Missed Opportunities in the Management of ST-Segment Elevation Myocardial Infarction in the Arab Middle East: Patient and Physician Impediments

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ABSTRACT

Background: Lack of timely reperfusion therapy in patients with ST-elevation myocardial infarction (STEMI) has been associated with worse outcomes. The aim of this study is to identify the frequency and predictors of delayed presentation and missed reperfusion in patients with STEMI in the Gulf Register of Acute Coronary Events (Gulf RACE) registry.
Delayed Presentation and missed reperfusion is associated with increased in hospital mortality in STEMI patients.

Methods: Gulf RACE is a prospective, multinational study of all consecutive patients hospitalized with the final diagnosis of acute coronary syndrome in 65 centers in 6 Arab countries. In this analysis, we included 3197 patients with STEMI. The independent predictors of delayed presentation and missed reperfusion therapy were identified using multivariate logistic regression.

Results: In total, 929 patients presented >12 hours after symptom onset. The independent predictors of late presentation are older age, atypical symptoms, no family history of coronary artery disease, and being in Yemen. Of the 2268 STEMI patients presenting early, a total of 205 patients (9.3%) did not receive reperfusion therapy despite no contraindications (shortfall). The independent predictors of not receiving appropriate reperfusion therapy are older age, prior stroke, being in Yemen, and atypical symptoms. Lack of reperfusion therapy due to shortfall or delayed presentation was associated with increased in-hospital mortality.

Conclusions: Nearly one-third of patients with STEMI in the Arab Middle East present to the hospital >12 hours after symptom onset, and nearly 1 in 10 eligible patients do not receive any reperfusion therapy. Community and physician awareness programs are needed to increase the utilization of appropriate lifesaving therapies.

Introduction

Prompt reperfusion in patients with ST-segment elevation myocardial infarction (STEMI) is essential to myocardial salvage and improved outcomes.[1,2] Delays from symptom onset to hospital presentation have been associated with reduced likelihood of receiving appropriate timely reperfusion therapy.[3–7] Late presenters have significantly longer delays prior to receiving evidence-based therapies.[6,8]

On the other hand, more than one-third of patients with STEMI do not receive appropriate reperfusion therapy despite early presentation.[9–13] Failure to receive reperfusion therapy has been associated with worse outcomes.[5,7,9,10,14,15] Most prior studies examining delays in presentation and the utilization of reperfusion therapy have been conducted in Western populations and developed countries. Practice patterns and patient characteristics in developing regions of the world may differ significantly from what has been observed in Western registries. In the Arab Middle East, appropriate use of reperfusion therapy in patients with STEMI has never been systematically examined. We thus evaluated the frequency and

predictors of delayed presentation and missed reperfusion in a contemporary cohort with STEMI, based on data from the largest prospective multinational registry of acute coronary syndrome (ACS) in the Middle East.[16]

Methods

Study Population

The Gulf Registry of Acute Coronary Events (Gulf RACE) is a prospective, multinational study of all consecutive patients hospitalized with the final diagnosis of ACS in 65 centers in 6 Arab countries (Kuwait, Oman, United Arab Emirates, Yemen, Qatar, and Bahrain). Patients were enrolled from January 2007 to June 2007. Details of study organization have been previously described.[17] All hospitals in Kuwait, Bahrain, and Qatar participated, and 90% of hospitals in United Arab Emirates and Oman and 85% of hospitals in Yemen participated. Nonparticipating hospitals were often small, with limited cardiac services. Of the 65 sites participating, only 18 had catheterization labs.

The definition of STEMI was based on the American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with ACS.[18] For the purposes of this analysis, patients with STEMI and new left bundle-branch block myocardial infarction (LBBB MI) were considered together, and are herein referred to as STEMI.

Data on baseline characteristics, duration of symptoms, admission profile, and in-hospital treatments and outcomes were prospectively collected by the treating physicians. Patients were divided into 2 groups based on whether or not they presented within 12 hours of symptom onset. Contraindications to thrombolytic therapy were also recorded, including any prior intracranial hemorrhage, severely elevated blood pressure, malignant intracranial neoplasm, known structural cerebral vascular lesion, aortic dissection, trauma and cardiopulmonary resuscitation of >20 minutes' duration, recent surgery, and pregnancy. Subsequently, patients presenting within 12 hours of symptom onset were divided into 2 groups based on whether or not they received reperfusion therapy (either thrombolytic therapy or primary coronary angioplasty).

Statistical Analysis

Continuous variables are summarized as median and interquartile ranges, and compared using the Wilcoxon rank sum test. Categorical variables are summarized as percentages, and compared using χ^2 tests. Separate stepwise multivariate logistic regression analyses were used to identify independent predictors of delay in presentation, failure to receive reperfusion therapy, and in-hospital mortality after adjusting for baseline covariates. Similarly, the association between delayed presentation and failure to receive timely reperfusion was examined using stepwise logistic regression models adjusting for age, gender, baseline covariates, and in-hospital treatment patterns. For all multivariate modeling, the threshold for variable entry into models was $P < 0.05$, and the threshold for variable removal was $P > 0.10$. Selection of variables for entry consideration was based on clinical judgment, results of previous publications, and the expertise of the investigators. Care was given to avoidance of model overfitting by maintaining an events to covariate ratio of at least 10 to 1. Analyses were performed with the SAS 9.1 statistical package (SAS Institute, Cary, NC).

Results

Delayed Presentation

A total of 3197 patients (mean age 54 ± 12 y, 14% female) presented to the emergency room (ER) with acute STEMI/new-onset LBBB MI, of which 929 (30%) presented >12 hours after symptom onset (Figure 1). The baseline characteristics of the delayed patients are shown in Table 1. These patients were older (58 ± 13 vs 52 ± 11 y), more often female (20% vs 11%), and had a higher prevalence of smoking (45% vs 53%), dyslipidemia (14% vs 18%), prior stroke (5% vs 2%), and atypical symptoms (13% vs 5%). The median door-to-needle time for patients presenting within 12 hours of symptom onset was 36 minutes (interquartile range was 20–65 min). There were regional variations in the frequency of late presentation, with patients from Yemen most often presenting >12 hours from symptom onset (59%). Late presenters had higher heart rate, lower systolic blood pressure, and a higher Global Registry of Acute Coronary Events (GRACE) score and Killip class (Table 1). In addition, delayed patients were less likely to receive evidence-based therapies in the first 24 hours of hospitalization, including β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and statins, and were less likely to undergo coronary angiography during the index admission.
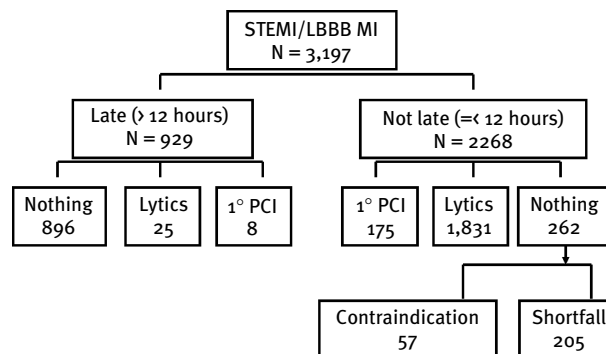

Figure 1. Characteristics of patients presenting with STEMI or LBBB MI. Abbreviations: LBBB MI, left bundle-branch block myocardial infarction; N, number of patients; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 1. Baseline Characteristics and In-hospital Outcomes of STEMI Patients Presenting >12 Hours and ≤12 Hours After Symptom Onset

	Presentation >12 h N = 929	Presentation ≤12 h N = 2268	P Value
Age, y	57 (50–67)	51 (45–60)	<0.0001
Female gender	19	11	<0.0001
Country			<0.0001
Bahrain (n = 88)	9	91	
Kuwait (n = 754)	15	85	
Oman (n = 479)	22	78	
Qatar (n = 155)	15	85	
UAE (n = 750)	14	86	
Yemen (n = 971)	59	41	
HT	32	33	0.56
DM	30	32	0.26
Prior MI	14	13	0.34
Prior PCI	3	6	0.0018
Prior CABG	2	1	0.08
Smoking	45	53	0.0002
HL	14	18	0.001
Family history of CAD	11	14	0.0066
MI location			<0.0001
Anterior	58	53	
Inferior	32	41	
Prior stroke	5	2	<0.0001
Chest pain	87	95	<0.0001
Resting HR (bpm)	88 (77–100)	80 (70–95)	<0.001
SBP (mm Hg)	130 (110–150)	135 (120–154)	<0.001
Peak CPK (mg/dL)	455 (210–1208)	1319 (446–2753)	<0.001
Peak CKMB (mg/dL)	71 (40–130)	111 (50–234)	<0.001
Ambulance use	12	19	<0.0001
Door-to-ECG time (min)	15 (8–21)	10 (5–18)	<0.0001
Killip class			<0.0001
I (n = 2555)	71	83	
II (n = 388)	18	10	
III (n = 153)	7	4	

Table 1. (continued)

	Presentation >12 h N = 929	Presentation ≤12 h N = 2268	P Value
IV (n = 94)	4	3	
GRACE score			<0.0001
Low (n = 1131)	28	47	
Intermediate (n = 812)	30	30	
High (n = 734)	42	23	
Medication use			
Aspirin	98	98	0.30
Clopidogrel	59	59	0.96
Unfractionated heparin	74	63	<0.0001
LMW heparin	22	31	<0.0001
IIb/IIIa inhibitors	6	9	0.0013
β-Blockers	55	65	<0.0001
ACEIs	71	65	0.0006
Statins	88	91	0.0233
Nitrates	79	72	<0.0001
Diuretics	22	16	<0.0001
Coronary angiography	12	20	<0.0001
EF (n = 2207)	48 (40–55)	46 (39–55)	0.08
Outcomes			
Death	10.4	3.9	<0.0001
Cardiogenic shock	13	6	<0.0001
New-onset heart failure	11	6	<0.0001
Major bleeding	1	1	0.72
Stroke	1	2	0.035

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CABG, coronary artery bypass graft; CAD, coronary artery disease; CK, creatine kinase; CK-MB, creatine kinase isoenzyme MB; DM, diabetes mellitus; ECG, electrocardiography; EF, ejection fraction; GRACE, Global Registry of Acute Coronary Events; HL, hyperlipidemia; HR, heart rate; HT, hypertension; LMW, low molecular weight; MI, myocardial infarction; n, number of patients; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; UAE, United Arab Emirates.
Continuous variables are summarized as median and interquartile ranges, and categorical variables are summarized as percentages.

Outcomes of Late Presenters

A total of 186 patients (5.8%) died during hospitalization, of whom 97 patients (52.2%) presented early and 89 (47.2%) were late presenters. Delayed presentation was associated

with significantly increased in-hospital mortality (10.4% vs 3.9%, $P < 0.0001$). In addition, delayed presentation was associated with increased incidence of cardiogenic shock and new-onset heart failure (Table 1).

The independent predictors of late presentation are shown in Table 2. After adjusting for potential confounders (age, gender, diabetes mellitus, hypertension, prior angioplasty, prior coronary artery bypass graft, smoking, family history of coronary artery disease [CAD], prior stroke, hyperlipidemia, presenting symptoms, country, use of ambulance, and interaction between age and gender), the independent predictors of late presentation were older age, atypical symptoms, family history of CAD, and being in Yemen (model c-index 0.782).

Reperfusion Shortfall

A total of 2268 STEMI patients presented within 12 hours of symptom onset, of whom 2006 patients received either thrombolytic therapy (80.2%) or primary percutaneous coronary intervention (PCI) (19.8%). A total of 57 patients (2.5%) did not receive reperfusion therapy because they had contraindication to lytics, and 205 patients (9.3%) did not receive reperfusion therapy despite no contraindications (shortfall). Patients who did not receive any reperfusion therapy despite no contraindications were older, more often female, and more likely to have atherosclerotic risk factors or prior cardiovascular disease (Table 3). Shortfall patients presented less often via ambulance and had a longer door-to-electrocardiography (ECG) time. They complained of chest pain less often and were sicker at presentation, with higher Global Registry of Acute Coronary Events (GRACE) score, higher heart rate, lower systolic blood pressure, and higher Killip class (Table 3). In addition to not receiving

Table 2. Independent Predictors of Delayed Presentation in Patients With STEMI in the Arab Middle East

	OR	95% CI	P Value
Age (per 10 year)	1.3	1.10–1.58	<0.0001
Prior PCI	0.45	0.27–0.73	0.0012
Atypical symptoms	1.2	1.10–1.30	<0.0001
Country: Yemen[a]	11.8	5.5–25.2	<0.0001
Family history of CAD	0.73	0.56–0.97	0.029

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; OR, odds ratio; PCI, percutaneous coronary intervention.
Model adjusted for age, gender, DM, HT, prior angioplasty, prior CABG, smoking, family history of CAD, prior stroke, HL, presenting symptoms, country, use of ambulance, and interaction between age and gender. Model c-index 0.782.
[a] Compared with the country with lowest delayed presentation, Bahrain.

Table 3. Comparison Between STEMI Patients Presenting Within 12 hours of Symptom Onset Based on Administration of Reperfusion Therapy

	Shortfall N = 205	Reperfusion N = 2006	P Value
Age, y	56 (48–65)	50 (44–58)	<0.0001
Female gender	20	80	<0.0001
Country			<0.0001
Bahrain (n = 77)	16	84	
Kuwait (n = 633)	7	93	
Oman (n = 369)	10	90	
Qatar (n = 128)	12	88	
UAE (n = 637)	4	96	
Yemen (n = 367)	21	79	
HT	46	31	<0.0001
DM	38	32	0.015
Prior MI	23	12	<0.0001
Prior PCI	10	5	0.0067
Prior CABG	2	1	0.27
Smoking	42	54	0.0015
HL	22	18	0.12
Family history of CAD	18	14	0.084
MI location			<0.0001
Anterior	54	53	
Inferior	32	41	
Prior stroke	4	1	0.0028
Chest pain	82	97	<0.0001
Resting HR (bpm)	84 (72–100)	80 (69–94)	0.030
SBP (mm Hg)	130 (110–150)	135 (120–152)	0.25
Peak CPK (mg/dL)	403 (175–161)	1471 (520–2903)	<0.0001
Peak CK-MB (mg/dL)	57 (26–120)	120 (56–244)	<0.0001
Ambulance use	14	20	0.032
Door-to-ECG time (min)	15 (10–30)	10 (5–16)	<0.0001
Killip class			<0.0001
I (n = 1862)	71	85	
II (n = 215)	16	9	
III (n = 79)	7	3	
IV (n = 49)	6	2	

	Shortfall N = 205	Reperfusion N = 2006	P Value
GRACE score			<0.0001
Low (n = 934)	33	49	
Intermediate (n = 598)	29	31	
High (n = 429)	38	20	
Medication use			
Aspirin	93	99	<0.0001
Clopidogrel	52	60	0.021
Unfractionated heparin	60	63	0.41
LMW heparin	33	31	0.60
IIb/IIIa inhibitors	10	9	0.73
β-Blockers	55	67	0.0008
ACEIs	54	66	0.0004
Statins	76	93	<0.0001
Nitrates	74	71	0.56
Diuretics	24	15	0.0002
EF (n = 1524)	50 (40–56)	48 (40–55)	0.34
Coronary angiography	17	21	0.204
Outcomes			
Death	9.3	2.8	<0.0001
Cardiogenic shock	13.7	6	0.0001
New-onset heart failure	22	14	0.0019
Major bleeding	1	1	0.92
Stroke	0	0.6	0.26

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CABG, coronary artery bypass graft; CAD, coronary artery disease; CK, creatine kinase; CK-MB, creatine kinase isoenzyme MB; DM, diabetes mellitus; ECG, electrocardiography; EF, ejection fraction; GRACE, Global Registry of Acute Coronary Events; HL, hyperlipidemia; HR, heart rate; HT, hypertension; LMW, low molecular weight; MI, myocardial infarction; n, number of patients; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; UAE, United Arab Emirates.
Continuous variables are summarized as median and interquartile ranges, and categorical variables are summarized as percentages.

reperfusion therapy, these patients received evidence-based therapies less often, including a lower rate of statins, β-blockers, and ACEIs. These patients had worse in-hospital outcomes, including higher rates of death (9.3% vs 2.8%), cardiogenic shock, and new-onset heart failure.

Table 4. Independent Predictors of Failure to Administer Appropriate Reperfusion Therapy Among STEMI Patients Presenting Within 12 Hours of Symptom Onset

	OR	95% CI	P Value
Age (per 10-y increase)	1.2	1.04–1.37	0.012
Prior stroke	5.3	2.6–10.5	<0.0001
No chest pain	1.6	1.4–1.8	<0.0001
HT	1.6	1.2-2.3	0.0046
Country: Yemen vs UAE	5.3	3.3–8.8	<0.0001

Abbreviations: CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; HT, hypertension; OR, odds ratio; SBP, systolic blood pressure; UAE, United Arab Emirates.
Model adjusted for age, gender, presentation heart rate, SBP, prior stroke, prior CAD, DM, use of ambulance, country, and chest pain on presentation (c-index 0.773).

The independent predictors of not receiving appropriate reperfusion therapy in the absence of contraindications are shown in Table 4 and include older age, prior stroke, being in Yemen, and lack of chest pain on presentation.

In-Hospital Mortality

In univariate analysis, lack of reperfusion therapy due to shortfall or delayed presentation was associated with increased in-hospital mortality (odds ratio [OR]: 3.9, 95% confidence interval [CI]: 2.9–5.4). Lack of appropriate reperfusion due to either delayed presentation or reperfusion shortfall was associated with a nearly 2-fold increase in in-hospital mortality (OR: 1.9, 95% CI: 1.2–3.0, $P = 0.0074$; c-index 0.889). Other independent predictors of increased mortality were female gender, prior angioplasty, atypical symptoms, and nonambulance presentation.

Discussion

Our analysis shows that in 2007, nearly one-third of patients with STEMI in the Arab Middle East presented to the hospital >12 hours after symptom onset, and nearly 1 in 10 eligible patients did not receive any reperfusion therapy. Lack of reperfusion was more common in sicker patients and those with prior stroke or no chest pain on presentation, and was independently associated with a >2-fold increase in short-term mortality.

This is the first report from the Arab Middle East that evaluated patient and physician factors associated with lack of appropriate reperfusion therapy. Our analysis is in agreement with previous reports from other registries. In a substudy of the National Registry of Myocardial Infarction (NRMI) in the United States, Ting and colleagues reported that the rate of delayed presentation (>12 hours) was 8.7%.[6,8] Older age, female gender, minority race, and diabetes mellitus were the independent predictors

of delayed presentation. Eagle et al reported that out of 2501 patients with STEMI enrolled in the GRACE study from 14 countries, only 1763 (70.5%) presented within 12 hours of symptom onset.[19] Cohen et al reported that 40% of acute STEMI patients presented >12 hours after symptom onset.[13] Recently, Tatu-Chitoiu et al reported that female gender and older age were independent predictors of late presentation in Romania.[12] In our study, nearly one-third of patients presented late. We also noted significant regional variation in the frequency of late presentation, suggesting that socioeconomic status and literacy rate may play an important role in late presentation. Future studies should evaluate potential factors contributing to delayed presentation and test whether specific programs directed toward this patient population impact the early presentation rate.

The lack of appropriate reperfusion therapy is not entirely the result of late presentation. Nearly 10% of early presenters did not receive appropriately indicated reperfusion therapy. This is lower than the previously reported shortfall rate that ranged from 22% in the Emergency Department Quality in Myocardial Infarction (EDQMI) registry to 30% in the GRACE registry.[7,13,19] However, we noted significant regional variability in the rate of shortfall (4%–21%), which raises the question of whether shortfall rate is a marker of quality of care. Our analysis supports this notion, because most patients who did not receive appropriate reperfusion therapy also did not receive other important evidence-based therapies. Increasing physician awareness of the evidence-based practice guidelines, including but not limited to indications of reperfusion therapy, may potentially increase the utilization of the urgently needed therapies and would potentially improve patient outcomes. In addition, wider availability of healthcare facilities with rigorous processes to improve STEMI patients' early identification and treatment may improve healthcare delivery and outcomes.

Our analysis also confirms the previous observations that lack of reperfusion therapy secondary to both late presentation or shortfall is an independent predictor of in-hospital mortality in patients with STEMI.[5,7] Given the high rate of late presentation in the Arab Middle East, community-awareness campaigns are needed, with special emphasis on women, older patients, and patients with prior stroke. Given the regional variation, these awareness campaigns may need to be prioritized to regions where late presenters are more frequent.

Our study has several limitations. Although our cohort included nearly consecutive patients with suspected ACS who live in 6 countries, we were able to include only 85% of patients in 3 of the countries. Nearly 60% of the study cohort had ejection fraction assessment, and only a minority of patients underwent coronary angiography. We did not have information about the socioeconomic status of patients and their literacy rate (the literacy rate is 28%, 53%, 89%, 89%, 91%, and 93% in Oman, Yemen, United Arab Emirates, Bahrain, Qatar, and Kuwait, respectively). Yemen is the largest country among the included countries and has the lowest income per capita.[20] In addition, we did not have information about the credentials of treating physicians, thus we could not evaluate the impact of specialized training on shortfall rate.

Conclusion

Nearly one-third of patients with STEMI in the Arab Middle East present to the hospital >12 hours after symptom onset, and nearly 1 in 10 eligible patients do not receive any reperfusion therapy. Community and physician awareness programs are needed to increase the utilization of appropriate lifesaving therapies.

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