Implementation of a Structured Guideline–Based Program for the Secondary Prevention of Ischemic Stroke in China

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Background and Purpose—High rates of ischemic stroke and poor adherence to secondary prevention measures are observed in the Chinese population.

Methods—We used a national, multicenter, cluster-randomized controlled trial in which 47 hospitals were randomized to either a structured care program group (n=23) or a usual care group (n=24). The structured care program consisted of a specialist-administered, guideline-recommended pharmaceutical treatment and a lifestyle modification algorithm associated with written and Internet-accessed educational material for patients for the secondary prevention of ischemic stroke. The primary efficacy outcome was the proportion of patients who adhered to the recommended measures at 12-month postdischarge. This trial is registered with ClinicalTrial.gov (NCT00664846).

Results—At 12 months, 1287 (72.1%) patients in the Standard Medical Management in Secondary Prevention of Ischemic Stroke in China (SMART) group and 1430 (72%) patients in the usual care group had completed the 12-month follow-up (P=0.342). Compared with the usual care group, those in the SMART group showed higher adherence to statins (56% versus 33%; P=0.006) but no difference in adherence to antiplatelet (81% versus 75%; P=0.088), antihypertensive (67% versus 69%; P=0.661), or diabetes mellitus drugs (73% versus 67%; P=0.297). No significant difference in the composite end point (new-onset ischemic stroke, hemorrhagic stroke, acute coronary syndrome, and all-cause death) was observed (3.56% versus 3.59%; P=0.921).

Conclusions—The implementation of a program to improve adherence to secondary ischemic stroke prevention efforts in China is feasible, but these programs had only a limited impact on adherence and no impact on 1-year outcomes. Further development of a structured program to reduce vascular events after stroke is needed.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00664846. (Stroke. 2014;45:00-00.)

Key Words: guideline • patient compliance • secondary prevention • stroke

Stroke, a global health problem, is ranked third as a cause of disability-adjusted life-years (DALYs) according to the study of global burden of disease 2010 (GBD 2010).1 In developing countries, premature loss of life and stroke-related disability are a heavy burden with increasing economic and social costs.2 In China, the government has identified stroke as a high priority for both primary and secondary prevention and has supported the organization and publication of several national stroke guidelines to improve standards of care; however, these efforts have had an unclear impact on patient outcomes.3–5

Many studies have shown major evidence-practice gaps, including a decline in the adherence of patients to treatments after discharge from the hospital.6 A variety of structured programs, such as the Get With the Guidelines (GWTG) stroke program in the United States,7 have been shown to improve the quality of in-hospital stroke treatment. Long-term adherence to treatments is critical to ensure that secondary ischemic stroke prevention measures are maximally effective. A similar program must be implemented to improve the quality of secondary stroke prevention after hospital discharge. A cluster-randomized, guideline-based, structured care program, known as the Standard Medical Management in Secondary Prevention of Ischemic Stroke in China (SMART) study, was performed to assess the feasibility and effectiveness of
structured care management and treatment to prevent recurrent ischemic stroke in China.

Methods and Patients

Patients

The details of the rationale and design of the SMART study have been published elsewhere. SMART was a national, multicenter, cluster-randomized controlled trial to assess the effectiveness of a guideline-based structured care program for secondary stroke prevention, as opposed to usual care, in China. For the trial, the following inclusion criteria were used: patients >18 years old; proven stroke because of cerebral infarction (according to standard clinical criteria with supporting brain imaging, either computer tomography or MRI), or transient ischemic attack; hospitalization within 30 days after the index event; clinical stability; and previous independence in their daily activities, as indicated by scores of 0 to 3 on the modified Rankin scale. The following exclusion criteria were used: radiological evidence of intracerebral hemorrhage; clear cause of stroke or transient ischemic attack unrelated to atherosclerosis (eg, cervical artery dissection or perivascular procedural stroke), although strokes resulting from cardioemboli were included; severe comorbid illness or unstable medical condition (eg, congestive cardiac failure, respiratory failure, renal failure, severe liver dysfunction, or malignancy with a likelihood of death within 2 years); significant memory or behavioral disorders requiring daily care; concurrent participation in another clinical trial; and pregnancy.

We obtained written informed consent from the participants or their legal surrogates. The study was approved by the central ethics committee at the principal study center at Peking Union Medical College Hospital and the ethics committees at the participating study sites.

We invited 48 hospitals (n=42 level-3 hospitals and n=6 level-2 hospitals) to participate in the study. The hospitals were stratified based on size (level-2 hospitals had ≥100 inpatient beds providing acute medical care and preventative care services to populations of ≤100,000; level-3 hospitals were major tertiary referral centers in provincial capitals and major cities and location (by province). The hospitals were randomized to either the SMART program or the usual care group using a simple cluster method. However, 1 hospital (level 3) withdrew from the study before it began, leaving 23 hospitals (level-3 hospitals, n=20; level-2 hospitals, n=3) in the SMART group and 24 hospitals (level-3 hospitals, n=21; level-2 hospitals, n=3) in the usual treatment group.

Procedure

All patients were evaluated and followed up by neurologists. The SMART program comprised a combination of interventions, consistent with the current guidelines for the secondary prevention of ischemic stroke: pharmaceutical treatment targeted toward specific pathological subtypes, according to Trial ORG10172 in the Acute Stroke Treatment (TOAST) criteria (ie, large-artery atherosclerosis, small-vessel occlusion, cardioembolism, stroke of other determined pathogenesis, and stroke of undetermined pathogenesis); lifestyle modification; and patient education (Appendix I in the online-only Data Supplement). We discussed lifestyle modification with the patients, including smoking cessation, healthy diet, and regular exercise. Patient education included an interactive education session emphasizing the importance of adhering to the SMART program: that is, accessing a unique password-protected website that outlined aspects of the prevention of ischemic stroke and using materials discussing the importance of adhering to measures, a generalized estimating equations linear regression model was used to account for the interdependence of members from same center. Times to event outcomes were analyzed using Cox proportional hazards models, including the SMART program as a factor and with adjustments for covariates.

Assessment of Outcomes

The primary efficacy outcome was the proportion of the patients who adhered to the secondary ischemic stroke prevention measures according to the recommendations of the SMART program. The secondary outcome was the composite of new-onset ischemic stroke, new-onset hemorrhagic stroke, acute coronary syndrome, and all-cause death. We recorded serious adverse events during follow-up, regardless of whether the local investigator considered the adverse effects related to the treatment (definite, uncertain, or no causality), and we reported all pertinent information to the data monitoring committee.

Statistical Analysis

The sample size estimation was 1771 patients per group, based on a 10% increase in the use of antiplatelet therapy in the SMART group versus a control usual care rate of 76%, assuming a 5% Type I error and a 2% allowance for variation using a 2-sided test. However, we estimated that a total of 4074 patients would be required for the study, assuming an overall dropout rate of 15% in each group. We compared the baseline patient characteristics of the randomized groups using the t test or χ² test, as appropriate. We calculated the adherence to each of the recommended measures for the hospital discharge and 12-month outcomes. To evaluate adherence, each measure for which a patient was eligible constituted an observation; the outcome was dichotomized as 1 (measure met) or 0 (measure not met) to indicate whether the recommended treatment was fulfilled. The percentage of adherence to each measure was defined as the total number of measures performed divided by the total number of eligible patients. To investigate the overall associations of the SMART program and the adherence to measures, a generalized estimating equations linear regression model was used to account for the interdependence of members from same center. Times to event outcomes were analyzed using Cox proportional hazards models, including the SMART program as a factor and with adjustments for covariates.

Table 1. Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>SMART Group (n=1795)</th>
<th>Usual Care Group (n=2026)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>67</td>
<td>69</td>
<td>0.24</td>
</tr>
<tr>
<td>Age (mean, SD), y</td>
<td>61.48 (11.47)</td>
<td>60.36 (11.66)</td>
<td>0.004</td>
</tr>
<tr>
<td>NIHSS (mean, SD)</td>
<td>4.90 (4.45)</td>
<td>4.32 (4.26)</td>
<td>0.001</td>
</tr>
<tr>
<td>Past medical history, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>24</td>
<td>23</td>
<td>0.20</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>7</td>
<td>7</td>
<td>0.77</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64</td>
<td>63</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24</td>
<td>21</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>17</td>
<td>14</td>
<td>0.04</td>
</tr>
<tr>
<td>TOAST classification, %</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>45</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Small-vessel disease</td>
<td>47</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other determined pathogenesis</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Undermined pathogenesis</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Lifelong nonsmoker</td>
<td>54</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>30</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale score; SMART, Standard Medical Management in Secondary Prevention of Ischemic Stroke in China; and TOAST, Trial ORG10172 in the Acute Stroke Treatment.
Table 2. Proportions of Medications Prescribed at Discharge

<table>
<thead>
<tr>
<th>Medication</th>
<th>SMART Group (n=1795)</th>
<th>Usual Care Group (n=2026)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>1245/1674 (85%)</td>
<td>1470/1795 (82%)</td>
<td>0.6963</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>757/1089 (70%)</td>
<td>790/1167 (68%)</td>
<td>0.4873</td>
</tr>
<tr>
<td>Antidiabetic</td>
<td>307/394 (78%)</td>
<td>264/379 (70%)</td>
<td>0.5532</td>
</tr>
<tr>
<td>Statin</td>
<td>991/1534 (65%)</td>
<td>802/1720 (47%)</td>
<td>1.007</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>17/41 (42%)</td>
<td>13/42 (31%)</td>
<td>0.1652</td>
</tr>
</tbody>
</table>

Adjusted for age and National Institutes of Health Stroke Scale (NIHSS) score. SMART indicates Standard Medical Management in Secondary Prevention of Ischemic Stroke in China.

A standard value of P<0.05 was considered statistically significant. We performed all data analyses using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Between April 1, 2008, and December 31, 2010, a total of 3821 patients were assigned to receive either care through the SMART program or usual care at 1 of the 47 participating hospitals. The baseline demographic and clinical characteristics demonstrated that the patients in the SMART group were slightly older (62±11 versus 60±12 years; P=0.004), had worse neurological impairments (ie, higher National Institutes of Health Stroke Scale [NIHSS] scores, 4.9±4.5 versus 4.3±4.3; P=0.001), were more likely to have a history of hypercholesterolemia (17% versus 14%; P=0.04), and were less likely to smoke (30% versus 34%; P=0.002) than the patients who received usual care (Table 1). After adjusting for age and NIHSS score, no significant difference in the proportion of medication use prescribed at discharge was observed between the 2 groups (Table 2).

Adherence to Secondary Stroke Prevention Measures

The levels of adherence to measures (antiplatelet, antihypertensive, and antidiabetic medications, and statin and warfarin use) for the secondary prevention of ischemic stroke were calculated at 6 (Table 3) and 12 months (Table 4) after the index ischemic stroke event. A significant difference in adherence to statin use between the 2 groups was observed at 12 months (SMART group: 56% versus usual treatment group: 33%; P=0.006), although there were no significant differences in adherence to other measures between the 2 groups: antiplatelet drug use (SMART group: 81% versus usual treatment group: 75%; P=0.088), antihypertensive drug use (SMART group: 67% versus usual treatment group: 69%; P=0.661), and antidiabetic drug use (SMART group: 73% versus usual treatment group: 67%; P=0.297). Of 1791 patients, the educational website recorded 1624 entries from the SMART group during the study or 0.91 per patient per annum.

There was no significant decrease in the secondary end point (new-onset ischemic stroke, intracranial hemorrhage, acute coronary syndrome, and all-cause death) in the SMART group compared with the usual care group (3.50% versus 3.59%; P=0.921; Table 5).

Discussion

This pragmatic, nationwide, multicenter, cluster-randomized controlled trial presents updated information and recommends adherence to medical treatments for the prevention of secondary ischemic stroke using a program of guideline-based structured care and patient education in China. Compared with usual care, our specially designed SMART program increased patient adherence to the medical regimen of statins, although not to antiplatelet drugs, antihypertensive drugs, antidiabetic drugs, or warfarin for the treatment of cardioembolic stroke, during a 12-month follow-up period. There was no difference between the groups in the composite vascular end point of ischemic stroke, new-onset hemorrhagic stroke, acute coronary syndrome, and all-cause mortality.

Despite strong evidence supporting therapies and multiple guidelines for their use, high-risk patients often discontinue prescribed therapies after discharge from the hospital. The current status of secondary stroke prevention in China is not satisfactory. A recent study on the secondary prevention of ischemic stroke in urban China (ChinaQUEST) revealed that the use of antiplatelet drugs and lipid-lowering therapy substantially declined after hospital discharge.10 These findings indicate that physicians and patients should focus more attention on improving the quality of secondary stroke prevention after hospital discharge, which is crucial for prevention outcomes. Concerted efforts have been made to improve acute stroke management in various countries and districts. The GWTG-Stroke program has been associated with increased adherence to all 7 prespecified performance measures for ischemic stroke in China.

Table 3. Adherence to Measures for Secondary Ischemic Stroke Prevention at 6-Months Poststroke

<table>
<thead>
<tr>
<th>Medication</th>
<th>SMART Group (n=1598)</th>
<th>Usual Care Group (n=1732)</th>
<th>Estimate</th>
<th>P Value*</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>1301/1563 (83%)</td>
<td>1305/1702 (77%)</td>
<td>1.683</td>
<td>0.071</td>
<td>2.809</td>
<td>0.916 8.611</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>692/1011 (68%)</td>
<td>766/1100 (70%)</td>
<td>0.421</td>
<td>0.541</td>
<td>1.523</td>
<td>0.395 5.874</td>
</tr>
<tr>
<td>Antidiabetic</td>
<td>280/370 (76%)</td>
<td>246/350 (70%)</td>
<td>0.862</td>
<td>0.346</td>
<td>12.367</td>
<td>0.395 14.191</td>
</tr>
<tr>
<td>Statin</td>
<td>866/1466 (59%)</td>
<td>604/1622 (37.2%)</td>
<td>1.697</td>
<td>0.005</td>
<td>5.456</td>
<td>1.689 17.633</td>
</tr>
<tr>
<td>Anticoagulation*</td>
<td>13/35 (37%)</td>
<td>11/30 (37%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Adjusted for age, hypercholesterolemia, and National Institutes of Health Stroke Scale (NIHSS) score. Anticoagulation drugs were not included in this analysis model because of the small number of patients. CI indicates confidence intervals; OR, odds ratio; and SMART, Standard Medical Management in Secondary Prevention of Ischemic Stroke in China.

*Statistical significance P<0.05.
in-hospital acute stroke care. A recent positive evaluation of the GWTG-Stroke program in Taiwan suggested that such initiatives are applicable outside the United States to improve the quality of stroke care. We suggest that similar programs for secondary stroke prevention be performed worldwide.

For patients with noncardioembolic ischemic stroke, antiplatelet agents are recommended to reduce the high risk of recurrent stroke and other cardiovascular events. Although these drugs are easy to use, inexpensive, and well tolerated, adherence to antiplatelet drugs is not optimal, as anticipated. The ChinaQUEST study demonstrated that antiplatelet use declined from 81% at the time of hospital discharge to 66% at 12 months poststroke. In contrast to antihypertensive therapy, in which blood pressure is monitored to achieve a treatment target, the effects of antiplatelet drugs are not visible, and patients might doubt the effectiveness of the treatment when recurrent ischemic events occur or worry about the risk of bleeding. Thus, patient education may be more critical than previously recognized to ensure good adherence to antiplatelet therapy.

In the present study, we demonstrated that patients with hypertension and those with diabetes mellitus exhibit consistent levels of adherence to antihypertensive and antidiabetic drugs. The randomized groups showed a minimal difference in use during 12 months, and this good adherence to antihypertensive drugs is consistent with the findings of a previous study. This adherence to medications might in part reflect the high level of awareness about the importance of hypertension as a major risk factor for stroke. In addition, the well-developed Chinese Hypertension Prevention and Treatment Guidelines and various medical and educational activities have contributed to increased public awareness of hypertension and diabetes mellitus.

In the present study, adherence to warfarin was only 28% in the SMART group and 29% in the usual care group 12 months poststroke. These figures are consistent with those obtained in a registry study in Taiwan, in which anticoagulant treatment (warfarin) was used by only 28% of patients with atrial fibrillation at the time of hospital discharge, and a recent German study, in which only 31% of patients with atrial fibrillation used anticoagulants. The main reason for the poor adherence to anticoagulant treatment is the inconvenience and complexities of regular monitoring. Strategies to improve adherence to anticoagulant treatment in China might include physician and patient education and easy access to facilities that provide international normalized ratio monitoring.

There is now strong evidence that the use of statins in the secondary prevention of ischemic stroke is beneficial. Although statin use was significantly higher in the SMART group than in the usual care group and statin use in the SMART group at 12 months after discharge was much higher than that observed in the ChinaQUEST study (56% versus 17%), the use of these drugs remains substantially lower than that in developed countries; statin use of 74% was observed in the Swedish Prescribed Drug Register at 12 months after stroke. This result indicated that patient education is effective in substantially increasing statin use in secondary ischemic stroke prevention; thus, these efforts should be strengthened in the future.

There were no significant differences in medication adherence (except statin use) and cardiovascular events compared with usual care. Several factors might account for the negative results. The primary reasons are likely the short follow-up time and small sample. Difference between SMART-based care and usual care might be more evident after long-term implementation in a larger population. In addition, the SMART

### Table 4. Adherence to Measures for Secondary Ischemic Stroke Prevention at 12 Months Poststroke

<table>
<thead>
<tr>
<th>Medication</th>
<th>SMART Group (n=1598)</th>
<th>Usual Care Group (n=1732)</th>
<th>Estimate</th>
<th>P Value*</th>
<th>OR*</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>1020/1258 (81%)</td>
<td>1050/1402 (75%)</td>
<td>1.139</td>
<td>0.088</td>
<td>3.468</td>
<td>0.830</td>
<td>14.494</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>555/830 (67%)</td>
<td>621/906 (69%)</td>
<td>0.365</td>
<td>0.661</td>
<td>1.440</td>
<td>0.283</td>
<td>7.338</td>
</tr>
<tr>
<td>Antidiabetic</td>
<td>220/303 (73%)</td>
<td>190/284 (67%)</td>
<td>1.016</td>
<td>0.297</td>
<td>2.761</td>
<td>0.409</td>
<td>18.642</td>
</tr>
<tr>
<td>Statin</td>
<td>660/1183 (56%)</td>
<td>442/1342 (33%)</td>
<td>1.712</td>
<td>0.006</td>
<td>5.539</td>
<td>1.629</td>
<td>18.831</td>
</tr>
</tbody>
</table>

Adjusted for age, hypercholesterolemia, and National Institutes of Health Stroke Scale (NIHSS) score. Anticoagulation drugs were not included in this analysis model because of the small number of patients. CI indicates confidence intervals; OR, odds ratio; and SMART, Standard Medical Management in Secondary Prevention of Ischemic Stroke in China.

*Statistical significance P<0.05.

### Table 5. End Points in the Randomized Groups at 12 Months Poststroke

<table>
<thead>
<tr>
<th></th>
<th>SMART Group (n=1795)</th>
<th>Usual Care Group (n=2026)</th>
<th>Hazard Ratio</th>
<th>95% CI for Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All end-point events</td>
<td>63 (3.50%)</td>
<td>73 (3.59%)</td>
<td>0.982</td>
<td>0.694</td>
<td>1.391</td>
</tr>
<tr>
<td>Ischemic stroke (%)</td>
<td>33 (1.84%)</td>
<td>38 (1.87%)</td>
<td>1.054</td>
<td>0.648</td>
<td>1.715</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>10 (0.56%)</td>
<td>10 (0.49%)</td>
<td>1.042</td>
<td>0.418</td>
<td>2.6</td>
</tr>
<tr>
<td>Nonfatal intracerebral hemorrhage</td>
<td>3 (0.17%)</td>
<td>4 (0.20%)</td>
<td>0.911</td>
<td>0.201</td>
<td>4.126</td>
</tr>
<tr>
<td>Nonfatal acute coronary syndrome</td>
<td>4 (0.22%)</td>
<td>6 (0.30%)</td>
<td>0.768</td>
<td>0.215</td>
<td>2.749</td>
</tr>
<tr>
<td>All-cause death</td>
<td>13 (0.72%)</td>
<td>15 (0.74%)</td>
<td>0.941</td>
<td>0.445</td>
<td>1.99</td>
</tr>
</tbody>
</table>

The data are presented as n (%). Adjusted for age, sex, history of ischemic stroke, smoking, hypertension, hypercholesterolemia, and National Institutes of Health Stroke Scale (NIHSS) score. CI indicates confidence intervals; and SMART, Standard Medical Management in Secondary Prevention of Ischemic Stroke in China.
program improved adherence to only 1 of the 5 drugs assessed. Improving adherence to the intervention is the first step toward reducing the likelihood of a recurring stroke. Achieving the treatment target may be the next important step. Moreover, most of the participating hospitals were large and located in urban areas (eg, level-3 hospitals), where physicians have the resources to provide high levels of medical care, potentially increasing adherence to guidelines. Although the physicians at the usual care facilities were not familiar with the SMART program, they may improve their practice through continuous medical education gained via experience. The improvement of their practice in this manner would underestimate the power of the SMART program and potentially yield negative results for the comparison of the SMART program with usual care.

With increasing use of the Internet and social media, Internet-based education likely plays an increasingly important role in medical care. However, the percentage of individuals with Internet access is only 2% among people >60 years old (which comprises the majority of patients with stroke), according to a survey performed by the China Internet Network Information Center (CNNIC) in 2009. Other strategies include educating caregivers to provide support and using mobile phone text messaging to send information and reminders for scheduling appointments, adhering to a medical regimen, and monitoring patient health status.

SMART is a nationwide, multicenter, cluster-randomized controlled trial that provides valuable information on the current status of secondary ischemic prevention. The results of the present study demonstrate that the SMART program is feasible and can improve adherence to statins. The results obtained from this study might provide valuable information for modifying strategies to further improve the quality of secondary stroke prevention.

The present study has several limitations. First, the drop-off rate was high, reflecting the current status of secondary stroke prevention. Patients and physicians typically pay more attention to in-hospital treatment during the acute phase of the illness than to long-term prevention after hospital discharge. Improvements to the SMART program may be necessary to reduce the observed drop-off rate, including methods for offsite follow-up such as regular telephone or text communication. Second, most stroke patients in China are treated in small, below-level-2 hospitals with limited high-quality medical resources; therefore, SMART should enroll more small hospitals to assess the effectiveness of the program. Third, there is an imbalance in the baseline characteristics, which likely reflects the cluster-randomized nature of the trial. A generalized estimating equations linear regression model was used to account for the interdependence of members from same center, and the analysis was adjusted for these imbalance characteristics. Finally, in addition to adherence to pharmacological interventions, adherence to various behavioral factors (eg, smoking cessation, healthy diet, and regular exercise) should be considered because these factors contribute to the prevention of cardiovascular events.

In conclusion, the implementation of a program to improve adherence to secondary ischemic stroke prevention efforts in China is feasible, but the current implementation had only a limited impact on adherence and no impact on 1-year outcomes. Further development of a structured program to reduce vascular events after stroke is needed.

Acknowledgments

We thank the Standard Medical Management in Secondary Prevention of Ischemic Stroke in China (SMART) investigators and centers (Appendix II in the online-only Data Supplement) for their participation in this trial. We thank all of the patients who participated in SMART study.

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Disclosures

None.

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Data Supplement (unedited) at:
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# SUPPLEMENTAL MATERIAL

## Appendix I
Interventions applied to patients in SMART group according the stroke subtype

<table>
<thead>
<tr>
<th>Stroke subtype</th>
<th>Recommended measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large-artery atherosclerosis</strong></td>
<td>Antiplatelet therapy if no contraindication: aspirin 75-150 mg/d or clopidigrel 75 mg/d</td>
</tr>
<tr>
<td><strong>Small-vessels occlusion</strong></td>
<td>Antihypertensive agents if eligible: diuretic agents or angiotensin-converting enzyme inhibitors (ACEIs)/ angiotensin receptor blockers (ARBs) or long-acting calcium channel blockers (CCBs) as the first line choice</td>
</tr>
<tr>
<td>Stroke patient with undetermined etiology having one of the following criteria:</td>
<td>Statins</td>
</tr>
<tr>
<td>1) &gt;50% stenosis of extra-intracranial large artery</td>
<td>Antidiabetic agents if eligible: not specified</td>
</tr>
<tr>
<td>2) Carotid artery atherosclerosis plaque and &gt;55 years old</td>
<td>Smoke cessation</td>
</tr>
<tr>
<td>3) Age 30-55 years with more than two risk factors of hypertension, diabetic mellitus, smoking, hyperlipidemia, or hyperhomocystinemia</td>
<td>Healthy diet, exercise, booklet on stroke prevention</td>
</tr>
<tr>
<td><strong>Cardioembolism</strong></td>
<td>Anticoagulation if no contraindication: warfarin</td>
</tr>
<tr>
<td></td>
<td>Antihypertensive agents if eligible: diuretic agents or angiotensin-converting enzyme inhibitors (ACEIs)/ angiotensin receptor blockers (ARBs) or long-acting calcium channel blockers (CCBs) as the first line choice</td>
</tr>
<tr>
<td></td>
<td>Antidiabetic agents if eligible: not specified</td>
</tr>
<tr>
<td></td>
<td>Smoke cessation</td>
</tr>
<tr>
<td>Stroke of other etiology</td>
<td>Healthy diet, exercise, booklet of stroke prevention education</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Manage underlying disease</td>
</tr>
<tr>
<td></td>
<td>Aspirin 75-150 mg/d or warfarin if no contraindication</td>
</tr>
</tbody>
</table>
Appendix II:

Institutions participating SMART study (with numbers of patients enrolled and local lead investigators)

Beijing Daxing District Hospital (53, LZ Zhao); Beijing Ji Shui Tan Hospital, (100, YH Sun); Beijing Shi JiTan Hospital (129, ML He); China PLA General Hospital (50, CQ Pu); China Rehabilitation Research Center (27, T Zhang); Daping Hospital (60, HD Zhou); First Affiliated Hospital of Xinjiang Medical University (38, XN Zhang); General Hospital of the Navy (60, XK Qi); Guangzhou First Municipal People’s Hospital (105, MY Li); Henan Provincial People’s Hospital (78, JW Zhang); Huashan Hospital Fudan University (31, Q Dong); Inner Mongolia Batou City Central Hospital (115, JF Zhang); Luhe Hospital of Tongzhou District (49, HS Du); Jilin University (99, J Wu); Nanjing General Hospital of Nanjing Military Command, (54, XF Liu); No 263 Hospital of PLA (127, JL Zhang); No 309 Hospital of PLA, (50, YP Chen); Peking Union Medical College Hospital (133, LY Cui); Peking University Third Hospital (49, DS Fan); Pinggu County Hospital (60, GY Zhang); Qilu Hospital of Shandong University (60, CZ Yan); Qinghai Provincial People’s Hospital (66, SZ Wu); Shanghai Changzheng Hospital (79, XY Chen); Second Affiliated Hospital of Zhejiang University College of Medicine (74, MP Ding); Southwest Hospital (49, SG Shi); The Affiliated Drumtower Hospital of Nanjing University Medical School (72, Y Xu); The Appurtenant Hospital of Chifeng University (106, QF Cui); The First Affiliated Hospital of China Medical Sciences University (101, CD Zhang); The First Affiliated Hospital of College of Medicine (71, JW Wang); The First Affiliated Hospital Sun Yat-Sen University (49, QS Zeng); The First Hospital of Harbin Medical University (100, WZ Wang); The First Hospital of Hebei Medical University (46, MW Wang); The General Hospital Under Tianjin Medical Sciences University (105, Y Cheng); The Second Hospital of Harbin Medical University (115, LM Zhang); The Second Hospital of Hebei Medical University (97, ZZ Li); The Second Hospital of Shandong University (59, W Shang); The
Second Affiliated Hospital of Soochow University (51, YJ Cao); The Third Hospital of Hebei North University (85, SM Yue); The Third Hospital of Hebei Medical University (64, JY Liu); The Third People's Hospital of Dalian (197, JB Zhang); The Zhongnan Hospital of Wuhan University (56, JJ Zhang); Tiantan Hospital, Capital Medical University (175, YJ Wang); Tianjin Third Central Hospital, (82, ZZ Zhang); West China Center of Medical Sciences (98, D Zhou); Xiangya Hospital of Central South University (107, J Xia); Xuanwu Hospital, Capital Medical University (89, JP Jia); Yutian County Hospital (101, JC Wang)
在中国开展的基于指南的规范缺血性卒中二级预防项目

Implementation of a Structured Guideline–Based Program for the Secondary Prevention of Ischemic Stroke in China

彭斌, 倪俊, Craig S Anderson, 朱以诚, 王建明, 周立新, 蒲传强, 吴江, 王拥军, 崔丽英, 代表 SMART 研究组

通讯作者: 崔丽英 中国医学科学院北京协和医院神经科

卒中是全球性健康问题,2010 年全球疾病负担研究(GBD2010)显示以疾病调整生命年(DALYs)评估,卒中居疾病负担第三位。在发展中国家,过早死亡与卒中相关疾病已导致日益增加的经济和社会负担。在中国,政府已认识到卒中一级二级预防的重要性,支持有关组织发布多项国家卒中指南以改善现状;但是指南对于患者结局的影响尚不清楚。

多项研究结果显示指南与临床实践中存在较大差距,尤其是患者出院后对预防措施的依从性明显下降。有研究显示规范的干预项目可改善住院期间卒中治疗的质量,如美国的跟着指南走 - 卒中项目(GWTG)。对干预措施的长期依从性对最大程度保障缺血性卒中二级预防有效性至关重要。应在患者出院后的二级预防中开展类似于住院期间的干预活动。我们开展实施一项全国多中心、区组随机对照、基于指南的规范干预项目 -- 规范化药物治疗研究(SMART)来评估缺血性卒中二级预防规范治疗的可行性和有效性。

研究过程

所有患者均被纳入临床试验。SMART项目包括基于目前指南推荐的多项缺血性卒中二级预防干预措施:针对不同卒中亚型 (TOAST 分型),如大动脉粥样硬化卒中,小血管闭塞性卒中,心源性卒中,其他病因卒中及原因未明卒中)的药物治疗方案;生活方式干预及健康教育。生活方式干预包括戒烟、健康饮食和规律的体育锻炼。患者健康教育包括随访时的宣讲,发放控制卒中危险因素的科普材料,突出对 SMART 项目依从性的重要性,还设立健康教育网站,患者进入专用的密码保护的健康教育网站获得有关知识。常规治疗组仅在随访时接受医师诊治,治疗方案由接诊医师根据其常识决定,不提供网站密码及书面科普材料。在中心集中开展培训后启动项目,各中心参加研究的主要研究者对入组患者进行筛查并填写病例记录表(CRF)。研究中心收集患者的基本信息及随访资料。项目组对各中心进行实地监测评估医师执行 SMART 项目的情况,检查核实医疗记录以评估实验数据的质量。

背景和目的:中国人群中缺血性卒中发病率高,但二级预防措施依从性低。

方法:我们开展一项全国多中心、区组随机对照研究,共 47 家医院参加,其中 23 家为规范治疗组,24 家为常规治疗组。规范治疗措施包括基于指南推荐的药物治疗方案和生活方式改进,采用书面材料和网络教育形式进行缺血性卒中二级预防健康宣教。主要有效性研究终点是患者在出院 12 个月时对二级预防措施的依从性。本研究在临床研究登记中心注册(NCT00664846)。

结果:出院 12 月时,规范治疗组(SMART 组)有 1287 名患者 (72.1%),常规治疗组有 1430 名患者 (72%)完成研究。SMART 组患者对他汀的依从性显著高于常规治疗组 (56% vs 33%; P=0.006),但两组在抗血小板药物 (81% vs 75%; P=0.088)、降压药物 (67% vs 69%; P=0.661) 和降糖药物 (73% vs 67%; P=0.297) 间没有显著差异。复合终点事件(复发缺血性卒中、出血性卒中、急性冠脉综合征和全因死亡)在两组间也没有显著性差异(5.6% vs 3.59%; P=0.921)。

结论:在中国推行旨在改善缺血性卒中二级预防卒中依从性的项目是可行的,但是目前本项目对依从性影响有限,并未改善卒中后 1 年的结局。应进一步完善项目以减少卒中后血管事件。

(Stroke. 2014;45:515-519.)
结局评估

研究主要有效性结局是患者对 SMART 项目中缺血性卒中二级预防措施的依从性。次要结局包括新发缺血性卒中、脑出血、急性冠脉综合征和全因死亡的复合终点。不论各中心研究者认为是否与治疗有关（明确相关、不确定或无关），均记录随访中发生的严重不良事件，并上报数据监测委员会。

统计分析

基于前期研究，抗血小板药物使用率为 76%，预测实施 SMART 项目后，与常规治疗组相比，SMART 组可提高抗血小板药物使用率 10%。基于此，以 2%作为允许差值，假设发生 1 类错误的概率为 5%，预测每组样本数为 1771。采用双向 t 检验。但项目组预计失访率为 15%，最终估计需入组 4074 名患者。

我们使用 t 检验或卡方检验比较两组间的基线资料。计算患者出院至 12 个月的依从性。依从性的评估采用如下方法：评估患者根据指南需要采用的措施，对每一项措施，采用二分法统计，1 代表执行该措施，0 代表未执行该措施。对每一项措施的依从性定义为实际执行措施的患者数与应该执行该项措施的患者数的比值。我们采用广义估计方程（GEE）线性回归法来评估 SMART 组与依从性的关系，采用 Cox 比例风险模型分析事件时间结局。

P<0.05 代表统计学显著性差异。所有统计分析在 SAS 9.2 统计软件进行（SAS Institute Inc, Cary, NC）。

结果

在 2008 年 4 月 1 日至 2010 年 12 月 31 间，47 家医院共入组 3821 名患者，患者基线资料显示与常规治疗组相比，SMART 组患者年龄略大（62±11 vs 60±12；P=0.004），神经功能损伤略重（NIHSS 评分 4.9±4.5 vs 4.3±4.3；P=0.001），高脂血症比例略高（17% vs 14%；P=0.04），吸烟患者略少（30% vs 34%；P=0.002）（表 1）。调整年龄、NIHSS 评分后，出院时药物使用率在两组间无显著性差异（表 2）。

二级预防措施依从性

分别计算出院时、6 个月（表 3）及 12 个月（表 4）患者对二级预防措施的依从性（抗血小板药物、降压药物、降糖药物、他汀和华法林）。尽管在 12 个月时抗血小板药物（SMART 组：81% vs 常规治疗组：67%；P=0.066）、降糖药物（SMART 组：73% vs 常规治疗组：67%；P=0.297）的依从性在两组间无显著性差别，但他汀药物的使用率显著高于常规治疗组（56% vs 33%；P=0.006）。在 SMART 组 1791 名患者中，记录 1624 次登陆网站记录（0.91 次/人年）。

次要终点结局（新发缺血性卒中、脑出血、急性冠脉综合征及全因死亡）在两组间无显著性差异（3.50% vs 3.59%；P=0.921；表 5）。

讨论

本研究是一项全国多中心、区组随机对照研究，提供了中国患者对规范缺血性卒中二级预防项目依从性的最新信息。与常规治疗组相比，尽管抗血小板药物、降压药物、降糖药物或他汀都依从性略低，但研究设计的 SMART 项目可提高 12 个月时患者对这些药物的依从性，复合血管事件在两组间未见显著性差异。

尽管强有力的证据及多个指南支持长期使用二级药物，但仍然存在很多高危患者在出院后停止用药。中国目前卒中二级预防现状并不令人满意。近来的一项中国城市缺血性卒中二级预防研究（ChinaQUEST）显示抗血小板药物和降脂药物使用率在出院后显著降低。这些现象提示临床医师及患者应更重视改进出院后卒中二级预防的依从性。我们应在世界范围内开展类似的卒中二级预防项目。

对于非心源性卒中患者均推荐抗血小板药物以降低卒中复发及其它心血管事件的风险。尽管药物使用方便且价格便宜，耐受性好，但抗血小板药物使用依从性并不乐观。ChinaQUEST 研究显示抗血小板药物使用率由出院时的 81% 下降至出院 1 年时的 66%。与降压药物不同，使用降压药物有血压测量的依据，使用抗血小板药物时还缺乏对有效性的可评价标准，一旦再次出现缺血性事件，患者就会质疑抗
血小板药物的有效性,有些患者还担心药物的出血性风险。因此,应更重视患者教育以提高抗血小板药物的依从性。

本研究结果显示患者对降压药物和降糖药物的依从性保持稳定。12 月的随访阶段差异不大,降压药物良好的依从性与其他研究类似。

这在一定程度反映对高血压作为卒中主要危险因素的重视。此外,中国高血压防治指南及其他医学教育活动也提高了公众对高血压和糖尿病的认识。

本研究中 12 个月时华法令的使用率在 SMART 组及常规治疗组仅为 28% 和 29%。这些数据与台湾登记研究的情况类似,出院时房颤患者华法令的使用率仅为 28%,德国的一项研究中房颤患者使用抗凝药物的比例也仅为 31%。抗凝药物使用率低的最主要原因是由于定期药物检测导致的使用不方便。在中国,提高抗凝药物使用率的策略包括对临床医师及患者的健康教育,以及为患者提供更方便的 INR 检测手段。

强有力的证据显示他汀在卒中二级预防中的有效性。尽管 12 个月时 SMART 组他汀使用率显著高于常规治疗组以及 ChinaQUEST Stroke February 2014
研究终点数据（56% vs 17%），但与发达国家相比仍有不小的差距。瑞典处方药物登记研究数据显示卒中后12个月时他汀药物使用率为74%。本研究结果提示在缺血性卒中二级预防中患者教育可显著提高他汀药物的使用率。因此，将来该项工作还应该得到加强。

与常规治疗组相比，SMART组心血管事件结局并未减少。这可能与下列几项原因有关。最主要的原因可能是随访时间相对较短，样本量略少，在大样本长期随访中，SMART项目可显著显示其有效性。其次，SMART项目仅提高了5项药物中的一种药物的使用率。提高依从性是减少卒中复发风险的第一步，达到治疗靶目标可能是更重要的阶段。第三，本研究绝大部分医院是位于城区的大医院（三级医院），临床医师的诊疗水平较高，可能提高患者对指南的依从性。尽管常规治疗组的医师并不知道SMART项目方案，但其可能通过患者教育提高依从性。常规治疗组医师水平的提高在一定程度上削弱了SMART项目的效应，可能导致阴性结果。

随着网络和社会媒体的广泛运用，基于网络的教育方式可能在医学教育中发挥重要作用。但是，中国网络信息中心的研究显示2009年超过60岁的人群中上网的比例仅为2%。应结合其他的策略来提高教育的依从性，如为护士提供健康教育、使用手机短信提醒定期随访信息、使用药物及监测患者健康状况。

SMART研究是一项全国多中心、区组随机对照研究，为当前缺血性卒中二级预防提供了有价值的信息。研究结果显示SMART项目是可行的，可提高他汀药物的依从性。本研究结果对今后进一步改进卒中二级预防策略提供依据。

本研究有几项局限。第一，患者脱落率较高，这也反映目前卒中二级预防的现状。临床医师和患者更重视急性期住院期间的治疗，对出院后的长期预防重视不够。应改进SMART项目以减少患者脱落率，如定期电话随访等。第二，中国绝大部分卒中患者在小医院治疗，二级以下的医院高质量的医疗资源有限。因此，SMART项目应该纳入更多小医院。第三，在基线数据中存在不平衡，可能是由于区组随机所致。我们使用采用广义估计方程（GER）线性回归模型来分析同一中心个体间的相互关系，并在统计分析时对这些不平衡因素进行校正。第四，除评估药物依从性外，还应考虑不同行为因素（如戒烟、健康饮食及规律的锻炼）的影响，这些因素也有助于预防心脏事件。

综上所述，在中国开展旨在提高缺血性卒中二级预防依从性项目是可行的。不过现行的方案对依从性的影响尚有限，并未影响1年时的结局。应进一步改进项目以减少卒中后血管事件复发。

参考文献