Pre-hospital Transport Times and Outcomes After Different Reperfusion Strategies for ST-Elevation Myocardial Infarction

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This study evaluated prehospital transport times and clinical outcomes after different reperfusion strategies for ST-elevation myocardial infarction in a real-world setting. We consecutively enrolled 27,205 patients who underwent percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction in Michigan from 2010 to 2016. Primary PCI was performed in 25,927 patients (95%), whereas 1,278 (5%) were treated with a pharmacoinvasive strategy. The overall use of a pharmacoinvasive strategy decreased during the study period ($p < 0.001$). Prehospital transport times were estimated by using the Google Maps API from the centroid of each home zip code tabulation area to the zip code tabulation area for the nearest hospital with PCI capability. The estimated prehospital transport time predicted the choice of reperfusion strategy ($p < 0.001$). Primary PCI was used in 97% of the patients living within 1 hour from a hospital with PCI capability compared with 48% with estimated transport times >1 hour. Bleeding and mortality rates were similar for patients treated with primary PCI or a pharmacoinvasive strategy (odds ratio 0.832, 95% confidence interval 0.649 to 1.067, $p = 0.147$). In conclusion, almost all patients in Michigan had timely access to a hospital with PCI capability and received treatment with primary PCI. The authors declare no conflicts of interests. **(Am J Cardiol 2019;123:375−381)**

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for patients with ST-elevation myocardial infarction (STEMI) when first-medical-contact-to-balloon time is within 90 minutes for direct admit patients and 2 hours for transfer patients.[1−7] When primary PCI cannot routinely be achieved within the recommended times, the most recent guidelines support a pharmacoinvasive strategy with fibrinolysis followed by either rescue PCI or routine early PCI.[1−3] Recent randomized trials and observational studies have shown comparable outcomes for primary PCI and a pharmacoinvasive strategy.[8−13] Although a pharmacoinvasive strategy can be initiated in any prehospital system, primary PCI can only be delivered at PCI-capable hospitals. Geographic factors might therefore impact the choice of reperfusion strategy for STEMI, although this has not been studied in detail. The aim of this study was to evaluate prehospital transport times and clinical outcomes in patients treated with different reperfusion strategies for STEMI in a real-world setting.

Methods

Patients who underwent PCI at all 47 nonfederal hospitals in Michigan participate in the Blue Cross Blue Shield of Michigan Cardiovascular Consortium. The details of the Blue Cross Blue Shield of Michigan Cardiovascular Consortium registry and its data collection and auditing process have been described previously.[14,15] Data include clinical, demographic, procedural, and angiographic characteristics, medications (before, during, and after PCI), and in-hospital outcomes. All data elements have been prospectively defined. In addition to a random audit of 2% of all cases, medical records are reviewed for all patients who underwent multiple procedures or coronary artery bypass graft surgery, and for patients who died in the hospital to ensure data accuracy.

The study population included all patients presenting with STEMI and treated with either primary PCI, rescue PCI, or routine early PCI in Michigan between January 2010 and December 2016. STEMI was diagnosed according to current guidelines.[1,2] Primary PCI was defined as PCI within 12 hours from symptom onset without previous fibrinolytic therapy. A pharmacoinvasive strategy was defined as initial fibrinolysis followed by either rescue PCI or routine early PCI, where rescue PCI was defined as PCI after unsuccessful fibrinolysis (continued chest pain and electrocardiogram

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ST-segment resolution < 50% within 60 to 90 minutes after initiating fibrinolytic therapy) and routine early PCI as PCI 3 to 24 hours after successful fibrinolysis.

Prehospital transport times were estimated using the Google Maps API from the centroid of each home zip code tabulation area to the zip code tabulation area for the nearest hospital with PCI capability and reflects weather and traffic conditions on the afternoon of Thursday October 8, 2015. To achieve a first-medical-contact-to-balloon time < 2 hours for transfer patients as recommended in the guidelines, we estimated that a prehospital transport time of < 1 hour was necessary to meet door-to-balloon criteria. Only patients with a valid, mappable Michigan zip code were included.

Fisher's exact and Pearson's chi-square tests were used with categorical variables, whereas Student's *t* tests were used to compare continuous variables in univariate comparisons of demographic, clinical, procedural, and outcome measures between PCI indications.

Preprocedural bleeding risk for each case was estimated using a validated risk tool that utilizes patient-level covariates including age, gender, estimated glomerular filtration ratio (Modification of Diet in Renal Disease estimate), coronary artery disease presentation (STEMI, non-STEMI, and other), cardiogenic shock, heart failure status, and New York Heart Association class if applicable, previous PCI, and previous peripheral artery disease.[16]

Estimated prehospital transport times were compared by Wilcoxon's test. Trends in choice of reperfusion strategy over time were evaluated by the Cochran-Armitage test of trend. Association between prehospital transport time and choice of reperfusion strategy (primary PCI vs a

Table 1
Baseline characteristics

Variable	Primary percutaneous coronary intervention (n = 25,927)	Pharmaco-invasive strategy (n = 1,278)	p-value	Rescue percutaneous coronary intervention (n = 758)	Routine early percutaneous coronary intervention (n = 520)	p-value
Age (years ± standard deviation)	61.66 ± 12.91	59.88 ± 11.52	< 0.001	59.67 ± 11.74	60.20 ± 11.18	0.417
Men	18,009 (69.5%)	954 (74.6%)	< 0.001	558 (73.6%)	396 (76.2%)	0.305
White	22,465 (86.6%)	1,205 (94.3%)	< 0.001	716 (94.5%)	489 (94.0%)	0.750
Black or African American	2,887 (11.1%)	13 (1.0%)	< 0.001	10 (1.3%)	3 (0.6%)	0.194
Asian	304 (1.2%)	3 (0.2%)	0.002	0 (0.0%)	3 (0.6%)	0.036
Other ethnicity	90 (0.4%)	9 (0.7%)	0.039	5 (0.7%)	4 (0.8%)	0.818
Current/recent smoker (w/in 1 year)	11,661 (45.0%)	633 (49.6%)	0.001	373 (49.3%)	260 (50.0%)	0.799
Uninsured	2,461 (9.5%)	186 (14.6%)	< 0.001	373 (49.3%)	260 (50.0%)	0.799
Body mass index (mean ± standard deviation, kg/m^2)	29.67 ± 7.06	30.68 ± 8.54	< 0.001	30.95 ± 9.85	30.28 ± 6.10	0.139
Hypertension	17,993 (69.4%)	838 (65.6%)	0.004	510 (67.3%)	328 (63.1%)	0.120
Dyslipidemia	15,892 (61.3%)	773 (60.5%)	0.541	470 (62.0%)	303 (58.3%)	0.180
Family history of premature coronary artery disease	4,361 (16.8%)	202 (15.8%)	0.341	124 (16.4%)	78 (15.0%)	0.513
Diabetes mellitus	6,743 (26.0%)	285 (22.3%)	0.003	169 (22.3%)	116 (22.3%)	0.996
Prior myocardial infarction	5,766 (22.2%)	252 (19.7%)	0.034	147 (19.4%)	105 (20.2%)	0.724
Prior heart failure	1,712 (6.6%)	38 (3.0%)	< 0.001	24 (3.2%)	14 (2.7%)	0.628
Prior valve surgery/procedure	187 (0.7%)	3 (0.2%)	0.041	3 (0.4%)	0 (0.0%)	0.151
Prior primary coronary intervention	6,060 (23.4%)	249 (19.5%)	0.001	149 (19.7%)	100 (19.2%)	0.850
Prior coronary artery bypass grafting	1,524 (5.9%)	71 (5.6%)	0.634	43 (5.7%)	28 (5.4%)	0.821
Comorbidities	6,357 (24.5%)	258 (20.2%)	< 0.001	154 (20.3%)	104 (20.0%)	0.890
Estimated glomerular filtration rate (mean ± standard deviation, mL/min/1.73 m^2)	74.66 ± 23.71	82.30 ± 21.48	< 0.001	80.47 ± 21.90	84.89 ± 23.71	< 0.001
Cardiogenic shock prior to procedure	2,043 (7.9%)	73 (5.7%)	0.005	67 (8.8%)	6 (1.2%)	< 0.001
Cardiac arrest prior to procedure	2,435 (9.4%)	102 (8.0%)	0.090	82 (10.8%)	20 (3.8%)	< 0.001
Pre-procedural bleeding risk score (mean ± standard deviation)	3.79 ± 3.84	2.93 ± 2.77	< 0.001	3.19 ± 3.15	2.56 ± 2.05	< 0.001

Hypertension was defined by any one of the following: (1) history of hypertension diagnosed and treated with medication, diet and/or exercise; (2) previous documentation of blood pressure > 140 mm Hg systolic and/or 90 mm Hg diastolic for patients without diabetes or chronic kidney disease, or previous documentation of blood pressure > 130 mm Hg systolic and/or 80 mm Hg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease; or (3) currently on pharmacologic therapy for treatment of hypertension. Hyperlipidemia was defined by any one of the following: (1) total cholesterol > 200 mg/dl (5.18 mmol/L); (2) low-density lipoprotein ≥ 130 mg/dl (3.37 mmol/L); or (3) high-density lipoprotein < 40 mg/dl (1.04 mmol/L). For patients with known coronary artery disease, treatment is initiated if LDL is > 100 mg/dl (2.59 mmol/L), and this would qualify as hypercholesterolemia. Co-morbidities included cerebrovascular disease, peripheral arterial disease, chronic lung disease, and renal disease currently treated with dialysis. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula. The first p-value is comparing primary PCI and rescue PCI, whereas the second p-value is comparing rescue PCI and routine early PCI.

pharmacoinvasive strategy) was assessed by generalized linear mixed effects regression models including a random hospital intercept as well as logistic regression models with cubic spline transform of time. Generalized linear mixed effects regression models were also used to assess the independent effect of the different reperfusion strategies on bleeding and in-hospital mortality after adjusting for patient baseline clinical and demographic characteristics. For the mortality model, all variables included other than predicted bleeding risk were adjusted for in the regression, whereas the bleeding outcome regression model adjusted for estimated preprocedural bleeding risk and access site (radial vs femoral access). A p value < 0.05 was considered statistically significant. Data were analyzed using the statistical software R version 3.1.[17]

Results

We included 27,205 patients presenting with STEMI at the 47 nonfederal hospitals with PCI capability in the state of Michigan during the 7-year study period. Baseline characteristics for patients treated with primary PCI or a pharmacoinvasive strategy are presented in Table 1.

Primary PCI was performed in 95% of patients and 5% were treated with a pharmacoinvasive strategy. In the pharmacoinvasive cohort, 59% of patients received rescue PCI and 41% routine early PCI (Figure 1). The overall use of a pharmacoinvasive strategy decreased over the study period ($p < 0.001$; Figure 2).

Figure 3 shows the estimated prehospital transport time to the nearest primary PCI hospital in relation to population density and choice of reperfusion treatment. The majority of patients (96%) lived within 1 hour from a hospital with PCI capability. The estimated prehospital transport time predicted the choice of reperfusion strategy for STEMI ($p < 0.001$; Figure 4). Primary PCI was used in 97% of patients with an estimated prehospital transport time of < 1 hour. In comparison, primary PCI was only used in 48% of patients with longer prehospital transport times. The median estimated prehospital transport time was 12 minutes (interquartile range 8 to 22) in patients treated with primary PCI compared with 59 minutes (interquartile range 39 to 88) in patients treated with a pharmacoinvasive strategy ($p < 0.001$).

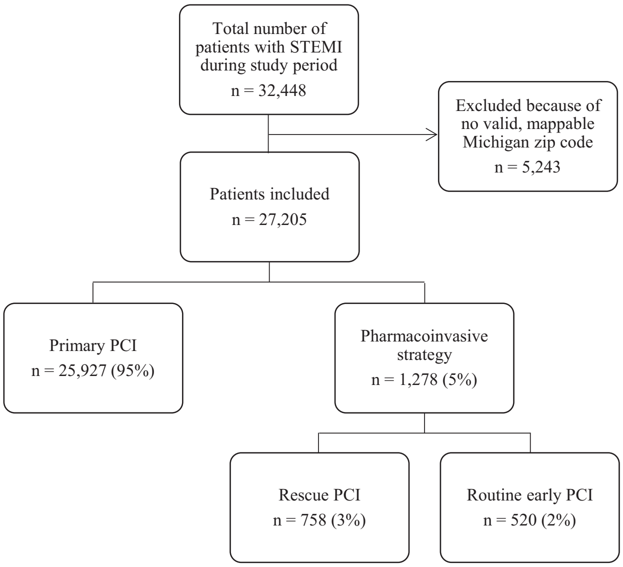

Figure 1. Flow chart showing inclusion of patients. PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

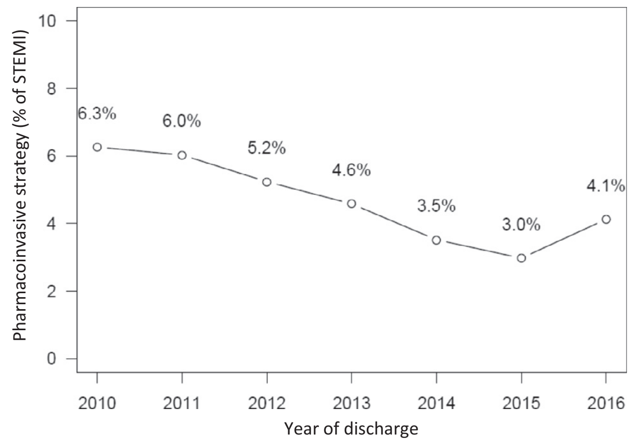

Figure 2. Proportion of STEMI cases treated with a pharmacoinvasive strategy. STEMI = ST-elevation myocardial infarction.

Time to treatment and PCI procedural data by reperfusion strategy for STEMI are presented in Table 2. Postprocedural bleeding and complication rates by reperfusion strategy for STEMI are presented in Table 3. Detailed bleeding complications by PCI access site are shown in Figure 5. In general, patients treated with primary PCI and rescue PCI had similar rates of postprocedural bleeding, other complications, and in-hospital mortality, whereas lower rates were seen in those treated with routine early PCI.

Radial compared with femoral artery access site was associated with a lower bleeding rate (odds ratio 0.723, 95% confidence interval 0.628 to 0.832, $p < 0.0001$). After adjusting for PCI access site and preprocedural bleeding risk, the overall postprocedural bleeding rate was comparable for those treated with primary PCI or a pharmacoinvasive strategy (odds ratio 0.832, 95% confidence interval 0.649 to 1.067, $p = 0.147$). The most common bleeding complication in both groups was access site bleeding. Intracerebral hemorrhage rates were low in both patients treated with primary PCI and a pharmacoinvasive strategy (Figure 5).

Discussion

Most patients in Michigan live within 1 hour of a PCI-capable hospital and were treated with primary PCI. As expected, the probability of receiving primary PCI decreased with longer estimated prehospital transport times to the nearest PCI-capable hospital. Although primary PCI was the treatment strategy of choice in almost all patients who lived within 1 hour from a PCI-capable hospital, primary PCI was only used in approximately half of the patients with longer prehospital transport times. In line with our findings, the proportion of patients receiving

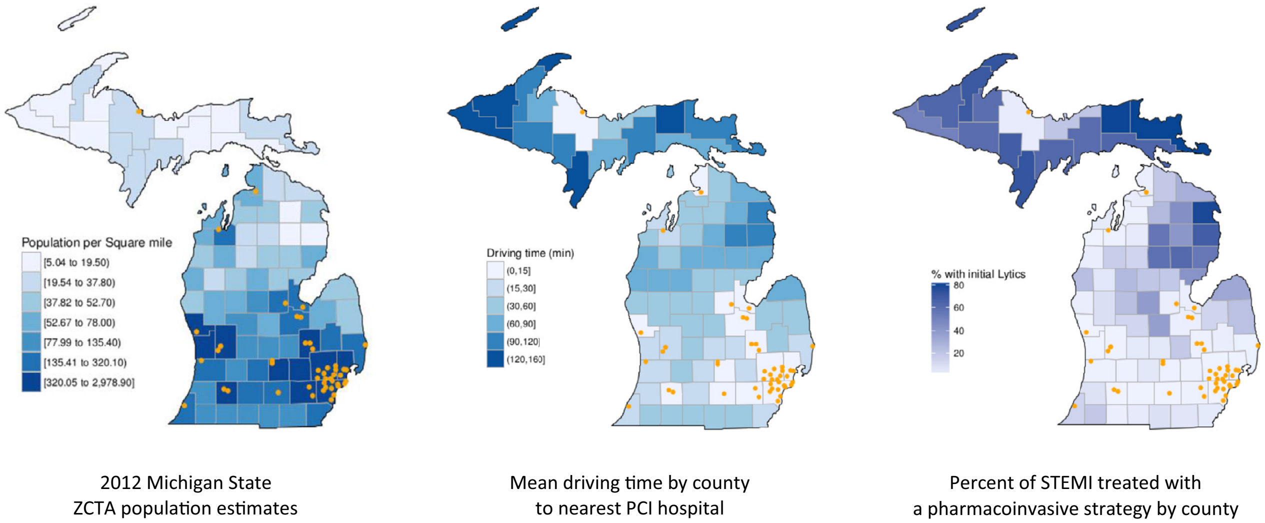

Figure 3. Estimated prehospital transport time to the nearest hospital with PCI capability in Michigan in relation to population density and choice of reperfusion treatment. *Yellow dots* represent hospitals with PCI capability. PCI = percutaneous coronary intervention. (Color version of figure is available online.)

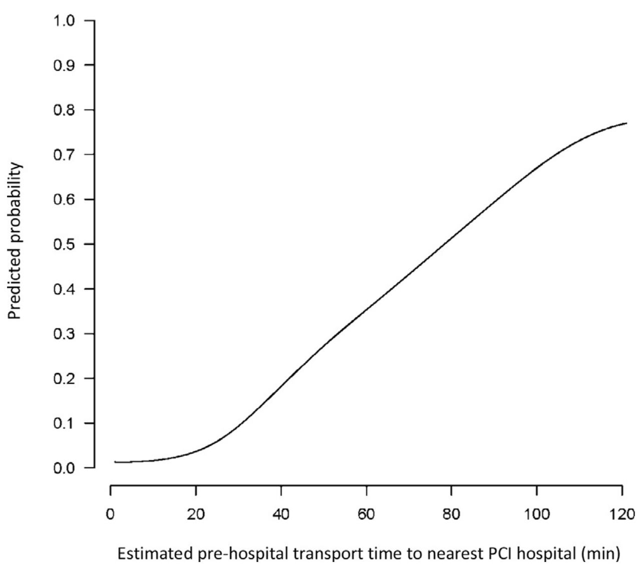

Figure 4. Predicted probability of treatment with a pharmacoinvasive strategy for STEMI by estimated prehospital transport time to the nearest primary hospital with PCI capability. PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

primary PCI has also been shown to decrease with longer estimated interhospital driving time.[18] For unknown reasons, the overall use of a pharmacoinvasive strategy decreased slightly over the study period.

The estimated prehospital transport time was based on driving times and did not take into account the actual mode of transport or any transport delays. Further, estimated prehospital transport times were calculated based on the patient home zip code and not the home address. For this reason, the estimated prehospital transport time does necessarily reflect the actual transport time for the individual patient. Several factors other than estimated transport time can influence the decision on reperfusion strategy for STEMI. For example, traffic delays and bad weather conditions can further prolong prehospital transport delays and favor the use of a pharmacoinvasive strategy. A pharmacoinvasive strategy is also more likely to be chosen in patients presenting to a hospital without PCI capability or outside of normal working hours at hospitals with limited PCI availability. Conversely, primary PCI is more likely to be chosen in patients with high bleeding risk, because fibrinolysis may be contraindicated. Unfortunately, we did not have detailed data on the specific reasons for choice of reperfusion treatment for the individual patient.

After adjusting for preprocedural bleeding risk and PCI access site, we found similar in-hospital bleeding, other complication, and mortality rates in patients treated with primary PCI or a pharmacoinvasive strategy. The rates of intracerebral hemorrhage were low in patients treated with either primary PCI or a pharmacoinvasive strategy. The lower rates of bleeding, other complications, and mortality found in patients who underwent routine early PCI are likely explained by a lower baseline risk in this patient group due to selection bias.

Our findings are consistent with the STREAM trial, which is the largest randomized controlled trial of primary PCI versus the pharmacoinvasive strategy in patients with STEMI.[10] The mortality and overall bleeding rates we found are also similar to those reported by 3 recent observational studies of the pharmacoinvasive strategy in a real-world setting.[11–13]

There are several limitations of this study. Most important, we did not have access to data on the total number of patients in Michigan triaged for STEMI who did not subsequently undergo PCI. Consequently, our findings might be prone to immortal time bias. One reason for not performing PCI could be patient death during transport. Another reason might be that coronary angiography did not show significant coronary artery stenosis. The first would underestimate, whereas the latter overestimate, the risks associated with a pharmacoinvasive strategy. Similarly, it is possible

Table 2
Key presentation and angiographic variables in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention compared with a pharmacoinvasive strategy

Variable	Primary PCI (n = 25,927)	Pharmacoinvasive strategy (n = 1,278)	p-value	Rescue PCI (n = 758)	Routine early PCI (n = 520)	p-value
Median symptom-onset-to-balloon time, minutes (inter quartile range)	168 (118-272)	N.A.	N.A.	N.A.	N.A.	N.A.
Median symptom-onset-to-needle time, minutes (inter quartile range)	N.A.	115 (71-200)	N.A.	110 (70-195)	124 (75−205)	0.104
Median needle-to-cath lab time, minutes (inter quartile range)	N.A.	223 (137-930)	N.A.	161 (120-228)	1035 (343-1554)	< 0.001
Radial arterial access site	3,702 (14.3%)	267 (20.9%)	< 0.001	135 (17.8%)	132 (25.4%)	0.001
No. of vessels treated with primary percutaneous coronary intervention						
1	23,916 (92.2%)	1,179 (92.3%)	0.999	693 (91.4%)	486 (93.5%)	0.202
2	1,301 (5.0%)	74 (5.8%)	0.859	47 (6.2%)	27 (5.2%)	0.466
≥ 3	118 (0.5%)	4 (0.3%)	0.665	4 (0.5%)	0 (0.0%)	0.151
Treated lesion data missing	592 (2.3%)	21 (1.6%)	0.147	14 (1.8%)	7 (1.3%)	0.655
Culprit lesion location						
Left main	170 (0.7%)	1 (0.1%)	0.005	0 (0.0%)	1 (0.2%)	0.407
Left anterior descendent artery	9,508 (36.7%)	403 (31.5%)	0.002	262 (34.6%)	141 (27.1%)	0.005
Left circumflex artery	3,727 (14.4%)	155 (12.1%)	0.024	69 (9.1%)	86 (16.5%)	< 0.001
Right coronary artery	10,895 (42.0%)	622 (48.7%)	< 0.001	368 (48.5%)	254 (48.8%)	0.955
Culprit lesion location not available	1,627 (6.3%)	97 (7.6%)	0.0678	59 (7.8%)	38 (7.3%)	0.830
Pre-procedural TIMI grade						
0	15,812 (61.0%)	317 (24.8%)	< 0.001	278 (36.7%)	39 (7.5%)	< 0.001
I	2,137 (8.2%)	109 (8.5%)	0.716	78 (10.3%)	31 (6.0%)	0.008
II	3,052 (11.8%)	246 (19.2%)	0.001	150 (19.8%)	96 (18.5%)	0.564
III	3,032 (11.7%)	443 (34.7%)	0.001	157 (20.7%)	286 (55.0%)	< 0.001
Not available	1,894 (7.3%)	163 (12.8%)	0.001	95 (12.5%)	68 (13.1%)	0.798
Post-procedural TIMI grade						
0	312 (1.2%)	7 (0.5%)	0.032	5 (0.7%)	2 (0.4%)	0.707
I	158 (0.6%)	8 (0.6%)	0.854	7 (0.9%)	1 (0.2%)	0.152
II	579 (2.2%)	31 (2.4%)	0.628	26 (3.4%)	5 (1.0%)	0.005
III	23,174 (89.4%)	1,123 (87.9%)	0.095	659 (86.9%)	464 (89.2%)	0.224
Not available	1,704 (6.6%)	109 (8.5%)	0.008	61 (8.0%)	48 (9.2%)	0.476
Culprit lesion diameter stenosis grade						
< 50%	27 (0.1%)	3 (0.2%)	0.165	1 (0.1%)	2 (0.4%)	0.570
50−74%	241 (0.9%)	67 (5.2%)	0.001	24 (3.2%)	43 (8.3%)	0.001
75−99%	8,048 (31.0%)	791 (61.9%)	0.001	391 (51.6%)	400 (76.9%)	0.001
100%	15,969 (61.6%)	316 (24.7%)	0.001	280 (36.9%)	36 (6.9%)	< 0.001
Not available	1,642 (6.3%)	101 (7.9%)	0.030	62 (8.2%)	39 (7.5%)	0.675

The first p-value is comparing primary PCI and rescue PCI, whereas the second p-value is comparing rescue PCI and routine early PCI.

Table 3
Postprocedural complications in patients treated with primary, rescue, or early routine percutaneous coronary intervention

Variable	Primary percutaneous coronary intervention (n = 25,927)	Pharmacoinvasive strategy (n = 1,278)	p-value	Rescue percutaneous coronary intervention (n = 758)	Routine early percutaneous coronary intervention (n = 520)	p-value
Cardiogenic shock	2,223 (8.6%)	6 (4.8%)	< 0.001	54 (7.1%)	7 (1.3%)	< 0.001
Heart failure	2,210 (8.5%)	89 (7.0%)	0.050	69 (9.1%)	20 (3.8%)	< 0.001
Reinfarction	524 (2.0%)	27 (2.1%)	0.823	23 (3.0%)	4 (0.8%)	0.006
Intracerebral hemorrhage	35 (0.1%)	4 (0.3%)	0.109	3 (0.4%)	1 (0.2%)	0.650
Any bleeding event	2,325 (9.0%)	84 (6.6%)	0.003	71 (9.4%)	13 (2.5%)	< 0.001
In-hospital mortality	1,513 (5.8%)	37 (2.9%)	< 0.001	36 (4.7%)	1 (0.2%)	< 0.001

that some patients developed intracerebral hemorrhage after receiving fibrinolytic therapy and did not undergo PCI. They would be excluded from our analysis and these numbers, therefore, may not reflect the true incidence of intracerebral hemorrhage after fibrinolysis.

Our findings are only applicable to patients who underwent PCI after STEMI, that is, primary PCI, rescue PCI, or routine early PCI. The findings might not be extrapolated to patients where a pharmacoinvasive strategy was intended but who ended up receiving fibrinolysis only.

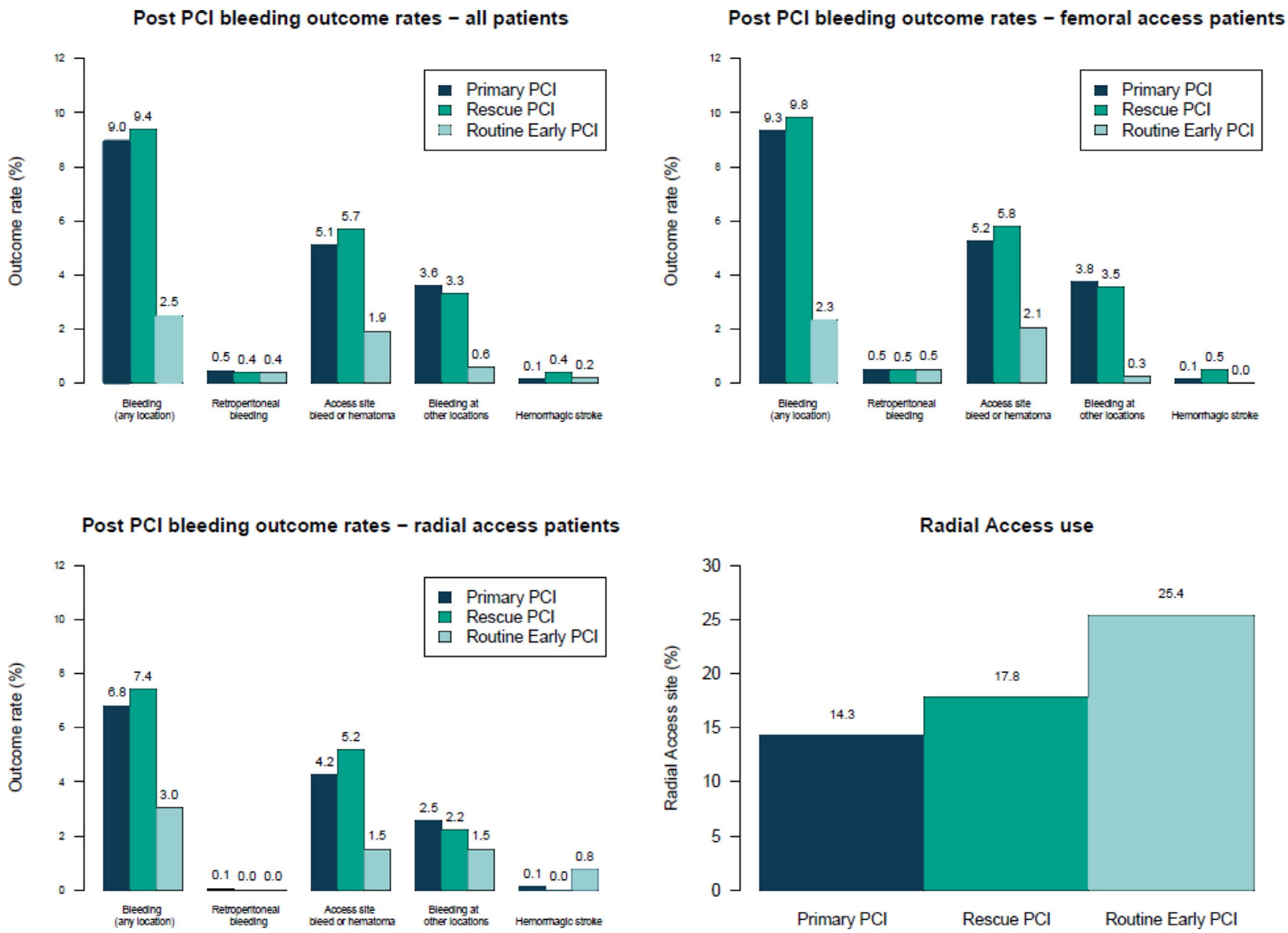

Figure 5. Bleeding complications in patients with ST-elevation myocardial infarction by treatment strategy. PCI = percutaneous coronary intervention.

Finally, there are regional differences in the organization of prehospital STEMI care. The findings of this study reflect STEMI treatment in the state of Michigan and may not apply to other STEMI systems of care. Patients living close to bordering states or Canada might have been transported to a PCI-capable hospital outside Michigan and were not included.

In conclusion, in this real-world registry of patients who underwent PCI for STEMI, the majority of patients lived within timely access of a PCI-capable hospital and were treated with primary PCI. The probability of receiving treatment with primary PCI decreased with longer estimated prehospital transport times. Bleeding complications and mortality rates were similar for patients treated with primary PCI and a pharmacoinvasive strategy.

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