Original Research

Factors Associated with Delay in Seeking Health Care for Hospitalized Patients with Acute Coronary Syndromes: The GREECS Study

Christos Pitsavos, Georgia Kourlaba, Demosthenes B. Panagiotakos*, Christodoulos Stefanadis; for the GREECS Study Investigators

*First Cardiology Clinic, School of Medicine, University of Athens, *Department of Dietetics – Nutrition, Harokopio University, Athens, Greece*

Key words:
Extent of pre-hospital delay, characteristics of patients, in-hospital mortality.

Objective: To examine the particular features that characterized patients who arrived in the hospital relatively early compared to those who arrived relatively late after the onset of cardiac symptoms.

Methods: A sample of 6 hospitals located in Greek urban and rural regions was selected. In these hospitals we recorded almost all non-fatal admissions with first event an acute coronary syndrome, from October 2003 to September 2004. 2172 patients were included in the study (76% men, 24% women). The time delay from symptom onset to hospitalization was recorded. Socio-demographic, clinical, dietary and other lifestyle characteristics were also recorded.

Results: The overall median (25th, 75th percentiles) delay time was 3.5 (2, 8) h. Patients with a history of hypertension or diabetes mellitus, as well as those receiving diuretics and calcium antagonists, were more likely to seek medical care more than 6 h after the onset of symptoms. Patients who died in hospital had sought medical care later than those who survived ($p=0.008$). Moreover, the administration of thrombolytic therapy was inversely related with the time interval between the onset of symptoms and presentation to hospital. Median (25th, 75th percentiles) delay time was 2 (1, 4) h for patients who received such therapy and 4 (2, 11) h for those who did not ($p<0.001$).

Conclusion: Our findings indicate the need for developing community-wide educational approaches to reduce delay.

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Address:
Demosthenes B. Panagiotakos

46 Paleon Polemiston St. 166 74 Glyfada, Greece
e-mail:
d.b.panagiotakos@usa.net

It has been reported that the administration of reperfusion agents is associated with a reduction of up to 25% in in-hospital mortality after acute myocardial infarction.[1-3] Moreover, several studies have suggested that both the use of reperfusion strategies and their efficacy are inversely correlated with the time between the onset of symptoms suggestive of acute coronary disease and patients' arrival at the hospital for treatment. Regarding eligibility for thrombolytic therapy, findings from the Worcester Heart Attack Study have demonstrated that patients seeking medical care within the first hour of the onset of symptoms are more than 6 times more likely to receive thrombolytic therapy than are patients who delayed more than 6 hours.[4] Concerning the association of pre-hospital delay and benefits of thrombolytic therapy, there is clear evidence that early treatment, especially within the first "golden hour", can reduce both infarct size and subsequent disability and mortality.[5,6]

Despite the known importance of early intervention, delay in seeking medical care is common and constitutes a major unre-

solved public health problem. Delaying presentation at the hospital after the onset of symptoms has been attributed to misunderstanding of the seriousness of the signs and symptoms, psychological denial[7] and concerns about the implications of hospitalization. Previous studies have investigated factors associated with the delay in seeking medical care and suggested that a variety of demographic, behavioral and clinical characteristics account for this delay.[8-12] However, information relating the extent of delay and factors associated with the delay for each type of acute coronary syndrome are limited, since all studies conducted in the past, with the exception of GRACE,[12] included only patients with acute myocardial infarction. Moreover, whereas the profile of coronary heart disease patients in Greece has been widely investigated in three large scale, population-based studies,[13-15] information concerning pre-hospital delay time in patients with acute coronary syndromes in Greece is lacking.

Therefore, the primary aim of this work was to examine the extent of the delay in seeking medical care for patients hospitalized with acute coronary syndromes in Greece, as well as to investigate whether particular features characterized patients who arrived in the hospital relatively early compared to those who arrived relatively late after the onset of symptoms. A second goal of this work was to investigate whether delayed arrival in hospital represents an independent risk factor for in-hospital mortality.

Methods

Population of the study

The design and rationale of this study have been described in detail previously.[16] Briefly, from October 2003 to September 2004 we enrolled almost all consecutive patients (participation rate=98%) who entered the cardiology clinics or the emergency units of six major general hospitals in Greece (Hippokration hospital in Athens, and the general hospitals in Lamia, Karditsa, Halkida, Kalamata and Zakynthos island). With the exception of Athens—where there are several other hospitals—these hospitals cover the entire population of their regions.

Diagnosis of acute coronary syndromes

Pre-established criteria were used for the diagnosis of acute coronary syndromes. The definitions take into account clinical presentation, electrocardiographic findings, and the results of serum biochemical markers of necrosis. In particular, acute myocardial infarction was defined by a typical rise and gradual fall (troponin) or a more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: (a) ischemic symptoms, (b) development of pathologic Q waves on the ECG, (c) ECG changes indicative of ischemia (ST segment elevation or depression), or (d) coronary artery intervention (e.g. coronary angioplasty).[17] Unstable angina was defined by the occurrence of one or more angina episodes, at rest, within the preceding 48-hours, corresponding to class III of the Braunwald classification.[18] Finally, the study included only cases with discharge diagnoses of acute coronary syndromes: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA).

The study was approved by the Medical Research Ethics Committee of our Institution and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Other characteristics of the participants

In all patients a detailed medical history was recorded, including previous hospitalization for cardiovascular disease (i.e. coronary heart disease, stroke or other cardiovascular disease), presence and management of hypertension (medical records of blood pressure greater or equal to 140/90 mmHg or use of antihypertensive drugs), hypercholesterolemia (medical records of total serum cholesterol greater than 200 mg/dl or use of lipid lowering agents), renal failure (medical records of serum creatinine greater than 1.7 mg/dl), and diabetes mellitus (use of anti-diabetic medication or blood glucose greater than 125 mg/dl). In addition, we recorded the patients' familial medical history.[16]

Socio-demographic characteristics (i.e. age, sex, years of school, marital status and financial situation) were recorded for each patient. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Patients' lifestyle and behavioural characteristics, such as smoking habits (current, former, and rare or non-smokers as well as exposure to environmental cigarette smoke) and physical activity were also recorded.

The patient's physical activity level during the last year was assessed in terms of frequency (times per

week), duration (in minutes per time) and intensity of sports or occupation-related physical activity, based on a modified version of a self-reported questionnaire provided by the American College of Sports Medicine.[19] Participants who did not report any physical activities were defined as sedentary. For the rest of the participants we calculated a combined score by multiplying the weekly frequency, duration and intensity of physical activity.

Delay time was defined as the interval between the self-reported time of the onset of symptoms suggestive of an acute coronary event and the arrival time in the hospital. Based on delay time, patients were divided initially into 3 categories: those arriving at the hospital within 2 h (early arrival), those admitted between 2 and 6 h (intermediate arrival), and those seeking medical care at least 6 h after the onset of symptoms (late arrival). These cut points were chosen taking into account the fact that patients arriving earlier for medical care are more likely to receive thrombolytic therapy and benefit from this than those presenting for treatment after more prolonged delay. Subsequently, patients were divided into those admitted within 2 h (≤2 hours) and those admitted after 2 h (>2 hours). This 2-hour time point was chosen because it has been shown that the beneficial effect of fibrinolytic therapy is substantially higher in patients presenting within 2 h after symptom onset compared to those presenting later.[3]

Statistical analysis

Continuous variables are presented as mean values ± standard deviation. The categorical variables are presented as absolute and relative (%) frequencies. Differences in the distribution of characteristics in patients classified according to extent of pre-hospital delay were examined by chi-squared test for discrete variables, while t test and analysis of variance were used to examine differences between the different delay groups for continuous variables. Discriminant function analysis was used to determine which of the socio-demographic, clinical and behavioural characteristics best distinguished the three delay groups. Wilks' Lambda (Λ) was used to evaluate the contribution of each variable to the discrimination between the three delay groups. The smaller the Λ, the greater is the contribution of the respective variable to the discrimination. Multiple logistic regression analysis was used to identify the predictors of late (>2 h) versus early (≤2 h) arrival. Both the discriminant and logistic regression analysis initially included patient age, sex, marital, financial and educational status, smoking habits, physical activity level, medical history and use of lipid lowering agents, anti-hypertensive and anti-diabetic drugs. Final models were constructed by using the stepwise regression procedure. Finally, the effect of pre-hospital delay time on the in-hospital mortality was evaluated by the use of multiple logistic regression analysis, after controlling for potential confounders. A probability value of 5% was considered as statistically significant. All statistical calculations were performed using SPSS version 12.0 software (SPSS Inc, Chicago, Il, USA).

Results

Distribution of delay times

Figure 1 illustrates the distribution of pre-hospital delay time between patients hospitalized with STEMI and those hospitalized with NSTEMI or UA. The overall median (25th, 75th percentiles) delay time was 3.5 (2, 8) h. The median delay time was higher in patients with NSTEMI (4 h), followed by patients with UA (3.5 h), and those with STEMI (3 h). Moreover, 38% of patients sought medical care at least 6 h after the onset of symptoms (33% of patients with STEMI, 38% of patients with NSTEMI and 37% of patients with UA, $p<0.001$), while only 22% of patients presented at the hospital within 2 h from the onset of symptoms. Regarding the centers participating in the study, the median (25th, 75th percentiles) delay time was 2 (1, 6) h for patients admitted to Hippokration Hospital in Athens and 4 (2, 9) h for those admitted to the other 5 general hospitals ($p<0.001$). Among patients admitted to Hippokration, 56% were admitted within 2 h and 23% after 6 h from the onset of symptoms, while for the other hospitals the percentages were 33% and 32%, respectively ($p<0.001$).

Characteristics associated with time to hospital presentation

Table 1 illustrates various demographic, clinical and lifestyle characteristics of those admitted within 2 h, between 2 and 6 h and after 6 h from the onset of symptoms. These results are presented separately for those with STEMI and those with NSTEMI/UA (combined group), because the use of fibrinolytic strategies is more mandatory and more beneficial in patients with STEMI. Among patients with STEMI,

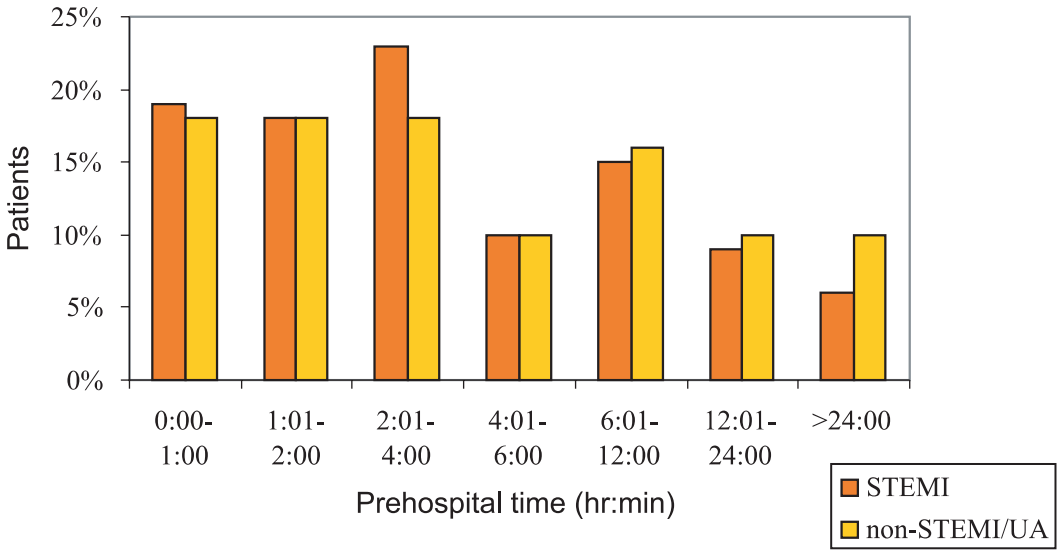

Figure 1. Distribution of pre-hospital delay time among patients with ST-segment elevation (STEMI) acute myocardial infarction and non-ST-segment elevation infarction or unstable angina (UA).

those who delayed seeking medical care for more than 6 h were more likely to be women, widowed, or elderly, to have a lower educational level, history of hypertension, diabetes mellitus, to be receiving diuretics and calcium antagonists, whereas they were less likely to be current smokers compared to those who arrived earlier. Regarding patients with NSTEMI /UA, those admitted early were more likely to have a history and family history of coronary heart disease, to be receiving calcium antagonists and to be current smokers, compared to those who delayed more than 2 h before seeking medical care.

A discriminant analysis was conducted to determine which factors from the socio-demographic, clinical and behavioral characteristics best discriminated between the three delay groups. It was observed that the factors that best distinguished group memberships were: center to which patients were admitted (urban versus rural centers) (Λ=0.956), treatment with calcium antagonists (Λ=0.984), history of coronary heart disease (Λ=0.987), smoking habits (Λ=0.989), gender (Λ=0.989), age (Λ=0.991).

Multiple logistic regression was performed to identify which socio-demographic, clinical or lifestyle characteristics of patients contributed statistically significantly to the prediction of late (>2 hours) versus early (≤2 hours) arrival at the hospital. The results of this analysis showed that elderly patients, those who had not experienced a prior coronary heart event, those receiving calcium antagonists and those living in rural regions (who sought medical care in the hospitals of Karditsa, Lamia, Halkida, Kalamata and Zakynthos island) were significantly more likely to delay seeking medical care (Table 2).

Delay time and in-hospital mortality

The median (25th, 75th percentiles) delay time was 6 (3, 11) h for patients who died and 3.5 (2, 8) h for those who survived (p=0.008). The inverse relationship between pre-hospital delay time and in-hospital mortality was stronger in patients with STEMI. Those who died included almost 4% of patients who presented at the hospital within 2 h and 11% of patients who sought medical attention 6 h after the onset of symptoms (p=0.04). Moreover, we observed that the likelihood of dying was almost 2.5 times higher in people who delayed coming to the hospital more than 2 h compared to those who arrived within 2 h (OR=2.3, 95% CI 1.23 to 4.22). To determine whether pre-hospital delay represents an independent risk factor for in-hospital mortality, we performed multiple logistic regression after controlling for baseline risk variables

Table 1. Characteristics associated with the extent of pre-hospital delay in patients with acute coronary syndromes.

	ST elevation AMI				Non-ST elevation AMI / Unstable Angina			
	<2 h 24%	2–6 h 43%	≥6 h 33%	p	<2 h 22%	2–6 h 41%	≥6 h 37%	p
Men	86%	85%	77%	0.021	76%	72%	70%	0.370
Age (years)	60±13	63±13	66±13	<0.001	66±13	67±12	68±12	0.03
Financial status:								
Low	11%	7%	8%		13%	10%	7%	
Medium	56%	60%	64%	0.230	58%	55%	57%	0.407
High	33%	33%	28%		29%	35%	36%	
Years of school	9±4	8±4	7±4	0.05	8±5	7±4	7±4	0.03
Marital status:								
Single	3%	7%	3%		6%	1%	5%	
Married	85%	82%	83%	0.003	76%	82%	79%	0.595
Divorced	5%	5%	1%		1%	2%	1%	
Widowed	7%	6%	13%		17%	15%	14%	
Hypertension	36%	48%	56%	0.002	57%	54%	59%	0.44
Hypercholesterolemia	52%	45%	46%	0.44	46%	48%	49%	0.79
Diabetes mellitus	27%	22%	34%	0.02	38%	31%	33%	0.216
Renal failure	2%	4%	6%	0.35	8%	4%	6%	0.38
Prior CHD	31%	28%	30%	0.856	66%	59%	50%	0.002
Family history of CHD	44%	36%	34%	0.152	46%	37%	33%	0.008
Physical inactivity	22%	21%	25%	0.61	20%	25%	18%	0.113
Current smoking	49%	45%	35%	0.01	34%	25%	24%	0.08
Prior medication:								
ACE inhibitors	6%	10%	14%	0.125	14%	16%	11%	0.202
B-blockers	7%	8%	8%	0.941	13%	12%	10%	0.715
Diuretics	3%	9%	12%	0.01	14%	13%	11%	0.739
Calcium antagonists	7%	7%	15%	0.014	10%	13%	20%	0.004
Statins	13%	12%	13%	0.849	21%	13%	16%	0.242

ACE – angiotensin converting enzyme; AMI – acute myocardial infarction; CHD – coronary heart disease.

Table 2. Factors significantly associated with prehospital delay of >2 h. Results from multiple logistic regression.

Characteristics	Overall Adjusted OR (95% CI)	ST-segment elevation AMI Adjusted OR (95% CI)	Non-ST-segment elevation AMI/Unstable Angina Adjusted OR (95% CI)
Hypertension (y/n)	-	1.55 (1.08-2.23)	-
Age (years)	1.01 (1.002-1.02)	1.02 (1.004-1.03)	-
Urban vs. rural region	0.40 (0.30-0.53)	0.28 (0.18-0.43)	0.45 (0.32-0.64)
History of CHD (n/y)	1.47 (1.17-1.84)	-	1.60 (1.21-2.11)
Calcium antagonism (y/n)	1.98 (1.38-2.84)	-	1.90 (1.26-2.87)

AMI – acute myocardial infarction; CHD – coronary heart disease; CI – confidence interval; OR – odds ratio.

Urban refers to Hippokration hospital, Athens, and rural to the general hospitals in Lamia, Karditsa, Halkida, Kalamata and Zakynthos island.

that could not be influenced by time between onset of symptoms and hospital arrival. From this analysis, we observed that the pre-hospital delay remained a statistically significant predictor of in-hospital mortality even after adjustment for potential confounders (Table 3).

Table 3. Effect of pre-hospital delay on in-hospital mortality after adjustment for potential confounders.

	OR	95% CI	p
Late vs. early arrival	3.2	1.22-8.59	0.018
Age (years)	1.08	1.03-1.12	<0.001
Male vs. female	0.56	0.26-1.18	0.128
Diabetes mellitus (y/n)	2.16	1.03-4.52	0.04
Hypertension (y/n)	0.53	0.25-1.10	0.09
Hypercholesterolemia (y/n)	1.88	0.90-3.94	0.09
Smokers vs. no smokers	0.91	0.31-2.64	0.871
BMI (kg/m2)	0.97	0.88-1.06	0.522
Renal failure (y/n)	4.27	1.68-10.8	0.002
History of CHD (n/y)	1.28	0.62-2.61	0.494

BMI – body mass index; CHD – coronary heart disease; CI – confidence interval; OR – odds ratio. Late arrival means >2 h, early arrival ≤2 h.

Delay time and management

Thrombolytic therapy was administered to 57% of STEMI patients. The administration of thrombolytic therapy was inversely related with the time interval between the onset of symptoms and admission. Median (25th, 75th percentiles) delay time was 2 (1, 4) h for patients who received such therapy and 6 (3, 12) h for those who did not ($p<0.001$). Among those admitted within the 2 first hours, 76% received fibrinolytic agents, while for those arriving at the hospital after between 2 and 6 h and those who delayed more than 6 h the respective percentages were 63% and 20% ($p<0.001$).

Discussion

In this paper we present the findings relating to the extent of delay in seeking medical care after the onset of symptoms in patients hospitalized with acute coronary syndromes in Greece. Our results demonstrate that delay time in Greece is prolonged. Median delay time was 3.5 hours, while more than one in three patients arrived at the hospital after 6 hours from the onset of symptoms. This median time is higher than those calculated in some previous studies and lower than in others. Recently, a study conducted to examine gender differences in the reasons for individual delay in seeking treatment for acute myocardial infarction symptoms found that the median delay time was 3.1 h (3.08 and 3.1 for men and women, respectively).[20] According to the results of the Second National Registry of Myocardial Infarction, median delay times did not change between 1994 and 1997 (2 hours).[10] Finally, a median delay of 2.0 hours was observed in patients enrolled in the large multicenter Rapid Early Action for Coronary Treatment trial.[21]

Regarding diagnosis, patients hospitalized with STEMI sought medical care earlier than patients with NSTEMI and those with UA (median delay time 3 h vs. 4 h vs. 3.5 h). That may be attributed to the more severe symptoms (i.e. stronger chest pain, dyspnea, etc.) that STEMI patients may have experienced. However, we observed that although patients with STEMI presented at the hospital earlier than patients with NSTEMI and UA, they still exhibited prolonged delay. The majority of STEMI patients (62%) delayed more than 2 h before being admitted to hospital, resulting in a reduced beneficial effects of reperfusion therapies.

A number of socio-demographic, clinical and behavioral factors have been associated with late presentation at hospital for treatment after the onset of acute coronary symptoms.[22,23] Our findings are in agreement with previous published reports declaring that older people experienced longer delay in seeking medical attention compared to younger.[8-12,24,25] This could be due to older people having limited access to medical care, especially when they live in rural areas or alone. Furthermore, elderly people may not recognize the symptoms of acute coronary disease or appreciate their severity.

Women delayed seeking medical care more than men.[8-12,24] This could be attributed to the low incidence of acute coronary syndromes in the female population. A frequent observation by women is that heart attack is “a male problem”; therefore, they ignore the signs and symptoms of coronary heart disease. Additionally, differences between men and

women in age, co-morbid conditions and other socio-demographic and behavioral characteristics may account for the discrepancy in delay time between genders. This conclusion is also supported by the fact that sex is not a statistically significant predictor for delay arrival in the multiple logistic model.

Our results indicate that patients with a history of coronary heart disease sought hospital care earlier than those without such history. This is understandable, since the former patients would have been counseled about the importance of seeking medical advice quickly if symptoms of acute coronary disease recurred.

Patients receiving calcium antagonists had a longer delay in seeking medical care after the onset of symptoms. This may be attributed to the false perception that patients who control their hypertension with medication cannot develop acute coronary disease. Also, psychological reasons, especially denial of the possibility that they may suffer from acute coronary disease, might cause this prolonged delay.

Concerning the relationship of pre-hospital time and in-hospital mortality, our results demonstrate that patients who arrived late at the hospital had a higher likelihood of dying than those who arrived within the 2 first hours from the onset of symptoms. Moreover, it was observed that late arrival was an independent predictor for in-hospital mortality of patients with acute coronary syndromes. This means that the baseline differences between early and late arrivers cannot explain the reduced benefit of interventions in acute myocardial infarction carried out late after the onset of chest pain. This is in contrast to the results of a previous study showing that the baseline differences between the populations account for the higher mortality rate among late arrivers.[24]

Study limitations

In our study we did not collect data for some variables that other studies have demonstrated might be associated with the duration of pre-hospital delay. These include the time of day that symptoms appeared, the symptoms which led them to seek medical care, and the means of transportation to the hospital. In addition, we did not record data about the use of aspirin or other antiplatelet drugs. Therefore, we cannot examine whether or not the use of these drugs can affect the delay time, as calcium antagonists do. Furthermore, the inclusion of only 6 hospitals from selected Greek regions makes the generalization of the findings of the study very difficult. Finally, concerns might be raised about the accuracy of the self-reported time of onset of acute symptoms that led them to seek medical advice.

Conclusions

Our findings indicate the need for developing community-wide educational approaches to reduce delay in seeking medical care. Patients with a history of diabetes mellitus and hypertension are at increased risk for acute myocardial infarction as well as for prolonged delay. Therefore, these patients constitute a high risk group towards whom educational efforts should be directed. In particular, these patients should receive instructions regarding the possible meaning of a change in symptoms, how to appreciate the severity of symptoms that should lead them to seek medical attention, and what they may gain from early presentation to the hospital after the onset of symptoms.

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