

Trends in acute reperfusion therapy for ST-segment elevation myocardial infarction from 1999 to 2006: we are getting better but we have got a long way to go

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Received 24 January 2007; revised 14 January 2008; accepted 1 February 2008

See page 571 for the editorial comment on this article (doi:10.1093/eurheartj/ehn277)

This paper was guest edited by Prof. Maarten L. Simoons, Dept. of Cardiology—Thoraxcenter, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands

Aim	Many patients who are eligible for acute reperfusion therapy receive it after substantial delays or not at all. We wanted to determine whether over the years more patients are receiving reperfusion therapy.
Methods and results	This analysis is based on 10 954 patients with ST elevation or left bundle-branch block presenting within 12 h of symptom onset and enrolled in the GRACE registry between April 1999 and June 2006. Over this time, there was an increasing trend in use of primary percutaneous coronary intervention (PCI) from 15% to 44% ($P < 0.001$), while use of fibrinolytic therapy decreased (from 41 to 16%; $P < 0.01$). No trend in median time to primary PCI was seen but that for fibrinolysis declined significantly (from 40 to 34%; $P < 0.0001$). Hospital mortality declined (6.9–5.4%; $P < 0.01$); the relationship between observed and expected mortality improved over time ($P = 0.06$). Nevertheless, 33% of patients still received no reperfusion therapy. Factors associated with reperfusion use included age; prior myocardial infarction, heart failure or coronary artery bypass graft surgery; history of diabetes; female sex; and delay from symptom onset to hospital arrival. In 2006, 52% of patients receiving fibrinolysis had door-to-needle times >30 min and 42% of those undergoing primary PCI had door-to-balloon times >90 min.
Conclusion	Primary PCI is now used much more than fibrinolysis. Although hospital mortality and delays to fibrinolytic reperfusion have improved, over 40% of patients reperfused still receive it outside the time window recommended, and one-third of potentially eligible patients receive no reperfusion.
Keywords	Reperfusion therapy • Fibrinolysis • Percutaneous coronary intervention • Hospital mortality

Introduction

Acute reperfusion therapy with either primary percutaneous coronary intervention (PCI) or fibrinolysis reduces mortality in eligible

patients with ST-segment elevation myocardial infarction (STEMI).^{1,2} Despite this, earlier reports suggest that a substantial proportion of patients receive inadequate therapy—either too late or, in some instances, not at all.^{3,4} Guidelines from both

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Europe and the United States have emphasized the need for identifying patients early and minimizing delays in the delivery of reperfusion therapy, citing studies that have established improved outcomes with rapid treatment.^{5,6} Recent meta-analyses of randomized clinical trials have suggested that primary PCI may offer some advantages when compared with fibrinolysis in patients who are eligible for both treatments.^{7,8} However, the primary objective of contemporary management for STEMI is to treat more patients with any type of reperfusion therapy.⁹ Depending on local facilities, the optimal approach is either immediate (including pre-hospital) fibrinolysis or rapid transfer to a high-volume tertiary care centre for primary PCI.⁹

The goals of this study were to assess overall trends in the use of reperfusion therapy for patients with STEMI using data from the Global Registry of Acute Coronary Events (GRACE). We were particularly interested in determining whether the number of eligible patients receiving any form of reperfusion therapy is increasing; if the speed with which reperfusion therapy is delivered is improving; and whether these potential trends are associated with changes in hospital mortality rates.

Methods

Population study

Detailed information on the data-collection methods for GRACE has been published elsewhere.^{10,11} Briefly, GRACE has been designed to reflect an unbiased, representative population of patients with acute coronary syndromes (ACS). However, the qualifying ACS must not have been precipitated by significant non-cardiovascular co-morbidity such as acute anaemia or hyperthyroidism. At each enrolling hospital, study investigators worked with their ethics or institutional review board to obtain appropriate approval to participate in data collection. To enrol an unselected population, the first 10–20 consecutive eligible patients were recruited from each site per month. Data were collected by trained coordinators using a standardized case report form. Demographic characteristics, medical history, presenting symptoms, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected. Standardized definitions for all patient-related variables and clinical diagnoses were used.^{10,11} Regular audits were performed at all participating hospitals. Hospital-specific feedback regarding patient characteristics, presentation, management, and outcomes were provided to each centre on a quarterly basis in the form of written reports.

For this analysis, we included all non-transfer patients enrolled at GRACE hospitals between 1999 and 2006 who presented within 12 h of symptom onset with new or presumed new ST-elevation and/or a presumed new left bundle-branch block (LBBB) pattern on the initial electrocardiogram (ECG). We examined patients in each of seven 12-month treatment periods, noting patient demographics, timing and type of reperfusion, and in-patient outcomes. Primary PCI was defined as any PCI provided within 12 h in a patient not receiving fibrinolysis.

Statistical analyses

Patients were categorized by hospital discharge date into one of seven 12-month periods from 1 July to 30 June the following year (the first period extended from 1 April 1999 to 30 June 2000). Only data from hospitals in which GRACE patients had been continuously enrolled for at least six contiguous years were analysed. A total of

54 hospitals in 12 countries were represented. All analyses were done using SAS software 9.1.

Trends in the percentage of patients reperfused were identified using the Cochran–Armitage test for linear trends. Trends in times to treatment and pre-hospital delay were evaluated by ranking all treatment times and calculating the mean rank for each year; a test for possible trends was then done by a linear regression of the mean ranks on study year.

The expected hospital mortality rates were calculated using the GRACE risk model variables (age, systolic blood pressure, heart rate, Killip class, cardiac arrest, elevated biomarkers, and creatinine concentration),¹¹ and were compared with the observed hospital mortality rates.

Logistic regression—no reperfusion

Stepwise logistic regression analysis was performed to assess the significance of factors generally thought to be related to the clinical decision-making process to use or not use reperfusion therapy, and to quantify their relative importance. The outcome was defined as 'no reperfusion'. Candidate variables included those related to patient and hospital characteristics and geographical differences, taken from a previous analysis of 'reperfusion-eligible' patients enrolled in GRACE.³ Variables considered were study year (as a continuous variable); age >75 years; sex; time from symptom onset to hospital arrival; access to a catheterization laboratory; 'hospital' (see below); history of congestive heart failure, CABG, myocardial infarction or diabetes; and all possible two-way interactions with study year.

The linear relationship between no reperfusion and continuous variables was assessed by plotting the logit for no reperfusion with means by time period. These steps were repeated for men and for women.

A Cochran–Armitage test for trends in reperfusion rates was performed for each enrolling hospital. All of the geographic regions represented (Europe, Argentina/Brazil, Australia/New Zealand/Canada, and the United States) included some hospitals that showed improvement and some with no improvement in reperfusion rates. The same was generally true for countries. Each hospital was categorized into one of three groups: decreasing trend, no trend, or increasing trend in no reperfusion. Logistic regression models showed the same candidate variables were statistically significant for each group with the exception of medical history of diabetes where the confidence intervals (CI) for the parameter estimates overlapped. The final logistic regression model therefore combined the three hospital trend groups and included the variable 'hospital'.

Logistic regression—hospital mortality

Stepwise logistic regression was performed to see if trends in no reperfusion or time to treatment were related to changes in hospital mortality. As there were no differences in mortality for the three trend groups previously examined for reperfusion, data for all hospitals were combined. The GRACE risk score variables¹¹ were analysed along with study year, sex, time from symptom onset to patient arrival, type of reperfusion (PCI alone, fibrinolytic alone, both or neither), and medical history of diabetes, congestive heart failure, CABG, and myocardial infarction.

Results

Patient population

Between 1999 and 2006, we identified 10 954 patients enrolled in GRACE who presented within 12 h of symptom onset with ST-elevation and/or LBBB. Patients' baseline characteristics are

Table 1 Patients' baseline characteristics according to discharge year

	April 1999 to June 2000 (n = 1733)	July 2000 to June 2001 (n = 1763)	July 2001 to June 2002 (n = 1625)	July 2002 to June 2003 (n = 1651)	July 2003 to June 2004 (n = 1657)	July 2004 to June 2005 (n = 1400)	July 2005 to June 2006 (n = 1215)
Demographics							
Median age, years (IQR)	65 (55–74)	65 (54–75)	64 (54–74)	64 (54–75)	64 (54–74)	64 (54–74)	63 (53–75)
Men, %	1254 (73)	1269 (72)	1148 (71)	1173 (71)	1130 (73)	1003 (72)	892 (74)
Median BMI, kg/m ² (IQR)	26 (24–29)	27 (24–29)	26 (24–29)	26 (24–29)	26 (24–29)	27 (24–29)	26 (24–29)
Medical history							
Angina, %	881 (51)	774 (44)	678 (42)	606 (37)	505 (32)	436 (31)	398 (33)
Myocardial infarction, %	394 (23)	345 (20)	325 (20)	320 (20)	321 (21)	259 (19)	238 (20)
Heart failure, %	137 (8.0)	89 (5.1)	102 (6.3)	87 (5.3)	97 (6.2)	70 (5.0)	62 (5.1)
Coronary intervention, %	102 (5.9)	127 (7.3)	123 (7.6)	152 (9.3)	148 (9.5)	126 (9.0)	127 (11)
CABG surgery, %	95 (5.5)	79 (4.5)	75 (4.6)	75 (4.6)	85 (5.5)	66 (4.7)	60 (5.0)
Cardiovascular risk factors							
Smoker (current or former), %	1065 (62)	1121 (64)	994 (62)	1036 (63)	965 (62)	858 (62)	757 (63)
Diabetes, %	347 (20)	335 (19)	332 (21)	309 (19)	335 (22)	266 (19)	250 (21)
Hypertension, %	862 (50)	865 (50)	808 (50)	851 (52)	809 (52)	735 (53)	673 (56)
Hyperlipidaemia, %	576 (34)	653 (38)	557 (35)	638 (39)	632 (41)	572 (41)	495 (41)
Clinical presentation							
Median pulse, bpm (IQR)	76 (65–90)	76 (64–90)	76 (65–90)	76 (64–90)	77 (65–90)	75 (63–90)	76 (65–90)
Median systolic BP, mmHg (IQR)	140 (120–160)	135 (120–155)	135 (118–155)	137 (117–155)	137 (120–156)	136 (120–155)	134 (117–154)
Median diastolic BP, mmHg (IQR)	80 (70–93)	80 (70–90)	80 (70–90)	80 (70–90)	80 (70–90)	80 (70–90)	80 (70–90)
Cardiac arrest, %	63 (3.7)	69 (4.0)	57 (3.6)	60 (3.7)	54 (3.5)	55 (3.9)	48 (4.0)
Killip class I, %	1371 (81)	1415 (82)	1286 (80)	1326 (82)	1278 (83)	1153 (84)	999 (85)
Killip class II, %	221 (13)	230 (13)	218 (14)	217 (13)	179 (12)	136 (9.9)	117 (10)
Killip class III, %	71 (4.2)	60 (3.5)	69 (4.3)	49 (3.0)	60 (3.9)	60 (4.4)	35 (3.0)
Killip class IV, %	35 (2.1)	31 (1.8)	32 (2.0)	33 (2.0)	24 (1.6)	24 (1.7)	23 (2.0)
Positive cardiac biomarkers, %	610 (36)	758 (44)	781 (49)	821 (51)	738 (49)	676 (53)	677 (57)
Median serum creatinine (mg/dL) (IQR)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	1.1 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.9–1.2)

BMI, body mass index, BP, blood pressure; bpm, beats per minute; IQR, interquartile range.

shown by study year in Table 1. The rates of previous angina, myocardial infarction, and heart failure generally decreased, whereas the rate of prior PCI increased. The proportion of patients with positive initial biomarkers of cardiac necrosis (CK-MB, troponin and/or creatine phosphokinase) increased from 36% in 1999 to 57% in 2006 ($P < 0.001$), likely due to increasing use of troponin as the biomarker of choice in the later study period.

Figure 1 demonstrates the year-by-year percentage of patients who received no reperfusion therapy, primary PCI, or fibrinolysis. No reperfusion was provided to 40% of patients in 1999 and to 33% of patients in 2006 ($P < 0.0001$ for trend). Among patients receiving reperfusion, we identified an increase in the use of primary PCI from 15 to 44% ($P < 0.0001$) between 1999 and 2006, whereas the use of fibrinolysis fell from 41 to 16% ($P < 0.0001$).

Table 2 and Figure 2 demonstrate the changes in median time to reperfusion therapy for patients receiving primary PCI and fibrinolysis, including time from symptom onset to hospital arrival, and time from hospital arrival to PCI or fibrinolysis (Table 2). Between 2000 and 2006, median door-to-balloon times for primary PCI remained relatively constant between 75 and 84 min, though median time was noticeably higher in 1999 (99 min). Median door-to-needle times fell from 40 min in 1999 to 34 min in 2006 ($P < 0.001$ for trend). Despite these improvements, 42% of patients receiving primary PCI alone in 2006 had door-to-balloon times >90 min and 52% of patients receiving fibrinolysis alone had door-to-needle times exceeding 30 min. In addition, time from symptom onset to hospital arrival showed no improvement.

Figure 3 shows the changes in expected and observed rates of hospital mortality for patients with ST elevation or LBBB. From 2003 onwards, trends for lower observed hospital mortality than

expected were observed. A portion of this difference likely reflects an overall increase in both early and later PCI during the study period as revealed by the logistic regression for hospital mortality. The hazard ratio for PCI alone was 0.70 (95% CI 0.55–0.88), indicating lower mortality compared with those not undergoing PCI.

Figure 4 illustrates the variables that were associated with a failure to provide reperfusion therapy as identified by multivariable logistic analysis. Four factors were strongly related, as evidenced by odds ratios (ORs) exceeding 2.0: prior heart failure, age >75 years, prior myocardial infarction, and prior CABG. Several additional patient factors also associated with no reperfusion were: female sex, diabetes, and delay from symptom onsets to hospital arrival (patient delay).

Discussion

There is clear evidence that timely delivery of acute reperfusion therapy for patients with STEMI substantially lowers hospital mortality.^{2,7,12,13} While fibrinolysis is acknowledged to be particularly more effective when initiated early after symptom onset,¹⁴ a recent meta-analysis demonstrated that primary PCI was associated with a reduction in the odds of 30-day mortality, regardless of the delay to treatment.⁸ Although the relationship between time delay and mortality may be less critical for primary PCI when compared with fibrinolysis,¹⁵ it does appear to matter and is increasingly being used as a key determinant in the selection of reperfusion therapy. Accordingly, guidelines have strongly encouraged hospitals to create care systems to maximize availability of reperfusion therapy to all eligible patients, and specifically fibrinolysis within 30 min (door-to-needle time) and primary PCI within 90 min (door-to-balloon time).^{5,6}

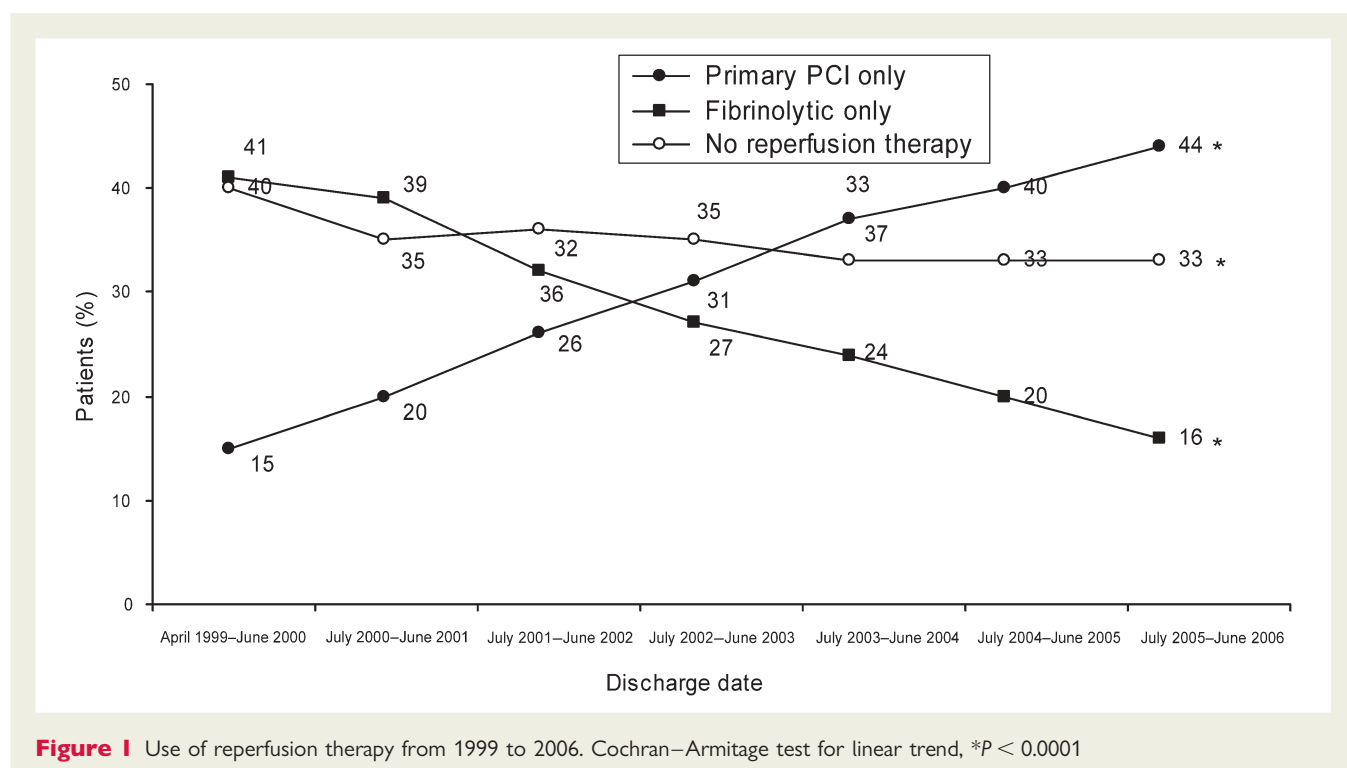


Table 2 Delays in reperfusion therapy by discharge year in GRACE

	April 1999 to June 2000	July 2000 to June 2001	July 2001 to June 2002	July 2002 to June 2003	July 2003 to June 2004	July 2004 to June 2005	July 2005 to June 2006
Prehospital delay (min)	120 (71–210)	129 (80–215)	125 (77–225)	130 (75–210)	125 (75–210)	126 (80–230)	133 (80–226)
Treatment delay (median min [interquartile range])							
From hospital arrival to PCI or fibrinolytic therapy							
PCI or fibrinolytic therapy	50 (28–95)	47 (25–85)	45 (25–90)	55 (30–106)	57 (30–96)	64 (31–106)	64 (30–110)
PCI only	99 (70–141)	75 (45–125)	75 (44–121)	84 (48–140)	75 (45–116)	80 (50–121)	80 (45–119)
Fibrinolytic therapy only	40 (23–70)	35 (21–62)	31 (20–57)	34 (20–61)	34 (19–60)	30 (19–70)	34 (17–62)
From symptom onset to PCI or fibrinolytic therapy							
PCI or fibrinolytic therapy	190 (130–310)	182 (128–295)	185 (123–299)	198 (130–325)	190 (130–310)	200 (133–319)	200 (135–330)
PCI only	235 (170–345)	230 (160–375)	225 (165–359)	232 (165–375)	216 (150–372)	230 (160–364)	228 (160–370)
Fibrinolytic therapy only	180 (120–295)	170 (115–270)	162 (106–255)	175 (105–273)	179 (110–264)	160 (105–265)	158 (105–258)

PCI, percutaneous coronary intervention.

This analysis from GRACE reveals important trends in the use of acute reperfusion therapy globally among 54 hospitals in 12 countries between 1999 and 2006. We see several encouraging developments, but at the same time we continue to see a substantial number of missed opportunities to impact hospital mortality with effective and timely reperfusion. What trends are favourable? First, the use of primary PCI has grown considerably among patients included in GRACE hospitals over the past 7 years. This is appropriate given evidence that, on average, rapidly delivered primary PCI may be associated with lower hospital mortality when compared with fibrinolysis.⁷ This is particularly true for patients who delay seeking treatment 3 h or more after symptom onset, in whom the success of fibrinolysis in opening the occluded artery falls.¹⁶

In our multinational study, the median time to fibrinolysis fell from 40 to 34 min between 1999 and 2006, but the delay to primary PCI remained unchanged. Similar results were reported from a US report from the National Registry of Myocardial Infarction, studying STEMI in the years from 1999 to 2002, which showed no significant improvement in average reperfusion time.¹⁷

A third trend, which is most encouraging, is the fact that the relationship between observed and expected hospital mortality rates appears to be improving. This may be due to greater use of PCI. The increasing use of adjunctive treatments with both forms of reperfusion, such as the addition of more effective antiplatelet drugs and anticoagulation, may also be responsible. Improvements in the hospital management of patients with an ACS and corresponding reductions in the rates of adverse outcomes including death have been reported recently in another analysis from the GRACE registry.¹⁸

Despite encouraging developments, important concerns are raised by these findings. Pre-hospital delay for patients receiving reperfusion treatment remained stable with an average median of 125 min from symptom onset to hospital arrival over the 7-year study period. This suggests that recent efforts to educate patients about the warning signs and symptoms of STEMI and ACS to encourage early presentation for STEMI have had little influence on patients. Better strategies for improving patient awareness and use of pre-hospital systems are urgently needed.¹⁹

The overall proportion of eligible patients who fail to receive any form of reperfusion therapy also remains unacceptably high. One-third of eligible patients with ST elevation or LBBB received no reperfusion therapy in 2006. Similar findings were reported in the second Euro Heart Survey, in which 36% of patients with STEMI did not receive reperfusion therapy; failure to provide reperfusion therapy included late arrival, uncertain admission diagnosis, and early ST resolution.²⁰ We believe there are several potential explanations based on our findings. Physicians are uncertain about the benefits of reperfusion in very old patients (>75 years), in part because the risks of reperfusion therapy are higher in this cohort. It may also be that clinicians are uneasy about extending reperfusion to more complex groups of patients that have been less frequently studied in clinical trials. For example, we found that clinicians were less likely to use reperfusion in patients who present atypically (e.g. with heart failure) instead of with classic chest pain or in those with prior CABG.²¹ Patients with a prior myocardial infarction or CABG were also less likely to receive reperfusion therapy, perhaps because it was unclear whether the ST elevation on the ECG was old or new. When

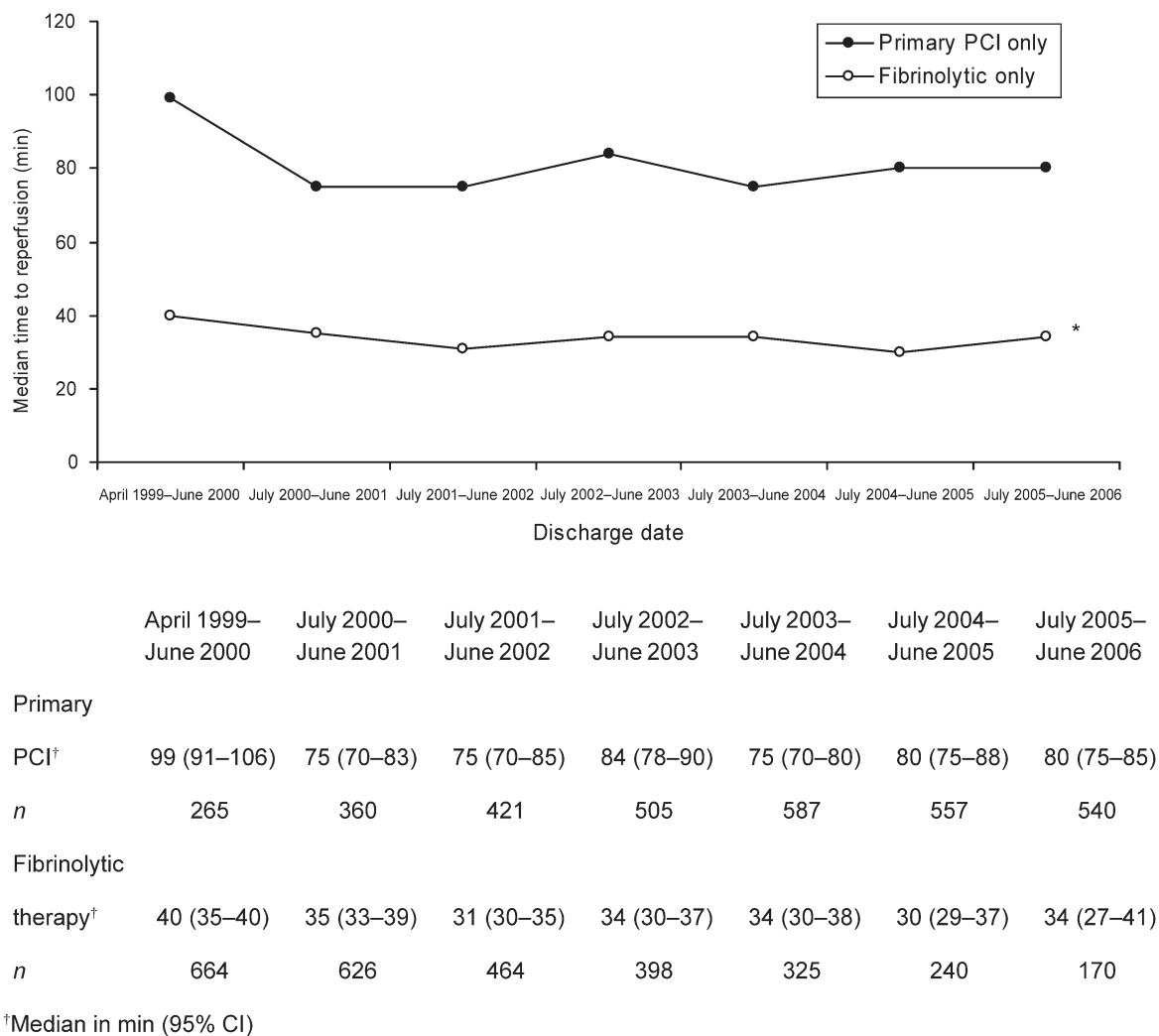
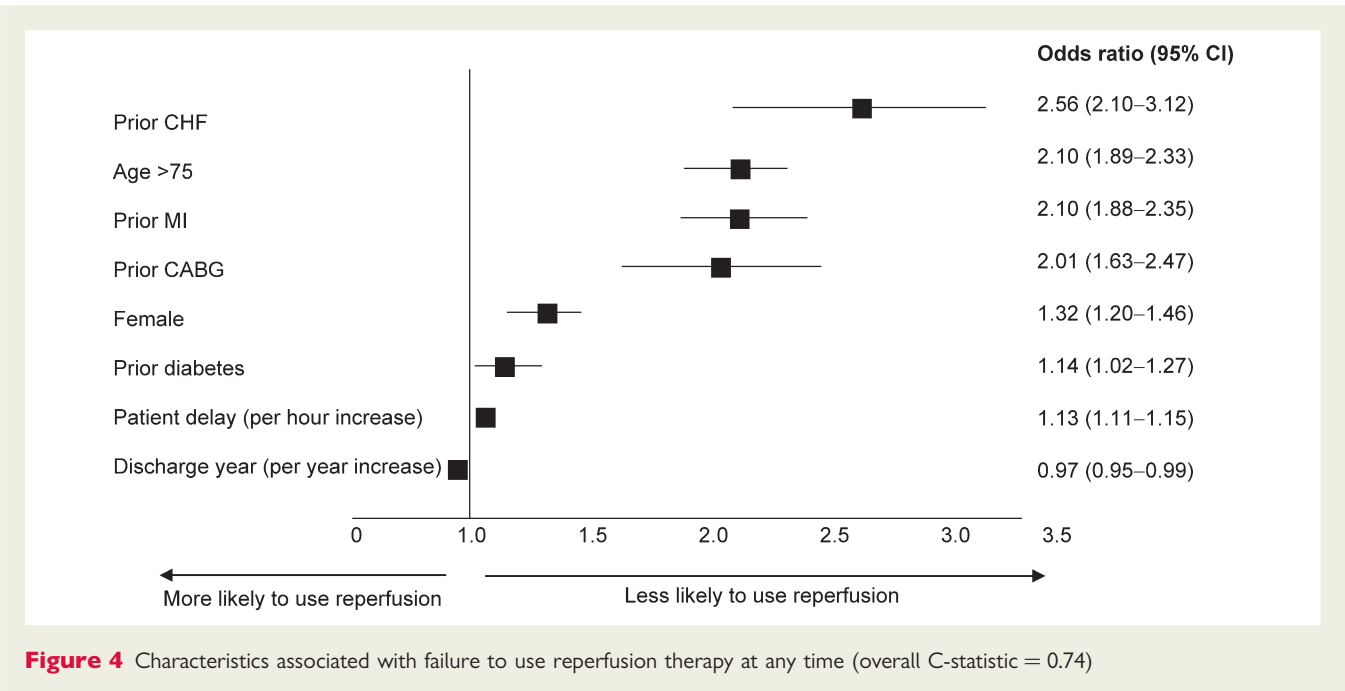
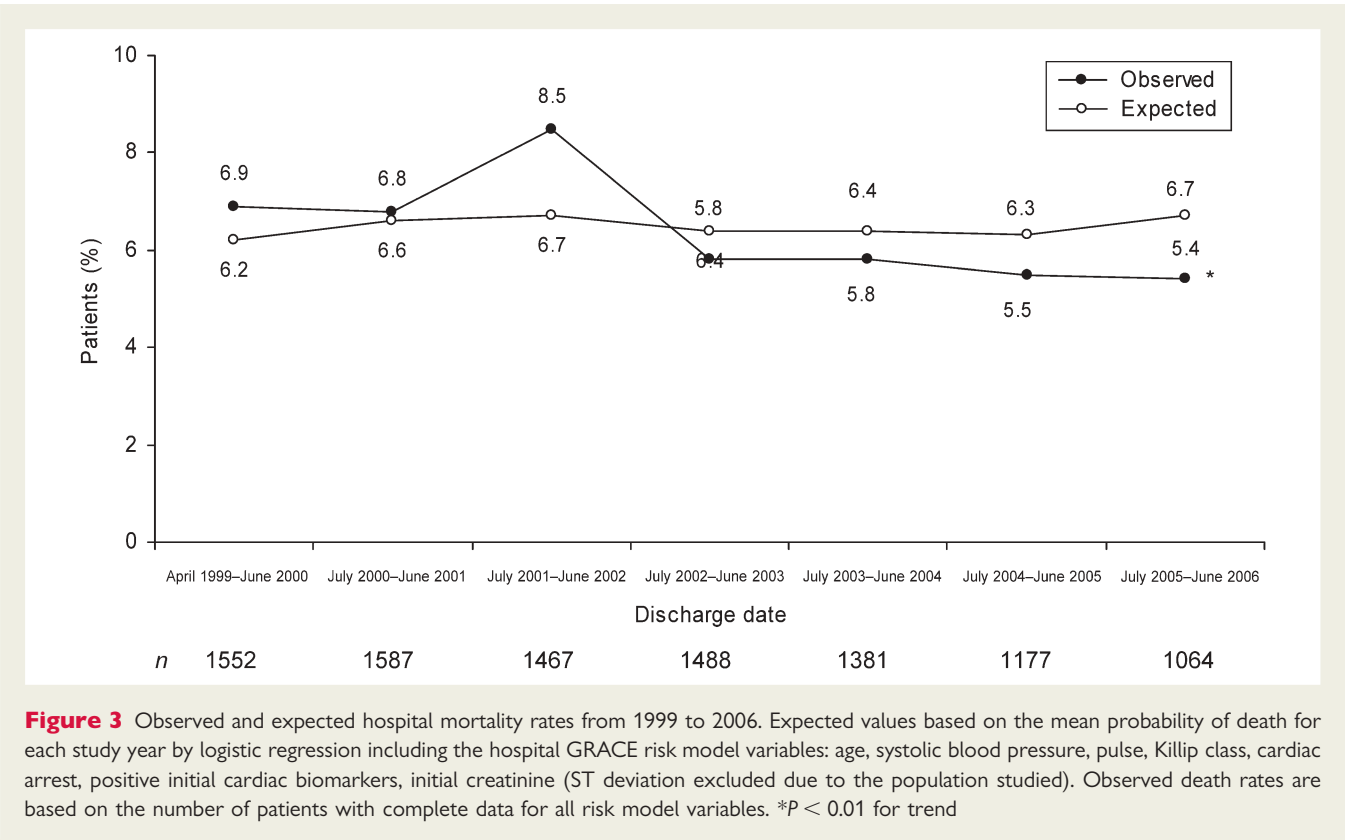


Figure 2 Time from hospital arrival to receipt of reperfusion therapy from 1999 to 2006. * $P < 0.001$ for trend

the variable indicating if the ECG abnormality was 'new' or 'unknown' was included in the final logistic model for no reperfusion, the trend in no reperfusion became non-significant (data not shown). Furthermore, there was a statistically significant increase in the proportion of patients whose ECG abnormality was 'new' vs. 'unknown' (82–89%). These data suggest that the decreasing trend in no reperfusion is due to increasing certainty in the newness of the ECG abnormality. Furthermore, patients with a prior CABG often have abnormal baseline ECGs including prior myocardial infarction and/or right branch block, in which cases treating physicians may be less certain about the indication for and benefits of reperfusion therapy. Another reason for failure to give reperfusion is that not all patients presenting with LBBB have coronary occlusion and a significant proportion do not have an ACS. However, in an individual with LBBB and concordant ST elevations, the likelihood of an AMI increases significantly.²²

Strengths and limitations of the study

GRACE is the largest multinational registry to include the complete spectrum of patients with ACS, including more than 65 000 patients from 14 countries. Standardized 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 of providing data on a heterogeneous patient population that includes groups who are often under-represented in randomized trials, which enhances the generalizability of the findings.¹¹ GRACE provides a representative sample of patients with ACS who are treated in a variety of hospital and healthcare systems. Nevertheless, as a non-randomized observational study, GRACE is subject to certain inherent limitations and potential biases including the collection of non-randomized 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. For example, the participating clusters reflect regional practices and outcomes, but do not necessarily reflect practice for specific countries.

Conclusion

While the global effort to improve reperfusion therapy for acute STEMI is having an impact, this 'report card' continues to identify substantial opportunities for improvement. Hospital

systems and professional and administrative leadership are key for this to occur.

Acknowledgements

We thank and express our gratitude to the physicians and nurses participating in GRACE. Dr Sophie Rushton-Smith provided editorial assistance and was funded by sanofi-aventis. We also thank Frederick Anderson Jr, PhD, the principal investigator of the GRACE registry, who is based at the Center for Outcomes Research at the University of Massachusetts Medical School.

Conflict of interest: Sanofi-aventis had no involvement in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the paper for publication. The design, conduct, and interpretation of the GRACE data are undertaken by an independent steering committee.

Funding

The GRACE registry (<http://www.outcomes-umassmed.org/grace>) is supported by an unrestricted educational grant from sanofi-aventis to the Center for Outcomes Research, University of Massachusetts Medical School.

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CLINICAL VIGNETTE

doi:10.1093/eurheartj/ehm437

Online publish-ahead-of-print 24 October 2007

Cabrol shunt for iatrogenic aortic dissection: evaluation with cardiac 64-slice CT

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A 63-year-old man was admitted with intractable angina and underwent elective coronary angiography. He had a history of percutaneous coronary intervention to the left circumflex artery five years previously. Coronary angiography revealed 90% stenosis of the proximal right coronary artery (RCA) (Panel A) and a 3 mm Cypher stent was placed across the lesion. The procedure was complicated by a RCA dissection with retrograde extension to the ostium and subsequently into the ascending aortic wall (Panel B). The patient was referred for urgent surgical repair. Extensive bleeding was encountered at surgery, and the false lumen of the aortic dissection was decompressed with a Cabrol shunt, whereby a dacron graft was interposed between the lower part of the false lumen and the right atrium.

Six weeks later a 64-slice cardiac CT was performed to non-invasively evaluate patency of the graft. It confirmed a persistent aortic dissection and a patent false lumen (Panel C). It also clearly depicted a widely patent Cabrol shunt, both at the proximal anastomoses with the false lumen and the distal anastomoses with the right atrium (Panel D). A multiphasic reconstruction cine loop throughout the cardiac cycle demonstrated a contrast shunt into the right atrium during ventricular systole (Supplementary data). The patient remains well at 6-month clinical follow-up.

The Cabrol shunt was first described in 1978 as a method for decompressing the false lumen of an aortic dissection complicated by excessive peri/post-operative haemorrhage. The shunt commonly closes during the first postoperative week although a small minority may remain open for longer periods of time. In recent years cardiac CT has become established as a highly accurate non-invasive method for evaluating coronary artery bypass grafts. We adapted it to evaluate the patency of the Cabrol shunt. It clearly demonstrated the proximal and distal graft anastomoses and the contrast shunt sign confirmed graft patency (Supplementary data). Such findings illustrate the increasing versatility of cardiac CT in providing accurate non-invasive evaluation of surgical grafts and shunts.

Panel A. Coronary angiogram demonstrated a 90% stenosis (arrow) in the proximal right coronary artery.

Panel B. Following percutaneous coronary intervention a coronary dissection extended into the wall of the ascending aorta (arrows). A Cabrol shunt was inserted for intractable bleeding at surgery (see Panel D).

Panel C. Cardiac CT performed six weeks later to evaluate the dissection confirms chronic aortic dissection with contrast in the false (straight arrow) and true lumens (hollow arrow).

Panel D. Cardiac CT coronal oblique image demonstrates the Cabrol shunt extending from the false lumen of the ascending aorta (straight arrow) to the right atrium (open arrow). Distally a contrast shunt (curved arrow) confirms the site of distal anastomoses and shunt patency.

Supplemental data: Multiphasic cardiac CT cine loop throughout the cardiac cycle demonstrates the Cabrol graft with a contrast shunt into the right atrium during ventricular systole.

Supplementary material is available at *European Heart Journal* online.

