European Heart Journal (2001) **22,** 1702–1715
doi:10.1053/euhj.2001.2583, available online at http://www.idealibrary.com on IDEAL®

Geographic variation in patient and hospital characteristics, management, and clinical outcomes in ST-elevation myocardial infarction treated with fibrinolysis

Results from InTIME-II

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Aims We examined the geographic variations in InTIME-II, a randomized double-blind trial comparing alteplase with lanoteplase for myocardial infarction.

Methods and Results We compared baseline characteristics, management, and outcomes in four regions (Western Europe, Eastern Europe, North America, and Latin America) and in countries with historically different management approaches (Germany vs the U.K., the U.S. vs Canada). Thirty-day mortality in Western Europe, Eastern Europe, North America and Latin America was 6·7%, 7·3%, 5·7%, 10·1%, $P<0·0001$. Adjusted mortality for Europe was intermediate between North America and Latin America (odds ratios (OR) [95% confidence intervals (CI)] compared to Western Europe: North America 0·84 [0·67–1·0], Eastern Europe 1·2 [1·0–1·4], and Latin America 1·8 [1·3–2·7]). Revascularization rates varied 10-fold but did not explain regional mortality differences. Germany and the U.K. had similar adjusted 1-year mortality (OR for the U.K. 1·16 [0·92–1·5]), although invasive procedures were four- to 10-fold more common in Germany. Similarly the U.S. and Canada had equal adjusted 1-year mortality (OR for Canada 0·85 [0·61–1·17]) despite three-fold higher use of invasive procedures in the U.S.

Conclusions Significant geographic variations in practice and adjusted mortality following fibrinolysis persist despite recent guidelines. These findings have important implications in the design and interpretation of international studies, identify under- and over-utilized therapies, and support further study of treatments with marked worldwide variations.

(Eur Heart J 2001; 22: 1702–1715, doi:10.1053/euhj.2001.2583)

Key Words: Myocardial infarction, fibrinolysis, geographic variation, management, outcomes.

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Introduction

Despite improvements in survival and myocardial salvage observed with the introduction of fibrinolytic therapy, cardiovascular disease remains the leading cause of loss of potential life-years under age 75 in the Western world[1]. Considerable practice variation and

Revision submitted 21 December 2000, and accepted 2 January 2001.

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The InTIME-II study was supported by Bristol-Myers Squibb.

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0195-668X/01/221702+14 $35.00/0

differences in mortality following acute myocardial infarction, particularly between the U.S. and other countries, have been reported in trials from the late 1980's and early 1990's[2–5]. Several analyses recently compared treatment and outcomes in Europe in patients with acute coronary syndromes (including some patients with acute ST-elevation myocardial infarction)[6–8]. However, little data exist comparing patients with ST-elevation myocardial infarction in Europe and the Americas following the revision of evidence-based myocardial infarction practice guidelines[9–11], and the impact of these updated guidelines on clinical practice variation and outcome is unknown.

The Intravenous nPA for Treatment of Infarcting Myocardium Early II trial[12] (InTIME-II) was a randomized, double-blind, double-dummy, clinical trial comparing 30-day mortality in patients with acute myocardial infarction randomized to either accelerated alteplase or single-bolus lanoteplase in 15 078 patients. The results of the primary study[12], conducted between July 1997 and November 1998, demonstrated that single-bolus lanoteplase was as effective as alteplase in patients presenting with ST-elevation myocardial infarction. Since patient management, other than the initial fibrinolytic assignment, aspirin and heparin co-therapy, was left to the discretion of the treating physician, InTIME-II permitted a comparison of other treatment patterns across geographic regions.

We hypothesized that those regions with greater use of proven therapies (beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and as an adjunct to percutaneous coronary intervention intravenous glycoprotein IIb/IIIa inhibitors) would have lower rates of cardiac morbidity and mortality. The practices and outcomes were compared in four regions (Western Europe, Eastern Europe, North America, and Latin America). In addition, we also compared two countries in each of two regions; Germany and the U.K. in Western Europe, and the U.S. and Canada in North America. Practice such as angiography, differs substantially between these countries[4,7,8,13–16], being quite frequent in Germany and the U.S., and relatively infrequent in the U.K. and Canada.

Methods

Patients and treatments

InTIME-II enrolled patients aged 18 years or older with onset of symptoms within 6 h who were eligible for fibrinolytic therapy. Clinical outcomes were assessed over 30 days and mortality for 6–12 months.

After giving informed consent, patients were randomly assigned in a 2:1 ratio to receive 120 KU . kg^{-1} single-bolus lanoteplase, or an accelerated infusion of alteplase administered as a bolus dose of 15 mg, an infusion of 0·75 mg per kilogram of body weight over a 30-min period (not to exceed 50 mg), followed by an infusion of 0·5 mg per kilogram (up to 35 mg) over the next 60 min. Aspirin was administered as soon as possible and then in a daily dose of 100–325 mg. Patients also received a bolus dose of 70 U . kg^{-1} (maximum 4000 units) of heparin, followed by an infusion of 15 U . h^{-1} (maximum 1000 units).

Geographic location

Patients were categorized by geographic location of the enrolling hospital into one of four groups: Western Europe, Eastern Europe, North America, or Latin America for the primary analysis. The four regions were defined by accepted geographic boundaries, with the exception of South Africa and Israel that were grouped with Western Europe. Secondary analyses compared Germany vs the U.K., and the U.S. vs Canada.

Characteristics of hospitals and patients

All participating hospitals completed a supplemental survey inquiring about the hospital locale, size, teaching status, physician specialty usually caring for patients with myocardial infarction after admission, and presence of on-site facilities (cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass graft surgery (CABG)). Data on patient demographic and clinical variables, procedures, and outcomes were collected via the case-report forms. A more detailed analysis of hospitals stratified by the on-site availability of coronary angiography is described elsewhere[17].

Clinical outcomes

The primary outcome was 30-day all-cause mortality. Secondary clinical outcomes at 30 days included post-infarction angina, Canadian Cardiovascular Society Class (CCSC) angina, recurrent myocardial infarction (as adjudicated by the Clinical Events Committee), emergency revascularization (as determined by the investigator), new/worsening heart failure, and cardiogenic shock. Primary safety outcomes included stroke (as adjudicated by the Neurologic Event Committee) and major bleeding (intracranial haemorrhage or bleeding requiring transfusion and resulting in haemodynamic compromise).

Statistical analysis

The chi-square test and analysis-of-variance were used to identify differences in baseline characteristics by geographic location. To evaluate the influence of baseline characteristics on outcomes, logistic models were constructed using both forward and backward stepwise procedures, which selected any baseline characteristic significantly associated ($P<0·05$) with the outcome of interest. Geographic location was forced into the model

Table 1 Participating countries

	No. hospitals	No. pts		No. hospitals	No. pts
Western Europe	**503**	**8884**	**Eastern Europe**	**91**	**2894**
United Kingdom	69	2360	Poland	28	1256
Germany	194	2331	Hungary	11	427
Netherlands	35	934	Russia	11	360
France	63	681	Czech Republic	11	256
South Africa	22	569	Turkey	10	197
Italy	38	562	Estonia	2	132
Spain	16	404	Slovakia	5	79
Belgium	18	288	Slovenia	5	74
Austria	9	211	Lithuania	2	42
Sweden	8	174	Latvia	1	36
Finland	9	93	Romania	5	35
Norway	5	81			
Switzerland	5	64	**Latin America**	**54**	**407**
Portugal	7	48	Argentina	21	141
Israel	1	47	Brazil	16	115
Denmark	3	21	Mexico	6	82
Ireland	1	16	Chile	9	61
			Uruguay	2	8
North America	**207**	**2875**			
Canada	77	1553			
United States	130	1322			

in the final step. Model results are presented as an odds ratio (OR) with 95% confidence intervals (CIs). The median lengths of hospital stay were compared using the Kruskal–Wallis test. A Cox regression model was used to analyse 1-year mortality data since the minimum follow-up for the trial was 6 months.

Mortality among the regions, and within the pairs of countries of interest, was also compared after stratification by the TIMI Risk Score for ST-elevation myocardial infarction[18], a weighted scale of seven independent predictors of 30-day mortality.

Results

All 855 hospitals responded to the survey. Thirty-day outcomes were available in 15 060 patients (99·9% enrolled), while 6-month and 1-year vital status were available in 14 815 (98·3%) and 9297 (61·7%) patients, respectively. The primary end-point of the main trial (30-day all-cause mortality) was equivalent for alteplase and lanoteplase (6·61% vs 6·75%, $P=0·04$ for equivalence)[12], thus the current analysis combines the results across fibrinolytic agent in any given region or country.

Geographic location

Table 1 lists the participating countries and the number of hospitals and patients enrolled per country. A majority of the patients (78%) and hospitals (70%) were from Europe (Western Europe: 59% patients, 59% hospitals; Eastern Europe 19% patients, 11% hospitals). North America and Latin America contributed 19% and 3% of patients, respectively, and accounted for 24% and 6% of participating hospitals. Countries with the highest enrollment were the U.K. (16%), Germany (15%), Canada (10%), and the U.S. (9%).

Characteristics of the hospitals

Hospitals participating in this trial tended to be medium (300–700 beds) to large-sized (>700 beds), urban, teaching centres, with the care for patients with myocardial infarction usually conducted by cardiologists (Table 2). On-site angiography, percutaneous coronary intervention, and CABG were available in 56%, 44%, and 30% of all hospitals. Although there were significant differences in hospital characteristics between the geographic regions, none of the hospital features themselves were independently associated with 30-day mortality.

Participating hospitals in the U.K. compared to Germany tended be larger, urban centres. However, fewer hospital in the U.K. had on-site angiography (29% vs 48%) and percutaneous coronary intervention (16% vs 43%) facilities compared to German hospitals ($P<0·0001$ for each comparison).

Only 24%, 20%, and 16% of Canadian hospitals had on-site angiography, percutaneous coronary intervention, CABG facilities, respectively, compared to 74%, 54%, and 50% in the U.S. ($P<0·0001$ for each). Patient care was almost always directed by a cardiologist in U.S. hospitals (95%), while in 39% of Canadian hospitals care was conducted by non-cardiologists.

Table 2 Profiles of participating hospitals

	All	WE	EE	NA	LA	Ger	U.K.	P*	U.S.	Can	P†
Number of hospitals	855	503	91	207	54	194	69	—	130	77	—
Number of patients	15060	8884	2894	2875	407	2331	2360	—	1322	1553	—
Urban[1]	69	65	97	57	96	53	81	<0·0001	52	65	0·08
Size of hospital											
<300 beds	32	24	13	57	54	29	12		54	61	
300–700 beds	44	50	35	37	33	54	58	0·004	41	31	ns
>700 beds	23	26	51	6	13	17	30		5	8	
Teaching[2]	62	61	87	51	78	63	55	ns	52	51	ns
MI care by cardiologist[3]	75	67	91	82	94	48	54	ns	95	61	<0·0001
On-site angiography											
24 h	31	26	27	38	57	22	10		52	14	
Day only	25	25	35	19	28	26	19	0·02	22	10	<0·0001
None	44	48	37	43	15	52	71		26	75	
On-site PCI											
24 h	29	24	27	37	56	21	10		49	14	
Day only	15	14	33	5	20	22	6	0·0003	5	6	<0·0001
None	56	62	40	58	24	57	84		46	79	
Mean primary PCI rate[4]	11	8	13	15	21	9	1	0·0002	22	2	<0·0001
On-site CABG available	30	17	53	37	83	7	10	ns	50	16	<0·0001

Data are % of hospitals unless otherwise indicated. $P<0·0001$ for all comparisons across the four regions.
[1]Urban=hospitals serving ≥100 000 persons, or hospitals that are considered regional referral centres.
[2]Teaching=hospitals where medical students, residents or cardiology fellows participated in the routine care of patients.
[3]MI care by cardiologist=hospitals in which the care of most patients with MI is by staff cardiologists or cardiology fellows.
[4]Mean primary PCI rate=% patients that undergo primary PCI on average in hospitals in the prior year in routine care (excluding clinical trials).
PCI=percutaneous coronary intervention.
CABG=coronary artery bypass graft surgery.
WE=Western Europe; EE=Eastern Europe; NA=North America; LA=Latin America; Ger=Germany; Can=Canada.
*Germany vs U.K.
†U.S. vs Canada.

Baseline patient clinical characteristics

Baseline patient characteristics demonstrated significant differences across the geographic regions (Table 3). Differences of potential clinical importance included fewer elderly patients (age ≥75 years) in Eastern Europe and Latin America, more patients with Killip class ≥II congestive heart failure in Western Europe and Eastern Europe, and longer time-to-treatment in Latin America. Patients in Germany (compared to the U.K.) were younger, with a lower likelihood of prior myocardial infarction, Killip class ≥2, and late presentation (>3 h); but were more likely to have diabetes, prior hypertension, or previous percutaneous coronary intervention. Patients in the U.S. (compared to Canada) were more likely to be female, have a history of diabetes, hypertension or prior percutaneous coronary intervention; but were less likely to have Killip class ≥2, and tended to present earlier following symptom onset.

Medication use

Use of aspirin and lipid-lowering therapy prior to enrollment was lowest in Eastern Europe and highest in North America, while rates of prior beta-blocker and ACE inhibitor/angiotensin receptor blocker use were more uniform across the regions (Table 4). Patients in the U.K. (compared to Germany) were more likely to be treated with aspirin, but less likely to be receiving ACE inhibitors/angiotensin receptor blockers or antiarrhythmics prior to presentation. U.S. patients were more likely to have been treated with aspirin prior to enrollment than Canadian patients.

In-hospital use of intravenous and oral beta-blockers both were lowest in Western Europe and Latin America and highest in North America. Lipid-lowering agents were used more frequently in Western Europe and North America compared to the other two regions. Patients enrolled in Germany (compared to the U.K.) were more likely to receive ACE inhibitors/angiotensin receptor blockers, and intravenous and oral beta-blockers during the index hospitalization. A similar pattern of more intensive medical therapy, including greater use of hypolipidaemic therapy, was present in the U.S. compared to Canada.

Of medical therapies consistently associated with improved survival following acute myocardial infarction, only ACE inhibitors/angiotensin receptor blockers were used more frequently in Eastern Europe and Latin America compared to Western Europe and North America. This may have been related to a greater proportion of patients with diabetes (Latin America), prior congestive heart failure (Eastern Europe), anterior infarction (both) and Killip Class ≥II (Eastern Europe).

Table 3 Baseline patient characteristics

	All	WE	EE	NA	LA	Ger	U.K.	P*	U.S.	Can	P†
Number of patients	15060	8884	2894	2875	407	2331	2360	—	1322	1553	—
Demography											
Mean age (years)	61·1	61·5	59·8	61·3	59·8	61·1	63·0	<0·0001	61·1	61·5	ns
Age ≥75 years	14	14	10	17	10	14	17	0·002	17	17	ns
Female	25	24	26	27	22	23	25	0·09	30	25	0·003
Risk factors											
Smoking	45	45	48	42	44	44	43	ns	41	43	ns
Diabetes	14	13	13	17	17	16	8	<0·0001	19	16	0·04
Hypertension	30	28	36	32	37	34	23	<0·0001	38	27	<0·0001
Cardiovascular history											
Myocardial infarction	16	15	18	19	13	14	19	<0·0001	19	20	ns
Heart failure	3	3	5	3	3	3	3	ns	3	4	ns
PCI	5	4	1	9	3	6	2	<0·0001	11	7	<0·0001
CABG	3	2	1	5	3	2	2	ns	7	4	0·02
Peripheral vascular disease	5	5	6	5	4	5	4	0·07	5	6	0·13
MI characteristics											
Anterior location	45	42	46	38	45	42	42	ns	36	39	ns
Killip ≥2	13	14	14	9	7	11	25	<0·0001	7	10	0·02
time to TX >3 h	46	46	49	37	67	40	50	<0·0001	35	38	0·12

Data in tables are % of patients unless otherwise indicated; *Germany vs U.K.; †U.S. Canada.
$P<0·0001$ for all comparisons across the four regions except for % female ($P=0·0003$).
Other abbreviations, see Table 2.

Use of cardiac procedures

Rates of angiography, percutaneous coronary intervention and CABG were lowest in Eastern Europe and highest in North America (Table 4). These differences were driven by high rates of procedures performed during the index hospitalization in the U.S. (angiography 79%, percutaneous coronary intervention 49%, CABG 15%). If coronary angiography was performed, the likelihood of having a revascularization procedure prior to discharge varied among the regions from a low of 45% in Eastern Europe to 76% in North America (four-way $P<0·0001$). Angiography was as likely to lead to revascularization in Germany as in the U.K. (57% vs 59%, P=ns) despite an eight-fold higher rate of angiography in Germany. However, angiography was more likely to lead to revascularization in the U.S. compared to Canada (79% vs 69%, $P<0·0001$), even though more than twice as many patients in the U.S. had angiography during the index admission. Adjunctive intravenous glycoprotein IIb/IIIa inhibitors were used in 39% of patients undergoing percutaneous coronary intervention in the U.S., but were infrequently used in other regions (1·2%–8%) during percutaneous coronary intervention.

A minority of the revascularizations (7%–16%) were performed between discharge and 30 days in the four regions (Table 4, Fig. 1). In the U.S., revascularization was performed early (median 2·4 days), in contrast to Canada and the other three regions (median 7·3–11·3 days), where the revascularization rates were fairly constant over the first 2 weeks (Fig. 1). The rate of revascularization in Germany (40%) and timing (median 8·7 days) was not as aggressive as in the U.S., while the utilization of invasive procedures in the U.K. were one-quarter that of Canada and nearly identical to the rates in Eastern Europe.

Mortality

Unadjusted 30-day mortality rates by geographic region were lowest in North America (5·7%), intermediate in Western Europe (6·7%) and Eastern Europe (7·3%) and highest in Latin America (10·1%) (Table 5). The majority of these deaths occurred between 24 h and discharge, and during this period differences between regions widened (Fig. 2, Table 5). Adjusted 30-day mortality (adjusted for significant baseline characteristics and prior medications listed in Tables 3–4) followed a similar pattern (Fig. 3). Of interest, adjusted 30-day mortality was similar in Germany and the U.K. (OR for the U.K. 1·2 [0·9–1·6], $P=0·16$), and was also similar in Canada and the U.S. (OR for Canada 0·95 [0·64–1·4], $P=0·78$) (Fig. 3). There were no statistically significant country effects (Germany–U.K., U.S.–Canada) in 30-day mortality stratified for baseline risk (Fig. 4a–b).

At 6 months and 1 year, adjusted mortality was not different in Germany and the U.K. (ORs for the U.K. 1·1 [0·86, 1·5] and 1·2 [0·92, 1·5] at these timepoints, respectively). Similarly, adjusted mortality was not different in the U.S. and Canada during the follow-up period (ORs for Canada 0·88 [0·61, 1·28] and 0·85 [0·61, 1·2] at 6 months and 1 year, respectively).

Among patients who underwent revascularization, unadjusted mortality was higher in Latin America (8·6%) compared to each of the other regions (Western

Table 4 Medications and procedures

	All	WE	EE	NA	LA	Ger	U.K.	P*	U.S.	Can	P†
Number of patients	15060	8884	2894	2875	407	2331	2360	—	1322	1553	—
Prior medications											
Aspirin	20	20	16	25	20	19	26	<0·0001	28	23	0·003
Beta-blockers	16	16	15	15	12	17	17	ns	16	15	ns
ACE inhibitors/ARBs	13	12	17	14	17	15	9	<0·0001	15	13	0·11
Hypolipidaemic	9	10	4	15	7	9	8	0·12	16	14	0·18
Antiarrhythmics	1	1	1	1	3	2	0·9	0·02	1	1	ns
In-hospital											
Medications											
Aspirin	96	96	95	96	95	95	95	ns	96	95	ns
IV beta-blockers	20	16	19	32	16	23	6	<0·0001	41	25	<0·0001
Oral beta-blockers	76	73	75	84	73	83	64	<0·0001	86	82	0·001
ACE inhibitors/ARBs	54	52	63	50	59	67	48	<0·0001	49	51	ns
Hypolipidaemic	33	42	13	27	12	46	55	<0·0001	34	21	<0·0001
Antiarrhythmics	16	13	19	23	19	12	11	ns	23	22	ns
Procedures											
Angiography	38	39	14	55	41	70	9	<0·0001	79	35	<0·0001
PCI	20	20	6	33	9	36	5	<0·0001	49	19	<0·0001
Adjunctive GP IIb/IIIa inhibitor	15	8	1	31	4	8	17	0·004	39	14	<0·0001
CABG	4	3	1	10	4	5	1	<0·0001	15	5	<0·0001
Any revascularization	24	23	7	42	23	40	6	<0·0001	63	24	<0·0001
Revascularization/angiography	62	58	45	76	55	57	59	ns	79	69	<0·0001
30 days											
PCI	22	22	6	35	22	38	6	<0·0001	51	21	<0·0001
CABG	5	4	1	11	5	6	2	<0·0001	17	6	<0·0001
Any revascularization	26	26	8	45	27	44	7	<0·0001	67	27	<0·0001

Data in table are % of patients; * Germany vs U.K.; †U.S. vs Canada.
$P<0·0001$ for all comparisons across the four groups except for prior beta-blocker ($P=0·09$), prior antiarrhythmic ($P=0·16$), and in-hospital aspirin (P=ns).
ARBs=angiotensin receptor blockers; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft surgery; Revascularization/angiography=ratio of patients who underwent revascularization among those with angiography.
Other abbreviations, see Table 2.

Europe 3·2% ($P=0·005$), Eastern Europe 2·6% ($P=0·02$), North America 2·9% ($P=0·003$)). There was a trend for higher mortality among non-revascularized patients in Latin America (10·5% vs 7·7% in all other regions combined, $P=0·067$) (Fig. 4). Overall, patients selected for revascularization in Latin America were not at higher risk for mortality compared to patients selected for revascularization in the other regions (data not presented). In a multivariate model that included baseline characteristics and pre-procedural complications, the adjusted mortality following revascularization was significantly higher in Latin America (OR for Latin America vs all other regions 3·7 [1·6–8·7], $P=0·002$). There were no significant differences between Western Europe, Eastern Europe, and North America or in the Germany–U.K. and U.S.–Canada comparisons in similar unadjusted and adjusted analyses stratified by revascularization.

Other clinical end-points

CCSC angina ≥II at 30 days was present in 15%, 24%, 15%, and 8% of patients enrolled in Western Europe, Eastern Europe, North America, and Latin America, respectively (4-way $P<0·0001$), and these differences persisted even after multivariate adjustment (OR for Eastern Europe 1·5 [1·4, 1·7], OR for Latin America 0·5, [0·3, 0·7] compared to Western Europe) (Table 5). Of note, patients enrolled in countries with a less invasive approach (the U.K., Canada) were more likely to experience CCSC angina ≥II (adjusted ORs 1·4 for the U.K. and 1·8 for Canada) and new/worsening chronic heart failure (adjusted ORs 1·4 and 1·3) at 30 days, compared to patients enrolled in their regional counterparts (Germany, U.S.) where invasive procedures were more frequently utilized.

No clear patterns in reinfarction, cardiogenic shock, total stroke or intracranial haemorrhage emerged in the four-region analysis. In the German–U.K. comparison, no differences in the rates of stroke or major haemorrhage were observed. However, U.S. patients experienced higher rates of total stroke, intracranial haemorrhage, and major bleeding compared to Canadian patients even after multivariate adjustment. Fatal intracranial haemorrhage was more frequent in the U.S. compared to Canada (1·3% vs 0·5%, $P=0·04$) and accounted for 25% of the deaths by 30 days in the U.S. (Fig. 5).

Among the four regions, median length of stay was longest in Eastern Europe (14 days) and shortest in

Table 5 Clinical outcomes

	All	WE	EE	NA	LA	*P**	Ger	U.K.	*P*	U.S.	Can	*P*
Number of patients	15060	8884	2894	2875	407	—	2331	2360	—	1322	1553	—
In-hospital												
24-h mortality, %	2·4	2·4	3·0	1·8	2·7	0·04	2·0	2·5	ns	1·4	2·2	0·14
Unadjusted OR (CI)		1·0	1·3 (1·0, 1·6)	0·8 (0·6, 1·0)	1·1 (0·6, 2·1)	—	1·0	1·3 (0·9, 1·9)	ns	1·0	1·5 (0·9, 2·7)	0·14
Adjusted OR (CI)		1·0	1·3 (1·0, 1·7)	0·7 (0·5, 1·0)	1·2 (0·6, 2·2)	—	1·0	1·3 (0·9, 2·0)	ns	1·0	1·3 (0·7, 2·5)	ns
Discharge mortality, %	6·1	6·0	7·0	5·0	9·1	0·0007	5·4	7·2	0·009	4·8	5·1	ns
Unadjusted OR (CI)		1·0	1·2 (1·0, 1·4)	0·8 (0·7, 1·0)	1·6 (1·1, 2·2)	—	1·0	1·4 (1·1, 1·7)	0·009	1·0	1·2 (0·8, 1·6)	ns
Adjusted OR (CI)		1·0	1·3 (1·1, 1·6)	0·9 (0·7, 1·1)	2·0 (1·4, 3·0)	—	1·0	1·0 (0·7, 1·4)	ns	1·0	0·9 (0·6, 1·3)	ns
Median hospital stay, d (25%, 75%)	9 (6, 15)	9 (6, 15)	14 (10, 19)	6 (5, 9)	8 (6, 11)	<0·0002	18 (13, 23)	6 (5, 8)	<0·0001	5 (4, 8)	7 (5, 11)	<0·0001
30 days												
All-cause mortality, %	6·7	6·7	7·3	5·7	10·1	0·003	5·5	8·4	0·0001	5·1	6·2	0·20
Unadjusted OR (CI)		1·0	1·1 (0·9, 1·3)	0·8 (0·7, 1·0)	1·6 (1·1, 2·2)	—	1·0	1·6 (1·2, 2·0)	0·0001	1·0	1·2 (0·9, 1·7)	0·20
Adjusted OR (CI)		1·0	1·2 (1·0, 1·4)	0·8 (0·7, 1·0)	1·8 (1·3, 2·7)	—	1·0	1·3 (1·0, 1·8)	0·054	1·0	1·0 (0·6, 1·5)	ns
CCSC ≥II angina, %	17	15	24	15	7·8	<0·0001	14	21	<0·0001	11	19	<0·0001
Unadjusted OR (CI)		1·0	1·7 (1·5, 1·9)	1·0 (0·9, 1·1)	0·5 (0·3, 0·7)	—	1·0	1·5 (1·3, 1·8)	<0·0001	1·0	1·8 (1·4, 2·2)	<0·0001
Adjusted OR (CI)		1·0	1·5 (1·4, 1·7)	1·0 (0·9, 1·1)	0·5 (0·3, 0·7)	—	1·0	1·4 (1·2, 1·7)	0·0001	1·0	1·8 (1·4, 2·2)	<0·0001
Non-fatal re-MI, %	4·7	4·5	3·8	4·8	2·2	0·03	4·3	5·0	ns	4·5	5·1	ns
Unadjusted OR (CI)		1·0	0·8 (0·7, 1·0)	1·1 (0·9, 1·3)	0·5 (0·3, 0·9)	—	1·0	1·2 (0·9, 1·5)	ns	1·0	1·1 (0·8, 1·6)	ns
Adjusted OR (CI)		1·0	0·9 (0·7, 1·1)	1·0 (0·8, 1·2)	0·5 (0·3, 1·1)	—	1·0	1·1 (0·9, 1·5)	ns	1·0	1·1 (0·8, 1·6)	ns
Cardiogenic shock, %	3·7	3·6	3·4	4·2	4·9	0·16	3·6	3·4	ns	4·6	3·9	ns
Unadjusted OR (CI)		1·0	1·0 (0·8, 1·2)	1·2 (0·9, 1·4)	1·5 (0·9, 2·3)	—	1·0	0·9 (0·7, 1·3)	ns	1·0	0·8 (0·6, 1·2)	ns
Adjusted OR (CI)		1·0	0·9 (0·7, 1·1)	1·2 (1·0, 1·6)	1·8 (1·1, 2·9)	—	1·0	0·8 (0·6, 1·2)	ns	1·0	0·7 (0·5, 1·1)	0·11
New/worse CHF, %	14	13	16	15	11	0·0002	11	15	<0·0001	13	17	0·003
Unadjusted OR (CI)		1·0	1·3 (1·2, 1·5)	1·2 (1·1, 1·4)	0·7 (0·5, 1·0)	—	1·0	1·5 (1·3, 1·8)	<0·0001	1·0	1·4 (1·1, 1·7)	0·003
Adjusted OR (CI)		1·0	1·2 (1·1, 1·4)	1·3 (1·1, 1·5)	0·8 (0·5, 1·1)	—	1·0	1·4 (1·1, 1·7)	0·002	1·0	1·3 (1·1, 1·7)	0·02
All stroke, %	1·8	1·7	1·6	2·1	2·2	ns	1·7	1·9	ns	2·6	1·5	0·04
Unadjusted OR (CI)		1·0	0·9 (0·7, 1·3)	1·2 (0·9, 1·6)	1·3 (0·7, 2·6)	—	1·0	1·1 (0·7, 1·7)	ns	1·0	0·6 (0·3, 1·0)	0·04
Adjusted OR (CI)		1·0	1·0 (0·7, 1·4)	1·2 (0·9, 1·7)	1·5 (0·7, 3·0)	—	1·0	1·0 (0·6, 1·6)	ns	1·0	0·6 (0·3, 1·0)	0·04
ICH, %	1·0	0·9	0·9	1·4	0·7	0·11	0·9	0·7	ns	1·7	1·0	0·10
Unadjusted OR (CI)		1·0	1·1 (0·7, 1·6)	1·6 (1·1, 2·3)	0·9 (0·3, 2·7)	—	1·0	0·8 (0·4, 1·4)	ns	1·0	0·6 (0·3, 1·1)	0·10
Adjusted OR (CI)		1·0	1·1 (0·7, 1·8)	1·5 (1·0, 2·2)	1·0 (0·3, 3·1)	—	1·0	0·8 (0·4, 1·5)	ns	1·0	0·5 (0·2, 1·0)	0·04
Major bleeding†, %	0·5	0·4	0·2	1·1	1·7	<0·0001	0·3	0·3	ns	1·5	0·6	0·02
Unadjusted OR (CI)		1·0	0·7 (0·3, 1·4)	2·8 (1·7, 4·6)	4·7 (2·1, 11)	—	1·0	0·7 (0·3, 2·1)	ns	1·0	0·4 (0·2, 0·9)	0·02
Adjusted OR (CI)		1·0	0·7 (0·3, 1·5)	2·3 (1·4, 3·9)	4·8 (2·1, 11)	—	1·0	0·7 (0·2, 2·1)	ns	1·0	0·5 (0·2, 1·1)	0·08
6-month												
Mortality, %	8·7	8·9	9·2	7·3	12·0	0·003	7·6	11·1	0·0001	7·0	7·5	ns
Unadjusted OR (CI)		1·0	1·0 (0·9, 1·2)	0·8 (0·7, 0·9)	1·4 (1·0, 1·9)	—	1·0	1·5 (1·2, 1·8)	0·0001	1·0	1·1 (0·8, 1·4)	ns
Adjusted OR (CI)		1·0	1·0 (0·9, 1·2)	0·8 (0·7, 1·0)	1·7 (1·2, 2·4)	—	1·0	1·1 (0·9, 1·5)	ns	1·0	0·9 (0·6, 1·3)	ns
1-year												
Mortality, %	9·7	9·7	10·9	8·0	12·3	0·0006	8·0	12·2	<0·0001	7·8	8·2	ns
Unadjusted OR (CI)		1·0	1·1 (1·0, 1·3)	0·8 (0·7, 0·9)	1·3 (1·0, 1·7)	—	1·0	1·5 (1·2, 1·7)	<0·0001	1·0	1·1 (0·8, 1·4)	ns
Adjusted OR (CI)		1·0	1·2 (1·0, 1·4)	0·8 (0·7, 0·9)	1·6 (1·2, 2·2)	—	1·0	1·2 (0·9, 1·5)	ns	1·0	0·8 (0·6, 1·2)	ns

Data in table are % of patients; *Four-way *P*-value across the regions; †Excluding intracranial haemorrhage.
CCSC=Canadian Cardiovascular Society Classification; ICH=intracranial haemorrhage.
Other abbreviations, see Table 2.

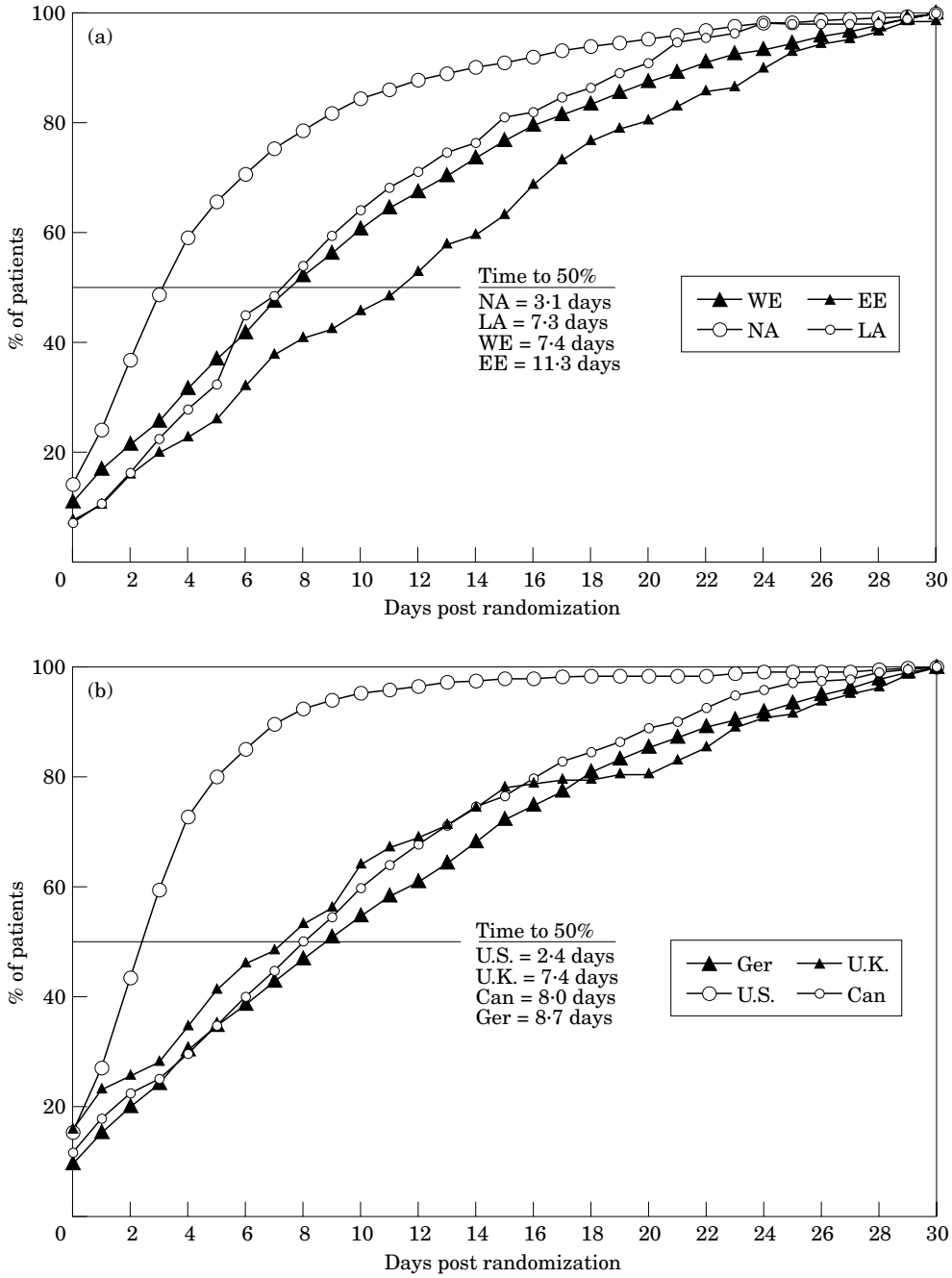

Figure 1 **Timing of revascularization through 30-days among patients who underwent a revascularization by (a) geographic region, and (b) specific countries. WE=Western Europe, EE=Eastern Europe, NA=North America, LA=Latin America, UK=United Kingdom, GER=Germany, US=United States, CAN= Canada.**

North America (6 days). Length of stay was markedly longer in Germany compared to the U.K. (18 vs 6 days, $P<0{\cdot}0001$), with nearly one in seven German patients still hospitalized at 30 days. This may reflect the German cultural practice to convalesce in local hospitals following myocardial infarction and revascularization, and the definition of initial hospitalization used in this trial which included transfers to other acute care facilities. In the U.S., the median hospital stay was 5 days (interquartile range 4–8), approximately 2 days shorter on average than in Canada (median 7, interquartile range 5–11, $P<0{\cdot}0001$).

Discussion

Despite recent dissemination of very similar practice guidelines in both hemispheres[9–11] this study demonstrated marked global regional variations in the use of

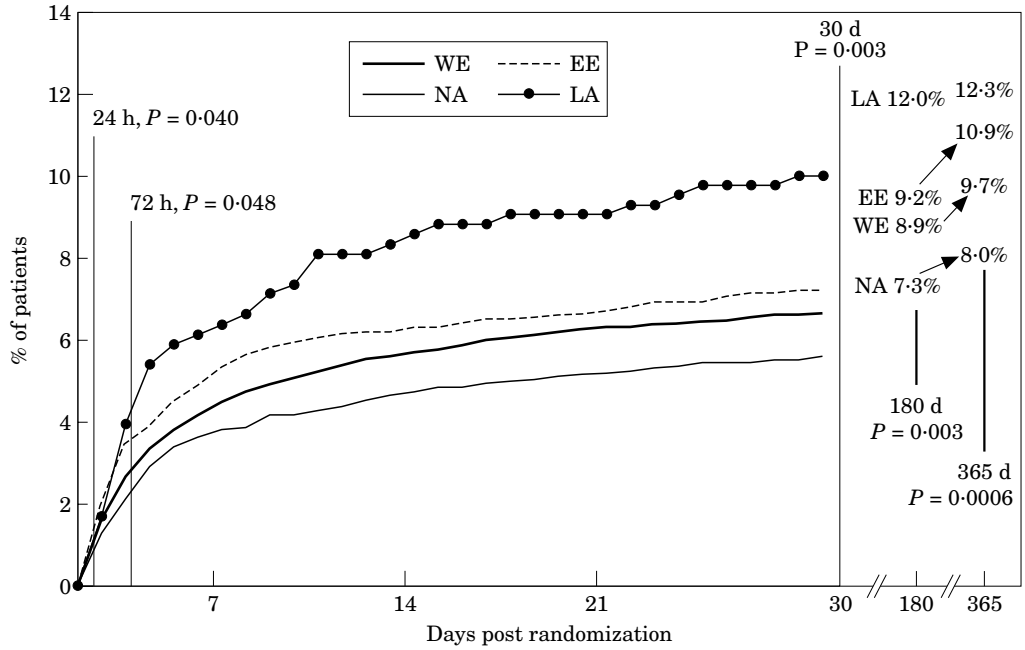

Figure 2 **Unadjusted mortality by geographic region. WE=Western Europe, EE=Eastern Europe, NA=North America, LA=Latin America.**

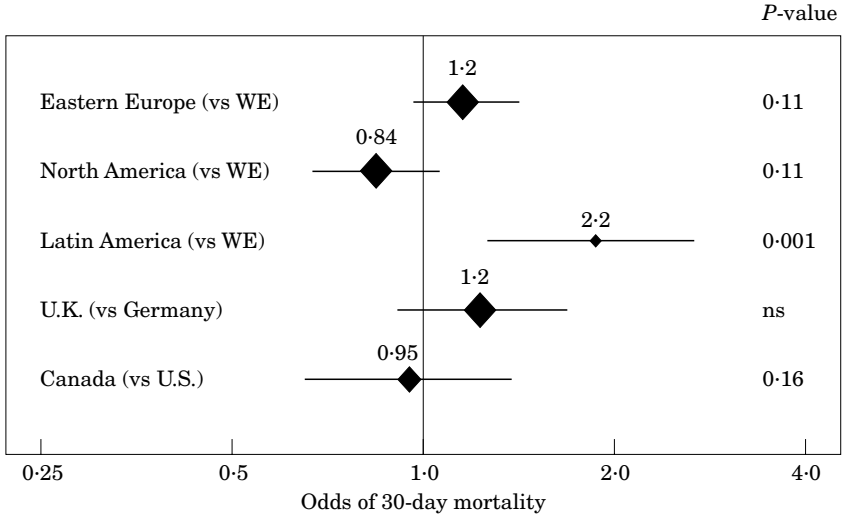

Figure 3 **Adjusted odds of 30-day mortality by geographic location. An odds ratio greater than 1·0 indicates a higher adjusted 30-day mortality for that region compared to Western Europe (Germany is the referent for the United Kingdom, United States is the referent for Canada). WE=Western Europe, GER=Germany, US=United States. Model is adjusted for the following variables: age; gender; smoking status; history of angina, MI, diabetes, hypertension, peripheral vascular disease; time to treatment; systolic blood pressure; heart rate; body weight; Killip class; location of MI; prior use of antiarrhythmics or lipid-lowering agents.**

medications and invasive procedures, and clinical outcomes in a large international trial of fibrinolysis for acute myocardial infarction. Our findings of geographic practice variation are analogous to those reported in recent studies of patients with unstable angina and non-ST-elevation myocardial infarction[6–8,19–21] and extend prior observations of differences between the U.S. and other countries in acute myocardial infarction[2,4,5] to additional international regions and countries.

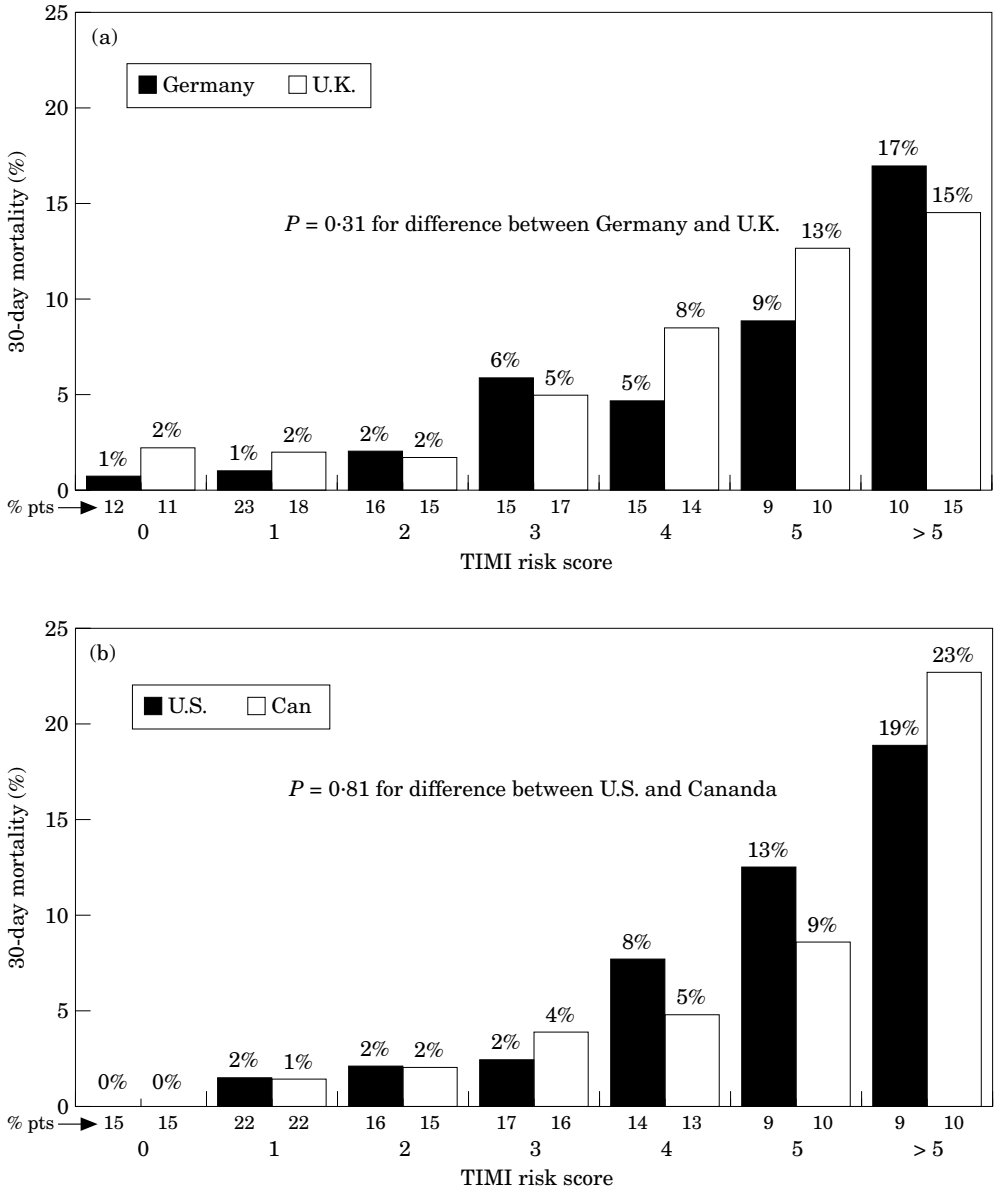

Figure 4 **Thirty-day mortality stratified by the TIMI Risk Score, a simple weighted integer scoring system that includes age, systolic blood pressure, Killip class heart failure, heart rate, cardiovascular risk factors, location of ST-elevation, and weight. (a) Compares Germany with the United Kingdom and (b) the United States with Canada. Numbers below the x-axis represent the percentage of patients in the corresponding country with the number of risk factors identified.**

Mortality findings

Adjusted 30-day mortality in InTIME-II was lowest in North America followed by Western Europe, Eastern Europe, and Latin America, and these results remained stable out to 1 year. Geographic variations in mortality are unlikely to be explained by any single factor given the complex interaction of a large number of variables that can influence survival following ST-elevation myocardial infarction[3]. Mortality differences in InTIME-II persisted despite consideration of baseline clinical and hospital characteristics, and stratification for baseline risk using known predictors of mortality in this dataset. The observed regional mortality differences may be related to four factors: (1) differences in the use of proven therapies, (2) higher than expected mortality following revascularization, (3) unmeasured covariates (e.g., socioeconomic variables), or (4) play of chance.

Less frequent use of intravenous and oral beta-blockers, lipid-lowering agents, and intravenous glycoprotein IIb/IIIa inhibitors as an adjunct to percutaneous coronary intervention may have played a role in the

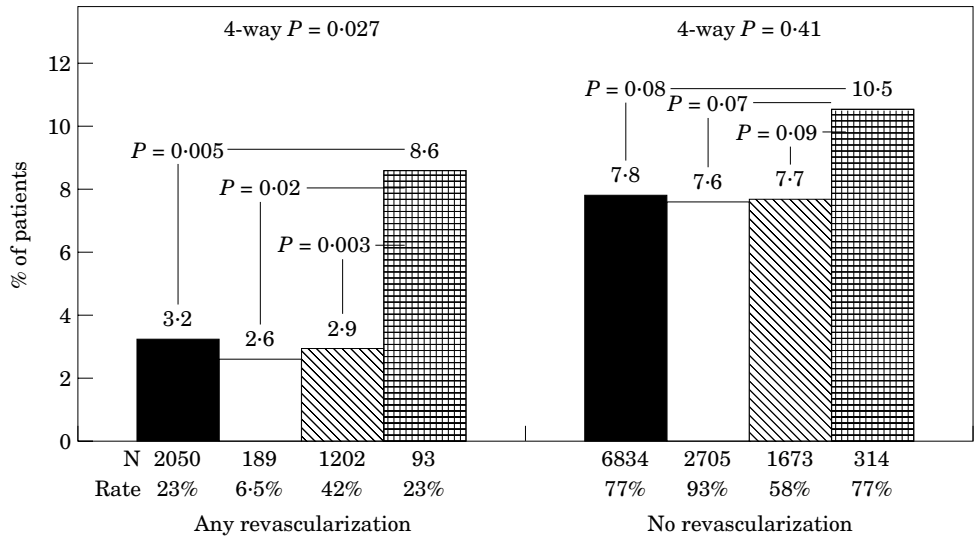

Figure 5 **Unadjusted 30-day mortality rates in each region stratified by the use of revascularization during the index hospitalization. Numbers below the x-axis indicate the absolute number and percentage of patients in each region. ■=Western Europe, □=Eastern Europe, ▨=North America, ⊞=Latin America.**

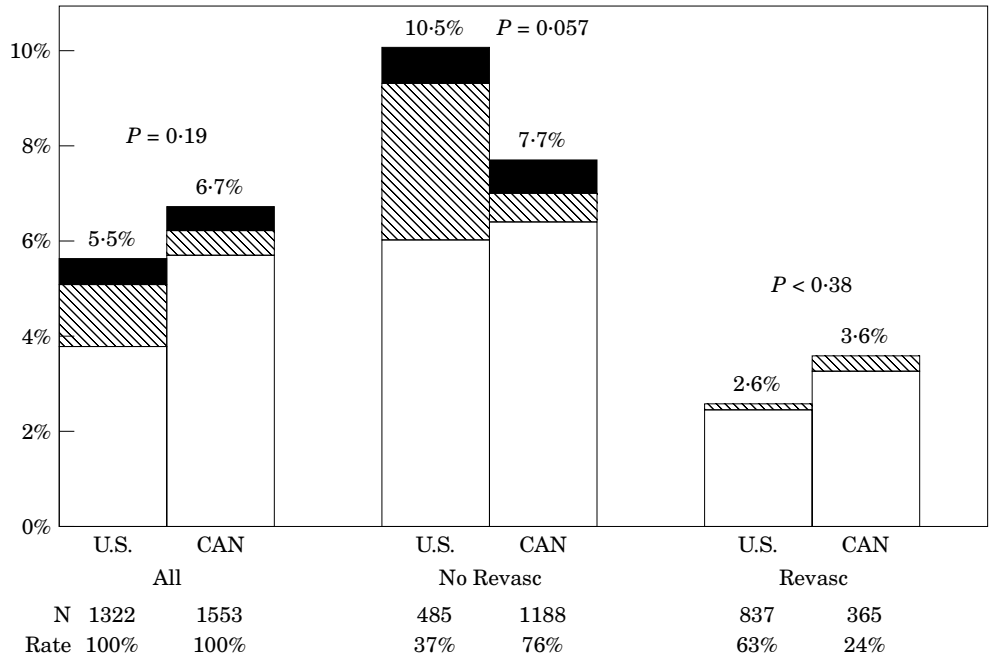

Figure 6 **Rates of death and intracranial haemorrhage in the U.S. and Canada at 30 days stratified by the use of revascularization during the index hospitalization. The absolute number of patients and percentage of patients in each strata are indicated below the x-axis. *P*-values compare the rate of death plus non-fatal intracranial haemorrhage between the U.S. and Canada for each strata. ■=Non-fatal intracranial haemorrhage; ▨=fatal intracranial haemorrhage; □=non-intracranial haemorrhagic death.**

higher mortality rate in Eastern Europe and Latin America. The higher mortality rate following revascularization in Latin America represents a small absolute number of deaths, and may be due to the play of chance. Of note, in patients with acute coronary syndromes *without* persistent ST-elevation, higher event rates in Latin America compared to other regions were also observed in both the PURSUIT[20] and ESSENCE trials[8,21].

Differences in observed mortality rates between Germany and the U.K., and between the U.S. and Canada, were largely explained by differences in baseline

patient characteristics, with the U.K. and Canada enrolling patients of higher risk for mortality, compared to Germany and the U.S., respectively. Data from the ENACT study[6], a pan-European survey of acute coronary syndromes, reported a higher rate of fibrinolytic therapy in the U.K. compared to other European countries. This is consistent with our observations that the U.K. hospitals participating in InTIME-II infrequently utilized primary percutaneous coronary intervention in ST-elevation myocardial infarction, and tended to enroll higher risk patients in the trial, thus explaining the higher unadjusted, but similar adjusted, mortality in the U.K. compared to Germany.

Use of invasive procedures

Markedly disparate use of invasive procedures following acute myocardial infarction has been previously reported[4,6,13–16]. In this analysis, rates of angiography, percutaneous coronary intervention, and CABG varied as much as 10-fold across the regions, with the lowest utilization in Eastern Europe and the highest in North America (particularly in the U.S.). In Western Europe, these procedures were performed much more frequently in Germany than in the U.K., while in North America they were more common in the U.S. than Canada. However, no clear, simple relationship between revascularization and short to medium-term survival is apparent.

While patients enrolled in the Germany were 6–7 times more likely to undergo revascularization than patients enrolled in the U.K., adjusted mortality was similar (adjusted ORs for the U.K. 1·2, 1·1, and 1·2 at 30 days, 6 months and 1 year, respectively). Similarly, in the U.S.–Canada comparison, a 2–3 fold-higher rate of revascularization in the U.S. was not associated with improved survival (adjusted ORs for Canada 0·95, 0·81, and 0·85 at 30 days, 6 months, and 1 year, respectively). Interestingly, even among relatively high risk patients (TIMI risk score ≥ 5), no differences between mortality in countries with very divergent practices were observed (Fig. 4). Meanwhile, patients enrolled in Western Europe and Latin America had nearly identical rates of revascularization but significantly different adjusted mortality (ORs for Latin America vs Western Europe 1·8 [1·3–2·7], $P=0·001$ at 30 days, 1·7 [1·2–2·4], $P=0·004$ at 6 months, and 1·6 [1·2–2·2], $P=0·003$ at 1 year).

Adjusted rates of CCSC $\geq$II angina and new/worsening chronic heart failure at 30-days were higher in the U.K. than Germany, and also in Canada compared to the U.S., suggesting a link between early revascularization and reduction in angina[14], and more myocardial salvage. Apparent global variation in CCSC anginal status (and to a lesser degree chronic heart failure) also may be affected by differences in reporting and/or variable interpretations of the qualitative grading systems; this sort of reporting bias can not be excluded.

Delayed use of revascularization was associated with longer hospital lengths of stay (Eastern Europe 14 days; Canada, Western Europe, Latin America 7–9 days; U.S. 5 days) (Fig. 1). Only 6·5% of patients in Eastern Europe underwent revascularization by 30 days (at a median of 11·3 days), while at the other extreme, nearly two-thirds of U.S. patients underwent revascularization, with procedures generally occurring quite early during the index admission (median 2·4 days). Meanwhile rates and timing of coronary revascularization procedures were intermediate and very similar in Western Europe, Canada, and Latin America (rates 23–24%; median time 7·3–7·4 days).

Implications

Our findings have several important research and clinical implications. First, they may assist in the interpretation of geographic variations in outcomes observed in clinical trials, and help optimize the design of future studies by bringing to light heterogeneities that can be expected in worldwide megatrials of acute myocardial infarction. For example, use of percutaneous coronary intervention with adjunctive glycoprotein IIb/IIIa inhibition was extremely low in Eastern Europe (1·2% compared to 39% in the U.S.). Thus a trial comparing an early invasive strategy including glycoprotein IIb/IIIa inhibitors vs routine care might be more feasible in Eastern Europe than in regions where this strategy is already commonly in use.

Secondly, these analyses can aid efforts in quality improvement in individual countries and regions by targeting specific proven therapies that appear to be under-utilized. Specifically, use of beta-blockers was relatively low in the U.K. (64%) compared to Germany, Canada, and the U.S. (82–86%) despite data that support their use[22–25]. Similarly, lipid-lowering agents and glycoprotein IIb/IIIa inhibitors (the latter as an adjunct to percutaneous coronary intervention), two promising new therapies recommended for selected patients in the revised American College of Cardiology/American Heart Association Guidelines[26], also appear to have been underutilized in this trial.

Lastly, practice patterns regarding the use and timing of angiography and revascularization post-infarction continue to demonstrate wide variation in regional use. In particular, there was a 4–10 fold higher rate of invasive procedures in Germany compared to the U.K., and a three-fold higher rate in the U.S. vs Canada. However, no difference in adjusted mortality at any timepoint through 1 year and only minor reductions in post-infarction angina and heart failure were observed with a more aggressive approach. Furthermore, the higher rate of invasive procedures may have been associated with higher rates of haemorrhage in the U.S. compared to Canada.

Limitations

These analyses, although pre-specified, were undertaken within non-randomized subgroups of a clinical trial

comparing two randomized therapies. The number of patients varied between regions, and multivariate modelling cannot completely control for all differences between the regions and countries (e.g. socioeconomic differences). Different thresholds for enrolling patients in this trial may have existed among the various hospitals and regions, particularly with respect to the availability of on-site catheterization facilities, which may introduce a selection bias. This issue is explored in detail in a separate paper[17]. Survival benefits of early revascularization (particularly CABG), may require longer follow-up than was available in this trial[28,29]. We did not assess the quality of life of patients beyond the four-level classifications of angina and heart failure at 30 days; such measures also may be favourably affected by higher rates of revascularization[30,31]. Lastly, adjustments for multiple comparisons were not made, and thus these subgroup findings should be considered hypothesis-generating, requiring confirmation in other prospective studies.

Conclusions

Practice patterns and outcomes varied markedly in this large international study of fibrinolytic therapy for acute ST-elevation myocardial infarction, despite similar practice guidelines recently published in each of the regions. Regional differences in mortality persisted even after adjustment for baseline patient characteristics and consideration of differences in hospital features, and are not explained by the observed wide variation in the use of revascularization. These differences in the use of post-infarction invasive procedures suggest that further and longer-term prospective evaluation in the modern era are needed to better delineate their optimal role in patient care.

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