TRANSIENT ISCHEMIC ATTACKS AND MINOR STROKES: HOW NEWER TECHNOLOGIES ARE HELPING IN BETTER DIAGNOSIS OF HIGH-RISK PATIENTS AND RESPONSE TO TREATMENT

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ABSTRACT

Stroke is a leading cause of disability and death. In more than 30% of patients a disabling stroke is preceded by milder transient symptoms. The risk of stroke in patients with transient ischemic attacks (TIAs) and minor stroke may be very high in the initial days following the symptoms. Identification of such patients and appropriate treatment can lead to a significant decrease in the risk of subsequent stroke. This review will focus on two important issues; the impact of introduction of newer technology on identification of high-risk patients and the recent advances in antithrombotic therapy in stroke prevention in patients with TIAs and minor stroke. Appropriate use of imaging and cardiac rhythm monitoring allow for identification of high risk patients and the use of dual antiplatelet therapy early, following an acute TIA or minor stroke, significantly reduces the risk of recurrence.

Key Words: transient ischemic attacks (TIAs), Stroke, Ischemic Stroke.

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INTRODUCTION

Worldwide, cerebrovascular disease (CVD) is the leading cause of chronic disability; the second most common cause of death and dementia; and a significant burden to patients, caregivers, and healthcare systems.[1-3] Recent epidemiological studies from Oxford reveal that the incidence of stroke is similar to ischemic heart disease (IHD), and that contrary to common belief, stroke manifests at an age similar to that of IHD.[4] In addition, brain imaging studies reveal "silent stroke" is 4-6 times more common than overt stroke in older segments of the population.[5] These lesions are not merely an epiphenomenon[6]; they have been shown to increase the risk of subsequent symptomatic stroke[5], and lead to cognitive decline[7] and dementia.[5,7] Taken together, silent stroke and symptomatic ischemic disease are a much bigger health care problem than are currently appreciated. Also alarmingly, the incidence of stroke is rising.

Stroke is however a preventable disease. While the incidence of stroke is increasing across the world, a continued decline in its incidence in the USA during the last 10 years is testament that efforts at prevention are effective.[8] This is unfortunately not the case in other parts of the world. Between 1990 and 2010, the global number of stroke deaths rose from 4.6 million to 5.8 million, an increase of 26%. This increase was mainly seen in low to middle income countries.[3]

Cerebrovascular disease is a complex process that begins with damage to the vascular endothelium decades before it becomes clinically symptomatic.[9-13] Treatable risk factors play an important role in evolution of the vascular injury.[14-18] Acute stroke is preceded by transient ischemic attacks (TIAs) in more than 30% of patients.[19-22] The risk of stroke following a TIA is especially high immediately following the event; most events occurring within the initial 24-48 hours.[20] Scores designed to identify patients at an especially high risk for recurrence have been designed, tested and validated.[22] There is also compelling evidence that 'same-day' evaluation and treatment of patients presenting with TIAs can result in a significant decrease in subsequent strokes of more than 80%.[20,23] Recent evidence shows that brief periods of dual antiplatelet treatment is superior to single antiplatelet following a TIA.[5,13] The study CHANCE[13] was completed in China and it is not clear if these results can be generalized to non-oriental population. The POINT trial[24], sponsored by NIH in the USA, is evaluating similar treatments in North America and will provide valuable data in a few years. In addition, newer drugs are being tested in TIA patients presenting within 24 hours from symptom onset. The SOCRATES study[25] is evaluating the effect of ticagrelor versus ASA in such patients. The study was

started in 2013 and will be enrolling 8000 patients with TIAs and minor stroke.

The risk of recurrent stroke is particularly high in patients with high-grade ipsilateral carotid stenosis. Immediate investigations of the neck vessels are therefore essential. Approximately 10% of patients with TIAs have significant ipsilateral carotid stenosis that may require urgent surgery. In an additional 20 % of patients, a cardiac source (most commonly atrial fibrillation) may be detected. In such patients development of thrombus formation in the left atrial appendage and its dislodgment and embolization may be the mechanism for the acute event. Whereas most patients with sustained or persistent atrial fibrillation can be diagnosed with routines electrocardiography, paroxysmal atrial fibrillation may require prolonged cardiac monitoring for 24 hours or longer. The yield for detection of atrial fibrillation increases from 2% to 16 percent if the duration of cardiac monitoring is increased from 24 hours to 30 days.[26,27] The technology to monitor the cardiac rhythm continues to improve and is becoming less expensive.

The presenting symptoms in patients with TIAs and minor stroke are abrupt and seldom last more than an hour in the majority of patients. Loss of function (focal weakness, decrease sensation, aphasia, ataxia) is the most common presenting symptom. Loss of consciousness is rarely a manifestation of cerebral ischemia. Similarly, 'positive symptoms' (for example; paresthesias, visual fortification spectra) are also not a feature of TIAs but more suggestive of migraine auras or rarely, focal seizures. After imaging of the brain (to rule out intracranial hemorrhage) the patient should be started on antiplatelet treatment as soon as possible. Most patients will also require appropriate control of hypertension and hyperlipidemia.

The investigations and management of TIAs and minor stroke has been the subject of many recent publications.[3,7,9,17] The main purpose of this review is to highlight recent advances in the determination of prognosis and in the management of patients presenting with acute TIAs or minor stroke.

A. DIAGNOSIS:

1. Risk of stroke following TIA and minor stroke.

Whereas TIAs have long been recognized as harbingers for stroke and heart disease, it has only recently been recognized that this risk is particularly high in the initial days following the acute event. These studies were summarized in systematic reviews.[1] Almost 50% of all strokes occurring within the first 3 months of TIA onset occur during the first two days.[1,2] Studies in Oxfordshire found the risk of stroke in the first 48 hours after TIA to be 10%,[3] about twice the risk of myocardial infarction or death in patients presenting with acute coronary syndromes.[4]

Similar to TIAs, the risk of recurrent stroke is also high after 'minor stroke'. In fact, compared to TIAs, event rates were higher for patients with minor ischemic stroke enrolled in the FASTER trial.[5] Risk of cardiac events is also elevated after TIA. In one large study, 2.6% were hospitalized for major cardiovascular events (myocardial infarction, unstable angina, or ventricular arrhythmia) within 90 days.[6] Given the high risk of stroke and MI in patients with TIAs and minor stroke, we believe the current management strategies are unfortunately not emergent enough and very inadequate.[7]

2. The underlying etiology for TIA and Minor Ischemic Stroke.

The underlying vascular lesion in most patients with TIAs and minor stroke is rupture of an unstable plaque in the neck or intra-cranial vessels.[8] The high incidence of stroke in such patients[3,6,9] may be related to severity of the underlying pathology.[10] The thrombosis at a ruptured atherosclerotic plaque is responsible for the initial ischemic event. Rapid recanalization and reperfusion likely is the mechanism for fast recovery. However, the plaque likely remains highly thrombogenic for days after the event, thereby elevating the risk of a subsequent ischemic event.

The underlying pathology of TIAs and minor stroke and the risk of recurrent stroke is very similar to that of acute coronary syndromes (i.e., unstable angina and non-Q-wave myocardial infarction) in which thrombosis and thrombolysis are acutely active and protracted.[11] It is possible that the cerebral ischemia that acutely recovers may be a marker for ongoing thrombosis-thrombolysis, whereas major ischemia that persists may be a result of a larger embolus that is not completely resolved and that is not amenable to acute antiplatelet therapy.[10]

3. Clinical clues to help identify patients at the highest risk of stroke following TIA and minor stroke.

Neurological symptoms in focal cerebral ischemia follow specific patterns and arise from dysfunction in specific brain regions. As the ischemic insult is sudden, the symptoms also develop very quickly. Thus the most important clinical hallmark of TIA and stroke is the abruptness of development of focal symptoms (stroke; as if struck by lightening). If the symptoms begin in one region of the body (for example the vision) and then march to another region (for example the arm or leg), especially if this movement occurs over a few minutes, the underlying etiology is unlikely to be focal ischemia. In such patients migraine aura is the likely mechanism for the symptoms. Focal seizures may be a less likely etiology. Other common mimics include hypoglycemia, inner ear disease or malingering and are listed in Table 1. In busy stroke prevention clinics non-ischemic symptoms account for 30% of patients referred as TIAs or minor strokes.[28]

TABLE 1: DIFFERENTIAL DIAGNOSIS OF TRANSIENT FOCAL NEUROLOGICAL SYMPTOMS

Transient Ischemic Atatcks and minor stroke
Migraine with and without aura
Focal seizures
Hypoglycemia
Hyperglycemia
Tumor attacks
Intracerebral hemorrhage
Peripheral (inner ear) vertigo
Focal neuropathy
Motor neuron disease
Malingering

Several clinical factors have been shown to predict increased stroke risk following TIA. The most extensively validated factors are the clinical elements that have come to constitute the ABCD2 score. Five simple independent risk factors for stroke within the 90 days after a TIA were identified in the original cohort study[6]: age ≥ 60 years, diabetes, duration ≥ 10 minutes, speech impairment, and weakness. In a meta-analysis combining two cohorts from California and Oxford and validating a new model

TABLE 2: THE ABCD2 AND RISK STRATIFICATION SCORING SHEET IN USE IN THE STROKE PREVENTION CLINIC AT UNIVERSITY OF ALBERTA HOSPITAL

APSS
Alberta Provincial Stroke Strategy

MINOR STROKE/TIA STROKE RISK ASSESSMENT

HIGH RISK:

- Symptom onset within the last 48 hours with any one of the following
  - ✓ Motor deficit lasting more than 5 minutes
  - ✓ Speech deficit lasting more than 5 minutes
  - ✓ $ABCD^2$ score ≥ 4
- Atrial fibrillation with TIA

MEDIUM RISK:

- Symptom onset between 48 hrs and 7 days with any one of the following:
  - ✓ Motor deficit lasting more than 5 minutes
  - ✓ Speech deficit lasting more than 5 minutes
  - ✓ $ABCD^2$ score ≥ 4

LOW RISK:

- Symptom onset >7 days
- Symptom onset ≤7 days without the presence of high risk symptoms (speech deficit or motor deficit or $ABCD^2$ score ≥4 or atrial fibrillation with TIA)

Note: Isolated syncope or dizziness is rarely a TIA and may not require Stroke Prevention Clinic referral

$ABCD^2$ SCORING CHART

		Yes	No
Age	≥ 60 yrs	1	0
BP	≥ 140/90	1	0
Clinical Features			
● Uniateral weakness (with or without speech disturbance)		2	0
● Speech deficit without weakness		1	0
Duration			
	> 10 min < 59 min	1	0
	≥ 60 min	2	0
Diabetes		1	0

Score ≥ 4 = High Risk

BP ≥ 140/90

Clinical Features

- Uniateral weakness (with or without speecl
- Speech deficit without v

Duration

> 10 min < 59 m
≥ 60 min

Diabetes

Score ≥ 4 = High Risk

Figure 1: CT scan of a patient with transient neurological symptoms showing an intracerebral hemorrhage.

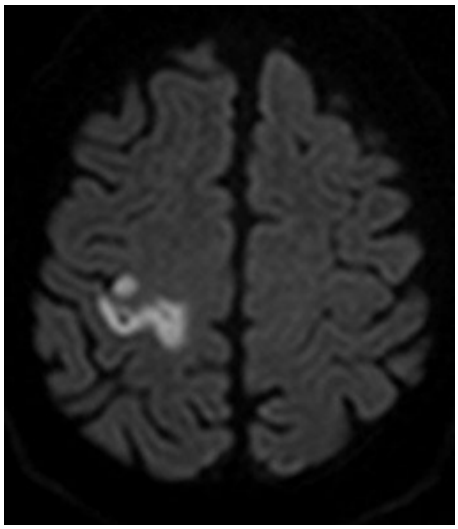

Figure 2: New MRI lesions in patients with TIAs and minor stroke. The risk of stroke recurrence is significantly higher in patients with abnormal MRI scans.

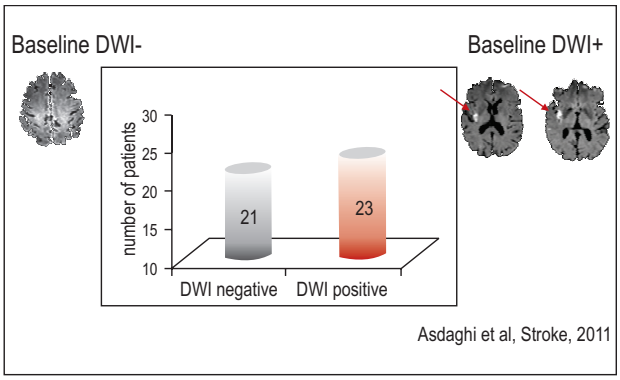

Figure 3: Risk of stroke increased in patients with DWI positive lesions on MRI. A

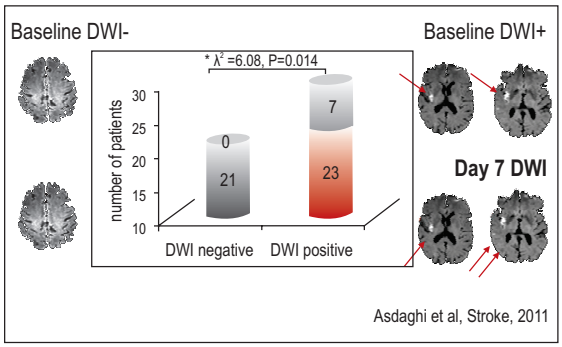

Figure 4 B

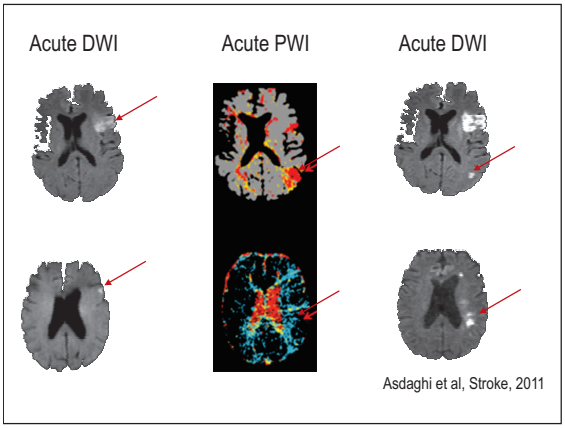

Figure 4: MRI scan with contrast enhancement studies. Patients with abnormal perfusion deficits are at the highest risk for new cerebral infarction during follow-up.

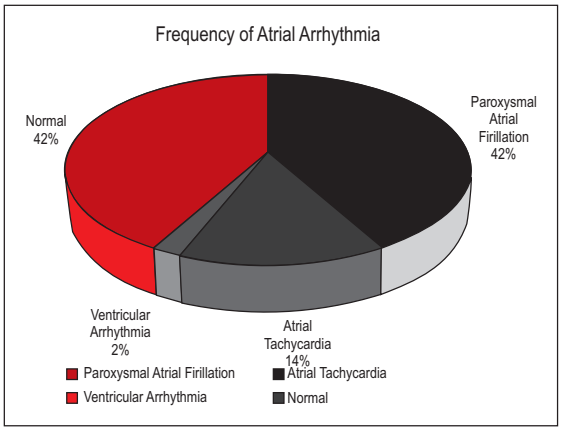

Figure 5: The risk for detection of new paroxysmal atrial fibrillation with prolonged monitoring.

in four remaining cohorts from the two regions, the ABCD2 score was created.[29] It includes all the elements of the original score and adds a couple of additional modifications. The score is created by summing points for each of several independent risk factors: age ≥ 60 years,[1] blood pressure ≥ 140/90 mmHg,[1] clinical symptoms of unilateral

weakness[2] or speech impairment without weakness,[1] duration 10-59 minutes[1] or ≥ 60 minutes[2], and diabetes.[1] Stroke risk was strongly associated with total score, increasing as the score increased with 90-day stroke risks ranging from 20% with a score of 6-7 to < 1% with a score of 0-1. The ABCD2 score is a useful tool to triage patients in busy emergency departments or stroke prevention clinics. Table 2 shows an example of a scoring system in use in our stroke prevention clinic to triage patients depending on the ABCD2 score. Another important determinant of stroke risk is time. The risk of recurrence is highest immediately following the acute event and for the subsequent 24-48 hours.[3] Thereafter it continues to decrease over time.

Although all patients with focal neurological symptoms require careful neurological evaluation, patients with higher ABCD2 scores should be examined immediately and evaluated with imaging of the neck vessels and the heart rhythm (see below). In addition, as the risk of stroke recurrence is very high early following the event, patients presenting within the initial 24-48 hours should have immediate access to imaging.

4. Sophisticated brain imaging studies to identify patients at highest risk of stroke following a TIA or minor stroke.

All patients with a suspected TIA and minor stroke should have imaging of the brain, neck vessels and the heart. A cranial CT scan is usually normal but may show a small ischemic stroke. It may also show silent asymptomatic strokes, especially in patients with a history of atrial fibrillation. Occasionally the transient symptoms may be secondary to a small brain hemorrhage or a brain tumor that may be diagnosed with the simple brain imaging with non-contrast CT scan as shown in Figure 1. The yield with MRI is significantly better than with CT scans. Imaging studies utilizing MRI have shown that approximately 40-50 percent of patients a recent TIA have abnormal MRI scans (32) The infarction are most often evident on diffusion weighted imaging (DWI) and can be cortical or subcortical as is evident from Figure 2. In addition to confirming the diagnosis, identification of ischemic lesion on MRI also provides important clues on prognosis. The risk of stroke recurrence is significantly higher in patients in whom new ischemic lesions are detected on MRI compared to patients with no new lesions on MRI following an acute TIA. In a recent study from our center, the risk of recurrent ischemic stroke was evaluated with repeated MRI studies. During follow-up, new lesions were reported in 23% of patients with abnormal MRIs compared to none in patients with normal MRIs (32). The results are shown in Figure 3. We have also shown that perfusion MRI studies can improve detection of patients at high risk for stroke recurrence following a TIA. New lesions are most likely to develop in regions of hypoperfusion identified on the brain imaging as shown in Figure 4.[30]

Although it is important to consider CT scans of the head in all patients with suspected TIAs, MRI of the brain should be reserved for patients at high risk of stroke. The technology is not widely available and is expensive. In patients with high ABCD2 score, especially if they are examined within the initial 24-48 hours may merit MRI evaluation.

5. Prolonged cardiac rhythm monitoring for detection of cardiac arrhythmias in patients with TIAs and minor stroke.

Similar to patients with completed large stroke, the underlying etiology of the event is not established despite extensive investigations in more than 30 to 40% of cases. In the reminder of patients common etiologies include significant ipsilateral carotid disease in 10% of patients, cardiac embolic disease in 20-30% of patients and small vessel intracranial disease (lacunar stroke) in another 20% of patients. Patients where no definite etiology is established are referred to as 'cryptogenic stroke'. More recently the condition is also being referred to as 'embolic stroke unknown source' or ESUS.[31] This group of patients with ESUS are of interest to stroke neurologists as a significant proportion of such patients may have paroxysmal atrial fibrillation (PAF) as the potential mechanism for the stroke. Conformation of PAF as the etiology is important as the treatment for prevention may require long-term anticoagulation therapy.

There has been recent interest in the use of long-term external and internal loop recorders in patients with cryptogenic stroke for the detection of PAF. Two recent studies have shown that the incidence of PAF may be between 8 and 16 percent in such patients. In the work completed in Canada, patients with cryptogenic stroke (and TIAs) were monitored with external loop recorders.[26] The diagnosis of cryptogenic stroke was entertained only if imaging of the neck vessels showed no significant stenosis and cardiac evaluation, including Holter monitoring for 24-48 hours and echocardiography was normal. Compared to repeat Holter monitoring where PAF was detected in 2% of patients, one month of recording revealed an additional 16% of new PAF. Our recent work has shown that such monitoring is important not only in patients with cryptogenic stroke but also in patients where a definite etiology is evident.[32] We evaluated 106 patients with recent stroke and TIAs with prolonged cardiac monitoring. PAF was evident in more than 40% of patients.[32] The data from our series is shown in Figure 5. The presence of a significant carotid stenosis or lacunar etiology does not rule out the presence of additional PAF. We recommend prolonged cardiac monitoring as an essential investigation

tool in patients where the etiology for a TIA or stroke is being investigated. The technology is becoming simpler and can be acquired by any busy stroke service.

B. Current Therapies to prevent stroke in patients with TIAs and minor strokes:

The accepted standard treatment for stroke prevention in TIA is the use of ASA, clopidogrel or a combination of ASA+dipyridamole.[33] These therapies together with early risk factor management have been the mainstay of stroke prevention for several years. In the EXPRESS study from Oxfordshire, early treatment with dual antiplatelet agents together with the liberal use of statins and ACE-inhibitors was noted to reduce the risk of early stroke by more than 80%.[3] Combination antiplatelet therapy, with its higher risk of hemorrhagic complications and no definite advantage from randomized trials was however not recommended for long term use by most experts.[14] Vascular wall injury resulting in platelet activation and aggregation are early initiating factors in most ischemic strokes. Platelet thrombi contribute to small vessel strokes, large vessel thombosis and embolism, and cardiac embolism. Inhibiting platelets reduces risk of ischemic stroke and is recommended in major guidelines.[15,16,33] The significant reduction in recurrent vascular events in EXPRESS[3] and SOS-TIA[17] studies suggests that the benefits of platelet inhibition begin immediately and may be greatest in the acute period.

The last decade has witnessed a large number of studies addressing important issues in stroke prevention in patients with TIAs and minor strokes. Research pertinent to the high-risk of stroke and other vascular events after TIA and minor stroke (especially within the initial 24-48 hours)[3,10] is nicely summarized in the review by Giles et al.[1] Additional important questions include the appropriateness of assessment of patients at the highest risk for stroke,[6] scoring system to make such identification easy for the general practitioner[9] and the use of imaging to predict patients most likely to develop early stroke.[10,34]

Current resources in most countries does not allow for extensive investigations for all patients presenting with transient symptoms. The medical community very frequently encounters transient neurological symptoms. Separating symptoms that may be serious and may be secondary to serious underlying mechanism such as a stroke from more benign conditions is important. This section of the current review will focus on three selected issues that can help identify high-risk patients.

Aspirin

Aspirin is the most commonly used medication in prevention of stroke in patients with TIAs and has been extensively studied in randomized trials, and reduces the incidence of stroke, myocardial infarction, and vascular death by 22%. Aspirin reduces recurrent stroke in patients with small vessel disease, large vessel disease, and also significantly in atrial fibrillation.[18]

Although earlier trials used a dose of 1300 mg of ASA per day, the best effects are likely evident with a dose in the range of 50-325 mg/day.[15,16] A loading dose of ASA (300 – 650mg) may lead to a rapid antithrombotic effect and is recommended by most experts.

Clopidogrel

Clopidogrel is a relatively newer agent that has not been tested as a single drug in patients with TIAs or minor stroke compared to placebo in reduction of recurrent vascular events. It is a thienopyridine derivative, inhibits platelet aggregation by blocking the P2Y12 ADP receptor.[19] Initial data on the efficacy of clopidogrel in reduction of stroke recurrence was evident in the CAPRIE trial where clopidogrel 75 mg/day reduced long-term risk of stroke, myocardial infarction, or vascular death by 8.7% relative to aspirin in patients with vascular disease. There was no increase in the risk of hemorrhage or other major side effects.[20]

In acute coronary syndromes, clopidogrel in combination with ASA has been shown to significantly reduce the risk of death compared to ASA alone.[12] With a loading dose of 600 mg, clopidogrel produces platelet inhibition faster than 300 mg, with greater inhibition at 3 and 4 hours after administration.[21] It has been shown to be effective and safe in trials of acute coronary syndrome (ACS) and coronary artery stenting.[12,22]

The recently completed CHANCE study showed that the combination of clopidogrel with ASA for 3 weeks significantly reduced the risk of stroke when patients were evaluated at 90 days. The trial was conducted in China and the effectiveness of the combination has not been tested in non-oriental population.[13] It is the currently subject of a large NIH funded POINT study in North America.

Clopidogrel-Aspirin combination.

Long-term use of combination of clopidogrel and aspirin in several trials of vascular disease, included two with stroke or TIA patients.[23,35] These studies enrolled the patients weeks to months after onset of symptoms. There was no improvement in stroke reduction but a statistically significant increase in the risk of hemorrhage in the combination group compared to single drug treated patients.

The mechanisms for antithrombotic effects of ASA and clopidogrel are separate and may be synergistic.[33] The combination of the two medications is routinely used in patients with coronary, carotid, and intracranial stenting.[22,26]

We need to evaluate critically the reasons for failure of the combination to reduce stroke in patients in previous

trials where patients with strokes and TIAs were enrolled over a time period of up to 6 months from the onset of symptoms. In the MATCH (Management of atherothrombosis with clopidogrel in high- risk patients with recent TIA or ischemic stroke) trial 7599 patients were enrolled.[33] Aspirin plus clopidogrel was compared to clopidogrel. The majority of patients (79%) enrolled suffered a prior stroke and at that, mostly subcortical lacunar stroke. Only a minority of patients enrolled suffered a TIA. The trial was negative showing a non-significant 1% absolute benefit in terms of reduced risk of ischemic events. The combination group had a 1% significant increased risk of major hemorrhage. It is however interesting to note that in the patients treated very early (within 7 days of the event) there was a trend toward greater benefit with a 17% RRR.[33] Similarly the CHARISMA trial which randomized patients with vascular disease to aspirin 75-162 mg/day and clopidogrel 75 mg or placebo, also showed negative results.[23] A small reduction in ischemic events balanced with a small significant increase in severe hemorrhages.

There are three trials where patients with TIAs and minor strokes were treated early after onset of symptoms with combination treatment with clopidogrel and ASA versus ASA alone. FASTER was a pilot trial based in Canada.[5] It evaluated clopidogrel (300 mg load and 75 mg/day afterwards) on a background of aspirin in patients presenting within 24 hours of a TIA or minor stroke. The trial enrolled 392 patients. The risk of stroke (ischemic or hemorrhagic) at 90 days was 11% in those treated with aspirin alone and 7% in those treated with clopidogrel and aspirin, a non-significant 36% RRR in this pilot trial (p=0.19). There were two ICHs and these were both in patients treated with clopidogrel and ASA.

The recently completed CHANCE trial (5170 patients enrolled within 24 hours of symptom-onset) from China showed that in patients with high-risk TIAs and minor strokes, there was a significant absolute reduction of early stroke at 90 days from 11.7 % to 8.2 % (HR 0.68, 95% CI 0.57-0.81; p<0.001) in patients treated with a combination of ASA and clopidogrel for 21 days compared to ASA alone.[13] Similar to the EXPRESS study,[3] most of the strokes developed in the initial days following the TIA. The observation that strokes occur very early, as is evident from EXPRESS and CHANCE suggests that perhaps the vascular pathology responsible for the events begins to heal rapidly once antiplatelet therapy is initiated. This allows for the possibility that shorter duration combination antiplatelet therapy may also be as effective as the 21 days treatment in CHANCE or the 30 days treatment in the NIH funded POINT trial. A prospective study that compares the outcome of stroke, MI or death at 90 days in patients treated with 10 days or 30 days of dual antiplatelet therapy will therefore be very useful. If the shorter duration dual antiplatelet therapy is as effective as the longer duration dual antiplatelet treatment, this will result in lower costs and the lower risk of side effects in stroke prevention in high-risk TIA patients.

The CARESS study also points to the usefulness of dual antiplatelet therapy in patients with TIAs, especially those at a very high risk of stroke.[36] In CARESS, a pilot double-blind, placebo-controlled trial, the effectiveness of clopidogrel- aspirin vs. aspirin alone was assessed by the presence of TCD micro-embolic signals in 107 patients with recently symptomatic carotid stenosis.[36] The primary end point was the detection of micro-embolic signals on TCD. At 7 days, 44% on the combination and 73% on aspirin alone had persistent micro-embolic signals (p=0.005), suggestive of a reduction in ongoing thrombo-embolism from the vulnerable plaque at the site of stenosis. There were more strokes and TIAs in the aspirin-only group (11 vs. 4) but the difference was not significant.

Finally in the meta-analysis of results from FASTER, CHARISMA, CARESS, and MATCH for patients enrolled within 24 hours of onset of TIA or stroke, there was a RRR of 34% with clopidogrel-aspirin vs. aspirin alone for the composite outcome measure of stroke, TIA, acute coronary syndrome, and all-cause death.[5] This together with the results from CHANCE study[13] provides strong support for the use of combination antiplatelet therapy in the setting of TIAs and minor stroke provided the treatment is initiated as soon as possible after the onset of symptoms.

Duration of antiplatelet medication combination.

Data from EXPRESS[3] and Northern California[6] shows that the risk of stroke after a TIA and minor stroke is highest in the initial 24-48 hours after the onset of symptoms. After the initial 48 hours, the risk of subsequent stroke subsides and continues to decrease for the 90-day observation in most recent studies. In the EXPRESS study, the majority of strokes prevented in the second arm of the study were in the initial 48 hours.[3] Similarly, in the CHANCE trial the best effect of the combination antiplatelet treatment was in the initial days following enrollment into the study.[13] The key to success is very early evaluation and initiation of treatment. It is likely that the vascular injury promoting thrombus formation may be very responsive to antithrombotic and heals quickly given the dual antiplatelet assault on the injury.

There are no studies determining the duration of optimal dual antiplatelet therapy in patients with TIAs and minor stroke. In the FASTER pilot study, duration of 90 days was arbitrarily selected because previous observational studies had evaluated prognosis at 90 days.[5] In the CHANCE study dual antiplatelet

treatment was offered for 21 days and the outcome was evaluated at 90 days.[13] In the on-going POINT study the duration of antiplatelet therapy, similar to FASTER, is 90 days.

The question relating to the duration of therapy to effectively reduce stroke in patients with TIAs and minor stroke is important for several reasons. Firstly, dual therapy is associated with a higher risk of major and minor hemorrhage. In the MATCH trial, the risk of major hemorrhage was twice that seen with single antiplatelet treatment.[24] In CHANCE, while the risk of major hemorrhage was equal in both arms, the risk of minor hemorrhage was almost double in the dual antiplatelet group compared to ASA alone.[13] Secondly, the cost of clopidogrel may be significant, especially in low to middle income countries. Thirdly, longer duration treatment, especially in the elderly may be associated with poor compliance and adherence to the use of dual medications.

CHANCE study[13] may have conclusively answered the question about the significantly better treatment with dual antiplatelet therapy in reducing the risk of stroke in the oriental population and POINT, when completed, will have similar answers in the Caucasian population. As yet unanswered question relates to the exact duration of dual therapy before the patient is switched to a single antiplatelet agent.

Summary:

Patients with TIAs and minor stroke require urgent attention. The speed with which patients are evaluated should be similar to evaluation of suspected acute coronary syndrome. All patients require imaging of the brain, neck vessels and elimination of a possible cardioembolic source. Clinical clues and abnormalities on brain imaging may help with the identification of patients at the highest risk for early stroke. Such patients may require dual antiplatelet therapy. Increasing use of prolonged monitoring of cardiac rhythm is very helpful in identification of patients with PAF. In such patients the appropriate treatment for prevention is the long-term use of anticoagulant therapy.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE

NIL

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