−7.47	0.7	1.7	−10.04	7.1	9.6	−8.70
XDB-DN tertile 3	6392	208 (179–249)	7.8	6.3	5.76	9.0	8.9	0.33	0.7	2.0	−10.77	9.4	9.6	−0.75

XDB indicates door-to-balloon time in transfer; DN, door-to-needle time; IQR, interquartile range; X-PCI, transfer primary percutaneous coronary intervention; O-FT, onsite fibrinolytic therapy; and MI, myocardial infarction.

time dependence of this benefit for the large group of STEMI patients in clinical practice. This analysis demonstrates that most STEMI patients undergoing X-PCI in the United States are not realizing a benefit over O-FT because of delays in implementation. Extensive delays reduce the mortality benefit of X-PCI (number needed to treat, 23 for PCI-related delay <60 minutes; number needed to treat, 44 for PCI-related delay 60–90 minutes; and number needed to treat, 250 for PCI-related delay >90 minutes). When delays related to implementation of X-PCI exceed ≈120 minutes, the mortality advantage of X-PCI over O-FT is likely negated. Such delays occur in 48% of patients.

Mortality increased as risk increased for both groups, and the benefit of X-PCI was greatest among those at highest risk (Thrombolysis in Myocardial Infarction risk score >5). Similarly, the absolute benefit of X-PCI over O-FT was greater among those presenting between 2 and 6 hours from symptom onset compared with ≤2 hours, suggesting an enhanced benefit X-PCI over O-FT with longer prehospital delay.

Previous analyses based on randomized data and short treatment times described the relationship of PCI-related delay and mortality as linear[7,16]; however, this analysis suggest a steeper relationship between mortality and delay with shorter PCI-related delays and a flatter relationship when PCI-related delays are longer. At no point was survival with X-PCI inferior to O-FT, but the comparative benefit of this strategy erodes rapidly with the rate of benefit for X-PCI flattening as delays become more extensive. Until the success achieved in randomized trials and selected centers can be achieved throughout the United States, the majority of transfer patients will still be subjected to extensive delays to reperfusion.

Substantial debate remains as to the appropriate role for FT added to PPCI and the appropriate timing of catheterization after FT. Specifically, increased mortality was seen with immediate PCI after FT[17] compared with PPCI alone, yet improved outcomes were seen in a strategy of routine transfer for PCI after FT[18] or half-dose FT.[19] This pharmacoinvasive strategy has improved outcomes for FT, most recently in the Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER)-AMI and Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI) trials.[18,20] Regionalized transfer protocols after pharmacotherapy have reduced reperfusion times for patients transferred for PCI.[21]

Nevertheless, pharmacoinvasive strategies are practiced infrequently in the United States. Because the purpose of this analysis was not to address whether a pharmacoinvasive strategy is superior to either O-FT alone or PPCI, a pharmacoinvasive strategy was excluded so that a specific comparison of O-FT and X-PCI could be studied. Nevertheless, these data suggest that because recurrent MI was a major limitation of O-FT, a pharmacoinvasive strategy may reduce complications, improving outcomes compared with X-PCI.

Recipient hospital volume indicators extended the equipoise between the X-PCI and O-FT strategies to a similar extent, suggesting that patient and hospital factors modify the time-dependent benefit of X-PCI over O-FT. Transferring hospitals should consider that the performance of higher-volume hospitals extended the time to implement X-PCI. This finding suggests that more investigation is necessary to evaluate the influence of hospital characteristics and performance among STEMI patients treated in transfer.

There remains a tremendous desire to identify a single protocol for patients with STEMI, 1 optimal XDB-DN time, and a universal reperfusion strategy for all STEMI patients at hospitals without PPCI; however, the significant variability in comparative outcomes with O-FT and X-PCI based on delay, patient, and hospital characteristics raises questions about the prudence of such a rigid approach. The ACC/AHA STEMI guidelines recommend that selection of the optimal reperfusion strategy should be based not only on the anticipated XDB-DN time but also on patient characteristics and systemic issues such as transport times and local hospital expertise. These data support each of those recommendations.[8,22] Because PPCI is not inferior at long treatment times, patients who are deemed to be at higher-than-average risk for stroke (elderly, congestive heart failure, low body mass index) may be better selected for X-PCI without O-FT even if a delay will ensue, whereas others may not receive the benefit of X-PCI if delays to treatment are extensive.[8,22] When a delay is anticipated, eg, related to transport or to exclude competing illness (stroke, pulmonary embolism, aortic dissection, etc), some patients may be best served with a strategy of FT followed by routine transfer.[18]

Limitations

Almost half of the O-FT patients were excluded because mortality data were not available; however, those who were included were quite representative of a general population of STEMI patients. Nevertheless, exclusion of these patients, patients unsuitable for PCI after angiography or too sick for transport, and those who died before transport limits the ability to generalize these findings beyond the population evaluated in this analysis.

This analysis is a nonrandomized analysis from registry data. Despite propensity score matching and other methods to correct for bias in the selection of patients for O-FT versus X-PCI, it is possible that both measured and unmeasured confounding may have influenced the decision to transfer for PCI and outcomes after reperfusion.

Various factors such as PPCI volume, age, duration of symptoms, and infarct location significantly modulate the magnitude of the comparative advantage of PPCI. Unfortunately, despite the large size of this data set, identification of the time of equipoise in X-PCI and O-FT in subgroups such as high-risk patients presenting late was limited by small numbers of patients in these groups after propensity matching. Certainly, there is complex interplay between the risks and benefits of the 2 reperfusion strategies that likely accounts for the variability in comparative efficacy with X-PCI and O-FT.

Conclusions

As XDB-DN times increase, the advantage of X-PCI over O-FT declines. The relationship is curvilinear. The optimum benefit of X-PCI over O-FT can be achieved if PCI-related delays (XDB-DN) are <120 minutes for mortality and <160 minutes for death/MI/stroke. As indicated in the ACC/AHA guidelines, the clinician should consider the anticipated PCI-related delay (XDB-DN time) and patient and hospital-based characteristics when selecting a reperfusion strategy. Systems of care must identify and implement ways to reduce transport times and overall ischemic times using environmental, operational, and cultural modifications.[23] The local environment, economic, and clinical realities must be considered when solutions such as creation of community PCI programs and adoption of pharmacoinvasive strategies are considered.

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CLINICAL PERSPECTIVE

The 2 major reperfusion strategies for ST-segment–elevation myocardial infarction are primary percutaneous coronary intervention (PCI) and fibrinolytic therapy (FT). Because not all hospitals perform primary on a full-time basis, patients with ST-segment–elevation myocardial infarction presenting to hospitals without primary PCI capability are often transferred for primary PCI (X-PCI) and do not receive onsite fibrinolytic therapy (O-FT). Although randomized trials support X-PCI over O-FT, these trials inform the clinician only about the comparative efficacy of the 2 strategies for the small group of ST-segment–elevation myocardial infarction patients who can be transferred rapidly with short treatment times. In the United States, the majority of patients who are transferred for PCI do not receive it in a timely fashion. This analysis evaluates the time-dependent loss of X-PCI benefit compared with O-FT and finds that the survival benefit of X-PCI over O-FT is lost after ≈120 minutes of PCI-related delay. Almost half of the patients transferred for PCI exceeded this threshold. The clinician should consider a patient's risk for ischemic complications, bleeding, and stroke and PCI-related delay when selecting X-PCI or O-FT for patients with ST-segment–elevation myocardial infarction presenting to hospitals without primary PCI capability.