# Decline in Rates of Death and Heart Failure in Acute Coronary Syndromes, 1999-2006

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**Context** Randomized trials provide robust evidence for the impact of pharmacological and interventional treatments in patients with ST-segment elevation and non–ST-segment elevation acute coronary syndromes (NSTE ACS), but whether this translates to changes in clinical practice is unknown.

**Objective** To determine whether changes in hospital management of patients with ST-segment elevation myocardial infarction (STEMI) and NSTE ACS are associated with improvements in clinical outcome.

**Design, Setting, and Patients** In the Global Registry of Acute Coronary Events (GRACE), a multinational cohort study, 44 372 patients with an ACS were enrolled and followed up in 113 hospitals in 14 countries between July 1, 1999, and December 31, 2006.

**Main Outcome Measures** Temporal trends in the use of evidence-based pharmacological and interventional therapies; patient outcomes (death, congestive heart failure, pulmonary edema, cardiogenic shock, stroke, myocardial infarction).

**Results** Use of pharmacological medications increased over the study period (β-blockers, statins, angiotensin-converting enzyme inhibitors, thienopyridines with or without percutaneous coronary intervention [PCI], glycoprotein IIb/IIIa inhibitors, low-molecular-weight heparin; all $P<.001$). Pharmacological reperfusion declined in patients with STEMI by –22 percentage points (95% confidence interval [CI], –27 to –17), whereas primary PCI increased by 37 percentage points (95% CI, 33-41). In patients with non-STEMI, rates of PCI increased markedly by 18 percentage points (95% CI, 15-20). Rates of congestive heart failure and pulmonary edema declined in both populations: STEMI, –9 percentage points (95% CI, –12 to –6) and NSTE ACS, –6.9 percentage points (95% CI, –8.4 to –4.7). In patients with STEMI, hospital deaths decreased by 18 percentage points (95% CI, –5.3 to –1.9) and cardiogenic shock by –24 percentage points (95% CI, –4.3 to –0.5). Risk-adjusted hospital deaths declined –0.7 percentage points (95% CI, –1.7 to 0.3) in NSTE ACS patients. Six-month follow-up rates declined among STEMI patients: stroke by –0.8 percentage points (95% CI, –1.7 to 0.1) and myocardial infarction by –2.8 percentage points (95% CI, –6.4 to 0.9). In NSTE ACS, 6-month death declined –1.6 percentage points (95% CI, –3.0 to –0.1) and stroke by 0.7 percentage points (95% CI, –1.4 to 0.1).

**Conclusions** In this multinational observational study, improvements in the management of patients with ACS were associated with significant reductions in the rates of new heart failure and mortality and in rates of stroke and mycoardial infarction at 6 months.

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RANDOMIZED TRIALS PROVIDE ROBUST evidence for the impact of pharmacological and interventional treatments in patients with ST-segment elevation and non–ST-segment elevation acute coronary syndromes (NSTE ACS), leading to changes in practice guidelines.[1-4] However, the extent and time course of changes in clinical practice are uncertain, and it is unknown whether such changes are associated with improved outcome. Previous studies have documented substantial gaps between guideline recommendations and clinical practice.[5-7] Thus, there is a clinical priority to determine the extent to which evidence is applied in practice, whether this is changing over time, and whether such changes are associated with improved outcomes.

Few studies in acute coronary disease offer a sufficiently long sampling interval with sufficiently robust sampling techniques to reveal changes in practice and outcome over time.[8-10] The Global Registry of Acute Coronary Events (GRACE)[7] is the only large-

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scale, multinational, observational study of the spectrum of patients hospitalized with an ACS, with continuous recruitment of patients for more than 6 years. Results from earlier studies suggest that hospital characteristics, access to resources, and geographic factors influence uptake of new therapies into practice.[7,11] The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE)[11] quality improvement initiative involves centers throughout the United States and provides valuable insights into selected care processes and patient outcomes as measures of hospital quality.

A total of 62 935 patients have been enrolled in GRACE since it was launched in 1999, and there is a sufficiently large sample size (16 814 patients with ST-segment elevation myocardial infarction [STEMI]; 27 558 with NSTE ACS; and 2067 in-hospital deaths) and sufficient study duration (6.5 years of recruitment) to define changes in management and outcome. The hypothesis for this analysis is that changes in hospital management of patients with ACS are associated with improvements in clinical outcome, and that these changes are independent of the risk status of the study population on presentation to hospital.

## METHODS

Full details of the GRACE methods have been published.[12,13] To be eligible, patients (≥18 years) had to be admitted for ACS as a presumptive diagnosis and have at least 1 of the following: electrocardiographic changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, documented coronary artery disease, or both. The qualifying patient with ACS must not have been precipitated by significant noncardiovascular comorbidity. Where required, study investigators received approval from their local hospital ethics or institutional review board for the conduct of this study and signed informed consent for follow-up contact was obtained from the patients at enrollment.

### Consistency of Sampling Techniques, End Point Definitions, and Methods of Analysis

The aim was to enroll an unselected population of patients with an ACS, irrespective of geographic region. Sites were encouraged to recruit the first 10 to 20 consecutive eligible patients each month, and regular audits were performed. Data were collected by trained study coordinators using standardized case report forms. Demographic characteristics, medical his-

**Table 1.** Patients' Baseline Characteristics According to Type of Acute Coronary Syndrome and Enrollment Period

| | ST-Segment Elevation MI | | NSTE ACS | |
|---|---|---|---|---|
| | July 1999 to June 2000 (n = 2564) | January to December 2005 (n = 2044) | July 1999 to June 2000 (n = 4699) | January to December 2005 (n = 3676) |
| Demographics | | | | |
| Men, No. (%) | 1803 (71) | 1456 (72) | 2961 (63) | 2393 (65) |
| Age, median (25th-75th percentiles), y | 65 (55-75) | 65 (54-75) | 67 (57-75) | 68 (57-77) |
| Index ECG abnormal for ischemia, No. (%) | 2558 (100) | 2042 (100) | 3299 (73) | 2290 (63) |
| Medical history, No. (%) | | | | |
| Angina | 1357 (53) | 604 (30) | 3661 (79) | 2131 (58) |
| Diabetes | 529 (21) | 435 (21) | 1178 (25) | 1039 (28) |
| Prior MI | 559 (22) | 387 (19) | 1803 (39) | 1297 (35) |
| Congestive heart failure | 202 (8) | 113 (5.6) | 626 (13) | 423 (12) |
| Stroke or transient ischemic attack | 165 (7) | 130 (6.4) | 413 (8.9) | 336 (9.2) |
| Prior PCI | 161 (6) | 211 (10) | 817 (18) | 893 (24) |
| Prior CABG | 156 (6) | 108 (5) | 758 (16) | 610 (17) |
| Peripheral arterial disease | 220 (9) | 131 (6) | 522 (11) | 402 (11) |
| Hypertension | 1301 (51) | 1143 (56) | 2945 (63) | 2591 (71) |
| Hyperlipidemia | 883 (35) | 774 (38) | 2239 (48) | 2101 (58) |
| Smoking status, No. (%) | | | | |
| Current | 829 (34) | 728 (36) | 926 (21) | 767 (21) |
| Former | 579 (24) | 467 (23) | 1411 (31) | 1168 (32) |
| Presenting characteristics | | | | |
| Positive initial enzymes, No. (%) | 1052 (41) | 1178 (61) | 1190 (26) | 1514 (43) |
| ST elevation, No. (%) | 2402 (94) | 1933 (95) | 173 (3.7) | 54 (1.5) |
| ST depression or T wave inversion | 1348 (53) | 1078 (53) | 2655 (57) | 1896 (52) |
| Systolic blood pressure, median, (25th-75th percentiles), mm Hg | 140 (120-160) | 137 (120-155) | 140 (125-160) | 140 (123-160) |
| Diastolic blood pressure, median (25th-75th percentiles), mm Hg | 80 (70-92) | 80 (70-90) | 80 (70-91) | 80 (70-90) |
| Pulse (25th-75th percentiles), beats/min | 77 (65-90) | 76 (65-90) | 76 (66-89) | 75 (65-89) |
| Killip class, No. (%) | | | | |
| I | 2025 (80) | 1673 (83) | 3866 (84) | 3093 (86) |
| II | 364 (15) | 224 (11) | 574 (13) | 366 (10) |
| III | 91 (3.6) | 71 (3.5) | 126 (2.7) | 115 (3.2) |
| IV | 38 (1.5) | 38 (1.9) | 21 (0.5) | 16 (0.4) |
| Creatinine, median (25th-75th percentiles), mg/dL | 1.02 (0.90-1.23) | 1.00 (0.88-1.20) | 1.02 (0.90-1.23) | 1.02 (0.89-1.30) |
| Serum cholesterol, median (25th-75th percentiles), mg/dL | 197 (168-231) | 184 (154-217) | 200 (169-232) | 177 (148-209) |

Abbreviations: CABG, coronary artery bypass graft; ECG, electrocardiogram; NSTE ACS, non–ST-segment elevation acute coronary syndromes; MI, myocardial infarction; PCI, percutaneous coronary intervention.
SI conversion factors: To convert cholesterol from mg/dL to µmol/L, multiply by 0.0259; and creatinine from mg/dL to µmol/L, multiply by 88.4.

tory, presenting symptoms, duration of prehospital delay, biochemical and electrocardiographic findings, treatment practices, and outcomes were collected. Patients with a non-ACS discharge diagnosis and patients transferred into a GRACE site from a non-GRACE site were excluded from the analysis. All cases were assigned to 1 of the following categories: STEMI (including left bundle-branch block), non-STEMI, unstable angina, and other cardiac or noncardiac diagnoses.[13] Hospital-specific feedback was provided to each center on a quarterly basis.

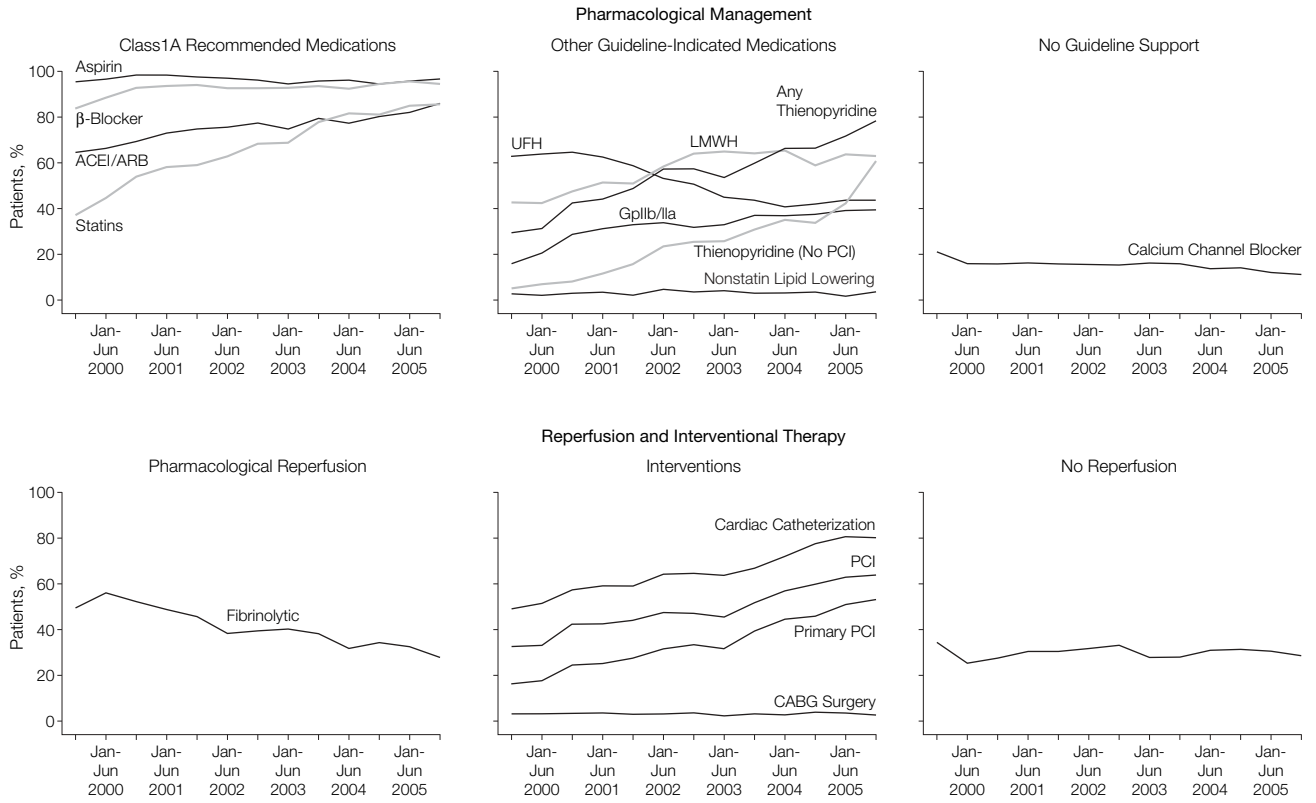
The primary outcomes for this study were in-hospital death, recurrent myocardial infarction, heart failure, stroke, and cardiogenic shock. At approximately 6 months after hospital discharge, patients were followed up for death, stroke or myocardial infarction. Of the patients who were alive at discharge from hospital, 2435 (16%) of 15 569 of those with STEMI and 3883 (15%) of 26 736 with NSTE ACS did not complete follow up. Standardized definitions of all patient-related variables, diagnoses, and in-hospital outcomes were used[13] (details available at http://www.outcomes.org/grace). We applied guideline-based criteria for identifying patients eligible for pharmacological treatments or mechanical interventions; specifics are available from the authors on request.

## Statistical Analysis

The analysis focuses on the populations of patients diagnosed with STEMI or NSTE ACS (non-STEMI and unstable angina). Data used were collected from July 1, 1999, through December 31, 2006. Data are summarized as frequencies and percentages for categorical variables. Continuous variables are presented as medians and 25th and 75th percentiles. The period of patient enrollment into GRACE was divided into 13 periods of 6 months each. Six-month follow-up data for each patient were reported under the same period as their enrollment. The double-sided Cochran-Armitage test for trend or logistic regression was used to evaluate time trends at a significance level of $\alpha = .05$. The analysis was performed using SAS software version 9.1 (SAS Institute Inc, Cary, NC).

To account for possible changes in patients' baseline risk characteristics, the probability of in-hospital death was calculated for each patient using the GRACE in-hospital risk score.[14] The average risk score for each time period was then calculated. Although patients with STEMI showed no change in predicted risk of mortality over time, there

**Figure 1.** Temporal Trends in Patients With ST-Segment Elevation Myocardial Infarction or Left Bundle-Branch Block, July 1999-December 2005




The sample size of the ST-segment elevation myocardial infarction cohort varied over time. Percentages are based on eligible patients for respective treatments in each period, shown in Table 2 for the first and last periods. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; Gp, glycoprotein; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

was a slight increase in risk for those with NSTE ACS. To account for this, adjusted rates were computed and normalized to those of the first time period. To calculate the adjusted rate, a difference between the observed and predicted death rates was computed for each time period.

## RESULTS

This study is based on data from 44 372 patients enrolled at 113 hospitals in 14 countries between July 1, 1999, and December 31, 2005, and were followed up for approximately 6 months after discharge. Of these patients, 27 558 were diagnosed with NSTE ACS and 16 814 with STEMI. Patients with STEMI were more often male and were slightly younger than those with NSTE ACS (TABLE 1). Patients with NSTE ACS had a more complex medical history than patients with STEMI but were less likely to be current smokers and more likely to be past smokers.

### ST-Segment Elevation Myocardial Infarction

**Temporal Trends in Pharmacological Management (Class 1A Indications).** Temporal trends in medication use and interventions in eligible STEMI patients are shown in FIGURE 1 and TABLE 2. Over the study period, the use of aspirin exceeded 94% in eligible patients (Figure 1) and the use of any oral antiplatelet drug (aspirin or thienopyridine) did not change (97% in 1999 to 99% in 2005; 4% increase; 95% confidence interval [CI], 0.5-3.2 for percentage difference in rates). Treatment with β-blockers increased by 11 percentage points (95% CI, 7.6-14), statins by 48 percentage points (95% CI, 45-52), and angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) by 22 percentage points (95% CI, 18-25) (Figure 1 and Table 2).

### Other Guideline-Indicated Medications

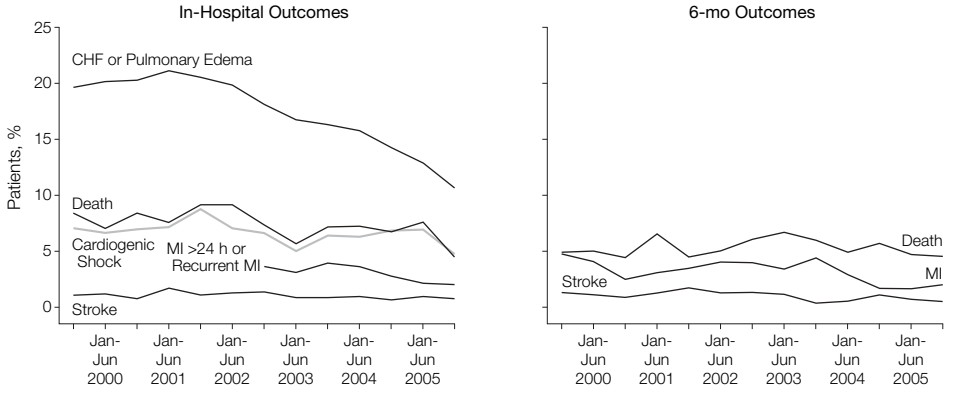
The use of low-molecular-weight heparin increased by 20 percentage points (95% CI, 16-24), whereas the use of unfractionated heparin declined by 19 percentage points (95% CI, –24 to –15) over the same period (Figure 1). Some patients received both low-molecular-weight heparin and unfractionated heparin during hospitalization.[15] Thienopyridine usage increased by 49 percentage points (95% CI, 45-53) overall, and by 56 percentage points (95% CI, 50-61) in the absence of percutaneous coronary intervention (PCI). Glycoprotein IIb/IIIa (GpIIb/IIIA) usage, overall, increased by 24 percentage points (95% CI, 20-27) over the course of the study, but among patients whose care was managed noninvasively, less than 1 in 10, received this therapy (2.3%-9.0%; 6.7 percentage points; 95%

**Table 2.** Changes in Therapy of 44 372 Patients Treated for STEMI and NSTE ACS, 1999 and 2005

| | No./Total (%) of Patients | | % Difference in Rates (95% Confidence Interval) | *P* Value for Linear Trends* |
|---|---|---|---|---|
| | July to December 1999 | July to December 2005 | | |
| ST-segment MI | | | | |
| Aspirin | 1064/1118 (95.1) | 815/842 (96.7) | 1.6 (–0.1 to 3.4) | <.01 |
| β-Blocker | 718/858 (83.6 ) | 603/639 (94.3) | 11 (7.6 to 14) | <.001 |
| Statin | 486/1302 (37.3) | 816/955 (85.4) | 48 (45 to 52) | <.001 |
| ACE inhibitor/ARB | 760/1181 (64.3) | 714/832 (85.8) | 22 (18 to 25) | <.001 |
| Low-molecular-weight heparin | 493/1151 (42.8) | 547/869 (62.9) | 20 (16 to 24) | <.001 |
| Unfractionated heparin | 720/1146 (62.8) | 367/864 (42.4) | –19 (–.24 to –15) | <.001 |
| Thienopyridine | | | | |
| Any | 329/1112 (29.5) | 664/849 (78.2) | 49 (45 to 53) | <.001 |
| No PCI | 39/759 (5.1) | 181/298 (60.7) | 56 (50 to 61) | <.001 |
| Glycoprotein IIb/IIIa antagonist | 184/1177 (15.6) | 343/875 (39.2) | 24 (20 to 27) | <.001 |
| Glycoprotein IIb/IIIa antagonist without PCI | 19/810 (2.3) | 28/310 (9.0) | 6.7 (3.3 to 10) | <.001 |
| Nonstatin lipid-lowering drug | 32/1287 (2.5) | 31/937 (3.3) | 0.8 (–0.6 to 2.2) | .49 |
| Calcium channel blocker | 255/1209 (21.1) | 102/915 (11.1) | –9.9 (–13 to –6.9) | <.001 |
| Fibrinolytic | 387/781 (49.5) | 144/517 (27.8) | –22 (–27 to –17) | <.001 |
| Cardiac catheterization | 602/1224 (49.1) | 738/925 (79.7) | 31 (27 to 34) | <.001 |
| Primary PCI | 177/1099 (16.1) | 406/769 (52.7) | 37 (33 to 41) | <.001 |
| PCI | 396/1219 (32.4) | 591/927 (63.5) | 31 (27 to 35) | <.001 |
| CABG | 39/1217 (3.2) | 25/920 (2.7) | –0.5 (–1.9 to 1.0) | .54 |
| No reperfusion | 365/1069 (34.1) | 216/754 (28.6) | –5.5 (–9.8 to –1.2) | .90 |
| NSTE ACS | | | | |
| Aspirin | 1897/2032 (93.3) | 1372/1430 (95.9 ) | 2.6 (1.1 to 4.1) | .02 |
| β-Blocker | 1496/1868 (80.0) | 1152/1280 (90.0) | 9.9 (7.5 to 12) | <.001 |
| Statin | 983/2442 (40.2) | 1420/1721 (82.5) | 42 (40 to 45) | <.001 |
| ACE/ARB | 1210/2300 (52.6) | 1100/1463 (75.1) | 23 (20 to 26) | <.001 |
| Low-molecular-weight heparin | 1020/2117 (48.1) | 1074/1515 (70.8) | 23 (20 to 26) | <.001 |
| Unfractionated heparin | 1105/2097 (52.6) | 507/1502 (33.7) | –19 (–22 to –16) | <.001 |
| Thienopyridine | | | | |
| Any | 401/2017 (19.8) | 1029/1447 (71.1) | 51 (48 to 54) | <.001 |
| No PCI | 112/1676 (6.7) | 569/929 (61.2) | 55 (51 to 58) | <.001 |
| Glycoprotein IIb/IIIa antagonist | 194/2157 (9.0) | 297/1513 (19.6) | 11 (8.3 to 13) | <.001 |
| Nonstatin lipid-lowering drug | 88/2412 (3.6) | 71/1685 (4.2) | 0.6 (–0.7 to 1.8) | .96 |
| Calcium-channel blocker | 879/2352 (37.3) | 415/1655 (25.0) | –12 (–15 to –9.4) | <.001 |
| Cardiac catheterization | 984/2379 (41.3) | 1045/1667 (62.6) | 21 (18 to 24) | <.001 |
| PCI | 403/2375 (16.9) | 581/1676 (34.6) | 18 (15 to 20) | <.001 |
| CABG | 161/2360 (6.8) | 85/1668 (5.1) | –1.7 (–3.2 to –0.3) | .04 |
| No revascularization | 1221/1776 (68.7) | 708/1224 (57.8) | –11 (–14 to –7.4) | <.001 |

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; MI, myocardial infarction; NSTE ACS, non–ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.
*Double-sided Cochran-Armitage test or logistic regression using data for all time periods.

**Figure 2.** In-Hospital and 6-Month Outcomes in Patients With ST-Segment Elevation Myocardial Infarction or Left Bundle-Branch Block




The sample size of the ST-segment elevation myocardial infarction cohort varied over time. Percentages are based on eligible patients for respective treatments in each period, shown in Table 3 for the first and last periods. CHF indicates congestive heart failure; MI, myocardial infarction. For in-hospital outcomes, $P<.01$ for recurrent MI or MI diagnosed 24 hours after presentation to hospital; $P=.02$ for shock; and $P<.001$ for death. For 6-month outcomes, $P=.01$ for MI and $P=.04$ for stroke.

**Table 3.** Changes in Clinical Outcomes in 44 372 Patients Treated for STEMI or NSTE ACS, 1999 and 2005

| | No./Total (%) of Patients | | % Difference in Rates (95% Confidence Interval) | *P* Value for Linear Trends* |
|---|---|---|---|---|
| | July to December 1999 | July to December 2005 | | |
| ST-segment MI† | | | | |
| In-hospital | | | | |
| Death | 112/1335 (8.4) | 45/992 (4.6) | –3.9 (–5.3 to –1.9) | <.001 |
| CHF or pulmonary edema | 265/1351 (19.5) | 106/993 (11) | –9.0 (–12 to –6) | <.001 |
| MI >24 h after presentation or recurrent MI | 14/390 (3.6) | 20/994 (2.0) | –1.6 (–3.6 to 0.5) | <.01 |
| Cardiogenic shock | 96/1354 (7.1) | 47/993 (4.7) | –2.4 (–4.3 to –0.5) | .02 |
| Stroke | 15/1356 (1.1) | 7/997 (0.7) | –0.4 (–1.2 to 0.4) | .08 |
| 6-mo Outcomes | | | | |
| Death | 54/1099 (4.9) | 28/620 (4.5) | –0.4 (–2.5 to 1.7) | .64 |
| Stroke | 14/1084 (1.3) | 3/601 (0.5) | –0.8 (–1.7 to 0.1) | .04 |
| MI | 7/147 (4.8) | 12/601 (2.0) | –2.8 (–6.4 to 0.9) | .01 |
| NSTE ACS† | | | | |
| In-hospital outcomes | | | | |
| Death | 2213 (2.9) | 1566 (2.2) | –0.7 (–1.7 to 0.3) | .02 |
| CHF or pulmonary edema | 2228 (13) | 1564 (6.1) | –6.5 (–8.4 to –4.7) | <.001 |
| MI >24 h after presentation or recurrent MI‡ | 696 (3.0) | 1556 (1.7) | –1.3 (–2.7 to 0.1) | .03 |
| Cardiogenic shock | 2230 (2.1) | 1565 (1.8) | –0.2 (–1.1 to 0.7) | .01 |
| Stroke | 2227 (0.2) | 1559 (0.6) | 0.3 (–0.1 to 0.7) | .18 |
| 6-mo Outcomes† | | | | |
| Death | 1942 (4.9) | 998 (3.3) | –1.6 (–3.0 to –0.1) | .04 |
| Stroke | 1901 (1.4) | 957 (0.7) | –0.7 (–1.4 to 0.1) | .01 |
| MI‡ | 2.5 | 2.9 | 0.4 (–1.7 to 2.5) | .43 |

Abbreviations: CHF, congestive heart failure; MI, myocardial infarction; NSTE, non–ST-segment elevation acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction.
*Double-sided Cochran-Armitage test or logistic regression using data for all time periods.
†Risk adjustment was applied to the NSTE ACS population as the risk profile increased over time. The risk profile of the STEMI population did not change. Of the 44 372 patients in the cohort, 16 814 were STEMI patients and 27 558 were NSTE ACS patients.
‡First time period was for July to December 2002.

CI, 3.3-10). The use of calcium channel blockers, with no guideline-supported indication in STEMI, declined by 9.9 percentage points (95% CI, –13 to –6.9) between 1999 and 2005 (Figure 1B; Table 2).

### Reperfusion and Interventional Therapy

Use of pharmacological reperfusion declined by 22 percentage points (95% CI, –27 to –17) (Figure 1; Table 2), whereas the rate of primary PCI increased by 37 percentage points (95% CI, 33-41) over the same interval (Figure 1; Table 2). Approximately one third of patients received primary or other PCI in 1999 and this increased to 64% of patients in 2005 (32.5 percentage points; 95% CI, 27-35). The proportion of patients with STEMI who did not receive pharmacological reperfusion therapy or primary rescue or facilitated PCI declined by 5.5 percentage points (95% CI, –9.8 to –1.2; Figure 1; Table 2).

### Outcome Measures Over Time in Patients With STEMI

The rates of death in hospital and cardiogenic shock declined in parallel, whereas the rate of stroke did not change significantly (FIGURE 2). Hospital deaths decreased by 3.9 percentage points (95% confidence interval [CI] –5.3 to –1.9) and cardiogenic shock by 2.4 percentage points (95% CI, –4.3 to –0.5; TABLE 3). The rate of in-hospital congestive heart failure or pulmonary edema declined by 9.0 percentage points (95% CI, –12 to –6; Table 3). Myocardial infarction diagnosed more than 24 hours after presentation to hospital or recurrent myo-

cardial infarction were collected systematically in the revised case report form July 2002. The rate of these events declined by 1.6 percentage points (95% CI, –3.6 to 0.5). A linear regression of mean risk scores at hospital presentation, over time, was nonsignificant (data available from authors on request).

The rate of myocardial infarction occurring between hospital discharge and 6-month follow-up decreased by 2.8 percentage points (95% CI, –6.4 to 0.9) and stroke by 0.8 percentage points (95% CI, –1.7 to 0.1; Figure 2; Table 3).

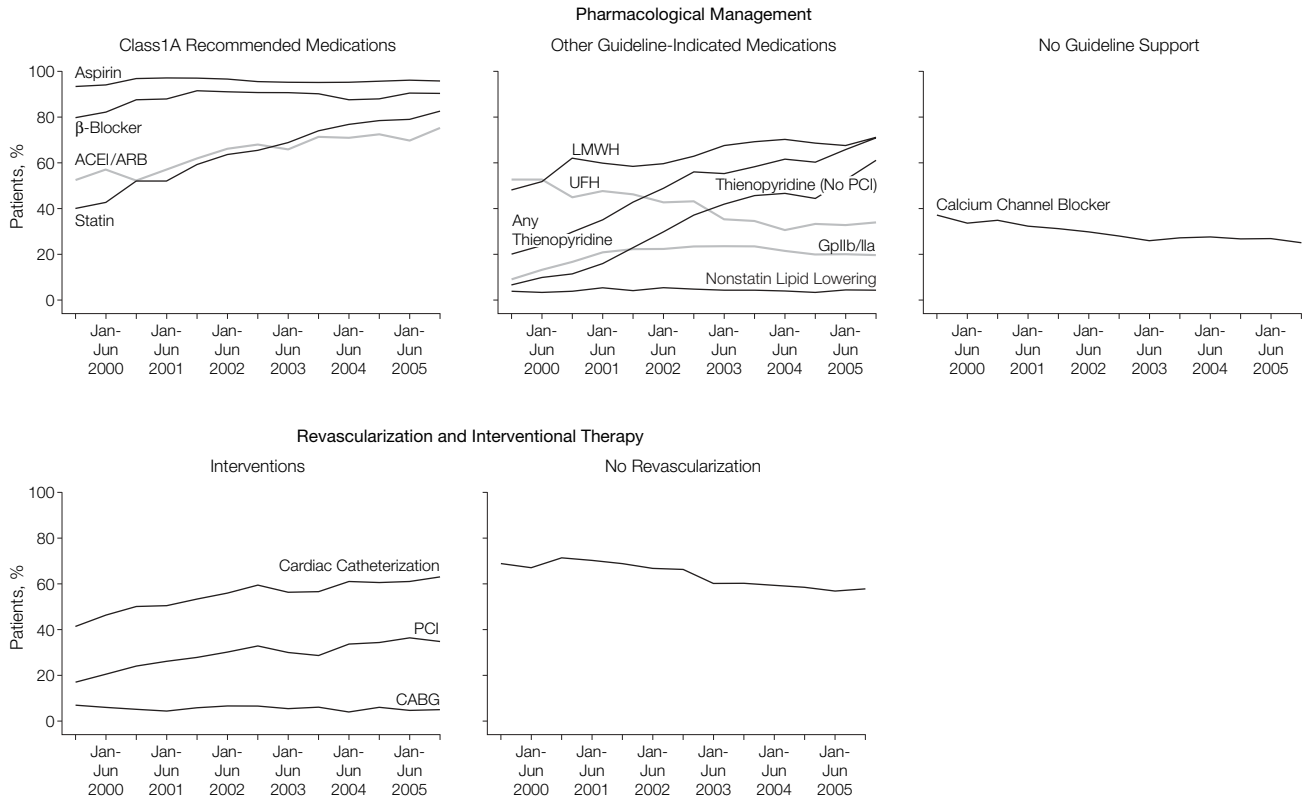
## Non-STEMI and Unstable Angina

**Temporal Trends in Pharmacological Therapies (Class 1A Recommendations).** Temporal trends in medication use in NSTE ACS patients without contraindications to these drugs are shown in FIGURE 3 and Table 2. The use of aspirin was high and increased modestly during the study by 2.6 percentage points (95% CI, 1.1-4.1). Similarly, the use of β-blockers increased by 9.9 percentage points (95% CI, 7.5-12). Use of ACE inhibitors (or ARBs) increased by 23 percentage points (95% CI, 20-26), statins by 42 percentage points (95% CI, 40-45), and thienopyridines by 51 percentage points (95% CI, 48-54). In contrast, the use of unfractionated heparin fell by 19 percentage points (95% CI, –22 to –16), whereas that of low-molecular-weight heparin increased by 23 percentage points (95% CI, 20-26; some patients received both low-molecular-weight heparin and unfractionated heparin during hospitalization[15]). Treatment with calcium-channel blockers (no class 1 recommendation) declined by 12 percentage points (95% CI, –15 to –9.4).

**Temporal Trends in Interventional Therapy**

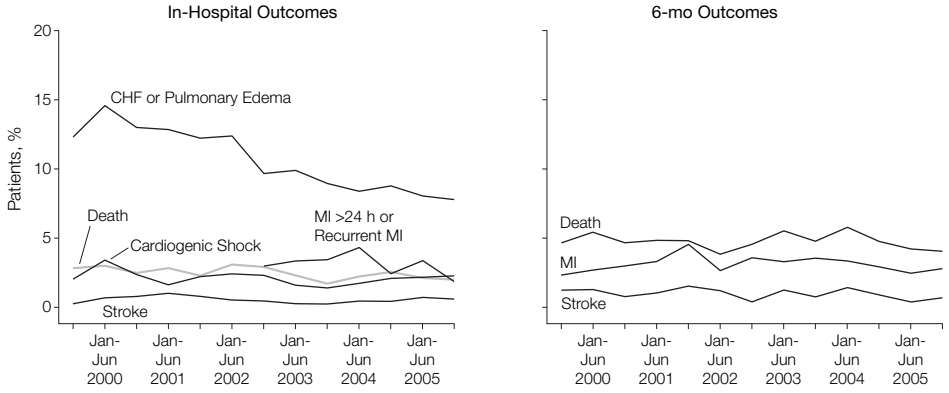
There was a modest decrease in the use of coronary artery bypass graft (CABG) surgery of 1.7 percentage points (95% CI, –3.2 to –0.3; Figure 3). The frequency of angiography increased markedly by 21 percentage points (95% CI, 18 to 24). The use of PCI increased substantially by 18 percentage points (95% CI, 15-20). Glycoprotein IIb/IIIa inhibitors exhibited an increase, with increasing usage between 1999 (9.0%, 194/2157) and 2003 (23%, 435/1859), then about 20% through 2005 (Figure 3) with an overall increase of 11 percentage points (95% CI, 8.3-13; Table 2). Glycoprotein IIb/IIIa usage in patients whose care was managed noninvasively was low, increasing from 2.7% (49/1792) in 1999 to 9.3% in 2002 and decreasing to 6.1% (123/2013) in 2005.

**Figure 3.** Temporal Trends in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes, July 1999-December 2005




The sample size of the ST-segment elevation myocardial infarction cohort varied over time. Percentages are based on eligible patients for respective treatments in each period, shown in Table 2 for the first and last periods. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; GP, glycoprotein; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

**Figure 4.** In-Hospital and 6-Month Outcomes in Patients With Non–ST-Segment Elevation Myocardial Infarction or Unstable Angina




The sample size of the ST-segment elevation myocardial infarction cohort varied over time. Percentages are based on eligible patients for respective treatments in each period, shown in Table 3 for the first and last periods. CHF indicates congestive heart failure; MI, myocardial infarction. For in-hospital outcomes, $P<.001$ for CHF or pulmonary edema and $P=.03$ for shock; recurrent MI or MI diagnosed 24 hours after presentation to hospital, and stroke. For 6-month outcomes, $P=.03$ for stroke.

### Outcome Measures Over Time in Patients With NSTE ACS

Risk-adjusted hospital deaths declined by 0.7 percentage points (95% CI, –1.7 to 0.3) in NSTE ACS patients (FIGURE 4; Table 3). The rate of stroke did not change significantly over time (Figure 4; Table 3). The rate of cardiogenic shock decreased slightly, but significantly, while the rate of congestive heart failure and pulmonary edema decreased by 6.5 percentage points (95% CI, –8.4 to –4.7). Myocardial infarction diagnosed more than 24 hours after presentation to hospital or recurrent myocardial infarction (recorded systematically in case report forms from July 2002) declined by 1.3 percentage points (95% CI, –2.7 to 0.1).

The rate of death between hospital discharge and 6-month follow-up decreased by 1.6 percentage points (95% CI, –3.0 to –0.1). Stroke decreased by 0.7 percentage points (95% CI, –1.4 to 0.1; Figure 4; Table 3).

### Risk Scores and Death Adjusted for Risk at the Start of the Study

The mean in-hospital risk score[14] for patients with NSTE ACS showed a significant ($P<.01$) increasing trend over the study period, from 120 (95% CI, 118-121) in 1999 to 125 (95% CI, 123-127) in 2007. Hence, if all else remained unchanged, the expected risk of death would have risen from 2.5% to 3.2%. Thus, although the unadjusted death rate remained unchanged, when adjusted for risk, deaths decreased by 0.7 percentage points (95% CI, –1.7 to 0.3) from 1999, a relative change of 24% (Figure 4; Table 3).

## COMMENT

These data, from the largest multinational observational cohort study of patients with an ACS, demonstrate evidence of a change in practice for both pharmacologic and interventional treatments in patients with either STEMI or NSTE ACS. These changes in practice are accompanied by significant decreases in the rates of in-hospital death, cardiogenic shock, recurrent myocardial infarction, and heart failure in patients presenting with STEMI and significant decreases in hospital death, heart failure, cardiogenic shock, and new myocardial infarction among patients with NSTE ACS. The risk status of patients at presentation with STEMI did not change over the course of the present study, so it is highly plausible that the changes in clinical outcomes are the direct consequence of changes in practice. The hospital death rate for patients with NSTE ACS showed a significant decrease after adjustment for baseline risk. It is disappointing that the proportion of patients who received no reperfusion therapy has not significantly improved over time.

The use of evidence-based therapies and PCI interventions increased in the STEMI population. This included the use of ACE inhibitors (or ARBs) and Gp IIb/IIIa inhibitors in patients undergoing PCI. This increase was matched by a statistically significant decrease in the rates of death, cardiogenic shock, and heart failure or pulmonary edema.

In patients with NSTE ACS, increases were observed in in-hospital treatment with low-molecular-weight heparin, thienopyridines, ACE inhibitors (or ARBs), and statins. Similarly, the rate of cardiac intervention (cardiac catheterization and PCI) increased. In contrast, the use of Gp IIb/IIIa inhibitors increased between 1999 and 2003 but changed little thereafter; a similar pattern was observed for Gp IIb/IIIa inhibitors without PCI. This change in practice may reflect a response to the findings from the Global Use of Strategies to Open Occluded Coronary Arteries-IV Acute Coronary Syndrome (GUSTO-IV ACS,[16] published in June 2001) and guidelines for managing patients with NSTE ACS (published in 2000[17,18] and 2002[4,19]). In the update, the use of Gp IIb/IIIa inhibitors was limited in patients who were to undergo PCI.

In NSTE ACS the rates of new heart failure or pulmonary edema, in hospital, decreased significantly. The risk score for patients with NSTE ACS increased modestly over the course of the study. After adjustment for risk status, the rate of hospital death declined by approximately a quarter. More marked changes may be evident with longer follow-up because the beneficial impact of interventional therapy may be seen with later follow-up.[20-23] The results of a meta-analysis of trials of interventional therapy suggest an additional hazard of death or myocardial infarction during the hospital phase that is subsequently overcome by postdischarge benefit.[23,24]

Since GRACE was launched in 1999, NSTE ACS guidelines from both the American College of Cardiology/American Heart Association (ACC/AHA)[1,2] and the European Society of Cardiology (ESC)[3,4] have been updated to include data from recent clinical trials. In an earlier study from the GRACE registry, data from nearly 13 000 patients with an ACS were analyzed to evaluate the uptake of selected cardiac medications and invasive therapies between 1999 and 2001 and to assess the impact of geographical and hospital characteristics on this pattern.[7] During this period, new guidelines were released by the ESC and the ACC/AHA, and the results of 2 major clinical trials (Fragmin during Instability in Coronary Artery Disease [FRISC] II,[25,26] GUSTO IV-ACS[27]) were published. The results of our earlier study suggest that hospital status, access to resources, and geographical factors, rather than the publication of guidelines, influence the uptake of new therapies into practice.[7] We also reported increases in the use of evidence-based cardiac medications between July 1999 and December 2001 but no significant decline in death rates was observed over that interval.[7] Data from the present study (1999 to 2006) demonstrate substantial temporal changes in the use of pharmacological and interventional therapies in ACS and clear evidence for a reduction in new heart failure and in-hospital deaths especially in patients with STEMI. Our multinational data, combined with those from CRUSADE,[28] suggest the potential for further reductions in patient outcomes with greater uptake of evidence-based therapies and interventions.

## Strengths and Limitations

GRACE is the largest multinational observational cohort study to include the spectrum of patients with ACS. GRACE is designed to be representative of regional communities and uses standardized criteria for defining ACS and hospital outcomes, rigorous quality control, and audit measures. The participating clusters reflect regional practices and outcomes but do not necessarily reflect practice for specific countries. Participating hospitals are sent feedback on a 6-month basis, so we cannot determine whether improvements in adherence to evidence-based medication are taking place nationwide or are limited to participating sites. Increasing use of troponin measurement throughout the study may have led to underestimation of the detection of small reinfarctions if troponin was already elevated at presentation and if the patient did not evolve new electrocardiographic changes of myocardial infarction.

## Conclusions

These contemporary multinational observational data show substantial changes in the management of patients with STEMI or NSTE ACS studied between 1999 and 2006. The main changes demonstrate a marked increase in interventional therapy in both ST elevation and NSTE ACS and changes in pharmacological therapy, including increases in use of β-blockers, statins, ACE inhibitors (or ARBs), and thienopyridines in patients with an ACS, and Gp IIb/IIIa inhibitors in patients with STEMI. The changes are consistent with trial evidence and national and international guidelines. The risk profile for patients with STEMI has not changed significantly over this interval, whereas the risk for patients with NSTE ACS has increased slightly. This study population is the first demonstration of significant reductions observed in hospital rates of new heart failure in ACS patients, over time, and of reductions in mortality.

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**Author Contributions:** Dr Fox had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Fox, Steg, Eagle, Goodman, Anderson, Granger, Budaj, Gore.
*Acquisition of data:* Fox, Steg, Eagle, Goodman, Anderson, Granger, Budaj, Gore.
*Analysis and interpretation of data:* Fox, Steg, Eagle, Goodman, Anderson, Granger, Flather, Budaj, Quill, Gore.
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*Study supervision:* Fox, Steg, Anderson, Gore.
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