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TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

Short-term prognosis after a TIA: A simple score predicts risk

ABSTRACT

Transient ischemic attacks (TIAs) are ominous and call for acute interventions, including hospitalization. TIAs are defined by complete resolution of an acute neurologic deficit, but any amount of recovery is probably the most important defining feature and, paradoxically, is strongly predictive of a subsequent event. Most patients should be hospitalized after a TIA, to provide an opportunity to monitor, thoroughly evaluate, and treat conditions promptly if indicated.

KEY POINTS

The risk of stroke after a TIA is very high overall and can be quickly stratified with a simple score based on age, blood pressure, history of diabetes, and the duration and features of the TIA.

TIA patients should be evaluated with a history and physical examination, laboratory tests, electrocardiography, and head and neck imaging.

Hospitalization allows neurologic monitoring after a TIA so that tissue plasminogen activator (tPA) can be given promptly if a subsequent event occurs. Hospitalization also increases the likelihood that atrial fibrillation, carotid artery stenosis, and other conditions will be quickly evaluated and treated.

Carotid endarterectomy, if indicated, should be performed as soon as possible after a TIA.

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TRANSIENT ISCHEMIC ATTACKS (TIAs) are common[1] and are often a harbinger of disabling strokes. But defining who is at risk for a subsequent event and what actions should be taken immediately remain important clinical issues. This article discusses the defining features of a TIA, a simple scoring system for determining the acute risk of stroke, and other aspects of the immediate evaluation and management of TIA.

TIAs ARE COMMON

Approximately 250,000 to 350,000 TIAs occur each year in the United States.[2–4] The median survival is more than 8 years,[5] and TIA survivors number approximately 2.4 million. A recent survey found that 1 in 15 people older than 65 years—equivalent to 2.3 million people in the United States—reported a history of TIA.[6] About 15% of patients who present with a stroke report having had a previous TIA.[7]

WHAT IS A TIA?

Traditional definition is symptom-based and problematic

A TIA is traditionally defined as a spell of neurologic impairment lasting less than 24 hours that is caused by focal ischemia in the brain or retina.

Although we have grown comfortable with this definition, it is problematic. Little agreement exists about which events are TIAs, even if they are independently evaluated by two neurologists.[8,9] In addition, 24 hours is a rather arbitrary time period and does not help to determine which events involve infarction; new infarction can occur within minutes and

TABLE 1

Predicting the risk of stroke after a transient ischemic attack: The California, ABCD, and ABCD² scores

CHARACTERISTIC	POINTS		
	CALIFORNIA	ABCD	ABCD²
Age ≥ 60 years	1	1	1
Blood pressure ≥ 140/90 mm Hg	—	1	1
Clinical features of transient ischemic attack			
Weakness[a]	1	2	2
Speech impairment[b]	1	1	1
Duration			
≥ 60 minutes	1	2	2
10–59 minutes	1	1	1
Diabetes	1	—	1
Total score	0–5	0–6	0–7

[a]Defined as any weakness (California score); unilateral weakness (ABCD and ABCD² scores)
[b]Regardless of weakness by the California score; in the absence of unilateral weakness by ABCD and ABCD² scores; the maximum possible score for clinical features of transient ischemic attack is thus 2 in all three scoring systems
ABCD = Age, Blood Pressure, Clinical Features, and Duration
ABCD² = Age, Blood Pressure, Clinical Features, Duration, and Diabetes

TIAs carry a substantial short-term risk of stroke, cardiac events, and death

can often be documented after TIA.[10] And why should the diagnosis require that symptoms resolve completely, particularly when we know that in such circumstances, infarction is often present?

New definition is tissue-based

A newer definition reclassifies TIA as an event with transient symptoms (typically lasting less than 1 hour) without evidence of acute brain infarction on imaging studies.[10] By the old definition, a patient with transient symptoms but an infarction evident by magnetic resonance imaging (MRI) had a TIA; by the new definition, this would be a stroke.

The new definition has some advantages for billing in that strokes are generally reimbursed more favorably than TIA. It is also conceptually simpler: infarction defines a stroke, and the reliance on time is reduced. But the definition also creates new problems. The likelihood of seeing evidence of infarction depends on the type of imaging study done: hospitals that routinely perform MRI diagnose fewer TIAs and more strokes. About 30% to 50% of patients with clinically defined TIA have evidence of ischemic abnormalities on diffusion MRI, most of which become permanent infarcts.[11]

The new definition is not universally accepted: the traditional one is more familiar and is easier to use. No solution is perfect, but a broader acceptance of the spectrum of acute ischemic cerebrovascular syndromes might be a good first step: TIA and stroke are more similar than different.

DO PATIENTS WHO HAD A TIA REQUIRE ACUTE CARE?

TIA and stroke share common causes, risk factors, pathophysiology, and treatment.[12] But regardless of which definition is used, TIA does not involve a neurologic deficit at the time of diagnosis. This leaves important clinical questions that are generally irrelevant to stroke management: Is prompt intervention or hospitalization required? Should a patient who had a TIA the previous day be told to make an appointment or go immediately to the emergency department?

Risk is high after a TIA

TIA carries a substantial short-term risk of stroke, hospitalization for cardiovascular events, and death. Most studies have found that the risk of stroke is more than 10% in the 90 days after a TIA,[2,13–24] with half of those strokes occurring within the first 2 days.[2,13,18,21,23–25] Studies in northern California and the United Kingdom found that the risk of stroke in the first 24 hours after a TIA is about 4%, which is about twice the risk of myocardial infarction or death in patients presenting with acute coronary syndromes.[13,26,27]

Paradoxically, the risk of a subsequent ischemic stroke may be less after a completed stroke than after a TIA, with reported 3-month risk generally ranging from 4% to 8%.[19 20,22,28–41] Thus, patients with TIA are actually more unstable in terms of new stroke than those presenting with an initial stroke.

The risk of cardiac events is also elevated after a TIA. Elkins et al[42] found that 2.6% of patients who were diagnosed with a TIA at an emergency department were hospitalized for a major cardiovascular event (myocardial infarction, unstable angina, or ventricular arrhythmia) within 90 days. Heyman et al[43] found that within 5 years after a TIA, the number of patients who had a myocardial infarction or sudden cardiac death nearly equaled the number who had a cerebral infarction.

ESTIMATING RISK OF STROKE AFTER TIA

Several studies have identified risk factors for stroke after TIA, and these risk factors may help guide initial management. Three similar formal prediction rules have been developed and cross-validated in California and the United Kingdom (**TABLE 1**). The scores are based on five factors. The California score predicts the risk of stroke within 90 days; the Age, Blood Pressure, Clinical Features, and Duration (ABCD) score predicts the risk at 7 days and at 90 days. The newer Age, Blood Pressure, Clinical Features, Duration, and Diabetes (ABCD^2) score, which was meant to replace the other two scores, incorporates elements from those scores and predicts the risk at 90, 30, 7, and 2 days (**FIGURE 1**).

The ABCD^2 score predicts risk of stroke after a transient ischemic attack

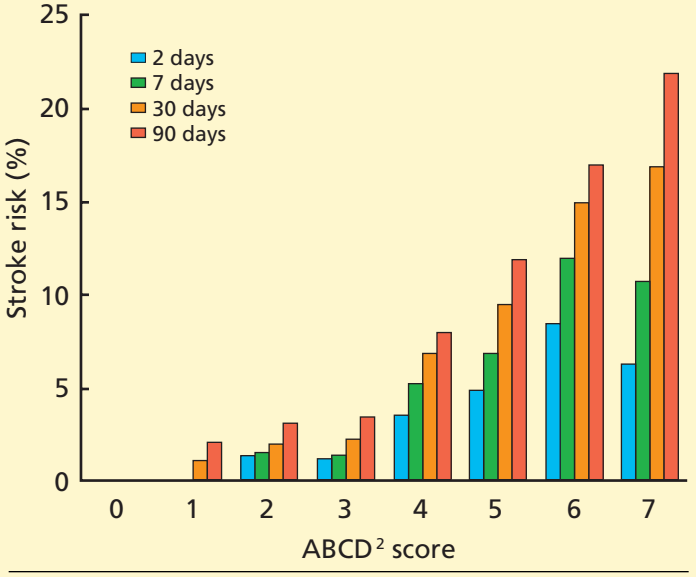

FIGURE 1. Stroke risk after TIA by Age, Blood Pressure, Clinical Features, Duration, and Diabetes (ABCD^2) score at 2 days, 7 days, 30 days, and 90 days after TIA in 4,809 patients treated in California and the United Kingdom.

JOHNSTON SC, ROTHWELL PM, NGUYEN-HUYNH MN, ET AL. VALIDATION AND REFINEMENT OF SCORES TO PREDICT VERY EARLY STROKE RISK AFTER TRANSIENT ISCHAEMIC ATTACK. LANCET 2007; 369:283–292.COPYRIGHT 1977, WITH PERMISSION FROM ELSEVIER

In a study of nearly 3,000 patients presenting with a TIA to clinics and emergency departments in the United Kingdom and the United States, using the ABCD^2 score, 21% of patients were classified as being at very high risk (score 6 or 7; 2-day risk of stroke 8.1%), 45% at moderate risk (score 4 or 5; risk 4.1%), and 34% at low risk (score 0–3; risk 1%).[44]

The scores do not account for imaging findings, which also have prognostic value. A new infarct seen on brain imaging (which is consistent with the traditional definition of TIA but would now lead to a diagnosis of stroke) is associated with a twofold to 15-fold increase in subsequent short-term risk of stroke.[18,22,45–48] Evidence of vessel occlusion on acute brain magnetic resonance angiography is also associated with a fourfold increased short-term risk of stroke.[48] MRI changes are associated with the clinical factors identified in prior prediction rules,[49] so it is unclear how much predictive power they would add to the scores.

Degree of acute recovery predicts stroke risk

Patients who have only partially recovered from an acute neurologic deficit after 24 hours are considered by both the traditional and new definitions to have had a stroke rather than a TIA, but partial recovery may actually indicate that they are at high risk of a subsequent event. Studies show that the greater the degree of acute recovery after a neurologic ischemic event, the greater the chance of neurologic deterioration over the subsequent 3 months.[50–54]

It is not clear why a patient who promptly and largely recovers from a major ischemic event is at such high risk of early and permanently disabling recurrence. The pathophysiology of TIA may be similar to that of acute coronary syndromes (eg, unstable angina and non-Q-wave myocardial infarction), in which thrombosis and thrombolysis are acutely active and protracted. Similarly, cerebral ischemia that rapidly resolves may be a marker for ongoing thrombosis and thrombolysis.

In contrast, major ischemia that persists may be a result of largely completed thrombosis that is not amenable to acute antithrombotic therapy. Aggressive, early antithrombotic therapy with combinations of new, potent agents is highly effective in acute coronary syndromes,[55–58] and such an approach should be tested in patients after a TIA.

Head imaging should be done on all TIA patients

'Benign recurrent' TIA may be migraine

Many patients who present in the emergency department or clinic have only sensory symptoms lasting less than 10 minutes. These patients are far less likely than other TIA patients to develop a stroke and are more likely to have recurrent episodes that completely resolve.[59] I believe these are not TIAs but are related to migraines. Treatment with calcium channel blockers can be effective.

EVALUATING TIA PATIENTS

A history and physical examination are essential to diagnosing a TIA.

Recommended laboratory tests—some of which can help identify conditions that mimic a TIA—include a complete blood cell count; blood levels of electrolytes, blood urea nitrogen, glucose, and calcium; the erythrocyte sedimentation rate; and a rapid plasma reagin test.

The appropriate cardiac evaluation is still being determined, but evidence supports performing electrocardiography (ECG) on all patients presenting with a TIA. ECG frequently reveals unexpected atrial fibrillation or a myocardial infarction or suggests a left ventricular aneurysm, all of which are important causes of cardiogenic emboli and have a high risk of recurrence. In addition, ECG abnormalities are independently associated with the risk of cardiac events in the 3 months after a TIA.[42] Most patients also would benefit from 2-day cardiac monitoring, which can identify patients with paroxysmal atrial fibrillation. Echocardiography is warranted in some patients, although transesophageal echocardiography is not used as often as it once was in patients with a TIA because of new evidence that correcting a patent foramen ovale does not help prevent strokes.

Head imaging should be done on all TIA patients, usually with computed tomography (CT). Hemorrhage, tumor, and multiple sclerosis, all of which could mimic a TIA, may be seen.

Neck imaging to look for carotid artery stenosis can be done by CT angiography, ultrasonography, or magnetic resonance angiography. We use CT angiography with perfusion, which is the fastest way to get all the information needed, entails a low risk from exposure to contrast agents, and often helps to determine treatment.

HOSPITALIZATION IS USUALLY INDICATED

The short-term prognosis after a TIA justifies a sense of urgency if interventions exist that can alter the outcome. Hospitalization may reduce the risk of stroke or other adverse events by hastening the workup and targeted therapy. Proven therapies are available for several important causes of TIA, and identifying and treating them should be a high priority.

The National Stroke Association guidelines for managing TIAs recommend hospitalizing patients at high risk of stroke or if a special treatment is needed (eg, for carotid stenosis or atrial fibrillation).[60] The guidelines came out before the ABCD^2 score was devel-

oped, so no specific thresholds of risk were advised. In the United States, a patient with an ABCD2 score of 6 or 7 should definitely be hospitalized, and those with a score of 4 or 5 should probably be hospitalized, although thresholds differ in other countries and even differ between similar hospitals within the United States.

Prompt tPA therapy if stroke occurs

If a patient is hospitalized after a TIA, he or she can be observed carefully to increase the likelihood of receiving tissue plasminogen activator (tPA, alteplase, Activase) promptly should ischemic symptoms recur, and this is probably enough to justify the costs of hospitalization. tPA can have a profound impact on a patient's outcome, and because the long-term costs associated with having a stroke are so high, averting even a small proportion of strokes makes hospitalization cost-effective.

Nguyen-Huynh et al[61] analyzed the cost-utility of 24-hour hospitalization at the University of California, San Francisco, for patients diagnosed with a recent TIA who were candidates for tPA if a stroke occurred. The overall cost-effectiveness ratio was $55,044 per quality-adjusted life-year (a value considered to be borderline cost-effective), and less for patients at higher risk of stroke.

This kind of analysis is highly affected by several variables: the degree of risk of stroke (as calculated by the ABCD2 score), the costs of hospitalization, and the ability to identify whether a patient is having a stroke during hospitalization. Monitoring neurologic status requires frequent examination; in most hospitals, such monitoring is not currently up to the standard of cardiac monitoring.

Detecting atrial fibrillation and starting treatment for it

Although data are sparse about the stroke risk early after a TIA, specifically in patients with atrial fibrillation, case series suggest that the risk is higher than in the general population: probably 10% to 15% in the first month after a TIA. In our study,[6] the 90-day risk was 13%, but many patients were already receiving anticoagulation, making this a conservative estimate.

ECG is necessary to confirm the diagnosis of atrial fibrillation, and cardiac monitoring may identify additional cases. CT of the head is necessary to rule out a hemorrhage, and echocardiography may demonstrate a clot but may not alter one's choice of therapy.

Multiple randomized trials have found that anticoagulation reduces the risk of stroke. The Heparin in Acute Embolic Stroke Trial[62] did not find low-molecular-weight heparin to be beneficial in patients with atrial fibrillation and acute stroke, but the trial was small. The risk of bleeding at the site of an ischemic stroke is likely to be much smaller after a TIA than after a stroke, and it is logical to anticipate that starting effective therapy earlier would reduce the risk of cardioembolic events sooner. Guidelines from the National Stroke Association and American Stroke Association recommend starting oral anticoagulation.

Prompt endarterectomy for carotid artery stenosis

Carotid artery atherosclerosis accounts for about 11% of TIAs. The risk of stroke in patients with carotid artery stenosis was as high as 20% at 90 days in one study.[18] Traditional teaching was that patients should wait 4 to 6 weeks after any neurologic event before undergoing endarterectomy or stenting, but new data strongly contradict this.

Hospitalization may reduce the risk of stroke by hastening workup, triage, and targeted therapy

The North American Symptomatic Carotid Endarterectomy Trial[63] found that in patients with medically treated high-grade internal carotid artery stenosis, 43.5% of those presenting with hemispheric TIA had a stroke within 2 years. Half the strokes occurred within the first month, suggesting that the danger is greatest acutely after a TIA. Patients were enrolled in the study up to 4 months after the initial TIA, so the immediate post-TIA period, during which the risk of stroke may have been even higher, was not studied.

Carotid endarterectomy, if indicated, should be performed as soon as possible after a TIA, and hospitalizing a patient after an event may help ensure that it is done promptly. Randomized trials have shown that carotid endarterectomy is beneficial for patients with TIAs in the distribution of a carotid stenosis of more than 60% to 70%.[64] Rothwell et al[65] analyzed pooled data from the European Carotid Surgery Trial and North American

Symptomatic Carotid Endarterectomy Trial and found that the benefit from surgery was greatest if it was performed within 2 weeks after the last ischemic event and fell rapidly with increasing delay: the absolute risk reduction at 5 years for stroke or operative death was 20% for patients with at least 50% stenosis if endarterectomy was done less than 2 weeks after the ischemic event, and was only 0.8% if done later.

Carotid ultrasonography, CT angiography, or magnetic resonance angiography should be performed in all patients with TIAs in the anterior circulation. Many experts think this should be performed within 24 hours of presentation because the early risk of stroke is so high.

National Stroke Association guidelines[66] recommend that endarterectomy be performed as soon as possible—preferably within 2 weeks—for those with 70% to 90% stenosis that is symptomatic, as well as for those with 50% to 69% stenosis who can be treated with a less than 6% risk of perioperative stroke or death.

Evaluating other problems

Other causes of TIA include small-vessel (lacunar) ischemia, intracranial atherosclerosis, aortic arch atheroma, and paradoxical emboli. These account for about 80% of all TIAs, so risks determined by larger studies are also applicable to these patients.

Evaluation should be individualized on the basis of history and comorbidities and may include transesophageal echocardiography, intracranial magnetic resonance angiography, catheter angiography, and laboratory tests for hypercoagulable states. Before subjecting patients to testing, one should take into account whether or not the findings would influence the choice of treatment.

OTHER TREATMENT CONSIDERATIONS

The National Stroke Association recently published updated guidelines for managing TIAs.[60] The American Stroke Association also recently published guidelines for secondary prevention that include TIA as well as ischemic strokes.[67]

These guidelines extensively review the evidence and opinion supporting other aspects of treatment that cannot be covered in detail in this short review highlighting the new aspects of TIA treatment distinct from stroke. Of course, all patients with non-cardioembolic stroke should receive an antiplatelet agent, and guidelines have implied that combined dipyridamole and aspirin is the best first choice, based on the European Stroke Prevention Study 2 and the European/Australasian Stroke Prevention in Reversible Ischaemia Trial,[68,69] with aspirin and clopidogrel as alternatives.[70] A high-dose, high-potency statin is also indicated for the vast majority of patients, and other risk factors for stroke, such as hypertension and diabetes, should be controlled. Clinical trials are still needed to help determine appropriate acute therapies for TIA. No single large-scale trial has been performed that treated TIA as an acute condition.

REFERENCES

1. **Brown RD Jr, Petty GW, O'Fallon WM, Wiebers DO, Whisnant JP.** Incidence of transient ischemic attack in Rochester, Minnesota, 1985–1989. Stroke 1998; 29:2109–2113.
2. **Kleindorfer D, Panagos P, Pancioli A, et al.** Incidence and short-term prognosis of transient ischemic attack in a population-based study. Stroke 2005; 36:720–723.
3. **Broderick J, Brott T, Kothari R, et al.** The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. Stroke 1998; 29:415–421.
4. **Williams GR, Jiang JG, Matchar DB, Samsa GP.** Incidence and occurrence of total (first-ever and recurrent) stroke. Stroke 1999; 30:2523–2528.
5. **Howard G, Toole JF, Frye-Pierson J, Hinshelwood LC.** Factors influencing the survival of 451 transient ischemic attack patients. Stroke 1987; 18:552–557.
6. **Johnston SC, Fayad PB, Gorelick PB, et al.** Prevalence and knowledge of transient ischemic attacks among US adults. Neurology 2003; 60:1429–1434.
7. **Brainin M, McShane LM, Steiner M, Dachenhausen A, Seiser A.** Silent brain infarcts and transient ischemic attacks. A three-year study of first-ever ischemic stroke patients: the Klosterneuburg Stroke Data Bank. Stroke 1995; 26:1348–1352.
8. **Koudstaal PJ, Gerritsma JG, van Gijn J.** Clinical disagreement on the diagnosis of transient ischemic attack: is the patient or the doctor to blame? Stroke 1989; 20:300–301.
9. **Kraaijeveld CL, van Gijn J, Schouten HJ, Staal A.** Interobserver agreement for the diagnosis of transient ischemic attacks. Stroke 1984; 15:723–725.
10. **Albers GW, Caplan LR, Easton JD, et al; TIA Working Group.** Transient ischemic attack—proposal for a new definition. N Engl J Med 2002; 347:1713–1716.
11. **Kidwell CS, Alger JR, Di Salle F, et al.** Diffusion MRI in patients with transient ischemic attacks. Stroke 1999; 30:1174–1180.
12. **Johnston SC.** Clinical practice. Transient ischemic attack. N Engl J Med 2002; 347:1687–1692.
13. **Johnston SC, Gress DR, Browner WS, Sidney S.** Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000; 284:2901–2906.
14. **Whisnant JP, Matsumoto N, Elveback LR.** Transient cerebral

ischemic attacks in a community. Rochester, Minnesota, 1955 through 1969. Mayo Clin Proc 1973; 48:194–198.
15. **Dennis M, Bamford J, Sandercock P, Warlow C.** Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. Stroke 1990; 21:848–853.
16. **Biller J, Bruno A, Adams HP, et al.** A randomized trial of aspirin or heparin in hospitalized patients with recent transient ischemic attacks. A pilot study. Stroke 1989; 20:441–447.
17. **Putman SF, Adams HP Jr.** Usefulness of heparin in initial management of patients with recent transient ischemic attacks. Arch Neurol 1985; 42:960–962.
18. **Eliasziw M, Kennedy J, Hill MD, Buchan AM, Barnett HJ; North American Symptomatic Carotid Endarterectomy Trial Group.** Early risk of stroke after a transient ischemic attack in patients with internal carotid artery disease. CMAJ 2004; 170:1105–1109.
19. **Humphrey PR, Marshall J.** Transient ischemic attacks and strokes with recovery prognosis and investigation. Stroke 1981; 12:765–769.
20. **Coull AJ, Lovett JK, Rothwell PM; Oxford Vascular Study.** Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004; 328:326–328.
21. **Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP.** The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology 2004; 62:2015–2020.
22. **Daffertshofer M, Mielke O, Pullwitt A, Felsenstein M, Hennerici M.** Transient ischemic attacks are more than "ministrokes." Stroke 2004; 35:2453–2458.
23. **Lisabeth LD, Ireland JK, Risser JM, et al.** Stroke risk after transient ischemic attack in a population-based setting. Stroke 2004; 35:1842–1846.
24. **Gladstone DJ, Kapral MK, Fang J, Laupacis A, Tu JV.** Management and outcomes of transient ischemic attacks in Ontario. CMAJ 2004; 170:1099–1104.
25. **Rothwell PM, Giles MF, Flossmann E, et al.** A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. Lancet 2005; 366:29–36.
26. **Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM.** Very early risk of stroke after a first transient ischemic attack. Stroke 2003; 34:e138–e140.
27. **Rao SV, Ohman EM, Granger CB, et al.** Prognostic value of isolated troponin elevation across the spectrum of chest pain syndromes. Am J Cardiol 2003; 91:936–940.
28. **Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO.** Survival and recurrence after first cerebral infarction: a population-based study in Rochester, Minnesota, 1975 through 1989. Neurology 1998; 50:208–216.
29. **Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C.** Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. Stroke 1994; 25:333–337. Erratum in: Stroke 1994; 25:1887.
30. **Sacco RL, Shi T, Zamanillo MC, Kargman DE.** Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. Neurology 1994; 44:626–634.
31. **Hankey GJ, Jamrozik K, Broadhurst RJ, et al.** Long-term risk of first recurrent stroke in the Perth Community Stroke Study. Stroke 1998; 29:2491–2500.
32. **Moroney JT, Bagiella E, Paik MC, Sacco RL, Desmond DW.** Risk factors for early recurrence after ischemic stroke: the role of stroke syndrome and subtype. Stroke 1998; 29:2118–2124.
33. **Lai SM, Alter M, Friday G, Sobel E.** A multifactorial analysis of risk factors for recurrence of ischemic stroke. Stroke 1994; 25:958–962.
34. **Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR.** Determinants of early recurrence of cerebral infarction. The Stroke Data Bank. Stroke 1989; 20:983–989.
35. **Hier DB, Foulkes MA, Swiontoniowski M, et al.** Stroke recurrence within 2 years after ischemic infarction. Stroke 1991; 22:155–161.
36. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. Lancet 1997; 349:1569–1581.
37. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997; 349:1641–1649.
38. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. JAMA 1998; 279:1265–1272.
39. **Kay R, Wong KS, Yu YL, et al.** Low-molecular-weight heparin for the treatment of acute ischemic stroke. N Engl J Med 1995; 333:1588–1593.
40. **Bath PM, Lindenstrom E, Boysen G, et al.** Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. Lancet 2001; 358:702–710. Erratum in: Lancet 2001; 358:1276.
41. **Wiebers DO, Whisnant JP, O'Fallon WM.** Reversible ischemic neurologic deficit (RIND) in a community: Rochester, Minnesota, 1955 1974. Neurology 1982; 32:459–465.
42. **Elkins JS, Sidney S, Gress DR, Go AS, Bernstein AL, Johnston SC.** Electrocardiographic findings predict short-term cardiac morbidity after transient ischemic attack. Arch Neurol 2002; 59:1437–1441.
43. **Heyman A, Wilkinson WE, Hurwitz BJ, et al.** Risk of ischemic heart disease in patients with TIA. Neurology 1984; 34:626–630.
44. **Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al.** Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007; 369:283–292.
45. **Douglas VC, Johnston CM, Elkins J, Sidney S, Gress DR, Johnston SC.** Head computed tomography findings predict short-term stroke risk after transient ischemic attack. Stroke 2003; 34:2894–2898.
46. **Purroy F, Montaner J, Rovira A, Delgado P, Quintana M, Alvarez-Sabin J.** Higher risk of further vascular events among transient ischemic attack patients with diffusion-weighted imaging acute ischemic lesions. Stroke 2004; 35:2313–2319.
47. **Ay H, Koroshetz WJ, Benner T, et al.** Transient ischemic attack with infarction: a unique syndrome? Ann Neurol 2005; 57:679–686.
48. **Coutts SB, Simon JE, Eliasziw M, et al.** Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. Ann Neurol 2005; 57:848–854.
49. **Crisostomo RA, Garcia MM, Tong DC.** Detection of diffusion-weighted MRI abnormalities in patients with transient ischemic attack: correlation with clinical characteristics. Stroke 2003; 34:932–937.
50. **Johnston SC, Easton JD.** Are patients with acutely recovered cerebral ischemia more unstable? Stroke 2003; 34:2446–2450.
51. **Johnston SC, Leira EC, Hansen MD, Adams HP.** Early recovery after cerebral ischemia and risk of subsequent neurological deterioration. Ann Neurol 2003; 54:439–444.
52. **Aslanyan S, Weir CJ, Johnston SC, Lees KR; GAIN International Steering Committee and Investigators.** Poststroke neurological improvement within 7 days is associated with subsequent deterioration. Stroke 2004; 35:2165–2170.
53. **Alexandrov AV, Felberg RA, Demchuk AM, et al.** Deterioration following spontaneous improvement: sonographic findings in patients with acutely resolving symptoms of cerebral ischemia. Stroke 2000; 31:915–919.
54. **Grotta JC, Welch KM, Fagan SC, et al.** Clinical deterioration following improvement in the NINDS rt-PA Stroke Trial. Stroke 2001; 32:661–668.
55. **Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators.** Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345:494–502.
56. **Antman EM, McCabe CH, Gurfinkel EP, et al.** Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. Circulation 1999; 100:1593–1601.

57. **Armstrong PW.** Pursuing progress in acute coronary syndromes. Circulation 1999; 100:1586–1589.
58. **Cohen M, Demers C, Gurfinkel EP, et al.** Low-molecular-weight heparins in non-ST-segment elevation ischemia: the ESSENCE trial. Efficacy and Safety of Subcutaneous Enoxaparin versus intravenous unfractionated heparin, in non-Q-wave Coronary Events. Am J Cardiol 1998; 82:19L–24L.
59. **Johnston SC, Sidney S, Bernstein AL, Gress DR.** A comparison of risk factors for recurrent TIA and stroke in patients diagnosed with TIA. Neurology 2003; 60:280–285.
60. **Johnston SC, Nguyen-Huynh MN, Schwarz ME, et al.** National Stroke Association guidelines for the management of transient ischemic attacks. Ann Neurol 2006; 60:301–313.
61. **Nguyen-Huynh MN, Johnston SC.** Is hospitalization after TIA cost-effective on the basis of treatment with tPA? Neurology 2005; 65:1799–1801.
62. **Berge E, Abdelnoor M, Nakstad PH, Sandset PM.** Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. Lancet 2000; 355:1205–1210.
63. **Streifler JY, Eliasziw M, Benavente OR, et al.** The risk of stroke in patients with first-ever retinal vs hemispheric transient ischemic attacks and high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial. Arch Neurol 1995; 52:246–249.
64. **Barnett HJ, Eliasziw M, Meldrum HE.** Drugs and surgery in the prevention of ischemic stroke. N Engl J Med 1995; 332:238–248.
65. **Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ ; Carotid Endarterectomy Trialists Collaboration.** Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. Lancet 2004; 363:915–924.
66. **Johnston SC, Nguyen-Huynh MN, Schwarz ME, et al.** National Stroke Association guidelines for the management of transient ischemic attacks. Ann Neurol 2006; 60:301–313.
67. **Sacco RL, Adams R, Albers G, Alberts MJ, et al; American Heart Association; American Stroke Association Council on Stroke; Council on Cardiovascular Radiology and Intervention; American Academy of Neurology.** Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006; 37:577 617.
68. **Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A.** European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143:1–13.
69. **ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A.** Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006; 367:1665–1673. Erratum in: Lancet 2007; 369:274.
70. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996; 348:1329–1339.

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