

Papers

Access to catheterisation facilities in patients admitted with acute coronary syndrome: multinational registry study

Frans Van de Werf, Joel M Gore, Álvaro Avezum, Dietrich C Gulba, Shaun G Goodman, Andrzej Budaj, David Brieger, Kami White, Keith A A Fox, Kim A Eagle, Brian M Kennelly, for the GRACE Investigators

Abstract

Objective To investigate the relation between access to a cardiac catheterisation laboratory and clinical outcomes in patients admitted to hospital with suspected acute coronary syndrome.

Design Prospective, multinational, observational registry.

Setting Patients enrolled in 106 hospitals in 14 countries between April 1999 and March 2003.

Participants 28 825 patients aged ≥ 18 years.

Main outcome measures Use of percutaneous coronary intervention or coronary artery bypass graft surgery, death, infarction after discharge, stroke, or major bleeding.

Results Most patients (77%) across all regions (United States, Europe, Argentina and Brazil, Australia, New Zealand, and Canada) were admitted to hospitals with catheterisation facilities. As expected, the availability of a catheterisation laboratory was associated with more frequent use of percutaneous coronary intervention (41% *v* 3.9%, $P < 0.001$) and coronary artery bypass graft (7.1% *v* 0.7%, $P < 0.001$). After adjustment for baseline characteristics, medical history, and geographical region there were no significant differences in the risk of early death between patients in hospitals with or without catheterisation facilities (odds ratio 1.13, 95% confidence interval 0.98 to 1.30, for death in hospital; hazard ratio 1.05, 0.93 to 1.18, for death at 30 days). The risk of death at six months was significantly higher in patients first admitted to hospitals with catheterisation facilities (hazard ratio 1.14, 1.03 to 1.26), as was the risk of bleeding complications in hospital (odds ratio 1.94, 1.57 to 2.39) and stroke (odds ratio 1.53, 1.10 to 2.14).

Conclusions These findings support the current strategy of directing patients with suspected acute coronary syndrome to the nearest hospital with acute care facilities, irrespective of the availability of a catheterisation laboratory, and argue against early routine transfer of these patients to tertiary care hospitals with interventional facilities.

Introduction

The optimal early management of patients presenting to hospital with acute coronary syndrome has been studied extensively over the past 10 years. Recent randomised trials and meta-analyses have shown better clinical outcomes in patients assigned to an early invasive strategy, including primary percutaneous coronary intervention for those with persistent ST segment elevation,¹ or early revascularisation with percutaneous coronary intervention or coronary artery bypass grafting in

those with non-ST segment elevation acute coronary syndrome.²⁻⁴ In these randomised trials a reduction in recurrent ischaemic events was consistently associated with the invasive strategy, while significant reductions in mortality were rarely observed. For example, in the latest study—the randomised intervention trial of unstable angina (RITA-3)—there was a 34% reduction in the risk of death, reinfarction, or refractory angina in the invasive group at four months, mainly due to a halving of the rise of refractory angina but without any survival benefit.⁴

In the “real world” the choice of a management strategy is often governed by the facilities available at the hospital at which patients initially present. Though thrombolytic and antithrombotic therapies are widely available, only 20% of emergency care departments have access to a catheterisation laboratory, and still fewer hospitals have the capability to perform immediate percutaneous coronary intervention or coronary artery bypass grafting.⁵ The issue of whether access to interventional facilities affects clinical outcomes in patients admitted with acute coronary syndrome is under scrutiny. A positive association between the availability of a catheterisation laboratory and improved outcomes would argue for a change in the routing of patients with acute coronary syndrome from the nearest community hospital to a regional specialised tertiary care hospital with immediate access to a catheterisation laboratory (similar to the handling of acute trauma cases).⁶

The global registry of acute coronary events (GRACE) is an ongoing, multinational, prospective registry of patients with the entire spectrum of acute coronary syndrome. The registry collects data on baseline characteristics, management, and clinical outcomes. We investigated the relation between access to a cardiac catheterisation laboratory and the use of percutaneous coronary intervention or coronary artery bypass grafting and clinical outcomes in patients admitted with suspected acute coronary syndrome.

Methods

Full details of the methods have been published previously.⁷⁻⁹ The global registry is designed to reflect an unbiased population of patients with acute coronary syndrome, irrespective of geographical region. A total of 106 hospitals located in 14 countries contributed data to this analysis.

Patients entered in the registry had to be at least 18 years old, be admitted with a presumed diagnosis of acute coronary



See bmj.com for three tables of additional data on baseline characteristics and use of revascularisation procedures in the three diagnostic subgroups and on regional differences in availability of catheterisation laboratories.

syndrome (that is, have symptoms consistent with acute ischaemia), and have at least one of the following: electrocardiographic changes consistent with acute coronary syndrome, serial increases in serum biochemical markers of myocardial necrosis, or documentation of coronary artery disease. The qualifying acute coronary syndrome must not have been precipitated by non-cardiovascular comorbidity (for example, anaemia or surgery). At about six months after discharge from hospital, patients were followed up by telephone, clinical visits, or through calls to their primary care physician to ascertain the occurrence of selected long term study outcomes.¹⁰

To ensure the enrolment of an unbiased population, each month we recruited the first 10 to 20 eligible consecutive patients from each site. We collected data on demographic characteristics, medical history, presenting symptoms, time from onset of symptoms to admission, biochemical and electrocardiographic findings, treatment practices, and various hospital outcomes. We used standardised definitions of all variables related to patients, clinical diagnoses, and hospital complications and outcomes. All cases were assigned to ST segment elevation myocardial infarction, non-ST segment elevation myocardial infarction, or unstable angina.

Patients were diagnosed with ST segment elevation myocardial infarction when they had new or presumed new ST segment elevation ≥ 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 measurements, whether qualitative or quantitative). In cases of non-ST segment elevation myocardial infarction at least one positive cardiac biochemical marker of necrosis without new ST segment elevation seen on the index or qualifying electrocardiogram had to be present. Unstable angina was diagnosed when serum biochemical markers indicative of myocardial necrosis were within the normal range. Patients originally admitted because of unstable angina but in whom myocardial infarction developed during the hospital stay were classified as having a myocardial infarction.

We analysed regional differences according to the distribution of centres in four geographical regions: Australia, New Zealand, and Canada (which were grouped together because they exhibited similar practice patterns with regards to the use of invasive procedures), Argentina and Brazil, Europe, and the United States.

Statistical analysis

We expressed categorical variables as frequencies and percentages and continuous variables as medians (interquartile range). We assessed differences in demographics, clinical characteristics, and outcomes between patients who were admitted to hospitals with or without access to a catheterisation laboratory using χ^2 tests for categorical variables and Wilcoxon rank sum or Kruskal-Wallis tests for continuous variables. Multiple logistic regression was used to examine the association between first admission to a hospital with catheterisation facilities or a hospital without such facilities and in clinical outcomes of major bleeding, stroke, and mortality, with adjustment for age, sex, Killip class (clinical estimate of severity of infarct), heart rate, systolic blood pressure, diastolic blood pressure, cardiac arrest at presentation, history of diabetes, previous myocardial infarction, stroke, positive stress test, percutaneous coronary intervention, coronary artery bypass graft, hypertension, and geographical region.⁹ Cox regression was used to examine the association between availability of catheterisation facilities at the hospital of first admission and mortality at 30 days and six months. We also

examined reinfarction at six months after hospital discharge. The statistical analysis was performed with SAS software, version 8.1.

Results

Study population

We analysed data from 28 825 patients with acute coronary syndrome enrolled between April 1999 and March 2003 from 106 hospitals in 14 countries. Baseline risk factors, use of percutaneous coronary intervention and coronary artery bypass graft, and clinical outcomes were stratified according to the presence or absence of a catheterisation laboratory. The crude model for death at 30 days and at six months was based on data from 28 371 (98%) patients, while the adjusted model was based on data from 25 402 (88%) patients. We collected data on myocardial infarction after discharge up to six months as of June 2000 and in 15 205 patients.

Baseline clinical characteristics and revascularisation procedures

We analysed baseline characteristics of the patient cohort according to the capability of the admitting hospital to carry out cardiac catheterisation (table 1). Most patients in this analysis (77%) were admitted to hospitals with catheterisation facilities with a consistent pattern across different regions (79% in the United States, 76% in Europe, 66% in Australia/New Zealand/Canada, and 83% in Argentina/Brazil). The median age of admitted patients was 66 years in units with catheterisation facilities and 68 years in units without such facilities. Overall, most patients admitted were male, but more female patients were admitted to hospitals without catheterisation facilities (32% *v* 37%). More patients who were first admitted to hospitals without catheterisation facilities were in a poor haemodynamic state (that is, Killip class $>I$).

Table 1 also shows the medical history of patients in each type of hospital facility. A history of previous myocardial infarction and hypertension was equally prevalent in the two groups. A history of diabetes mellitus was more common in patients admitted to hospitals with catheterisation facilities (25% *v* 23%), as was the previous use of invasive procedures.

In patients admitted to hospitals with catheterisation facilities, percutaneous coronary intervention procedures and coronary artery bypass graft during the index admission were significantly more common than in patients first admitted to hospitals without facilities: 41% *v* 4% for percutaneous coronary intervention and 7% *v* $<1\%$ for coronary artery bypass graft (table 1). The largest difference in percutaneous coronary intervention was found in Europe, with 48% in hospitals with and 2% in hospitals without catheterisation facilities, respectively. For coronary artery bypass graft the largest differences between hospitals with and without facilities were found in the United States (11% *v* 1.6%) and Argentina/Brazil (10% *v* 1%).

Clinical outcomes

The figure shows the observed clinical outcomes, the absolute differences in outcome between patients first admitted to hospitals with or without catheterisation facilities, and the unadjusted and adjusted odds ratios/hazard ratios in the total acute coronary syndrome population. Tables 2 and 3 show the results for the diagnostic subgroups of patients with acute coronary syndrome.

In the total population of patients with acute coronary syndrome, and after adjustment for baseline characteristics, medical history, and geographical region, patients first admitted

Table 1 Key baseline characteristics and revascularisation procedures by type of hospital (n=28 825)

Characteristic	Catheterisation laboratory		P value
	Yes	No	
No (%) of patients	22 096 (77)	6729 (23)	
Median (interquartile range) age (years)	66 (55-75)	68 (57-76)	<0.001
No (%) of men	14 888 (68)	4232 (63)	<0.001
Killip class* (%):			
I	17 629 (82)	5254 (80)	<0.001 (4×2 comparison)
II	2745 (13)	995 (15)	
III	834 (3.9)	308 (4.7)	
IV	282 (1.3)	46 (0.7)	
Medical history (%):			
Stroke	1831 (8.4)	541 (8.1)	0.486
PCI	3818 (17)	557 (8.3)	<0.001
CABG	2947 (13)	577 (8.6)	<0.001
Coronary angiogram	6603 (31)	1154 (18)	<0.001
Positive stress test	2291 (11)	666 (10)	0.215
Myocardial infarction	6633 (30)	2102 (31)	0.07
Hypertension	13 069 (60)	3921 (59)	0.162
Diabetes mellitus	5487 (25)	1559 (23)	0.005
ACS subgroup (%):			
STEMI	7847 (36)	1986 (30)	<0.001 (3×2 comparison)
Non-STEMI	6991 (32)	2016 (30)	
Unstable angina	7258 (33)	2727 (41)	
Revascularisation (%):			
PCI	8941 (41)	253 (3.9)	<0.001
CABG	1554 (7.1)	46 (0.7)	<0.001

ACS=acute coronary syndrome; CABG=coronary artery bypass grafting; CAD=coronary artery disease; non-STEMI=non-ST segment elevation myocardial infarction; PCI=percutaneous coronary intervention; STEMI=ST segment elevation myocardial infarction.

*Clinical signs of worsening left ventricular function from class I to IV.

to hospitals with catheterisation facilities were at a 14% increased risk of death at six months. The risk of in hospital stroke or major bleeding was also higher (53% and 94% respectively). There was,

however, a trend towards a lower risk of reinfarction after discharge in such patients (hazard ratio 0.86, 0.69 to 1.08).

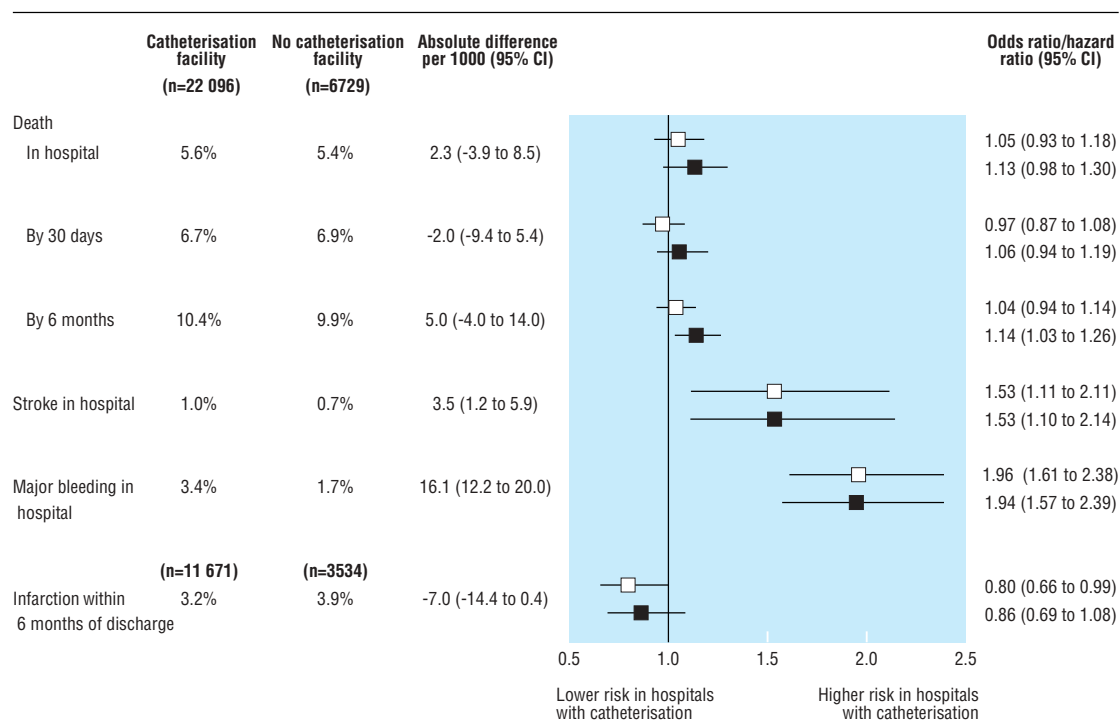
The pattern of increased risk of death at six months and increased risk of major bleeding or stroke in hospitals with catheterisation facilities remained consistent across the three subgroups. There was a significant reduction in the risk of reinfarction after discharge in the patients with non-ST segment elevation myocardial infarction (tables 2 and 3). In all hospitals, the highest rates of stroke were observed in patients with ST segment elevation myocardial infarction, while major bleeding complications were less common in patients with unstable angina.

Discussion

This analysis from a large multinational observational registry indicates that the availability of a catheterisation laboratory is associated with more use of percutaneous coronary intervention and coronary artery bypass graft in patients presenting with acute coronary syndrome. Despite this, after we adjusted for baseline variables, medical history, and geographical region, patients admitted first to hospitals with catheterisation facilities did not have a survival benefit but seemed to have higher rates of major bleeding and stroke in hospital than those first admitted to hospitals without such facilities.

Bleeding complications and strokes

The higher rates of major bleeding in hospital can be explained by the higher rate of invasive procedures. Randomised studies of acute coronary syndrome have shown that an invasive approach is associated with an increase in bleeding complications (mainly puncture related).¹⁻⁴ Rates of stroke were higher in patients with ST segment elevation myocardial infarction than in those with non-ST segment elevation myocardial infarction or unstable angina, with a consistent excess across the three diagnostic groups in patients admitted to hospitals with catheterisation



Clinical outcomes for all patients with acute coronary syndrome, for patients admitted to hospitals with or without catheterisation laboratory (open squares are unadjusted ratios and closed squares are adjusted ratios)

Table 2 Clinical outcomes by final diagnosis of acute coronary syndrome and access to catheterisation facility. Figures are numbers (percentages) of patients

	STEMI		Non-STEMI		Unstable angina	
	Access	No access	Access	No access	Access	No access
No of patients	7847	1986	6991	2016	7258	2727
Died in hospital	611 (7.8)	140 (7.1)	393 (5.7)	122 (6.1)	226 (3.1)	97 (3.6)
Died by 30 days	632 (9.0)	154 (9.0)	433 (7.1)	139 (8.2)	239 (3.7)	110 (4.5)
Died by 6 months after discharge	820 (12.4)	202 (12.4)	673 (11.7)	187 (11.6)	405 (6.8)	158 (6.8)
Stroke in hospital	115 (1.5)	26 (1.3)	69 (1.0)	11 (0.6)	41 (0.6)	8 (0.3)
Major bleeding in hospital	314 (4.1)	36 (1.8)*	287 (4.2)	55 (2.8)**	128 (1.8)	25 (0.9)**
Infarction up to 6 months after discharge†	126 (3.3)	35 (3.6)	148 (4.0)	63 (6.2)**	79 (2.2)	30 (2.3)

ACS=acute coronary syndrome; non-STEMI=non-ST segment elevation myocardial infarction; STEMI=ST segment elevation myocardial infarction.

*P<0.001.

**P<0.05.

†Base numbers were 3981, 1027, 3860, 1118, 3830, and 1389, respectively.

facilities. This excess could also be attributed to the more frequent use of invasive procedures. The highest rates of stroke in patients first admitted to hospitals without catheterisation facilities were found in those with ST segment elevation myocardial infarction, in whom the difference with the patients admitted to hospitals with catheterisation facilities was also the smallest. These findings could be explained by additional haemorrhagic strokes due to the use of thrombolytic therapies, especially in patients first admitted to hospitals without catheterisation facilities.

No improvement with invasive facilities

In the total population of patients studied, mortality at six months after admission was 14% higher in hospitals with catheterisation facilities after we adjusted for differences in baseline risk, medical history, and geographical region (figure). We found a consistent pattern in the three diagnostic groups (tables 2 and 3).

With regard to patients with ST segment elevation myocardial infarction, our results support the findings of the national registry of myocardial infarction 2, and other recent studies, that the use of intervention procedures in patients with ST segment elevation myocardial infarction is influenced by the interventional facilities of the admitting hospital.^{5 11–13} Not surprisingly, rates of percutaneous coronary intervention and coronary artery bypass graft seem to be significantly higher in patients with ST segment elevation myocardial infarction who first presented to hospitals with access to a catheterisation laboratory. In patients receiving fibrinolytic therapy in the global use of strategies to open occluded coronary arteries I trial (GUSTO-I), those admitted to hospitals without revascularisation facilities had similar outcomes to those admitted to hospitals with such facilities, provided that recommended therapies were given and patients were transferred to tertiary hospitals if necessary.¹⁴ Similarly, the thrombolysis in myocardial infarction II trial (TIMI

(n=1461) reported no significant differences in mortality between a conservative and an invasive approach, although the invasive strategy was associated with higher rates of percutaneous coronary intervention and an increased rate of haemorrhage than treatment in community hospitals.¹² The RESCATE study¹¹ and the European network for acute coronary treatment (ENACT)¹³ reported concordant results. Meta-analyses of randomised trials, on the other hand, have shown primary percutaneous coronary intervention to be associated with short and long term reductions in mortality when compared with thrombolytic therapy, regardless of whether the patient was transferred from a community hospital.¹ However, time delays between admission to the community hospital and first balloon inflation in the tertiary care facility were much shorter in the randomised studies than in the real world.¹⁵ Interpretation of these randomised studies is further complicated because of the selection of patients considered safe for transportation and, in some studies, the exclusion of procedure related reinfarctions from the primary end point.¹⁶ In our registry study the risk of death in patients with ST segment elevation myocardial infarction first admitted to a hospital with catheterisation facilities did not differ significantly from that in patients admitted to a hospital without catheterisation facilities, despite the fact that primary percutaneous coronary intervention was more common in the hospitals with such facilities (26% v 0.9%).

Earlier randomised studies in patients with unstable angina and non-ST segment elevation myocardial infarction^{17 18} did not show a clear benefit of a routine invasive approach, but more recent randomised studies have reported a better clinical outcome, mainly attributable to a reduction in the risk of reinfarction.^{2–4} In the current registry, early and late mortality in patients with unstable angina or non-ST segment elevation myocardial infarction who were first admitted to hospitals without catheterisation facilities were similar to those in patients first admitted to hospitals with facilities, despite a lower use of invasive procedures and a higher risk of reinfarction after discharge. Concordant results were reported in 7984 patients with unstable angina and non-ST segment elevation myocardial infarction studied by the organisation to assess strategies for ischaemic syndrome (OASIS)¹⁹ and in 791 patients with unstable angina from the RESCATE study.²⁰

The observed differences in mortality between patients first admitted to hospitals with or without catheterisation facilities were small and the odds or hazard ratios close to 1, suggesting that an invasive approach, as often applied to patients admitted to hospitals with catheterisation facilities, does not result in a clear survival benefit. Although the lack of an early survival benefit could be attributed to mortality related to the procedure, the higher mortality at six months suggests that the much more fre-

Table 3 Adjusted odds or hazard ratios (95% confidence intervals) for patients first admitted to hospitals with or without catheterisation facilities according to final diagnosis of acute coronary syndrome

	STEMI	Non-STEMI	Unstable angina
Died in hospital	1.15 (0.92 to 1.43)	1.04 (0.74 to 1.31)	0.98 (0.40 to 1.31)
Died by 30 days	1.12 (0.93 to 1.36)	0.98 (0.80 to 1.20)	0.88 (0.68 to 1.13)
Died by 6 months	1.09 (0.93 to 1.29)	1.15 (0.97 to 1.37)	1.03 (0.84 to 1.26)
Infarction (up to 6 months after discharge)	1.02 (0.68 to 1.52)	0.72 (0.52 to 0.99)	0.85 (0.52 to 1.36)
Stroke in hospital	1.15 (0.74 to 1.80)	1.80 (0.92 to 3.55)	1.75 (0.81 to 3.80)
Major bleeding in hospital	2.22 (1.55 to 3.18)	1.65 (1.20 to 2.26)	1.69 (1.08 to 2.64)

Non-STEMI=non-ST segment elevation myocardial infarction; STEMI=ST segment elevation myocardial infarction.

quent, and probably unselective, performance of revascularisation procedures in these patients is not beneficial. Although the detection of a possible survival benefit of revascularisation may require a longer follow up, a total reversal of the observed difference in risk of mortality is unlikely.

Comparison with randomised studies

Our results are supported by other registry data but are at variance with those of recent randomised trials. Discrepancies between randomised trials and registries are well known but not fully understood. One of the most important reasons is the reluctance of investigators to include high risk patients in randomised studies. With regard to trials in acute coronary syndrome it is well known that elderly and female patients are largely under-represented.²¹ A more selective use of invasive procedures in the high risk patients of this registry may be partly responsible for the favourable outcomes observed in those first admitted to community hospitals without catheterisation facilities. More particularly, the significantly lower incidence of stroke and major bleeding complications can be explained by the lower rate and more selective performance of invasive procedures.

Study limitations

Notwithstanding the large number of patients, the standardised criteria to define diagnostic subgroups and clinical outcomes, and the quality control and audit measures, the limitations of a registry-type study apply. Therefore, caution should be exercised with the interpretation of our results. Though we performed multivariable adjustments, unmeasured variables may exist that we did not account for. In some centres, patients may have been discharged for subsequent readmission for cardiac catheterisation and percutaneous coronary intervention, and these data may not have been captured in our study. It was also not possible to account for the sampling fraction in the analysis. This may increase the uncertainty in the results beyond the reported confidence intervals, although the effect is probably small.

Clinical implications

Our results do not suggest that an invasive approach to patients with acute coronary syndrome is harmful but that a more restrictive selective use of invasive procedures, as usually applied to patients first admitted to a community hospital, is at least as effective as a more liberal routine use. This analysis therefore supports the current strategy of admitting patients with acute coronary syndrome as rapidly as possible to the nearest hospital, irrespective of the availability of a catheterisation laboratory, and argues against the early routine transport of these patients to a specialised regional tertiary care hospital with interventional facilities.

We thank the physicians and nurses participating in the global registry of acute coronary events (GRACE) and Sophie Rushton-Mellor for preparing the manuscript. The GRACE scientific advisory committee comprises Keith A A Fox, UK; Joel M Gore, US (co-chairs); Kim A Eagle, US; Gabriel Steg, France (publication committee co-chairs); Giancarlo Agnelli, Italy; Frederick A Anderson Jr, US; Álvaro Avezum, Brazil; David Brieger, Australia; Andrzej Budaj, Poland; Marcus D Flather, UK; Robert J Goldberg, US; Shaun G Goodman, Canada; Christopher B Granger, US; Dietrich C Gulba, Germany; Enrique P Gurfinkel, Argentina; Brian M Kennelly, US; Werner Klein, Austria; José López-Sendón, Spain; Gilles Montalescot, France; Frans Van de Werf, Belgium. Further information about the project, along with a complete list of the GRACE participants, can be found at www.outcomes.org/grace

Contributors: All authors were responsible for the study concept and design and acquisition of data. KW was responsible for statistics. FVdeW is guarantor and drafted the manuscript, which was critically revised by all other authors.

What is already known on this topic

In patients with acute coronary syndrome evidence from randomised clinical trials has shown better outcomes in those who undergo an early invasive strategy

It is unclear whether access to interventional cardiology facilities in routine practice improves outcomes among these patients

What this study adds

Access to cardiac catheterisation is associated with more invasive intervention among patients with acute coronary syndrome

After adjustment for confounders there was no increase in survival at 30 days or six months and higher rates of major bleeding and stroke among patients with such access than among patients without such access

The results do not support the early routine transfer of these patients to specialist centres with interventional cardiology facilities

Funding: The GRACE registry is supported by an unrestricted educational grant from Aventis Pharma (Bridgewater, NJ) to the Center for Outcomes Research, University of Massachusetts Medical School (Worcester, MA).

Competing interests: FVdeW has received research grants from Aventis, Boehringer Ingelheim, and Genentech. KAAF has received funding from Aventis, BMS, and Sanofi Synthelabo. KAE has received grants from Pfizer, Aventis, and Blue Cross Blue Shield of Michigan and is consultant for Sanofi and the NIH Heart, Lung, and Blood Institute. BMK is scientific adviser to Aventis.

Ethical approval: Where required, local approval from institutional review boards was obtained.

- 1 Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13-20.
- 2 Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Fragmin and fast revascularization during instability in coronary artery disease investigators. *Lancet* 1999;354:708-15.
- 3 Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.
- 4 Fox KA, Poole-Wilson PA, Henderson RA, Clayton TC, Chamberlain DA, Shaw TR, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomised intervention trial of unstable angina. *Lancet* 2002;360:743-51.
- 5 Rogers WJ, Canto JG, Barron HV, Boscarino JA, Shultz DA, Every NR. Treatment and outcome of myocardial infarction in hospitals with and without invasive capability. Investigators in the national registry of myocardial infarction. *J Am Coll Cardiol* 2000;35:371-9.
- 6 Topol EJ, Kereiakes DJ. Regionalization of care for acute ischemic heart disease: a call for specialized centers. *Circulation* 2003;107:1463-6.
- 7 GRACE Investigators. Rationale and design of the GRACE (global registry of acute coronary events) project: a multinational registry of patients hospitalized with acute coronary syndromes. *Am Heart J* 2001;141:190-9.
- 8 Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, Lopez-Sendon J. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the global registry of acute coronary events (GRACE). *Lancet* 2002;359:373-7.
- 9 Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A validated prediction model for all forms of acute coronary syndromes: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;291:2727-33.
- 10 Goldberg RJ, Currie K, White K, Brieger D, Steg PG, Goodman SG, et al. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the global registry of acute coronary events (GRACE)). *Am J Cardiol* 2004;93:288-93.
- 11 Marrugat J, Sanz G, Masia R, Valle V, Molina L, Cardona M, et al. Six-month outcome in patients with myocardial infarction initially admitted to tertiary and nontertiary hospitals. RESCATE investigators. Recursos Empleados en el Síndrome Coronario Agudo y Tiempos de Espera. *J Am Coll Cardiol* 1997;30:1187-92.
- 12 Feit F, Mueller HS, Braunwald E, Ross R, Hodges M, Herman MV, et al. Thrombolysis in myocardial infarction (TIMI) phase II trial: outcome comparison of a "conservative strategy" in community versus tertiary hospitals. The TIMI research group. *J Am Coll Cardiol* 1990;16:1529-34.

- 13 Gabriel Steg P, Lung B, Feldman LJ, Maggioni AP, Keil U, Deckers J, et al. Determinants of use and outcomes of invasive coronary procedures in acute coronary syndromes: results from ENACT. *Eur Heart J* 2003;24:613-22.
- 14 Mehta RH, Criger DA, Granger CB, Pieper KK, Califf RM, Topol EJ, et al. Patient outcomes after fibrinolytic therapy for acute myocardial infarction at hospitals with and without coronary revascularization capability. *J Am Coll Cardiol* 2002;40:1034-43.
- 15 Antman EM, Van de Werf F. Pharmacoinvasive therapy: the future of treatment for ST elevation myocardial infarction. *Circulation* 2004;109:2480-6.
- 16 Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;349:733-42.
- 17 TIMI IIIB Investigators. Effect of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction results of the TIMI IIIB trial. *Circulation* 1994;89:1545-56.
- 18 Boden WE, O'Rourke RA, Crawford MH, Blaustein AS, Deedwania PC, Zoble RG, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs non-Q-wave infarction strategies in hospital (VANQWISH) trial investigators. *N Engl J Med* 1998;338:1785-92.
- 19 Yusuf S, Flather M, Pogue J, Hunt D, Varigos J, Piegas L, et al. Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. OASIS (organisation to assess strategies for ischaemic syndromes) registry investigators. *Lancet* 1998;352:507-14.
- 20 Lupon J, Valle V, Marrugat J, Elosua R, Seres L, Pavesi M, et al. Six-month outcome in unstable angina patients without previous myocardial infarction according to the use of tertiary cardiologic resources. RESCATE Investigators. Recursos Empleados en el Síndrome Coronario Agudo y Tiempos de Espera. *J Am Coll Cardiol* 1999;34:1947-53.
- 21 Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *Jama* 2001;286:708-13.

(Accepted 30 November 2004)

doi 10.1136/bmj.38335.390718.82

Universitair Ziekenhuis Gasthuisberg, Herestraat 49, Leuven, Belgium 3000
Frans Van de Werf *cardiologist*

University of Massachusetts Memorial Health Care, Worcester, MA 01655, USA
Joel M Gore *cardiologist*

University of Massachusetts Medical School, Worcester, MA 01604, USA
Kami White *statistician*

Research Division, Dante Pazzanese Institute of Cardiology, 04012-909, San Paulo, Brazil

Alvaro Avezum *cardiologist*

Krankenhaus Düren, Düren, NRW Germany 52351

Dietrich C Gulba *cardiologist*

Canadian Heart Research Centre and Terrence Donnelly Heart Centre, Division of Cardiology, St Michael's Hospital, University of Toronto, Toronto, ON, Canada

M5B 1W8

Shaun G Goodman *cardiologist*

Postgraduate Medical School, Grochowski Hospital, Centrum Medycznego

Kształcenia Podyplomowego, Warsaw, Poland 04-073

Andrzej Budaj *cardiologist*

Concord Repatriation General Hospital, Coronary Care Unit, Concord, NSW,

Australia 2139

David Brieger *cardiologist*

Royal Infirmary of Edinburgh, University of Edinburgh, Edinburgh EH16 4SB

Keith A A Fox *professor*

University of Michigan Cardiovascular Center, Ann Arbor, MI 48109-0477, USA

Kim A Eagle *cardiologist*

Hoag Memorial Hospital Presbyterian, Newport Beach, CA 92658-6100, USA

Brian M Kennelly *cardiologist*

Correspondence to: F Van de Werf frans.vandewerf@uz.kuleuven.ac.be

Amendment

This is version 2 of the paper. In this version the figure legend has been amended to clarify that the closed squares show adjusted ratios.