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Fibrinolytic Therapy Versus Primary Percutaneous Coronary Interventions for ST-Segment Elevation Myocardial Infarction in Kentucky: Time to Establish Systems of Care?

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Abstract

Background—Fibrinolytic therapy is recommended for ST-segment myocardial infarctions (STEMI) when primary percutaneous coronary intervention (PPCI) is not available or cannot be performed in a timely manner. Despite this recommendation, patients often are transferred to PPCI centers with prolonged transfer times, leading to delayed reperfusion. Regional approaches have been developed with success and we sought to increase guideline compliance in Kentucky.

Methods—A total of 191 consecutive STEMI patients presented to the University of Kentucky (UK) Chandler Medical Center between July 1, 2009 and June 30, 2011. The primary outcome was in-hospital mortality and the secondary outcomes were major adverse cardiovascular events, extent of myocardial injury, bleeding, and 4) length of stay. Patients were analyzed by presenting facility—the UK hospital versus an outside hospital (OSH)—and treatment strategy (PPCI vs fibrinolytic therapy). Further analyses assessed primary and secondary outcomes by treatment strategy within transfer distance and compliance with American Heart Association guidelines.

Results—Patients presenting directly to the UK hospital had significantly shorter door-to-balloon times than those presenting to an OSH (83 vs 170 minutes; $P < 0.001$). This did not affect short-term mortality or secondary outcomes. By comparison, OSH patients treated with fibrinolytic therapy had a numeric reduction in mortality (4.0% vs 12.3%; $P = 0.45$). Overall, only 20% of OSH patients received timely reperfusion, 13% PPCI, and 42% fibrinolytics. In a multivariable model, delayed reperfusion significantly predicted major adverse cardiovascular events (odds ratio 3.87, 95% confidence interval 1.15–13.0; $P = 0.02$), whereas the presenting institution did not.

Conclusions—In contemporary treatment of STEMI in Kentucky, ongoing delays to reperfusion therapy remain regardless of treatment strategy. For further improvement in care, acceptance of transfer delays is necessary and institutions should adopt standardized protocols in association with a regional system of care.

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Keywords

primary percutaneous coronary intervention; fibrinolytic therapy; ST-segment myocardial infarction; systems of care

Significant advances in treating ST-segment myocardial infarctions (STEMI) have led to decreases in cardiac mortality during the last several decades.[1] Restoration of myocardial perfusion to the infarct zone by mechanical or pharmacological means has become the cornerstone of modern therapy for STEMI. Mechanical revascularization, or primary percutaneous coronary intervention (PPCI), of the infarct artery is the preferred method of restoring coronary perfusion because of its superior efficacy and decreased risk of complications compared with fibrinolytic therapy.[2] The efficacy of PPCI diminishes, however, with increasing time from symptom onset to restoration of flow.[3] PPCI also requires the availability of qualified catheterization laboratories with experienced personnel on a 24-hour basis. When STEMI patients present to facilities with no PPCI capabilities, it is critically important to consider transfer to a PPCI facility versus the administration of fibrinolytic therapy. When PPCI is not available or cannot be performed in a timely manner, fibrinolytic therapy is recommended. Despite this recommendation, patients presenting to sites without PPCI capability are often transferred to PPCI centers that have prolonged transfer times. In an effort to reduce barriers to timely access to reperfusion, regional networks have been established to increase the number of patients who receive the appropriate reperfusion therapy.[4–6] Factors specific to each region of the country, such as availability of air transport, prevailing weather patterns, and other factors affect the optimal method of reperfusion for a given patient.

The University of Kentucky (UK) Chandler Medical Center is the largest academic medical center in Kentucky and one of only a few tertiary referral centers. In addition to receiving STEMI patients from its own vicinity, the UK hospital frequently receives transferred STEMI patients from the central, eastern, southeastern, and southern parts of the state. We sought to evaluate practice patterns at our institution and objectively critique compliance with existing guidelines to better understand how to implement a successful regional system of STEMI care in central Kentucky.

Methods

Sample

The institutional review board at the UK College of Medicine approved this study. The sample consisted of consecutive patients presenting to the UK hospital for treatment of acute STEMI between July 1, 2009 and June 30, 2011. A total of 197 patients were identified. Six patients were excluded as not being candidates for reperfusion because of "comfort care" (n = 1), a refusal to undergo catheterization (n = 2), late presentation (n = 2), or death before the start of the procedure (n = 1). The study design was a retrospective cohort analysis in which cardiac outcomes were analyzed based on treatment strategy directed by the referring facility.

Outcomes

Personnel blinded to the study design extracted prespecified outcomes and catheterization data from our institutional case report forms submitted to the National Cardiovascular Data Registry (NCDR) database. The NCDR case report forms include patient demographics, risk factors, cardiac status at the time of presentation, coronary anatomy, intracoronary device utilization, and adverse event rates.[7] Key patient times were tracked for performance

measures, including symptom onset to presentation, door-to-needle (DTN), door-to-door, door-to-balloon (DTB), and other timing metrics where "door" represents a patient's arrival to the facility. The primary outcome was in-hospital mortality. Secondary outcomes were major adverse cardiovascular events (MACE); extent of myocardial injury as defined by peak cardiac biomarker levels (troponin, creatinine kinase [CK]-MB) and left ventricular ejection fraction; bleeding as assessed by vascular complications, transfusion, and major bleeding; and length of stay.[8]

Statistical Analysis

Outcomes were compared by presenting facility, the UK hospital versus an outside hospital (OSH) and reperfusion strategy (PPCI vs fibrinolytic therapy). The subgroups analyzed included patients with a transfer distance of <45 mi and those with a transfer distance of ≥45 mi. In addition, patients who met the American Heart Association (AHA)/American College of Cardiology (ACC) standards for reperfusion (<90 minutes DTB for PPCI, <30 minutes DTN for fibrinolytics) were compared with those who did not.[9] Patients meeting the upper limit of the 2004 DTB guidelines of 90 minutes ± 30 minutes were compared with those who did not (<120 minutes DTB for PPCI, <60 minutes DTN for fibrinolytics). Dichotomous outcomes are summarized by percentages, with Fisher exact tests used for comparisons. Normally distributed outcomes were summarized by means and standard deviations, with *t* tests used for comparisons. Numeric but non-normally distributed outcomes are summarized by medians and interquartile ranges, with rank sum tests used for comparisons. $P < 0.05$ was considered statistically significant. Version 9.3 of SAS software (SAS Institute, Cary, NC) was used for data analysis.

Associations between MACE and individual patient factors were estimated and tested for statistical significance. MACE was defined as death, MI, stroke, shock, or major bleeding. Patient factors examined in univariable logistic regression models were time to presentation, presenting facility, timely access to reperfusion therapy, and infarct size as estimated by peak CK-MB and troponin levels. Patient factors with $P < 0.20$ in univariable logistic regression models along with presentation site were subsequently included in a multivariable logistic regression model. In univariable logistic regression modeling, associations between MACE and individual patient factors were summarized by unadjusted odds ratios, for which both point estimates and 95% confidence intervals were obtained. Potential interactions also were assessed for patient factors that were statistically significant in multivariable logistic regression modeling.

Results

Patient Population

Of the 191 STEMI patients included in the study, 82 presented to the UK hospital, whereas the remaining 109 presented to an OSH before being transferred. Of those presenting to an OSH, 82 (75%) were transferred for PPCI, whereas 27 (25%) were treated with fibrinolytics. Of the 27 patients who received fibrinolytics, 17 eventually underwent rescue PCI, 8 were treated with routine PCI within 24 hours of presentation, and 2 were treated medically. Baseline characteristics were generally well balanced between patients presenting directly to the UK hospital (n = 82) versus those presenting to an OSH (n = 109), although fewer nonwhite patients presented to an OSH (Table 1). There were no significant differences identified between patients transferred from an OSH for PPCI (n = 82) versus those treated with fibrinolytics (n = 27). Each referring location for STEMI is identified and scaled by number of patients transferred from each site in Figure 1.

PCI Procedure

Table 2 displays the procedural characteristics of the sample. There were 164 patients who received PPCI and were equally divided between direct presentation to the UK hospital for PPCI and those transferred from an OSH. Patients presenting to the UK hospital had an average DTB time of 83 minutes (median 72), whereas average patient DTB time was more than doubled for those presenting as transfers at 170 minutes, median 145 ($P < 0.01$). Figure 2 displays additional key performance measures. More OSH patients were in cardiogenic shock at the time of PCI (7.3% vs 4.9%), although the difference was statistically nonsignificant ($P = 0.56$). At angiography, the majority of patients (86.5%) were found to have flow-limiting lesions, as defined by a Thrombolysis in Myocardial Infarction score of ≤ 2, balanced between the groups (86.4% vs 86.6%; $P = 1.00$). The majority of patients were successfully revascularized percutaneously (96.9%), with two requiring urgent or emergent coronary artery bypass grafting (1.1%), one patient died before PCI (0.5%), one PCI was unsuccessful (0.5%), and three (1.6%) patients were treated medically, two of whom had received fibrinolytic therapy.

Outcomes

In-hospital mortality was similar between patients presenting to the UK hospital and those transferred from OSH facilities (Table 2). Among OSH patients, those transferred for PPCI had a higher mortality (10 of 82) than those who received fibrinolytics (1 of 27 or 12.3% vs 4.0%), but given the modest sample size, this difference was not statistically significant ($P = 0.45$).

Patients presenting to the UK hospital had significantly lower peak CK-MB levels than those presenting to an OSH, whereas peak troponin levels showed a similar pattern, but the difference was not statistically significant. The ejection fractions at discharge were similar regardless of the presentation site (43.6% vs 43.9%; $P = 0.90$), and the development of symptomatic congestive heart failure was uncommon in both groups. Among OSH patients there was a trend toward less symptomatic congestive heart failure in patients who initially underwent PPCI (3.7% vs 14.8%; $P = 0.06$); otherwise, there were no significant differences between patients treated with fibrinolytics and PPCI. There was a low rate of catheterization-related complications, including procedural cerebrovascular accident, vascular complications, major bleeding, and a need for dialysis in both groups.

Figure 3 displays compliance with AHA guidelines (DTB <90 minutes and DTN <30 minutes) by site and reperfusion strategy. Guideline compliance was considerably higher among patients presenting to the UK hospital than those transferred from an OSH for PPCI (71% vs 13%). OSH patients who received fibrinolytic therapy had intermediate compliance (42%) with AHA-recommended DTN times <30 minutes. When more liberal reperfusion targets were applied (DTB <120 minutes or DTN <60 minutes), 87% of patients presenting to the UK hospital, 30% transferred from an OSH for PPCI, and 69% receiving fibrinolytics met criteria. Despite a clinically impressive difference in mortality among patients meeting the target times for reperfusion, a statistically significant mortality benefit was not observed (0% vs 12.8%; $P = 0.20$); however, when considering the more liberal reperfusion targets, significantly lower mortality occurred in patients who met the more liberal targets than those who did not (2.4% vs 15.3%; $P = 0.04$). No other significant differences were detected on subgroup analyses (Table 3).

Results from univariable and multivariable logistic regression models relating MACE to individual patient factors are summarized in Figure 4. Delayed reperfusion was estimated to almost triple the odds of MACE, and the association of delayed reperfusion with MACE became even stronger after adjustment for presenting facility and peak CK-MB. Peak CK-

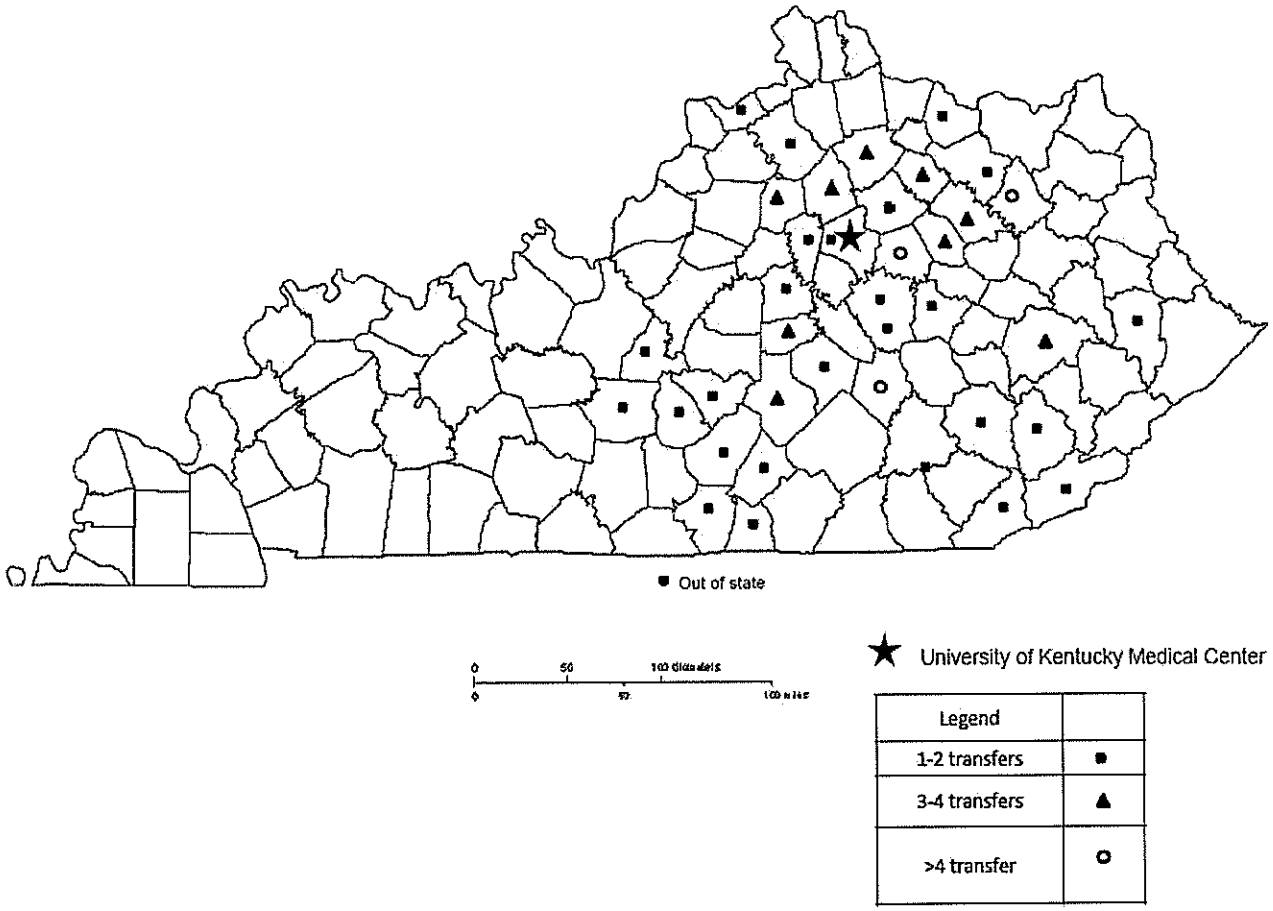

Fig. 1.
Map of Kentucky with county lines shown. Each referring location for ST-segment myocardial infarctions (STEMI) is identified and scaled by number of patients transferred from each site.

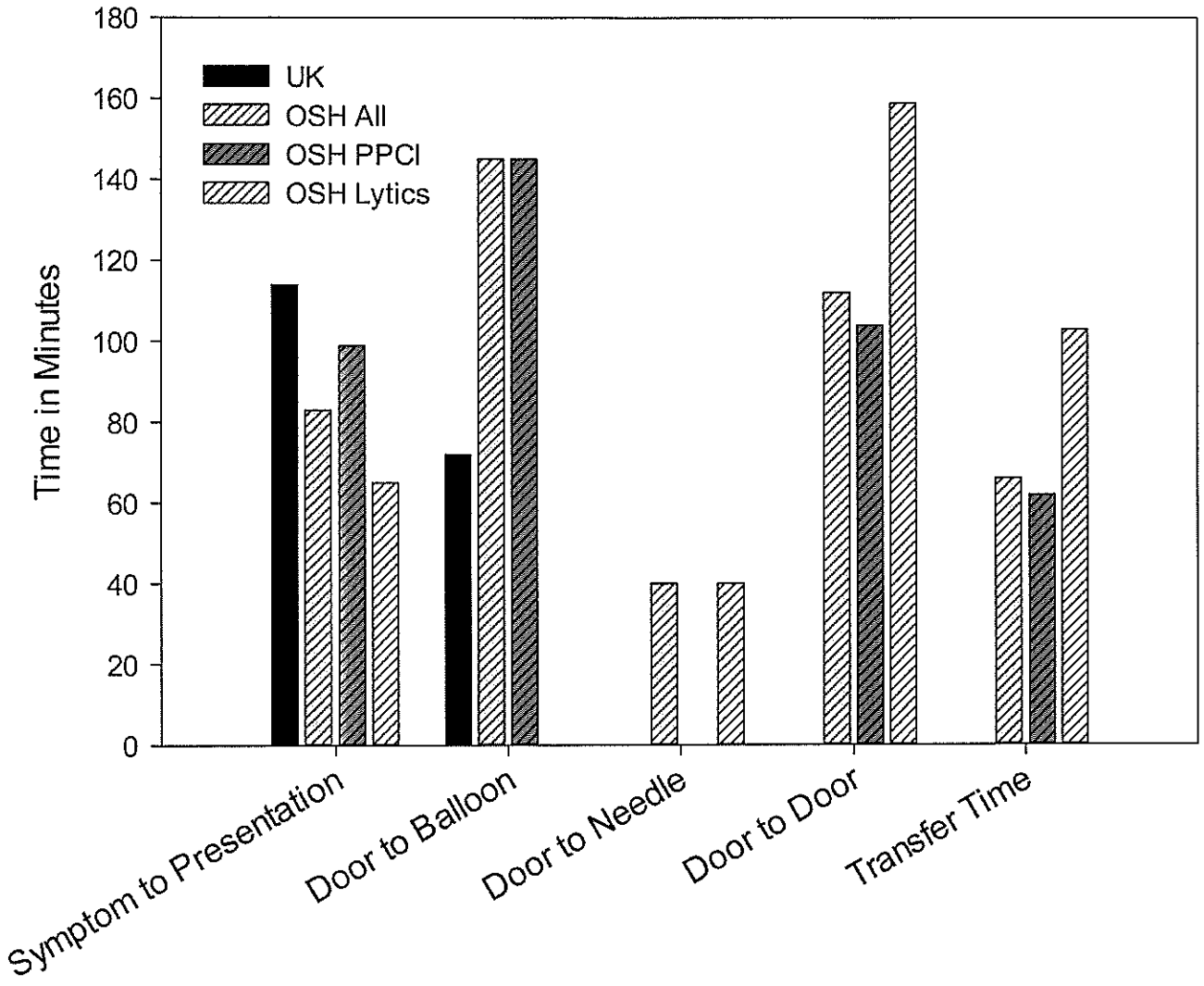

Fig. 2.

Mean reperfusion times for patients presenting to our institution (black bars) and those presenting to an outside hospital (OSH) receiving primary percutaneous coronary intervention (PPCI; light gray bars) or fibrinolytic therapy (lytics; dark gray bars). As shown, door-to-balloon times were significantly longer for OSH patients and outside the American College of Cardiology/American Heart Association guideline recommendations of <120 minutes. In addition, median door-to-needle time was also outside the guideline recommended time of <30 minutes.

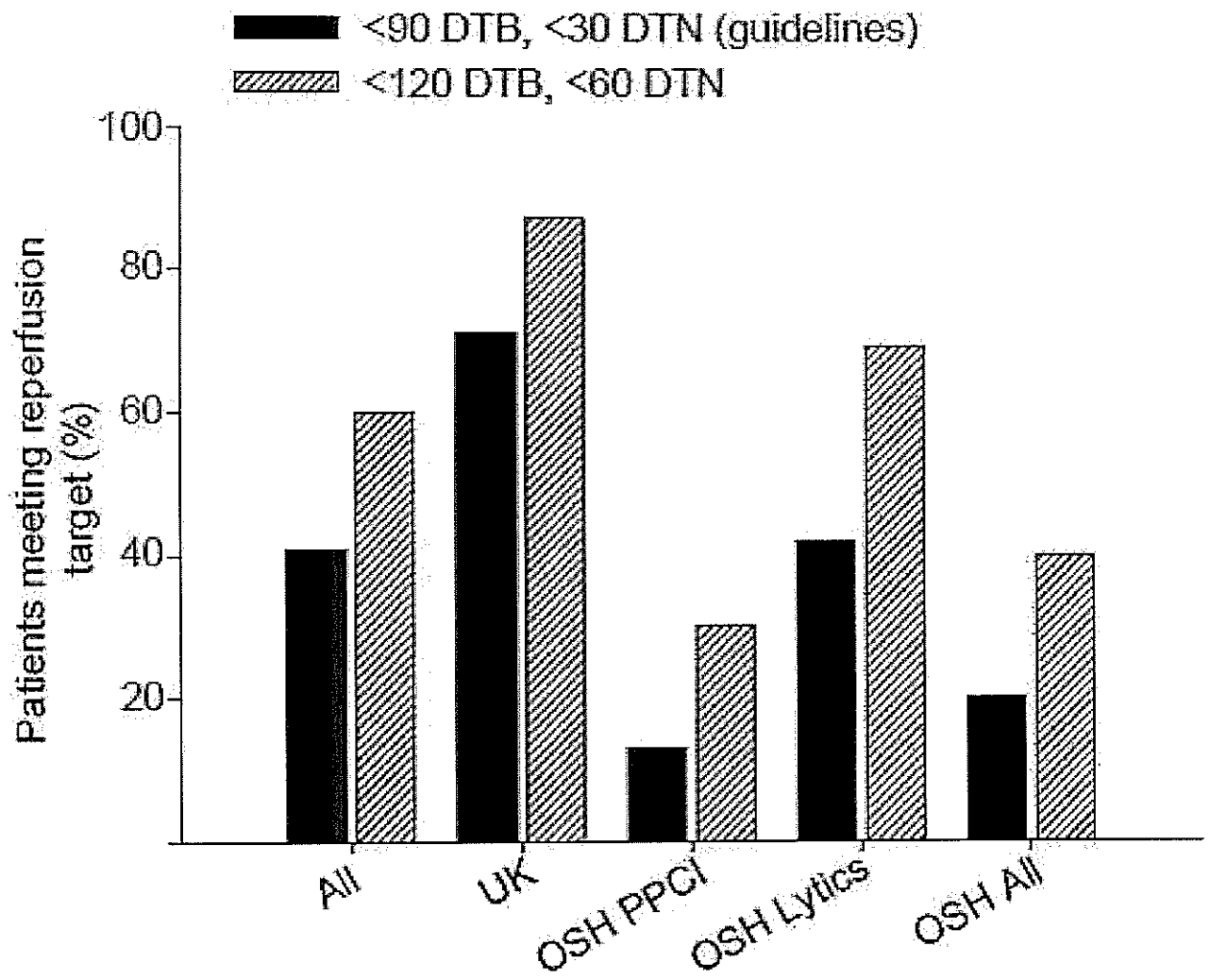

Fig. 3.

Percentage of patients meeting current reperfusion guidelines (black bars) and upper limits of acceptability (striped bars). Times are displayed in minutes. DTB, door-to-balloon; DTN, door-to-needle; lytics, fibrinolytic therapy; OSH, outside hospital; PPCI, primary percutaneous coronary intervention; UK, University of Kentucky Chandler Medical Center.

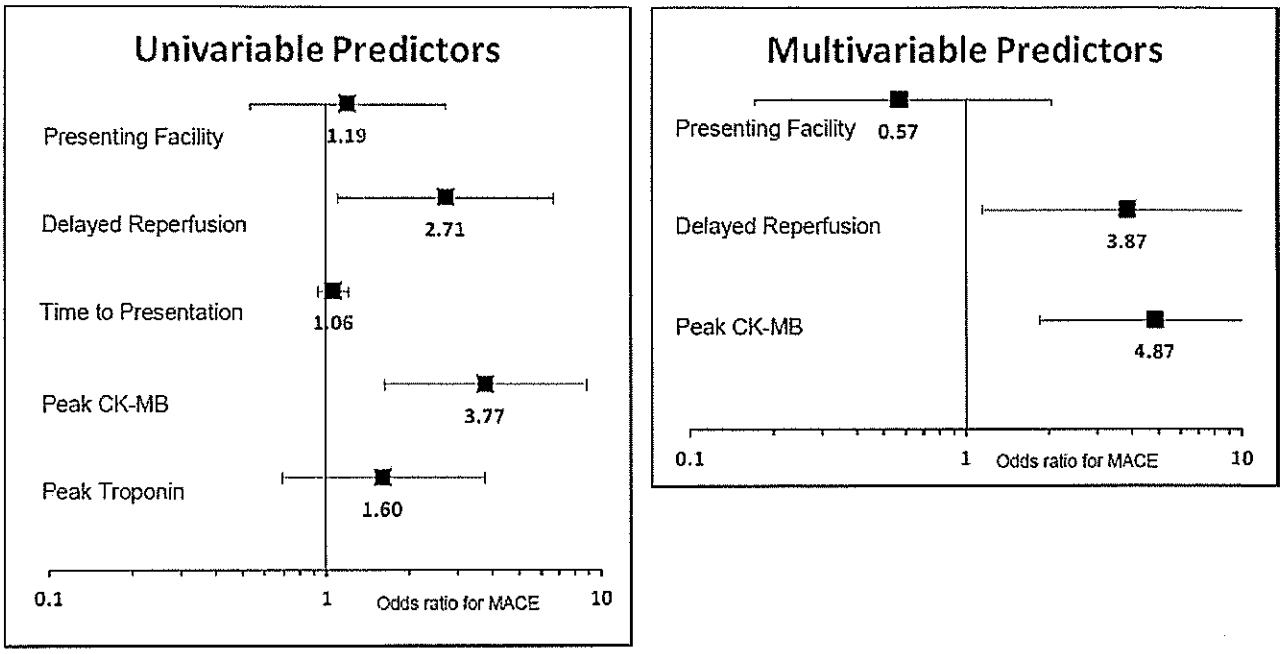

Fig. 4.

Potential predictors of major adverse cardiac events (death, myocardial infarction, stroke, shock, or major bleeding) in univariable and multivariable logistic regression models are listed with point estimates of their odds ratios and 95% confidence intervals. Timely reperfusion and peak creatinine kinase (CK)-MB predict adverse events in both univariable and multivariable models. The odds ratios for presenting facility (University of Kentucky Chandler Medical Center vs outside hospital) for delayed reperfusion are for <120 minutes door-to-balloon and <30 minutes door-to-needle versus otherwise, and the odds ratios for time to presentation are per hour of delay from onset of chest pain until emergency department presentation. MACE, major adverse cardiovascular events.

Table 1

Patient demographics

Demographics	All	UK ED	OSH (all)	*P*	OSH PPCI	OSH lytics	*P*
No. subjects	191	82	109		82	27	
Age, y, mean ± SD	57.9 ± 12.1	58.0 ± 11.1	57.8 ± 12.9	0.88	58.2 ± 13.3	56.4 ± 11.7	0.52
Male sex, %	69.6	69.5	69.7	1.00	65.9	81.5	0.15
White, %	93.2	86.6	98.2	<0.01	97.6	100.0	1.00
Tobacco, %	67.5	61.0	72.5	0.12	70.7	77.8	0.62
Hypertension, %	73.8	75.6	72.5	0.74	72.0	74.1	1.00
Hyperlipidemia, %	69.6	72.0	67.9	0.63	68.3	66.7	1.00
Family history, %	16.8	15.9	17.4	0.85	17.1	18.5	0.54
Diabetes, %	23.6	28.0	20.2	0.23	22.0	14.8	0.58
Prior MI, %	20.9	23.2	19.3	0.59	23.2	7.4	0.09
CHF, %	5.2	7.3	3.7	0.33	4.9	0.0	0.57
Prior PCI, %	20.4	22.0	19.3	0.72	22.0	11.1	0.27
Prior CABG, %	4.2	4.9	3.7	0.73	2.4	7.4	0.23
BMI, kg/m^2, mean ± SD	28.5 ± 5.5	29.0 ± 5.7	28.2 ± 5.3	0.35	27.9 ± 5.3	29.2 ± 5.0	0.27
Creatinine, mg/dL, mean ± SD	1.1 ± 0.5	1.1 ±0.6	1.2 ±0.2	0.75	1.2 ± 0.2	1.2 ± 0.2	0.93

BMI, body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; ED, emergency department; lytics, fibrinolytic therapy; MI, myocardial infarction; OSH, outside hospital; PPCI, primary percutaneous coronary intervention; SD, standard deviation; UK, University of Kentucky Chandler Medical Center.

Table 2

Procedural details and outcomes

	All	UK ED	OSH (all)	*P*	PPCI	Lytics	*P*
Procedural details							
Transfer distance, mi (range)		N/A	45 (24–59)		35 (18–59)	52 (44–86)	0.02
Cardiogenic shock, %	6.3	4.9	7.3	0.56	8.5	3.7	0.68
TIMI 3 flow pre-PCI, %	13.5	13.6	13.4	1.00	13.4	N/A	
TIMI 3 flow post-PCI, %	95.2	93.8	96.2	0.59	98.8	88.0	0.01
Left anterior descending artery, %	41.0	44.4	37.4	0.37	35.4	44.0	0.65
Circumflex artery, %	15.4	11.1	18.7	0.22	19.5	16.0	0.77
Right coronary artery, %	42.6	42.0	43.0	1.00	43.9	40.0	0.65
Bypass graft, %	2.7	3.7	1.9	0.65	2.4	0.0	1.00
Dissection/perforation, %	2.2	2.5	1.9	1.00	1.2	4.0	0.44
Successful PCI, %	96.9	96.3	97.2	1.00	98.8	92.6	0.15
DES, %	23.9	29.5	19.8	0.17	14.8	36.0	0.047
CABG, %	1.1	1.2	0.9	1.00	1.2	0.0	1.00
Medical management, %	1.6	1.2	1.8	1.00	0.0	7.4	0.06
Outcomes							
Death (%)	19 (10.0)	8 (9.9)	11 (10.1)	1.00	10 (12.3)	1 (4.0)	0.45
Length of stay, wk (range)	3 (2–4)	3 (2–6)	3 (2–3)	0.02	3 (2–3)	3 (2–4)	0.11
Peak CK-MB (range)	198 (96–300)	167 (57–292)	244 (106–,302)	0.02	245 (106–302)	238 (117–301)	0.86
Peak troponin I (range)	50 (21–96)	38 (16–95)	53 (26–96)	0.26	50 (24–96)	76 (29–95)	0.77
EF at discharge	43.8 ± 12.1	43.6 ± 11.6	43.9 ± 12.6	0.90	44.3 ± 13.1	42.5 ± 11.0	0.51
Shock (%)	6 (3.1)	3 (3.7)	3 (2.9)	1.00	2(2.4)	1 (3.7)	1.00
CHF (%)	10 (5.2)	3 (3.7)	7 (6.4)	0.52	3 (3.7)	4 (14.8)	0.06
CVA (%)	1 (0.5)	0 (0)	1 (0.9)	1.00	0 (0.0)	1 (3.7)	0.25
Hemorrhagic CVA (%)	1 (0.5)	0 (0)	1 (0.9)	1.00	0 (0.0)	1 (3.7)	0.25
Dialysis (%)	1 (0.5)	1 (1.2)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00
Vascular complications (%)	1 (0.5)	1 (1.2)	0 (0.0)	1.00	0 (0.0)	0 (0.0)	1.00
Major bleeding at 72 h (%)	4 (2.1)	2 (2.4)	2 (1.8)	1.00	1 (1.2)	1 (3.7)	0.44
Transfusion (%)	12 (6.3)	7 (8.5)	5 (4.6)	0.36	5 (6.1)	0 (0.0)	0.33

Medical management refers to patients in whom revascularization was not performed. Length of stay, CK-MB, and troponin I outcomes are median followed by interquartile range. Categorical variables are listed as total number of events and percentages. EF is shown as mean and standard deviation. CABG, coronary artery bypass graft; CHF, congestive heart failure; CK-MB, creatinine kinase-MB; CVA, cerebrovascular accident; DES, drug-eluting stents; ED, emergency department; EF, ejection fraction; lytics, fibrinolytic therapy; OSH, outside hospital; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; UK, University of Kentucky Chandler Medical Center.

Table 3

Outcomes by distance and time

	Distance <45 mi			Distance >45 mi		
	PPCI	Lytics	*P*	PPCI	Lytics	*P*
Total (n)	46	7		34	19	
Death (%)	6 (13.3)	0 (0.0)	0.58	4 (11.8)	1 (5.9)	0.65
Length of stay, wk (range)	3 (2–3)	3 (3–8)	0.11	3 (2–3)	3 (2–4)	0.33
Peak CK-MB (range)	242 (102–302)	284 (198–302)	0.38	226 (108–302)	195 (67–281)	0.49
Peak troponin I (range)	50 (20–96)	94 (76–96)	0.17	46 (28–97)	41 (25–95)	0.32
EF at discharge	44.9 ± 13.4	35.9 ± 12.7	0.10	44.0 ± 12.3	44.4 ± 9.6	0.89
Major bleeding (%)	1 (2.2)	1 (14.3)	0.25	0 (0)	0 (0)	N/A
	DTB <90 or DTN <30 min			DTB <120 or DTN <60 min		
	Met	Not met	*P*	Met	Not met	*P*
Total (n)	18	86		41	63	
Death (%)	0 (0)	11 (12.8)	0.20	1 (2.4)	10 (15.3)	0.04
Length of stay, wk (range)	3 (2–3)	3 (2–3)	0.21	3 (2–3)	3 (2–3)	0.21
Peak CK-MB (range)	193 (100–300)	248 (106–302)	0.63	246 (115–300)	247 (104–302)	0.82
Peak troponin I (range)	31 (25–96)	61 (25–96)	0.29	45 (24–96)	58 (27–96)	0.72
EF at discharge	45.1 ± 10.2	44.0 ± 13.0	0.73	43.0 ± 11.1	45.0 ± 13.4	0.44
Major bleeding (%)	1 (5.6)	1 (1.1)	0.31	2 (4.9)	0 (0)	0.15

Categorical variables are listed as total number of events and percentages. Ejection fraction is shown as mean ± standard deviation. Length of stay, CK-MB, and troponin I outcomes are median followed by interquartile range. Referring sample sizes do not sum to 109 and some percentages are out of slightly smaller denominators than "total(n)" because of missing data. CK-MB, creatinine kinase-MB; DTB, door-to-balloon; DTN, door-to-needle. EF, ejection fraction; lytics, fibrinolytic therapy; PPCI, primary percutaneous coronary intervention.