ACUTE CORONARY SYNDROMES

Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events

B K Nallamothu, K A A Fox, B M Kennelly, F Van de Werf, J M Gore, P G Steg, C B Granger, O H Dabbous, E Kline-Rogers, K A Eagle, on behalf of the GRACE Investigators

Heart 2007;**93**:1552–1555. doi: 10.1136/hrt.2006.112847

See end of article for authors' affiliations

Correspondence to: Kim A Eagle, University of Michigan Cardiovascular Center, 300 N. Ingalls, 8B02, Ann Arbor, MI 48109-0477, USA; keagle@umich.edu

Accepted 3 April 2007
Published Online First 25 June 2007

Objective: Treatment delays may result in different clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) who receive fibrinolytic therapy vs primary percutaneous coronary intervention (PCI). The aim of this analysis was to examine how treatment delays relate to 6-month mortality in reperfusion-treated patients enrolled in the Global Registry of Acute Coronary Events (GRACE).
Design: Prospective, observational cohort study.
Setting: 106 hospitals in 14 countries.
Patients: 3959 patients who presented with STEMI within 6 h of symptom onset and received reperfusion with either a fibrin-specific fibrinolytic drug or primary PCI.
Main outcome measures: 6-month mortality.
Methods: Multivariable logistic regression was used to assess the relationship between outcomes and treatment delay separately in each cohort, with time modelled with a quadratic term after adjusting for covariates from the GRACE risk score.
Results: A total of 1786 (45.1%) patients received fibrinolytic therapy, and 2173 (54.9%) underwent primary PCI. After multivariable adjustment, longer treatment delays were associated with a higher 6-month mortality in both fibrinolytic therapy and primary PCI patients ($p<0.001$ for both cohorts). For patients who received fibrinolytic therapy, 6-month mortality increased by 0.30% per 10-min delay in door-to-needle time between 30 and 60 min compared with 0.18% per 10-min delay in door-to-balloon time between 90 and 150 min for patients undergoing primary PCI.
Conclusions: Treatment delays in reperfusion therapy are associated with higher 6-month mortality, but this relationship may be even more critical in patients receiving fibrinolytic therapy.

Treatment delays in the delivery of fibrinolytic therapy and primary percutaneous coronary intervention (PCI) are associated with increased rates of mortality in patients with ST-segment elevation myocardial infarction (STEMI).[1 2] However, there is controversy as to whether treatment delays in primary PCI are less important than those in fibrinolytic therapy, especially when fibrin-specific agents are utilised.[3] This is important because a differential effect of treatment delays on outcomes may influence the selection between these two reperfusion strategies.[3–7] Accordingly, using data from the ongoing, multinational Global Registry of Acute Coronary Events (GRACE), we examined how treatment delays relate to 6-month mortality in patients with STEMI who received fibrinolytic therapy with a fibrin-specific agent or primary PCI. GRACE provides an ideal resource for such an investigation because it includes patients who received both types of reperfusion strategies, and the data for each strategy are collected under identical circumstances.

METHODS

Study population

GRACE is a prospective, observational cohort study designed to reflect an unselected population of patients with acute coronary syndromes (ACS). To date, a total of 106 hospitals in 14 countries in Europe, North and South America, Australia and New Zealand have contributed data to the study. Full details of the GRACE methods have been published elsewhere.[8 9]

In brief, patients admitted with ACS as a presumptive diagnosis (ie, have symptoms consistent with acute myocardial ischaemia) are screened for at least one of the following: electrocardiographic changes consistent with ACS, serial increases in serum cardiac biomarkers, and/or documentation of coronary artery disease. In addition, the qualifying ACS must not have been precipitated by significant noncardiovascular comorbidity such as acute anaemia or hyperthyroidism. To enrol an unselected population of patients with ACS, sites are encouraged to recruit the first 10–20 consecutive eligible patients each month. Regular audits are performed at all participating hospitals.

Data were collected by trained abstractors using a standardised case report form. Demographic characteristics, medical history, presenting symptoms, biochemical and electrocardiographic findings, treatment practices and a variety of hospital outcome data were collected. Standardised definitions for all patient-related variables and clinical diagnoses were used. At discharge, all cases were assigned to STEMI, non-STEMI, or unstable angina categories. At approximately 6 months after hospital discharge, patients who survived were contacted to ascertain vital status. Standardised definitions were used for selected hospital complications and outcomes. At each institution, study investigators worked with the ethics or institutional review boards to obtain appropriate approval to participate.

Abbreviations: ACS, acute coronary syndromes; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombosis in Myocardial Infarction

For this analysis, we limited our study population to those patients aged ⩾18 years, admitted with STEMI, who presented to the admitting hospital within 6 h of symptom onset, and who received reperfusion therapy with either fibrinolytic therapy with a fibrin-specific agent or primary PCI. We specifically excluded patients receiving streptokinase to better represent contemporary fibrinolytic therapy with fibrin-specific drugs.[10] However, the inclusion of patients who received streptokinase (n = 950) in a sensitivity analysis did not qualitatively affect our results (data not shown).

Statistical analysis

The primary end point for this analysis was 6-month mortality. The predictor variable of interest was time to treatment, which was defined as the door-to-needle time for patients receiving fibrinolytic therapy and the door-to-balloon time for patients undergoing primary PCI. Unadjusted analyses evaluated differences in baseline characteristics between patients who underwent primary PCI and those who received fibrinolytic therapy using Wilcoxon sum-rank test for continuous variables and chi-squared tests for categorical variables.

Multivariable logistic regression was used to assess the relationship between 6-month mortality and treatment delays separately in both groups of patients. We modelled treatment delay as a quadratic term in both models to account for the possibility of a nonlinear relationship. In addition, we adjusted for several covariates associated with in-hospital and 6-month mortality from the GRACE risk scores[11 12]—age, cardiac arrest, Killip classification, systolic blood pressure, pulse, creatinine, ST-changes, and elevated biomarkers—as well as the time from symptom onset to presentation.

We report the relationship between each additional minute of treatment delay and increasing 6-month mortality for both groups as treatment delay extended beyond guideline-recommended goals: from 30 to 60 min for door-to-needle time in fibrinolytic therapy, and from 90 to 150 min for door-to-balloon time in primary PCI. Estimates of 6-month mortality were calculated after setting additional covariates to the mean values for the entire cohort. A p value of less than 0.05 was considered statistically significant. All analyses were performed using Stata version 8 (Stata Corporation, College Station, TX) and SAS version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 3959 patients were included in the final analysis. Of these, 1786 (45.1%) received fibrinolytic therapy, and 2173 (54.9%) underwent primary PCI. Table 1 lists the baseline characteristics in the fibrinolytic therapy and primary PCI patients. In comparison with patients treated with fibrinolytic therapy, those undergoing primary PCI were younger (median age, 61 vs 63 years; p = 0.06), more likely to have had prior PCI (9.5% vs 5.6%; p<0.001), and had longer delays from symptom onset to presentation (median delay, 120 vs 104 min; p⩽0.001). These differences in baseline characteristics between the two groups reflect potential biases in the selection of a particular reperfusion strategy for individual patients. In addition, patients who received fibrinolytic therapy had a median door-to-needle time of 35 min (interquartile range (IQR), 20 to 62 min), and patients who underwent primary PCI had a median door-to-balloon time of 78 min (IQR, 47 to 120 min).

After multivariable adjustment, longer treatment delays were associated with a higher 6-month mortality in both fibrinolytic therapy and primary PCI patients (p<0.001 for both cohorts). For patients who received fibrinolytic therapy, 6-month mortality increased by 0.30% per 10-min delay in door-to-needle time between 30 and 60 min (95% confidence interval, 0.22% to 0.40% per 10-min delay) (fig 1). For patients who underwent primary PCI, 6-month mortality increased by 0.18% per 10-min delay in door-to-balloon time between 90 and 150 min (95% confidence interval, 0.08 to 0.35% per 10-min delay) (fig 2).

DISCUSSION

We found that treatment delays with either fibrinolytic therapy or primary PCI were associated with a higher 6-month mortality in patients with STEMI receiving reperfusion therapy. Furthermore, this relationship appeared to be less steep in patients undergoing primary PCI than in those receiving fibrinolytic therapy. Understanding the overall association between treatment delays and outcomes in reperfusion therapy for STEMI is critical for improving the selection and delivery of both fibrinolytic therapy and primary PCI in individual patients.

Primary PCI is widely recognised as superior to fibrinolytic therapy for establishing reperfusion in patients with STEMI. However, PCI is unavailable in many hospitals, and there are potential delays in its delivery particularly for patients presenting during off-hours or those undergoing inter-hospital transfer.[13 14] Fibrinolytic therapy has the advantage of being delivered rapidly without the need for specialised resources or personnel, but it is associated with higher rates of reinfarction and intracerebral haemorrhage. The relationship between treatment delay and clinical outcomes is increasingly being recognised as a key determinant in the choice between reperfusion therapies. This is one reason why current STEMI guidelines from the American Heart Association/American College of Cardiology do not recommend one universal approach for all patients in all settings.

Our finding of a steeper relationship between treatment delay and clinical outcomes in patients who received fibrinolytic therapy was not entirely unexpected, and we postulate two reasons for this difference. First, the efficacy of fibrinolytic therapy at re-establishing TIMI 3 flow diminishes with longer treatment delays leading to worse clinical outcomes.[15] This is potentially due to enhanced thrombus organisation over time within the infarct-related artery. Primary PCI ''mechanically'' disrupts the thrombus, and therefore its ability to re-establish TIMI 3 flow is less time-dependent.[16] Another possibility is that longer treatment delays are associated with more complex patients—for example, older, more comorbidities, longer delays to presentation—who may be more likely to have bleeding complications with fibrinolytic therapy.

Our findings add to previous literature on the relationship between treatment delays and clinical outcomes for reperfusion therapy. Recent observations have confirmed a direct relationship between treatment delays and clinical outcomes in patients treated with primary PCI.[17 18] In 2003, Schomig and colleagues evaluated the relationship between treatment delays from symptom onset and myocardial salvage after reperfusion using scintigraphic examinations in patients with STEMI.[19] In that study, treatment delays were closely related to myocardial salvage in patients treated with fibrinolytic therapy but had less impact on those who underwent primary PCI. A recent report by Stenestrand *et al*[20] found that primary PCI demonstrated substantial benefits when compared with in-hospital and prehospital fibrinolytic therapy despite the potential for greater treatment delays. Pinto *et al*[21] also showed that treatment delays may be better tolerated with primary PCI; however, these investigators noted that the choice of reperfusion therapy also depended on other factors like age and infarct location. Our findings confirm and expand on these earlier observations by focusing on the important time interval from hospital arrival to treatment and addressing long-term clinical outcomes.

Table 1 Baseline characteristics in patients treated with either fibrinolytic therapy or primary percutaneous coronary intervention

	Fibrinolytic therapy (n = 1786)	Primary PCI (n = 2173)
Demographics		
Median age, years (IQR)	63 (53 to 73)	61 (53 to 72)
Women, %	26	24
Clinical characteristics, %		
Prior myocardial infarction	17	14
Prior heart failure	4.2	2.0
Prior coronary intervention	5.6	9.5
Prior bypass surgery	3.6	2.8
Smoker (current or former)	64	64
Diabetes	17	18
Hypertension	45	48
Hyperlipidaemia	35	38
Clinical presentation		
Median pulse, beats per min (IQR)	74 (62 to 87)	75 (64 to 88)
Median systolic blood pressure, mm Hg (IQR)	138 (120 to 157)	130 (114 to 151)
Median diastolic blood pressure, mm Hg (IQR)	80 (70 to 92)	80 (69 to 90)
Cardiac arrest, %	4.1	4.7
Killip class II, %	11	11
Killip class III, %	2.3	1.8
Killip class IV, %	1.0	2.9
ST-segment deviation on electrocardiogram, %	99	99
Positive cardiac biomarkers, %	38	49
Median serum creatinine, mg/dL (IQR)	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.2)
Median time delay, min (IQR)		
From symptom onset to presentation	104 (60 to 108)	120 (70 to 186)
From door to treatment*	35 (20 to 62)	78 (47 to 120)

*For fibrinolytic therapy, door-to-needle time; for primary PCI, door-to-balloon time.
IQR, interquartile range; PCI, percutaneous coronary intervention.

STRENGTHS AND LIMITATIONS

GRACE is the largest multinational registry to include the complete spectrum of patients with ACS, including almost 70 000 patients from 14 countries. The participating centers reflect regional practices and outcomes but do not necessarily reflect practice for specific countries. Standardised criteria are employed for defining ACS and hospital outcomes, and rigorous quality control and audit measures are employed. ''Real life'' studies such as GRACE offer the advantage that they provide data on a heterogeneous patient population that includes groups who are often under-represented in randomised trials, such as women and older people, which enhances the generalizability of the study findings to various hospital and healthcare systems.[11] Nevertheless, as a non-randomised observational study, GRACE is subject to certain inherent limitations and potential biases including the collection of non-randomised data, missing or incomplete information, and potential confounding by drug indication or other unmeasured covariates, which must be kept in mind when interpreting the study results. Despite our use of validated clinical risk-adjustment models during our analyses, residual confounding may still explain some of the difference in treatment delays between patients treated with fibrinolytic therapy and those who underwent primary PCI. This is important because there were considerable differences between patients who received these two reperfusion strategies. For example, patients treated with fibrinolytic therapy were younger and more likely to have had prior PCI, but had longer delays from symptom onset to presentation. If these differences led to varying degrees of

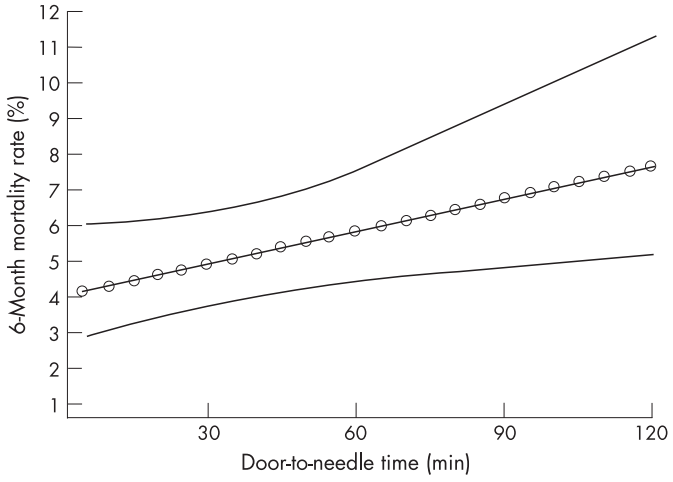

Figure 1 Relationship between door-to-needle time and 6-month mortality in patients who received fibrinolytic therapy. 95% confidence intervals are shown.

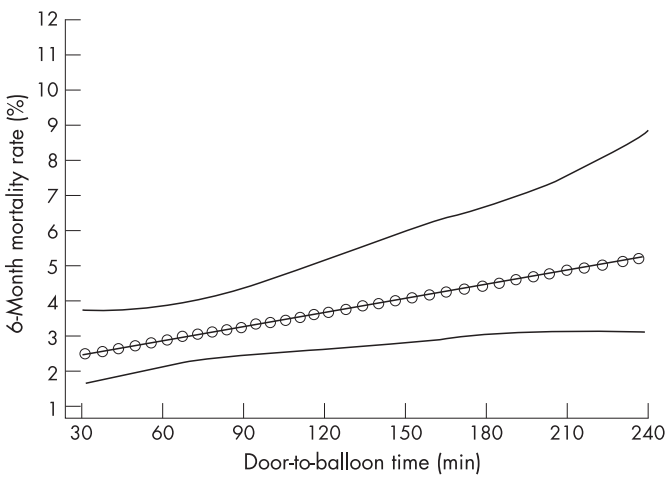

Figure 2 Relationship between door-to-balloon time and 6-month mortality in patients who underwent primary percutaneous coronary intervention. 95% confidence intervals are shown.

residual confounding across the two groups, our findings may be somewhat biased. This issue also limits our ability to interpret the absolute differences in 6-month mortality between patients treated with fibrinolytic therapy and those who underwent primary PCI.

CONCLUSIONS

Treatment delays in the delivery of fibrinolytic therapy and primary PCI increase mortality in patients with STEMI. Although treatment delays are longer in primary PCI, their relationship with clinical outcomes is more gradual than that seen with fibrinolytic therapy. This important differential effect of treatment delays on outcome may influence the selection between these two reperfusion strategies in STEMI patients.

ACKNOWLEDGEMENTS

The authors thank the physicians and nurses participating in GRACE. Further information about the project, along with the complete list of participants, can be found at http://www.outcomes.org/grace. The authors are grateful to Sophie Rushton-Smith, PhD, for editorial support in the preparation of this manuscript.

CONTRIBUTORS

GRACE Scientific Advisory Committee: Keith A A Fox, UK; Joel M Gore, USA (GRACE Co-Chairs); Kim A Eagle, USA; Philippe Gabriel Steg, France (GRACE Publication Committee Co-Chairs); Frederick A Anderson Jr, USA (Director, GRACE Study Coordinating Center); additional Members of the GRACE Scientific Advisory Committee: Giancarlo Agnelli, Italy; Álvaro Avezum, Brazil; David Brieger, Australia; Andrzej Budaj, Poland; Marcus D Flather, UK; Robert J. Goldberg, USA; Shaun G Goodman, Canada; Christopher B Granger, USA; Dietrich C Gulba, Germany; Enrique P Gurfinkel, Argentina; Brian M Kennelly, USA; Werner Klein (deceased), Austria; José López-Sendón, Spain; Gilles Montalescot, France; Frans Van de Werf, Belgium.

Authors' affiliations

B Nallamothu, VA Health Services Research & Development Center of Excellence, Ann Arbor VA Medical Center, Ann Arbor, USA
K A A Fox, Cardiovascular Research, Division of Medical & Radiological Sciences, The University of Edinburgh, Edinburgh, UK
B M Kennelly, Department of Cardiology, Hoag Memorial Hospital Presbyterian, Newport Beach, USA
F Van de Werf, Department of Cardiology, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium
J M Gore, Division of Cardiovascular Medicine, University of Massachusetts Medical School, Worcester, USA
P G Steg, Cardiology, Hôpital Bichat, Paris, France
C B Granger, Duke University Medical Center, Durham, USA
O H Dabbous, Center for Outcomes Research, University of Massachusetts Medical School, Worcester, USA
K A Eagle, E Kline-Rogers, University of Michigan Medical School, Ann Arbor, USA

Funding: GRACE is funded by an unrestricted educational grant from sanofi-aventis (Paris, France) to the Center for Outcomes Research, University of Massachusetts Medical School (Worcester, MA).

Competing interests: B K Nallamothu: none. K A A Fox: British Heart foundation, Medical Research Council, The Wellcome Trust, Aventis, Sanofi Synthelabo, GlaxoSmithKline, Bristol-Myers Squibb. B M Kennelly: sanofi-aventis. F Van de Werf: sanofi-aventis. J M Gore: sanofi-aventis. P G Steg: Speakers bureau; Boehringer-Ingelheim, BMS, GSK, MSD, Novartis, Nycomed, sanofi-aventis, Sankyo, Servier, ZLB-Behring. Consulting/advisory board: AstraZeneca, BMS, GSK, MSD, Pfizer, sanofi-aventis, Servier, Takeda. Stockholding: none. C B Granger: sanofi-aventis, Procter and Gamble, Alexion, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Novartis, The Medicines Company. O H Dabbous: none. E Kline-Rogers: none. K A Eagle: Biosite, Bristol Myers Squibb, Cardiac Sciences, Blue Cross Blue Shield of Michigan, Hewlett Foundation, Mardigian Fund, Pfizer, sanofi-aventis, Varbedian fund, National Heart, Lung & Blood NIH.

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