Validation of the Stroke Prognostic Instrument-II in a Large, Modern, Community-Based Cohort of Ischemic Stroke Survivors

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Background and Purpose—The risk of recurrent stroke in the modern era of secondary stroke prevention is not well defined. Several prediction models, including the Stroke Prognostic Instrument-II (SPI-II), have been created to identify patients at highest risk, but their performance in modern populations has been infrequently tested. We aimed to assess the 1-year risk of recurrence after hospital discharge in a recent, large, community-based cohort of patients with ischemic stroke and to validate the SPI-II prediction model in this cohort.

Methods—From 2004 through 2006, 5575 patients with acute ischemic stroke were prospectively identified and followed for recurrent events. Kaplan-Meier statistics were used to analyze the cumulative incidence of recurrent ischemic stroke. Harrell c-statistic was calculated to determine the performance of SPI-II in predicting stroke or death at 1 year, and the log-rank test was used to compare the differences among low-, middle-, and high-risk groups.

Results—Among 5575 patients with ischemic stroke, recurrence was observed in 221 during the subsequent year. Kaplan-Meier estimates of cumulative rates of recurrent stroke were 2.5%, 3.6%, and 4.8% at 3, 6, and 12 months, respectively. Rates of stroke or death for SPI-II in the low-, middle-, and high-risk groups were 8.2%, 24.5%, and 35.6%, respectively (trend, \( P = 0.001 \)). The c-statistic for SPI-II was 0.62 (95% CI, 0.61–0.64).

Conclusions—The modern 1-year rate of recurrent stroke after hospital discharge is low but still substantial at 4.8%. SPI-II is a modestly effective tool in identifying patients with ischemic stroke at highest risk of developing recurrence or death. (Stroke. 2011;42:00-00.)

Key Words: outcome prediction tool recurrent stroke risk factors

Approximately 20% of ischemic strokes are recurrences, and these cause greater disability, financial burden, and mortality than first strokes.1,2 The risk of recurrence is highest during the first year and then decreases steadily with time.3-5 Prior large-scale studies report recurrence rates of 4% to 17% in the year after stroke, but these studies may not apply to contemporary patients because they occurred over a decade ago, before advancements in diagnostic neuroimaging and secondary stroke prevention.1,3-10 Many of these studies are also limited by insufficient power, inclusion of transient ischemic attacks (TIAs) and hemorrhagic stroke, and exclusion of major stroke.

Predictors of recurrent ischemic stroke are not well characterized. Multiple clinical variables have been identified as possible risk factors, but none has been consistently demonstrated across different populations.1-10 Reasons for contradictory results include small sample sizes, lack of multivariate analyses, and differing patient baseline characteristics and stroke subtypes. Nevertheless, several prognostication models using clinical variables have been created to better identify patients at highest risk of developing recurrent ischemic stroke.11-13 One of the most commonly used tools is the Stroke Prognostic Instrument-II (SPI-II).12 SPI-II uses 7 clinical factors to estimate the risk of stroke or death in patients with prior TIA or nondisabling ischemic stroke. It has been validated in 4 independent cohorts as a modestly effective tool (c-statistic of 0.63–0.65) for stratifying patients into low-, middle-, and high-risk groups for recurrent stroke or death.12,14 However, the use of SPI-II and its subsequent validations has been limited by application of the score to heterogeneous cerebrovascular cohorts that included patients with TIA, who are likely more predisposed to future ischemic stroke than patients with completed infarction, particularly in the short term,15 at the same time as excluding patients with major strokes who are more clinically unstable than patients with nondisabling strokes and are at an increased risk of death.
from recurrent infarction or secondary complications of their index event. In an effort to better define the risk of recurrent ischemic stroke, we investigated a large, modern, prospectively assembled cohort of patients with ischemic strokes of all severities. We also tested the performance of the SPI-II score in discriminating the risk of recurrent stroke or death within 1 year in this cohort.

Subjects and Methods

Study Setting
Our cohort was selected from members of the Kaiser Permanente Medical Care Plan (KPMCP), which is a large, integrated healthcare delivery system with >3 million members who are ethnically, racially, and socioeconomically heterogeneous and are reflective of the local northern Californian population except for underrepresentation of the very rich and very poor.

Design and Study Population
We prospectively identified a cohort of consecutive adults hospitalized with ischemic stroke from 2004 through 2006 and followed them during the year after discharge for new diagnoses of recurrent ischemic stroke. Patients were identified in parallel with the Quality Improvement in Stroke Prevention (QUISP) study, a cluster-randomized trial of standardized discharge order sets. Full details of QUISP have been published elsewhere, but in brief, 12 of 16 KPMCP hospitals were randomized through a matched-pair design to continue best medical care or to implement standardized discharge orders for patients with ischemic stroke. The impact of this intervention was then assessed in patients admitted with ischemic stroke to these 12 and 2 other KPMCP hospitals between January 1, 2004, and December 31, 2006. Patients enrolled into the study received routine clinical follow-up after discharge. Eligible patients were identified by searching computerized hospital records for International Classification of Diseases, 9th Revision primary discharge diagnoses of ischemic stroke (codes 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91). Patients were included if they had brain imaging performed during the hospitalization to confirm ischemic stroke, were ≥40 years, had full KPMCP pharmacy benefits, and had been discharged to home or to a facility other than a hospice. In a validation study, the diagnosis of acute ischemic stroke was confirmed in a sample of 731 cases reviewed by a nurse medical records analyst.

Outcome Measures
Our primary outcome of recurrent ischemic stroke was identified by searching broadly for International Classification of Diseases, 9th Revision codes 430.xx to 434.xx in the primary hospital discharge code position in an automated hospital discharge diagnosis database and a billing claims database listing hospitalizations outside of the KPMCP system. Because KPMCP pays for emergent hospitalization outside its system, a careful record of these is maintained and follow-up is very complete. This broad International Classification of Diseases, 9th Revision code search (includes codes for hemorrhagic stroke) was conducted to ensure that all recurrent ischemic stroke events were identified. All potential recurrent ischemic stroke diagnoses were independently reviewed and adjudicated by 2 neurologists with a third resolving any disagreements. Patients with recurrent events before initial hospital discharge were excluded from analysis (median length of stay, 3 days; interquartile range, 0–6 days). Our secondary outcome was a composite consisting of recurrent ischemic stroke or death. The rate of death was determined by searching a KPMCP mortality database that contains death certificate information for members who have died in California since 1970.19,20 A tertiary outcome was an acute myocardial infarction, which was identified through an electronic medical records search (International Classification of Diseases, 9th Revision codes 410.x); previous work has validated this end point.20 We used electronic medical records to obtain patients’ demographic characteristics, study site, and medical history, including the presence of hypertension, hyperlipidemia, diabetes, congestive heart failure, coronary artery disease, atrial fibrillation, prior myocardial infarction, peripheral vascular disease, and prior stroke. Records of written and filled prescriptions were used to determine medication use.

Testing the Performance of SPI-II
SPI-II assigns points to 7 clinical factors based on their predictive significance: congestive heart failure (3 points), diabetes mellitus (3 points), prior stroke (3 points), age >70 years (2 points), stroke as index event (2 points), severe hypertension (1 point), and coronary artery disease (1 point).21 The summed score determines assignment into a risk group: 0 to 3 points for low risk; 4 to 7 for middle risk; and 8 to 15 for high risk.21 All variables except severe hypertension were identified by searching electronic medical records using previously validated methodologies.20 SPI-II used different definitions of severe hypertension in different cohorts. For instance, the Northern Manhattan Stroke Study (NOMASS) classified severe hypertension as a hospital blood pressure measurement of >180 mm Hg systolic or 100 mm Hg diastolic, whereas the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events trial used self-reported history.5,12,21 We defined severe hypertension as a recorded blood pressure >180/100 mm Hg at discharge and performed sensitivity analyses using a discharge blood pressure >140/90 mm Hg.

Statistical Analysis
The rates of new diagnoses of recurrent ischemic stroke, acute myocardial infarction, and the composite outcome of recurrent ischemic stroke or death were calculated using Kaplan-Meier survival statistics. Follow-up was censored when patients experienced the outcome, died, or left the health plan. To test the performance of the SPI-II, we calculated survival free of recurrent stroke or death, then stratified this Kaplan-Meier plot by the SPI-II score, and compared the groups using the log-rank test. We quantified the predictive validity of the model by computing Harrell c-statistic. In an exploratory analysis, we also assessed the discriminatory performance of the SPI-II score for predicting its individual elements: recurrent stroke and death independently. Our study was approved by the Committee on Human Research at the University of California, San Francisco and the Kaiser Institutional Review Board. Informed consent was waived because of minimal risk to patients. Data analyses were performed with Stata, Version 10 (College Station, TX).

Results
We identified 5575 patients with ischemic stroke over a 3-year period. The demographics and medical comorbidities of our patients were similar to those reported in prior epidemiological studies of stroke (Table).22 Most patients were white (69%), whereas 13% were black, 10% were Asian, 7% were Hispanic, and 1% were of other races. After the initial stroke hospitalization, patients were discharged to home (41%) or long-term care facilities (59%). Outpatient follow-up was excellent with 95% of patients remaining KPMCP members for the full year after discharge, and 91% having at least 1 office visit in the 6 months after initial stroke. Of patients with known atrial fibrillation, 60% were prescribed anticoagulation at 1 month and 49% at 6 months. We could not determine the rate of antiplatelet therapy because aspirin is often taken over the counter and our medication records relied on filled pharmacy prescriptions. Statins were prescribed to 65% of patients at 1 month and to 51% at 6 months. Blood pressure was <140/90 mm Hg at the 6 month follow-up visit in 62% of patients.
Patients who had a recurrent stroke in the year after discharge had similar rates of secondary stroke prevention measures as compared with the overall cohort; statins were prescribed to 69% of patients at 1 month and 53% at 6 months; blood pressure was <140/90 mm Hg at the 6-month follow-up visit in 58% of patients; and anticoagulation was prescribed to 50% of patients with known atrial fibrillation at 1 month and 6 months.

Overall, 221 patients (4.0%) had a recurrent ischemic stroke in the year after discharge, 124 of which occurred within 3 months and 172 within 6 months. Death occurred in 1201 (21.5%) patients in the year after initial stroke. Kaplan-Meier rates of recurrent ischemic stroke were 2.5%, 3.6%, and 4.8% at 3, 6, and 12 months, respectively (Figure 1). Kaplan-Meier rates of the composite outcome of recurrent stroke or death were 15.3%, 19.7%, and 25.4% at 3, 6, and 12 months, respectively. Acute myocardial infarction occurred in 88 (1.6%) patients in the year after index stroke with associated Kaplan-Meier event rates of 0.8%, 1.1%, and 1.6% at 3, 6, and 12 months, respectively.

The performance of SPI-II in stratifying patients’ risk of recurrent ischemic stroke or death after hospital discharge is shown in Figure 2. Most patients fell into the middle- (n=2979) or high-risk (n=1717) groups rather than the low-risk group (n=879). Outcome rates for SPI-II in the low-, middle-, and high-risk groups were 8.2%, 24.5%, and 35.6%, respectively (trend, P=0.001). The c-statistic for SPI-II was 0.62 (95% CI, 0.61–0.64). Sensitivity analyses using different definitions of severe hypertension did not affect these results. When narrowing the outcome measure to recurrent stroke (without death), the score’s performance declined with outcome rates in the low-, middle-, and high-risk groups of 3.6%, 4.5%, and 5.9%, respectively (trend, P=0.069) and a c-statistic of 0.55 (95% CI, 0.51–0.59). Conversely, the SPI-II’s discriminatory ability remained unchanged when the outcome of interest was death with outcome rates in the low-, middle-, and high-risk groups of 5.4%, 22.0%, and 33.4%, respectively (trend P<0.001) and a c-statistic of 0.64 (95% CI, 0.62–0.66).

**Discussion**

In this modern, prospectively assembled, community-based cohort of 5575 patients with ischemic stroke, the 1-year rate of recurrent ischemic stroke after hospital discharge was 4.8%. The Oxfordshire Community Stroke Project prospectively followed 675 patients with stroke from 1981 to 1986 and found a 13% rate of recurrent stroke at 1 year (Figure 3).<sup>6</sup> However, their cohort included patients with intracerebral and subarachnoid hemorrhage (only 81% had an ischemic stroke), and many patients did not receive secondary stroke prevention measures (6% of patients on antiplatelet agents and 1% on anticoagulants).<sup>6</sup> The Mayo Clinic reported a recurrent stroke rate of 12% at 1 year among 1111 patients who had a first cerebral infarction from 1975 through 1989; they did not, however, exclude hemorrhagic strokes and only 80% of patients had brain imaging or autopsy to confirm diagnosis.<sup>4</sup> Analysis of 1273 patients in the Stroke Data Bank in 1991 demonstrated a 1-year recurrent stroke rate of approximately 8% (estimated per graph) and a 2-year recurrent stroke rate of 14.1%.<sup>7</sup> However, patients were mostly
black (57%) and were only enrolled from tertiary care centers. The Life Long After Cerebral Ischemia study reported a 4.7% cumulative rate of recurrent stroke at 1 year in 2473 patients with TIA or minor ischemic stroke; however, their rate is likely an underestimation because potentially half of early strokes may have been missed because enrollment was allowed up to 3 months after initial stroke.

Other published 1-year rates for recurrent ischemic stroke in large, observational cohorts of patients with ischemic stroke but not TIA are 7.7% in NOMASS, 12.5% in the Perth Community Stroke Study, 9% in the Lehigh Valley Recurrent Stroke Study, 6.3% in the North East Melbourne Stroke Incidence Study, and 11.2% in the Nanjing Stroke Registry Program; all are well above our rate of 4.8%. Although methodological heterogeneity may account for some of the differences, it is possible that advances in secondary stroke prevention over the past 20 years have led to an improved natural history in stroke survivors. These advances include widespread, evidence-based practices such as routine use of antiplatelet therapy, statins, anticoagulation in patients with atrial fibrillation, aggressive blood pressure control, and early carotid revascularization in patients with symptomatic carotid stenosis. Alternatively, our low rate may be an underestimation of the true risk because we did not evaluate for recurrent strokes during the initial hospitalization and thus may have missed some early recurrences (approximately 1%–4.3% published rate of recurrent stroke at 7 days).

The SPI-II was created in 2000 to assist in identifying patients with recent TIA or minor stroke at greatest risk of developing recurrent stroke or death. Previous validation of the model in hospital-based cohorts and patients enrolled in randomized controlled trials demonstrated a c-statistic of 0.63 to 0.65. When applied to our cohort of patients with minor and major ischemic stroke, SPI-II demonstrated similar ability to discriminate outcomes with a c-statistic of 0.62. This similar discriminatory ability despite a different inception cohort and time period suggests that the model may have use as a risk stratification tool in clinical practice and research; however, its discriminatory performance as judged by the c-statistic is only fair. In addition, its poor performance in stratifying recurrent stroke in isolation as compared with the composite of recurrent stroke and death demonstrates that the score’s performance is driven mostly by its ability to predict death, thus highlighting the need for better clinical tools to predict stroke recurrence. To illustrate this, a Bayesian analysis indicates that the probability of recurrence as predicted by the SPI-II score would be 8.2% in the low-risk group and 10.9% in the high-risk group, assuming a 9.5% overall rate of recurrent stroke, which is the weighted average of the studies in Figure 3. This suggests that although the SPI-II score is modestly effective in predicting the composite of death or recurrent stroke, it does not provide useful information on stroke recurrence in isolation.

Strengths of our study include its large sample size, community-based cohort, prospective data gathering, adjudicated diagnoses, and inclusion of only patients with ischemic stroke. There are several limitations to our study, the first and most important being lack of data regarding recurrent strokes during initial hospitalization, long-term functional outcomes, incident and recurrent stroke subtypes, and certain secondary stroke prevention measures such as carotid revascularization and antihypertensive and antiplatelet medicines. Second, patient follow-up was incomplete (95% at 1 year); thus, some recurrent strokes may have been missed. Third, recurrent stroke was identified on the basis of hospital discharge diagnoses, and therefore strokes managed on an outpatient basis were not captured. Lastly, our results may not be generalizable beyond an integrated healthcare delivery system with underrepresentation of the very rich and very poor and a strong focus on quality of care.

Figure 2. Kaplan-Meier plot of survival free of recurrent ischemic stroke or death stratified by risk group from the Stroke Prognosis Instrument-II.

Figure 3. Summary of annual rates of recurrent stroke in published cohorts from the last 30 years; studies including patients with a diagnosis of TIA as their index event or with a sample size of <350 are excluded. Years (x-axis) correspond to the median year of enrollment for the respective studies. TIA indicates transient ischemic attack.
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Disclosures
None.

References
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