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HEALTH CARE RESOURCE USE AND STROKE OUTCOME

Multinational Comparisons within the GAIN International trial

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Abstract

Background and Purpose: Outcome in patients hospitalized for acute stroke varies considerably between populations. Within the framework of the GAIN International trial, a large multicenter trial of a neuroprotective agent (gavestinel, glycine antagonist), stroke outcome in relation to health care resource use has been compared in a large number of countries, allowing for differences in case mix.
Methods: This substudy includes 1,422 patients in 19 countries grouped into 10 regions. Data on prognostic variables on admission to hospital, resource use, and outcome were analyzed by regression models.
Results: All results were adjusted for differences in prognostic factors on admission (NIH Stroke Scale, age, comorbidity). There were threefold variations in the average number of days in hospital/institutional care (from 20 to 60 days). The proportion of patients who met with professional rehabilitation staff also varied greatly. Three-month case fatality ranged from 11% to 28%, and mean Barthel ADL score at three months varied between 64 and 73. There was no relationship between health care resource use and outcome in terms of survival and ADL function at three months. The proportion of patients living at home at three months did not show any relationship to ADL function across countries.
Conclusions: There are wide variations in health care resource use between countries, unexplained by differences in case mix. Across countries, there is no obvious relationship between resource use and clinical outcome after stroke. Differences in health care traditions (treatment pathways) and social

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context seem to be major determinants of resource use. In making comparisons between countries, great care should be exercised in using outcome variables as indicators of quality of stroke care.

Keywords: Health care resource use, Length of hospital stay, Survival, Functional outcome

Stroke places a heavy burden not only on the person affected but also on the family, the health care system, and the society at large. Among people over 45 years of age, stroke is the leading cause of disability-adjusted life years (DALYs) lost worldwide (14;15). In affluent countries, stroke ranks third, behind ischemic heart disease and depression, as a cause of DALYs lost with all age groups included (15). The burden on the health care system and social services includes hospitalization, supportive and residential care, and rehabilitation, with hospitalization and other institutional care representing a major component of the cost burden, particularly over a shorter time frame (5–7;20;26). The provision of stroke care differs markedly between countries and national regions (3;9;22;25). Accordingly, estimates of resource use and cost of stroke have reported large variations between different countries. Much of this variation can be ascribed to differences in the costs included (for instance, whether or not indirect costs have been taken into account) and different methodologies used to collect data (6;7).

Stroke outcome also varies very considerably between regions and countries. In the WHO MONICA Project, in which a uniform methodology has been applied in 15 populations in Europe and China, early case fatality varied threefold between countries (23). Similar large differences in case fatality during the acute phase were observed in a European Union survey of stroke management, and the very large differences were only partly explained by differences in case mix (24;25). The European Stroke Care Inventory found higher 30-day case fatality in Eastern European countries compared with Western European countries (1). More than twofold variations in six-month case fatality were observed in the International Stroke Trial, and the differences persisted after adjustment for case mix (21).

For persons surviving a stroke, few multinational comparisons of stroke outcome using uniform data collection procedures have been reported (3;9;21). Different functional outcomes may depend on age at stroke, co-morbidity, severity of the stroke, and possibly also gender (10). Both survival and functional outcome may also be affected by medical interventions in the acute phase and early rehabilitation, most convincingly shown in randomized trials of stroke units vs. stroke care in general wards (11).

In this report, we use data collected within the framework of a multinational clinical trial of gavestinel, a glycine antagonist, in patients with acute ischemic stroke (12) to describe regional/national differences in health care resource use, survival, and functional outcome. Possible explanatory factors for these differences are explored, such as patient differences in baseline characteristics and stroke severity, the duration of treatment in hospital and use of other care in hospital, and posthospital discharge disposition.

METHODS

These data were collected as part of a multinational clinical trial conducted in 21 countries to evaluate the safety and efficacy of adding treatment with gavestinel (GV150526), a newly developed neuroprotective therapy against cerebral damage, to standard care after acute ischemic stroke (12). There were no significant differences between treatment groups in survival or functional outcomes at three months after stroke for patients with confirmed ischemic stroke (12). Therefore, data from the active treatment and placebo groups have

been pooled in the present study when comparing the three-month burden of stroke care and treatment across national regions.

The GAIN International study, including collection of data on resource use, was approved by all local or national ethical committees concerned. Written or witnessed oral consent to take part in study was obtained for all participants, either from the patient or from his/her representative.

Previously functionally independent persons presenting to hospital within six hours of onset of symptoms of a moderately severe stroke were entered in the study, unless subarachnoid hemorrhage was diagnosed or suspected. A total of 1,804 patients were randomized and admitted to hospital for a minimum three-day ward stay. All patients had CT or MRI scan within first 18 hours to confirm stroke type (ischemic or hemorrhagic). The ward type and other care in hospital and after discharge were at the discretion of the treating clinician. Patients were assessed at hospital discharge or seven days after randomization and followed at one and three months after discharge for survival and functional outcome as assessed by the Barthel ADL index (13). Information on residence, employment status, and paid and unpaid home assistance were collected both at baseline and at three-month follow-up. Data on health care resource use, such as length of stay in hospital, rehabilitation facility or assisted living environments, number of rehabilitation sessions as inpatient and outpatient, and number of outpatient visits to a physician, were also collected at the three-month follow-up.

The present study was restricted to patients in the GAIN International study that had ischemic stroke. Due to the small numbers of patients (22 and 11, respectively) and no obvious grouping partner(s), South Africa and Israel were not included in further comparisons. To improve the statistical power, some of the remaining 19 countries with a relatively small number of patients included in the study were grouped together, resulting in 10 regions/countries (Table 1). The grouping was based on geography (neighboring countries), and on similarities in OECD data on health indicators (life expectancy), health care resources (number of inpatient beds per capita, expenditure on health per capita), and similar social services for elderly and disabled people (16). Each of the 10 regions/countries was represented by 4–30 different hospitals (mean 17). Primary intracerebral hemorrhage was

Table 1. Patient Characteristics on Admission to Hospital for Acute Stroke by National Region

Country/region	*N*	Age, proportion >75 years (%)	Male sex (%)	Concomitant disorders			Stroke severity (NIHSS at baseline) mean ± SD
				Diabetes (%)	Atrial fibrillation (%)	Previous myocardial infarction (%)	
Australia/New Zealand	137	34	56	21	32	15	14.1 ± 6.7
Austria/Germany	158	39	57	27	28	14	10.0 ± 5.3
Belgium/Netherlands	294	40	56	17	29	17	13.7 ± 6.2
Denmark/Finland/ Iceland/Norway/ Sweden	203	38	59	10	28	17	12.8 ± 5.8
France	142	32	63	10	27	16	14.7 ± 5.9
Greece	72	39	58	19	38	6	12.0 ± 6.1
Hong Kong/Singapore	85	32	49	38	28	14	12.5 ± 7.8
Italy	117	45	56	17	26	12	11.8 ± 6.2
Portugal/Spain	128	46	52	26	37	4	14.6 ± 6.1
United Kingdom	86	38	52	8	29	22	13.6 ± 6.5

present in 333 patients. In 16 patients, the drug was not given and participation in the trial was terminated early. After these exclusions, 1,422 patients with acute ischemic stroke remained in the present study.

Stroke outcomes of survival, survivors' living setting at three months, and mean Barthel ADL score were compared across regions. Regions were first compared on observed outcomes, then outcomes after adjusting for differences in patient case mix, and finally outcomes after adjusting for differences in hospital duration as well as case mix. The variables used to adjust for case mix were sex, age, severity of stroke on admission to hospital (measured by NIH Stroke Scale) and comorbidity (atrial fibrillation, diabetes, and history of myocardial infarction). In some models, outcome was also adjusted for length of hospital stay, as described in the appropriate tables. Regression procedures were used to select meaningful explanatory variables. Thus, for each outcome, stepwise regression (logistic regression for categorical outcomes) was used to select variables that contribute significantly to variability between regions, and the overall effect of region was tested after entering all meaningful explanatory variables. Models were fitted, and adjusted least squares mean estimates were calculated for quantitative outcomes (mean Barthel score) using SAS procedure GLM. SAS was also used for logistic regression models that were fitted for binary outcomes (survival, living at home at three months). The levels of statistical significance were adjusted for multiple comparisons.

RESULTS

Case Mix

Table 1 displays the patient case mix on admission to hospital for acute stroke in each of the 10 regions/countries. Whereas gender distribution and the severity of stroke showed only small or moderate differences between the regions/countries, there were considerable variations in age structure and presence of comorbidity. Therefore, in the following analyses, outcome data are presented both unadjusted and adjusted for case mix on admission to hospital.

Health Care Resource Use

In Figure 1, the regions/countries are ranked by the mean time survivors spent in institutional care during the first three months after stroke. The total number of hospital days was found to be statistically significantly different between regions (p value $<.0001$). The duration of hospital stay was about twice as long in the UK and Belgium/The Netherlands compared with the Mediterranean countries (Greece, Italy, and Portugal/Spain). When all institutional care during the first three months was combined, there were, after adjustment for case mix at onset of stroke (sex, age, NIH Stroke Scale at baseline, atrial fibrillation, diabetes, and previous myocardial infarction), threefold differences between the countries with the shortest (Greece 20.3 days) and the longest institutional stay (Austria/Germany 60.6 days and France 60.0 days).

As shown in Table 2, regions were also found to differ significantly in the proportion of patients to receive inpatient and outpatient rehabilitation (p value $<.0001$). The proportions treated in hospital by physiotherapists, occupational therapists, and speech therapists were considerably smaller in France, Greece, Italy, and Portugal/Spain than in the other participating regions/countries.

After discharge from hospital, there were also very marked differences between regions/countries in the proportion of survivors who had access to outpatient rehabilitation during the period from discharge to follow-up at three months (Table 2). Physiotherapy and speech therapy were provided more often in Belgium/The Netherlands and Australia/

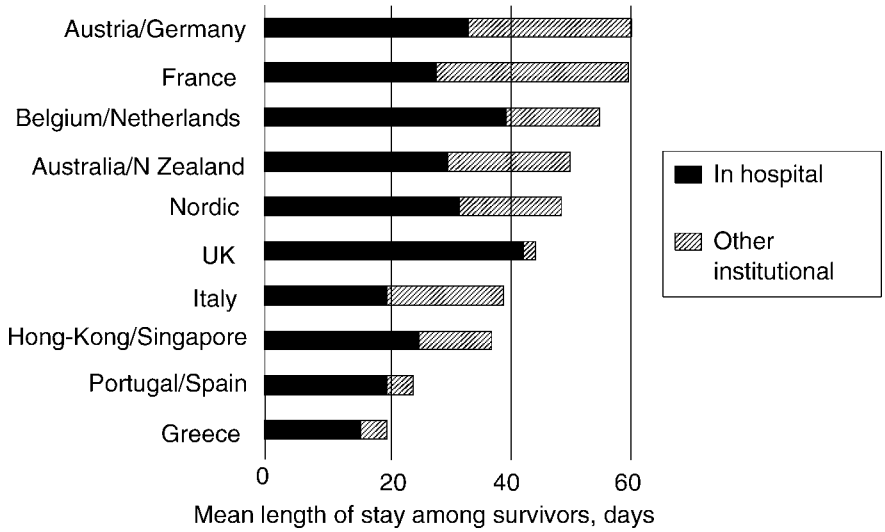

Figure 1. Mean length of initial hospital stay and other institutional stay during the first three months after stroke by region/country. Data were restricted to patients surviving the first 90 days and were adjusted for differences in case mix on inclusion into the GAIN International trial.

New Zealand than in the other regions/countries. Outpatient occupational therapy was nonexistent in the Greek and Italian centers, whereas more than half of the survivors were treated by an occupational therapist as outpatients if they had been discharged from a hospital in Australia/New Zealand.

Outcome in Relation to Case Mix and Health Care Resource Use

There was a statistically significant difference in survival at three months across regions (Table 3) that remained after adjustment for the case mix of patients (p value =.0001; variables that contributed significantly to the model are given in the table) as well as after adjustment for both case mix and duration of the initial hospital stay (p value =.0001).

Table 2. Inpatient and Outpatient Rehabilitation

	Percentage of patients with inpatient			Percentage of patients with outpatient		
	O.T./ Physio (%)	Speech therapy (%)	Other therapy (%)	O.T./ Physio (%)	Speech therapy (%)	Other therapy (%)
Australia/New Zealand	93	81	60	73	25	14
Austria/Germany	78	41	12	28	4	4
Belgium/Netherlands	85	54	9	72	32	5
Denmark/Finland/Iceland/ Norway/Sweden	77	22	7	47	10	6
France	54	19	4	39	14	5
Greece	44	1	0	55	7	5
Hong Kong/Singapore	88	62	0	42	14	0
Italy	47	16	3	32	13	1
Portugal/Spain	57	7	2	49	8	0
United Kingdom	86	58	10	35	17	4

Table 3. Survival to Three Months

Country/region	*N*	Survival to three months		
		Observed (%)	Adjusted for case mix[a]	Adjusted for case mix, hospital LOS[b]
Australia/New Zealand	137	87	89	88
Austria/Germany	158	85	80	78
Belgium/Netherlands	294	77	79	74
Denmark/Finland/Iceland/ Norway/Sweden	203	78	77	78
France	142	71	72	74
Greece	72	82	80	86
Hong Kong/Singapore	85	89	89	91
Italy	117	82	81	86
Portugal/Spain	128	80	85	90
United Kingdom	86	79	80	75

[a] Adjusted for case mix (age, NIH Stroke Scale at baseline, atrial fibrillation, prior myocardial infarction.
[b] Adjusted for case mix as well as total number of days in initial hospitalization. LOS, length of stay.

When compared with France (lowest survival), survival was significantly higher in Italy, Portugal/Spain, Australia/New Zealand, and Hong Kong/Singapore.

For patients surviving to three months, the functional outcomes shown as categories of the Barthel score and the proportion of patients living at home at three months are shown in Table 4. There was a considerable variation in mean Barthel scores at follow-up, ranging from 59 to 73 points. After adjustment for case mix at onset of stroke (variables that contributed significantly to the model are given in the table), this variation was considerably reduced (64 to 73 points) and did not reach statistical significance (p value $=.255$). On the other hand, there was a statistically significant (p value $<.0001$) difference in place of living at three months across regions with the lowest proportion of surviving patients

Table 4. Stroke Survivor Outcomes at Three Months: Mean Barthel ADL Scores and Proportion Living at Home

Country/region	*N*	Barthel ADL score, mean points		Proportion of patients living at home at 3 months	
		Observed	Adjusted for case mix[a]	Observed (%)	Adjusted for case mix[b] (%)
Australia/New Zealand	119	70	73	60	63
Austria/Germany	135	73	64	66	58
Belgium/Netherlands	227	64	67	49	52
Denmark/Finland/Iceland/ Norway/Sweden	159	73	71	59	58
France	101	70	71	56	57
Greece	59	71	68	95	92
Hong Kong/Singapore	76	70	69	78	76
Italy	96	72	70	80	78
Portugal/Spain	102	59	67	74	80
United Kingdom	68	71	72	69	70

[a] Adjustment variables chosen by logistic regression forward selection were age, baseline NIH Stroke Scale score, and diabetes.
[b] Adjustment variables chosen by logistic regression forward selection were age, baseline NIH Stroke Scale score, and history of myocardial infarction.

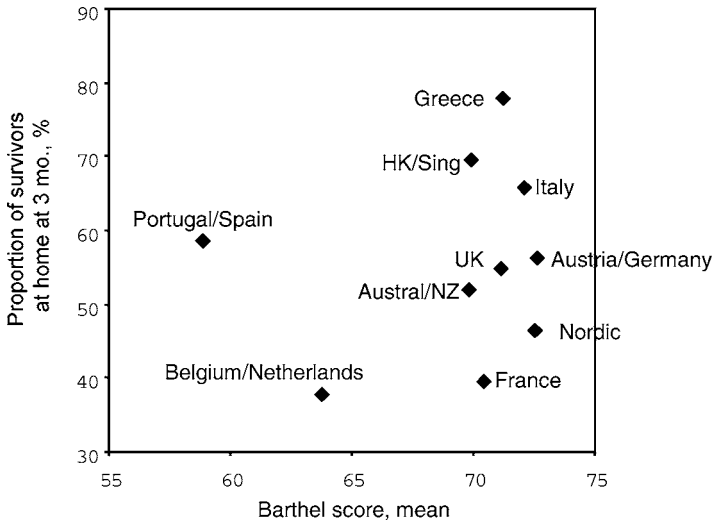

Figure 2. Relationship between mean Barthel score and the proportion of surviving patients living at home at three months follow-up. Unadjusted data.

living at home in Belgium/The Netherlands and the highest proportion in Greece (Table 4). There was, however, no relationship at all between functional outcome (Barthel index) and the proportion of survivors living at home three months after their stroke (Fig. 2). With the same mean Barthel index (unadjusted), the proportion living at home ranged from 39% in France to 78% in Greece. In Portugal/Spain, with the poorest functional outcome, the proportion at home at three months was considerably higher than in the Nordic countries with the highest mean Barthel score at follow-up.

Across regions/countries, functional outcome in survivors measured as Barthel score at three months adjusted for case mix did not correlate with resource use in terms of length of initial hospital stay, also adjusted for case mix (Fig. 3, left panel), or total time spent in

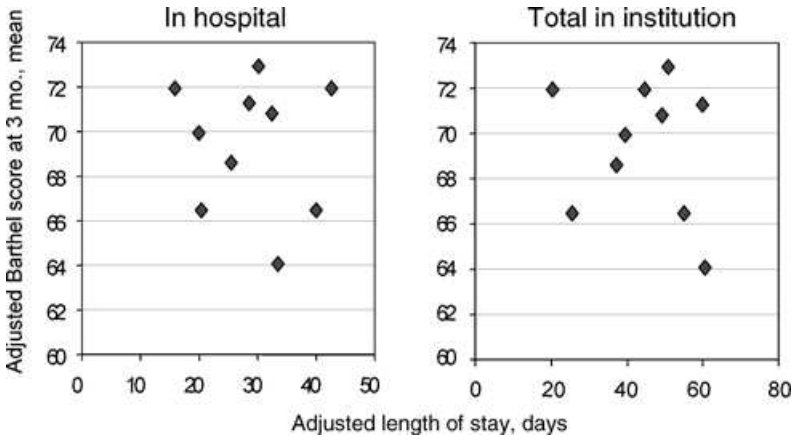

Figure 3. Relationship between length of initial hospital stay (left panel) or total length of institutional stay (right panel), both adjusted for differences in case mix at onset of stroke, and mean Barthel index at three months' follow-up, adjusted for case mix. The variables used for adjustment of case mix were sex, age, stroke severity on admission to hospital, presence of atrial fibrillation and diabetes, and history of myocardial infarction.

institutional care (Fig. 3, right panel). For instance, with the same length of hospital stay (20 days), mean Barthel score at follow-up ranged from 55 in Portugal/Spain to 71 in Italy.

DISCUSSION

To make multinational comparisons of health care resource use and outcome in patients presenting with ischemic stroke, we have used data collected within a setting of a three-month clinical trial. The strengths of the study include (1) the prospective data collection with uniform predefined criteria for various type of resources used, and (2) the careful clinical assessment of all patients at entry into the study and during follow-up, which made it possible to perform detailed adjustments for differences in case mix. The GAIN International trial was conducted to the highest standards and, despite the failure to demonstrate any beneficial effects of the glycine antagonist gavestinel, it has been regarded as a model stroke trial (8).

The present results may not be entirely representative for the general stroke population or for the care of stroke patients in the participating countries. First, the GAIN International study protocol excluded patients with mild and very severe symptoms at onset. Second, participation in a clinical trial may sometimes preclude very early discharge from hospital because of the need to collect follow-up data. Third, there may be intangible reasons for patients in a clinical trial to receive care that is different from routine stroke management. Fourth, centers participating in an international randomized trial on acute stroke are not necessarily representative of their regions/countries. It is reasonable to assume, for instance, that the intensity of rehabilitation is greater for centers that participated in GAIN International than the average for each region/country. However, the large number of participating centers (average 17 per region/country) reduces the risk that a single nonrepresentative center affects the results from a particular region/country. Combining some of the countries, each with a limited number of patients, into regions serves the same purpose. Geographically neighboring countries with similar health care systems were grouped together.

In all estimates of the costs of stroke, the dominant component, by far, is hospital and institutional care, in particular during the first months after stroke (3;6;7;20). Other direct costs, such as those for currently available drugs, outpatient visits, and social services contribute a relatively small share. Also indirect costs incurred by early death, early retirement, and sickness benefits play a minor role early after stroke, because most patients are elderly (20). The straightforward approach used in this study to compare health care resource use between regions/countries by length of hospital and other institutional care, therefore, covers a very large proportion of the total costs. Measuring the input of rehabilitation staff should, in the present study, be regarded as reflecting access and ambitions in an important component of stroke management, rather than being an important contributing factor to total costs.

Statistically significant differences between national regions were found in patient survival, which remained after adjustment for age, stroke severity, risk factors, and duration of stay in initial hospitalization. After adjustment for prognostic factors at entry into the trial, three-month case fatality was more than twice as high in France, Belgium/Netherlands, and the UK compared with regions/countries with the lowest case fatality rate (Australia/New Zealand, Portugal/Spain, and Hong Kong/Singapore). Previous direct comparisons based on hospital- based series of stroke patients (9;25) and patients participating in clinical trials (3;4;21) have consistently indicated that case fatality is high in the UK when compared with other Western countries, even after adjustment for known prognostic factors. In contrast to the present findings, case fatality has been low in the Nordic countries in previous international comparisons (9;21;23), and our observations of a relatively high case fatality in France and Belgium/Netherlands have not been documented in other studies.

The very low case fatality rates observed in some of the regions/countries, particularly Hong-Kong/Singapore, Portugal/Spain, and Australia/New Zealand are noteworthy and encouraging. This finding may well reflect excellence in stroke care, but other explanations must also be considered. There may be differences in the natural history of ischemic stroke or case mix that are not reflected by prognostic indictors measured in the present trial (age and sex, stroke severity as measured by the NIH scale, and comorbidity). For instance, it has been reported that a high proportion of patients with ischemic stroke have lacunar infarcts in East Asian populations (19) compared with Caucasian populations (18). This finding may affect the prognosis independently of the severity of neurological symptoms at onset as measured by the NIH scale. As another putative explanation, there may have been differences in the socioeconomic of the stroke patients between the regions with effects on the clinical course. In some regions/countries with private hospitals participating in the GAIN International trial, there may have been a selection of relatively affluent patients, whereas in countries with publicly financed health care systems patients may have been more unselected. It should be pointed out, however, that it has been more difficult to demonstrate an effect of social class on the clinical course of stroke than of myocardial infarction (17).

As discussed in detail by Weir et al. (21), it is unlikely that very large variations in case fatality (as in the International Stroke Trial) can be explained solely by variations in the quality of stroke care. Much of the variation can probably be attributed to differences in unmeasured baseline variables. There is also the possibility that differences in diagnostic criteria and detection of comorbidity (such as diabetes and previous myocardial infarction) may have influenced, to some extent, the case mix adjusted case fatality rates.

For patients surviving to three months, functional outcome measured by the Barthel ADL index was shown to vary considerably between regions/countries, although less so after adjusting for the patient case mix at onset of stroke. Among interventions in the acute phase of stroke, dedicated stroke units have been best documented to affect functional outcome after stroke (11). To what extent the apparently good functional outcome in some regions in the present study can be ascribed to good access to stroke units cannot be determined, because data on the proportions of patients that were cared for in stroke units were not systematically collected.

In some countries, particularly in Greece, Portugal, and Spain, a large proportion of surviving patients were managed at home by their families, despite being severely ADL-dependent, whereas in the Nordic countries and France, these patients were usually in institutional care. Comparing costs for institutional care and home care by families is notoriously difficult. The limited data available in the scientific literature suggest, however, that costs for home and institutional care for patients with severe disability after stroke are of similar order of magnitude (2). Our results agree with observations in the multinational lubeluzole trials (3;4) in that a relatively high proportion of patients are in institutional care at three months follow-up in the Nordic countries and in Austria/Germany. The most evident difference between the GAIN International and the lubeluzole trials were observed for France, with a high proportion of patients in institutional care at three months in our study but relatively low proportion in the lubeluzole studies. The two lubeluzole trials did not recruit patients in the countries with a very low use of institutional care in the present study (Greece, Portugal, and Spain).

There was no apparent relationship across regions between resource use, in terms of length of hospital or other institutional stay, and functional outcome. Similarly, there was no relationship between mean ADL proficiency and the proportion living at home at three months after stroke. Together, these observations indicate that differences in health care culture/traditions are major determinants of the extent of resources used for stroke care, rather than the patients' condition. For instance, in-hospital rehabilitation is approved

before starting in fixed sets of multiples of 15 working days in Germany, whereas the length of in-hospital rehabilitation is more flexible and dependent on the patient's progress in many other countries.

The access to outpatient rehabilitation and institutional care for severely disabled persons is another obvious determinant of total use of resources. Cost-effectiveness comparisons of stroke care between countries with different health care systems will continue to be problematic, as long as an incomplete range of costs is measured and a truly societal perspective fails to be applied. When making multinational comparisons of the burden of stroke, the burden on the family seems to be a crucial, but hitherto a much neglected component. Nevertheless, our failure to demonstrate any clear relationships between health care resource use and outcome, whether in terms of survival or ADL function, indicates that those involved in organizing stroke services and in caring for stroke patients in different countries have a great deal to learn from each other to develop their own stroke services in a cost-effective manner.

We conclude that there are wide variations between regions/countries in both health care resource use for stroke care and short-term outcome of stroke patients. Most of these variations remain after adjustment for case mix on hospital admission. The adjusted case fatality differences are substantial and merit further exploration. There is, across regions/countries, no apparent relationship between health care resource use in terms of length of hospital/institutional stay or access to rehabilitation and outcome measured as survival or ADL function at three months after stroke. Instead, it seems that variations in the resources used for stroke care reflect, to a large extent, differences in health care culture/traditions and in societal context, such as access to long-term institutional care for severely disabled stroke patients and the involvement of family members in long-term stroke care. Finally, as amply pointed out by the International Stroke trial investigators (21), there is a need for caution in the interpretation of comparisons between countries of observational (nonrandomized) data on outcome after stroke.

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