In-Hospital Initiation of Secondary Stroke Prevention Therapies Yields High Rates of Adherence at Follow-up

Bruce Ovbiagele, MD; Jeffrey L. Saver, MD; Andre Fredieu, MD; Shuichi Suzuki, MD, PhD; Scott Selco, MD, PhD; Venkatakrishna Rajajee, MD; Norma McNair, RN; Tannaz Razinia, BS; Chelsea S. Kidwell, MD

Background and Purpose—The Stroke PROTECT (Preventing Recurrence Of Thromboembolic Events through Coordinated Treatment) program systematically implements, at the time of acute transient ischemic attack (TIA) or ischemic stroke admission, 8 medication/behavioral secondary prevention measures known to improve outcome in patients with cerebrovascular disease. The objective of this study was to determine if the high utilization rates previously demonstrated at hospital discharge were maintained at 90 days after discharge.

Methods—Data were prospectively collected on consecutively encountered ischemic stroke and TIA patients admitted to a university hospital stroke service beginning September 1, 2002. PROTECT interventions were initiated before hospital discharge in all PROTECT-target (underlying stroke mechanism large vessel atherosclerosis or small vessel disease) and PROTECT–ACS (At-risk for Coronary Sequelae) patients. Adherence to program goals was assessed 3 months after discharge.

Results—During the period from September 2002 to August 2003, 144 individuals met criteria for PROTECT intervention. Of the 130 patients (90%) with available day 90 follow-up data, mean age was 72 (range, 37 to 95), and 63% were male. Adherence rates in patients without specific contraindications were 100% for antithrombotics, 99% for statins, 92% for angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and 80% for thiazides. Awareness of the importance of calling 911 in response to stroke was 87%. Adherence to diet and exercise guidelines were 78% and 70%, respectively. Of the 24 smokers, tobacco cessation was maintained in 20 (83%).

Conclusions—High rates of adherence to PROTECT therapies were maintained at 90 days after hospital discharge. (Stroke. 2004;35:2879-2883.)

Key Words: atherosclerosis ■ stroke management ■ stroke prevention

Use of evidence-based therapies for the prevention of ischemic stroke in patients receiving conventional care remains inadequate, despite the available data and the current national guidelines that support their use.1,2 Because the occurrence of a previous stroke or transient ischemic attack (TIA) is a major risk factor for a recurrent event, secondary stroke prevention offers a unique opportunity to decrease stroke rates and mitigate the devastating consequences of this disease.3

The importance of early diagnosis and aggressive initiation of secondary prevention strategies for patients with acute ischemic cerebrovascular syndromes is reinforced by recent community-based data that confirm a much higher early risk of subsequent stroke than was previously appreciated in patients with TIA or minor stroke.5,6 On the basis of these findings, the initiation of effective secondary prevention strategies would need to be implemented early (before disabling stroke occurs), monitored frequently, and maintained long-term after an index cerebrovascular event.7-9 However, suboptimal adherence to these measures, particularly in this period of highest risk for recurrence, could significantly influence the effects of any stroke prevention strategies.10 Various studies indicate that there is marked room for improvement in the implementation of antithrombotics, lipid-lowering therapies, antihypertensives, and smoking cessation counseling in individuals who have experienced a cerebrovascular event.11-13

The inpatient setting provides a unique window of opportunity for the initiation of secondary prevention measures.14 Missing this window may lead to patients not being started on these preventive therapies at all, or to delayed initiation, thereby exposing the patient to a potential event during the period of...
TABLE 1. Definition of Adherence for Each of the Program Behavioral Goals

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking Cessation</td>
<td>No smoking activity beyond 1 month of index event.</td>
</tr>
<tr>
<td>Exercise</td>
<td>Moderate exercise was defined by walking, running, or swimming for 30 minutes at least 4 days per week or physical or occupational therapy of a similar duration and frequency; activity must have been performed for at least 8 of 12 weeks beyond index event.</td>
</tr>
<tr>
<td>Diet</td>
<td>Diet that includes at least 5 servings of fruits and/or vegetables per day, at least 2 servings of fish per week; and at least 1 fiber-rich meal per day; less than one-third of daily intake attributable to fat. Activity must have been performed for at least 4 of 7 days of the week, for at least 8 of 12 weeks beyond index event.</td>
</tr>
<tr>
<td>Stroke Awareness</td>
<td>Stroke risk factors: Individual awareness of at least 2 of his or her modifiable stroke risk factors. Warning signs: Individual awareness of at least 3 of the 5 common stroke warning signs.*</td>
</tr>
</tbody>
</table>

*Five common stroke-warning signs: (1) sudden numbness or weakness of face, arm, or leg, especially on one side of the body; (2) sudden confusion, trouble speaking, or understanding; (3) sudden trouble seeing in one or both eyes; (4) sudden trouble walking, dizziness, loss of balance, or coordination; and (5) sudden severe headache with no known cause.

The Stroke PROTECT (Preventing Recurrence Of Thromboembolic Events through Coordinated Treatment) program systematically implements 8 medication/behavioral secondary prevention measures known to improve outcome in patients with cerebrovascular disease at the time of acute TIA or stroke admission. The program’s treatment algorithms center on evidence-based combination of medical and behavioral therapies that target the underlying atherosclerotic process. The 4 medication goals are initiation of an antithrombotic, a statin, an angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), and a thiazide diuretic. The 4 behavioral interventions are smoking cessation counseling, exercise counseling, diet counseling, and education about personal stroke risk factors, and the need to call 911 if new stroke symptoms occur. A detailed description of the program can be found on the PROTECT web site at www.strokeprotect.mednet.ucla.edu.

PROTECT has previously been shown to substantially increase treatment utilization at the time of hospital discharge. The objective of this study was to determine if the high utilization rates demonstrated by PROTECT at hospital discharge would be maintained at 90 days after hospitalization.

Subjects and Methods

Data were collected prospectively by program personnel on all patients aged 18 years or older with ischemic stroke or TIA admitted to the stroke service at a university teaching hospital from September 1, 2002 to August 31, 2003. Patients with a diagnosis of cerebral hemorrhage, migrainous aura, seizure, or any other nonischemic pathology were excluded.

Individuals eligible for PROTECT follow-up were classified into 2 categories: PROTECT-target or PROTECT–ACS groups. The PROTECT–target cohort included individuals with ischemic stroke or TIA whose underlying stroke mechanism was suspected to be caused by large vessel atherosclerosis or intracranial branch atherosclerosis/lipohyalinosis (small vessel disease). The PROTECT–ACS cohort included individuals with ischemic stroke or TIA whose underlying stroke mechanism was suspected to be caused by other mechanisms of stroke (cardioembolism, dissection, hypercoagulability, etc) but who had either a history of coronary artery disease or a history of a modified National Cholesterol Education Panel (NCEP) coronary artery disease risk equivalent. Modified NCEP–coronary artery disease risk equivalents were presence of cervicocephalic atherosclerosis >50%, diabetes mellitus, peripheral arterial disease, and abdominal aortic aneurysm.

Data obtained during hospitalization included patient demographics, stroke subtype per modified TOAST classification, and achievement by discharge of program goals.

The PROTECT outpatient algorithm was summarized on a patient calendar card and given to the patient and/or relative on discharge home, or placed in a transfer package sent to the appropriate rehabilitation center, nursing home, or other postacute hospital discharge facility. A 2- to 4-week telephone interview was conducted to coincide with the time when most generalists and neurologists tend to see their posthospital discharge stroke patients in follow-up. The 6-week lipid panel was performed to ensure that liver enzymes were not significantly elevated with statin use and to determine if any adjustments in statin medication dose were needed to meet national low-density lipoprotein (LDL) guidelines. PROTECT mandated that all individuals in the target and ACS cohorts be on statin therapy to achieve the NCEP goal of LDL level <100 mg/dL.

Maintenance of program goals was assessed at 3 months after hospitalization at a scheduled follow-up clinic visit. For patients unable to attend the 3-month clinic visit, a structured telephone interview was performed. During clinic visits, patients and/or family members were given a PROTECT self-monitor log to complete while in the physician’s waiting room. This questionnaire contained nonleading questions assessing the patient’s knowledge of his/her medications, risk factors, stroke warning signs, and recent blood pressure levels. The self-monitor log was then reviewed with the patient in the physician’s office. If a medication differed from the discharge medications, the questionnaire was extended to reveal the person who initiated the discontinuation or change (general practitioner, physician at rehabilitation facility, patient, unknown) and the reasons for the change or discontinuation (side effects, contraindication, inefficacy, other [for example, costs, drug interaction], unknown). Compliance definitions for the behavior goals are provided in Table 1. Log questions were asked verbally to patients whose 3-month encounter took place by structured phone interview.

The 3-month encounters also included questions regarding interval vascular events such as death, recurrent cerebral ischemia or hemorrhage, angina, myocardial infarction, and peripheral arterial occlusion. Recurrent stroke and TIAS were identified as any new neurological deficit after 24 hours because of new cerebral ischemic events, not because of nonischemic causes like edema, hemorrhagic transformation, or intercurrent illness. Deficits occurring in the first 21 days after index event had to be corroborated by neuromaging as caused by a lesion distinct from that of the index stroke to be counted as a new stroke. This definition for recurrence of stroke was in part...
derived from previous population studies. Confirmation of an interval vascular event was made preferably through medical record documentation of the event, as evidenced by a complete discharge summary, emergency room, or clinic encounter note. In situations in which this was not feasible, verbal confirmation had to be obtained from the patient’s treating physician via the phone.

The occurrences of prespecified common and life-threatening medication reactions were elicited from the patients through structured interviews used during the clinic visit. Potential severe idiosyncratic reactions were also noted.

The PROTECT program was initiated as an ongoing quality-improvement initiative. Analysis and reporting of program data (with identifying information removed) were approved by the institutional review board.

Analyses
Analyses focused on the proportion of patients treated with each of the 4 PROTECT medication interventions, the proportion of individuals compliant with PROTECT lifestyle modification interventions at 3 months, and the frequency of recurrent vascular events. Differences in endpoints were analyzed with the McNemar paired comparison test.

Results
During the period from September 2002 to August 2003, 207 individuals with stroke or TIA were admitted to the stroke service. Of these, 95 met PROTECT–target and 35 PROTECT–ACS cohort criteria, including 102 with ischemic stroke and 28 with TIA. Among the PROTECT groups, day 90 follow-up data were available for 130 out of 144 patients (90%); 10 patients were lost to follow-up and 4 had died. Ninety-six clinic visits and 34 telephone interviews were conducted.

Baseline demographics and characteristics for the 130 PROTECT target and ACS patients with 3-month follow-up can be found in Table 2. Median admission National Institutes for Health Stroke Scale was 5 (range, 0 to 22). Seventy-eight individuals (60%) were discharged home, 39 (30%) to a rehabilitation facility, 7 (5%) to another hospital, and 6 (4%) to a skilled nursing facility. Overall, PROTECT medication adherence rates at 3 months were: antithrombotic in 130 patients (100%), statin in 118 patients (91%), ACEI/ARB in 109 patients (84%), and thiazide in 83 patients (64%). The number of individuals for each PROTECT medication goal without any prespecified protocol contraindications at the time of hospital discharge were: 129 for antithrombotics, 118 for statins, and 116 for ACEI/ARB and thiazides. Utilization rates at the time of hospital discharge, compared with those at 3 months, among individuals without any prespecified protocol contraindications at the time of discharge are shown in Figure 1. Factors contributing to the nonutilization of PROTECT medications at day 90 are shown in Table 3. Medication treatment complications during the postdischarge period are provided in supplementary Table I (available online at http://www.strokeaha.org).

Awareness and adherence rates for smoking cessation, diet, and exercise are shown in Figure 2. The stroke management awareness intervention compliance rates were: 114 (88%) of patients (or relative/caregiver) were aware of the need to call 911 in the event of a stroke-like symptoms, 108 (83%) were aware of the individual patient’s own stroke risk factors, and 91 (70%) of the cohort were aware of common stroke warning signs.

Figure 3 depicts the statistically significant difference between admission and 3-month LDL levels and smoking cessation rates within the cohort. Fifty-eight of the 60 individuals with LDL levels <100 mg/dL on admission had proportions of 100% and 98% respectively, for antithrombotics and statins. The other medication groups all had lower adherence rates, with 94% adherence for ACEI/ARB and 92% for thiazide.

Table 2. Clinical Characteristics of Patients (PROTECT–target and PROTECT–ACS Patients Combined)

<table>
<thead>
<tr>
<th>Variable</th>
<th>PROTECT–Target and PROTECT–ACS Patients (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean, range)</td>
<td>72 (37–95)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td>Female 48 (37)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td>White 99 (76)</td>
</tr>
<tr>
<td>Hispanic 7 (6)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic 123 (94)</td>
<td></td>
</tr>
<tr>
<td>Medical history, no. (%)</td>
<td>Hispanic 7 (6)</td>
</tr>
<tr>
<td>Hypertension 101 (78)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia 60 (46)</td>
<td></td>
</tr>
<tr>
<td>Stroke or TIA 36 (28)</td>
<td></td>
</tr>
<tr>
<td>Diabetes 48 (37)</td>
<td></td>
</tr>
<tr>
<td>CURRENT smokers 24 (19)</td>
<td></td>
</tr>
<tr>
<td>Intracranial stenosis: &gt;50% 27 (21)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation 22 (17)</td>
<td></td>
</tr>
<tr>
<td>Abdominal aortic aneurysm 2 (2)</td>
<td></td>
</tr>
<tr>
<td>Current stroke/TIA subtype, no. (%)</td>
<td>LV atherosclerosis 53 (41)</td>
</tr>
<tr>
<td>Small vessel disease 42 (32)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolism 31 (24)</td>
<td></td>
</tr>
<tr>
<td>Undetermined 4 (3)</td>
<td></td>
</tr>
</tbody>
</table>

LV indicates large vessel; CAD, coronary artery disease; PAD, peripheral artery disease; TIA, transient ischemic attack; NISSS, National Institutes of Health stroke scale.

Figure 3. Discharge and day 90 adherence rates to PROTECT medication interventions among individuals without PROTECT protocol contraindications at the time of hospital discharge.
LDL levels <100 mg/dL at 3 months. None of the individuals who were not smoking on admission had started smoking at 3 months after hospitalization.

Vascular events during the 3 months after discharge were noted with the following frequency: 10 (7.7% of cohort) had recurrent ischemic strokes, 6 (4.6% of cohort) had TIA, 3 (2.3%) had angina, and 2 (1.5%) had myocardial infarcts. No individual had >1 event. No incidents of intracranial hemorrhage or peripheral arterial occlusion were documented at 90 days after hospitalization.

Discussion
This study has demonstrated that the PROTECT program was an effective means of maintaining high adherence to evidence-based secondary stroke prevention strategies in high-risk individuals within 90 days of hospital discharge. Compared with other cohort studies, PROTECT was associated with higher day 90 adherence rates in the use of antithrombotic and antihypertensive agents. Furthermore, PROTECT was also associated with greater adherence to target national guideline goals of cholesterol levels in vascular patients at high risk, as well as smoking cessation rates among the highest ever reported. This increase in treatment adherence was associated with a favorable clinical event rate, with substantially fewer recurrent vascular events within the PROTECT cohort of individuals compared with results from other 3-month postevent/hospitalization cohort studies.

The PROTECT program differs from previous secondary stroke prevention initiatives in several ways, including: (1) its focus on the implementation of goals during the initial hospitalization; (2) an aggressive medication approach designed to slow or halt the underlying atherosclerotic process based on the most recent clinical trial evidence; and (3) systematic application of mutually reinforcing tools, including bedside teaching, patient logs, information brochures, and handoff letters to primary care physicians. It is well known that those who have just experienced a vascular event are at extremely elevated risk for recurrent vascular events, particularly in the first days to weeks after the index event.6 The acute stroke hospitalization setting represents the ideal opportunity to institute evidence-based prevention therapies and education in behavioral modification strategies. The PROTECT Program helps to ensure that patients are not discharged from the hospital without initiation of secondary prevention measures proven to alter the natural history of atherosclerosis and decrease recurrent cerebrovascular events. As can be gleaned from Table 3, the leading factor for medication...

---

**Table 3. Nonutilization Factors for Statins and Antihypertensives at 3 Months Postevent**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Nonutilization Factor</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>Nonmedication initiation at hospital discharge because of presupposed protocol contraindications*</td>
<td>10 (8)</td>
</tr>
<tr>
<td></td>
<td>Discontinuation in rehabilitation facility</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Discontinuation in nursing home/other hospital</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Discontinuation by primary care physician</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>Nonmedication initiation at hospital discharge because of presupposed protocol contraindications†</td>
<td>14 (11)</td>
</tr>
<tr>
<td></td>
<td>Discontinuation in rehabilitation facility</td>
<td>6 (5)</td>
</tr>
<tr>
<td></td>
<td>Discontinuation in nursing home/other hospital</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>Discontinuation by primary care physician</td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>Discontinuation by patient or family</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Alanine aminotransferase level >3 times baseline; total cholesterol <135 mg/dL.
†Fixed arterial stenosis ≥50%; orthostasis; symptomatic hypotension.

---

**Figure 2.** Day 90 adherence rates for lifestyle modification goals.

**Figure 3.** Smoking rates and low-density lipoprotein (LDL) levels on admission and at day 90.
nonutilization at 3 months after discharge was nonutilization at the time of discharge, suggesting that perhaps in-hospital treatment, or the lack thereof, is a critical determinant of subsequent care in the community.

Also noteworthy is the low rate of medication discontinuation, which further underscores the likelihood that hospital care predicts future community care. Although not high, some medication discontinuations occurred in the rehabilitation setting, which may have been attributable to medication induced orthostasis or a breakdown in effective communication about PROTECT goals between the stroke and rehabilitation facilities.

It is difficult to effect a change in behavior, particularly diet, exercise, and tobacco use, in the short-term and even more so in the longer-term. However, our study suggests that for patients with ischemic cerebrovascular events, initiating counseling during the acute stroke hospitalization and directly linking the index event with lifestyle habits increase the likelihood of behavior modification. For instance, all 20 smokers not smoking 3 months after discharge had stopped immediately after the index stroke and had this cessation reinforced by PROTECT program bedside counseling and written materials. It is likely that postdischarge reinforcement in the form of the PROTECT telephone call at 2 to 3 weeks after discharge, and the 6-week lipid panel check, contributed to increased adherence of program goals. Outpatient encounters not only provide an opportunity to assess the patient’s postdischarge condition but also can be used to encourage adherence to medication and behavioral goals.

This analysis has a number of limitations. The study was observational and performed in a single center with no control group and a relatively small sample size. However, the Stroke PROTECT program was designed to be easily adaptable to a variety of health care systems. Future controlled studies will be required to demonstrate the impact of the PROTECT program on long-term maintenance of target therapies and the prevention of recurrent vascular events, and are currently ongoing. Individuals who were lost to follow-up, refused follow-up, or who had died may have been less compliant with treatment, which may have led to an overestimation of compliance. Finally, some endpoints were based on information obtained from our patients and we cannot rule out inaccurate reporting. However, the substantial improvement in NCEP–target LDL goals suggests that most patients were complying with program intervention.

In conclusion, inpatient health care professionals could play a pivotal role in influencing not only acute stroke care management needs but also the longer-term clinical outcome of their patients. This study suggests that systematic in-hospital initiation of secondary prevention therapies in stroke patients can be safe, may improve 3-month adherence rates, and also enhance compliance with national guidelines for the treatment of individuals at high-risk for vascular events.

Acknowledgments

This study was supported in part by NIH-NINDS Award K23 NS 02088 (C.S.K.) and NIH-NINDS Award K24 NS 02092 (J.L.S.). Funding for data collection within this study was supplied in part by unrestricted educational grants from Bristol-Myers-Squibb and Sanofi Pharmaceuticals. This work was presented in part at the 56th American Academy of Neurology Annual Meeting, April 28 2004, San Francisco, California.

References

In-Hospital Initiation of Secondary Stroke Prevention Therapies Yields High Rates of Adherence at Follow-up

Bruce Ovbiagele, Jeffrey L. Saver, Andre Fredieu, Shuichi Suzuki, Scott Selco, Venkatakrishna Rajajee, Norma McNair, Tannaz Razinia and Chelsea S. Kidwell

Stroke. 2004;35:2879-2883; originally published online October 28, 2004;
doi: 10.1161/01.STR.0000147967.49567.d6

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/35/12/2879

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/