Health Care Resource Use After Acute Stroke in the Glycine Antagonist in Neuroprotection (GAIN) Americas Trial

Tanja Rundek, MD, PhD; Kirsten Nielsen, PhD; Stephen Phillips, MD, FRCPC; Karen C. Johnston, MD, MSc; Marg Hux, MSc; David Watson, MSc; for the GAIN Americas Investigators

**Background and Purpose**—To compare 3-month stroke outcomes and stroke-related health care resource use between the US and Canada in the Glycine Antagonist in Neuroprotection (GAIN) Americas study. Delivery of medical care for stroke patients, often driven by efforts to curb costs, varies substantially between countries. Data on the potential impact of these variations on clinical outcomes are sparse.

**Methods**—The analysis of health care resource included total length of stay (LOS) in hospital, intensive care unit (ICU), and acute-care ward or rehabilitation unit, or both; number of outpatient rehabilitation sessions and visits to a physician; place of residence after discharge; and employment status. Cox proportional hazards models and logistic regression were used to calculate survival hazards and predictors of favorable functional outcome (Barthel Index of 95 to 100).

**Results**—One thousand six hundred four patients who were independent before stroke (mean age: 69.9 ± 12.7 years, 53% men, 85% ischemic stroke, 69% in the US) were included. Three-month survival and functional outcome did not differ between the US and Canada. Survival rate was 80% in both countries. Favorable functional outcome was achieved in 43% of Canadian and 47% of US patients. Fewer Canadian patients received treatment in ICU (19% versus 63% in the US), and Canadians had longer stays in hospital or rehabilitation facility (median: 33 days versus 16 days in the US).

**Conclusion**—Despite similar 3-month survival and functional outcome, patterns of health care resource varied substantially between the US and Canada. US patients had more intensive early care; Canadian patients had longer hospitalizations and rehabilitation care. Further research is required to determine the most cost-effective treatment and rehabilitation plan for people who have a stroke. (*Stroke*. 2004;35:1368-1374.)

**Key Words:** stroke outcome ■ survival ■ outcome ■ health resources/utilization ■ economics, medical
In this study, we report a comparison of stroke outcomes and stroke-related health care resource use within 3 months after acute stroke in the GAIN Americas study, a randomized, placebo-controlled, clinical trial of the putative neuroprotective agent GV150526 conducted in the US and Canada between 1998 and 2000.23

**Patients and Methods**

GAIN Americas included 1604 previously functionally independent patients presenting within 6 hours of onset of symptoms of a moderate to severe ischemic stroke or intracerebral hemorrhage. Patients were randomly allocated to receive intravenous GV150526 or placebo over 72 hours and followed-up for 3 months. Randomization was stratified by age and stroke severity, but not by country. All aspects of care were at the discretion of the responsible physician and health care standards of the participating institutions. The protocol did not require the admission of patients to intensive care unit (ICU). A protocol-specified secondary aim of the GAIN Americas study was to compare health care resource use between the 2 treatment groups. Because the study drug did not influence the primary outcome, data from the GV150526 and placebo groups were pooled for this analysis.23

Patients were assessed at baseline, hospital discharge, or 7 days after randomization (whichever was sooner), and at 1 and 3 months. Functional outcome was measured by the Barthel Index (BI).24 Baseline assessments included demographics (age, gender, country), medical history, prestroke functional level by the modified Rankin Scale (mRS),25 stroke severity by the National Institutes of Health Stroke Scale (NIHSS) (categorized into prespecified groupings of: mild, 2 to 5; moderate, 6 to 13; or severe, 14 to 41),26-28 and stroke type by the Oxfordshire Community Stroke Project classification.28 At day 7 or hospital discharge, the mechanism of stroke was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.29 Ischemic stroke patients who received intravenous recombinant tissue-type plasminogen activator (rt-PA) within 3 hours of onset were eligible for the GAIN Americas trial if they met the study-specific eligibility criteria after completion of rt-PA (ie, a minimal NIHSS score of 2 on the motor arm and leg item).23

Data on health care resource use included hospital LOS, discharge destination, and number of outpatient rehabilitation sessions and physician visits. Total hospital LOS was defined as the initial period of hospitalization including inpatient rehabilitation if a patient was transferred (not discharged) to an in-hospital rehabilitation unit (ie, if the transfer was considered part of the initial hospitalization). Lengths of stay in ICU and an acute-care ward were also calculated. Because there were significant differences in treatment received in ICU between the 2 countries, we performed further analysis of ICU use, especially with respect to stroke severity and use of rt-PA. LOS in a rehabilitation facility after discharge was calculated, as was total LOS in a treatment facility including the initial hospitalization and subsequent stay in a rehabilitation facility. Information on place of residence and employment status was collected at baseline and at 3-month follow-up.

**Statistical Analyses**

Health care resource use was summarized using medians, means, and standard deviations, or proportions, as applicable. When appropriate, a t-test or χ² test was used to compare patient characteristics between countries. In the case of multiple comparisons, a Bonferroni correction was performed. The Kaplan-Meier product limit method was used to estimate the probability of 3-month survival. Survival rates between countries were compared by the log-rank test. Cox proportional hazards models with a step-wise forward selection procedure were used to calculate adjusted survival hazard ratios and 95% confidence intervals for demographics (age, sex, country), clinical features (baseline NIHSS score, atrial fibrillation, hypertension, diabetes, previous stroke, and myocardial infarction) and health resource use. For survivors, favorable functional outcome (BI: 95 to 100) was modeled using logistic regression with a step-wise forward selection procedure. All P were 2-tailed and considered significant at α of 0.05.

**Results**

The mean age of the study population was 69.9 ± 12.7 years, and 53% were men (Table 1.). The majority of patients had...
moderate (41%) or severe (47%) stroke at onset, and 85% had ischemic stroke. Sixty-nine percent of patients were enrolled in the US and 31% in Canada. Most baseline characteristics were balanced between countries. Canadian patients, however, were slightly older, fewer were hypertensive, and fewer were employed before stroke.

Survival and Functional Outcome
There was no significant difference in 3-month survival between countries (Figure). In the US, 78.7% of patients (875/1112), and in Canada, 79.1% (389/492), survived to 3 months (P=0.864). Fifty percent of those who died in the US died within 11 days of stroke onset (mean time to death: 21±15 days). In Canada, median time to death was 15 days (mean: 25.9±24 days). There were no significant between-country differences in early (7-day or 30-day) or late (90-day) survival rates.

For patients who survived 3 months after stroke, 3-month functional outcome was similar between countries. Favorable functional outcome (BI: 95 to 100) was achieved in 43% of Canadian and in 47% of US patients. Half of the patients were independent by mRS (0, 1, or 2) in the US, and 45% of the patients were independent by mRS in Canada.

Health Care Resource Use
There were significant differences in the treatment received in hospital among US and Canadian patients (Table 2). Fewer Canadian patients received treatment in ICU (19% versus 63% in the US). Fewer Canadian patients were treated with rt-PA (11% versus 31% in the US), likely related to rt-PA’s approval in Canada occurring 1 year into the GAIN Americas trial. Demographic characteristics and risk factor profiles were similar between countries, although there was a trend for younger patients to be treated in ICU in the US (data not shown). Most patients treated in ICU had ischemic strokes (82% in the US versus 85% in Canada). Stroke severity and ICU LOS differed significantly between countries. Proportion of patients staying in ICU for up to 12 hours was 2% in both countries. In the US, 23% of patients stayed in ICU for 12 to 24 hours in comparison to 9% in Canada. A stay of >24 hours was observed in 38% in the US and 9% in Canada.

More patients with mild strokes (NIHSS score 2 to 5) were treated in ICU in the US (10%) than in Canada (3%). The proportions of moderate and severe strokes were similar...
between countries. All patients treated with rt-PA were placed in ICU in both countries. The proportion of patients treated in a rehabilitation facility was the same in both countries (44% in Canada, 48% in the US). Canadian patients had an overall longer stay in hospital or inpatient rehabilitation (median 33 days and mean 41 days versus median 16 and mean 22 days in the US), but a shorter stay in ICU (mean 0.6 days versus 2.9 days in the US). Canadian patients also had longer stays on in-hospital rehabilitation wards and longer stays in rehabilitation facilities after discharge, so their stays in rehabilitation overall were longer (mean stay 19 days versus 12 days in the US). More US patients were discharged to intermediate-care or full-care facilities such as nursing homes (13% versus 6% in Canada). More Canadian patients were still in hospital, including inpatient rehabilitation at the end of the 3-month follow-up (31% versus 6% in the US).

Use of outpatient health care resources, including number of physiotherapy, occupational, and speech therapy sessions, was greater in the US (Table 3). By 3 months after stroke, more patients were living at home in the US (76%) than in Canada (58%). Among patients who were working before stroke, only 27% of US and 29% of Canadian patients returned to work (Table 3). Most were unable to work

### TABLE 3. Summary of Outpatient Rehabilitation Therapy for 1264 Patients Who Survived 3 Months After Acute Stroke Onset

<table>
<thead>
<tr>
<th></th>
<th>USA (N = 875)</th>
<th>Canada (N = 389)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient rehabilitation therapy [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational therapy</td>
<td>350 (40.0)</td>
<td>81 (20.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>428 (48.9)</td>
<td>108 (27.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Speech therapy</td>
<td>231 (26.4)</td>
<td>41 (10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychotherapy</td>
<td>19 (2.2)</td>
<td>4 (1.0)</td>
<td>0.160</td>
</tr>
<tr>
<td>Status at 3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living at home [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In institution [n %]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing home (NH)</td>
<td>140 (16.4)</td>
<td>34 (8.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intermediate care (IC)</td>
<td>14 (1.6)</td>
<td>8 (2.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rehabilitation facility (RF)</td>
<td>32 (3.7)</td>
<td>77 (20.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospitalized for stroke- and nonstroke-related reasons (H)</td>
<td>22 (2.6)</td>
<td>42 (10.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total (in NH, RF, IC, or in H)</td>
<td>208 (24.3)</td>
<td>161 (41.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients employed before stroke who returned to work [n %]</td>
<td>61 (26.9)</td>
<td>20 (29.0)</td>
<td>0.773</td>
</tr>
</tbody>
</table>

### TABLE 4. Factors Associated With 3-Month Mortality (Nonadjusted and Adjusted Cox Proportional Hazard Ratios, N=1604)

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and clinical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (1-year increase)</td>
<td>1.05 (1.04, 1.06)</td>
<td>1.03 (1.02, 1.04)</td>
</tr>
<tr>
<td>Male</td>
<td>0.86 (0.69, 1.06)</td>
<td></td>
</tr>
<tr>
<td>Baseline NIHSS (1-point increase)</td>
<td>1.12 (1.11, 1.14)</td>
<td>1.10 (1.08, 1.12)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.40 (1.93, 2.98)</td>
<td>1.28 (1.02, 1.61)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.63 (1.26, 2.11)</td>
<td>1.42 (1.10, 1.84)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.12 (0.87, 1.42)</td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.34 (1.05, 1.72)</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.10 (0.88, 1.38)</td>
<td></td>
</tr>
<tr>
<td>Country (US/Canada)</td>
<td>0.97 (0.77, 1.22)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.10 (0.82, 1.48)</td>
<td></td>
</tr>
<tr>
<td>Resource use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU use</td>
<td>1.66 (1.34, 2.07)</td>
<td>1.47 (1.18, 1.84)</td>
</tr>
<tr>
<td>In-patient rehabilitation†</td>
<td>0.12 (0.09, 0.17)</td>
<td>0.13 (0.09, 0.18)</td>
</tr>
</tbody>
</table>

*Adjusted hazard ratio for variables included in the final model.
†Rehabilitation within the hospital that provided acute care and/or separate rehabilitation facility. HR indicates hazard ratio; MI, myocardial infarction; ICU, intensive care unit.
because of health-related reasons after stroke (61% in the US, 59% in Canada).

Factors Associated With Mortality and Functional Outcome
Factors significantly associated with 3-month mortality were increased age, greater NIHSS score at baseline, atrial fibrillation, hypertension, previous myocardial infarction, use of ICU, and lack of use of rehabilitation services during the period of initial hospitalization or after discharge (Table 4). Mortality was not affected by country.

Factors significantly associated with 3-month favorable functional outcome among 1264 stroke survivors were younger age, male gender, lower NIHSS score at baseline, ischemic stroke subtype, absence of atrial fibrillation, hypertension or previous stroke, and shorter stay in all health care units (Table 5). Country did not significantly influence favorable functional outcome.

Discussion
Using data from GAIN Americas, a large acute stroke clinical trial, a striking difference between the US and Canada was observed in the pattern of use of stroke-related health care resources within 3 months after stroke. Hospital LOS, admission to ICU, and pattern of use of rehabilitation services differed significantly between countries. However, survival and functional outcome did not differ. In both countries, most patients had good outcomes: 80% survived 3 months after stroke, and approximately half of survivors were independent at 3 months.

LOS in hospital and disability level after discharge are the most important determinants of cost after stroke. In our study, despite similar demographics and clinical characteristics of stroke patients, LOS in hospital or rehabilitation facility was significantly longer in Canada (median: 33 days versus 16 in the US). However, fewer Canadian patients received treatment in ICU and were discharged to intermediate-care or full-care facilities. Use of outpatient health care resources was greater in the US, adding to total resource intensity in the US. By 3 months after stroke, significantly more Canadian patients remained in hospital, which we hypothesize to be a result of differences in the structure of the health care systems, because clinical outcomes were equivalent. The larger number of ICU admissions in the US could reflect the greater availability of high-technology (and high-cost) procedures and facilities in the US, whereas longer hospital stays in Canada could reflect lower pressure to discharge patients from hospital. All of these are most likely a reflection of differences in payment structures, incentives for use of certain care types, and infrastructure between the health care systems.

Influence of age and stroke severity on stroke outcome and effectiveness of stroke unit care has been demonstrated previously. In this study, younger age, male sex, less severe stroke, and absence of history of previous stroke were predictors of favorable functional outcome, but country was not. Other major predictors observed by others, including stroke type and congestive heart failure, were not predictors in this study.

The best available evidence concerning the organization of care for stroke patients comes from the systematic review by the Stroke Unit Trialists’ Collaboration, which found that patients who received coordinated multidisciplinary care on a geographically defined stroke unit were more likely to be alive and independent 1 year later than were those who...
received conventional care on a general medical ward. Most of the trials studied comprehensive stroke units that accepted patients acutely but also provided rehabilitation for at least several weeks if necessary. This type of care was not provided in the majority of hospitals in the GAIN Americas trial. Only 1 trial in the systematic review evaluated an acute stroke unit with no continuing rehabilitation—the type of care provided by US and many Canadian acute-care hospitals—and no firm conclusions can be drawn from the data. Our study does not provide evidence of benefit from early intensive care and suggests that lower-intensity long inpatient stays lead to outcomes that are as good as those from short-term intensive inpatient care combined with intensive outpatient rehabilitation. In fact, we observed that ICU use was associated with a higher risk of death in the first 3 months after stroke and that longer LOS in ICU was associated with poorer clinical outcome. This was most likely because of the fact that sicker patients, with poor prognosis, were admitted to ICU.

The strengths of using a clinical trial for the analyses of health care resource use include the prospective, systematic, and uniform collection of detailed clinical information, standardized identification of risk factors, comorbid conditions, clinical outcomes and adverse reactions, assessment of outcome by trained and certified personnel, few missing data, and overall good quality of recorded data.

Several limitations of this study should be noted, mainly related to the specific patient selection criteria and short duration of the study. GAIN Americas was designed to exclude very mild and very severe strokes. Generalizability of the presented results to the whole stroke population may therefore be limited. Although the data collection was standardized, differences between US and Canada health care systems may have caused variation in interpretation of health care resource use. Some health care systems, for instance, allowed patients to be transferred to a rehabilitation unit during the initial stroke hospitalization, whereas others had to discharge the patients and admit them to a rehabilitation unit, although in the same institution. This may have caused disparities in length of hospital stay between the 2 countries. Also, the finding that more patients were placed in nursing homes in the US than in Canada may be explained by the relatively short duration of the study. The difference in the proportion of patients requiring nursing home care would be attenuated if a substantial number of the Canadian patients who were still in hospital or inpatient rehabilitation at 3 months (31% of the Canadian cohort) were ultimately discharged to a long-term care facility.

No formal stroke treatment pathways were operational at participating hospitals in the GAIN Americas trial. The relatively high proportion of patients treated in ICU in the US (63% versus 19% in Canada) could not be fully explained by the administration of rt-PA (31% treated with rt-PA in the US and 11% in Canada), and most likely reflects physician preference, different admission criteria, and standards of practice. Patients treated with rt-PA represented a highly selected group of patients, because only those who did not improve immediately after administration of rt-PA were included in GAIN Americas. Furthermore, the use of rt-PA in Canada was approved 1 year into the trial (in February 1999). Therefore, use of rt-PA was not considered a confounder in the outcome analyses caused by the possible selection bias. The step-wise selection methodology may have resulted in identification of relationships that are specific to this data set. Although the predictors of functional outcome observed in our study have been previously reported, we did not find the associations with some co-morbidities observed by others. Validation of these relationships in other data sets is necessary.

Finally, a thorough cost analysis of stroke care was not performed, mainly because of the large differences between health care systems and difficulty in obtaining accurate cost data. Consequently, we were unable to determine whether the expense of greater use of intensive care facilities in the US was offset by the longer duration of inpatient rehabilitation in Canada.

Despite its limitations, we believe that our study is still a useful addition to the growing literature on health care use after acute stroke as it relates to outcome and differences between health care systems in the US and Canada. These data may serve to prompt a reexamination of the services provided to stroke patients. More research is needed to determine the most cost-effective way of delivering care to people after stroke, and the burgeoning stroke epidemic requires that this information be acquired soon.

Acknowledgments

This study was supported in part by GlaxoSmithKline, Research Triangle Park, NC. Dr T. Rundek is supported by the Hazel K. Goddess Fund for Stroke Research in Women. Dr K. Johnston is supported by the National Institutes of Health–National Institute of Neurological Disorders and Stroke (K23NS01268-01). The authors gratefully acknowledge the contribution of the GAIN Americas investigators, without whose efforts this work would not have been possible.

References


Health Care Resource Use After Acute Stroke in the Glycine Antagonist in Neuroprotection (GAIN) Americas Trial
Tanja Rundek, Kirsten Nielsen, Stephen Phillips, Karen C. Johnston, Marg Hux and David Watson
for the GAIN Americas Investigators

Stroke. 2004;35:1368-1374; originally published online April 29, 2004;
doi: 10.1161/01.STR.0000127084.26321.7a

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/35/6/1368

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at: http://stroke.ahajournals.org//subscriptions/