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From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes

The Global Registry of Acute Coronary Events (GRACE)

Keith A. A. Fox[a]*, Shaun G. Goodman[b], Frederick A. Anderson Jr.[c], Christopher B. Granger[d], Mauro Moscucci[e], Marcus D. Flather[f], Frederick Spencer[c], Andrzej Budaj[g], Omar H. Dabbous[c], Joel M. Gore[c], on behalf of the GRACE Investigators[1]

[a] *The University and The Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK*
[b] *Canadian Heart Research Centre and Terrence Donnelly Heart Centre, Division of Cardiology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada*
[c] *University of Massachusetts Medical School, Worcester, MA, USA*
[d] *Duke University Medical Center, Durham, NC, USA*
[e] *University of Michigan Health System, Ann Arbor, MI, USA*
[f] *Royal Brompton & Harefield NHS Trust, London, UK*
[g] *Postgraduate Medical School, Grochowski Hospital, Warsaw, Poland*

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Aims The extent to which hospital and geographic characteristics influence the time course of uptake of evidence from key clinical trials and practice guidelines is unknown. The gap between evidence and practice is well recognized but the factors influencing this disjunction, and the extent to which such factors are modifiable, remain uncertain.

Methods and results Using chronological data from the GRACE registry (n=12 666, July 1999 to December 2001), we test the hypothesis that hospital and geographic characteristics influence the time course of uptake of evidence-based guideline recommendations for acute coronary syndromes (ACS) with and without ST elevation. Certain therapies were widely adopted in both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) patients (aspirin >94% of all patients; beta-blockers 85–95%) and changed only modestly over time. Significant increases in the use of low-molecular-weight heparins and glycoprotein IIb/IIIa inhibitors occurred in STEMI and NSTEMI patients in advance of published practice guidelines (September/November 2000) with marked geographical differences. The highest use of LMWH was in Europe in NSTEMI (86.8%) and the lowest in the USA (24.0%). Contrasting geographical variations were seen in the use of percutaneous coronary intervention (PCI) in NSTEMI: 39.5% USA, 34.6% Europe, 33.5% Argentina/Brazil, 25.0% Australia/New Zealand/Canada (July–December 2001). The

* Corresponding author: Professor Keith A. A. Fox, Department of Cardiology, University of Edinburgh, Edinburgh EH3 9YW, UK. Tel.: +44-131-536-2742; fax: +44-131-536-2744
[1] A complete list of investigators and institutions can be found in Appendix A
E-mail address: k.a.a.fox@ed.ac.uk (K.A.A. Fox).

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use of PCI was more than five times greater in hospitals with an on-site catheterization laboratory compared to centres without these facilities, and geographic differences remained after correction for available facilities.
Conclusions Hospital and geographical factors appear to have a marked influence on the uptake of evidence-based therapies in ACS management. The presentation and publication of major international guidelines was not associated with a measurable change in the temporal pattern of practice. In contrast, antithrombotic and interventional therapies changed markedly over time and were profoundly influenced by hospital and geographic characteristics.

Introduction

The past decade has witnessed a rapid evolution in therapeutic options for patients with acute coronary syndromes (ACS). These changes reflect improved understanding of pathogenic mechanisms and the impact of a complex array of clinical trials. How do the data from the rapidly evolving evidence base translate into clinical practice and how do guidelines and hospital characteristics influence the temporal patterns of uptake of novel therapies and strategies?

Based on analyses of the published trial data, and meta-analyses, guideline groups from the American College of Cardiology (ACC), American Heart Association (AHA) and the European Society of Cardiology (ESC) have reached largely consistent interpretations and recommendations.[1,2] Nevertheless, substantial gaps exist between guidelines for the management of ACS and current practice.[3–6] Further, geographical factors, hospital characteristics and access to resources may have a profound influence on the uptake of evidence-based recommendations.

The large-scale multinational observational GRACE (Global Registry of Acute Coronary Events) registry was established in 1999 with the aim of providing reliable and precisely defined data on the treatment, practice patterns and long-term outcomes of patients with ACS, and initial results have recently been published.[7–9] With continuous data collection and consistent recruitment populations in 14 countries, GRACE provides the opportunity to analyse data on the temporal characteristics of pharmacological treatment and coronary interventions from geographically diverse but representative communities. Data from the GRACE registry were used to test the hypothesis that geographical factors and the hospital characteristics may influence the rate of uptake of evidence-based therapeutic approaches into clinical practice.

Methods

Full details of the GRACE rationale and methodology have been published.[10.] Briefly, GRACE is designed to reflect an unbiased population of patients with ACS, irrespective of geographic region. Currently, 94 hospitals located in 14 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, United Kingdom, United States) are participating in this observational study.

Patients entered in the registry had to be at least 18 years old and alive at the time of hospital presentation, be admitted for ACS as a presumptive diagnosis and have symptoms consistent with acute ischaemia in addition to at least one of the following: electrocardiographic changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, and/or documentation of coronary artery disease. The qualifying ACS must not have been precipitated by significant comorbidity, trauma or surgery. At approximately 6 months after hospital discharge, patients were followed up to ascertain the occurrence of selected longer-term study outcomes. Where required, study investigators received approval from their local hospital ethics or institutional review board.

Data were collected at each site by a trained coordinator using a standardized case report form. Demographic characteristics, medical history, presenting symptoms, duration of prehospital delay, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected. Standardized definitions of all patient-related variables and clinical diagnoses were used. For each category of treatment only eligible patients without exclusion characteristics were analyzed (see Appendix B). All cases were assigned to one of the following categories:

- ST-segment elevation myocardial infarction (STEMI): new or presumed new ST-segment elevation $\geqslant$1 mm seen in any location or new left bundle branch block on the index or qualifying electrocardiogram with at least one positive cardiac biochemical marker of necrosis (including troponin).
- Non-ST-segment elevation myocardial infarction (NSTEMI): presence of at least one positive cardiac biochemical marker of necrosis without new ST-segment elevation seen on the index or qualifying electrocardiogram.
- Unstable angina: absence of ST-segment elevation on the electrocardiogram and serum biochemical markers indicative of myocardial necrosis within each hospital laboratory's normal range but with a discharge diagnosis of ACS. Patients originally admitted for unstable angina but in whom myocardial infarction occurred during the hospital stay were classified as having a myocardial infarction.
- Other cardiac/non-cardiac diagnoses: cases where the presumptive admission diagnosis was acute coronary syndrome or 'chest pain/rule out myocardial infarction'; however, these patients were subsequently shown to have some other cardiac or non-cardiac cause for their presentation.

Standardized definitions were also used for selected hospital complications and outcomes.[10]

Statistical analysis

The analysis focuses on the populations of patients diagnosed with STEMI and those with NSTEMI. The two and half years of patient enrolment into GRACE were divided into five time periods of 6 months each. Chi-square test for trend was used

Table 1 Baseline patient characteristics

	STEMI[a] patients (*n*=6625)	NSTEMI[b] patients (*n*=6041)
Median age (years)	64 (54, 74)	69 (58, 77)
Male gender (%)	71.0	66.6
Previous medical history (%)		
Angina	46.8	62.2
Myocardial infarction	19.1	32.3
PCI[c]/CABG[d]	10.6	23.0
Smoking	62.5	57.4
Diabetes mellitus	21.0	27.0
Hypertension	50.1	61.0
Hyperlipidaemia	36.0	45.3
Participant in clinical trial	7.4	5.0

[a]STEMI, ST-segment elevation myocardial infarction.
[b]NSTEMI, non-ST-segment elevation myocardial infarction.
[c]PCI, percutaneous coronary intervention.
[d]CABG, coronary artery bypass graft.

to test that the proportions in each of the five groups were increasing or decreasing in a linear fashion. The test was double-sided and considered to be statistically significant at $\alpha<0.05$. The analysis was performed with SAS software package (version 8.2, SAS Institute, Cary, NC).

Results

Study population

Data from the first 12 666 unselected patients with ACS (6041 with NSTEMI and 6625 with STEMI) from 94 hospitals in 14 countries were analysed and categorized according to sequential 6-month intervals and also by geographical region. The use of hospital medication and revascularization (PCI or coronary artery bypass grafting [CABG]) and the influence of hospital status (teaching and non-teaching) were stratified according to clinical presentation (STEMI, NSTEMI). The presence or absence of a catheterization laboratory in the hospital of patient presentation was also recorded in relation to patient diagnosis and treatment. Data from patients enrolled in GRACE between July 1999 and December 2001 were analysed according to temporal intervals (6-month periods) to evaluate the chronological pattern in treatment usage, particularly in relation to the publication of ACC/AHA and ESC guidelines and major trials in ACS.[1,2,11–13]

Baseline patient characteristics

The demographic characteristics and previous medical history of patients included in this analysis are shown in Table 1. The median age was 64 years in patients with STEMI and 69 years in patients with NSTEMI. In both the STEMI and NSTEMI cohorts, approximately two-thirds of the patients were male. In patients with a STEMI diagnosis, the percentage of patients with a history of angina, myocardial infarction and previous PCI or CABG was 46.8%, 19.1%, and 10.6%, respectively. Corresponding percentages in the NSTEMI group were 62.2%, 32.3%, and 23.0%, respectively. Overall, 7% of STEMI patients and 5% of NSTEMI patients were also participants in a clinical trial.

Temporal trends: NSTEMI

Outcome measures over time

In patients with NSTEMI outcome changed little over the 2.5-year period (death 5.3% July–December 1999 to 4.8% July–December 2001 [not significant, NS], cardiogenic shock 3.6% and 4.0% for the respective periods, and congestive heart failure 18.9% to 19.4%).

Widely used therapies without a change in practice

Certain therapies were widely adopted and changed only modestly over time (Table 2). Aspirin was prescribed in 94.0% of NSTEMI patients in July–December 1999, 97.8% in the period July–December 2001 ($P<0.0001$). Similarly beta-blocker use increased from 84.8% to 94.7% ($P<0.0001$) in the same interval. Calcium-channel blockers were less frequently used but also varied little (30.8% to 28.1%, P=NS). No major trials were published in this interval relating to these agents, nor were guidelines altered.

Widely used therapies with a change in practice

Antithrombotic therapy

During the study interval data were published from major trials in ACS, including LMWH (FRISC II [Fragmin in Fast Revascularisation during instability in coronary artery disease]),[12] glycoprotein IIb/IIIa inhibitors (GUSTO [Global Utilisation of STreptokinase in occluded arteries] IV-ACS)[13] and new guidelines were produced which included both classes of agent.[1,2]

The temporal trends in the usage of antithrombotic medication in the cohort of patients with NSTEMI are shown in Table 2. In July–December 2001, 62.1% of NSTEMI patients were prescribed LMWH, compared with 48.8% in the corresponding period in 1999. Prescribing of GP IIb/IIIa inhibitors increased in the 2-year study period from 16.6% in July-December 1999 to 31.2% of patients in the same period of 2001. The use of both LMWH and GP IIb/IIIa inhibitors increased in advance of the publication of ESC and ACC/AHA guidelines (September–November 2000).[1,2] Thrombolytic agents were prescribed at a consistently low level in these patients, reflecting the initial presentation with NSTEMI; 6.9% of patients received thrombolytics at the start of the observational period, a figure that decreased to 4.7% by the end of 2001.

Temporal trends in NSTEMI patients: hospital procedures

The temporal trends in the prevalence of PCI, CABG and cardiac catheterization are depicted in Table 2. Cardiac catheterization was a common procedure among patients admitted with NSTEMI, increasing to a moderate extent from 52.3% in July-December 1999 to 60.5% in that same period in 2001. The rate of PCI increased substantially

Table 2 Temporal trends in the management and in-hospital outcomes of 6041 patients with NSTEMI[a] in GRACE (July 1999–December 2001): percentages based on eligible patients for respective treatments (for definitions, see Appendix B)

	Jul-Dec 1999 (*n*=1242)	Jan–Jun 2000 (*n*=1166)	Jul–Dec 2000 (*n*=1193)	Jan–Jul 2001 (*n*=1352)	Jul–Dec 2001 (*n*=1088)	*P* value (Jul–Dec 1999 vs Jul–Dec 2001)	*P* value (5-way)
Management							
Aspirin (%)	94.0	94.0	97.0	96.2	97.8	<0.0001	<0.0001
LMWH[b] (%)	48.8	50.2	58.2	60.0	62.1	<0.0001	<0.0001
Ticlopidine/clopidrogrel (%)	28.1	28.0	36.2	41.3	46.4	<0.0001	<0.0001
Glycoprotein IIb/IIIa inhibitors (%)	16.6	20.4	26.8	30.0	31.2	<0.0001	<0.0001
Statins (%)	42.1	40.0	52.8	53.2	57.4	<0.0001	<0.0001
Beta-blockers (%)	84.8	85.6	91.1	90.0	94.7	<0.0001	<0.0001
Calcium-channel antagonists (%)	30.8	28.2	28.7	28.1	28.1	0.1603	0.1718
ACE[c] inhibitors (%)	52.4	55.7	56.3	60.0	64.2	0.2643	0.0005
Thrombolytics (%)	6.9	5.4	5.0	3.7	4.7	0.2994	0.0698
Cardiac catheterization (%)	52.3	53.4	57.4	55.6	60.5	<0.0001	<0.0001
PCI[d] (%)	28.3	26.0	30.0	31.0	33.4	0.0365	0.0059
CABG[e] (%)	11.8	9.1	10.5	7.7	8.9	0.0944	0.0250
Outcomes[f]							
CHF[g] (%)	18.9	23.4	19.9	19.5	19.4	0.7910	0.4572
Cardiogenic shock (%)	3.6	6.4	4.5	3.4	4.0	0.5835	0.2558
Death (%)	5.3	6.5	5.4	5.1	4.8	0.5739	0.2592

[a] NSTEMI, non-ST-segment elevation myocardial infarction.
[b] LMWH, low-molecular-weight heparins.
[c] ACE inhibitors, angiotensin-converting enzyme inhibitors.
[d] PCI, percutaneous coronary intervention.
[e] CABG, coronary artery bypass graft.
[f] Total patients, unadjusted by eligibility criteria.
[g] CHF, congestive heart failure.

between 1999 and 2001 (from 28.3% to 33.4%), but the increase was gradual and the trend was apparent before the publication of the ESC or ACC/AHA guidelines.[1,2] In contrast, the number of patients who underwent CABG declined from 11.8% in July-December 1999 to 8.9% in the same period in 2001.

Temporal trends in NSTEMI patients: prescribing other hospital medications

While in hospital, patients with a diagnosis of NSTEMI were commonly prescribed beta-blockers, and the use of this therapy remained consistently high throughout the study, the prescription rate being 84.8% at the start of the observational period and 94.7% by the end of 2001 (Table 2). In July–December 2001, angiotensin-converting enzyme (ACE) inhibitors and statins were given to 64.2% and 52.4% of patients, respectively, during their hospital stay. Increased use of ACE inhibitors was evident following the publication of the ESC and ACC/AHA ACS management guidelines at the end of 2000,[1,2] whereas an increase in the prescribing of statins was seen from early 2000. Calcium-channel antagonists were not frequently prescribed to patients with NSTEMI (30.8% of patients in 1999, decreasing gradually to 28.1% in 2001).

Temporal trends in the management of patients with STEMI

Outcome measures over time

Little change was evident in the frequency of death between July–December 1999 and 2001 (8.0% and 9.5%, respectively). The frequency of cardiogenic shock and of congestive heart failure was unchanged (Table 3).

Widely used therapies without a change in practice

Aspirin was consistently prescribed for the majority of patients (95.7% in 1999 and 97.3% in 2001, P=0.0449; Table 3). As for NSTEMI, beta-blockers were commonly prescribed (86.5% in 1999, 93.7% in 2001, P<0.0001) and increased by 7% during the study period. In contrast, calcium-channel antagonist use decreased in STEMI from 16.8% in 1999 to 13.6% in 2001 (P=0.0247; Table 3).

Temporal trends in STEMI patients: use of antithrombotic medication

The use of thrombolytic agents in patients with an admission diagnosis of STEMI decreased from 54.1% prior to mid 2000 to approximately 47% thereafter (Table 3). LMWH was prescribed for an increasing proportion of patients (40.6% increasing to 49.7% by end 2001); the upward trend was apparent from the start of the observation period but was most evident over the year 2000 (Table 3). The use of GP IIb/IIIa inhibitors in patients with STEMI increased markedly over the study period, from 19.5% to 36.8%.

Temporal trends in STEMI patients: hospital procedures

Trends in the frequency of hospital intervention procedures (cardiac catheterization, PCI and CABG) in patients with STEMI were similar to those presented for the cohort of patients with NSTEMI. By the end of the study period (December 2001) catheterization rates were similar for both STEMI and NSTEMI patients (approximately 60%). PCI was carried out in almost 50% of STEMI patients and in one-third of NSTEMI patients (Tables 2 and 3). In addition, the proportion of primary PCIs increased over the study period, from 15.1% at the start of the study period to 26.7%. Whereas the frequency of PCI increased over time, CABG procedures were uncommon in patients with STEMI, being consistently carried out in approximately 4% of patients across the observation period.

Temporal trends in STEMI patients: other hospital medications

In-hospital use of the lipid-lowering statins increased dramatically from 39.6% in 1999 to 59.2% of patients with STEMI in the period July–December 2001. The greatest increase in statin prescribing occurred between January–June 2000 and July–December 2000.

Geographical variations in ACS management

Marked geographical variations were evident for antithrombotic therapy and intervention therapy (Figs. 1–3). In contrast, the use of aspirin, statins, calcium-channel antagonists and ACE inhibitors varied only modestly by geographical region (data not shown).

LMWH

The use of LMWH in NSTEMI patients showed a marked geographical variation (Fig. 1), with treatment uptake being notably higher in Europe and the Australia/New Zealand/Canada region than in the United States or Argentina/Brazil. A similar pattern was evident for STEMI. The highest use of LMWH was in Europe (62.7%) and the lowest was in the United States (19.4%). In the United States the use of LMWH increased subsequent to the publication of the ESC and ACC/AHA guidelines,[1,2] but the values of use were two to three times lower than in other geographical regions (Fig. 1).

By the end of 2001, a substantially higher proportion of patients were prescribed LMWH as antithrombotic medication in non-teaching hospitals than in those with teaching status (70.6% versus 58.3%, respectively). This represents a reversal of the situation in 1999, in which 49.4% of patients in teaching hospitals received LMWH compared with 47.6% in non-teaching centres (Fig. 1).

Glycoprotein IIb/IIIa inhibitors

Wide geographical differences (two- to three-fold) in the prescribing pattern for GP IIb/IIIa inhibitors were also observed (Fig. 2). In 2001, 51.5% of patients with NSTEMI in the United States received GP IIb/IIIa therapy compared with 26.8% of patients in European hospitals and approximately 20% of patients in Australia/New Zealand/Canada and Argentina/Brazil. The use of these agents increased in all four regions over the 2-year period of this study. The rate of uptake in Europe increased most markedly between the period January–June 2000 and

Table 3 Temporal trends in the management and in-hospital outcomes of 6625 patients with STEMI[a] in GRACE (July 1999–December 2001): percentages based on eligible patients for respective treatments (for definitions, see Appendix B)

	Jul–Dec 1999 (*n*=1412)	Jan–Jul 2000 (*n*=1336)	Jul–Dec 2000 (*n*=1359)	Jan–Jul 2001 (*n*=1382)	Jul–Dec 2001 (*n*=1136)	*P* value (Jul–Dec 1999 vs Jul–Dec 2001)	*P* value (5-way)
Management							
Aspirin (%)	95.7	96.4	97.5	98.6	97.3	0.0449	0.0004
LMWH[b] (%)	40.6	41.7	45.0	50.0	49.7	<0.0001	<0.0001
Ticlopidine/clopidrogrel (%)	36.2	33.5	45.8	46.0	51.7	<0.0001	<0.0001
(without PCI)	5.9	7.6	9.0	11.4	15.0	<0.0001	<0.0001
Glycoprotein IIb/IIIa inhibitors (%)	19.5	21.6	32.1	33.0	36.8	<0.0001	<0.0001
(without PCI)	2.9	6.0	8.8	8.4	9.7	<0.0001	<0.0001
Statins (%)	39.6	42.8	54.0	58.5	59.2	<0.0001	<0.0001
Beta-blockers (%)	86.5	88.8	91.8	93.1	93.7	<0.0001	<0.0001
Calcium-channel antagonists (%)	16.8	13.6	12.9	14.6	13.6	0.0247	0.0650
ACE[c] inhibitors (%)	63.3	63.0	72.1	73.6	77.3	0.0736	<0.0001
Thrombolytics (%)	54.1	56.0	49.7	49.8	47.0	0.0034	0.0002
No reperfusion[d] (%)	32.4	31.4	29.3	28.8	30.2	0.3213	0.1126
Cardiac catheterization (%)	55.3	51.7	59.6	60.8	59.2	0.0050	<0.0001
PCI[e] (%)	40.8	37.0	48.0	47.4	49.0	0.0009	<0.0001
-Primary PCI within 12 h (%)	15.1	16.8	25.3	24.6	26.7	<0.0001	<0.0001
CABG[f] (%)	4.3	4.2	5.2	4.8	4.2	0.9651	<0.0001
Outcomes[g]							
CHF[h] (%)	21.5	21.2	21.0	21.1	21.1	0.7812	0.7250
Cardiogenic shock (%)	8.2	7.6	6.4	7.1	8.7	0.6107	0.7836
Death (%)	8.0	7.0	6.6	8.0	9.5	0.1678	0.1260

[a] STEMI, ST-segment elevation myocardial infarction.
[b] LMWH, low-molecular-weight heparins.
[c] ACE inhibitors, angiotensin converting enzyme inhibitors.
[d] No thrombolysis and no PCI.
[e] PCI, percutaneous coronary intervention.
[f] CABG, coronary artery bypass graft.
[g] Total patients, unadjusted by eligibility criteria.
[h] CHF, congestive heart failure.

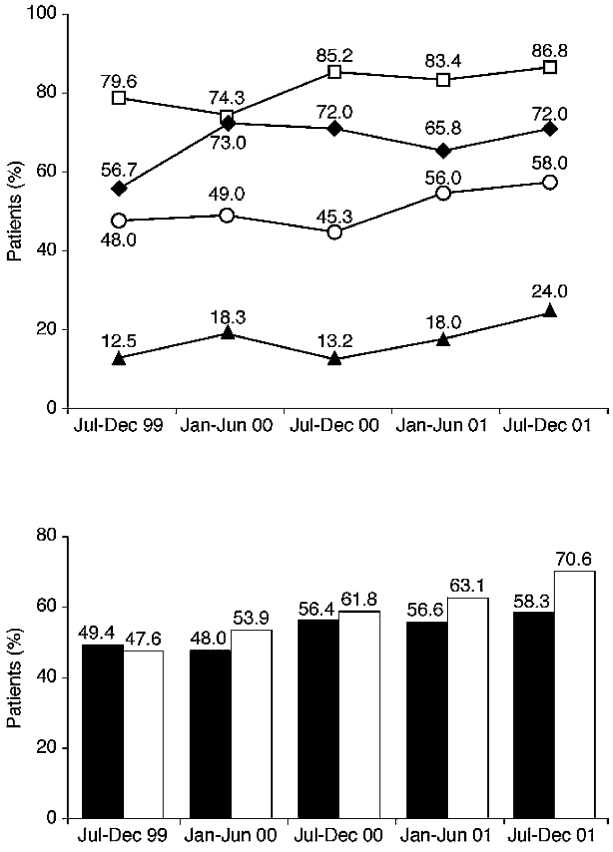

Fig. 1 (a) Geographic variation in rate of uptake of low-molecular-weight heparin (LMWH) treatment in non-ST-segment elevation myocardial infarction patients. (□) Europe; (◆) Australia/New Zealand/Canada; (○) Argentina/Brazil; (▲) United States. (b) Influence of hospital status on prescribing rate. (■) Teaching hospitals; (□) non-teaching hospitals.

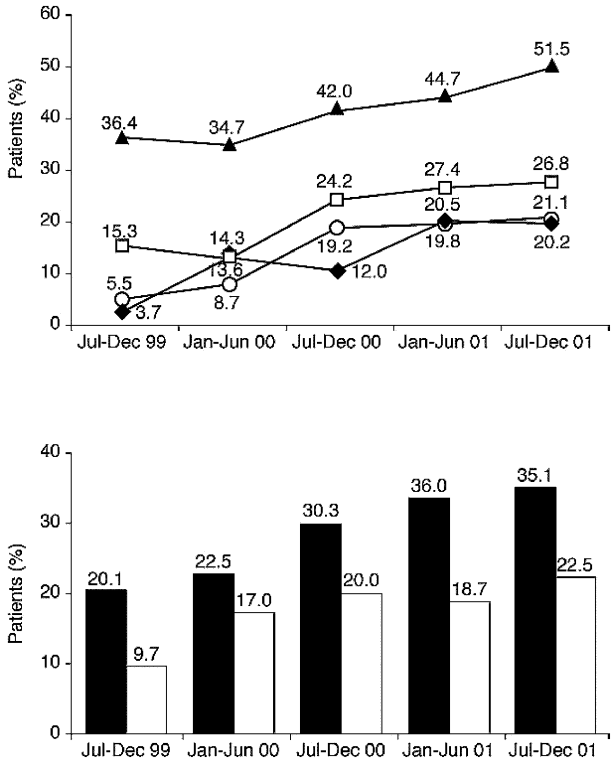

Fig. 2 (a) Geographic variation in prescription of glycoprotein IIb/IIIa inhibitors in non-ST-segment elevation myocardial infarction patients. (□) Europe; (◆) Australia/New Zealand/Canada; (○) Argentina/Brazil; (▲) United States. (b) Influence of hospital teaching status. (■) Teaching hospitals; (□) non-teaching hospitals.

July–December 2000 (from 15.3% to 26.8%). Evidence-based guidelines supporting the clinical use of these agents in non-ST-segment elevation ACS were published in the later part of 2000.[1,2]

There was a wide discrepancy in the usage pattern of GP IIb/IIIa inhibitors according to hospital status. At the end of 2001, the prescribing rate in teaching hospitals was substantially higher than that in non-teaching units (35.1% versus 22.5%, respectively; Fig. 2). This observational trend is similar to that described for PCI procedures.

PCI

In 2001, the highest percentage of patients with NSTEMI undergoing PCI was reported in the United States (39.5%; Fig. 3). This was similar to the PCI rate reported in 1999 (41.4%). Increased use of PCI was observed in Europe and the patterns of practice varied by geographical region (Fig. 3).

The number of PCI procedures carried out in patients with a NSTEMI diagnosis is significantly greater in hospitals with teaching status than in those without (36.4% vs 28.2%, respectively, at the end of 2001), and this trend was reported consistently across all the whole study period (Fig. 3).

Influence of the availability of on-site catheterization facilities on the incidence of PCI

The GRACE registry data were also used to evaluate the influence of an on-site cardiac catheterization laboratory on the use of PCI procedures (Fig. 4). The PCI procedure rate for all ACS patients was significantly higher in hospitals with direct access to a catheterization laboratory: 44.0% versus 5.2% in those without direct access. The respective PCI rates for STEMI were 61.0% vs 5.8%.

Discussion

A key aim of this study was to evaluate the temporal pattern of management of ACS, and to assess the impact of geographical factors and hospital characteristics (e.g. teaching status) on this pattern. Two sets of key evidence-based guidelines have been published since the GRACE study was launched in 1999: the ESC published Task Force recommendations in September 2000 and the joint guidelines from the ACC/AHA were published two months later, in November 2000. Two major clinical trials also reported results in the study period: FRISC II[11,12] and GUSTO IV-ACS.[13] FRISC II, published in August 1999, showed a clear advantage of an early interventional approach to ACS management—particularly in high-risk

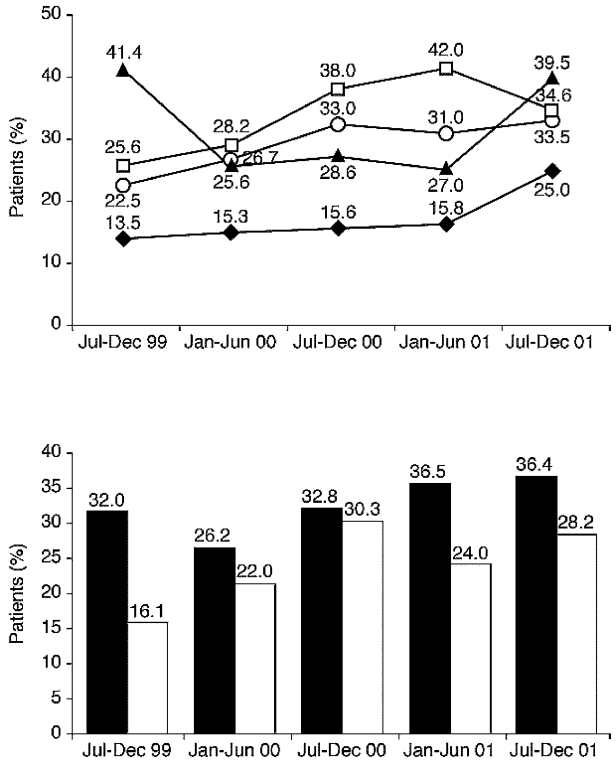

Fig. 3 (a) Geographic variation in the percentages of patients with non-ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention (PCI). (□) Europe; (◆) Australia/New Zealand/Canada; (○) Argentina/Brazil; (▲) United States. (b) Influence of hospital teaching status. (■) Teaching hospitals; (□) non-teaching hospitals.

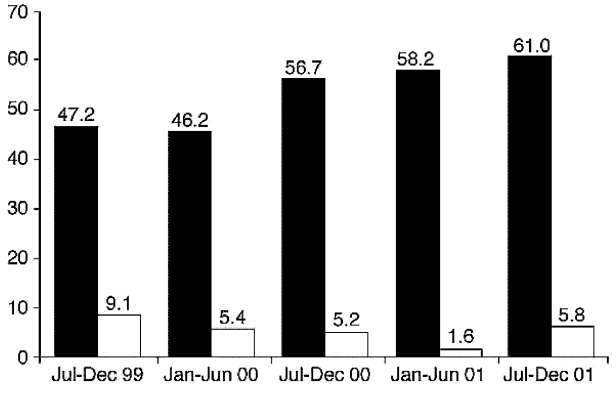

Fig. 4 Influence of on-site catheterization facilities on the frequency of percutaneous coronary intervention in ST-segment elevation myocardial infarction patients. (■) Catheterization laboratory; (□) No catheterization laboratory.

patients—and reported improved clinical outcomes in ACS patients given LMWH therapy.[11,12] The findings of GUSTO IV-ACS, published in June 2001, showed no evidence for benefit with abciximab in patients predominantly managed medically with ACS. This was in contrast to previous clinical trials that showed consistent benefit of abciximab therapy in NSTEMI patients undergoing PCI.[13]

Our data demonstrate that a consistently high proportion of patients, with either STEMI or NSTEMI, now receive aspirin and beta-blocker therapy in the acute phase of hospital management, as recommended in the treatment guidelines. These recent data contrast with lower use seen in EUROASPIRE II, conducted in 1999–2000.[4] In-hospital use of LMWH and GP IIb/IIIa also showed marked increases over the study period in all patients; however, this trend occurred in advance of the publication of the ESC and ACC/AHA guidelines advocating the use of these therapies in ACS management. There was no measurable impact on the temporal pattern of practice of the results of FRISC II or GUSTO IV-ACS, although FRISC II may have contributed to an increase in uptake of LMWH therapy.[11–13] More than half of all ACS patients in the study received lipid-lowering statin treatment during their hospital stay despite a lack of large-scale evidence or guideline recommendations to support this practice.

The ESC Euro Heart Survey of ACS, which recently published data on the use of in-hospital ACS therapies during the last quarter of 2000,[3] provides cross-sectional data which confirm the frequency of use of specific medications and interventions seen in the same period in this study. However, only 10% of all NSTEMI patients in the Euro Heart Survey received a GP IIb/IIIa inhibitor and only 27% of NSTEMI patients undergoing PCI received this therapy.[3] The present study reports that 26.8% of NSTEMI patients received GP IIb/IIIa inhibitor therapy at the end of 2000 (24.2% in Europe); this figure was 56.4% in patients undergoing PCI (52.0% in Europe). In patients with STEMI, the rate of use of thrombolytics declined over the study period. This reduction was compensated for by an increase in the use of PCI, and the overall rate of reperfusion remained unchanged.

The results reported in this paper demonstrate that cardiac catheterization is now a routine procedure in ACS patients with either STEMI or NSTEMI, but they reveal major differences in procedure rates according to hospital characteristics (teaching status, catheterization facilities). Rates of catheterization and PCI/CABG procedures were significantly higher in teaching centres and in those with on-site access to a catheterization laboratory. These two factors are not entirely separable (hospitals with teaching status are highly likely to have on-site catheterization laboratory facilities). Correspondingly, GP IIb/IIIa inhibitors are also prescribed more frequently in hospitals with teaching status due to their use as procedural antiplatelet agents in PCI.

Interestingly, despite the uptake of a variety of new treatments and the use of cardiac interventions, the mortality rate for both STEMI and NSTEMI patients did not alter throughout the duration of the study. In the NRMI 1, 2 and 3 studies, among 1 161 550 patients with myocardial infarction, the hospital mortality rate fell from 11.2% in 1990 to 9.4% in 1999.[14] The latter figure is similar to that for STEMI patients in the current study, which started in 1999, suggesting that the introduction of new therapies has not led to a noticeable reduction in in-hospital mortality.

Wide differences in practice patterns were seen according to geographical region, consistent with previous cross-sectional reports.[3,4] However, the magnitude of these differences (up to 2.5 fold) was substantially larger (Figs. 1–3) than could be accounted for as a result of differences in hospital characteristics. Furthermore, the temporal patterns, comparing geographical regions, were markedly discordant despite similar access to published trial data and international guidelines. Additional studies are merited to help explain the striking differences in practice in the face of common evidence. This is illustrated in the comparison of US and European data, where similar rates of interventions, and use of aspirin, beta-blockers, statins and other therapies are seen, but widely different rates of use of GP IIb/IIIa inhibitors and LMWHs are apparent.

The frequency of interventions was substantially lower in Australia/New Zealand/Canada compared with the data from Europe and the United States. This variation in intervention rates may be due to the impact of established practice patterns rather than access to evidence-based guidelines. The Euro Heart ACS survey found that angiography and PCI were performed according to hospital standard routines.[3] Interestingly some therapies increased in uptake in advance of published evidence and guidelines (e.g. LMWH in STEMI, GP IIb/IIIa inhibitors in STEMI) or in the absence of such evidence (in-hospital use of statins).

The present report provides large-scale temporal data as further evidence of the gap between the emergence of international evidence-based clinical practice recommendations and their implementation in clinical practice. In 1994, Rogers et al. reported observations from the National Registry of Myocardial Infarction (NRMI) suggesting that the management of myocardial infarction in the United States failed to conform to the recommendations of recent clinical trials.[5] Local factors, such as national healthcare policies and the availability of resources, appear to have a profound influence on the extent and time course of uptake of such therapies. EUROASPIRE, conducted in 1999 to 2000, described wide geographical variations in clinical practice across Europe.[4] Similarly, the PRAIS-UK survey, in NSTEMI patients only, highlighted the low rates of angiography, PTCA and CABG in the UK compared to both current recommendations and the treatment patterns of other European countries such as Germany, France and Italy.[15] A major challenge exists to bridge the gap between evidence and practice and to expedite the uptake of international guidelines.

Strengths and limitations

GRACE is the largest multinational registry study to include the complete spectrum of ACS patients. It is designed to be representative of regional communities and employs standardized criteria for defining ACS and hospital outcomes and quality control and audit measures. As in the MONICA (MONitoring trends and determinants In CArdiovascular diseases) study, such regional data may accurately represent the local populations but may not be representative of the countries as a whole. We are unable to examine the influence of national guidelines and the availability of resources on the rate of uptake of various treatments.

Conclusions

Hospital status, access to local resources and other geographical factors appear to have a marked influence on uptake of evidence-based therapies into clinical practice. In contrast, no clear temporal relationship was apparent between the publication of the ESC and ACC/AHA guidelines in 2000 and the rate at which treatment recommendations enter into hospital practice. Local and national patterns of practice appear to determine which therapies are implemented, some in advance of the evidence and others only slowly despite robust evidence and guidelines.

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Appendix A

GRACE Scientific Advisory Committee

Keith A. A. Fox, The Royal Infirmary of Edinburgh, Edinburgh, Scotland, UK; Joel M. Gore, University of Massachusetts Medical School, Worcester, Massachusetts, U.S.A. (GRACE Co-Chairs); Kim A. Eagle, University Hospital, Ann Arbor, Michigan, USA; Ph. Gabriel Steg, Hôpital Bichat, Paris, France (GRACE Publication Committee Co-Chairs); Giancarlo Agnelli, University of Perugia, Perugia, Italy; Frederick A. Anderson Jr, University of Massachusetts Medical School, Worcester, MA, USA; Álvaro Avezum, CTI-A Hospital Albert Einstein, São Paulo, Brazil; David Brieger, Concord Hospital Sydney, Australia; Andrzej Budaj, Grochowski Hospital, Warsaw, Poland; Marcus D. Flather, Royal Brompton & Harefield NHS Trust, London, UK; Robert J. Goldberg, University of Massachusetts Medical School, Worcester, MA, USA; Shaun G. Goodman, St. Michael's Hospital, Toronto, Ontario, Canada; Christopher B. Granger, Duke University Medical Center, Durham, North Carolina, USA; Dietrich C. Gulba, Cardiology Krankenhaus Düren Medizinische Klinik Düren Germany; Enrique Gurfinkel, Buenos Aires University, Buenos Aires, Argentina; Brian M. Kennelly, Hoag Memorial Hospital Presbyterian, Newport Beach, California, USA; Werner Klein, Medizinische Universitätsklinik, Graz, Austria; José

López-Sendón, Hospital Universitario Gregorio Marañon, Madrid, Spain; Gilles Montalescot, Pitié-Salpétrière Hospital, Paris, France; Frans Van de Werf, University of Leuven, Leuven, Belgium.

Appendix B

Treatment eligibility criteria: exclusions

Aspirin

1 Patients who died or were transferred out on the same date of hospital admission
2 Medical history of bleeding and haemorrhagic stroke
3 In-hospital bleeding and haemorrhagic stroke
4 Patients on prior warfarin therapy
5 Any contraindication to aspirin

Heparin

1 Patients who died or were transferred out on the same date of hospital admission
2 Medical history of bleeding and haemorrhagic stroke
3 In-hospital bleeding and haemorrhagic stroke
4 Contraindications to heparin including known thrombocytopenia

Thienopyridines

1 Patients who died or were transferred out on the same date of hospital admission
2 Medical history of bleeding and haemorrhagic stroke
3 In-hospital bleeding and haemorrhagic stroke
4 Patients on prior warfarin therapy

Glycoprotein IIb/IIIa inhibitors

1 Patients who died or were transferred out on the same date of hospital admission
2 Medical history of bleeding and haemorrhagic stroke
3 In-hospital bleeding and haemorrhagic stroke
4 Contraindications to heparin including known thrombocytopenia

Statins

1 Patients who died or were transferred out on the same date of hospital admission

Beta-blockers

1 Patients who died or were transferred out on the same date of hospital admission
2 Pulse <60 while not on beta-blockers
3 Atrioventricular block
4 Systolic blood pressure <90 mmHg
5 Killip class (II, III or IV)
6 In-hospital cardiogenic shock
7 Any contraindication to beta-blockers

Angiotensin-converting enzyme (ACE) inhibitors

1 Patients who died or were transferred out on the same date of hospital admission
2 In-hospital cardiogenic shock
3 Killip class IV
4 Serum creatinine >2.5 mg/dl
5 Any contraindication to ACE inhibitors

Thrombolytics (STEMI patients)

1 Medical history of bleeding and haemorrhagic stroke
2 In-hospital bleeding and haemorrhagic stroke
3 Chest pain to needle >12 h
4 In-hospital cardiogenic shock

Percutaneous coronary intervention (PCI)

1 Patients who were transferred out on the same date of hospital admission
2 Time to PCI >12 h

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