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## **Stroke Outcome in Clinical Trial Patients Deriving from Different Countries**

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**Conflicts of interest**

VISTA is a not-for profit collaboration of researchers from academia and commercial organisations. The VISTA steering Committee members have each contributed to the organisation of contributing trials and where 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.

**Cover Title: Stroke Outcome in Patients from Different Countries**

**Tables included:**

**Table 1: Baseline characteristics and concomitant diseases**

**Figures included:**

**Figure 1:** **a)** Proportion of Patients from Each Geographic Region **b)** Odds ratio for mild index stroke (NIHSS  $\leq 5$ ) amongst different regions (adjusted for age, medical history and year of trial enrolment) **c)** Odds Ratio for good functional outcome at 90 days (mRS  $\leq 1$ ) amongst different regions (adjusted for case mix and year of trial enrolment) **d)** Odds Ratio for good neurological outcome at 90 days (NIHSS  $\leq 1$ ) amongst different regions (adjusted for case mix and year of trial enrolment).

**Figure 2:** Hazard ratio for survival at 90 days amongst different regions, (adjusted for case mix and year of trial enrolment).

**Word Count:** 4637

**Keywords:** Acute Care, Clinical trials, Database, Epidemiology, Outcomes

## **Abstract**

**Background:** 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 analysed 3284 patients from the Virtual International Stroke Trials Archive (VISTA). We used logistic regression to examine the incidence of mild index stroke, functional (mRS) and neurological (NIHSS) 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 & Canada had the most severe index strokes. Those recruited in Austria & Switzerland had the best functional and neurological outcomes at 90 days ( $p < 0.05$ ), while 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 & 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 ischaemic stroke clinical trials over the last 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.

## **Background**

Worldwide, stroke is one of the leading causes of mortality and morbidity. There are prominent variations in stroke incidence and outcome amongst countries (1-3). Stroke incidence in Asia is generally higher than in the US (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 five 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 suffer more severe strokes, from which the recovery is poorer.

These differences are not confined to the East-West European axis, but are also found amongst 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., (2003) 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 (12). 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 centres usually deliver the highest standards of care

in the country and are associated with improved outcome (16). A confounding impact of stroke care on an assessment of geographical variation in outcome should be minimized by utilizing 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 Ischaemic 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, amongst different trial centres using the Virtual International Stroke Trials Archive (VISTA) (18).

## **Methods**

We collated anonymised 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 Score (mRS) available for baseline and follow up periods, had experienced an ischaemic stroke, where previous medical history variables were available, an onset to inclusion time of 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, mRS and NIHSS score at 90 days. In order to examine regional influences, whilst 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 & Canada were used as a reference against which we compared index stroke severity, neurological and functional recovery in other

regions, as 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 mRS, NIHSS and survival at 90 days following 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  $\leq 5$ . 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 mRS score of  $\leq 1$ , and good neurological outcome as attainment of a NIHSS score of  $\leq 1$ . 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 amongst regions after accounting for year of recruitment, initial stroke severity, age, and medical history.

Missing data were handled by imputing the worst possible outcome where 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 anonymised data on 3284 patients who met the stated eligibility criteria. The majority of patients in this dataset were from USA & 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 Table 1. Median age across the regions ranged from 66 (IQR [58, 72]) in Germany, to 76 (IQR [64, 81]) in Greece & Israel. Median baseline NIHSS score ranged from 10.5 (IQR [6, 15]) in Austria & Switzerland, to 15 (IQR [10, 20]) in the USA & 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 original trials' eligibility criteria could confound analyses by examining the distribution of mRS across regions, stratified by trial source. These distributions revealed that eligibility criteria did not contribute to an overall difference in outcomes amongst 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 enrolment. Patients who were enrolled in Austria & Switzerland had the mildest index stroke in our sample ( $p=0.0001$ , adjusted odds ratio for mild stroke=72.8, 95% confidence interval [22.0, 240.4]), closely followed by patients enrolled in Germany ( $p=0.01$ , adjusted odds ratio for mild stroke=52.3, 95% Confidence Interval [15.0, 182.9]) (Figure 1b). In this analysis patients who were recruited after 1998 had more severe index strokes ( $p= 0.006$ , adjusted odds ratio for mild stroke =0.22, confidence interval [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 & Switzerland attained a significantly better functional outcome at 90 days compared with those recruited in USA & Canada ( $p=0.023$ , adjusted odds ratio for good functional outcome=1.96, 95% confidence interval [0.90, 4.27]), closely followed by patients enrolled in Italy, ( $p=0.036$ , adjusted odds ratio for good functional outcome=1.78, 95% confidence interval [0.85, 3.75]). Patients recruited in Germany had a significantly worse functional outcome at 90 days ( $p=0.013$ , adjusted odds ratio for good functional outcome=0.31, 95% confidence interval [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 & Switzerland had a significantly better neurological outcome at 90 days ( $p=0.034$ , adjusted odds ratio for good neurological outcome= 2.42, 95% confidence interval [1.08, 5.41]) when compared with those enrolled in the USA & Canada (figure 1d). 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 following acute ischaemic stroke in order 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 & Canada ( $p<0.05$ ) (Figure 2), with those enrolled in Spain & Portugal having the best survival rate in our sample ( $p<0.0001$  hazard ratio for survival=1.70, 95% confidence interval [1.31, 2.20]).

## Discussion

Investigating stroke incidence in different parts of the world increases our understanding of aetiology and prevention (19). Epidemiological studies form the basis for future research (20); knowledge of disease patterns and regional differences assist the targeting of programs which 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 under-represented, therefore some analyses lacked power. We overcame this by grouping countries together according to geographical location. We recognise that the participating centres may represent some of the more organised 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 minimised.

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 & Canada ( $p < 0.05$ ). This trend towards better recovery was also reflected in the neurological outcomes of patients recruited in Austria & 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 rt-PA (22). Moreover, it is possible that the increased use of rt-PA within the 3 hour time window could have led to some selection of more severe

patients for trials after 1998. Survival across the different regions varied, with patients enrolled in Australia, New Zealand, Austria, Switzerland, Belgium, Netherlands, Finland, Germany, Greece, Israel, Spain and Portugal all reporting a significantly better survival rate than those enrolled in USA & 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 amongst 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 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 amongst 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 socio-economic status, a predictor of stroke both in poor and developed countries (28-30), were not available and may have influenced outcome. Socio-economical 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 & Canada. This finding was supported by Asplund et al., (2003) (12) Gray et al., (36) and Holland (1991) (37). Both Grieve et al., (2001) (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 & 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., (1997) (19) reported that comparisons of stroke incidence in different regions are only meaningful if investigations utilise 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 ischaemic stroke using a novel therapy, and as such, data collection was not specifically tailored for an epidemiological investigation. Numerous socio-economic 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 & Canada had the worst index stroke severity. Patients recruited in Austria & 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. Since the differences in outcome between countries are larger than the expected treatment effects of some interventions, the findings here echo the need for rigorous randomisation practices for active and control groups within multinational trials so as 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 which 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 randomised patients

within centres 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 which are under represented within VISTA. This could include an investigation of stroke subtypes, time from stroke onset to treatment, the underlying socio-economic influences, access to and use of health care resources within countries which 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.

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## Tables

**Table 1: Baseline characteristics and concomitant diseases**

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

<b>UK</b>	53	1.6	71 [64, 77]	14 [8, 19]	43.4	52.8	35.7	54.8	26.2	10.9
<b>USA &amp; Canada</b>	1919	58.4	72 [63, 79]	15 [10, 20]	49.4	47.4	25.9	71.7	20.2	24.6

b)

**Figures included:**

**Figure 1:** **a)** Proportion of Patients from Each Geographic Region **b)** Odds ratio for mild index stroke ( $\text{NIHSS} \leq 5$ ) amongst different regions (adjusted for age, medical history and year of trial enrolment) **c)** Odds Ratio for good functional outcome at 90 days ( $\text{mRS} \leq 1$ ) amongst different regions (adjusted for case mix and year of trial enrolment) **d)** Odds Ratio for good neurological outcome at 90 days ( $\text{NIHSS} \leq 1$ ) amongst different regions (adjusted for case mix and year of trial enrolment).

**Figure 2:** Hazard ratio for survival at 90 days amongst different regions, (adjusted for case mix and year of trial enrolment).