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International differences in in-hospital revascularization and outcomes following acute myocardial infarction

A multilevel analysis of patients in ASSENT-2

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Background Revascularization rates vary substantially between countries in patients with acute ST-elevation myocardial infarction (STEMI). The impact of early revascularization on clinical outcomes in such patients remains uncertain. The ASSENT-2 fibrinolytic trial provides the opportunity to compare revascularization rates following STEMI in patients across 29 countries, and to explore the relationship between revascularization and clinical outcome.
Methods Countries participating in ASSENT-2 were grouped into tertiles according to their in-hospital revascularization rates (<15%, 15–39%, >39%). Baseline characteristics, medication and procedure use, and clinical outcomes of the 16 949 patients enrolled were compared. Multiple Cox regressions were used to assess the relationship between the tertiles and 30-day mortality, the primary endpoint of the ASSENT-2 trial. Multilevel logistic regression models were developed to validate and further extend the findings from the single-level analyses.
Results Patients in highest tertile countries were younger, heavier, and more often diabetic or hypertensive. They were more likely to have had a previous myocardial infarction or revascularization procedure. Time to treatment and hospital length of stay were shorter in the highest tertile, and beta-blocker use was more frequent. Stroke rates were low and similar across tertiles, with no statistically significant difference in rates of intracranial haemorrhage. Recurrent ischaemia and reinfarction were less common in the highest tertile. Mortality rates at 30 days were lower for countries with the highest revascularization rates (5.1% vs 6.9% vs 6.5% for the lower

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two tertiles, $P<0.001$). At 1 year, mortality remained significantly lower in the highest tertile countries (8.4% vs 10.6% vs 9.9%, $P=0.001$). Following adjustment for baseline patient characteristics, Cox regression analysis confirmed an excess of 30-day and 1-year mortality in the lowest and intermediate tertiles compared to the highest tertile. The multilevel analyses validated these findings, and demonstrated that a country's life expectancy and the hospital volume were inversely related to both 30-day and 1-year mortality.

Conclusions The highest rate of in-hospital revascularization following fibrinolytic therapy for acute myocardial infarction in this international study was associated with a reduction in recurrent ischaemia, reinfarction, and improved survival at both 30 days and at 1 year. The optimal rates of revascularization in this setting remain to be determined.

Introduction

Significant variations exist between countries in the use of coronary angiography and revascularization in patients with acute coronary syndromes. These international variations in practice patterns may relate to differences in physician attitudes, variable access to advanced cardiovascular care, and to differences in the financing of healthcare systems. Initial studies comparing aggressive to conservative revascularization strategies in patients with non-ST-elevation myocardial infarction (NSTEMI) demonstrated reductions in recurrent angina and improved functional status.[1–3] Despite significant reductions in re-infarction, no benefit was seen on mortality. Similar observations have also been made in NSTEMI registries.[4] In fact, the VANQWISH study suggested an increase in mortality with an aggressive revascularization approach following NSTEMI.[5] Recently, randomized clinical trials such as FRISC II and TACTICS-TIMI 18 have demonstrated that early angiography and revascularization in NSTEMI result in a significant reduction in the composite clinical end-point of death and myocardial infarction.[6,7]

There have been fewer prospective studies exploring the role of early revascularization following fibrinolytic therapy in the setting of acute ST-elevation MI (STEMI). These trials have demonstrated wide variation in the rates of early angiography and revascularization in such patients. Although selected studies have revealed improved functional status, for example in US vs Canadian patients, little or no impact has been observed on mortality.[8–11] Since then however, significant advances in the efficacy of pharmacologic regimens as well as early revascularization have occurred, suggesting the need to revisit the potential benefits of early revascularization following STEMI.

Accordingly, we undertook this initiative in the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) study, a large, international, multicentre, randomized, and controlled mortality study involving 29 countries on five continents, which compared two different fibrinolytic treatments in patients with STEMI. In particular, we examined international rates of revascularization using a novel multi-level analytical approach not previously employed in such studies, thereby affording us a unique opportunity of comparing the relationship between early revascularization and outcome following acute myocardial infarction.

Methods

Patients

The ASSENT-2 trial has been previously described.[12] A total of 16 949 patients with ST-elevation MI within 6 h of symptom onset were randomly assigned to treatment with either accelerated-protocol alteplase or single-bolus injection of tenecteplase (bodyweight-adjusted). Patients were recruited at 1021 hospitals in 29 countries between October 1997 and November 1998. The primary hypothesis was proven, that of equivalence in all-cause mortality at 30 days. All patients received concomitant therapy with aspirin (160—325 mg) and intravenous unfractionated heparin adjusted for bodyweight. The use of other medications, coronary angiography and revascularization were left to the discretion of the individual investigator/clinician.

Statistical analysis

For the purposes of our study, all participating countries were grouped into tertiles according to their in-hospital revascularization rates. Those countries with revascularization rates of 40% or greater constituted the highest tertile, those with rates between 15 and 39% the intermediate tertile, and those with revascularization rates below 15% formed the lowest tertile. Rates of major haemorrhage, reinfarction, and recurrent ischaemia were also determined across these tertiles, using previously defined definitions. Baseline characteristics, medication and procedure use, and clinical outcomes were first compared across the three tertiles using the chi-square test. A multiple proportional hazards regression model was then developed to assess the relationship between the tertiles and the primary endpoint of the ASSENT-2 trial (i.e. 30-day mortality), after adjusting for baseline patient characteristics. A similar model was also developed for 1-year mortality. All analyses were performed using the SPSS version 11.0, with the level of significance set at 5% based on two-sided tests.

In addition, we developed multilevel (hierarchical) logistic regression models to validate and extend the findings of conventional single-level logistic regression analyses. Multilevel modelling incorporates the hierarchical nature of our data, which is structured into several levels: patient, hospital, and country. Two hospital- and country-level variables were also included in such modelling: at the hospital level, a volume indicator was constructed by classifying the participating hospitals into

Table 1 In-hospital revascularization rates and 30-day mortality

Country[a]	Number of sites	Number of patients	Revascularization	CABG	PCI	CATH	30-day death
High tertile	436	5693	56.5	11.6	45.7	73.3	5.1
US	375	3660	60.7	14.6	49.2	80.5	5.7
France	34	355	51.8	2.8	49.3	85.0	4.2
Switzerland	5	121	48.8	3.3	45.5	64.5	4.1
Israel	22	1557	41.3	6.7	35.5	55.2	4.1
Intermediate tertile	311	5456	23.9	4.3	19.8	43.7	6.9
Germany	72	771	38.8	4.8	34.2	64.7	7.7
Ireland	9	121	31.4	9.1	23.1	49.6	8.3
Belgium	62	770	29.6	5.6	24.0	59.7	8.1
Portugal	15	261	27.2	1.9	25.3	43.7	5.7
Brazil	16	280	25.0	6.1	23.9	75.4	10.0
Czechoslovakia	1	39	23.1	5.1	17.9	20.5	2.6
Mexico	13	137	21.9	2.9	19.0	35.8	10.2
Spain	32	752	18.0	1.6	16.6	31.0	6.3
Australia	25	871	17.3	4.9	13.5	40.6	4.5
Canada	51	1106	17.3	4.0	13.7	26.6	5.9
Austria	15	118	16.1	2.5	13.6	30.5	9.3
Low tertile	275	5800	10.4	1.5	8.9	20.1	6.5
South Africa	19	230	14.8	4.3	10.4	28.3	11.3
Netherlands	22	852	13.7	2.2	11.5	24.6	5.6
Italy	66	1075	13.4	1.2	12.4	32.8	4.9
Argentina	30	303	12.5	3.0	10.6	30.0	10.9
Turkey	4	103	11.7	1.0	12.6	34.7	7.8
Sweden	43	1070	11.6	2.1	9.6	14.6	6.5
Finland	10	139	10.1	5.0	5.0	10.0	7.2
Poland	11	436	9.6	0.2	9.6	21.8	6.2
NZ	8	249	8.4	1.6	6.4	12.9	5.6
UK	19	451	8.0	1.3	6.7	14.0	9.3
Greece	20	380	7.4	0.5	6.8	24.2	5.5
Denmark	11	288	3.1	0.3	3.1	3.8	8.3
UAE	2	218	2.3	0.0	2.3	3.2	3.7
Norway	10	236	1.7	0.4	1.3	3.0	7.2

[a]Participating countries are listed in descending order according to revascularization rates.

quartiles according to the number of patients enrolled in the ASSENT-2 trial: ≦16, 17–27, 28–43, and >43. At the country level, we used the life expectancy at birth in 1997 for the participating country as contained in the *World Health Report 1998*.[13] Unlike single-level logistic regression, our methodology takes into account data that are correlated within patient subgroups, and enables quantification of the effects of all levels of covariates on hospital- and country-level variations in outcomes. HLM 5 (SSI Scientific Software International) was used to perform three-level analyses.

Results

The ranking of countries by rates of revascularization is depicted in Table 1. Countries were grouped into tertiles based upon their individual rates of in-hospital revascularization (n=5693, 5456, 5800 highest to lowest tertiles). The United States had the highest rate of revascularization (61%), whereas Norway and the United Arab Emirates had the lowest (2%).

Coronary angiography was performed in 73% of patients in countries comprising the highest tertile, and in 20% of patients in the lowest tertile (Table 1). Similarly, there was a five-fold variation in the frequency of coronary angioplasty, and almost an eight-fold difference in the frequency of bypass surgery between highest and lowest tertiles. Rates of stent use during percutaneous coronary intervention were greatest in highest tertile countries (82%) as compared with the intermediate and lowest tertile countries (72% each; P<0.001): the overall rate was 78%. Selected patient characteristics according to revascularization tertile are depicted in Table 2. No difference in gender distribution or smoking rates was noted between tertiles. Patients in the highest tertile were younger, heavier, and more often diabetic and hypertensive. As well, patients in the highest tertile were more likely to have had a prior myocardial infarction or revascularization procedure, and were more often taking aspirin prior to hospital presentation. At presentation, patients in the highest tertile were also less likely to have an anterior myocardial infarction or higher Killip class than patients in the intermediate and lowest tertiles.

Time from onset of symptoms to treatment with fibrinolytic therapy was significantly shorter among patients in the highest tertile compared to intermediate and lowest tertiles (2.52 h vs 2.75 h vs 2.93 h, P<0.001). Patients in the highest tertile also had the shortest median length of hospital stay (6 days vs 8 days vs 9 day, P<0.001).

Table 2 Baseline characteristics and care processes

Variable	Highest tertile	Intermediate tertile	Lowest tertile	*P*-value
n	5693	5456	5800	
Age, years	60 (50, 69)	62 (52, 71)	63 (53, 71)	<0.001
Female, %	24	23	23	0.293
Height, cm	172 (165, 178)	170 (164, 176)	170 (165, 175)	<0.001
Weight, kg	80 (71, 91)	76 (68, 86)	75 (69, 85)	<0.001
Diabetes, %	19	16	13	<0.001
Hypertension, %	43	38	34	<0.001
Current smoker, %	45	43	45	0.139
Prior MI, %	17	14	3	<0.001
Prior PTCA, %	9	4	3	<0.001
Prior CABG, %	6	4	2	<0.001
Prior ASA use, %	58	45	32	<0.001
Killip class >I, %	8	15	13	<0.001
Anterior MI, %	38	40	43	<0.001
Systolic BP, mmHg	132 (116, 149)	132 (120, 150)	135 (120, 150)	<0.001
Heart rate, bpm	74 (63, 85)	73 (62, 86)	72 (60, 84)	<0.001
Hours to treatment	2.52 (1.8, 3.7)	2.83 (1.9, 4.0)	2.75 (2.0, 3.9)	<0.001
In-hospital use				
Beta-blocker, %	85	79	78	<0.001
Nitrate, %	84	67	66	<0.001
ACE-inhibitor, %	52	59	50	<0.001
Days to revascularization	3 (1, 6)	7 (2, 12)	5 (1, 11)	<0.001
Days to PTCA	1 (0, 3)	5 (0, 9)	3 (0, 7)	<0.001
Days to CABG	5 (1, 9)	10 (5, 15)	7 (1, 8)	<0.001
Revascularization ≦1 day, %	14	5	3	<0.001

Table 3 Clinical outcomes

Variable	Highest tertile	Intermediate tertile	Lowest tertile	*P*
Death in 30 days, %	5.1	6.9	6.5	<0.001
Reinfarction, %	3.3	4.1	4.5	<0.001
Recurrent ischaemia, %	7.6	7.9	9.9	ns[a]
Stroke, %	1.6	1.9	1.7	ns[a]
Intracranial haemorrhage, %	0.9	1.1	1.0	ns[a]
Major bleed, %	8.2	4.4	3.3	<0.001

[a] ns, not significant.

The use of both ASA and heparin following randomization were mandated by the ASSENT II protocol and therefore were similar across tertiles. Angiotensin-converting-enzyme inhibitors were used most often in intermediate tertile countries and least often in lowest tertile countries (52% vs 59% vs 50%, *P*<0.001). Nitrates and beta-blockers were more often used in highest tertile countries (84% vs 67% vs 66%, for nitrates; 85% vs 79% vs 78% for beta-blockers, *P*<0.001 for both).

Clinical outcomes by tertile are summarized in Table 3. Rates of in-hospital recurrent myocardial infarction and recurrent ischaemia were lowest in the highest tertile (3.3% vs 4.1% and 4.3%, *P*=0.003, for recurrent myocardial infarction ; 7.6% vs 7.9% and 9.9%, *P*<0.001, for recurrent ischaemia). Mortality rates at 30 days were lower for patients in countries with the highest revascularization rates (5.1% vs 6.9% vs 6.5% for the lower two tertiles, *P*<0.001) and at 1 year mortality remained significantly lower in the highest tertile countries vs those in intermediate or lowest tertiles (8.4% vs 10.6% vs 9.9%, respectively, *P*=0.001). Following adjustment for baseline patient characteristics such as age, sex, hypertension, Killip class, anterior myocardial infarction location, prior myocardial infarction , prior percutaneous coronary intervention, heart rate, systolic blood pressure, and time from symptom onset to treatment, Cox regression analysis confirmed an excess of 30-day and 1-year mortality in the lowest tertile (hazard ratio=1.17 and 1.17, 95% confidence interval=1.00–1.37 and 1.03–1.34, respectively) and intermediate tertile (hazard ratio=1.20 and 1.21, 95% confidence interval=1.03–1.40 and 1.06–1.37, respectively) compared to the highest tertile (Fig. 1). These results were further refined by the multilevel modelling below.

No statistically significant difference was noted across tertiles in the rates of either stroke (1.6%, 1.9% and 1.7%, *P*=0.410) or intracranial haemorrhage (0.9%, 1.1%, and 1.0%, *P*=0.596). Bleeding rates (excluding intracranial

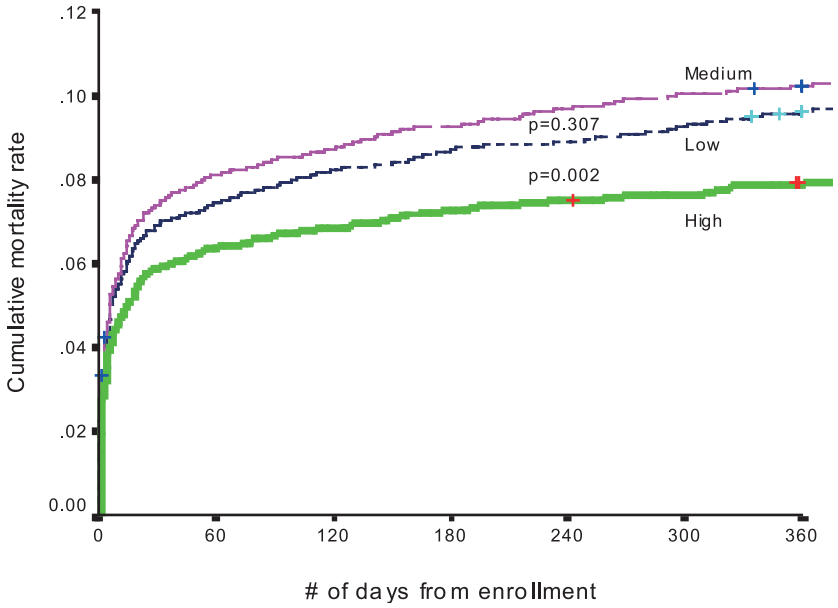

Fig. 1 Kaplan–Meier 1-year mortality curves by tertile of countries' revascularization rates. Significant differences were shown between the mortality curves between the highest and the other lower tertiles, but no differences between the intermediate and the lowest tertile by the log rank test.

haemorrhage) were greatest in the highest tertile and followed an inverse gradient according to revascularization rate (P<0.001). Major bleeding, excluding intracranial haemorrhage, was more common in countries with high revascularization rates (8.2%, 4.4% and 3.3%, respectively, P<0.001). The multilevel analyses are summarized in Table 4a and Table 4b. To reaffirm the previous results, the variance of 30-day mortality was first examined in the empty multilevel model (Model 1, Table 4a), which only included the identifiers for patients, hospitals and countries and not any predictor variable, to show that there was a small but significant inter-country variance of 0.057 (P<0.001) and a non-significant inter-hospital variance of 0.073 (P=0.184). In Model 2 a single variable, the previously defined tertiles of patients according to countries' revascularization rates, was included at the patient level. This resulted in a reduction of 36% in the inter-country variance to 0.036 (P<0.001), but the inter-hospital variance was reduced only by 4% to 0.070 (P=0.101). The mortality rate was significantly lower for patients in the highest tertile than in the other tertiles, as indicated by the highly significant odds ratios and 95% confidence intervals of 1.57 (1.21–2.03) for the intermediate tertile and 1.44 (1.12–1.85) for the lowest tertile. After adjusting for the same patient-level baseline characteristics as in single-level modelling such as age, sex, hypertension, Killip class, anterior myocardial infarction , prior myocardial infarction , prior percutaneous coronary intervention, heart rate, systolic blood pressure, and time to treatment in Model 3, these odds ratios were somewhat lowered but remained highly significant: 1.46 (1.11–1.92) for the intermediate tertile and 1.38 (1.09–1.71) for the lowest tertile, P=0.007 for both. However, this adjustment had little effect on reducing the variation either between hospitals or between countries.

In Model 4, two new predictor variables were introduced: a volume indicator (the quartile of the number of patients enrolled) at the hospital level and life expectancy at the country level. The life expectancy of the country of enrolment was a strong predictor of 30-day mortality, and accounted for almost all of the variation in mortality between countries and rendered the remaining variance of 0.0006 non-significant (P>0.500). A volume-outcome relationship was also evident with a lower mortality associated with hospitals that enrolled more than 27 patients, but the inter-hospital variation was only reduced by 15% to 0.062 from 0.073 and remained statistically non-significant after adjusting for hospital volume and life expectancy. Since 70% of deaths within 1 year occurred during the first 30 days of index hospitalization, it is not surprising that the results of multilevel analyses for 1-year mortality were similar to the above with minor variations (Table 4b). These results were further validated using a number of alternative methods including propensity analyses, analyses of country-level revascularization rates without grouping into tertiles, sensitivity analyses of countries belonging to the European Union, and the landmark analyses to assess the impact of early revascularization. These are presented in Appendix A.

Discussion

Our study provides novel insights into the impact of international rates of early angiography and revascularization following fibrinolysis for acute myocardial infarction, which varied significantly in ASSENT-2. A greater use of revascularization in those countries comprising the upper tertile was associated with improved 30-day and 1-year survival. This finding has not been previously observed in a large STEMI trial.

Table 4a Multilevel models for 30-day mortality

	Patient-level effects			Hospital-level effects		Country-level effect	
	OR	95% CI	*P*	Variance	*P*	Variance	*P*
Model 1. Empty model				0.073	0.184	0.057	<0.001
Model 2. Tertiles: revasc. rates							
Tertiles (Ref. highest)				0.070	0.101	0.036 (−36%)	<0.001
Intermediate	1.57	(1.21–2.03)	0.001				
Lowest	1.44	(1.12–1.85)	0.005				
Model 3. Adjusted for patient-level baseline characteristics							
Tertiles (Ref. highest)				0.068	0.159	0.052	<0.001
Intermediate	1.46	(1.11–1.92)	0.007				
Lowest	1.38	(1.09–1.71)	0.007				
Age	1.07	(1.06–1.08)	<0.001				
Female sex	1.24	(1.09–1.41)	0.001				
Hypertension	1.36	(1.20–1.56)	<0.001				
Killip class	2.06	(1.77–2.39)	<0.001				
Anterior MI	1.45	(1.27–1.65)	<0.001				
Prior MI	1.35	(1.19–1.43)	<0.001				
Prior PCI	0.77	(0.61–0.97)	0.025				
Heart rate	1.02	(1.02–1.02)	<0.001				
Systolic BP	0.98	(0.98–0.98)	<0.001				
Time to treatment	1.02	(1.00–1.04)	0.086				
Model 4. Adjusted for patient-level characteristics and country-level life expectancy and hospital patient volumes							
Tertiles (Ref. highest)				0.062	0.287	0.0006	>0.500
Intermediate	1.14	(0.99–1.30)	0.060				
Lowest	1.19	(1.02–1.39)	0.027				
Age	1.07	(1.06–1.08)	<0.001				
Female sex	1.23	(1.09–1.40)	0.002				
Hypertension	1.34	(1.16–1.54)	<0.001				
Killip class	2.04	(1.74–2.39)	<0.001				
Anterior MI	1.45	(1.27–1.67)	<0.001				
Prior MI	1.36	(1.20–1.54)	<0.001				
Prior PCI	0.78	(0.62–0.98)	0.030				
Heart rate	1.02	(1.02–1.02)	<0.001				
Systolic BP	0.98	(0.98–0.98)	<0.001				
Time to treatment	1.02	(1.00–1.04)	0.104				
Life expectancy	0.93	(0.91–0.95)	<0.001				
Site enrolment (Ref. ≦16)							
16–27	0.95	(0.80–1.11)	0.511				
28–43	0.79	(0.65–0.96)	0.016				
>43	0.84	(0.70–1.00)	0.051				

An important element of our analysis was multilevel modelling uncommonly employed in cardiovascular research. Although Yusuf and colleagues also used multilevel modelling in the OASIS study to provide patient level estimates adjusted for inter-country differences,[4] they did not quantify the relative contributions of factors from different levels to explain outcome variation between countries. Our use of multilevel modelling validated and extended the results from single level logistic regression, showing better 30-day and 1-year mortality outcomes in the highest tertile before and after the baseline adjustments. These results were further validated by alternative multilevel analyses based on propensity modelling, country-level revascularization rates analyses without resorting to a tertile grouping, sensitivity analyses of patients enrolled in EU countries, and landmark assessments of the impact of early revascularization. Furthermore, multilevel modelling provided additional quantitative information on the effect of patient- and country-level covariates on inter-country variation in mortality, in addition to gaining new insights into the volume-outcome relationship at the hospital level and the significance of life expectancy, a proxy for a country's general well-being, including the quality of the health-care system. This life-expectancy indicator turned out to be a crucially important predictor of mortality outcomes and accounted for much of the variation in mortality between countries. Such enriched results were not possible based only on single-level analyses.

Several prospective randomized trials in the early 1990's suggested that there was no benefit of routine revascularization on the composite endpoint of myocardial infarction and death in patients with NSTEMI.[2,5] In these studies however, there was only a modest difference in revascularization rates between the routine and conservative arms, which may have minimized any real benefit of the routine strategy. More recently, two large randomized trials have demonstrated a significant

Table 4b Multilevel models for 1-year mortality: ASSENT-2 international comparisons

	Patient-level effects			Hospital effects		Country effect	
	OR	95% CI	*P*	Variance	*P*	Variance	*P*
Model 1. Empty model				0.0871	<0.001	0.0589	<0.001
Model 2. Tertiles: revasc. rates							
Tertiles (Ref. highest)				0.0843 (−3%)	<0.001	0.0443 (−25%)	<0.001
Intermediate	1.50	(1.19–1.89)	<0.001				
Lowest	1.27	(1.10–1.69)	0.005				
Model 3. Adjusted for patient-level baseline characteristics							
Tertiles (Ref. highest)				0.0775	<0.001	0.0798	<0.001
Intermediate	1.45	(1.08–1.95)	0.013				
Lowest	1.32	(1.06–1.63)	0.012				
Age	1.07	(1.07–1.08)	<0.001				
Female sex	1.16	(1.04–1.30)	0.011				
Hypertension	1.44	(1.33–1.57)	<0.001				
Killip class	2.00	(1.79–2.24)	<0.001				
Anterior MI	1.30	(1.16–1.45)	<0.001				
Prior MI	1.49	(1.31–1.69)	<0.001				
Prior PCI	0.84	(0.68–1.04)	0.114				
Heart rate	1.02	(1.02–1.02)	<0.001				
Systolic BP	0.98	(0.98–0.99)	<0.001				
Time to treatment	1.02	(1.00–1.04)	0.018				
Model 4. Adjusted for patient-level characteristics and country-level life expectancy and hospital patient volumes							
Tertiles (Ref. highest)				0.0671	<0.001	0.0067	0.256
Intermediate	1.07	(0.92–1.26)	0.372				
Lowest	1.12	(0.98–1.28)	0.090				
Age	1.08	(1.07–1.08)	<0.001				
Female sex	1.16	(1.03–1.29)	0.013				
Hypertension	1.42	(1.31–1.56)	<0.001				
Killip class	1.99	(1.77–2.25)	<0.001				
Anterior MI	1.30	(1.16–1.47)	<0.001				
Prior MI	1.50	(1.32–1.71)	<0.001				
Prior PCI	0.84	(0.68–1.05)	0.126				
Heart rate	1.02	(1.02–1.02)	<0.001				
Systolic BP	0.98	(0.98–0.99)	<0.001				
Time to treatment	1.02	(1.00–1.04)	0.019				
High life expectancy	0.92	(0.90–0.94)	<0.001				
Site enrolment (Ref. ≦16)							
16–27	0.93	(0.81–1.07)	0.339				
28–43	0.85	(0.72–1.00)	0.045				
>43	0.85	(0.75–0.97)	0.017				

advantage of routine angiography and revascularization in patients with unstable angina and NSTEMI.[6,7] This discrepancy in outcomes between the earlier and more recent trials may relate to study design and to the use of adjunctive therapies. In the FRISC-2 study, low molecular weight heparin was used in all patients rather than unfractionated heparin, which was used in the earlier trials. In the TACTICS-TIMI 18 study, all patients received the intravenous glycoprotein IIb/IIIa inhibitor tirofiban, and stent use was very frequent. Low molecular weight heparins,[14] glycoprotein IIb/IIIa inhibitors[15] and stents[16] have all been shown to be superior to conventional treatments for acute coronary syndromes.

Much less data exist regarding the role of early revascularization following fibrinolytic therapy for STEMI. Three randomized trials of routine intervention vs conservative therapy following STEMI failed to demonstrate any significant differences in outcome.[10,11,16] These studies however may have been underpowered to detect a true difference, since the crossover rates from conservative to aggressive therapy were fairly high. In contrast, the DANAMI study did show a reduction in recurrent myocardial infarction and unstable angina, with no difference in mortality.[9] This study randomized 1008 patients with inducible ischaemia following fibrinolytic therapy for STEMI to an invasive strategy or to conservative treatment, with very little crossover. The suggested benefit of revascularization in this study was not surprising given that all patients randomized had evidence of provokable ischaemia following fibrinolysis.

The basis for our findings may relate in part to significant advances, which have occurred in both percutaneous coronary intervention and coronary bypass surgery over the past decade. The introduction of intravascular stents to reduce the risk of abrupt closure and circumvent the need for emergency bypass surgery and repeat procedures coupled with the advent of glycoprotein IIb/IIIa inhibitors and oral thienopyridines have

clearly impacted outcomes following revascularization.[14,15,17] Improved surgical techniques in the use of arterial grafts as well as more aggressive use of lipid-lowering therapy with HMG-CoA reductase inhibitors may also partly explain our findings compared to previous studies.[18,19] Although we adjusted for baseline differences between the tertiles in our study we cannot be certain that unmeasured variables may have played a role in our findings. These could include process of care issues highlighted by the shorter time to treatment in the tertile of countries with the greatest revascularization rates. It should be noted that we cannot be certain our sample adequately represents each country as a whole, but this should not undermine the importance of our findings. More detailed information regarding the use of concomitant therapy, especially as it relates to the performance of percutaneous coronary intervention, was unavailable. The alignment of reduced re-infarction and recurrent ischaemia suggests that these events likely mediated, at least in part, the reduction in mortality. Greater use of beneficial medications such as beta-blockers and statins in the highest tertile cohort may also be responsible for its better outcomes. These benefits, however, did come at the expense of an approximate doubling in major bleeding, with no apparent increase in risk of stroke or intracranial haemorrhage.

Recently the In-TIME II investigators also reported substantial variation in revascularization but could not explain regional mortality differences based on this diversity.[20] Reasons for the differences between our observations and theirs may reflect a smaller gradient in revascularization across the four geographic regions shown and the differences in analytical approaches employed. Recent data from Stenestrand and Wallentin in patients with both NSTEMI and STEMI from a Swedish registry seem to reaffirm our finding of a mortality benefit in the first year from revascularization following STEMI.[21]

Conclusions

Our study provides novel insights into the role of early revascularization following fibrinolysis for ST-elevation myocardial infarction and is the first to associate this with a reduction in total mortality in a large scale fibrinolytic trial. Our finding of benefit from revascularization (especially percutaneous coronary intervention) using single-level logistic modelling is further strengthened by the use of multilevel modelling, showing also that variation in the rates of percutaneous coronary intervention among countries is a more important factor than inter-country differences in patient baseline factors in explaining differences in mortality rates among countries. Coupled with the results of previous observational and randomized studies, it seems likely that early intervention following fibrinolytic therapy in patients with ST elevation is beneficial. This benefit may be partly dependent upon the appropriate use of adjunctive pharmacologic treatments and technical refinements that have been shown to improve outcome and reduce procedural risks. The exact magnitude of benefit and optimal rate of revascularization remains unclear, however, and warrants further evaluation.

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Appendix A

Propensity analyses (Table 5, Part A)

To further validate our results, we first performed a propensity analysis. Model 1 is the same empty model as in Table 4a and Table 4b. Next, a propensity score, the probability of enrolling in a high-tertile country for each patient, was calculated for each patient based on logistic regression. The most significant baseline characteristics associated with this propensity were body weight, diastolic blood pressure, prior percutaneous coronary intervention, Killip class, white race, sex, prior CABG, hypertension, and heart rate. As shown in Model 2, the resulting high propensity score by itself was predictive of elevated mortality (P=0.001), but had no effects in reducing variations between hospitals and countries. The propensity score remained a strong predictor of 30-day mortality after adjusting for hospital volume and life expectancy at the country level, which reduced the inter-country variation by 81% from 0.057 to a non-significant variance of 0.011 (P=0.134).

Country-level revascularization rates (Table 5, Part B)

Since the tertile-method of grouping countries by their revascularization rates is not unique, we tested our 30-day mortality results using an alternative approach to multilevel modeling of 30-day mortality *without grouping of countries* (Table 5). In Models 4–6, the effects of revascularization rates were shown to be of borderline significance before adjustment and became more significant after adjustment for baseline patient characteristics and angiography rates at the country level, although it had little effect on inter-hospital or inter-country variation.

Sensitivity analyses for participating EU countries (Table 5, Part C)

Because of a concern for the heterogeneity of participating countries within each of the tertiles, we further tested our results on patients enrolled in countries in the European Union (n=8232). The findings were similar, except that the inter-country variance was smaller and non-significant (P=0.135) even in the empty model (Model 7). The tertile variable had a much more profound impact on mortality and on further reducing the inter-country variation to a totally non-significant level (P>0.500, Model 8); of note, variation between the participating EU countries nearly disappeared after adjusting for patient baseline characteristics (Model 9). The highest-tertile countries continued to be associated with lower 30-day mortality with further adjustment for life expectancy and the hospital volume, which remained

Table 5 Alternative multilevel analyses for 30-day mortality

	Patient-level effects			Hospital-level effects		Country-level effect	
	OR	95% CI	*P*	Variance	*P*	Variance	*P*
Model 1. Empty model				0.073	0.184	0.057	<0.001
A. Propensity analyses							
Model 2. Propensity for enrollment in a high tertile country only							
Propensity scores	0.25	(0.16–0.56)	0.001	0.076	0.149	0.055	<0.001
Model 3. Propensity scores adjusted for life expectancy and hospital volume							
Propensity scores	0.24	(0.10–0.56)	0.001	0.077	0.222	0.011	0.134
B. Country-level revascularization rates							
Model 4. Country-level revascularization rates only							
Revascularization rate	0.99	(0.99–1.00)	0.054	0.074	0.149	0.050	<0.001
Model 5. Adjusted for baseline patient characteristics							
Revascularization rate	0.99	(0.99–1.00)	0.041	0.069	0.183	0.059	<0.001
Model 6. Adjusted for patient characteristics and country angiography rates							
Revascularization rate	0.97	(0.95–0.99)	0.015	0.072	0.110	0.074	<0.001
Angiography rate	1.01	(1.00–1.02)	0.021				
C. Restricted to EU countries (*n*=8232)							
Model 7. Empty model				0.064	0.055	0.015	0.135
Model 8. Tertiles: revasc. rates							
Tertiles (Ref. highest)				0.064	0.033	0.003	>0.500
Intermediate	1.77	(1.58–1.99)	<0.001				
Lowest	1.55	(1.33–1.81)	<0.001				
Model 9. Adjusted for patient-level baseline characteristics							
Tertiles (Ref. highest)				0.092	0.037	0.00002	>0.500
Intermediate	1.61	(1.11–2.34)	0.011				
Lowest	1.47	(1.00–2.17)	0.050				
Model 10. Adjusted for patient-level characteristics and country-level life expectancy and hospital patient volumes							
Tertiles (Ref. highest)				0.073	0.089	0.00009	>0.500
Intermediate	1.50	(1.10–2.04)	0.011				
Lowest	1.47	(1.03–2.09)	0.032				
Age	1.08	(1.07–1.10)	<0.001				
Female sex	1.20	(1.02–1.42)	0.031				
Hypertension	1.29	(1.08–1.55)	0.006				
Killip class	1.92	(1.48–2.48)	<0.001				
Anterior MI	1.46	(1.17–1.82)	0.001				
Prior MI	1.24	(1.07–1.54)	<0.001				
Prior PCI	0.70	(0.41–1.19)	0.190				
Heart rate	1.01	(1.01–1.02)	<0.001				
Systolic BP	0.98	(0.98–0.99)	<0.001				
Time to treatment	1.02	(0.98–1.07)	0.279				
Life expectancy	0.96	(0.93–0.99)	0.023				
Site volume (Ref. ≦16)							
16–27	0.98	(0.82–1.17)	0.844				
28–43	0.75	(0.59–0.96)	0.023				
>43	0.87	(0.69–1.11)	0.267				

significant and showing a tendency for a high volume to be associated with low mortality (Model 10).

Landmark analyses (Table 6)

Landmark analysis is a method of discounting early events in order to reduce selection bias between comparison groups.[22] A series of landmarks, at the end of day 1, day 3, and day 7, were used to assess the possible impact of early vs later revascularization. Of particular interest were the results of the 30-day mortality model for 1-day survivors, and the 1-year mortality model for 7-day survivors, which were summarized in Table 6. The results were consistent with the baseline models (Table 4a and Table 4b). The highest tertile countries were associated with lower 2–30-day mortality, both before and after baseline adjustment (Models 2–3), and revascularization performed within 1 day of hospital admission was associated with higher adjusted 2–30-day mortality (Model 4).

Among the 7-day survivors, countries with the highest revascularization rates continued to have lower 1-year mortality, and revascularization procedures were associated with lower 1-year mortality regardless of whether they were performed during day 1, day 2–3, or day 4–7, although only those performed in day 2–3 and day 4–7 were statistically significant (Models 5–8). However, the tertile variable became non-significant, indicating that the effects of the tertile variable was

Table 6 Landmark analyses of early & late revascularization: three-level, logistic regression

	Patient-level effects			Hospital effects		Country effect	
	OR	95% CI	*P*	Variance	*P*	Varience	*P*
One-day survivors (n=16632) for 30-day mortality							
Model 1. Empty model				*0.085*	*0.179*	*0.059*	*<0.001*
Model 2. Tertiles only							
Tertiles (Ref. highest)				0.085	0.107	0.034	0.003
Intermediate	1.60	(1.29–2.00)	<0.001				
Lowest	1.50	(1.21–1.84)	<0.001				
Model 3. Adjusted for patient baseline characteristics							
Tertiles (Ref. highest)				0.078	0.124	0.047	<0.001
Intermediate	1.48	(1.15–1.91)	0.003				
Lowest	1.40	(1.15–1.71)	0.001				
Model 4. Adjusted for patient baseline characteristics and early revascularization (≦1 day)							
Tertiles (Ref. highest)				0.078	0.111	0.047	0.001
Intermediate	1.51	(1.17–1.93)	0.002				
Lowest	1.43	(1.18–1.74)	0.001				
Revascularization ≦1 day	1.26	(1.06–1.49)	0.010				
Seven-day survivors (n=16632) for 1-year mortality							
Model 5. Empty model				*0.118*	*0.001*	*0.051*	*0.003*
Model 6. Tertiles only							
Tertiles (Ref. highest)				0.114	<0.001	0.037	0.015
Intermediate	1.46	(1.16–1.85)	0.002				
Lowest	1.33	(1.07–1.66)	0.010				
Model 7. Adjusted for patient baseline characteristics							
Tertiles (Ref. highest)				0.091	0.004	0.079	<0.001
Intermediate	1.48	(1.09–2.01)	0.011				
Lowest	1.36	(1.55–1.76)	0.021				
Model 8. Adjusted for patient baseline characteristics and early revascularization (≦1 day)							
Tertiles (Ref. highest)				0.088	0.011	0.079	<0.001
Intermediate	1.38	(1.00–1.91)	0.052				
Lowest	1.24	(0.93–1.67)	0.147				
Revascularization							
≦1 day	0.87	(0.60–1.25)	0.452				
2–3 day	0.69	(0.55–0.88)	0.003				
3–7 day	0.70	(0.48–1.01)	0.058				

partially accounted for by another patient-level variable that indicated whether or not the patient underwent revascularization within 1 day, 2–3 days or 4–7 days. As in baseline models (Table 4a and Table 4b), country-level variation in these multilevel landmark analyses remained significant even after adjustment for baseline patient characteristics.

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