CAN WE AFFORD TO NEGLECT PATIENTS WITH TRANSIENT ISCHEMIC ATTACK?

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ABSTRACT

Approximately 30-40% of patients with ischemic stroke have a preceding transient ischemic attack (TIA) or a minor stroke. Most of these patients have underlying vascular risk factors which until the index event were probably unidentified or inappropriately treated. Unfortunately, in most health care systems across the world there are long delays before a TIA patient is seen by a specialist. During this time period, many 'preventable' strokes may occur with devastating effects on the victims and their care givers. This evidence-based review discusses the prognosis, evaluation and treatment of patients presenting with a TIA or minor stroke. We present data from recently published studies indicating high risk of early stroke after a TIA or minor stroke. We also show emerging evidence that urgent evaluation and early treatment results in dramatic reduction of early stroke risk in a vast majority of such patients.

Worldwide, stroke remains the leading cause of death, and a major cause of morbidity, long-term disability and hospital admission.[1] There is popular belief that ischemic heart disease is the most common form of vascular disease. Recent evidence, however, suggests that the incidence of stroke may in fact be higher than that of acute coronary syndromes.[2] It is anticipated that as the world population ages, the incidence of stroke will rise 25% by the year 2020.[3] Most patients with acute coronary syndromes are admitted and treated on an urgent basis in acute coronary care units. On the other hand, the majority of patients with a transient ischemic attack (TIA) or minor stroke are prescribed aspirin and discharged from emergency departments without undergoing appropriate investigations and imaging.

In comparison to a TIA or minor stroke, morbidity associated with a major ischemic stroke is devastating. About 30-40% of ischemic strokes are preceded by TIA or minor stroke.[4] Hence there is a potential window of opportunity to prevent a major stroke. This window of opportunity is being neglected because of multiple reasons, including a general nihilistic approach towards stroke care, absence of painful symptoms (which would prompt patients to seek urgent medical advice), and lack of resources in our health care systems for providing the same urgent attention to these patients as is provided to patients with acute coronary syndromes. In the past, the risk of stroke after a TIA has been considered to be low (1-2% at one week and 2-4% at one month),[5,6] and many clinical services have been organized accordingly. More recent studies, however, suggest that after a TIA the 90-day risk of subsequent stroke may be as high as 10.5%, and almost half of these strokes could occur in first 48 hours.[7] The results of the Early use of Existing Preventive Strategies for Stroke (EXPRESS) study[8] published recently show that urgent evaluation and treatment of patients with TIA or minor stroke results in a dramatic reduction of 90-day stroke risk by 56%.

EVIDENCE FOR INCREASED RISK OF EARLY STROKE AFTER TIA/MINOR STROKE

In 2001, Johnston et al published an important study[7] reporting prognosis in over 1700 patients diagnosed with transient ischemic attack in 16 hospitals in Northern California. These patients were evaluated in 1997 and 1998, and followed up for 90 days thereafter. During this period, 10.5% suffered from an ischemic stroke. Alarmingly, half of these strokes occurred in the first 2 days after the TIA. The proportion approaches 25% if all vascular events (cardiac events, recurrent TIAs, vascular death) are included. Half of these vascular events occurred within the first 10 days of initial presentation. Most patients in this study were assessed and treated by

emergency physicians and discharged on anti-platelet therapy. The findings of this study also indicate that certain TIA patients are at particularly high risk of early stroke. Important characteristics of these high-risk patients are shown in Table 1. Several other studies report reliable estimates of the true early risk of stroke after TIA or minor stroke. Re-analysis of data from the Oxfordshire community stroke project found stroke risk from the date of onset of first TIA to be 8.6% at 7 days and 12% at 30 days.[9] A study from Alberta, Canada, reported that among 2285 patients with a TIA the estimated risk of stroke at 30 days was 6.7% and 9.5% at 90 days.[10] Another study on the timing of TIA preceding an ischemic stroke suggests that the time window for prevention is short. In this study 17% TIAs had occurred on the day of stroke and 43% during a seven-day period prior to the index stroke.[11]

PATHOPHYSIOLOGY OF TIA

TIA or minor stroke can be caused by multiple mechanisms. Most patients have underlying vascular risk factors, such as uncontrolled hypertension, smoking, diabetes, obesity and a sedentary lifestyle.[12] Many patients also have a history of coronary artery disease and peripheral arterial disease. Patients with underlying coronary artery disease and/or peripheral arterial disease are at particularly high risk for cerebrovascular disease.[13] The so-called vascular risk factors can be separated into modifiable and non-modifiable factors. Age remains the most important non-preventable risk factor for stroke. There is sufficient evidence to suggest that in high risk individuals aggressive treatment of hypertension and the use of statins can decrease the risk of stroke and other vascular events.[12] In the majority of TIA patients, the underlying mechanisms include injury to the endothelium and media, development of atheroma with thrombus formation, and artery-to-artery emboli, all of which may cause ischemic injury and development of focal neurological deficits. In most TIA patients, these emboli

TABLE 1

Clinical Indicators of High Risk TIAs (California Score, from ref. 7)

	Odds Ratio	95% Confidence interval	p value
Age>60	1.8	1.3 - 4.2	0.005
DM	2.0	1.4 - 2.9	0.001
>10 min	2.3	1.3 - 4.2	0.005
Weakness	1.9	1.4 - 2.6	0.001
Speech	1.5	1.1 - 2.1	0.01

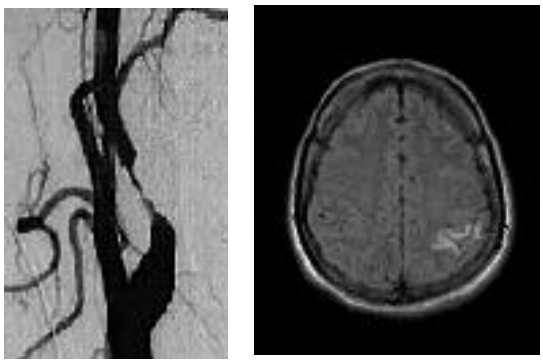

Figure 1. A young patient with transient neurological symptoms. (A) Angiogram shows significant stenosis secondary to internal carotid artery dissection. (B) MRI reveals left parietal infarct.

tend to be small and resolve rapidly resulting in complete resolution of symptoms in less than 24 hours. This definition has been based on the assumption that TIAs are associated with complete resolution of brain ischemia and no permanent brain injury. However, in recent years, studies using MRI techniques have shown that a substantial percentage of patients with TIA are left with permanent brain injury (Figure 1).[14,15] Based on these findings, the time-based definition of TIA has been challenged. It has been proposed by some experts that the definition should include clinical features as well as findings on diagnostic imaging that indicate the presence or absence of cerebral infarction.[16] Most patients in whom artery-to-artery emboli are suspected as the likely mechanism for cerebral ischemia will not have arterial stenosis greater than 50%. There is evidence that approximately only 10% of these patients may have a surgically correctable lesion in the neck vessels and hence the need for carotid imaging in patients presenting with symptoms related to anterior circulation territory.[17] Cardiac disease accounts for the second most common cause of emboli producing TIA or stroke.[17] Atrial fibrillation is the commonest cardiac cause and becomes particularly important as the population ages.[17] In the developing world, especially in younger individuals, one may also frequently see rheumatic heart disease as a common cause of valvular atrial fibrillation and embolic disease. In individuals with uncontrolled hypertension or diabetes, small-vessel disease may on occasion present as TIA, although most patients with small-vessel disease will have a stroke with no preceding transient symptoms.[18] Atherosclerosis is a lifelong process that continues to erode the endothelium and makes the lumen more susceptible to thrombus formation. Thrombi may originate in vessels with significant stenosis, although such a stenosis is not necessary for endothelial injury or thrombus formation. In a smaller percentage of patients,

an embolus would arise from the heart or in primary intracranial arterial disease. In certain ethnic groups the incidence of intracranial disease is particularly high.[19,20]

IS IT POSSIBLE TO IDENTIFY INDIVIDUALS AT HIGH RISK OF STROKE AFTER TIA?

Data from published studies suggest that approximately 22-30% of patients with suspected TIA have a diagnosis other than TIA or minor stroke.[21,22] It is extremely important to identify these low risk patients as they do not need costly urgent investigations and therapies that could have potentially serious side effects. Moreover, most patients with a confirmed diagnosis of TIA are not at risk of early stroke. Validated models predicting long-term stroke risk after TIA or minor stroke are available. There is increasing evidence that early risk of stroke after TIA can be predicted by using these scoring systems based on clinical features.

TABLE 2
[ABCD]^2 Score

Age ≥ 60 years	1 point
BP ≥ 140/90	1 point
Unilateral weakness	2 points
Speech impairment without weakness	1 point
Duration ≥ 60 minutes	2 points
Duration 10 - 59 minutes	1 point
Diabetes	1 point

The study by Johnston et al[7] identified five risk factors (California scores) independently associated with high risk of recurrent stroke at 3 months in a large cohort of patients with TIA (Table 1). Similarly, Rothwell and colleagues studied predictors of stroke during the first 7 days after a TIA in two independent population-based studies from Oxfordshire, UK, and developed a 6-point ABCD (age, blood pressure, clinical features, duration of symptoms) score.[23] The validity of the ABCD score was challenged in a population-based study from the United States.[24] More recently, Johnston, Rothwell and colleagues validated the California and ABCD scores in four independent groups of patients diagnosed with TIA in the US and UK and derived a unified score [ABCD]^2 which is highly predictive of 2-day stroke risk (Tables 2 and 3).[25]

Brain imaging also appears to be of prognostic value in patients with TIA. Presence of infarction on an initial CT scan can be highly predictive of recurrent stroke.[26] However, diffusion weighted imaging (DWI) on MRI seems to have greater clinical utility. In one recent study in which patients were scanned within 24 hours of TIA, the reported 90-day stroke risk was 32.6% in the presence of both ischemic lesions on DWI and vessel occlusion.[27] These findings were in comparison to a risk of under 4% in patients without DWI abnormality. Other recent studies show similar trends.[28] It is unclear, however, if imaging abnormalities provide additional prognostic value when compared with scoring systems based on clinical features alone. It is also important to emphasize that the numbers of patients in these studies are small and much more data is needed before one can advocate widespread use of these costly imaging modalities for routine evaluation of patients with TIA or minor stroke.

At a minimum, patients with TIA or minor stroke with symptoms related to the anterior circulation should have imaging of their neck vessels (carotid doppler ultrasound, CT angiogram or magnetic resonance angiography). In current practice, conventional contrast angiography is seldom used to evaluate extracranial vascular stenosis in the neck. CT scan of the brain should be performed to rule out other causes of neurological deficits (such as hemorrhage or subdural hematoma). Electrocardiogram should be obtained to exclude atrial fibrillation. Echocardiogram should be done in patients suspected to have underlying cardiac abnormalities.

CHANGING STRATEGIES FOR SUCCESSFUL MANAGEMENT OF PATIENTS WITH TIA AND MILD STROKE

As noted, not all patients with TIA and minor stroke are at high risk for early stroke, and high-risk patients may be identified by using scoring models as described above. Before a passionate appeal is made for urgent evaluation of these patients, treatment efficacy in prevention of early recurrent stroke needs to be demonstrated.

TIAs and minor strokes can be considered equivalent to acute coronary syndromes which if untreated carry a poor prognosis and are associated with early risk of myocardial infarction and cardiac death. Unfortunately, despite the fact that both conditions are associated with poor outcomes, major discrepancies persist in the way we manage these two patient groups. Most patients presenting with chest pain and suspected acute coronary syndrome are admitted to hospital for observation and intensive investigations. All patients with chest pain receive such urgent attention despite the fact that approximately 30-40% of them will have a non-cardiac cause for their symptoms. In contrast, even in university

hospitals most patients with suspected TIA are assessed in emergency departments on a non-urgent basis, followed by referral to either a stroke clinic, if one is available, or the on call neurologist. In smaller centers where access to a neurologist may not be available, such patients are discharged back to their general practitioner or referred to an internal medicine specialist. There may be a delay of several days or weeks before these patients receive follow-up appointments and then there are further delays before all relevant investigations can be undertaken.

Over the last 10 years our practice has been to screen patients referred to our stroke prevention clinic into three groups: (a) patients with symptom onset of < 24 hours, with motor and/or speech symptoms, with prolonged symptoms, or with vascular risk factors (these are seen urgently within 24-48 hours); (b) patients with similar symptoms but with days to weeks since symptom onset (these are seen less urgently, within 1-2 weeks); and (c) all other patients with nonspecific symptoms (such as syncope, numbness or dizziness) are seen electively over a month or longer. Our stroke prevention clinic runs five days per week and we see in excess of 2000 patients per year. The clinic has its own doppler facility, immediate access to CT scan and, where appropriate, MR imaging and cardiac evaluation.

Another important observation relates to the urgency in initiating therapy. Previously, attention has been focused on antithrombotic therapy and carotid surgery while management of risk factors such as hypertension, diabetes or high cholesterol was left to the referring physician. Earlier studies from a few years ago indicate that in the vast majority of these patients recommendations were either ignored or followed only by a minority of patients.[29] Our current practice is to initiate treatment for all risk factors in our clinic. We have also found that addition of a dietician, psychologist and social worker is of added value for the program.

Several treatments are likely to be effective in preventing stroke in the phase immediately following TIA or minor stroke. Patients who are naïve to antithrombotics and in whom there is no evidence for atrial fibrillation or other potential cardio-embolic source may be started on aspirin (acetylsalicyclic acid or ASA) 50-160 mg/day. Patients already taking ASA may either continue the same or may be switched to a combination of extended release dipyridamole (200 mg) plus ASA (25 mg) twice daily, or clopidogrel 75 mg/day. It is important to keep in mind that in stroke prevention studies the newer antiplatelet agents were shown to be only marginally better than ASA.[30,31] In our opinion, if the patient is unable to afford the more costly medication, it is quite appropriate to continue with ASA as long as they are compliant with treatment. In the MATCH trial,[32] long-term therapy with combination of ASA and clopidgrel in patients with ischemic stroke and TIA did not offer any additional benefit over clopidogrel alone, and in fact increased the risk of life-threatening hemorrhage at 18 months. However, more recent evidence has emerged that dual therapy might have a better risk-benefit ratio in selected patients,[33] or if started earlier after TIA, when the risk of stroke recurrence is higher.[8,34] We believe that combination therapy (ASA + clopidogrel) may be initiated early after the event in high-risk patients and can be continued for the first 2-3 months. Patients with underlying atrial fibrillation should receive long-term anticoagulation with warfarin. In patients with >50% symptomatic carotid stenosis, carotid endarterectomy is highly effective within 1-2 weeks after TIA or minor stroke.[35]

TABLE 3

Grouped score strata for low, moderate, and high risk TIAs (From ref.25)

ABCD2 score	2-day risk	7-day risk	90-day risk
Less than 4	1 %	1.2%	3.1%
4 to 5	4.1 %	5.9 %	9.8 %
Greater than 5	8.1 %	11.7 %	17.8 %

Three recent studies now suggest a radical change in the way we manage patients with TIAs and mild strokes. In the Early use of Existing Preventive Strategies for Stroke (EXPRESS) study,[8] investigators compared the usual UK practice of delayed assessment and treatment of patients with TIA or minor stroke (phase 1) with a revised protocol of prompt assessment and introduction of therapy within 24 hours of the event (phase 2). Their findings show that rapid assessment and early treatment after TIA results in a dramatically lower 90-day risk of recurrent stroke (10·3% in phase 1 versus 2·1% in phase 2, p=0·0015). In the study's phase 2 arm, a little over 50% patients were treated with a combination of aspirin and clopidogrel for the first three months. Blood pressure lowering treatment and statin therapy were initiated in the clinic. Patients with atrial fibrillation and with clinically significant carotid artery stenosis were also managed in an expeditious way. The data, however, needs cautious interpretation as the numbers of events were low in both study groups.

The second study, FASTER (Fast Assessment of Stroke in Transient ischemic attack to prevent Early Recurrence)[34] was a predominantly Canadian study. This pilot study randomized patients with TIA or mild stroke within 12 hours of the qualifying event to either aspirin or aspirin plus clopidogrel. In the second arm of this study simvastatin 40 mg was compared with placebo. The authors presented preliminary findings at the European Stroke conference in May 2007 held in Glasgow, UK. Their findings suggest that the addition of clopidogrel to ASA may be associated with a reduction of stroke after TIA or minor stroke. Early use of simvastatin did not seem to be of benefit. In this study, again, the number of patients was very small and data need cautious interpretation.

Another recently published study, Feasibility and impact of TIA clinic with Round-the-Clock Access: SOS-TIA21 evaluated a TIA clinic based in Paris, France. This clinic offered 24-hour access to patients with TIA for urgent evaluation and treatment. From January 2003 until December 2005 investigators treated 1085 patients with suspected TIA and reported a 3-month stroke rate of 1.24% versus a predicted rate from [ABCD]^2 of 5.96%. There was no control group in this study so once again the data require cautious interpretation.

CONCLUSIONS

Patients with TIA or minor stroke are not disabled, but they are at high risk of recurrent stroke during the first few days after the ischemic event. Currently, validated risk scores are available to aid in triage of patients at particularly high risk of early stroke. The EXPRESS, FASTER and SOS-TIA studies offer a ray of hope for these high-risk individuals, as their findings show that early and aggressive treatment may substantially reduce the risk of recurrent stroke after TIA or minor stroke. Worldwide the majority of these patients are treated on a non-urgent basis. A compelling case can now be made that patients presenting with symptoms suggestive of TIA or minor stroke need urgent evaluation. Patients classified as high-risk may require admission to the hospital for rapid investigations, treatment and observation. Early treatment of vascular risk factors, use of antithrombotic medication, and early carotid endarterectomy may result in a significant decrease in subsequent ischemic stroke in these individuals.

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