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Stroke Outcome in Clinical Trial Patients Deriving From Different Countries

Myzoon Ali, M.Res; Sari Atula, MD; Philip M.W. Bath, MD, FRCP; James Grotta, MD; Werner Hacke, MD, PhD; Patrick Lyden, MD, FAAN; John R. Marler, MD; Ralph L. Sacco, MD, MS; Kennedy R. Lees, MD, FRCP; for the VISTA Investigators

Background and Purpose—Stroke incidence and outcome vary widely within and across geographical locations. We examined whether differences in index stroke severity, stroke risk factors, mortality, and stroke outcome across geographical locations remain after adjusting for case mix.

Methods—We analyzed 3284 patients from the Virtual International Stroke Trials Archive (VISTA). We used logistic regression to examine the incidence of mild index stroke, functional, and neurological outcomes after accounting for age, medical history, year of trial recruitment, and initial stroke severity in the functional and neurological outcome analyses. We examined mortality between geographical regions using a Cox proportional hazards model, accounting for age, initial stroke severity, medical history, and year of trial recruitment.

Results—Patients enrolled in the USA and Canada had the most severe index strokes. Those recruited in Austria and Switzerland had the best functional and neurological outcomes at 90 days ($P<0.05$), whereas those enrolled in Germany had the worst functional outcome at 90 days ($P=0.013$). Patients enrolled in Austria, Switzerland, Belgium, Netherlands, Finland, Germany, Greece, Israel, Spain, and Portugal had a significantly better survival rate when compared with those enrolled in USA and Canada. Patients enrolled in trials after 1998 had more severe index strokes, with no significant difference in outcome compared with those enrolled before 1998.

Conclusion—We identified regional variations in index stroke severity, outcome, and mortality for patients enrolled in ischemic stroke clinical trials over the past 13 years that were not fully explained by case mix. Index stroke severity was greater in patients enrolled after 1998, with no significant improvement in outcomes compared to those enrolled before 1998. **(*Stroke*. 2009;40:35-40.)**

Key Words: acute care ■ clinical trials ■ database ■ epidemiology ■ outcomes

Worldwide, stroke is one of the leading causes of mortality and morbidity. There are prominent variations in stroke incidence and outcome among countries.[1–3] Stroke incidence in Asia is generally higher than in the USA.[4–6] Strokes are more frequent in Eastern than in Western Europe, with incidence varying from 660 per 100 000 men in Russia to 303 per 100 000 men in Sweden.[7] Stroke mortality is also 5-times higher in Eastern Europe compared with Western Europe.[7,8] This phenomenon could also be attributed to a higher frequency of risk factors such as hypertension and smoking[9,10] in the Eastern European population. These patients tend to have more severe strokes, from which the recovery is poorer.

These differences are not only confined to the East–West European axis but also are also found among the countries in Western Europe. Stroke incidence is lower in France and the United Kingdom compared with Germany. One-year mortality for stroke is lowest in France and highest in the United Kingdom.[7] The causes of this are still open to question but are thought to be partially related to the variation in risk factors, baseline characteristics of the patients, and acute stroke care between the countries.[11]

Asplund et al[12] reported that rehabilitation such as physiotherapy and speech therapy was provided more often in the Netherlands, Belgium, Australia, and New Zealand compared with other regions. The standard of stroke care within countries can vary widely.[13] The availability of resources for acute stroke care and rehabilitation can influence functional outcome and survival.[14] The International Stroke Trial investigators observed the lowest case fatality rates in Scandinavian patients, which were thought to be attributed to the availability of acute stroke units for these patients.[15] Stroke trial centers usually deliver the highest standards of care in the country and are associated with

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From Department of Medicine & Therapeutics (M.A., S.A., K.R.L.), Gardiner Institute, Western Infirmary, Glasgow, UK; Division of Stroke Medicine (P.M.W.B.), University of Nottingham, UK; Department of Neurology (J.G.), University of Texas, Houston Medical School, Houston, Tex; Department of Neurology (W.H.), University of Heidelberg, Germany; University of California and VA Stroke Center (P.L.), San Diego, Calif; National Institute of Neurological Disorders and Stroke (J.R.M.), Bethesda, Md; Miller School of Medicine (R.L.S.), University of Miami, Miami, Fla.

Correspondence to M. Ali, Division of Cardiovascular and Medical Sciences, University Department of Medicine & Therapeutics, Gardiner Institute, 44 Church St, Glasgow G11 6NT, UK. E-mail myzoonali@clinmed.gla.ac.uk

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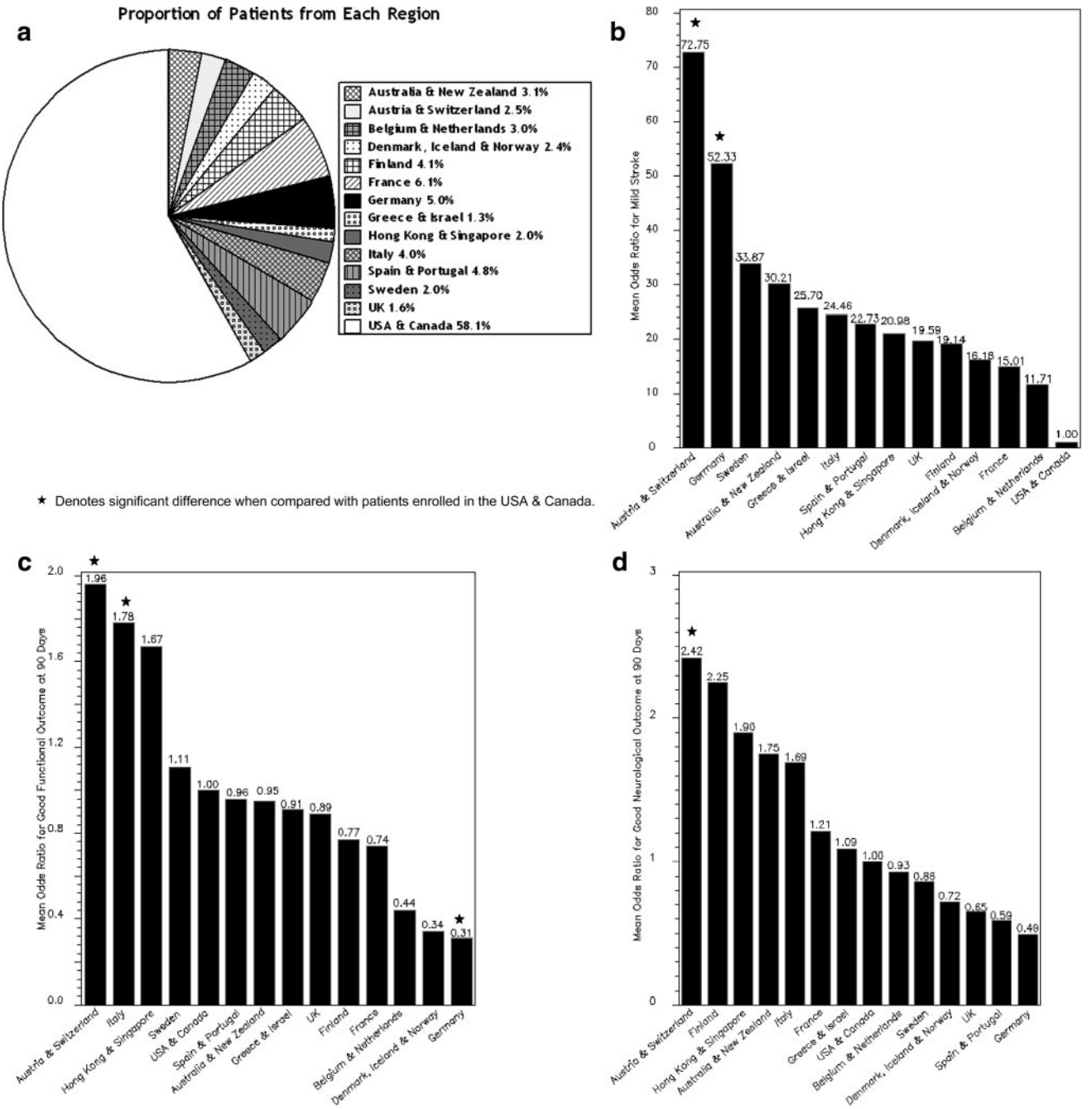

Figure 1. Proportion of patients from each geographic region (a). OR for mild index stroke (NIHSS ≤5) among different regions adjusted for age, medical history, and year of trial enrollment (b). OR for good functional outcome at 90 days (modified Rankin Scale score ≤1) among different regions adjusted for case mix and year of trial enrollment (c). OR for good neurological outcome at 90 days (NIHSS ≤1) among different regions adjusted for case mix and year of trial enrollment (d).

improved outcome.[16] A confounding impact of stroke care on an assessment of geographical variation in outcome should be minimized by using patients treated in this setting. Nevertheless, adjustment of outcome for multiple case mix and service quality variables did not remove substantial differences in functional outcome and death between countries in the Tinzaparin in Acute Ischemic Stroke Trial (TAIST).[17] We intended to examine the impact of geographical location on index stroke severity, stroke outcomes, and mortality after adjusting for case mix, among different trial centers using the Virtual International Stroke Trials Archive (VISTA).[18]

Patients and Methods

We collated anonymous data from VISTA on patients who were recruited into clinical trials across different geographical locations. Anonymity agreements for use of VISTA preclude identification of the trial sources. However, we identified eligible patients who were at least 18 years old, had documented National Institutes of Health Stroke Scale (NIHSS), and modified Rankin Scale score available for baseline and follow-up periods, had experienced an ischemic stroke, previous medical history variables were available, an onset to inclusion time was within 24 hours, and for whom no thrombolysis or active intervention was performed. Variables of interest for our study included baseline NIHSS score, age, sex, medical history, geographical region, modified Rankin Scale score, and NIHSS score

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Table. Baseline Characteristics and Concomitant Diseases

Region	Frequency, n	Frequency, %	Age, Median (IQR)	BNIH, Median (IQR)	Sex, % Male	Hemisphere, % Right	Atrial Fibrillation, % Present	Hypertension, % Present	MI, % Present	Diabetes, % Present
Australia & New Zealand	102	3.1	70 (62–77)	13 (9–19)	56.9	48.0	31.4	64.0	16.3	16.7
Austria & Switzerland	82	2.5	68 (59–77)	10.5 (6–15)	59.8	51.3	20.3	55.4	9.5	18.5
Belgium & Netherlands	99	3.0	71 (63–78)	13 (8–18)	62.6	45.9	38.5	48.4	15.4	14.9
Denmark, Iceland, & Norway	78	2.4	67.5 (57–73)	11 (7–16)	60.3	42.5	11.9	32.2	17.0	5.8
Finland	133	4.1	69 (64–75)	12 (7–18)	51.1	54.7	19.6	32.1	10.7	10.5
France	194	5.9	68 (55–74)	14 (10–19)	62.9	51.9	24.7	54.6	5.2	10.2
Germany	161	4.9	66 (58–72)	12 (7–15)	61.5	64.2	14.18	50.8	9.7	15.5
Greece & Israel	43	1.3	76 (64–81)	12 (7–17)	58.1	55.8	41.5	75.6	9.8	22.0
Hong Kong & Singapore	66	2.0	74 (68–79)	12 (8–18)	48.5	43.9	40.4	66.7	3.5	28.1
Italy	130	4.0	72 (65–78)	12 (7–18)	62.3	45.4	22.1	61.1	6.2	14.4
Spain & Portugal	158	4.8	70 (64–76)	14 (9–19)	55.7	43.6	26.3	48.3	8.5	20.3
Sweden	66	2.0	73 (69–77)	13 (6–19)	74.2	47.7	33.3	43.9	15.8	21.9
UK	53	1.6	71 (64–77)	14 (8–19)	43.4	52.8	35.7	54.8	26.2	10.9
USA & Canada	1919	58.4	72 (63–79)	15 (10–20)	49.4	47.4	25.9	71.7	20.2	24.6

IQR indicates interquartile range; MI, myocardial infarction.

at 90 days. To examine regional influences while accounting for low sample numbers in some regions, countries within a similar geographic location were grouped together into datasets of at least 40 patients. Data from patients enrolled in the USA and Canada were used as a reference against which we compared index stroke severity and neurological and functional recovery in other regions, because this group had the largest sample size and therefore offered the strongest statistical power for comparison.

Statistical Analyses

Our primary outcome measures were the NIHSS scores at baseline and the modified Rankin Scale score, and survival at 90 days after index stroke. We used logistic regression to examine whether the geographical region of trial recruitment was a significant predictor of mild index stroke, defined as NIHSS score at baseline of ≤5. We included age and medical history as covariates in this model. We accounted for potential shifts in treatment patterns over time by including a binary covariate in our logistic regression analyses, representing patient recruitment between 1994 and 1997 or 1998 and 2000, respectively.

We defined good functional outcome at 90 days as attainment of a modified Rankin Scale score of ≤1, and good neurological outcome as attainment of a NIHSS score of ≤1. We performed logistic regression using these functional and neurological outcomes to determine whether recruitment region was a significant predictor of good outcome after accounting for age, initial stroke severity, medical history, and year of trial recruitment. Finally, we used a Cox proportional hazards model to examine whether survival differed among regions after accounting for year of recruitment, initial stroke severity, age, and medical history.

Missing data were handled by imputing the worst possible outcome when the patient had died within the follow-up period. All other missing data were coded as lost to follow-up. All analyses were performed using a SAS 9.1 statistical package.

Results

Demographic Data

We extracted anonymous data on 3284 patients who met the stated eligibility criteria. The majority of patients in this dataset were from USA and Canada (58%), 5% were from Australia, New Zealand, Hong Kong, or Singapore, and 36% were from European countries (Figure 1a). Details of case mix across the different regions are presented in the Table. Median age across the regions ranged from 66 (interquartile range, 58–72) in Germany to 76 (interquartile range, 64–81) in Greece and Israel. Median baseline NIHSS score ranged from 10.5 (interquartile range, 6–15) in Austria and Switzerland to 15 (interquartile range, 10–20) in the USA and Canada. The most frequent stroke risk factor present was hypertension. Greece and Israel had the highest proportion of patients with hypertension (76%) and atrial fibrillation (41%).

We accounted for the possibility that the eligibility criteria of the original trials could confound analyses by examining the distribution of modified Rankin Scale score across regions, stratified by trial source. These distributions revealed that eligibility criteria did not contribute to an overall difference in outcomes among the regions examined.

We first examined the variation in initial stroke severity in patients who were recruited into clinical trials from different regions after accounting for age, medical history, and year of enrollment. Patients who were enrolled in Austria and Switzerland had the mildest index stroke in our sample ($P=0.0001$; adjusted OR [OR] for mild stroke=72.8; 95% CI, 22.0–240.4), closely followed by patients enrolled in Germany ($P=0.01$; adjusted OR for mild stroke=52.3; 95% CI, 15.0–182.9; Figure 1b). In this analysis patients who were recruited after 1998 had more severe index strokes ($P=0.006$; adjusted OR for mild stroke=0.22; CI, 0.07–0.64).

In our analysis set only 3% of patients were lost to follow-up at 90 days. Functional outcome at 90 days after stroke varied by region, even after adjusting for initial stroke severity, age, medical history, and year of enrolment. Patients who were recruited in Austria and Switzerland attained a significantly better functional outcome at 90 days compared

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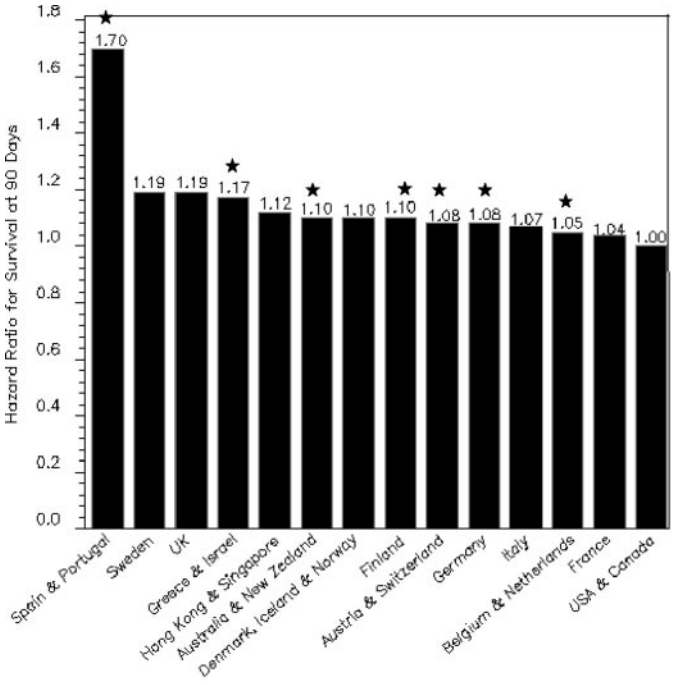

Figure 2. Hazard ratio for survival at 90 days among different regions adjusted for case mix and year of trial enrollment.

★ Denotes significant difference when compared with patients enrolled in the USA & Canada.

with those recruited in USA and Canada ($P=0.023$; adjusted OR for good functional outcome=1.96; 95% CI, 0.90–4.27), closely followed by patients enrolled in Italy ($P=0.036$; adjusted OR for good functional outcome=1.78; 95% CI, 0.85–3.75). Patients recruited in Germany had a significantly worse functional outcome at 90 days ($P=0.013$; adjusted OR for good functional outcome=0.31; 95% CI, 0.13–0.76; Figure 1c). Trial recruitment after 1998 was not a significant predictor of good functional outcome at 90 days ($P=0.42$).

Patients enrolled in Austria and Switzerland had a significantly better neurological outcome at 90 days ($P=0.034$; adjusted OR for good neurological outcome=2.42; 95% CI, 1.08–5.41) when compared with those enrolled in the USA and Canada (Figure 1 d). Likewise, trial recruitment after 1998 was not a significant predictor of good neurological outcome at 90 days ($P=0.87$).

We examined survival at 90 days after acute ischemic stroke to determine if mortality varied between geographical locations after adjusting for case mix. A Cox proportional hazards model showed that patients enrolled in Australia, New Zealand, Austria, Switzerland, Belgium, Netherlands, Finland, Germany, Greece, Israel, Spain, and Portugal had a significantly better survival rate when compared with those enrolled in USA and Canada ($P<0.05$; Figure 2), with those enrolled in Spain and Portugal having the best survival rate in our sample ($P<0.0001$; hazard ratio for survival=1.70; 95% CI, 1.31–2.20).

Discussion

Investigating stroke incidence in different parts of the world increases our understanding of etiology and prevention.[19] Epidemiological studies form the basis for future research;[20] knowledge of disease patterns and regional differences assist the targeting of programs that could help reduce risk factors and distribute resources for stroke management.[21] We aimed to identify region specific differences in index stroke, outcome, and mortality after accounting for case mix.

In our analysis set, patient observations from some countries were underrepresented; therefore, some analyses lacked power. We overcame this by grouping countries together according to geographical location. We recognize that the participating centers may represent some of the more organized hospitals in their country and that this may diminish country-specific differences; however, this strengthens rather than weakens our conclusions as the impact of standard of care on outcome is minimized.

After accounting for initial stroke severity, age, year of recruitment, and medical history, we found that trial recruitment in Austria, Switzerland, and Italy was a significant predictor of good functional outcome at 90 days when compared with the USA and Canada ($P<0.05$). This trend toward better recovery was also reflected in the neurological outcomes of patients recruited in Austria and Switzerland ($P=0.03$). Adjustment for period of trial recruitment revealed a trend for more severe stroke in trials conducted after 1998, with no improvement in functional or neurological outcome when compared with earlier trials. This may be a reflection of the increasing severity of index stroke after 1998, along with the lack of clinical impact of new drugs since the licensing of recombinant tissue plasminogen activator.[22] Moreover, it is possible that the increased use of recombinant tissue plasminogen activator within the 3-hour time window could have led to some selection of patients with more severe cases for trials after 1998. Survival across the different regions varied, with patients enrolled in Australia, New Zealand, Austria, Switzerland, Belgium, Netherlands, Finland, Germany, Greece,

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Israel, Spain, and Portugal all reporting a significantly better survival rate than those enrolled in USA and Canada.

Our dataset did not contain any patients who were enrolled in the Far East or South America. Our findings are therefore only applicable to a subset of stroke trial patients; these are typical of internationally conducted trials over the last decade. Disparity in outcome could be partially explained by variations in stroke care[17] per capita expenditure on health care, health care policy, and availability of rehabilitation resources among the regions examined. It has been previously documented that dedicated stroke units can reduce disability.[16] For example, the Scandinavian stroke unit model combines both acute and rehabilitation stroke units nationwide, and this was reflected in low case fatality.[23] However, not all stroke patients have access to these units.[17] Despite the established benefits, it is still uncommon for patients to be admitted into stroke units in many Italian regions; patients are most commonly admitted into general wards.[24] The proportion of patients who receive brain imaging, neurosurgery, physiotherapy, speech therapy, and occupational therapy[25] and the degree of governmental expenditure on health care can influence outcome. For example, the United States government in 2003 spent USD $2548 per capita on health care. In contrast, government expenditure on health care in Singapore in 2003 was USD $348.[26] Distribution of health care workers also differ among regions, with Belgium reporting a greater number of physicians per 1000 people (4.49) compared with Canada (2.13).[27] These factors in combination can impact the standards of care available and contribute to disparity. We lacked data on the standard of stroke care available to each patient and therefore could not consider this as a covariate in this analysis.

Although we noted a variation in functional outcome at 90 days between different regions, we are unable to draw inferences regarding its cause. Data on socioeconomic status, a predictor of stroke both in poor and developed countries,[28–30] were not available and may have influenced outcome. Socioeconomical factors are complex in their nature and influence both risk factors and standards of care.[28,31] Risk factors vary across the lifespan and show regional and international variations.[21] Recording of patient lifestyle is imperfect in its nature and, particularly in our series, some lifestyle and social factors that may have impacted outcome, such as the degree of family support available,[32] were not recorded. This may have confounded our results. In addition, factors such as ethnicity[33–35] and stroke subtype may have had an impact on outcome in our sample. Both stroke subtype and ethnicity were not included as covariates in our analyses but should be taken into account when interpreting outcome.

We found significant differences in mortality in many European countries compared with the USA and Canada. This finding was supported by Asplund et al,[12] Gray et al,[36] and Holland.[37] Both Grieve et al[38] and Holland[37] reported that stroke outcome was worst in the UK. Our findings are congruent with these investigations. We found no significant difference in the outcome or survival of patients enrolled in the UK compared with those recruited in the USA and Canada, which had the worst survival rate in our study. Our mortality results could also be explained by the use of optimal patient selection during the trial recruitment phase; the trials may have excluded patients with a poorer prognosis.

Sudlow et al[19] reported that comparisons of stroke incidence in different regions are only meaningful if investigations use standard definitions and methods. The strengths of our analysis lay in the robust data collection protocols implemented within VISTA and the depth of patients variables available. However, data were extracted from trials that were primarily concerned with the treatment of ischemic stroke using a novel therapy and, as such, data collection was not specifically tailored for an epidemiological investigation. Numerous socioeconomic factors that impact stroke recovery were not recorded within VISTA.

We conclude that recruitment in recent trials was associated with more severe index stroke, but not with significant difference in outcome when compared with earlier trial enrolment. Variation in stroke outcome across different geographical regions was evident after adjustment for case mix. Patients recruited in the USA and Canada had the worst index stroke severity. Patients recruited in Austria and Switzerland had the best functional and neurological outcome at 90 days after adjusting for case mix. Patients enrolled in Spain and Portugal had the best survival rate. Because the differences in outcome between countries are larger than the expected treatment effects of some interventions, the findings here echo the need for rigorous randomization practices for active and control groups within multinational trials to avoid false treatment effects in regions where placebo-treated patients achieve a good outcome after accounting for case mix.[39] Our findings may be pertinent to trials that do not include ethnicity or country of recruitment as a covariate in analyses. We consider it unlikely that these findings would explain discrepant results between consecutive trials of the same drugs, for example, the Lubeluzole North American trial,[40] and the subsequent neutral European Lubeluzole trial,[41] or the failure of SAINT II compared with SAINT I.[42] These trials randomized patients within centers or countries and some included geographical site or country as a covariate in analysis;[42,43] overall, severity and outcomes were similar between trials.

Further investigation of the causes of regional differences in outcome would be beneficial particularly in developing countries that are underrepresented within VISTA. This could include an investigation of stroke subtypes, time from stroke onset to treatment, the underlying socioeconomic influences, and access to and use of health care resources within countries that have reported a poorer outcome. Additionally, more emphasis on risk factor reduction, secondary prevention, and rehabilitation may redress the changes in stroke severity and outcome observed in our time course analysis.

Appendix

VISTA Steering Committee: Lees KR (chair), Bath PMW, Bluhmki E, Claesson L, Curram J, Davis SM, Diener HC, Donnan GA, Fisher M, Gregson BA, Grotta J, Hacke W, Hennerici MG, Hommel M, Kaste M, Lyden P, Marler J, Muir K, Sacco RL, Shuaib A, Teal P, Wahlgren NG, Warach S, and Weimar C.

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Disclosures

VISTA is a not-for profit collaboration of researchers from academia and commercial organizations. The VISTA Steering Committee members have each contributed to the organization of contributing trials and when these involved industry support have acknowledged that within the original publications. No author has any additional conflict of interest to declare in relation to this work, which was not externally supported.

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