The Prescribing Patterns of Antithrombotic Agents for Prevention of Recurrent Ischemic Stroke

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Abstract-

Objectives: Antithrombotic agents are effective in the secondary prevention of ischemic strokes. In the present study, we sought to determine the antithrombotic prescribing patterns of neurologists in patients with first-ever ischemic stroke and also to identify the factors influencing the choice of a specific agent and what changes are made when a recurrent stroke occurs in these patients.

Methods: We retrospectively reviewed the medical records of neurology patients who were diagnosed with first-ever ischemic stroke and were antithrombotic naïve from January 1, 2000 to December 31, 2000. Patients' antithrombotic agents at discharge and during the follow-up period were reviewed to identify factors affecting the choice of antithrombotic agents.

Results: A total of 376 patients experienced non-fatal first-ever ischemic stroke. Of these, 351 were prescribed antithrombotic agents at discharge, while the remaining 25 were not on antithrombotic treatment. Low-dose aspirin was the most commonly prescribed agent (65%). The most important determinant for the choice of other antiplatelet agents was aspirin intolerance. Not surprisingly, only 36% of the patients with atrial fibrillation were treated with oral anticoagulants at the time of hospital discharge.

Conclusion: Aspirin remains the most commonly used antithrombotic agent for the prevention of recurrent stroke among antithrombotic naïve patients with a first-ever ischemic stroke in our institution. Our results demonstrate that current recommendations find their way into clinical practice, but to a limited extent. We aim that all patients discharged from our hospital after strokes must receive appropriate antithrombotic drugs for prevention of recurrent strokes provided if there are no contraindications to therapy.

Key Words: Antithrombotic therapy, Antiplatelet agents, Recurrent stroke, Stroke prevention

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INTRODUCTION

The efficacy of antithrombotic medication in preventing recurrent strokes or other major vascular events has been proven in several trials[1-4]. They are an important component of the neurologist's armamentarium for

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stroke prevention. Aspirin has remained an important and most widely used preventive medical therapy in patients with ischemic cerebral events[5]. In the past 10 to 15 years, newer antiplatelet agents have been approved for stroke prevention, and at least as effective as aspirin in secondary prevention. They provide additional choices and physicians are often left to make the decision as to which agent to choose in a patient-by-patient basis.

In the present study, we therefore sought to look at the prescribing patterns of neurologists and identify the factors influencing the choice of a specific agent over another and what changes are made when a recurrent stroke occurs in these patients.

METHODS

We retrospectively reviewed the medical records of all patients who were admitted to the neurology service with the diagnosis of ischemic stroke at Mackay Memorial Hospital from January 1, 2000 to December 31, 2000. Mackay Memorial Hospital is a 2060-bed medical center in the northern part of Taipei, Taiwan serving a population of heterogeneous social class. Patients were excluded in the analysis if their strokes were recurrent or fatal, if they were on antithrombotic agents prior to the first-ever ischemic stroke, or those who were lost to follow-up after the first-ever ischemic stroke. Antithrombotic agents available on formulary included aspirin, ticlopidine, standard-release dipyridamole and warfarin. All our patients have had national health insurance which could be a factor influencing our clinical decision making among different antiplatelet therapies. We looked at the antithrombotic agents that patients were placed on at discharge and during the 5 years follow-up in order to determine if there were other factors that affected the choice of a specific antiplatelet agent. In addition, stroke recurrences were also analyzed to determine what changes were made after recurrent strokes occurred. We defined recurrence as new neurological deficits lasting for more than 24 hours in another part of the brain or worsening of the previous deficits not considered to be caused by edema, hemorrhagic transformation or intercurrent illness.

RESULTS

A total of 780 ischemic stroke patients were admitted to our ward. Of these, 431 patients had first-ever ischemic stroke and were antithrombotic naïve. Fifty-five patients were excluded because of lost to follow-up, leaving 376 patients included for analysis. All of these remaining patients were not on antithrombotic therapy prior to hospitalization. Of the 376 patients, 351 (93.4%) were discharged on antithrombotic medication, and 25 (6.6%) were not treated either on discharge or during the follow-up period. Baseline characteristics of the patients are listed in Table 1. Multiple risk factors were identified in all of the patients. However, we were not able to determine the exact mechanism of the qualifying events because this study was done retrospectively through chart review. Nevertheless, the subtype of ischemic stroke may be classified as presumably noncardioembolic in 332 patients and cardioembolic for the remaining 44 patients. The antithrombotic agents prescribed on discharge are identified in Table 2. Table 3 demonstrates the changes in therapy among different antithrombotic agents during the 5 years follow-up. We found that monotherapy with low-dose aspirin remained the initial choice in nearly 65% (227) of patients. The dosage of

Table 1. *Baseline characteristics of the 376 patients*

Characteristic	
Age - years	
Mean ± SD	65.2 ± 12.3
Range	23 - 91
Sex - number (%)	
Male	235 (62.5%)
Female	141 (37.5%)
Risk factors - number (%)	
Hypertension	310 (82.4%)
Hyperlipidemia	157 (41.8%)
Tobacco use	154 (41.0%)
Cardiac disease	147 (39.1%)
Ischemic heart disease	103 (27.4%)
Atrial fibrillation	44 (11.7%)
Diabetes	142 (37.8%)

Table 2. *Antithrombotic medication prescribed at discharge*

Antithrombotic medication	
On discharge medication - number (%)	
Overall	
Yes	351 (93.4%)
No	25 (6.6%)
Presumed noncardioembolic stroke - 332 (88.3%)	
Yes	307 (92.5%)
No	25 (7.5%)
Antiplatelet only	
Aspirin	199 (64.8%)
Ticlopidine	93 (30.3%)
Standard-release dipyridamole	7 (2.3%)
Aspirin + standard-release dipyridamole	2 (0.6%)
Anticoagulant only	6 (2.0%)
Presumed cardioembolic stroke - 44 (11.7%)	
Yes	44 (100%)
No	0
Antiplatelet only	28 (63.6%)
Anticoagulant only	13 (29.5%)
Anticoagulant + antiplatelet	3 (6.8%)

Table 3. *Number of patients and reasons for changes of antithrombotic medication*

Antithrombotic medication	
1. *Aspirin - number (%)*	
At discharge	227 (65%)
Changed to other antithrombotic agents during 5 years follow-up	28 (12%)
Ticlopidine	18 (64%)
Gastrointestinal bleeding or ulcers	13 (72%)
Recurrent stroke	5 (28%)
Standard - release dipyridamole	7 (25%)
Gastric discomfort	4 (57%)
Recurrent stroke	1 (14%)
Ischemic heart disease	1 (14%)
Uremia	1 (14%)
Warfarin	3 (11%)
Atrial fibrillation	2 (67%)
Intracranial stenosis	1 (33%)
2. *Ticlopidine - number (%)*	
At discharge	93 (26%)
Changed to other antithrombotic agents during 5 years follow-up	5 (5.4%)
Aspirin	5 (100%)
No explicit reasons	4 (80%)
Recurrent stroke	1 (20%)
3. *Warfarin - number (%)*	
At discharge	22 (6.3%)
Changed to other antithrombotic agents during 5 years follow-up	5 (23%)
Aspirin	5 (100%)
Bleeding and questionable compliance	5 (100%)
4. *Overall - number (%)*	
Changed antithrombotic agent	38 (11%)
Receiving the same antithrombotic agent	313 (89%)

aspirin used was 100 mg per day in all patients. Of the 227 patients, 28 patients had their antiplatelet regimen altered during the follow-up period. Of these, 18 were changed to ticlopidine due to gastrointestinal bleeding or ulcers in 13 and recurrent ischemic strokes in 5. Seven patients were switched to standard-release dipyridamole due to gastric discomfort in 4, and recurrent ischemic stroke, ischemic heart disease and uremia in the 3 other patients. The remaining 3 patients had their aspirin changed to oral anticoagulants due to atrial fibrillation in 2, and severely stenosed intracranial vessels in 1. Two patients received combination of antiplatelet agents due to a coexisting coronary artery disease. Ticlopidine monotherapy was prescribed on discharge to 93 patients primarily due to a history of gastric ulcers or gastrointestinal bleeding, multiple risk factors and concurrent peripheral arterial diseases. Of these, 4 patients had their antiplatelet agent switched to aspirin without explicit reasons but 1 was due to recurrent ischemic stroke. Seven patients were placed on standard-release dipyridamole at discharge and received the same agent at follow-up due to coexisting ischemic heart disease. A total

of 22 patients were discharged on oral anticoagulants, 73% (16) of them had atrial fibrillation, while the remaining 6 patients had stenoses of intracranial arteries. In 5 of these patients, an oral anticoagulant was switched to an antiplatelet agent during the follow-up period because of bleeding and questionable compliance. Not surprisingly, a rate of oral anticoagulation in patients with atrial fibrillation was only 36%. We found another 3 patients who were discharged on a combination therapy of antiplatelet and oral anticoagulant due to coexisting atrial fibrillation and coronary artery diseases. During the 5 years follow-up period, 40% of the 25 patients not receiving antithrombotic therapy had recurrent ischemic strokes, whereas only 48 (13.7%) of the 351 patients placed on antithrombotic medication had a recurrent ischemic stroke. All of them were still on antithrombotic treatment, and 89% received the same antithrombotic agent as prescribed on discharge.

DISCUSSION

The most effective strategy to reduce the burden of stroke is to prevent recurrent stroke. Other than risk factor management, antithrombotic agents have a well-established and important role in secondary prevention of ischemic stroke[6]. The emergence of newer antiplatelet agents provides additional choices for physicians to choose. Physicians may then ask the questions: which antiplatelet regimen to use, and how long to continue the treatment? Even though numerous recommendations and clinical guidelines about the choice of antiplatelet agent in the secondary prevention of stroke have been published[7-10], antiplatelet therapy still must be tailored for each individual patient based on the risk factors, side effects of therapy, and cost considerations[11]. Furthermore, there are no available guidelines regarding the occurrence of recurrent strokes despite administration of antithrombotic therapy. For this reason, we choose year 2000 to look at the experience in our institution and attempt to determine what are the factors influencing the choice of a specific antithrombotic therapy and what changes are made to the antithrombotic agents when a recurrent stroke occurs in these patients despite being on treatment.

Although data from randomized controlled trials have clearly demonstrated the value of antithrombotic therapy in the secondary prevention of ischemic stroke, there is still a gap between routine clinical practice and evidence-based clinical guidelines. The REACH Registry demonstrateed a pattern of underutilization of antiplatelet therapy among patients with or at risk for atherothrombosis[12,13]. However, the Taiwanese patients in the REACH Registry received antiplatelet therapy more frequently than the patients from other geographical regions (84.7% vs. 78.6%)-prescribed in 85.28% of patients with cerebrovascular diseases. Of these, 55% received aspirin and the remaining patients received other antiplatelet agents[13]. The results from our study also show a considerably high rate of patients discharged from the hospital with the prescription of antithrombotic medication. For the presumed noncardioembolic stroke, 92.5% (307) of patients received antiplatelet therapy. Aspirin was prescribed in 65% (199) of patients, while the remaining 35% had been taking other antiplatelet agents. The rate of patients receiving aspirin observed in our study was higher than that reported in the Taiwan REACH Registry (65% vs. 55%)[13]. Despite evidence from randomized controlled clinical trials demonstrating the substantial benefit of warfarin in reducing the risk for ischemic stroke in patients with atrial fibrillation[14,15], practice pattern evaluations consistently identify underuse[16]. Several studies showed that only 15% to 44% of patients with atrial fibrillation and no contraindication to warfarin therapy were prescribed warfarin. The use of warfarin in patients with atrial fibrillation at our institution is likewise in a suboptimal level, achieving only 36%.

To the best of our knowledge, this is the first time that a study has evaluated the prescribing patterns of antithrombotic agents not only at the time of discharge but also during the 5 years follow-up period. This study is also unique due to the fact that all patients had a first-ever ischemic stroke and were not on prior antithrombotic therapy. In looking at the prescribing patterns of our institution, low-dose aspirin remains to be the most commonly used first-line therapy for prevention of recurrent stroke. Ticlopidine and standard-release dipyridamole are used instead of clopidogrel and combination of

extended-release dipyridamole and aspirin because these agents were not available in our institution until later in the study.

Mayer et al.[17] reported in their study that individual risk factors do not appear to play a major role in the therapeutic decision making when determining the choice of antithrombotic therapy. However, in our study we found that they might appear to be a driving factor in a minority of our patients. About 36% of our patients with atrial fibrillation were discharged on an oral anticoagulant instead of an antiplatelet agent. Additionally, some patients with stenosed intracranial vessels received oral anticoagulants despite a lack of evidence regarding its efficacy in this situation. Furthermore, 2 patients with coexisting coronary artery diseases were also placed on a combination therapy. Individual experiences, costs of the drug, and patient characteristics were the probable reasons why a specific agent was preferred over another at our institution. Moreover, we found that the most important factor influencing the use or nonuse of a specific antithrombotic medication was divergent interpretations of the existing evidence among neurologists.

No clinical trials have directly addressed the issue about what should be the subsequent therapy for patients who experienced recurrent strokes while on antithrombotic therapy[17,18]. In our study, there were 48 patients who had experienced recurrent strokes while on antithrombotic therapy. Although it may seem plausible to switch to an alternative drug, only 7 patients in our study had their treatment regimen changed. The remaining patients were maintained on the same antithrombotic agent as prescribed on discharge. The potential reason for this is that neurologists at our institution believed that efforts should be focused on modification of vascular risk factors rather than switching to other antithrombotic agents.

This study has potential limitations. It was a retrospective study conducted through chart review in patients admitted in the neurological department. We were unable to determine the exact mechanisms of stroke, therefore we cannot exclude the possibility that type of stroke play a role in prescribing patterns. Formulary and health insurance were the other factors that may influence the choice of a specific therapy. Another limitation is that some of the newer agents may not have been approved in our country at the time of their discharge, but this issue was reevaluated during the follow-up period and the results were similar.

In conclusion, our results demonstrated that low-dose aspirin is the most widely used first-line agent for prevention of recurrent stroke. All patients with a history of ischemic stroke and atrial fibrillation, in whom anticoagulation is indicated and who do not have contraindications should receive warfarin. More clearly defined guidelines are urgently needed for patients who experienced a recurrent ischemic stroke while on appropriate antithrombotic treatment. Results from the on-going trials will be the only way to determine if a combination therapy may be more superior to monotherapy with respect to specific patient groups[19].

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