Articles

Difference in countries' use of resources and clinical outcome for patients with cardiogenic shock after myocardial infarction: results from the GUSTO trial

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Summary

Background Use of aggressive and invasive interventions is more common in the USA than in other countries. We have compared use of resources for patients with cardiogenic shock after myocardial infarction in the USA and in other countries, and assessed the association between use of resources and clinical outcomes.

Methods We analysed data for patients with cardiogenic shock after myocardial infarction who were enrolled in the GUSTO-I trial (1891 treated in the USA, 1081 treated in other countries). Patients were randomly assigned combinations of streptokinase, heparin, and accelerated tissue-plasminogen activator (t-PA), then decisions about further interventions were left to the discretion of the attending physician. The interventions included in our analysis were: pulmonary-artery catheterisation, cardiac catheterisation, intravenous inotropic agents, ventilatory support, intra-aortic balloon counterpulsation (IABP), percutaneous transluminal coronary angioplasty (PTCA), and coronary bypass graft surgery (CABG). The primary outcome measure was death from any cause at 30 days of follow-up.

Findings Patients who were treated in the USA were significantly younger than those treated elsewhere (median 68 [IQR 59–75] *vs* 70 [62–76], p<0·001), a smaller proportion had anterior infarction (49 *vs* 53%, p<0·001), and they had a shorter time to treatment (mean 3·1 *vs* 3·3 h, p<0·001). Aggressive diagnostic and therapeutic procedures were used more commonly in the USA than in the other countries: cardiac catheterisation (58 *vs* 23%); IABP (35 *vs* 7%); right-heart catheterisation (57 *vs* 22%); and ventilatory support (54 *vs* 38%). 483 (26%) of the patients treated in the USA underwent PTCA, compared with 82 (8%) patients in other countries. Patients who underwent revascularisation had better survival in all countries. Adjusted 30-day mortality was significantly lower among patients treated in the USA than among those treated elsewhere (50 *vs* 66%, p<0·001). The difference in mortality remained at 1 year—56% of patients treated in the USA died versus 70% of patients treated elsewhere (hazard ratio 0·69 [95% CI 0·63–0·75], p<0·001).

Interpretation 30-day and 1-year mortality was significantly lower among patients treated in the USA than among those treated in other countries. This difference in mortality may be due to the greater use of invasive diagnostic and therapeutic interventions in the USA.

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Introduction

Use of resources for treatment of acute myocardial infarction varies greatly throughout the world.[1–6] The more invasive and costly procedures, such as cardiac catheterisation, percutaneous transluminal coronary angioplasty (PTCA), and coronary bypass graft surgery (CABG), are used more commonly in the USA than in other countries.[5,6] The extent to which this difference in use affects outcome, particularly in high-risk patients who may have the most to gain from effective treatment strategies, is not clear.

Patients with acute myocardial infarction who are at greater risk of death are those with cardiogenic shock.[7–9] In the GUSTO-I trial of 41 021 patients, cardiogenic shock was identified on a prospectively collected data form in 2972 (7·2%) patients. These patients had a 30-day mortality of 55% and accounted for 59% of all deaths in the trial.[7]

We have compared use of resources for patients with cardiogenic shock in the USA and in other countries, and assessed the association between use of resources and clinical outcome.

Methods

The GUSTO-I trial has been previously described in detail.[10,11] 41 021 patients from the USA and 14 other countries who had symptoms of acute myocardial infarction and ST-segment elevation were enrolled and randomly assigned one of four thrombolytic regimens: 1·5 million units of streptokinase and subcutaneous heparin; 1·5 million units of streptokinase and intravenous heparin; accelerated tissue-plasminogen activator (t-PA) and intravenous heparin; or a combination of streptokinase, t-PA, and intravenous heparin. The primary endpoint was death from any cause by 30 days of follow-up. All patients gave informed consent to take part in the trial. The study protocol was approved by the institutional review board at each hospital.

Patients who had cardiogenic shock were a predefined subgroup for whom we used additional prospectively designed data-collection forms. The GUSTO protocol defined cardiogenic shock as a systolic blood pressure of 90 mm Hg or less for more than 1 h despite a fluid challenge, together with signs of

	USA (n=1891)	Other countries (n=1081)	p
Median (IQR; range) age in years	68 (59–75; 30–108)	70 (62–76; 30–90)	<0·001
Median (IQR) systolic blood pressure (mm Hg)	114 (97–130)	120 (100–135)	<0·001
Baseline Killip class			
I	1240 (66%)	596 (55%)	<0·001
II	350 (19%)	281 (26%)	
III	91 (5%)	75 (7%)	
IV	188 (10%)	127 (12%)	
Median (IQR) heart rate (bpm)	80 (66–96)	80 (67–98)	0·255
Location of myocardial infarction			
Anterior	930 (49%)	573 (53%)	<0·001
Inferior	917 (49%)	464 (43%)	
No MI	2 (<1%)	1 (<1%)	
Other	35 (2%)	40 (4%)	
Previous myocardial infarction	463 (25%)	280 (26%)	0·469
Median (IQR) height (cm)	170 (163–178)	168 (160–175)	<0·001
Time to treatment (h)			
Mean (SD)	3·1 (1·8)	3·3 (1·6)	<0·001
Median (IQR)	3 (2–4)	3 (2–4)	
Range	0·1–23·1	0·2–17·5	
Diabetes mellitus	374 (20%)	184 (17%)	0·061
Median (IQR) weight (kg)	76 (66–87)	72 (65–80)	<0·001
Smoking status			
Current	647 (35%)	329 (31%)	0·020
Ever	1171 (65%)	581 (56%)	<0·001
Previous CABG	146 (8%)	47 (4%)	<0·001
History of hypertension	864 (46%)	414 (39%)	<0·001
Previous cerebrovascular disease	78 (4%)	38 (4%)	0·398

bpm=beats per min.

Table 1: **Baseline characteristics of patients with cardiogenic shock**

hypoperfusion or a cardiac index of 2·2 L min^{-1} m^{-2} or less, judged by the physician to be secondary to cardiac dysfunction. The definition of shock also included those patients in whom systolic blood pressure increased to more than 90 mm Hg within 1 h of administration of inotropic agents.

Decisions about further interventions (ie, diagnostic procedures and adjunctive therapies) were left to the discretion of the attending physician. We compared use of interventions at centres in the USA and in other countries. The procedures and therapies included in our analysis were: pulmonary-artery catheterisation; cardiac catheterisation; intravenous inotropic agents; ventilatory support; intra-aortic balloon counterpulsation (IABP); PTCA; and CABG.

We assessed the potential effect of differences in the baseline characteristics of patients on outcome. For this analysis we selected those characteristics found to be the most important factors associated with mortality in the GUSTO-I trial: age, systolic blood pressure, Killip class on entry, heart rate, location of myocardial infarction (anterior *vs* inferior), history of previous infarction, height, weight, time to treatment, diabetes mellitus, history of cigarette smoking, current smoking, previous CABG, history of hypertension, and previous cerebrovascular disease. Lee at al[12] have shown that five of these factors in the entire GUSTO-I trial—age, systolic blood pressure, Killip class on entry, heart rate, and location of infarction—accounted for 90% of the ability of the model to predict outcome. In addition to these significant factors, the effects of ethnic origin, sex, diastolic blood pressure, previous PTCA, and previous angina were also analysed.

We used standard contingency table χ^2 tests or Fisher's exact tests to assess geographical differences in intervention and outcome between groups of patients defined by categorical variables. The Wilcoxon rank-sum test was used for analysis of continuous variables. After adjustment for the five significant factors identified by Lee et al,[12] we used multivariate logistic regression to assess the effect of geographical location on 30-day mortality.

Intervention	USA (n=1891)	Other countries (n=1081)	p*
Cardiac catheterisation	1092 (58%)	253 (23%)	<0·001
IABP	652 (35%)	80 (7%)	<0·001
Right-heart catheterisation	1074 (57%)	236 (22%)	<0·001
Ventilatory support	1021 (54%)	405 (38%)	<0·001
CABG	295 (16%)	43 (4%)	<0·001
PTCA	483 (26%)	82 (8%)	<0·001
Inotropic agent	1850 (98%)	998 (93%)	<0·001
β-blocker	1024 (54%)	410 (38%)	<0·001
Aspirin	1768 (94%)	1016 (94%)	0·610

*Data on types of interventions used for some patients were not available; differences between geographical locations were assessed only for patients whose data were available.

Table 2: **Use of interventions and medications by geographical location**

For the analysis of the effect of intervention on 30-day mortality by geographical location, we adjusted for those patients who did not survive long enough to receive an intervention. If the non-intervention groups were credited with all these early events, the beneficial effect of an intervention would be unfairly inflated. Thus, we used a time-dependent Cox proportional hazards model of 30-day mortality, which treated patients as non-procedure patients until the start of an intervention. The types of intervention included as time-dependent covariates in this modelling were PTCA, CABG, cardiac catheterisation, and IABP. We excluded right-heart catheterisation and ventilator use from time-dependent modelling because the date of the use of these procedures relative to cardiogenic shock was not known. Similarly, we used time-dependent modelling to assess the effect on 1-year mortality of USA versus non-USA location, according to use of revascularisation. All p values are two tailed.

Results

Of the 40 736 patients, for whom complete data on shock were available, 22 883 (56·2%) were treated in the USA and 17 853 (43·8%) in other countries. Cardiogenic shock occurred in a greater proportion of patients treated in the USA than in those treated elsewhere (1891 [8·3%] *vs* 1081 [6·1%], p<0·001). In most cases, cardiogenic shock developed after admission; in the USA and the other countries only 0·8% and 0·7% of patients, respectively, had shock on admission.

There were significant differences in baseline characteristics of patients with cardiogenic shock between those treated in the USA and those treated elsewhere (table 1). Patients treated in the USA were significantly younger than those treated in other countries, a smaller proportion had anterior myocardial infarction, and they had a slightly shorter time to treatment. A greater proportion of patients treated in the USA than those treated elsewhere had undergone CABG previously.

Intervention	USA	Other countries	p
All patients			
n	1891	1081	
Deaths by 30 days	936 (50%)	711 (66%)	<0·001
CABG			
n	295	43	<0·001
Deaths by 30 days	81 (27%)	17 (38%)	0·722*
PTCA			
n	483	82	<0·001
Deaths by 30 days	84 (30%)	39 (48%)	0·090*

*Value for differential effect of intervention in patients from USA *vs* patients from other countries.

Table 3: **Outcome of cardiogenic shock by 30 days and type of revascularisation used**

Predictor	χ^2, p	Predictor	χ^2, p
Age	104, <0·001	Time to treatment	10, <0·002
SBP	54, <0·001	Height	11, 0·025
USA *vs* non-USA	51, <0·001	Previous CABG	4, 0·047
MI location	26, <0·001	Age×Killip	4, 0·286
Baseline Killip	25, <0·001	Treatment	3, 0·392
Smoking	23, <0·001	Previous CVD	0·1, 0·805
Pulse	21, <0·001	Hypertension	<0·01, 0·949
Previous MI	20, <0·001	Weight	<0·01, 0·996
Diabetes	17, <0·001		

SBP=systolic blood pressure; MI=myocardial infarction; CVD=cerebrovascular disease.

Table 4: **30-day mortality model for patients with cardiogenic shock by baseline characteristics**

Predictor	χ^2, p	Predictor	χ^2, p
SBP	88, <0·001	Time to treatment	9, 0·003
Age	81, <0·001	Diabetes	9, 0·004
USA *vs* non-USA	48, <0·001	Height	9, 0·050
Baseline Killip	26, <0·001	Previous CABG	7, 0·009
MI location	24, <0·001	PTCA	3, 0·078
Pulse	22, <0·001	Treatment	2, 0·658
Age×Killip	18, <0·001	CABG	0·9, 0·343
Smoking	16, <0·001	Hypertension	0·4, 0·551
CC	15, <0·001	Weight	0·2, 0·676
Previous MI	12, <0·001	Previous CVD	0·01, 0·927
IABP	9, 0·002		

SBP=systolic blood pressure; MI=myocardial infarction;CVD=cerebrovascular disease; CC=cardiac catheterisation.

Table 5: **30-day mortality model for patients with cardiogenic shock by baseline characteristics and type of intervention**

Use of aggressive diagnostic and therapeutic interventions was more common in the USA than in the other countries (table 2). Pulmonary-artery catheterisation, cardiac catheterisation, IABP, PTCA, and CABG were done significantly more frequently in the USA than in other countries (p<0·001, table 2). Similarly, ventilatory support was more widely used in the USA than elsewhere (p<0·001).

Differences in the use of medication between the USA and the other countries were less consistent (table 2). As previously reported in the GUSTO-I trial,[10] intravenous or oral β-blockers were more commonly administered to patients with cardiogenic shock in the USA than in the other countries. Intravenous inotropic agents were used commonly in the USA and other countries, but use was significantly more frequent in the USA. There was no geographical difference in the frequency of aspirin use.

The 30-day mortality rate among patients with cardiogenic shock was significantly lower in the USA than in the other countries (50 *vs* 66%, p<0·001; table 3). After adjustment for the baseline characteristics of patients, those treated in the USA had significantly lower mortality than patients treated elsewhere. In the multivariate analysis, only two factors—age and systolic blood pressure—were more strongly associated with increased mortality than was geographical location (tables 4, 5). Adjustment for all potential baseline factors did not attenuate the association between treatment in the USA and improved outcome (p <0·0001). This finding did not change after adjustment for both interventions and the significant baseline factors (p <0·001).

30-day mortality after revascularisation was lower among patients with cardiogenic shock treated in the USA than among those treated elsewhere. After PTCA, there was a significant difference in 30-day mortality between the USA and the other countries (table 3). In patients who underwent CABG, 30-day mortality was 27% in the USA and 38% elsewhere; however this difference was not significant (p=0·722).

Table 6 shows mortality at 1 year. The unadjusted 1-year survival rate was higher among patients treated in the USA than among those treated elsewhere (44 *vs* 30%, p<0·001). In all countries, mortality at 1 year was lower for patients who underwent PTCA (p<0·001). By contrast, there was no significant difference in unadjusted 1-year mortality between patients who did and patients who did not undergo CABG (p=0·553).

After adjustment for baseline factors that had a significant effect on outcome, patients treated in the USA had significantly lower 1-year mortality than those treated elsewhere (p<0·001, table 6). Similarly, the adjusted 1-year mortality was lower in patients who had PTCA than in those who did not (p<0·001), but CABG did not significantly affect the adjusted 1-year mortality (p=0·445). Overall, the outcome for patients with cardiogenic shock was significantly better at 1 year in the USA than in the other countries, irrespective of whether revascularisation had been done. This finding did not change after adjustment for revascularisation (p<0·001).

Discussion

This analysis shows that the use and outcome of aggressive and invasive interventions for patients with acute myocardial infarction complicated by cardiogenic shock differed significantly between the USA and other countries. Patients treated in the USA had significantly lower mortality at 30 days and 1 year than patients who were treated in other countries.

Previous studies have reported differences in countries' assessment, treatment, and outcome for patients with myocardial infarction.[1,3–5] Among the 13 countries included in Barbash and colleagues' study,[3] 30-day mortality ranged from 4·2% to 14·8%, but differences in baseline characteristics between countries did not account for the geographical differences in mortality. The investigators suggested different countries' use of adjunctive post-thrombolytic treatment strategies together with genetic and environmental factors might modify the risk of myocardial infarction.

	1-year mortality			
	Unadjusted hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)*	p
Single-factor comparisons				
USA *vs* other countries	0·69 (0·63–0·75)	<0·001	0·70 (0·64–0·78)	<0·001
PTCA *vs* no PTCA	0·67 (0·58–0·78)	<0·001	0·81 (0·70–0·94)	<0·005
CABG *vs* no CABG	0·95 (0·78–1·14)	0·553	1·08 (0·89–1·30)	0·445
Multiple-factor comparisons				
USA, revascularisation	0·59 (0·45–0·79)	<0·001	0·55 (0·41–0·73)	<0·001
Other countries, revascularisation	0·95 (0·73–1·24)	0·707	1·21 (0·92–1·58)	0·168
USA, no revascularisation	0·73 (0·66–0·81)	<0·001	0·73 (0·66–0·82)	<0·001
Other countries, no revascularisation†	1·00		1·00	

*Adjusted for baseline characteristics of patients with a significant effect on 30-day mortality. †Reference group for multiple-factor comparisons.

Table 6: **1-year mortality**

Mark and colleagues[5] assessed the use of medical resources and outcome for 2600 patients in the USA and 400 patients in Canada who were randomly selected from the GUSTO trial. That study showed no significant difference in 30-day survival between countries (93·0% for the USA *vs* 92·4% for Canada, p=0·33). However, after adjustment for baseline clinical characteristics associated with mortality, patients from the USA had significantly better survival than Canadian patients (p=0·02). In addition, coronary angiography, coronary angioplasty, and bypass surgery were used more frequently in the USA than in Canada. Whether this difference in resource consumption accounted for the small difference in 30-day mortality was not clear. Van de Werf and colleagues[4] showed that more invasive procedures were done in the USA than in the other countries in the GUSTO trial, but that this difference was associated with only a small decrease in short-term mortality.

We found small but significant differences in baseline clinical characteristics of patients with cardiogenic shock between those treated in the USA and those treated elsewhere. However, these differences did not fully account for the significant difference in 30-day mortality. Indeed, the difference remained after adjustment for the baseline characteristics. In our multivariate analysis, age and systolic blood pressure were the only factors more strongly associated than geographical location with increased mortality. Even after adjustment for all baseline characteristics of patients, those treated in the USA had sigificantly lower mortality at 30 days (p<0·0001). This difference in mortality persisted at 1 year, even after adjustment for differences in revascularisation procedures.

Our study showed that patients with cardiogenic shock in the USA undergo more aggressive interventions, both diagnostic (eg, cardiac catheterisation) and therapeutic (eg, IABP, PTCA, CABG), more frequently than do patients in other countries. However, we were not able to find out whether the lower 30-day mortality in patients treated in the USA reflected selection bias or the benefits of these aggressive adjunctive therapies. Hochman and colleagues[8] examined whether selection bias affected mortality in patients treated for cardiogenic shock, and found that patients selected to undergo catheterisation had a lower mortality than those who were not selected for this procedure, irrespective of whether revascularisation was done.[8] Since the use of resources was not mandated by the GUSTO protocol but left to the discretion of the attending physician, differences in interventions and outcome may partly reflect the facilities available at different hospitals. In addition, the attitudes of patients, physicians, and society towards treatment for patients with emergency medical conditions may also be important factors.

We cannot say for certain that the difference in survival between the USA and other countries was the result of more aggressive treatment strategies. In our subgroup of patients with cardiogenic shock, the early mortality rate was high. Thus, many patients did not survive long enough to receive any intervention. Although we used time-dependent modelling to avoid inflating the beneficial effect of a procedure, this model may not have fully compensated for the large number of early deaths. Bias in the selection of patients who received more aggressive interventions could have had a substantial effect on the differences in mortality. Nonetheless, several retrospective studies have shown that early revascularisation is associated with better outcome.[13–16] In the entire GUSTO-I trial, the mortality of patients who developed cardiogenic shock and were treated with PTCA was 32%, compared with 61% in patients who did not undergo PTCA.[7] Other treatments such as the use of IABP could also have been important.

Although cardiogenic shock was defined at the start of GUSTO-I by specific criteria, this definition is somewhat subjective because it depends on how closely patients were monitored and the clinical judgments made about the cause of hypotension. Thus, closer monitoring of patients in the USA could have identified patients earlier in the course of shock, and thereby affected outcome. In addition, differences in selection criteria for more aggressive treatment strategies could have affected outcome.

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