SUMMARY
Anticoagulant therapy to halt or limit a potentially devastating stroke carries both risk and an unproven benefit. Two case reports highlight potential pitfalls. Antiplatelet agents are indicated for ischemia secondary to artery-to-artery embolism. Anticoagulation should be undertaken only when a demonstrated cardiac embolic source places a patient at ongoing risk of repeated embolic stroke. This article reviews rational approaches to anticoagulation for neurologic patients.

RÉSUMÉ
L'anticoagulothérapie visant à arrêter ou à limiter un accident vasculaire cérébral potentiellement dévastateur comporte à la fois des risques et des avantages non prouvés. Deux études de cas soulignent les embâches potentielles. Les agents antiplaquettaires sont indiqués dans les cas d'ischémie secondaire à une embolie d'une artère vers une autre artère. On devrait réservé l'anticoagulothérapie aux seuls cas où la source prouvée de l'embolie d'origine cardiaque place le patient à risque continu d'accident vasculaire cérébral répété d'origine cardiaque. Cet article passe en revue les approches rationnelles à l'anticoagulothérapie chez les patients atteints de troubles neurologiques.

Guidelines for use and monitoring of anticoagulants to prevent stroke are evolving. Two brief case reports highlight the potential pitfalls of this therapy. We review the literature in an attempt to provide a rational approach to anticoagulation for neurologic patients.

Case 1
A 60-year-old man presented with a 3-month history of progressive, stepwise, monocular visual loss. His family physician believed that he was suffering from multiple emboli to the retina, was worried that he was at risk for stroke, and treated him with warfarin. The physician also thought a structural lesion should be excluded and obtained computed tomography 1 month later. The CT study showed a suprasellar mass lesion (Figure 1).

Neurosurgical consultation was sought and the patient's INR was returned to normal immediately. Angiography confirmed an aneurysm of the internal carotid-ophthalmic artery junction (Figure 2). Craniotomy was performed to clip the aneurysm, and the patient made an excellent recovery.

JENNIFER BROWN, MD, CM
MARK BERNSTEIN, MD, FRCSC

Dr Brown is a Neurosurgery resident at the University of Toronto in Ontario.
Dr Bernstein is Head of the Division of Neurosurgery at the Toronto Hospital.

Case 2
A 60-year-old woman had received warfarin for 20 years for atrial fibrillation secondary to a myocardial infarction. She was found unconscious in her home by members of her weekly bridge club and brought to the emergency room. On examination she was deeply obtunded and hemiplegic on the left. Urgent CT demonstrated acute on chronic subdural hemorrhage on the right with midline shift (Figure 3). Her initial prothrombin time was 47/11 seconds (INR was not available at the time the measurements were made). Coagulation status was returned to normal.

Figure 1. Axial CT scan with intravenous contrast demonstrating a contrast-enhancing suprasellar mass

Figure 2. Cerebral angiogram, left internal carotid injection, demonstrating an aneurysm at the carotid-ophthalmic artery junction

Figure 3. Axial CT scan of the head without intravenous contrast demonstrating an acute on chronic right subdural hemorrhage with mass effect
immediately and the subdural hemorrhage evacuated by craniotomy.

The patient made an excellent recovery and was discharged to a rehabilitation hospital 4 weeks after admission. At discharge she had no weakness but was still somewhat confused and forgetful. The risk of anticoagulation was believed to outweigh its benefits for this patient, and she was given acetylsalicylic acid for ongoing stroke prophylaxis.

Discussion
These two cases raise several pivotal questions. Are transient neurologic symptoms necessarily due to ischemia? What investigations are required to confirm an ischemic etiology? If ischemia is diagnosed, will patients benefit from anticoagulation? What are the contraindications to and risks of anticoagulation? Which agent should be used? How long should therapy be continued? What ongoing monitoring is required?

Investigations. Strokelike symptoms must be diagnosed before initiating any treatment. Clinical diagnosis is insufficiently accurate to differentiate ischemia from infarction or “tumor attack” or to undertake anticoagulant therapy on this basis alone. A CT scan or magnetic resonance imaging of the head must be obtained before anticoagulation therapy is instituted. Once ischemic stroke has been diagnosed, the cause of the stroke must be determined.

Subclassification of ischemic stroke into arterioto-artery embolism, cardioembolic stroke, small vessel cerebrovascular disease, or other origin (such as dissection) should be attempted. The subclassification scheme for ischemic stroke proposed by Adams and colleagues requires a high-risk cardioembolic source to diagnose cardioembolism (Table 1).

One third of patients with progressive or fluctuating ischemic symptoms will further deteriorate. This group has been targeted for aggressive antithrombotic therapies based on the assumption that deterioration is secondary to propagation of the thrombus, which occludes more vessels and renders more of the brain ischemic. Hemorrhagic conversion, local or systemic metabolic abnormalities, edema, time-dependent deterioration of function in the “ischemic penumbra,” or seizure activity could equally explain progression, however. Progressive symptoms after ischemic stroke are an indication for repeat imaging; the cause of deterioration must be diagnosed before therapy is undertaken.

Contraindications. Obvious contraindications to anticoagulation include systemic bleeding tendencies, intracranial hemorrhage or mass lesion visible during neuroimaging, lack of appropriate neuroimaging, uncontrolled hypertension, and known allergies to the proposed agent.

Relative contraindications include massive hemispheric infarction and cardioembolic stroke, as these patients appear to have an increased risk of brain hemorrhage. Anticoagulation is contraindicated in profound ischemia, suggested by notable hypodensity on CT scan less than 24 hours after symptom onset or severe, persistent neurologic deficit and a final diagnosis of cerebral infarction. Multiple infarcts and a known source of embolus are additional risk factors for hemorrhage in patients receiving anticoagulants. Advanced age can also be considered a relative contraindication.

Advanced age should be defined physiologically rather than chronologically, but Barnett and associates note that patients older than 75 years are at higher risk for hemorrhagic complications of anticoagulation, and Ramirez-Lassem and Quinones note that it is difficult to establish the precise role of age. They observed hemorrhagic complications among men older than 50 and women older than 60 in their own series and cite Ruff and Dougherty, who observed “most” hemorrhagic complications among patients older than 60 years.

The use of anticoagulants in ischemic neurologic disorders has been advocated in analogy to their use in cardiovascular ischemia, but the risks of anticoagulation in acute cerebrovascular disease are greater than in cardiac disease, and neuronal tissues recover from ischemia less easily.
than the myocardium. Deciding not to anticoagulate remains entirely defensible in most neurologic settings. In the presence of relative contraindications, antithrombotic therapy should be omitted or delayed until a CT scan 48 hours or more after the onset of symptoms shows no hemorrhagic transformation.

**General considerations for clinical trials.**
Patients are selected for anticoagulation therapy on the basis of the origin of their strokes and the absence of risk factors for hemorrhage.

The clinical evidence for efficacy of anticoagulants in cerebrovascular disease is weak and tremendously flawed.9,12 Important limitations of studies include inability to enrol stroke patients early in the course of ischemia when some potential for recovery remains, contraindications to initiating antithrombotics in this early period, and the variable natural history of ischemic stroke: deficits tend to improve but also have the potential to worsen spontaneously. These factors obscure the benefits and hazards of anticoagulation in all but the most rigorously controlled clinical trials.12

Given the inconclusive nature of studies to date, a conservative approach to anticoagulation is recommended. Antiplatelet agents should be used for artery-to-artery emboli.

**Specific clinical trials.** Common sense suggests that patients with progressing ischemic symptoms are most likely to benefit from anticoagulation. Yet, in a double-blind placebo-controlled trial of 225 patients with acute, partial, stable thrombotic stroke, anticoagulants had no statistically significant benefit over placebo. The incidence of stroke progression or degree of neurologic change at 7 days or functional activity level of survivors at 7 days, 3 months, or 1 year after stroke was similar in both groups.7 Failure to demonstrate a benefit from anticoagulation therapy could be due to small sample size or because stroke progression does not always reflect progression of thrombosis.

Smaller studies show only an insignificant trend toward decreased progression in groups receiving heparin.8,13 Use of intravenous heparin in progressive stroke must be considered empiric and confined to clinical trials.1,8,9 The value of thrombolytic therapy is currently under study for this group of patients.14-17

<table>
<thead>
<tr>
<th>Table 1. Risk factors for cardioembolic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH-RISK SOURCES</strong></td>
</tr>
<tr>
<td>Mechanical prosthetic valve</td>
</tr>
<tr>
<td>Mitral stenosis with atrial fibrillation</td>
</tr>
<tr>
<td>Atrial fibrillation (other than lone atrial fibrillation)</td>
</tr>
<tr>
<td>Left atrial or aural appendage thrombus</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
</tr>
<tr>
<td>Recent myocardial infarction (&lt;4 weeks)</td>
</tr>
<tr>
<td>Left ventricular thrombus</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Akinetic left ventricular segment</td>
</tr>
<tr>
<td>Atrial myxoma</td>
</tr>
<tr>
<td>Infective endocarditis</td>
</tr>
<tr>
<td><strong>MEDIUM-RISK SOURCES</strong></td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Mitral annulus calcification</td>
</tr>
<tr>
<td>Mitral stenosis without atrial fibrillation</td>
</tr>
<tr>
<td>Left atrial turbulence in smokers</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>Atrial flutter</td>
</tr>
<tr>
<td>Lone atrial fibrillation</td>
</tr>
<tr>
<td>Bioprosthetic cardiac valve</td>
</tr>
<tr>
<td>Nonbacterial thrombotic endocarditis</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Hypokinetic left ventricular segment</td>
</tr>
<tr>
<td>Myocardial infarction (&gt;4 weeks, &lt;6 months)</td>
</tr>
</tbody>
</table>

Data from Adams and colleagues.6
Antithrombotic CME

Antithrombotic therapy for patients with stroke symptoms

Antiplatelet agents and subcutaneous administration of heparin are unproven for progressive stroke, although patients with severe leg weakness could receive them to prevent deep venous thrombosis or pulmonary embolism. These patients should be studied for possible beneficial effects on stroke recurrence or progression.

Cardioembolic stroke has been treated with anticoagulation in a small randomized trial. A trend toward decreased risk for recurrent embolism did not reach statistical significance. These patients comprise one of the high-risk groups for hemorrhagic conversion. Treating them with heparin in the acute period increases this risk, but they are also at considerable risk for recurrent emboli. Anticoagulants for these patients are best restricted to properly designed clinical trials in the acute phase after cardioembolic stroke unless rheumatic heart disease or demonstrable intracardiac thrombus is present. After a delay of 1 to 2 weeks and correction of risk factors for hemorrhage, such as uncontrolled hypertension, patients with a high-risk or moderate-risk cardiac embolic source (Table 1) should undergo full anticoagulation.

Anticoagulation should be initiated with heparin in hospital and continued with warfarin upon discharge. Ongoing use of warfarin in this group must be monitored by blood tests to keep the INR between 1.5 and 2.7 for atrial fibrillation or 3.0 to 4.5 for high-risk sources, such as mechanical valves. Monitoring can be reduced to every 3 to 6 months once stable levels have been achieved in asymptomatic patients. Monitoring must be accompanied by patient education about the indications for and complications of anticoagulation.

When patients with medium-risk cardiac lesions reach advanced age or have survived a hemorrhagic complication like our second patient had, conversion to an antiplatelet agent should be considered. When such patients present with neurologic symptoms, diagnosis using imaging is essential because the mimics of cerebral ischemia include hemorrhagic entities, such as chronic subdural hemorrhage. When these complications occur, urgent reversal of anticoagulation and surgical treatment of the lesion are required.

Symptomatic carotid stenosis, including transient ischemic attacks and minor stroke with good neurologic recovery, should be treated with antiplatelet agents. The dosage of ASA is controversial, but 325 to 1300 mg daily is an acceptable range.

Ticlopidine hydrochloride conveys greater risks than ASA as well as greater potential benefit. The most important risk is a 1% risk of neutropenia, although this condition reverses when therapy is terminated. There is some evidence that, in women particularly, ticlopidine is more effective than ASA. This agent should be considered for women, patients who cannot take ASA, and patients who experience recurrent symptoms while using ASA. Patients receiving ticlopidine should be closely monitored for neutropenia and for elevated serum cholesterol levels.

In addition to antiplatelet agents, patients with more than 70% carotid stenosis on the side ipsilateral to the affected hemisphere should be referred to a neurosurgeon for assessment of eligibility for carotid endarterectomy. Ongoing trials will define the role of endarterectomy in cases of milder stenosis and in asymptomatic carotid stenosis.

No clinical trials. Unusual or complex cases might not be amenable to study by clinical trials. In such cases we must be guided by analogy to simpler entities and by common sense.

For example, a patient with a high-risk cardiac source of embolism, such as a mechanical prosthetic valve, who undergoes a cerebral ischemic event while receiving anticoagulants presents a management challenge. Risk of recurrent emboli is undefined in such patients, but there is risk of hemorrhagic conversion if the stroke appears anatomically large from clinical and imaging features. If hemorrhage is absent on CT and the event is a transient ischemic attack or small infarct, continuing anticoagulation therapy is reasonable. Anticoagulation must be stopped if neuroimaging demonstrates hemorrhage or a large hemispheric hypodensity.
hypodensity is present, restarting anticoagulation may be considered if no hemorrhage is present 48 hours after the event and no other contraindications are present.

Neurologic deficits more frequently progress in vertebrobasilar disease than in carotid distribution atherosclerosis, and thus heparin has been considered for posterior circulation ischemia. Only a randomized clinical trial could show definitive support for using heparin because of the variable natural history of the disease, but such a study would be difficult to do because the condition is uncommon. Patients with vertebrobasilar ischemia were included in a Canadian study that showed reduced risk of repeat ischemic attacks, stroke, or death among patients who received 325 mg of ASA four times daily.2

Anticoagulation therapy is sometimes advocated for patients with large vessel atherosclerosis who are not surgical candidates due to inaccessibility of the lesion or medical contraindications.25 The advantages of anticoagulant over antiplatelet agents have not been demonstrated in this group, and we cannot support this recommendation.

Unusual causes of stroke, such as dissection and acute occlusion of a major artery, have not been extensively studied, but they could be associated with unstable intraluminal clots particularly prone to propagation or local embolism. Some experts advocate using heparin followed by warfarin for about 2 months to allow the clot to stabilize, but this treatment for unusual causes of stroke is unproven.25,26 Surgical removal of accessible, symptomatic intracarotid thrombi has also been recommended, but these patients face higher risks during surgery, and this recommendation is founded on anecdotal evidence alone. The optimal treatment has not been defined.25

Conclusion
Evidence that solidly supports the use of anticoagulant therapy in the face of cerebral ischemia has been elusive despite numerous attempts to define indications for various agents.1,8,9,12,21,27

The treatment is not without risks and a conservative approach is recommended. Candidates for anticoagulation include survivors of cardioembolic stroke who have a continuing risk of cardiac emboli and have been allowed to stabilize for a period, and patients with small infarcts associated with high-risk cardiac sources of emboli, such as demonstrable intracardiac thrombus or rheumatic valve disease. The benefit of anticoagulation for symptomatic, demonstrated intraluminal thrombus of the large cervical and cerebral vessels is likely to remain unproven.

Candidates for antiplatelet therapy include patients with good or complete recovery from small strokes or transient ischemic attacks secondary to artery-to-artery emboli, including those awaiting carotid endarterectomy and those who are not candidates for this procedure.

No antithrombosis for new neurologic symptoms should ever be undertaken in the absence of neuroimaging, even if the study requires some delay in initiating treatment. If a prolonged delay is unavoidable, referral to a centre with facilities for expedient neuroimaging and initiation of treatment is recommended. The use of anticoagulants in cerebral ischemia is associated with significant risks and is at best unproven and at worst unfounded.

Correspondence to: Dr Mark Bernstein, 2-405, McLaughlin Pavilion, Toronto Western Division, 399 Bathurst St, Toronto, ON M5T 2S8

References
**INDICATIONS AND CLINICAL USE:** Seasonal allergic rhinitis including hay fever. Perennial rhinitis poorly responsive to conventional treatment. Regular usage is essential for full therapeutic benefit since maximum relief may not be obtained until after 2-3 days of treatment.

**CONTRAINDICATIONS:** History of hypersensitivity to any ingredient. Active or quiescent tuberculosis, or untreated fungal, bacterial and viral infections.

**WARNINGS:** in patients previously on systemic steroids, either on prolonged or intermittent therapy, topical corticosteroids can be accompanied by symptoms of withdrawal e.g. postural and muscular pain, lassitude, and depression and, in severe cases, adrenal insufficiency may occur, necessitating transient replacement of systemic steroid therapy. Careful attention must be given to patients in whom a rapid decrease in systemic steroids may result in other symptoms.

**PRECAUTIONS:** Patients should be informed that the full effect of fluticasone propionate therapy is not achieved for 2 to 3 days. Treatment of seasonal rhinitis should be started before the episode begins. An abnormally prolonged initial flare of a challenge of seasonal allergens may necessitate additional therapy. Treatment with corticosteroids should not be stopped abruptly, but should be tapered gradually. Replacement of systemic steroids with fluticasone propionate must be gradual and carefully supervised. Corticosteroids may mask infections. New infections may occur as resistance to local infections is decreased through the use of corticosteroids. During long-term therapy, HPA axis function and hematological status should be assessed. Long-term effects of fluticasone propionate on the growth plate in children and on local effects, possibility of atrophic rhinitis and pharyngal candidiasis should be kept in mind. Enhanced effect of corticosteroids in children and in those with diabetes. Acyclovir acid should be used cautiously in conjunction with corticosteroids in hypothyroidism. In patients who have had recent nasal surgery or trauma, the corticosteroid should be used with caution until healing has occurred. Patients should be advised to inform subsequent physicians of prior use of corticosteroids. Pregnancy: Safety has not been established. Women expected benefits against potential hazards to the fetus, particularly during the first trimester of pregnancy. It is teratogenic to human species (see PRODUCT MONOGRAPH). Fluticasone propionate nasal sprays are only safe at high systemic exposure levels, direct intranasal application ensures minimal systemic exposure. Relevance to humans not established. Infants born to mothers who have received systemic corticosteroids during pregnancy should be carefully observed for hypoadrenalism. Lactation: Fluticasone propionate is not known to be excreted in human breast milk. When plasma levels were obtained in lactating laboratory rats following subcutaneous administration there was evidence of fluticasone propionate in the plasma, but no intranasal administration to primates, no drug was detected in plasma, it is unlikely that the drug would be excreted in milk. Women should be advised of potential hazards to the neonate. Children: Adverse effects have been reported in children under the age of 12.

**ADVERSE REACTIONS:** Adverse reactions in controlled clinical studies have been primarily associated with irritation of nasal mucous membranes, and are consistent with those expected from application of topical medication to an already irritated mucous membrane. Adverse reactions reported were similar to those reported by patients receiving placebo. The most frequently reported adverse reactions in children (n = 100) and adults (n = 940) were nasal allergic rhinopathy at 200 mcg per day nasal burning (3.4%), pharyngitis 1.6%, runny nose 1.6%, blood in nasal mucosa 1.6%, sneezing < 1.2%, headache 2.5%, epistaxis 1.1%, nasal ulcer 1.2%, In adults, allergic rhinitis (n = 33) adverse reactions similar to seasonal except epistaxis 13.5%, blood in nasal mucosa 0.5%, nasal sores 3.2%, nasal congestion 5.2%, sneezing 5.2%, rhinorrhea 6.2%, nasal discharge 1.5%, localized burning 1.5%, localized irritation 1.5%, localized pruritus 1.5%, localized edema 1.5%, localized swelling 1.5%. **DOSAGE AND ADMINISTRATION:** The therapeutic effects of corticosteroids are not immediate. Effect occurs in regular use. Adults and Children 12 years of age or older dosage is two sprays (50 mcg each) in each nostril once a day (total daily dosage). 200 mcg. Severe rhinitis may benefit from two sprays in each nostril every 12 hours. Recommended minimum daily dose is 400 to 400 mg each in each nostril. Children 4-11 years of age: Usual dosage is one or two (50 mcg)actuation) sprays in each nostril every 12 hours. The recommended maximum daily dose is 200 mcg (two sprays in each nostril). Improvement of symptoms usually appears within a few days after start of therapy. However, symptom relief does not occur in all patients treated. As long as two weeks, FLONASE should not be continued beyond these three weeks absence of significant improvement of symptoms. In presence of excessive nasal mucous, crusting may occur. The drug may fail to remove crusts. In such cases it is advisable to use nasal vasoconstrictor for two to three days to remove crusts. Before FLONASE and/or chronic usage. Patients should be instructed on the correct method of use, which is to blow the nose, then insert the nozzle carefully into the nostril, compress the opposite nostril and actuate the spray while inhaling through the nose, with the mouth closed. Careful attention is given to patients previously treated for prolonged periods with systemic corticosteroids when using FLONASE. Consult product monograph for transitional periods and dosage recommendations. Store between 4°C and 30°C (39°F). Shake gently before use. AVAILABLE: Aqueous suspension of microfine fluticasone propionate 0.05% were for topical administration to nasal mucosa by metering, atomizing spray pump. Each 100 mg of spray (1 actuation) contains 50 mcg of fluticasone propionate in a pre-formed atomizer bottle containing sufficient suspension for 100 metered actuations (10 g weight) or 120 metered actuations (10 g weight). Fluticasone propionate nasal spray are drug mark of Group Limited, Glaxo Wellcome Inc., licensed use. "The appearance, namely the colors, shapes and sizes, of the Flonase® and Becloforte® actuator are trade-marks of Glaxo Group Limited, Glaxo Wellcome Inc., licensed use. Full prescribing information contact Glaxo Wellcome Inc., 7333 Mississauga Rd. North, Mississauga, Ontario, L5W 4L5.