Trends in Management and Outcome of Hospitalized Patients With Acute Stroke and Transient Ischemic Attack
The National Acute Stroke Israeli (NASIS) Registry

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**Background and Purpose**—Improving stroke management, guideline adherence, and outcome is a global priority. Our aim was to examine trends in nationwide use of reperfusion therapy, stroke in-hospital management, and outcome.

**Methods**—Data were based on the triennial 2-month period of the National Acute Stroke Israeli registry (February to March 2004, March to April 2007, April to May 2010). The registry includes unselected patients admitted to all hospitals nationwide. There were in total 6279 patients: ischemic stroke, 4452 (70.9%); intracerebral hemorrhage, 485 (7.7%); undetermined stroke, 97 (1.6%); and transient ischemic attacks, 1245 (19.8%).

**Results**—Overall use of reperfusion therapy for acute ischemic stroke increased from 0.4% in 2004% to 5.9% in 2010 ($P<0.001$; adjusted OR, 17.0; 95% CI, 7.5–38.7). Use of CT or MR angiography for ischemic events increased from 2.1% in 2004% to 16.6% in 2010 ($P<0.001$; adjusted OR, 9.7; 95% CI, 6.8–13.9). Overall use of antithrombotics and anticoagulation for atrial fibrillation did not differ between periods, whereas clopidogrel use increased nearly 3-fold to 41% and statin use nearly 2-fold to 68%. The relative odds of providing reperfusion therapy, using CT or MR angiography, and prescribing anticoagulants for atrial fibrillation were higher among hospitals with large compared with small stroke patient volumes. In-hospital mortality after acute ischemic stroke decreased from 7.2% in 2004 to 3.9% in 2010 ($P<0.001$; adjusted OR, 0.7; 95% CI, 0.4–1.0), whereas there was no significant change in odds of poor functional outcome.

**Conclusions**—Based on a nationwide stroke registry, use of reperfusion therapy, vascular imaging, and statins is steadily increasing, whereas in-hospital mortality is decreasing. 

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**Key Words:** outcomes ■ registry ■ stroke management

**Materials and Methods**

**Study Setting**

The study population of the NASIS registry includes patients with acute stroke or TIA aged ≥18 years admitted to any of the 28 hospitals operating throughout Israel. The registry is conducted triennially during a 2-month period (February to March 2004, March to April 2007, and April to May 2010) by the Israeli Neurological Association in collaboration with the Israel Center for Disease Control, Israeli Ministry of Health and under the auspices of the Israeli Medical Association. The number of patients admitted during the 2-month periods were 2171 in 2004, 2102 in 2007, and 2006 patients in 2010. Admission policies have not changed between periods. Formal use of recombinant tissue-type plasminogen activator within a 3-hour window was approved in Israel in July 2004 and reimbursement codes for intravenous recombinant tissue-type plasminogen activator and for endovascular thrombectomy were introduced during September 2008. The study was approved by the institutional ethical committees of participating hospitals.

**As the management of acute ischemic stroke advances, widespread implementation of optimal stroke care continues to pose enormous challenges for healthcare systems. Clinical guidelines have been developed to provide timely and appropriate decisions for patients admitted with acute stroke.**

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Data Collection and Definition of Variables

Study procedures have previously been published.5 A coordinating physician responsible for data collection throughout all hospital wards was designated to each participating medical center. Stroke and TIA were diagnosed, as reported by each department, in accordance with the medical report on discharge from the hospital. In cases in which there was doubt regarding diagnosis, the decision was made by a central adjudication committee. Ischemic stroke and intracerebral hemorrhage were differentiated by findings from brain imaging and were regarded as undetermined stroke if brain CT or MRI was not performed. Stroke severity was assessed using the National Institutes of Health Stroke Scale score and handicap with the modified Rankin Scale.6

A standardized case report form was used with uniform definitions for patient-related variables, clinical diagnoses, diagnostic tests performed, treatment modalities, in-hospital complications, and outcome. For uniformity of data collection, study investigators received a detailed study manual of operation and underwent specific training on details of data collection. See the online-only Data Supplement for the operational definitions of main variables in the NASIS registry. Data entry, analysis, and logistics were conducted at a central coordinating center. Data were computer-processed by means of a system designed using the SAS software (SAS Institute, Cary, NC). Data checks for completeness and consistency were based on the discharge medical reports and on computerized data queries. Information was verified using online checks incorporated into the data entry interface and by batch logical checks applied to the database following the data entry process. Study neurologists resolved all queries at the coordinating center based on information included in discharge summaries.

Study Outcomes

Trends in patients’ characteristics, diagnostic tests performed, in-hospital care, complications, and in-hospital outcome during 2004 to 2010 were assessed. Poor outcome at discharge was defined as modified Rankin Scale ≥2 or discharge to a nursing home or in-hospital death.

Statistical Analysis

Differences in age by study period were assessed with analysis of variance. Trends in the distribution of sex, vascular risk factors, and comorbidities as well as event type and severity were studied using the Mantel-Haenszel χ2 test. Management of stroke and outcomes including in-hospital complications, mortality, and poor functional outcome were assessed by study period nationwide. Performance measures were also presented for the best ranking centers defined according to 90th percentile for each measure. Number of patients with stroke and TIA admitted annually to each hospital was estimated based on the 3 registry periods and categorized into 3 groups (≤400, 401–700, >700 patients) corresponding to 3 levels of hospital stroke and TIA volume. Logistic regression models were computed for each management and outcome variable, assessing trends between registry periods and differences by hospital stroke and TIA volume. All models were adjusted for age, sex, stroke severity, hypertension, dyslipidemia, current smoking, peripheral artery disease, prior stroke, malignancy, and prior disability (modified Rankin Scale ≥2). The potential effect of having a neurology residency or an interventional stroke program was separately assessed in alternative models (data not tabulated). The SAS 9.2 software (SAS Institute) was used for statistical analysis.

Results

In total, 6279 patients were included in the registry: ischemic stroke, 4452 (70.9%); intracerebral hemorrhage, 485 (7.7%); undetermined stroke, 97 (1.6%); and TIA, 1245 (19.8%). There was a 1-year decrease in the mean age between periods (70.6±13.2 in 2004 to 69.5±14.1 in 2010) and no significant difference in the distribution by sex (53%–56% men). Baseline characteristics and comorbidities of patients by registry period are presented in Table 1. The prevalence of dyslipidemia, hypertension, and current smoking increased over the years, whereas peripheral artery disease, prior stroke, and prior disability became less prevalent. In addition, rates of mild strokes rose over the years.
Management and outcome by period are summarized in Table 2 and Figures 1 and 2. Adjusted ORs and 95% CIs for trends between periods are shown in Table 3. Median (interquartile range) length of hospital stay during the periods was 5 (3–9) days in 2004, 4 (2–7) days in 2007, and 4 (2–8) days in 2010. Overall use of reperfusion therapy for acute ischemic stroke increased from 0.4% in 2004 to 1.5% in 2007 and 5.9% in 2010, and among patients <80 years, rates increased from 0.6% to 2.1% and 6.9%, respectively (Figure 1A). Regarding reperfusion modality, in 2010, 5.5% of patients received intravenous recombinant tissue-type plasminogen activator and 0.9% endovascular therapy with or without bridging thrombolysis. Best ranking centers (90th percentile for reperfusion) provided during 2010 reperfusion therapy to 13.2% of patients (Figure 1B). Corresponding rates for use of intravenous recombinant tissue-type plasminogen activator among patients arriving early after symptoms onset are provided in Table 2. Adjusting for potential confounders, use of reperfusion therapy was overall 17-fold higher (adjusted OR, 17.0; 95% CI, 7.5–38.7) in the 2010 period compared with the 2004 period. Among patients arriving within the first 3.5 hours, adjusted OR for use of intravenous recombinant tissue-type plasminogen activator increased nearly 40-fold between periods.

Use of CT or MR angiography for ischemic events increased from 2.1% in 2004 to 7.9% in 2007 and 16.6% during 2010 (adjusted OR, 9.7; 95% CI, 6.8–13.9). Best ranking centers for this measure use CT or MR angiography in 30.2% of patients during 2010. Overall use of antithrombotics at discharge among patients with ischemic events or TIAs did not differ between periods and was 94.7% during 2010, whereas there was an increase in clopidogrel use from 14.3% in 2004 to 32.2% in 2007 and 40.5% in 2010 (P<0.001). No significant difference in rates of anticoagulation use at discharge for patients with atrial fibrillation was found between study periods. During 2010, the overall rate was 53.5%, and after exclusion of patients with several selected contraindications, the rate of anticoagulation at discharge was 57.3% (Table 2). Rates of statin use among patients with ischemic events increased from 42.3% during 2004 to overall 67.9% during 2010. The rate of statin use during 2010 among the best ranking centers for this measure was 82.1%.

Among patients with ischemic stroke, in-hospital mortality decreased from 7.2% in 2004 to 5.2% in 2007 and 3.9% in 2010. Reperfusion therapy (%)

<table>
<thead>
<tr>
<th>Period</th>
<th>2004</th>
<th>2007</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ischemic stroke</td>
<td>6.9</td>
<td>5.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Age&lt;80 years</td>
<td>6.9</td>
<td>5.9</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Figure 1. A, Percentages of reperfusion therapy for all ischemic stroke (n=4452) and for age <80 years (n=3171) by study period. B, Percentages of center reperfusion therapy by deciles of center performance during the 2010 period. For ranking purposes, 4 centers with <60 patients with stroke/TIA admitted annually were grouped into 1 group. TIA indicates transient ischemic attack.
2010 (Figure 2A; P<0.001) and poor outcome from 69.5% in 2004 to 63.0% in 2010 (Figure 2B; P<0.001). The proportion of patients with ischemic stroke without recorded in-hospital complications increased from 68.5% in 2004 to 76.4% in 2010 (Figure 2C; P<0.001). Similar trends were observed among all strokes. Adjusting for potential confounders, in-hospital mortality for acute ischemic stroke decreased between periods by 30%, whereas there was no difference in rates of poor outcome.

The relative odds of providing reperfusion therapy, performing CT/MR angiography, and prescribing anticoagulants at discharge in patients with atrial fibrillation were higher among hospitals with large as compared with small stroke patient volumes, adjusting for potential confounders and for registry period (Table 3). Among hospitals with neurology residency programs, adjusted odds for any reperfusion therapy were 3.9-fold higher, for use of CT/MR angiography 4.5-fold higher, and for prescribing anticoagulants in patients with atrial fibrillation 1.8-fold higher (P<0.005 for all). Among hospitals with interventional stroke programs, adjusted odds for any reperfusion therapy was 5-fold higher, for use of CT/MR angiography 4.6-fold higher, and for prescribing anticoagulants 1.8-fold higher.

Table 3. Multivariable Logistic Regression Models (Adjusted ORs and 95% CI) of Management and Stroke Outcomes by Trends Over Time and Hospital Annual No. of Admitted Patients With Stroke/TIA

<table>
<thead>
<tr>
<th>Management</th>
<th>Registry Period</th>
<th>Annual Patients With Stroke/TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2004</td>
<td>2007</td>
</tr>
<tr>
<td><strong>In-hospital mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IS and ICH, n=4937</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IS, n=4452</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>In-hospital mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IS and ICH, n=4937</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IS, n=4452</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Poor outcome‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IS and ICH, n=4937</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IS, n=4452</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lipid-lowering medication at discharge (IS and TIA†), n=5218</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Models included registry period, hospital no. of patients with stroke/TIA admitted annually, age, sex, stroke severity, hypertension, dyslipidemia, current smoking, peripheral artery disease, prior stroke, malignancy, and prior disability (modified Rankin Scale ≥2).

TIA indicates transient ischemic attack; rtPA, recombinant tissue-type plasminogen activator; IS, ischemic stroke; ICH, intracerebral hemorrhage; AFib, atrial fibrillation.

*Patients with no history of dementia or malignancy or peptic disease and no reports on bleeding during hospitalization.
†Patients with low-density lipoprotein ≥100 mg/dL or treated with lipid-lowering medication on admission or low-density lipoprotein not documented.
‡Poor outcome was defined as modified Rankin Scale ≥2 at discharge or discharge to a nursing home or in-hospital death.
ing anticoagulants in patients with atrial fibrillation 1.8-fold higher compared with centers with no interventional programs ($P<0.005$ for all; data not tabulated).

**Discussion**

Although thrombolysis has been shown to have a clear benefit-to-risk ratio as treatment for acute ischemic stroke, there were barriers to its implementation in routine clinical practice. Most of the available information is based on highly experienced selected centers or from stroke treatment networks rather than on unselected nationwide data. We have found during a 6-year period, a 17-fold increase in the overall use of reperfusion therapy and a nearly 30-fold increase among patients arriving in the first hours after symptom onset with rates reaching 13.2% among best performing centers. The formal approval for use of recombinant tissue-type plasminogen activator in Israel, the introduction of relevant reimbursement codes, and the extension of the proven time window of recombinant tissue-type plasminogen activator to 4.5 hours boosted this substantial improvement.

Globally data vary, but generally, dissemination of thrombolysis therapy has been relatively slow. National data show that in Sweden, the use of thrombolysis increased from 0.9% in 2003 to 6.6% in 2008. In the United States during 2009, it was estimated that 3.4% to 5.2% of patients with ischemic stroke received thrombolytics, approximately double the rate of treatment in 2005, whereas in the Get With The Guidelines–Stroke (GWTG-S) program, however, represents hospitals that are more likely to be larger teaching hospitals with a strong interest in stroke and quality improvement. In Taiwan, the rate of thrombolysis among patients arriving within 2 hours was approximately 9% during 2006 to 2008, and in Germany during 2000, 3% of all patients with ischemic stroke and 10% of patients admitted within 3 hours of stroke onset received thrombolytic therapy. In an audit from England, Wales, and Northern Ireland during 2008, 1.4% of the total stroke population and 10% of eligible patients received thrombolysis within 3 hours.

Some time trends in the prevalence of vascular risk factors were noted over the years, in particular an increasing prevalence of dyslipidemia. In addition, mild strokes were more prevalent over the years. Because use of lipid-lowering drugs before the index event was part of the operational definition, this increase likely reflects the increased clinicians’ awareness of the importance of lipid-level control rather than a true rise in dyslipidemia prevalence. Changes in other risk factors, comorbidities, and stroke severity could reflect differences in screening, mere chance, or an improvement in prevention therapies. Future information in the ongoing NASIS registry will allow for further evaluation of these trends.

Overall use of antithrombotics at hospital discharge after ischemic events and anticoagulation in patients with atrial fibrillation did not differ between periods, whereas clopidogrel use increased by nearly 3-fold to 41% and statin use by almost 2-fold to 68%. Antithrombotics at discharge were provided in Taiwan to 86% and anticoagulation for atrial fibrillation in 28%, whereas in the GWTG-S, rates increased, respectively, from 93% to 98% and from 60% to 93%. Satins were prescribed in Sweden to 36% of patients during 2005 and in Taiwan to 39% of patients, whereas the corresponding GWTG-S figure increased from 43% in 2003 to 86% in 2009. Given well-established benefits and authoritative guidelines, statin use and anticoagulation for cardioembolic stroke prevention remain understudied and active educational programs should be applied to increase their use in appropriate patients. The relative odds of providing reperfusion therapy, using CT/MR angiography, and prescribing anticoagulants in patients with atrial fibrillation were higher among hospitals with large as compared with small stroke patient volumes as well as in hospitals with neurology residency programs or with interventional stroke programs. Also in the GWTG-S program, the greatest rates of improvement were seen in larger hospitals with the largest annual stroke discharge rates and those identified as teaching hospitals. Mortality rates have impressively decreased during the registry period by approximately one third, whereas there was no significant change in rates of poor outcome. In the United States, the percentage of stroke hospitalizations resulting in death decreased over a decade by approximately 10%. The reasons underlying the observed decrease in mortality rates are multifactorial and cannot be explained by the increase in the use of reperfusion therapy that is yet applicable to a minority of patients. Trends in mortality rates likely reflect advancements in acute stroke care, additional unmeasured factors, or lower rates of severe stroke. Indeed, wider use of preventative therapies might potentially reduce the severity of stroke when it occurs.

This study demonstrates the value of an ongoing national registry, supporting national surveillance and quality improvement efforts, and facilitating evidence-based stroke care. The triennial 2-month period design provides an efficient high-quality approach for the assessment of in-hospital trends in stroke management and outcome. The registry includes unselected patients admitted to all hospitals nationwide, thus avoiding institution and patient selection bias. Due to the medical insurance coverage of the total population by law, there are no barriers for hospital admission after acute stroke in Israel. Information was, however, restricted to admitted patients and to their hospital admission period. Data were not collected for patients discharged from the emergency department. The prevailing policy in Israel is, however, to admit patients presenting to the emergency department with a recent acute cerebrovascular event. Finally, residual measured and unmeasured confounding may have influenced the results of the multivariable analyses.

In summary, we have found substantial improvements in the use of reperfusion therapy and in selected performance measures and a decrease in rates of in-hospital mortality. The superior performance measures observed among the best ranking centers can be regarded as national aims for the management of stroke. The NASIS ongoing nationwide registry will allow for future surveillance of measures of performance and for the study of trends in adherence to stroke management guidelines.
Appendix

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Disclosures
None.

References
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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/43/8/2136

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/05/09/STROKEAHA.111.647610.DC1
Table S1: Operational definitions of main variables in the NASIS registry

<table>
<thead>
<tr>
<th>Operational definitions</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>History of or diagnosis of hypertension (&gt;140/90 mmHg) before the index stroke/TIA with or without medical treatment.</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Total cholesterol above 200 mg/dl (5.18 mmol/L), or LDL cholesterol above 130 mg/dl (3.37 mmol/L), or HDL cholesterol below 40 mg/dl (1.04 mmol/L), or triglycerides above 200 mg/dl (1.69 mmol/L), or current lipid-lowering medical treatment.</td>
</tr>
<tr>
<td>Current smoking</td>
<td>Currently smoking or stopped smoking &lt;1 month before the index stroke/TIA.</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>Intermittent claudication or peripheral arterial disease requiring angioplasty or bypass surgery, or limb amputation, or Ankle Brachial Index &lt;0.8, or known aortic aneurysm.</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>History of prior single or multiple strokes.</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Known malignancy that could potentially affect life expectancy, not including basal cell carcinoma or squamous cell carcinoma of the skin.</td>
</tr>
<tr>
<td>Prior disability (mRS≥2)</td>
<td>mRS≥2 prior to the index event.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Known diabetes requiring diet or oral hypoglycemic medications or insulin, or fasting glucose above 126 mg/dl (7 mmol/L) prior to the index event.</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Documentation of paroxysmal or chronic atrial fibrillation prior to the index stroke/TIA.</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>Documentation of active or prior angina pectoris, or prior diagnosis of single/multiple myocardial infarctions (including silent MI).</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Prior diagnosis of congestive heart failure, or signs or symptoms indicative of congestive heart failure, or ejection fraction&lt;30%.</td>
</tr>
<tr>
<td>Valve disease</td>
<td>Artificial (mechanical or biological) heart valve.</td>
</tr>
<tr>
<td>Pre-stroke dementia</td>
<td>Diagnosis or symptoms indicative of dementia prior to the index event, with or without medical treatment.</td>
</tr>
</tbody>
</table>