Practice patterns and outcomes after stroke across countries at different economic levels (INTERSTROKE): an international observational study

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Summary

Background **Stroke disproportionately affects people in low-income and middle-income countries. Although improvements in stroke care and outcomes have been reported in high-income countries, little is known about practice and outcomes in low and middle-income countries. We aimed to compare patterns of care available and their association with patient outcomes across countries at different economic levels.**

Methods **We studied the patterns and effect of practice variations (ie, treatments used and access to services) among participants in the INTERSTROKE study, an international observational study that enrolled 13 447 stroke patients from 142 clinical sites in 32 countries between Jan 11, 2007, and Aug 8, 2015. We supplemented patient data with a questionnaire about health-care and stroke service facilities at all participating hospitals. Using univariate and multivariate regression analyses to account for patient casemix and service clustering, we estimated the association between services available, treatments given, and patient outcomes (death or dependency) at 1 month.**

Findings **We obtained full information for 12 342 (92%) of 13 447 INTERSTROKE patients, from 108 hospitals in 28 countries; 2576 from 38 hospitals in ten high-income countries and 9766 from 70 hospitals in 18 low and middle-income countries. Patients in low-income and middle-income countries more often had severe strokes, intracerebral haemorrhage, poorer access to services, and used fewer investigations and treatments ($p<0·0001$) than those in high-income countries, although only differences in patient characteristics explained the poorer clinical outcomes in low and middle-income countries. However across all countries, irrespective of economic level, access to a stroke unit was associated with improved use of investigations and treatments, access to other rehabilitation services, and improved survival without severe dependency (odds ratio [OR] 1·29; 95% CI 1·14–1·44; all $p<0·0001$), which was independent of patient casemix characteristics and other measures of care. Use of acute antiplatelet treatment was associated with improved survival (1·39; 1·12–1·72) irrespective of other patient and service characteristics.**

Interpretation **Evidence-based treatments, diagnostics, and stroke units were less commonly available or used in low and middle-income countries. Access to stroke units and appropriate use of antiplatelet treatment were associated with improved recovery. Improved care and facilities in low-income and middle-income countries are essential to improve outcomes.**

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Introduction

Stroke is the second most common cause of death worldwide and one of the leading causes of disability.[1-3] Although prevention strategies can reduce this burden of disease,[4,5] effective and affordable treatments are essential for reducing mortality and morbidity in those who have already had a stroke. Aspirin,[4,5] intravenous thrombolysis,[4,5] and mechanical thrombectomy[6] for acute ischaemic stroke, plus stroke unit care and early rehabilitation services for all stroke patients[4,5] can reduce mortality and morbidity.

Results of the 2014 PURE study[7] showed that clinical outcomes after stroke were substantially poorer in low-income and middle-income countries than in high-income countries. Whether this finding reflects differences in the patient population, services available, or treatments received is uncertain. In many high-income countries, clinical practice guidelines and national strategies now recommend the establishment of stroke units in all hospitals that care for patients with acute stroke.[8–13] This practice has been linked to an increased provision of evidence-based care[14–19] and improved patient

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Research in context

Evidence before this study

We searched MEDLINE, Embase, and PubMed from Jan 1, 2000, to May 24, 2017, for large stroke register studies using Medical Subject Headings including the following search terms: "stroke OR cerebral hemorrhage OR cerebral infarction AND quality indicator OR performance indicator OR quality improvement OR quality of care OR quality of health care OR registry OR register OR audit AND outcome OR mortality OR case fatality OR survival OR disability OR function OR recovery OR discharge OR discharge destination OR return home OR complications". We identified 20 studies but none had been done in low or middle-income country settings.

Added value of this study

This is the first large study to use standardised, prospective data collection across a range of World Bank country income categories levels in more than 12 000 carefully characterised acute stroke patients from 108 hospitals in 28 countries. We have found that evidence-based treatments, diagnostics, and availability of stroke units were less common in low-income and middle-income countries. Access to stroke units and appropriate antiplatelet treatment were consistently associated with improved recovery.

Implications of all the available evidence

This analysis supports the widespread provision of appropriate early antiplatelet treatment and stroke unit care within hospitals in low-income and middle-income country settings. A certain basic standard of care and supporting resources are likely to be needed to fully achieve these benefits. Further research needs to develop and test methods of effectively implementing lower-cost, regionally appropriate models of stroke unit care.

outcomes.[17–20] However the greatest adoption of these practices has been in high-income countries, where most clinical trials of stroke units have been done. The number of stroke units in low-income and middle-income countries is unknown, along with whether these are associated with improved outcomes.[4,5,8] Such information could inform the establishment of stroke units in low-income and middle-income countries.

INTERSTROKE was an international observational stroke study done in 32 countries at different economic levels.[21] Individuals who had had a stroke were selected using standardised criteria and were characterised in detail. In this study we use INTERSTOKE data to compare patterns of care available and their association with patient outcomes, across a much broader range of health-care settings than has previously been possible.

Methods

Study design and participants

INTERSTROKE was an international case-control study of risk factors for first stroke,[21] which enrolled 13 447 stroke patients from 142 clinical sites in 32 countries between Jan 11, 2007, and Aug 8, 2015. For this analysis of practice patterns, our hypotheses were that, across all countries studied, there would be variations in access to stroke treatments and services and that, after adjusting for variations in patient casemix, patient outcomes would be affected by the treatments and services they can access. We proposed that outcomes would be better where health-care resources were greater, guideline investigations and treatments were provided, and guideline services (especially stroke units) were available at the hospital.

Data collection operated at two levels. First, individual stroke patient data included the following: demographic features (age, sex, level of education), risk factors, pre-stroke disability (using the modified Rankin Scale[22]), comorbidity (based on the Charleston Comorbidity Index[23]), stroke characteristics (including haemorrhage or infarct classified with the Oxfordshire Community Stroke Project classification,[24] modified Rankin score[22] at baseline, level of consciousness at baseline), and acute management received at enrolment in the study (brain imaging, antiplatelet treatment, thrombolysis, lipid-lowering treatment, and blood pressure-lowering treatment).

Second, service-level data were collected. Using a short questionnaire (appendix), we collected information about service features at every participating hospital: local and national health-care characteristics (eg, source of health funding and items for payment); hospital characteristics and resources (eg, tertiary or secondary level hospital, and departments and beds available); stroke service characteristics (eg, presence of stroke unit and stroke unit characteristics and resources); and additional features (ie, other aspects of patient care such as post-discharge rehabilitation). The survey was first circulated by e-mail from the coordinating centre via national leads in June, 2011; if there was no reply by early 2012, the e-mail was re-sent.

The study was approved by the ethics committees in all participating centres.[21] Participants, or their proxy, provided written informed consent.

Outcomes

Patient outcomes were recorded at 1 month follow up[21] and included death, discharge disposition after hospital (home, rehabilitation centre, or nursing home), dependency using the modified Rankin score,[22] and length of hospital stay. Patient details were collected from the participants or from a proxy respondent.[21]

Statistical analysis

We described patient characteristics and clinical practice (ie, investigations, treatments, and services provided) at recruiting hospitals grouped by the 2011 World Bank Country Income Categories using χ^2 and t tests.

We did multivariate analyses using SPSS (version 23) and SAS (version 9.4) to calculate casemix adjusted outcomes and a two-level multivariable model using random intercepts to take into account potential clustering of clinical practice by centre. We used multivariable logistic regression models to adjust for casemix covariates that are known to affect patient outcomes[25]—ie, age, sex, level of education, pre-stroke disability, number of comorbidities, stroke type and classification, and initial stroke severity. No significant multi-collinearity was identified. Adjustment was also made for country wealth (ranked by gross domestic product [GDP]) and clustering by centre. We then used binary logistic regression to identify variables that had the closest association with patient outcomes. Subgroup analyses stratified results by key patient and service characteristics. Availability of a stroke unit was clustered in regions and correlated with patient age, level of consciousness, and stroke severity. Therefore we also sought to confirm our findings in a propensity-matching analysis accounting for these variables. Finally, we did exploratory sensitivity analyses of the association between patient outcomes and access to stroke units (with or without particular characteristics). These comparisons were based on stroke unit quality criteria[26] in terms of the following: the presence of a discrete ward, multidisciplinary care, staff specialist interest in stroke, programmes of staff education, patient management protocols, and information for patients and families; staffing levels that meet basic benchmark levels for nursing and medical and treatment staff;[26] stroke unit capacity (ability to manage >50% of the stroke patients in the hospital); and access to post-discharge rehabilitation.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.

Results

Between Jan 11, 2007, and Aug 8, 2015, the INTERSTROKE study[21] enrolled 13 447 acute stroke patients from 142 centres; 34 centres (1105 participants) did not provide information about the service survey. We therefore had complete individual patient data and service information from 12 342 participants from 108 hospitals in 28 countries covering western Europe, east and central Europe, the Middle East, Africa, South Asia, China, southeast Asia, Latin America, North America, and Australia.

Table 1 outlines the characteristics of patients, investigations, and treatments provided and the services available. 38 hospitals (2576 participants) were in high-income countries (Australia, Canada, Croatia, Denmark, Germany, Ireland, Poland, Sweden, United Arab Emirates, and the UK) and 70 hospitals (9766 participants) in low-income and middle-income countries. The latter consisted of 50 hospitals (5859 participants) in upper-middle-income countries (Argentina, Brazil, Chile, China, Columbia, Ecuador, Malaysia, Peru, Russia, South Africa, and Turkey), 17 hospitals (3361 participants) in lower-middle-income countries (India, Nigeria, Pakistan, Philippines, Sudan), and three hospitals (546 participants) in low-income countries (Mozambique, Uganda). Hospitals in low-income and middle-income countries recruited patients who were on average younger, less well educated, had fewer comorbidities, more severe strokes, and more intracerebral haemorrhage (all p<0·0001; table 1). Although CT scanning was mandated for all INTERSTROKE patients, those from high-income countries were more likely to have imaging on the day of admission. Other investigations were also more readily available (table 1). Patients from high-income countries were more likely to receive antiplatelet treatment, intravenous thrombolysis, or a carotid intervention after an ischaemic stroke, but any variations

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	High-income country (2576 participants; 10 countries)	Upper-middle-income country (5859 participants; 11 countries)	Lower-middle-income or low-income country (3907 participants; 7 countries)	p value
Patient characteristics				
Age (years)	65·8 (13·8)	62·7 (13·3)	59·1 (13·5)	<0·0001
Sex				
Men	1543 (60%)	3331 (57%)	2359 (60%)	0·001
Women	1034 (40%)	2528 (43%)	1548 (40%)	0·001
Education				
None or primary	449 (17%)	3832 (66%)	2234 (58%)	<0·0001
High school, trade college, or university	2127 (83%)	2025 (34%)	1673 (42%)	..
Comorbidities				
None	730 (28%)	1886 (32%)	1430 (37%)	<0·0001
One or more	1845 (72%)	3972 (68%)	2477 (63%)	..
Pre-stroke independence				
mRS score 0–2	2481 (96%)	5794 (99%)	3871 (99%)	0·001
Stroke classification				
Intracerebral haemorrhage	258 (10%)	1666 (28%)	1275 (32%)	<0·0001
Infarct, total anterior circulation	111 (4%)	280 (5%)	208 (5%)	..
Infarct, partial anterior circulation	1022 (40%)	1927 (33%)	1319 (34%)	..
Infarct, posterior circulation	406 (16%)	549 (9%)	311 (8%)	..
Infarct, lacunar	706 (27%)	1149 (20%)	574 (15%)	..
Unclassified	70 (3%)	288 (5%)	219 (6%)	..
Level of consciousness reduced	189 (7%)	1640 (28%)	2116 (54%)	<0·0001
Stroke index severity				
Mild (mRS 0–2)	1605 (62%)	2180 (37%)	894 (23%)	<0·0001
Moderate (mRS 3)	472 (18%)	1636 (28%)	994 (25%)	
Severe (mRS 4)	373 (15%)	1391 (24%)	1076 (28%)	
Very severe (mRS 5)	126 (5%)	651 (11%)	942 (24%)	
Mean length of stay in hospital (days)	9	16	6	<0·0001

(Table 1 continues on next page)

	High-income country (2576 participants; 10 countries)	Upper-middle-income country (5859 participants; 11 countries)	Lower-middle-income or low-income country (3907 participants; 7 countries)	p value
(Continued from previous page)				
Investigations done in hospital				
CT scan on day 1	2460 (96%)	5567 (95%)	3455 (89%)	<0·0001
MRI scan	503 (20%)	611 (10%)	43 (1%)	<0·0001
Holter monitoring	608 (24%)	94 (2%)	2 (1%)	<0·0001
Carotid doppler	1653 (64%)	1175 (20%)	76 (2%)	<0·0001
Treatments given in hospital				
Antiplatelet drugs for cerebral infarct	2344 (91%)	5121 (87%)	3116 (85%)	<0·0001
Lipid lowering for cerebral infarct	1865 (72%)	4222 (72%)	3140 (80%)	<0·0001
Intravenous thrombolysis for infarct*	463 (20%)	168 (4%)	73 (3%)	<0·0001
Carotid intervention for infarct*†	79 (3%)	16 (<1%)	2 (<1%)	<0·0001
BP lowering for any stroke	1818 (71%)	3881 (66%)	2972 (76%)	<0·0001
Services available at centre				
Tertiary (*vs* secondary or local)	1839 (72%)	3090 (53%)	2690 (69%)	<0·0001
Any stroke specialist available	2397 (96%)	5155 (88%)	2410 (62%)	<0·0001
Capacity to look after >50% of patients	2259 (90%)	4805 (82%)	1512 (39%)	<0·0001
Stroke unit availability				
Any stroke unit available	2370 (92%)	1323 (23%)	2362 (61%)	<0·0001
Capacity to look after >50% of patients	2236 (89%)	1297 (22%)	1334 (34%)	<0·0001
Unit meets all key characteristics‡	1767 (71%)	1088 (19%)	783 (20%)	<0·0001
Unit meets all staffing benchmarks§	475 (18%)	408 (7%)	723 (18%)	<0·0001
Post-discharge rehabilitation				
Any service available	2357 (92%)	2170 (37%)	1214 (31%)	<0·0001
Family training in rehabilitation	2169 (84%)	4418 (75%)	2509 (64%)	<0·0001

Data are n, mean (SD), or n (%). All recruited patients were expected to have brain imaging (usually a CT scan) and a 12-lead electrocardiogram. mRS=modified Rankin Scale. BP=blood pressure. *Substantial missing data that were assumed to suggest non-treatment. †Usually carotid endarterectomy (a few patients had carotid stenting). ‡The stroke unit characteristics included[26] discrete ward, staff who specialise in stroke, regular multidisciplinary team meetings, protocols for care in place, programmes of education and training for staff, information provided for patients and carers. §Basic stroke unit staffing was benchmarked[26] at a staff complement (to cover all shifts) of 1·0 whole time equivalent of nursing staff per bed, 0·1 whole time equivalent of therapist, and 0·1 whole time equivalent of doctor. All comparisons are at the level of the patient. Because the services available were clustered at centres, we also confirmed any differences at the level of the centres.

Table 1: **Patient and practice characteristics categorised by World Bank country income category**

in blood pressure-lowering treatments and lipid-lowering treatment were not linked clearly to World Bank country income categories. Data reporting was almost complete (12 266; 99%) for all reported variables with the exception of thrombolysis and carotid interventions for which non-reporting was assumed to indicate that the treatment was not given.

Table 1 also summarises the services available in each site. 6055 (49%) patients were admitted to hospitals reporting that they had some form of stroke unit available; (95% of centres and 92% of patients in high-income countries; 30% of centres and 38% of patients in low-income and middle-income countries). However there was no clear gradient by World Bank country income categories, with the fewest stroke units being available in upper-middle-income countries. When present, stroke units in low-income and middle-income countries were less likely to meet all of the six key quality characteristics[26] or to report having sufficient capacity to accommodate most hospitalised stroke patients (table 1). This was corroborated by information that, for the same number of admissions (a median of 50 stroke patient admissions per month), stroke units in high-income countries reported having a median of 18 beds available compared with eight beds in units in low-income and middle-income countries.

Stroke patients from wealthier countries had better outcomes at 1 month. When grouped as high-income countries versus low-income and middle-income countries, the number surviving, and surviving without major dependency, as defined by a modified Rankin Scale score of 0–3, were 2501 (98%) and 2308 (90%), respectively in high-income countries compared with 8580 (88%) and 7536 (78%) in low-income and middle-income countries. This finding was confirmed when outcomes were regressed against country wealth; ranked from lowest to highest country GDP (table 2). Differences in patient characteristics seemed to explain much, but not all, of the variation by country wealth. After adjusting for baseline patient casemix variables (age, sex, education, pre-stroke disability, stroke type, number of comorbidities, level of consciousness, and modified Rankin score at baseline) the association between country income and recovery was reduced but not abolished (table 2). There was no further attenuation of the association after including common drugs given (antiplatelet, lipid lowering, and BP-lowering treatment and thrombolysis), and access to services (medical stroke specialist, stroke unit, and rehabilitation post discharge). These results suggest that the incrementally better patient outcomes recorded in wealthier countries were partly explained by patient casemix.

We then explored the associations between treatments given, services available, and patient outcomes across all World Bank country income category settings (table 3). For these analyses we included all treatments and services that were less common in centres in low-income and middle-income countries (table 1). We did not include carotid interventions because this applied to only 97 (1%) patients overall. After adjustment for patient casemix and country wealth, the appropriate provision of antiplatelet treatment (prescribed for those with cerebral infarction), and the availability of stroke unit care and post-discharge rehabilitation were each associated with a greater chance of survival without severe dependency (table 3). The appropriate provision of antiplatelet treatment and availability of stroke unit care and post-discharge rehabilitation were also associated with a

	Univariate analysis	Multivariate analysis A*	Multivariate analysis B†	Multivariate analysis C‡	Multivariate analysis clustered by centre§
Full recovery (mRS 0–1) *vs* worse	1·05 (1·04–1·05); p<0·0001	1·01 (0·99–1·01); p=0·72	1·00 (0·99–1·01); p=0·91	1·01 (0·99–1·01); p=0·07	1·01 (0·99–1·01); p=0·08
Independent (mRS 0–2) *vs* worse	1·05 (1·05–1·06); p<0·0001	1·00 (0·99–1·01); p=0.95	1·00 (0·99–1·01); p=0·99	1·00 (0·99–1·01); p=0·99	1·01 (0·99–1·01); p=0·43
No major dependency (mRS 0–3) *vs* worse	1·06 (1·05–1·08); p<0·0001	1·00 (0·99–1·01); p=0·59	1·00 (0·99–1·01); p=0·47	0·99 (0·99–1·02); p=0·07	1·00 (0·99–1·01); p=0·70
Without very severe dependency (mRS 0–4) *vs* worse	1·10 (1·09–1·10); p<0·0001	1·02 (1·01–1·04); p<0·0001	1·03 (1·02–1·04); p<0·0001	1·02 (1·01–1·03); p=0·0005	1·03 (1·02–1·04); p<0·0001
Alive (mRS 0–5) *vs* dead	1·12 (1·11–1·14); p<0·0001	1·05 (1·04–1·06); p<0·0001	1·05 (1·04–1·06); p<0·0001	1·05 (1·03–1·06); p<0·0001	1·06 (1·04–1·07); p<0·0001

Data are odds ratio (95% CI); p value. Exploration of the association between country wealth and odds of patients having a better outcome (graded by the modified Rankin Scale; mRS) and the gross domestic product (GDP) ranked from lowest to highest income. The univariate analysis includes only country GDP ranked from the highest to lowest of the 28 included countries. *Outcomes adjusted for country GDP ranking plus participant age, sex, education, pre-stroke disability, stroke type (haemorrhage or Oxfordshire Community Stroke Project category of infarct), number of comorbidities (Charleston comorbidity index), level of consciousness, and modified Rankin score at baseline (always recorded within 5 days of stroke onset). †Outcomes adjusted for all of the above plus common drugs given (antiplatelet, lipid-lowering, blood pressure-lowering treatment, and thrombolysis). ‡Outcomes adjusted for all of the above plus accounting for services available (medical stroke specialist, stroke unit, and rehabilitation post discharge). §Outcomes adjusted for those in ‡ plus clustering by centre.

Table 2: **Patient outcomes at 1 month by country wealth**

higher probability of survival at 1 month (table 3). When the analysis also took into account clustering by centre (table 3), the availability of stroke unit care and post-discharge rehabilitation were each associated with a greater chance of survival without severe dependency (table 3). The appropriate provision of antiplatelet treatment and availability of post-discharge rehabilitation were associated with a higher chance of survival at 1 month when taking into account clustering by centre.

Using a forward binary logistic regression, including all variables listed in table 3, we noted that survival without severe dependency as defined by modified Rankin Scale 0–3 was greater with access to stroke unit care and appropriate antiplatelet treatment. Significant covariates were pre-stroke disability plus the five patient variables (age, comorbidities, baseline modified Rankin Scale, level of consciousness, and stroke classification). Survival at 1 month was best explained by appropriate antiplatelet treatment, access to stroke unit care, and access to post-discharge rehabilitation. Significant covariates were country GDP ranking, patient education, and the five patient variables above.

Table 4 highlights the univariate and multivariate analyses exploring the association of access to a stroke unit with the provision of other stroke treatments and with patient outcomes. Admission to a hospital with a stroke unit was associated with increased odds of receiving all the other process measures plus increased survival and survival without severe dependency. However after adjusting for clustering by centre, access to a stroke unit was only associated with increased access to CT scanning and post-discharge rehabilitation and with survival without severe dependency (1·29; 1·14–1·44).

As stroke unit availability was unevenly distributed between regions, we used a matched propensity analysis that excluded the five regions where availability was either universal (western Europe, eastern Europe, North America, and Australia) or absent (Middle East). Variables that were related to patient outcomes and also closely

	Univariate analysis	Multivariate analysis A*	Multivariate analysis B†	Multivariate analysis C‡
Alive without severe dependency (mRS 0–3)				
Antiplatelet therapy for infarct	1·84 (1·61–2·10); p<0·0001	1·28 (1·08–1·51); p=0·0050	1·29 (1·09–1·53); p=0·0030	1·12 (0·95–1·34); p=0·19
Thrombolysis for infarct	1·13 (0·91–1·41); p=0·28	1·09 (0·83–1·43); p=0·54	1·06 (0·80–1·39); p=0·69	0·90 (0·68–1·18); p=0·44
Medical stroke specialist available§	1·79 (1·61–1·98); p<0·0001	1·04 (0·91–1·18); p=0·61	0·97 (0·82–1·14); p=0·69	0·91 (0·77–1·08); p=0·93
Stroke unit available§	1·25 (1·14–1·36); p<0·0001	1·42 (1·27–1·59); p<0·0001	1·42 (1·27–1·60); p<0·0001	1·29 (1·14–1·44); p<0·0001
Post-discharge rehabilitation available§	1·55 (1·43–1·70); p<0·0001	1·20 (1·06–1·35); p=0·0030	1·37 (1·20–1·57); p<0·0001	1·18 (1·03–1·35); p=0·0210
Alive (mRS 0–5)				
Antiplatelet therapy for infarct	2·47 (2·07–2·96); p<0·0001	1·65 (1·34–2·03); p<0·0001	1·62 (1·32–1·99); p<0·0001	1·39 (1·12–1·72); p=0·0030
Thrombolysis for infarct	1·67 (1·15–2·43); p=0·0070	1·43 (0·94–2·17); p=0·09	1·10 (0·72–1·69); p=0·66	0·85 (0·55–1·31); p=0·46
Medical stroke specialist available§	1·62 (1·32–2·00); p<0·0001	1·22 (0·97–1·54); p=0·09	1·26 (0·99–1·59); p=0·05	1·20 (0·94–1·52); p=0·14
Stroke unit available§	1·23 (1·09–1·39); p=0·0010	1·17 (1·01–1·34); p=0·0340	1·18 (1·03–1·36); p=0·0200	1·00 (0·86–1·16); p=0·99
Post-discharge rehabilitation available§	3·79 (3·28–4·38); p<0·0001	2·26 (1·91–2·66); p<0·0001	1·90 (1·58–2·28); p<0·0001	1·54 (1·28–1·85); p<0·0001

Data are odds ratio (95% CI); p value. The multivariate analysis used multivariate regression to show casemix adjusted outcomes. mRS=modified Rankin Scale. *Outcomes adjusted for participant age, sex, education, pre-stroke disability, stroke type (haemorrhage or Oxfordshire Community Stroke Project category of infarct), number of comorbidities (Charleston comorbidity index), level of consciousness, and modified Rankin score at baseline (always recorded within 5 days of stroke onset). †Outcomes adjusted for all of the above plus country income (GDP ranking). ‡Outcomes adjusted for all those in † plus centre. §Service available at the recruiting centre but not necessarily received by every patient.

Table 3: **Association of treatments available with patient outcomes at 1 month**

	Stroke unit available	Stroke unit not available	Univariate analysis	Multivariate analysis*	Multivariate analysis†
Process measures					
CT scan on day of admission	5727 (95%)	5754 (92%)	1·69 (1·45–1·95); p<0·0001	1·66 (1·43–1·94); p<0·0001	1·35 (1·10–1·66); p=0·0040
Antiplatelet for infarct	4148 (86%)	3554 (80%)	1·49 (1·31–1·63); p<0·0001	1·40 (1·24–1·58); p<0·0001	1·16 (0·99–1·34); p=0·06
Lipid lowering for infarct	3366 (70%)	2772 (63%)	1·35 (1·23–1·47); p<0·0001	1·33 (1·21–1·47); p<0·0001	1·17 (0·76–1·81); p=0·48
Thrombolysis for infarct	580 (12%)	123 (3%)	4·74 (3·88–5·78); p<0·0001	3·65 (2·96–4·50); p<0·0001	Insufficient data
BP lowering therapy for any stroke	4357 (72%)	4313 (69%)	1·17 (1·09–1·27); p<0·0001	1·29 (1·18–1·41); p<0·0001	0·93 (0·73–1·17); p=0·52
Post-discharge rehabilitation provided	4564 (75%)	1198 (19%)	13·0 (11·9–14·2); p<0·0001	18·2 (16·4–20·3); p<0·0001	86·7 (66·4–1·13); p<0·0001
Clinical outcomes at 1 month					
Alive without severe dependency (mRS 0–3)	4936 (82%)	4907 (79%)	1·25 (1·14–1·36); p<0·0001	1·41 (1·26–1·58); p<0·0001	1·29 (1·14–1·44); p<0·0001
Alive (mRS 0–5)	5492 (91%)	5588 (89%)	1·23 (1·09–1·39); p=0·0010	1·30 (1·12–1·49); p<0·0001	1·00 (0·86–1·16); p=0·99

Data are n (%) or odds ratio (95% CI); p value. The table shows the number (%) of patients in both service groups in each category of process measure (care received up to 1 month) and outcome measure (degree of recovery at 1 month post stroke). Univariate analyses show the unadjusted odds ratio and 95% (CI) for the association between access to stroke unit care and a better clinical outcome. The multivariate analysis used multivariate regression to show casemix adjusted outcomes. BP=blood pressure. mRS=modified Rankin Scale. *Outcomes adjusted for participant age, sex, education, pre-stroke disability, stroke type (haemorrhage or Oxfordshire Community Stroke Project category of infarct), number of comorbidities (Charleston comorbidity index), level of consciousness, and modified Rankin score at baseline (always recorded within 5 days of stroke onset), plus country income (GDP ranking). †Outcomes adjusted for all of the above plus centre.

Table 4: **Association of access to stroke unit care with processes of care and patient outcomes at 1 month**

associated with stroke unit availability were patient age and stroke severity. Therefore, we compared two groups of 3466 stroke participants with or without access to a stroke unit who were matched on age (mean age, years), reduced level of consciousness (45%), and baseline modified Rankin Scale score (mean score 3·40). Admission to a hospital that had a stroke unit was again associated with increased odds of survival (1·15; 1·01–1·31) and of survival without major disability (1·30; 1·17–1·44).

In view of the imbalance between high-income countries and low-income and middle-income countries in the numbers of patients with intracerebral haemorrhage, we repeated the analyses excluding intracerebral haemorrhages (appendix). On multivariate analyses, patients with ischaemic stroke had increased survival without severe dependency (1·42; 1·23–1·64; p<0·0001) if admitted to a hospital with a stroke unit. Results were directionally consistent but non-significant for survival (1·15; 0·96–1·39; p=0·14).

Further subgroup analyses found a consistent association between access to stroke unit services and patient outcomes across a range of patient and service subgroups (figure 1). The association of improved outcomes with antiplatelet drug use was seen across all subgroups (figure 2) except for stroke type where no benefit was recorded for the very small number of haemorrhage patients given aspirin.

Finally, in sensitivity analyses we repeated the analysis in table 4 for the outcome of survival without severe dependency (modified Rankin Scale 0–3) but compared stroke units with and without specific quality characteristics (as described in table 1). The association with improved outcomes was greater in the presence of quality features compared with absence: if the stroke unit was described as having the six key characteristics (1·32; 1·11–1·56); if stroke unit staffing met basic benchmark levels (1·34; 1·11–1·62); and if the stroke unit had the capacity to house at least 50% of stroke patient admissions (1·20; 1·00–1·45). The availability of post-discharge rehabilitation was not associated with additional benefit in this analysis (1·08; 0·67–1·33).

Discussion

We had anticipated that INTERSTROKE patients enrolled from hospitals in low-income and middle-income countries would have poorer access to investigations, treatments, and services than those enrolled from hospitals in high-income countries. However, these patients also had poorer clinical outcomes (survival 88% *vs* 98% in high-income countries; survival without severe disability 78% *vs* 90%), which could only be partly explained by the inclusion of more severe stroke patients. Across all countries studied, the practice variables most consistently associated with improved patient outcomes were access to stroke unit care and post-discharge rehabilitation plus receiving appropriate antiplatelet treatment. This could reflect more limited access to state or insurance-funded health-care services.

The poorer stroke prognosis in low and middle-income countries has been described previously.[2,3,7,27] We have confirmed that stroke in poorer countries seems to be either a more severe disease (ie, more intracerebral haemorrhage) or has different referral patterns (patients admitted to hospital are more likely to have severe stroke). The potential role of stroke units and antiplatelet treatment in low-income and middle-income country settings has not been described before but is potentially complex. Access to drugs or services could not explain differences between patient outcomes in wealthy versus less wealthy countries but they did seem to explain associations across all countries. This might reflect the observation that access to a stroke unit varied greatly within as well as between wealth categories.

Several observational studies[16,18,20,28] have reported on the association of appropriate antiplatelet treatment (ie, early use in acute cerebral ischaemia) with improved survival and reduced disability. Additionally, a 2016 meta-analysis of aspirin trials[29] confirmed an important

short-term benefit of aspirin treatment to prevent recurrent cerebral ischaemia. However, these studies have almost all been done in high-income settings.[27,28] Earlier access to brain imaging could facilitate earlier antiplatelet use.

In the INTERSTROKE study, the apparent benefit of stroke units is similar to that reported in randomised clinical trials[4] and seems to be due to a combination of an intrinsic stroke unit effect as well as stroke unit patients having better access to antiplatelet treatment, risk factor modification, and post-discharge rehabilitation. The apparent benefits were recorded across a range of stroke patient groups and tended to be greater if the stroke unit was reported to be well staffed, to meet recognised service standards, and to have sufficient capacity to provide care for most stroke patients admitted to hospital. Our findings suggest that stroke units can have a similar benefit in low-income and middle-income countries as has been noted in high-income countries.

At present few hospitals in low-income and middle-income countries have stroke units. Even in our study, which is likely to have included a higher proportion of better-resourced tertiary care centres (with better access to imaging and drug therapies) than in most hospitals in low-income and middle-income countries, only 38% had stroke units. Our study suggests that establishment of simple stroke units could enhance the level and organisation of care and improve stroke outcomes in low-income and middle-income countries. WHO has targeted a 25% reduction in premature mortality from cardiovascular disease globally by 2025. This is unlikely to be achieved by risk-factor reduction alone but also requires investment in medical treatments and organisation of better systems of care. Investment in specialised stroke units is likely to be cost effective and should be a priority worldwide.

Limitations of this study include the observational design, which cannot completely exclude the possibility of residual confounding. We did several analyses, which raises the possibility of chance findings. However, use of the 99% confidence threshold would not alter our main conclusions. Service features were described at the level of the hospital so we cannot be certain which specific patients were actually admitted to a stroke unit. Although this introduces some uncertainty, it also reduces any potential bias resulting from selective admission of patients with better prognosis within a hospital to the stroke unit; it is testing the effect of the stroke unit on all patients at that hospital. Of note, the sensitivity analyses suggest improved outcomes where stroke units had greater capacity to accept most stroke patients. As only a proportion of patients were enrolled in INTERSTROKE, it is possible (but unlikely) that stroke unit sites enrolled patients with a better prognosis. An additional challenge was that service characteristics tended to cluster together in hospitals, countries, and regions making it difficult to separate the

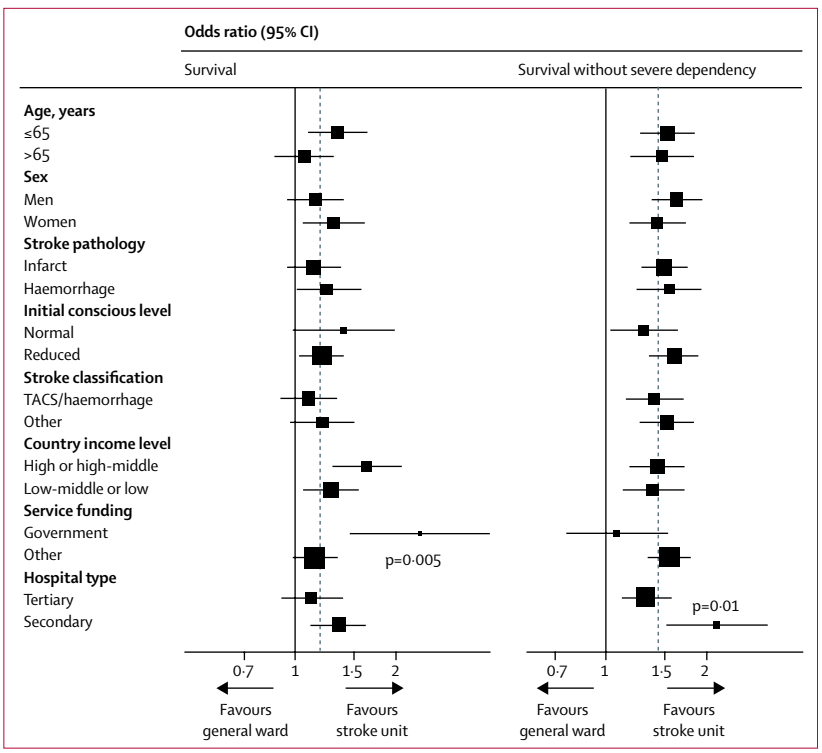

Figure 1: **Association between admission to a hospital with a stroke unit and patient outcomes at 1 month**
Subgroup analysis by patient and service characteristics. p values indicate subgroup interactions at p<0·05.

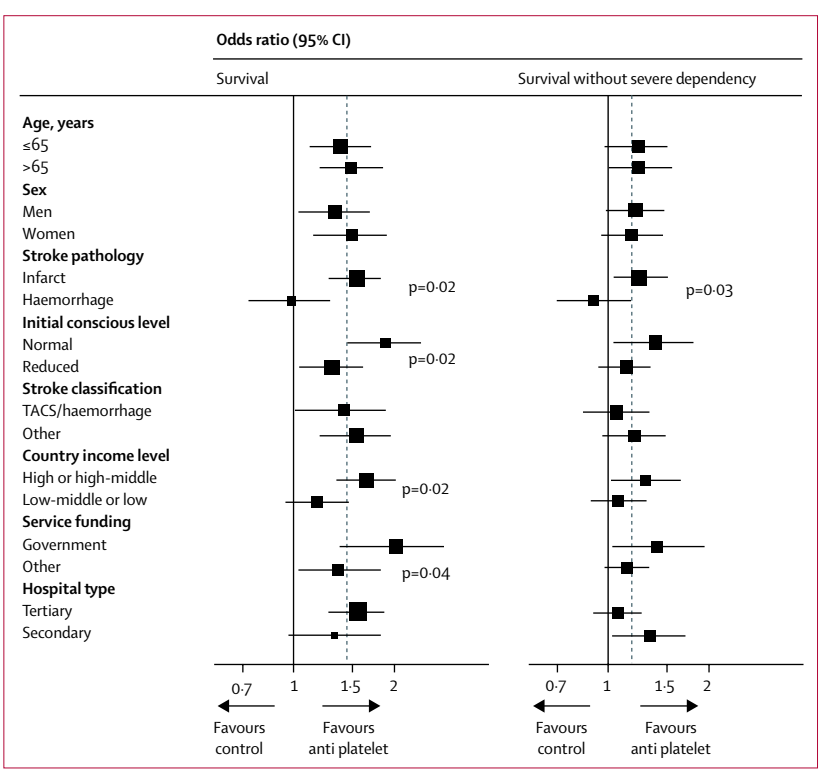

Figure 2: **Association between use of antiplatelet treatment in hospital and patient outcomes at 1 month**
Subgroup analysis by patient and service characteristics. p values indicate subgroup interactions at p<0·05.

effect of different aspects of service delivery. In particular, the availability of post-discharge rehabilitation services was closely related to stroke units. Finally, several regions had no variation in the provision of stroke units, although exclusion of these regions from the analysis did not alter our conclusions.

The strengths of our study are that we collected standardised information from more than 12 000 well characterised acute stroke patients including an independent assessment of outcome at 1 month. We recruited from a large number of hospitals in diverse settings with variations in care. This was facilitated by national coordinators and investigators who were trained in collecting data in a standardised manner. The study investigators had a research interest in stroke epidemiology, but there was not usually a special interest in service delivery. Although we recognise that the hospitals participating in INTERSTROKE are likely to have had a higher level of resources and support than is typical of poorer resourced areas, we know of no other study that has obtained such a broad range and quality of data using such standardised and prospective methods. If the centres participating in INTERSTROKE were better equipped than the average centres in each country (especially in low-income and middle-income countries), the gaps between high-income countries and low-income and middle-income facilities, organised care, treatments, and outcomes for stroke patients might be even greater than what we report.

Several previous studies have explored the potential effect of indicators of service quality in routine hospital settings;[27,28] however, almost all have been done in high-income countries. The most recent review of low and middle-income countries[8] could only identify limited observational information that could not adjust for confounders. Individual case studies in India, Thailand, South Africa, and Mauritania[8] suggested that stroke unit care could have a beneficial effect in those settings. Only two studies have explored the effect of antiplatelet agents in low-income and middle-income countries and their results were inconclusive.[28]

In conclusion, we believe that this analysis supports the widespread provision of appropriate early antiplatelet treatment and stroke unit care within hospitals in low-income and middle-income settings. It also indicates that a certain basic standard of care and supporting resources are likely to be needed to fully realise these benefits. These include adequate staffing and the capacity to accept the majority of stroke patients. Further research needs to develop and test methods of effectively implementing lower-cost, regionally appropriate models of stroke unit care.

Contributors

This subproject of INTERSTROKE was conceived and jointly led by PL and MJO'D in conjunction with the study secretariat comprising the key national coordinators and members of the coordinating team at Population Health Research Institute. PL and MJO'D designed the study, planned analyses, and wrote the first draft of the report. PL, MT, and MJM did statistical analyses. All authors contributed to the collection of data, discussion and interpretation of the data, and to the writing of the report. All authors had full access to data and reviewed and approved the drafts of the report. MJO'D and SY jointly designed and led the overall INTERSTROKE study.

Declaration of interests

GJH reports personal fees from Bayer and Medscape, outside of the submitted work. H-CD has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth, and Yamanouchi; financial support for research projects provided by AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis, and Talecris; served as editor of *Aktuelle Neurologie*, *Arzneimitteltherapie*, *Kopfschmerznews*, *Stroke News*, and the Treatment Guidelines of the German Neurological Society within the past year; and served as co-editor of *Cephalalgia*, and on the editorial board of *The Lancet Neurology*, *Stroke*, *European Neurology*, and *Cerebrovascular Disorders*. All other authors declare no competing interests.

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