Very late presentation in ST elevation myocardial infarction: Predictors and long-term mortality

Patrick W. McNair [a,1], Kenneth C. Bilchick [a,1], Ellen C. Keeley [b,*,1]

[a] Department of Medicine, Division of Cardiology, University of Virginia, Charlottesville, VA, United States of America
[b] Department of Medicine, Division of Cardiovascular Medicine, University of Florida, Gainesville, FL, United States of America

ARTICLE INFO

ABSTRACT

Background: Despite improvements in ST elevation myocardial infarction (STEMI) care, total ischemic time remains long in patients who present late. Our goal was to identify predictors of very late presentation (≥12 h) of STEMI and determine long-term mortality.
Methods: We retrospectively examined consecutive patients admitted with STEMI to our institution using the ACTION Registry™. Time of symptom onset to first medical contact (FMC) was calculated and categorized as <12 h or ≥12 h. Predictors of very late presentation were determined.
Results: Compared to patients who presented <12 h (n = 365), those who presented ≥12 h (n = 49) after symptom onset were more likely women, diabetics, and those with prior coronary revascularization. In addition, patients who presented ≥12 h had worse ventricular function, were less likely to report chest pain, and were less likely to be transported by ambulance and to undergo coronary angiography. Late presenters had higher rates of heart failure, longer hospitalizations, and were less likely to be discharged home. Diabetes, female sex, and absence of chest pain were strong predictors of late presentation. Long-term survival was significantly lower in late presenters (73% vs. 93%, p = 0.007).
Conclusions: Female sex, diabetes, and absence of chest pain are strong predictors of presentation delay, and long-term mortality is significantly increased in those presenting very late.

1. Introduction

Current guidelines recommend first medical contact (FMC) to device time of ≤90 min in the treatment of ST elevation myocardial infarction (STEMI) [1]. These guidelines underscore the importance of total ischemic time (time of vessel occlusion and symptom onset to the re-establishment of antegrade blood flow) and pre-hospital initiatives aimed to decrease it. Despite continued improvements in STEMI system-based care, total ischemic time remains unacceptably long in patients who are slow to recognize symptoms and seek medical attention. Prior studies assessing predictors of presentation delay in STEMI primarily focus on delays of <6 h [2–4]. However, the 12-hour mark after symptom onset remains relevant because it is the accepted timepoint used in decision-making regarding candidacy for reperfusion

therapy [1]. The aim of this study was to determine predictors of very late (≥12 h) presentation of STEMI and to assess long-term mortality in this patient population.

2. Methods

2.1. Study design

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the University of Virginia investigational review board. Due to the retrospective nature of the study protocol, the requirement for written informed consent from each patient was waived. We retrospectively examined consecutive patients admitted with STEMI to the University of Virginia using the ACTION Registry™ from January 2011 to December 2016. STEMI was defined by electrocardiogram (ECG) criteria as new ST segment elevation at the J-point in at least two contiguous leads of ≥0.2 mm in men or ≥1.5 mm in women in leads V_2-V_3 and/or ≥1 mm in other leads [1]. Reasons for exclusion included: unresponsive or cardiac arrest at FMC, a diagnosis other than STEMI, and undocumented symptom onset time or symptom description.

---

* Corresponding author at: University of Florida, Division of Cardiovascular Medicine, 1600 SW Archer Road, PO Box 100277, Gainesville, Florida 32610-0277, United States of America.
E-mail address: Ellen.Keeley@medicine.ufl.edu (E.C. Keeley).
[1] This author takes the responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

2.2. Data collection

Demographics, co-morbidities, presenting symptom (presence or absence of chest pain), time of symptom onset, time of FMC, vital signs at FMC, laboratory and echocardiographic data, coronary angiographic data, in-hospital outcomes, and long-term all-cause mortality were collected. In-hospital outcomes included acute heart failure, cardiogenic shock, cardiac arrest, stroke, and death. Time of symptom onset to FMC was calculated for each patient and categorized as <12 h or ≥12 h.

2.3. Statistical analysis

Continuous variables are displayed as medians with interquartile ranges and compared with Wilcoxon Rank Sum test. Categorical variables are displayed as absolute values with percentages of the total and compared using Chi-Square or Fisher's Exact test. Statistical analysis was 2-tailed and p-values of <0.05 were considered to be statistically significant. Based on the two-group Wilcoxon Rank Sum or Chi-Square tests, clinically relevant differences between the two groups were evaluated with univariable logistic regression models. A stepwise, multivariable logistic regression was performed using a p-value < 0.2 to enter the model and a p-value of <0.05 to remain in the model. Odds ratios and 95% confidence intervals (CI) were calculated. Long-term survival curves using Kaplan-Meier methodology were constructed and compared using the log-rank test. Hazard ratios with 95% CI were calculated using Cox proportional hazards regression. Mortality at 1 year was compared using Chi-Square. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

A total of 559 patients with STEMI between 2011 and 2016 were available in the ACTION Registry™ in our institution. A total of 145 were excluded (34 were unresponsive at FMC, 35 had a diagnosis other than STEMI, and 76 did not have their symptom onset or description documented). The analysis was based on the remaining 414 patients, of whom 365 (88%) had symptom onset to FMC time of <12 h, and 49 (12%) with symptom onset to FMC time of ≥12 h.

Nearly half of the very late presenters were women compared to 28% of patients presenting <12 h, and those who presented very late had higher rates of diabetes and prior coronary artery bypass surgery (Table 1). At FMC, very late presenters had higher heart rates and lower systolic blood pressures, and were less likely to be transported by emergency medical services (Table 2). Those who presented very late were less likely to report chest pain as their presenting symptom, and had lower left ventricular ejection fractions on the initial echocardiogram.

Very late presenters were less likely to be referred for coronary angiography or to undergo PCI (Table 3). During the index hospitalization, they were also more likely to develop acute heart failure, have longer lengths of stay, were less likely to be discharged to home, and more likely to be discharged to a rehabilitation center. In multivariable analysis, diabetes, female sex, and absence of chest pain were strongly associated with late presentation (c-statistic = 0.70) (Table 4).

Median follow-up for the entire cohort was 2.8 years (IQR 1.1–4.6). Survival was significantly lower in very late presenters at 1-year follow-up (73% vs. 93%, log-rank p ≤0.0001). A Kaplan-Meier survival curve showed increased long-term mortality in very late presenters (log-rank p = 0.007) (Fig. 1). Cox proportional hazard analysis calculated a hazard ratio of 2.3 (95% CI, 1.2–4.3, p = 0.009) for very late presenters compared to those presenting <12 h.

Table 1
Baseline patient characteristics.

Variable	<12 h	≥12 h	p-Value
	N = 365	N = 49	
Female sex	101 (28%)	23 (47%)	0.006
Age (years)	58 (50,68)	61 (54,71)	0.095
Race			0.380
White	306 (84%)	37 (76%)	
African American	42 (12%)	7 (14%)	
Hispanic	8 (2%)	2 (4%)	
Asian	9 (2%)	3 (6%)	
Body mass index (kg/m^2)	29 (26,34)	29 (25,33)	0.535
Family history of coronary artery disease	203 (56%)	26 (53%)	0.738
Tobacco use	256 (70%)	34 (69%)	0.914
Hypertension	231 (63%)	31 (63%)	0.998
Hyperlipidemia	169 (46%)	26 (53%)	0.373
Diabetes mellitus	91 (25%)	27 (55%)	<0.0001
Chronic obstructive pulmonary disease	33 (9%)	5 (10%)	0.791
Prior coronary artery disease	102 (28%)	12 (24%)	0.611
Prior myocardial infarction	82 (22%)	7 (14%)	0.191
Prior percutaneous coronary intervention	79 (22%)	7 (14%)	0.233
Prior coronary artery bypass surgery	9 (2%)	5 (10%)	0.005
Prior congestive heart failure	22 (6%)	6 (12%)	0.104
End stage renal disease on dialysis	6 (2%)	0 (0%)	1.000
Prior stroke	22 (6%)	5 (10%)	0.348
Peripheral arterial disease	34 (9%)	3 (6%)	0.600
Medications			
Aspirin	123 (34%)	15 (31%)	0.716
P2Y12 inhibitor	28 (8%)	2 (4%)	0.558
Anticoagulation	16 (4%)	3 (6%)	0.475
Beta-blocker	97 (27%)	14 (29%)	0.712
Angiotensin converting enzyme inhibitor	93 (25%)	15 (31%)	0.399
Statin	118 (32%)	20 (41%)	0.202

Data presented as number (%), median (IQR).

4. Discussion

We found that 12% of STEMI patients presented very late (≤12 h) after symptom onset. Patients who presented very late were more likely to be women and diabetics, and were less likely to present with chest pain. We also found that patients who presented very late were less likely to call 911 and be transported by ambulance, suggesting they did not perceive their symptoms to be an emergency. Our results concur with prior reports focused on predictors of delayed presentation in STEMI [2–6], and now extend to patients who present very late.

Longer total ischemic time has been associated with larger infarct size and increased mortality [7,8]. In a recent study, STEMI patients with pre-hospital delays of ≥12 h had worse left ventricular systolic function and higher rates of acute heart failure [5]. Similarly, we found

Table 2
Clinical data at first medical contact and test results.

Variable	<12 h	≥12 h	p-Value
	N = 365	N = 49	
Heart rate (beats per minute)	77 (65,90)	89 (74,106)	0.001
Systolic blood pressure (mmHg)	143 (124,167)	133 (110,157)	0.018
Acute congestive heart failure	49 (13%)	10 (20%)	0.189
Cardiogenic shock	24 (7%)	4 (8%)	0.760
Cardiac arrest	21 (6%)	3 (6%)	1.000
Transported by EMS (air and ground)	245 (67%)	22 (45%)	0.005
First medical contact to device (minutes)	93 (74,113)	104 (75,121)	0.264
Chest pain	312 (85%)	35 (71%)	0.012
No chest pain	53 (15%)	14 (29%)	
Chest pain within past 30 days	120 (33%)	11 (22%)	0.141
Initial troponin (ng/mL)	0.1 (0.0,0.8)	11.9 (2.5,24.9)	<0.0001
Peak troponin (ng/mL)	43 (17,91)	37 (13,113)	0.600
Initial creatinine (mg/dL)	1.0 (0.8,1.1)	1.0 (0.8,1.3)	0.586
Initial hemoglobin (g/dL)	14 (13,15)	13 (12.5,15)	0.033
Left ventricular ejection fraction (%)	48 (38,58)	43 (33,53)	0.003

Data presented as number (%), median (IQR).

Table 3
In-hospital outcomes and discharge status.

Variable	<12 h	≥12 h	p-Value
	N = 365	N = 49	
Referred for coronary angiography	360 (99%)	46 (94%)	0.023
Percutaneous intervention	346 (94%)	37 (76%)	<0.0001
Right coronary artery	170 (49%)	20 (54%)	0.259
Left anterior descending	123 (36%)	9 (24%)	
Left circumflex	45 (13%)	8 (22%)	
Other[a]	8 (2%)	0 (0%)	
Stent placement	315 (86%)	29 (59%)	<0.0001
Coronary artery bypass graft surgery	9 (2%)	1 (2%)	1.000
Cardiogenic shock	30 (8%)	8 (16%)	0.065
Acute congestive heart failure	18 (5%)	8 (16%)	0.002
Cardiac arrest	23 (6%)	3 (6%)	1.000
Stroke	1 (0.3%)	1 (2%)	0.223
Death	10 (3%)	2 (4%)	0.642
Hospital length of stay (days)	3 (2,4)	3 (3,7)	0.006
Discharge status			0.004
Home	345 (95%)	41 (84%)	
Rehabilitation	8 (2%)	5 (10%)	
Hospice	2 (1%)	1 (2%)	

Data presented as number (%), median (IQR).
[a] Other includes: Left Main, Ramus, and Internal Mammary Arterial graft.

that very late presenters had more hemodynamic compromise with higher heart rates and lower blood pressures on presentation. During the index hospitalization, very late presenters were found to have higher initial troponin levels, worse left ventricular systolic function, and higher rates of acute heart failure compared to patients who presented earlier, indicating a sicker patient population.

Previous evidence has associated increased pre-hospital delay with increased in-hospital mortality [9]. While we did not find a difference in in-hospital mortality between the groups, long-term mortality was significantly higher in very late presenters. This was largely driven by increased death within the first 6 months. We contend that very late presenters remain at increased risk for death after hospital discharge and may benefit from increased post-discharge surveillance. Our results are different from a recent study of long-term mortality in STEMI patients which did not find increased mortality in those presenting late, however, in this study "late" was defined as >60 min [6].

While prior studies have shown improved outcomes with revascularization in STEMI patients presenting between 12 and 48 h after symptom onset [10–12], current guidelines, partly based on the findings from the Occluded Artery Trial [13], recommend deferring reperfusion in patients presenting >12 h who do not show evidence of ongoing ischemia [1]. Nevertheless, reperfusion with primary PCI >12 h from symptom onset may attenuate the increased long-term mortality associated with very late presentation [11].
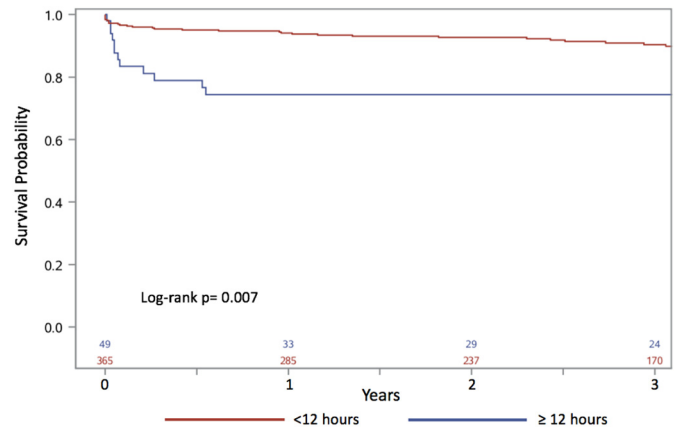
Despite significant reductions in door-to-balloon times through the mid-2000s [14,15], more recently this trend has plateaued [16], suggesting little room for further improvement. Moreover, pre-hospital

Fig. 1. Kaplan-Meier time to event model for long-term mortality.

delay for at-risk populations have decreased marginally [2], underscoring potential improvement possibilities within this metric. Despite impressive advances in STEMI care, a sizable proportion of patients (12% in our study) continue to present very late and are subjected to longer total ischemic times. While prior efforts to reduce pre-hospital delay have been suboptimal [17], novel educational initiatives regarding STEMI symptoms (including lack of chest pain) and the importance of seeking medical attention early should continue with a special focus on vulnerable populations, including women and diabetics.

4.1. Study limitations

Our study has several limitations. First, it was a retrospective study. Second, the population was predominantly white and our results may not be applicable to other patient populations. Third, symptom onset time was based on self-reported data which can be subject to recall bias. Fourth, we do not have information regarding the incidence of atrial fibrillation or mechanical complications of STEMI in our patient cohort.

5. Conclusions

Female sex, diabetes, and absence of chest pain are strong predictors of presentation delay in STEMI, and long-term mortality is significantly increased in those presenting very late.

Authors contributions

PWM and ECK designed this study. PWM collected data and entered it into a database. PWM, ECK and KCB analyzed the data. All authors wrote and critically revised the manuscript and all have approved the final submitted version.

Conflicts of interest

None.

Grant support

References

[1] P.T. O'Gara, F.G. Kushner, D.D. Ascheim, et al., 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, J. Am. Coll. Cardiol. 61 (2013) e78–140.

Table 4
Univariable and multivariable logistic regression.

Patient characteristic	Univariable		Multivariable	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Female sex	2.3 (1.3–4.2)	0.007	2.0 (1.1–3.8)	0.025
Age (by decade)	1.2 (1.0–1.5)	0.099		
Diabetes mellitus	3.7 (2.0–6.8)	<0.0001	3.4 (1.8–6.4)	<0.0001
Prior myocardial infarction	0.6 (0.2–1.3)	0.195		
Prior heart failure	2.2 (0.8–5.7)	0.111		
Prior coronary artery bypass	4.5 (1.4–14.0)	0.010		
Absence of chest pain during presentation	2.4 (1.2–4.7)	0.014	2.4 (1.2–4.8)	0.016
Chest pain in past 30 days	0.6 (0.3–1.2)	0.144		

OR = odds ratio.
CI = confidence interval.

[2] H.H. Ting, E.H. Bradley, Y. Wang, et al., Factors associated with longer time from symptom onset to hospital presentation for patients with ST-elevation, Arch. Intern. Med. 168 (2008) 959–968.

[3] R.J. Goldberg, P.G. Steg, I. Sadiq, et al., Extent of, and factors associated with delay to hospital presentation in patients with acute coronary disease (The GRACE Registry), Am. J. Cardiol. 89 (2002) 791–796.

[4] C. Nielsen, K.G. Laut, L.O. Jensen, J. Ravkilde, C.J. Terkelsen, S.D. Kristensen, Patient delay in patients with ST-elevation myocardial infarction: time patterns and predictors for a prolonged delay, Eur. Heart J. Acute Cardiovasc. Care (2016) 1–9.

[5] E. Cerrato, D. Forno, S. Ferro, A. Chinaglia, Characteristics, in-hospital management and outcomes of late acute ST-elevation myocardial infarction presenters, J. Cardiovasc. Med. 18 (2017) 567–571.

[6] B. Jager, S. Farhan, M. Rohla, et al., Clinical predictors of patient related delay in the VIENNA ST-elevation myocardial infarction network and impact on long-term mortality, Eur. Heart J. Acute Cardiovasc. Care 6 (3) (2017) 254–261.

[7] A. Guerchicoff, S.J. Brener, A. Maehara, et al., Impact of delay to reperfusion on reperfusion success, infarct size, and clinical outcomes in patients with ST-segment elevation myocardial infarction: the INFUSE AMI Trial (INFUSE-Anterior Myocardial Infarction), JACC Cardiovasc. Interv. 7 (2014) 733–740.

[8] A.E. Denktas, H.V. Anderson, J. McCarthy, R.W. Smalling, Total ischemic time: the correct focus of attention for optimal ST-segment elevation myocardial infarction care, JACC Cardiovasc. Interv. 4 (2011) 599–604.

[9] H.H. Ting, E.H. Bradley, Y. Wang, et al., Delay in presentation and reperfusion therapy in ST-elevation myocardial infarction, Am. J. Med. 121 (2008) 316–323.

[10] A. Schomig, J. Mehilli, D. Antoniucci, et al., Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset, JAMA 293 (2005) 2865–2872.

[11] A. Schomig, G. Ndrepepa, A. Kastrati, Late myocardial salvage: time to recognize its reality in the reperfusion therapy of acute myocardial infarction, Eur. Heart J. 27 (2006) 1900–1907.

[12] M. Gierlotka, M. Gasior, K. Wilczek, et al., Reperfusion by primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction within 12 to 24 hours of the onset of symptoms, Am. J. Cardiol. 107 (2011) 501–508.

[13] J.S. Hochman, G.A. Lamas, C.E. Buller, et al., Coronary intervention for persistent occlusion after myocardial infarction, N. Engl. J. Med. 355 (2006) 2395–2407.

[14] D.S. Menees, E.D. Peterson, Y. Wanj, et al., Door-to-balloon time and mortality among patients undergoing primary PCI, N. Engl. J. Med. 369 (2013) 901–909.

[15] A. Flynn, M. Moscucci, D. Share, et al., Trends in door-to-balloon time and mortality in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, Arch. Intern. Med. 170 (2010) 1842–1849.

[16] M.B. Yudi, G. Hamilton, O. Farouque, et al., Trends and impact of door-to-balloon time on clinical outcomes in patients aged <75, 75-84, and ≥85 years with ST-elevation myocardial infarction, Am. J. Cardiol. 120 (2017) 1245–1253.

[17] K. Dracup, S. McKinley, B. Riegel, et al., A randomized clinical trial to reduce patient prehospital delay to treatment in acute coronary syndrome, Circ. Cardiovasc. Qual. Outcomes 2 (2009) 524–532.