The High-Risk TIA Patient:
Part Two—Management

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Presented at the University of Toronto's Saturday at the University, January 2006.

Part one of this article discussed the diagnostic evaluation of patients with transient ischemic attack (TIA). Part two outlines treatment approaches and incorporates recommendations from new guidelines[1-3] and recent trials of clinical importance.

Preventing strokes due to carotid artery disease

About 10% to 20% of ischemic strokes are caused by symptomatic extracranial carotid artery disease. Therefore, rapid identification of TIA patients with symptomatic carotid stenosis who would be candidates for carotid revascularization is a top management priority.

Stroke prevention surgery with carotid endarterectomy is highly beneficial for secondary prevention in patients with a recently symptomatic severe carotid artery stenosis (70% to 99%) and it is also beneficial for selected patients with moderate stenosis (50% to 69%).[4] Endarterectomy is not indicated for patients with mild (< 50%) carotid stenosis or in cases of complete (100%) carotid occlusion.

The benefit of carotid endarterectomy is highly dependent on the *timing* of surgery after the presenting event. A pooled analysis demonstrated that surgery is most effective when performed *within two weeks* of the index TIA or stroke event and the benefit declines rapidly with time.[5] For example, in patients with symptomatic carotid stenosis of 70% to 99% who have surgery within two weeks, only three patients need to be operated on to prevent one stroke in five years (NNT is three). The benefit of endarterectomy is much lower if surgery is delayed more than three months. This time-dependent decline in benefit is especially pronounced for patients with moderate carotid stenosis. In such patients, surgery is most beneficial when performed within the first two weeks of the ischemic event; the benefit is essentially lost if surgery is delayed more than two weeks, with net harm if surgery is performed after more than three months in unselected patients.[3]

Published recommendations now call for early surgery. According to the American Academy of Neurology, "for patients with severe stenosis and a recent TIA or non-disabling stroke, carotid endarterectomy should be performed without delay, preferably within two weeks."[6] Similarly, the 2006 National Stroke Association guidelines on TIA management recommend that "surgery should be performed as soon as the patient is fit for the procedure, preferably within two weeks of TIA."[3]

Carotid endarterectomy is most effective when performed soon after a TIA or stroke, ideally within two weeks of the event.

The practice implication is that we should aim to minimize any unnecessary delays in the initial assessment, diagnosis, referral and surgery for patients with recently symptomatic carotid artery disease. The consequences of such delays have been reported—in one population-based study of all patients with recently symptomatic carotid stenosis

referred for endarterectomy, one in three patients had a recurrent stroke while awaiting surgery.[7]

Carotid angioplasty and stenting is an alternative to surgery, particularly for individuals who are at too high a risk for surgery or in cases where endarterectomy is technically not feasible. Recent clinical trials have provided conflicting results, with some studies showing that carotid stenting has comparable efficacy and safety to surgery, while others demonstrated higher complication rates with stenting. At present, many authorities view carotid stenting as an investigational procedure, pending the results of ongoing randomized trials and longer-term safety data. The Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) is currently underway and will hopefully provide more definitive data on the role of carotid stenting for stroke prevention. A useful review of carotid stenting is available online.[8]

Preventing strokes due to AF

Atrial fibrillation (AF) is the most common cardiac cause of stroke, accounting for about one in six ischemic strokes overall. Warfarin is highly beneficial for stroke prevention in AF. For patients with AF who have had a TIA or ischemic stroke, the two-year risk of recurrent stroke is about 20% without antithrombotic therapy. This risk is reduced to about 16% with ASA and it is reduced to 7% with warfarin.[9]

Unfortunately, warfarin remains underutilized in patients who would benefit from it. Physicians tend to underestimate the benefit of warfarin, overestimate its risks and overestimate the benefit of ASA. An excellent patient decision aid that explains the benefits and risks of warfarin vs. ASA is available at www.canadianstrokenetwork.ca and can be helpful for counselling patients and families and encouraging medication compliance.[7] The target INR should be 2.5 (range 2.0 to 3.0) for most patients. Updated practice guidelines are available.[10]

A trial of ASA combined with clopidogrel for stroke prevention in AF found that this combination was associated with less efficacy and greater bleeding rates than warfarin.[11] Some clinicians initiate anticoagulation with low molecular weight heparin after a TIA until the INR is therapeutic on warfarin. Warfarin is not generally recommended for stroke prevention in individuals with a non-cardioembolic TIA or ischemic stroke, as several large trials have shown that warfarin provides no added benefit over antiplatelet therapy in such patients and is associated with higher bleeding risks.

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Optimizing BP

Hypertension is the single most important modifiable risk factor for both ischemic stroke and intracerebral hemorrhage and it is a major contributor to small-vessel "silent" brain infarcts that can lead to vascular cognitive impairment and dementia. By regularly monitoring and treating BP in the office, FPs play a critical role in both primary and secondary stroke prevention. We recommend following the Canadian Hypertension Education Program guidelines, aiming for a target < 140/90 mmHg (< 130/80 mmHg in patients with diabetes or chronic renal disease).[12] Given that there is a continuous relationship between increasing BP and increasing stroke risk even

within the "normal" range of < 140/90 mmHg,[13] many believe that the lower the BP the better for stroke prevention. Even small magnitude reductions (*e.g.*, reduction of diastolic pressure by 5 mmHg to 6 mmHg, maintained over five years) translate into major benefits (42% relative risk reduction for stroke).[14] Most patients require more than one antihypertensive agent for adequate control. Lifestyle modifications, such as reducing dietary sodium and regular physical activity are strongly advised. Reducing daily sodium intake to between 1,200 mg and 1,500 mg is estimated to reduce the prevalence of hypertension by 30%.

Antiplatelet therapy options

Antiplatelet therapy options for secondary prevention after a non-cardioembolic TIA or ischemic stroke include either enteric-coated ASA, usually low dose preferred (*e.g.*, 81 mg q.d.), ASA (25 mg)/extended-release dipyridamole (200 mg) combination b.i.d., or 75 mg q.d. of clopidogrel. For patients already taking ASA who have a TIA, switching to either ASA/extended-release dipyridamole or clopidogrel is generally recommended rather than increasing the ASA dose.[4] The recently published European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) provides further data in support of the ASA/dipyridamole combination as superior to ASA alone for secondary prevention.[15] The largest stroke prevention trial to date, whose results are expected sometime in 2008, is the Prevention Regimen For Effectively avoiding Second Strokes (PROFESS) trial, which compares the efficacy and safety of clopidogrel vs. ASA/extended-release dipyridamole for secondary stroke prevention. This study is also investigating the effects of an ARB (telmisartan) in this population.

Lifestyle modifications, such as reducing dietary sodium and regular physical activity are strongly advised.

The routine long-term use of dual antiplatelet therapy with ASA and clopidogrel is not indicated for primary stroke prevention and is not generally recommended after a TIA or ischemic stroke (except for patients post-coronary stent who may need to be maintained on such therapy). According to the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial and the Management of AtheroThrombosis with Clopidogrel in High-risk patients with recent transient ischemic attacks or ischemic stroke (MATCH) trial, the long-term use of ASA plus clopidogrel was associated with increased adverse bleeding events with little or no net benefit.[16,17] The potential role of short-term (*e.g.*, one to three months) use of this combination for stroke prevention is the focus of ongoing research; short-term use of such combination therapy showed a trend toward a small benefit in a recent pilot trial.[18]

For acute treatment with ASA, a loading dose of at least 160 mg is recommended to achieve rapid platelet inhibition. Similarly, clopidogrel

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can be started with a loading dose of 300 mg after an acute TIA. To minimize the chance of headache as a potential side-effect when initiating ASA/extended-release dipyridamole combination, some clinicians start with once daily dosing for one week (overlapping with ASA 81 mg q.d.), then increasing to the standard twice daily dosing thereafter and discontinuing ASA.

Finally, caution is advised when discontinuation of long-term antiplatelet therapy for minor procedures is contemplated; it is estimated that the risk of ischemic stroke or TIA is increased threefold within one month after the discontinuation of antiplatelet therapy.[19]

Patients presenting with a suspected acute high-risk TIA or minor stroke should be evaluated promptly, ideally within 24 hours.

Lipid lowering

Current Canadian guidelines recommend a target LDL-C < 2.0 mmol/L for high-risk patients and a total cholesterol to HDL-C ratio < 4.0 mmol/L.[20] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was a secondary stroke prevention trial that investigated atorvastatin 80 mg vs. placebo in patients who had a TIA or stroke within the preceding one to six months, a baseline LDL-C of 2.6 mmol/L to 4.9 mmol/L and no known coronary disease. Over a median follow-up of nearly five years, there was a significant reduction in stroke events (relative risk reduction 16% for total strokes, 21% for ischemic strokes) in addition to major coronary events (35% relative risk reduction).[21]

The practice implication is that patients with noncardioembolic TIA or ischemic stroke should be treated with a statin, unless contraindicated, especially those with evidence of atherosclerotic vascular disease (*e.g.*, carotid stenosis). In a post hoc analysis of patients in the SPARCL trial who had a recurrent stroke during follow-up, there was a reduction in stroke severity in the statin-treated patients compared to the placebo-treated patients.

Overall safety and tolerability of high-dose statin therapy was confirmed in this study, with a 2.2% incidence of liver enzyme elevation greater than three times the upper limit of normal. Some concern has been raised by the observation in this trial of a significantly higher rate of hemorrhagic stroke in those treated with high-dose statin therapy compared to placebo (2.3% vs. 1.4%), although a meta-analysis of statin trials did not show an increased risk of hemorrhage.

Referral for patients

Patients with a suspected acute high-risk TIA or stroke should ideally be referred to an ED for initial assessment if rapid access to an outpatient stroke prevention clinic is not available. The main reason for emergency assessment is to enable appropriate diagnostic investigations to be obtained rapidly and to minimize delays in initiating stroke prevention therapies. Some patients with non-resolving, disabling stroke symptoms may qualify for treatment with thrombolytic therapy within the first three hours of symptom onset.

A brief hospital admission for patients with high-risk TIA or minor stroke has been recommended by some, but remains controversial and many institutions do not have a policy to admit such patients.[5,22] Rapid outpatient TIA clinics may be preferable to inpatient care, so long as they are rapid enough. In Ontario, 24 regional stroke prevention clinics have been established recently as part of a provincial plan supported by

the Ministry of Health and the Heart and Stroke Foundation and similar initiatives are underway across the country as part of the Canadian Stroke Strategy. The recently published early use of EXisting PREventive Strategies for Stroke (EXPRESS) study demonstrated the effectiveness of urgent, aggressive outpatient management of TIA and minor stroke patients. This study showed that the 90-day stroke risk could be reduced from 10% (with usual care) to 2% (in a clinic model where patients receive immediate treatment with a standardized protocol).[23]

Conclusions

A TIA represents a potential vascular and neurological emergency. Patients presenting with a suspected acute high-risk TIA or minor stroke should be evaluated promptly, ideally within 24 hours according to new guidelines. The two most important etiologies not to be missed are:

- Symptomatic carotid artery stenosis that would benefit from stroke prevention surgery with carotid endarterectomy
- AF (which is often paroxysmal) that would benefit from anticoagulation with warfarin for secondary stroke prevention

Carotid endarterectomy is most effective when performed within the first two weeks after a cerebral ischemic event and its benefit declines sharply with time elapsed thereafter.

All patients benefit from general risk factor management, especially BP control. To encourage medication compliance, patients should be reminded that their antihypertensive, antiplatelet and lipid lowering drugs are indeed considered "stroke prevention pills."

Patients and families should be educated to recognize the warning symptoms of TIA/stroke and to respond by calling 911. Some ischemic strokes are treatable in the ED with tissue plasminogen activator administered within the first three hours of stroke onset. With rapid initiation of secondary prevention therapies for patients with TIA or minor stroke, the early stroke recurrence risk may be reduced by as much as 80%.

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For references, please contact **cme@sta.ca**

Acknowledgements

Dr. Gladstone is supported by a Clinician Scientist Award from the Heart and Stroke Foundation of Ontario, the Heart and Stroke Foundation Centre for Stroke Recovery and the Department of Medicine, Sunnybrook Health Sciences Centre and University of Toronto.