THEORY AND METHODS

Are international differences in the outcomes of acute coronary syndromes apparent or real? A multilevel analysis

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Study objective: International variation in the outcomes of patients with acute coronary syndromes (ACS) has been well reported. The relative contributions of patient, hospital, and country level factors on clinical outcomes, however, remain unclear, and thus, was the objective of this study.
Design: Multilevel logistic regression models were developed for death/(re)infarction (MI) at 30 days and death in one year, with patients (1st level) nested in hospitals (2nd level) and hospitals in countries (3rd level).
Settings: The GUSTO IV ACS clinical trial was carried out at 458 hospital sites in 24 countries.
Patients: 7800 non-ST segment elevation (NSTE) ACS patients.
Main results: There were substantial variations among countries in the processes and outcomes of care at 30 days, ranging from 5.4% to 50.0% for percutaneous coronary intervention, 4.3% to 21.2% for coronary artery bypass graft surgery, 5.0% to 13.9% for 30 day death/(re)MI, and 4.9% to 14.8% for one year mortality. However, the residual inter-country variations in 30 day death/(re)MI and one year mortality became non-significant and nearly disappeared ($p>0.500$ for both) after adjusting for key baseline patient characteristics and hospital factors, which became significant ($p<0.01$ for both). Patient level factors accounted for 96%–99% of total variation in these end points, leaving the remaining 1% and 4% of variance attributable to hospital level factors.
Conclusion: The international differences in clinical outcomes in this study of NSTE ACS are primarily accounted for by the patient level factors, with hospital level factors playing a minor part, and the country level factors a negligible one. These findings have significant policy and research implications involving international collaboration and comparisons.

Disparities in cardiovascular and other health outcomes across geographical regions are common, and yet not well understood.[1 2] Even after adjustment for baseline patient characteristics, significant variations in clinical outcomes often persist in acute coronary syndrome (ACS) patients.[3–9] Although some studies have not shown mortality differences in either ST segment elevation (STE)[10–16] or non-ST segment elevation (NSTE) ACS patients,[17 18] others have reported better quality of life and mortality outcomes in countries with high revascularisation rates.[3 12 19] Such disparities in outcomes provide incentives to further investigate the underlying factors, including patient and provider characteristics, socioeconomic and cultural factors, healthcare practices, and other characteristics of healthcare systems.

To our knowledge, however, no study has formally identified and quantified the sources of inter-country variations in the ACS literature, although some have offered opinions on this.[6 8 20] To gauge the amount of variation in outcomes among countries attributable to patient compared with non-patient level factors, we applied multilevel modelling techniques that took into account the hierarchical and correlated nature of healthcare data.[21–24] In such data, findings are generally correlated among patients in the same subgroup, for instance, those cared for at the same hospital or in the same country. Thus, conventional, single level analyses that treat the data as if there were no hierarchical structures violate the assumption of independence of findings required for such methods, and result in suboptimal estimation of the effects of hospital and country level factors.[21–24] Moreover, single level analyses are not designed to assess the components of variation attributable to individual (patient level) compared with contextual (hospital and country level) effects. Thus, our objectives were: (1) to assess the extent of international differences in patient characteristics, care processes, and clinical outcomes, and (2) to determine the extent to which the observed inter-country variations in the composite of 30 day death or post-admission myocardial infarction (MI) and one year all cause mortality can be explained by patient, hospital, and country level factors.

METHODS

Patients and study design

Data from the global utilisation of strategies to open occluded coronary arteries IV acute coronary syndromes (GUSTO IV ACS) were used. The details of this trial have been previously reported.[25 26] Briefly, 7800 patients from the 458 participating hospitals in 24 countries were enrolled between July 1998 and April 2000 (table 1).

Eligible patients were 21 years or older, had at least one episode of angina lasting five minutes or more within the preceding 24 hours without persistent ST segment elevation, and a positive cardiac troponin T or I test (determined using a

Abbreviations: NSTE, non-ST segment elevation; ACS, acute coronary syndrome; GUSTO IV ACS, global utilisation of strategies to open occluded coronary arteries IV acute coronary syndromes trial; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; PCV, proportional change in variance; ICC, intraclass correlation coefficient; MI, myocardial infarction; STEMI, ST segment elevation myocardial infarction

Table 1 Number of study sites and patients and selected baseline patient level factors of each country* participating in the GUSTO IV ACS trial

Country	Sites (n)	Patients (n)	Median age	Female (%)	Prior MI (%)	Diabetes (%)	TnT (%)	ST depression (%)	Creatinine clearance (%)	CRP (%)	Enrolment MI (%)
North America											
Canada	31	642	65	31	34	25	46	28	79	59	36
United States	48	462	66	42	33	33	39	36	71	68	34
Western Europe											
Austria	8	78	66	33	30	35	81	32	66	36	13
Belgium	9	163	66	33	31	21	74	43	73	24	36
France	15	197	68	27	26	17	71	29	67	24	25
Germany	32	395	68	34	26	25	75	42	75	29	28
Greece	15	259	66	35	26	31	66	49	73	24	20
Ireland	5	40	64	15	40	10	83	23	78	43	23
Italy	29	486	66	34	30	21	76	42	71	27	27
Netherlands	27	570	66	33	26	11	71	43	83	25	31
Portugal	8	88	68	25	23	19	83	38	75	25	36
Spain	11	362	68	29	20	23	74	40	75	29	40
Switzerland	7	38	65	32	29	11	82	43	76	34	34
UK	15	124	64	30	36	16	77	32	76	29	35
Scandinavia											
Denmark	12	149	66	28	29	10	80	38	80	35	31
Finland	2	79	66	32	34	18	80	42	79	22	28
Norway	10	91	64	42	23	21	84	26	78	23	31
Sweden	28	544	70	34	31	16	88	31	73	22	33
Eastern Europe											
Czech	16	765	69	49	38	31	71	51	66	26	29
Poland	24	1657	65	49	34	17	50	44	81	19	26
Other											
Australia	9	118	66	35	27	14	64	40	64	40	40
Israel	13	265	63	26	35	30	78	39	76	34	27
New Zealand	3	54	61	20	33	13	94	26	80	24	43
South Africa	10	144	60	22	17	19	76	34	80	33	41
All countries	**387**	**7800**	**66**	**38**	**31**	**22**	**66**	**40**	**75**	**31**	**28**

*The actual number of sites from 458 possible sites that had enrolled at least one patient. CRP, C reactive protein >1110 mg/l; creatinine clearance<58.4 ml/min; MI, myocardial infarction; ST segment depression ⩾1mm; TnT, troponin T >0.01 μg/l. All missing data were imputed as positive for these indicators.

local qualitative or quantitative assay) or at least 0.5 mm transient or persistent ST segment depression on admission. They were randomly assigned to one of the three treatment groups: abciximab therapy for 24 hours (0.25 mg/kg bolus followed by a 0.125 μg/kg per minute infusion up to 10 μg/kg for 24 hours), abciximab therapy for 48 hours (same bolus and infusion for 48 hours), or matching placebo (bolus and 48 hour infusion). Coronary angiography was not to be performed during or within 12 hours after the completion of the study agent administration, unless the patient had recurrent or continuing ischaemia at rest associated with ischaemic ST/T segment changes that were not responsive to medical treatment. A clinical end point committee, which was unaware of treatment assignment, adjudicated all possible incidences of MI and, when requested by the Safety and Efficacy Monitoring Committee, also, the cause of death within 30 days. An independent neurologist adjudicated all suspected occurrences of stroke and intracranial haemorrhage. The ethics committees of the participating hospitals approved the protocol, and patients gave informed consent.

Statistical analysis

The primary end point for the GUSTO IV ACS trial (and for this study) was 30 day death/(re)MI, and one year mortality was a secondary end point. Because no treatment effect was found, the three treatment arms were combined. Biomarkers and renal function were grouped into tertiles to examine their relations with the primary end points: troponin T (TnT) ⩽0.01, 0.01–0.5, and >0.5 μg/l; and C reactive protein (CRP) ⩽4, 4–10, and >10 mg/l; creatinine clearance ⩽58.4, 58.4–76.9, and >76.9 ml/min; and the extent of ST segment depression into <1 (or no ST segment depression), 1–1.5, and ⩾2 mm. For ease of presenting variation among countries, we further dichotomised these data after examining their relations with outcomes, and defined an increased value as follows: >0.01 μg/l for TnT, ⩾1 mm for ST segment depression, >58.4 ml/min for creatinine clearance, and >10 mg/l for CRP. The results were presented in terms of percentages for categorical variables and medians (interquartile ranges) for continuous variables.

To assess the relative contributions of patient and non-patient level factors on outcomes, we began with two level "null" models (that is, without containing any independent variables), with patients at the first level and countries at the second. We then developed three level "null" models by including hospitals as an additional level to further identify the variance component attributable to the hospital effects, which has been distributed to both patient and country effects.[28] Thereafter, we developed nested three level models by successively incorporating patient age, other patient baseline characteristics, and the country level percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) rates (as estimated from our dataset). The amount of variance explained was calculated by the proportional change in variance (PCV), or the percentage reduction from the estimated variance in the null model as a result of incorporating a new factor(s) in the model—that is, $PCV = (V_0–V_1)/V_0$, where V_0 is the estimate of the initial (null) variance at the country or hospital level before adjusting for any compositional or contextual factor in the model, and V_1 was the country or the hospital level residual variance after adjusting for covariates.[23] The proportions of total variance related to hospital and country factors were estimated by the intraclass correlation coefficient (ICC) using the formula $V/(V+\pi^2/3)$, where $V = V_0$ or V_1, and $\pi^2/3$ is the fixed variance at the patient level as suggested by Snijders and Bosker.[28] Each model parameter was estimated using the restricted penalised quasilikelihood function in HLM version 6.0 (Lincolnwood, IL, USA) or MLwiN 2.1a (University of

Table 2 Use of evidence based drugs before and during hospitalisation according to country

	Aspirin (%)		Clopidogrel (%)		ACE inhibitors (%)		β blockers (%)		Nitrates (%)		Calcium channel blockers (%)	
Country	**Before**	**During**	**Before**	**During**	**Before**	**During**	**Before**	**During**	**Before**	**During**	**Before**	**During**
North America												
Canada	90	98	1	11	27	43	57	86	37	63	29	32
United States	84	96	4	19	28	40	54	83	34	59	26	26
Western Europe												
Austria	78	95	1	22	46	49	63	89	32	39	27	26
Belgium	79	94	0	0	17	25	66	87	25	52	23	22
France	52	96	3	10	18	22	66	81	82	82	41	43
Germany	80	99	4	12	44	72	55	81	35	66	24	15
Greece	69	96	0	0	41	51	49	73	41	85	40	36
Ireland	95	75	0	0	28	38	60	63	25	38	25	30
Italy	66	96	0	0	31	47	45	78	26	70	32	38
Netherlands	71	97	0	4	14	23	57	86	21	56	24	41
Portugal	90	100	0	1	38	63	53	89	50	81	30	18
Spain	89	96	1	4	17	32	34	66	44	74	32	50
Switzerland	87	97	0	37	24	40	68	84	24	37	21	21
UK	90	100	0	9	21	27	60	85	43	56	40	42
Scandinavia												
Denmark	90	98	0	7	17	21	58	86	34	46	33	38
Finland	100	100	0	4	23	35	95	99	54	77	17	17
Norway	92	96	0	1	10	20	70	96	17	44	24	21
Sweden	87	97	1	15	17	28	81	93	34	51	20	24
Eastern Europe												
Czech	81	98	0	0	35	48	53	78	58	79	20	16
Poland	91	98	0	0	48	63	63	84	65	90	25	28
Other												
Australia	95	98	2	11	27	38	59	81	42	53	31	40
Israel	84	99	0	0	29	54	54	83	26	57	24	23
New Zealand	100	100	0	0	26	30	67	85	46	44	35	35
South Africa	71	98	0	0	24	30	31	63	28	44	13	23
All countries	**84**	**97**	**1**	**5**	**31**	**43**	**58**	**83**	**46**	**61**	**26**	**29**

ACE inhibitors, angiotension converting enzyme inhibitor.

London, London, UK), which also provides standard errors and *t* tests for fixed effects and χ^2 tests for random effects. Each variance estimate was presented with a standard error and a p value based on the χ^2 test. All other descriptive analyses were performed using SPSS version 11.0 (Chicago, IL, USA).

RESULTS

Variations among countries

The baseline patient characteristics differed significantly among the 24 countries participating in the study (table 1). Variation in other aspects of health care such as the use of evidence based drugs was also noticeable, and except for calcium channel blockers, their use increased substantially during hospitalisation (table 2).

The diversity was even greater for invasive procedures at 30 days, and there was a threefold variation in the median length of hospital stay (table 3).

Differences in outcomes across countries were also pronounced: 5.0% to 13.9% in 30 day death/(re)MI, 2.5% to 8.0% in 30 day mortality, and 4.9% to 14.8% in one year mortality (table 3).

Sources of variation in 30 day death/(re)MI and in one year mortality

Table 4 shows the results of our multilevel analyses for 30 day death/(re)MI.

A small but significant intercountry variance of 0.036 ($p = 0.004$) was first shown in the two level null model after factoring out the patient level effects. To further exclude the hospital level effects that were distributed to both the patient level and country level effects in the two level model, we developed a series of three level models that also included the hospital level factors and showed, first of all, that the intercountry variance was reduced by 22.7% to 0.028 and became non-significant ($p = 0.072$) in the null model (model 1). This variance was further reduced and became negligible ($p>0.500$) after successively controlling for age, for all baseline patient characteristics, and then also for country level PCI and CABG rates (models 2–4), so that these factors explained nearly all (99.6%) the residual intercountry variation. In contrast, the estimated interhospital variance of 0.086 was significant ($p = 0.003$) in the three level null model, but was only reduced to 0.046 ($p = 0.032$) in the full model (model 4). The reduction in country level variance is depicted in ''caterpillar'' plots for shrunken residuals (logarithmic odds ratios) before and after adjusting for baseline patient factors (fig 1A). Similar plots for hospital level variance are given in figure 1B.

The ICC further shows that 1.09% of the total variation was related to country factors (with the remaining 98.91% related to patient factors) based on the two level null model (table 4). This proportion was reduced in the three level models to 0.82%, 0.36%, 0.03%, and 0.00% in models 1–4, respectively. By contrast, the intrahospital correlation coefficient was reduced from 2.53% in the three level null model to 1.38% in the full, three level model (model 4). Thus, 3.4% ((0.0279+0.0862)/(0.0279 +0.0862+3.29)) of the total variance was situated at the hospital and country level in the null model (model 1), and as a proportion of the hospital and country variance, 24.5% (0.0279/(0.0279+0.0862)) and 75.5% were at the country and the hospital level, respectively. After adjusting for baseline patient characteristics in model 3, however, such substantial country level effects were reduced from 24.5% to 2.6%. The patient factors, in contrast, accounted for 98.6% of the total variation.

The same multilevel analyses performed for one year mortality also confirmed that the country level factors, which was significant in the two level null model, played a negligible part (0%) in explaining the intercountry variation in one year mortality according to the three level models:

Table 3 Median length of stay and rates of revascularisation (PCI or CABG) and of (re)-myocardial infarction, and/or death at 30 days, and death at one year according to country

Country	Median LOS (days)	30 day						One year death (%)
		CABG (%)	PCI (%)	Revasculation (%)	(re)MI (%)	Death (%)	Death/(re)MI (%)	
North America								
Canada	8	14	25	39	8.4	3.7	5.5	8.1
United States	7	21	27	47	12.6	4.5	9.1	10.6
Western Europe								
Austria	14	5	10	15	8.5	4.2	5.9	11.9
Belgium	11	21	38	58	6.7	3.1	4.1	8.3
France	11	12	36	48	8.6	4.6	4.6	9.1
Germany	15	13	27	40	9.9	5.8	5.6	8.4
Greece	8	6	5	12	6.9	3.1	3.9	7.3
Ireland	15	10	13	20	5.0	5.0	0.0	10.0
Italy	11	16	25	40	9.9	4.5	6.4	8.6
Netherlands	9	12	21	33	6.7	3.7	3.7	7.0
Portugal	10	10	39	49	13.6	8.0	8.0	14.8
Spain	12	8	22	30	8.0	4.4	4.4	8.0
Switzerland	11	11	50	61	7.9	2.6	7.9	7.9
UK	9	7	19	25	8.1	4.8	4.8	10.5
Scandinavia								
Denmark	8	15	18	32	8.7	4.0	5.4	8.1
Finland	9	18	19	35	13.9	2.5	12.7	8.9
Norway	7	10	15	25	6.6	4.4	3.3	7.7
Sweden	8	15	24	39	9.6	2.9	7.9	6.4
Eastern Europe								
Czech	11	4	7	11	11.1	5.4	7.2	12.8
Poland	12	5	7	12	5.9	2.5	4.1	6.9
Other								
Australia	6	8	40	47	10.3	5.1	6.4	6.4
Israel	9	19	40	58	7.5	3.0	5.7	4.9
New Zealand	5	15	11	26	9.3	7.4	1.9	9.3
South Africa	6	21	26	46	6.9	2.8	4.9	5.6
All countries	**10**	**11**	**19**	**30**	**8.4**	**3.9**	**5.5**	**8.3**

CABG, coronary artery bypass graft surgery; LOS, length of stay; PCI, percutaneous coronary intervention; (re)-MI, (re)-myocardial infarction.

97.0% was explained by the patient level factors and the remaining 3% by hospital level factors (model 4, table 4).

DISCUSSION

International comparisons of population health, the incidence and prevalence of disease, and the impact of healthcare organisations and interventions on health outcomes are of great interest.[1 2] The proliferation of large international clinical trials in cardiovascular and other areas of medicine in the past two decades further stimulated investigation into the variations in practice patterns and outcomes among countries and geographical regions. These variations in health status and treatment outcomes, if real, are of particular concern, as they raise a host of questions concerning the efficacy, effectiveness, efficiency, and equity of the social and healthcare systems as well as the diagnostic and therapeutic procedures used within and among these countries and geographical regions. Identifying the sources of variation in patient outcomes is important, as it may have enormous implications for the design, analysis, and interpretation of such studies. For example, abciximab was not shown to be beneficial in the overall GUSTO IV ACS sample except in North America, where a beneficial effect of a borderline significance was seen. Nevertheless, the Food and Drug Administration (FDA) in the USA has not approved abciximab for frontline medicinal treatment of ACS patients based on the conventional view that subgroup results are less reliable.[27] Our findings of negligible country effects and of comparatively small hospital effects on outcomes in the GUSTO IV ACS trial lend support to the FDA's decision, although the reasons for better performance in North America deserve further investigations.

To our knowledge, however, there has not been a rigorous study performed to quantify the sources of intercountry variations in treatment outcomes for ACS patients. In this paper we showed that patient level factors explained 96%–99% of total NSTE ACS outcome variations. Similar findings were obtained in our previous studies of ST segment elevation myocardial infarction (STEMI)[3 29] where significant variations in 30 day and one year mortality were related mainly to patient characteristics. However, variation in one year mortality among countries remained highly significant for the STEMI sample even after adjusting for baseline patient characteristics, which was not the case for the NSTE ACS cohort. Whereas the residual intercountry variation was explained primarily by the country level life expectancy among STEMI patients, the patient and hospital level factors explained that variation in NSTE ACS patients. Such differences may be related to the finding from these studies that variation was greater among countries but smaller among hospitals in STEMI than in NSTE ACS patients, and that life expectancy as a proxy for the state of the nation's health and healthcare system had a greater impact on the outcomes of STEMI than of NSTE ACS. Further research is clearly required on this intriguing contrast.

It is noteworthy that our results are in agreement with those in other NSTE ACS studies.[7 17 18] Although significant international differences persisted in the efficacy and safety of subcutaneous enoxaparin in non-Q wave coronary events (ESSENCE) trial,[8] that study was based on very small samples from the outlier countries. Thus, our results were aligned with those obtained from a Swedish study that used two level modelling of 30 day mortality after a heart failure,[23] which confirmed that variation among hospitals in mortality after hospitalisation was mainly explained by the differences in baseline patient characteristics. A recent three level analysis of AMI patients in Ontario, Canada further showed that 96.6% of variation in one year mortality was related to patient level factors, leaving 2.8% and 0.6% to physician and

Table 4 Analysis of the hospital and country level effects on 30 day death/(re)MI and one year mortality

Variable	Hospital level effects		Country level effects		Intrahospital correlation (%)	Intracountry correlation (%)
	Variance (SE, p)	% Explained	Variance (SE, p)	% Explained		
30 day death/(re)MI						
Two level null model	–		0.0361 (0.024; p=0.004)			1.09
Three level models						
Model 1: null	0.0862 (0.046; p=0.003)		0.0279 (0.023; p=0.072)	22.7	2.53	0.82
Model 2: age only	0.0718 (0.044; p=0.010)	16.7	0.0122 (0.017; p=0.456)	56.3	2.13	0.36
Model 3: all baseline factors*	0.0419 (0.041; p=0.014)	51.4	0.0011 (0.012; p>0.500)	96.1	1.26	0.03
Model 4: Baseline+country level CABG-rate†	0.0462 0.039; (p=0.032)	46.4	0.0001 (0.001; p>0.500)	99.6	1.38	0.00
One year death						
Two level null model	–		0.0369 (0.024; p=0.005)			1.11
Three level models						
Model 1: null	0.179 (0.058; p=0.001)		0.0172 (0.022; p=0.312)	46.6	5.13	0.49
Model 2: age only	0.170 (0.059; p=0.002)	4.9	0.0068 (0.018; p>0.500)	60.5	4.91	0.20
Model 3: all baseline factors*	0.124 (0.054; p=0.014)	30.6	0.00002 (0.015; p>0.500)	99.7	3.64	0.00
Model 4: Baseline+country level CABG-rate†	0.103 (0.050; p=0.008)	42.5	0.00023 (0.001; p>0.500)	99.4	3.03	0.01

*Adjusted for age, prior myocardial infarction, prior transient ischaemic attacks, prior stroke, prior coronary artery bypass graft surgery, prior use of calcium channel blockers and β blockers, ST segment depression, troponins T, creatinine clearance, and time to randomisation. †Adjusted for country level coronary artery bypass graft surgery (CABG) rate.

hospital level factors, respectively.[21] Similarly, another Ontario study showed that socioeconomic status, although a significant predictor of patient level mortality, had a minimal impact on hospital mortality rates after adjusting for age, sex, and illness severity[30]; as well, a study of social context on heart disease mortality in Texas, USA showed that 95% of the total variance was accounted for by variation at the individual level, leaving the rest to variations in socioeconomic and ethnic factors at the census tract and the county level.[22]

It is also of interest to note that the country level revascularisation rates played a comparatively minor part in further reducing variations among hospitals and countries. Although we also found a negative relation between country level revascularisation and mortality rates, variation among countries remained significant after adjusting for the country level revascularisation rate. It should be noted here that these findings are contextual in nature, and they in no way imply that invasive procedures did not influence the outcomes of ACS at the patient level. To make such an inference is to commit a so called ecological fallacy, to infer an individual level relation on the basis of group level associations.[31]

As in other NSTE ACS studies,[5 7–9 18 32] we also found significant intercountry differences in drug and procedure use. In particular, in-hospital aspirin use was mandated in the protocol and given at a high rate across all regions (except for Irish patients) as recommended by the 2002 ACC/AHA and ESC guidelines.[33 34] The use of other efficacious drugs such as ACE inhibitors, β blockers, and long acting nitrates also increased after hospital admission, and their rates were consistent with those found in other studies.[7–9 18] Our finding of significant variations in practice patterns even within the context of rigorously designed clinical trials shows that opportunities exist to increase adherence to practice guidelines.

Several limitations of our study should be noted. Firstly, despite the detailed clinical data that had been collected in the GUSTO IV ACS trial, specific characteristics of hospitals (for example, information of on-site interventional facilities) and physician level data were unavailable.[27 35] Secondly, the GUSTO IV ACS sample may differ from the general population of patients with ACS, as it was not based on a representative sample in participating countries. In particular, coronary angiography was not performed within 12 hours of the completion of study agent infusion, which is the common practice in most hospitals without interventional facilities in North America and Europe. However, this is unlikely to change the main findings of our study in view of other studies also showing the predominance of patient level factors accounting for clinical outcomes.[21 23] Thirdly, we based our multilevel modelling on a latent variable approach, which assumed an underlying continuous dependent variable.[36] It should be noted that there are other methods of calculating the intraclass correlations and of summarising contextual level variances, for example, in terms of the median odds ratio.[28 37] However, the use of measures such as the median odds ratios[37] only confirms the findings of this study, and hence is not presented in this paper.

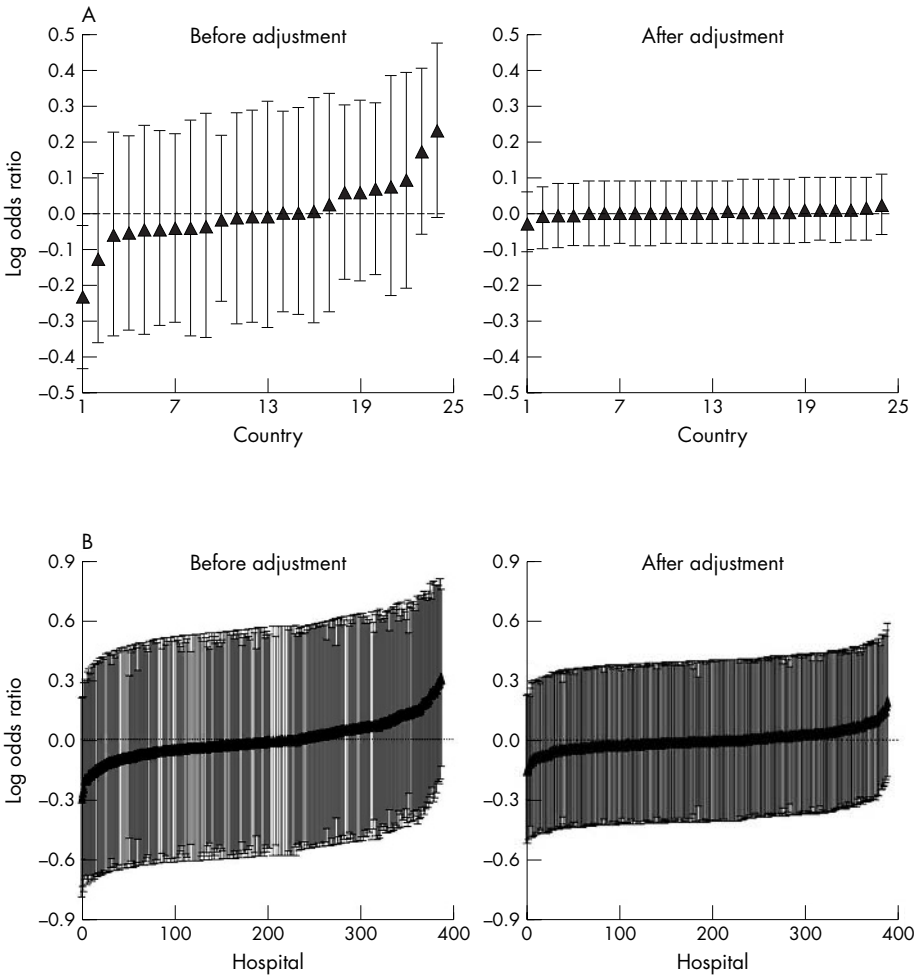

Figure 1 Logarithmic odds ratio and 90% confidence intervals for predicting 30 day death/(re)MI (ranked in ascending order) for each country (A) and for each hospital (B) before and after adjustment for baseline patient level factors.

Notwithstanding these limitations and considerations, our approach to the analysis of geographical variations has wider applications.

In conclusion, we found that practice patterns as well as patient characteristics differ among countries in a large, contemporary sample of NSTE ACS patients, and that variations in outcomes were related primarily to patient level factors and only small but significant proportions were related to hospital and country level factors. The variation between countries, which was smaller than that between hospitals, became negligible after controlling for patient and hospital effects. Greater attention to collecting data on hospital and physician characteristics in future NSTE ACS international studies and clinical trials, in addition to further exploring and refining patient level data, should provide insights into patient outcomes and optimising care in all healthcare settings.

Policy implications

- Variations in health status and treatment outcomes are of particular interest, as are those in diagnostic and therapeutic procedures used within and among countries and geographical regions. They raise a host of questions regarding the efficacy, effectiveness, efficiency, and equity of the social and healthcare systems.
- The multifactorial sources of these variations should be accounted for in the design, analysis, and interpretation of clinical and population based studies.
- Greater attention to collecting higher level data such as hospital and physician characteristics should provide insights into patient outcomes and optimising care.
- Identifying the components of these variations may further refine the approval process of novel treatments by regulatory agencies.

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