TIA: prevent a stroke

Transient ischaemic attacks (TIAs) should be considered as medical emergencies. A patient with a TIA needs rapid assessment and immediate treatment to reduce the risk of stroke and heart attack.

MARTIN KRAUSE
FRACP

Dr Krause is Associate Professor of Neurology, University of Sydney Medical School – Nepean Campus, Nepean Hospital, Penrith, NSW.

Stroke is a major contributor to disease burden in Australia. In 2003, there were about 346,700 Australians who had experienced a stroke at some time in their life, and about 146,400 Australians who had a disability that was mainly attributed to stroke. One in five people having a first-ever stroke died within one month, and one in three died within a year.[1]

Around 9000 deaths in Australia in 2003 were caused by stroke, and there were 68,866 hospital presentations with a principal diagnosis of stroke, in 2002 to 2003, accounting for 1,073,645 patient days. Around 80% of those people who have a stroke are aged 60 years or older.[2] Due to the ageing population in this country, the incidence rate of stroke will increase, with probably about 60,000 strokes occurring in 2009.[3] Each year, stroke costs Australia approximately $1.3 billion in accrued lifetime costs,[4] making it one of the most expensive diseases in the country.

Stroke prevention is the most important means for reducing the societal burden of stroke. There is no higher risk of stroke than in people who have experienced a recent cerebrovascular event such as a transient ischaemic attack (TIA) or a minor ischaemic stroke.[5] Johnston and colleagues demonstrated in a Californian cohort study that patients diagnosed in an emergency department with a TIA had a 25% risk of stroke, recurrent TIA, cardiovascular event or death within the next 90 days.[6] Coull and colleagues found the risks of stroke within seven days after TIA and minor stroke were 8% and 11.5%, respectively.[7] Some facts about TIAs in Australia are listed in Table 1.[3]

The perception of stroke, and even more of TIA, as an emergency among health care professionals and patients is insufficient, and ambulance

IN SUMMARY

- **Patients with transient ischaemic attacks (TIAs) have up to a 25% risk of a stroke, a cardiovascular event or death within the next three months. Most of these events will occur within two days after a TIA.**
- **Urgent assessment and intervention after a TIA can reduce the risk of such an event by up to 80%.**
- **Assessment of atrial fibrillation, diabetes, hypertension and age allows stroke risk stratification of patients. Patients with a moderate or high risk profile need immediate referral to a TIA clinic or a hospital with the capacity to treat acute stroke.**
- **Patients with TIA should be treated as soon as is feasible with a statin and a platelet inhibitor, unless they suffer from atrial fibrillation or have a prosthetic heart valve. In that case, they require an anticoagulant instead of a platelet inhibitor.**
- **First-line antiplatelet therapy is aspirin 75 to 150 mg daily. For recurrent ischaemic events, second-line treatment is aspirin plus dipyridamole or clopidogrel alone.**
- **All patients should receive a statin after a TIA, regardless of their cholesterol level.**
- **Patients with symptomatic moderate- or high-grade internal carotid artery stenosis benefit from immediate endarterectomy. This benefit wears off with time and is much less if endarterectomy is performed later than two weeks after the event.**

Table 1. Facts about TIAs in Australia[3]

- Stroke is the second most common cause of death
- Stroke is the most common cause of disability
- A stroke occurs every 10 minutes
- Up to 25% of all patients with a TIA will experience a stroke, heart attack or death within three months
- Urgent treatment of a TIA reduces the risk of early major stroke by 80%

response to stroke is disparate within each state of Australia. Only 23% of eligible public hospitals provided organised stroke services in 2004, and assessment tools like the ABCD2 score are not consistently applied in identifying patients at high risk of TIA.

Concept and evolving definition of TIA

The concept of TIA originates from a time when modern brain imaging was not available, and TIA was defined as an ischaemic event with the resolution of symptoms within 24 hours. Magnetic resonance imaging (MRI), however, has demonstrated new infarction (stroke) in up to 50% of the patients with transient neurological symptoms lasting longer than one hour.[8,9] Therefore, most intervention trials widened the concept to TIA or minor stroke, and the American Heart Association has recently endorsed a new imaging-based definition of TIA as a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, without infarction.[8] This definition, however, is MRI-based and presumes the high sensitivity of MRI and the vascular cause of symptoms.

There are insufficient data on the incidence of TIAs because many patients do not present to healthcare professionals if symptoms resolve within a short timeframe. According to the Oxfordshire Community Stroke Project (1981 to 1986), the incidence of first presentation with a TIA without preceding stroke or TIA was 42 per 100,000 people per year,[10] which is in line with other studies.

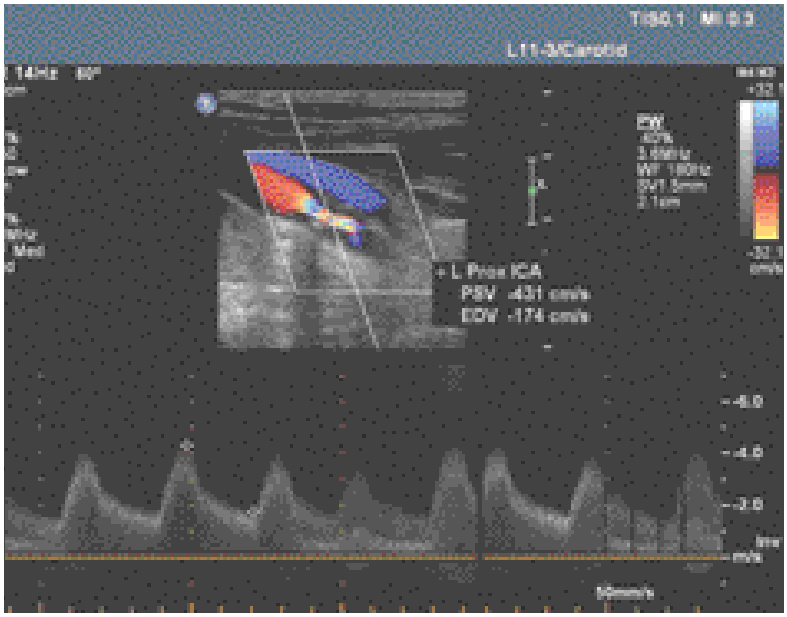

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Figure. Doppler image of a high-grade internal carotid artery stenosis.

Symptoms

The symptoms of a TIA vary substantially and may be difficult to recognise. Symptoms are likely to be a neurovascular incident if they have:

- sudden onset
- a distinct pattern, such as hemiparesis, aphasia, double vision, hemianopia
- occurred in the context of vascular risk factors.

Common symptoms in patients with TIA or stroke are the same and are listed in Table 2.

Sometimes patients might not be aware of their deficits – for example, patients with visual neglect may only present because others notice that they run into objects or have difficulties reading. Some of the deficits become evident only when a thorough neurological examination is conducted – for example, patients with aphasia may seem confused but in fact are having difficulty understanding others and expressing themselves. Even a sudden onset of confusion or dizziness and vertigo can indicate a stroke.

A drop attack is a rare symptom in patients with a TIA, and can be related to TIA in the posterior (vertebrobasilar) circulation. Strokes in the posterior circulation more commonly cause death and severe disability, so it is important to value and investigate such a symptom carefully.

Although the definition of TIA states a resolution of symptoms within 24 hours, symptoms normally last for a much shorter period, mostly only

Table 2. Symptoms of TIA

- Double or blurred vision (diplopia or nystagmus)
- Monocular loss of vision (amaurosis)
- Binocular partial loss of vision (homonymous hemi-/quadrantanopia)
- Facial droop (upper motor neuron facial weakness)
- Speaking difficulties such as slurred or hoarse speech (dysarthria or dysphonia)
- Language difficulties such as difficulty understanding others and/or expressing themselves (aphasia)
- Confusion
- Weakness in one limb or on one side of the body
- Impairment of fine motor skills (clumsy hand)
- Numbness or pins and needles in one limb or on one side of body
- Gait disorder with broad-based or unsteady gait
- Ataxia
- Vertigo
- Syncope with no other cause
- Drop attack

minutes. If symptoms are persisting on presentation, the patient needs an immediate referral to an emergency department with a stroke service.

It is now generally agreed that it is important to investigate a patient with a TIA and address vascular risk factors within a short timeframe. If this is done, the risk of a recurrent or first-time stroke can be reduced by up to 80%, which will reassure the patient much more than leaving him or her with a vague differential diagnosis.

Ischaemic cerebrovascular events are mostly painless, but ischaemic strokes involving the posterior cerebral artery are not infrequently associated with headaches,[11] and it can be difficult to differentiate these strokes from migraine attacks.

Table 3. Common differential diagnoses of TIA

- Migraine
- Vestibular disorder
- Bell's palsy (lower motor neuron facial weakness)
- Epileptic seizure
- Nerve or nerve root impingement
- Metabolic disorder, e.g. hypoglycaemia
- Sepsis
- Cardiac failure
- Somatoform and conversion disorders

Differential diagnoses

The common differential diagnoses of TIA are listed in Table 3, and some are discussed below.

Migraine

Patients with a history of migraine often present with neurological deficits. These patients generally present with a fairly stereotypical aura (which might be visual symptoms such as light flashes or hemianopia), vertigo and dizziness; double vision may also be a feature. Patients with the rare familial form of migraine – familial hemiplegic migraine – may present with severe neurological deficits that last for many hours or even days.[12]

In general, the neurological deficits associated with migraine precede the headaches and have the tendency to evolve fairly slowly; sensory symptoms present with a slow march and disappear when the headache starts. Migraine headaches are predominant on one side of the head, throbbing in character, build up over several minutes to hours and last for hours to even days. They are mostly associated with nausea, photophobia and phonophobia. Patients tend to retreat to a quiet and dark location or go to bed.

Epileptic seizure

Neurological deficits can persist after an epileptic fit, and may mimic a stroke. However, these deficits are preceded by a seizure.

Vestibular disorder

Vertigo is commonly confused with dizziness. Vertigo is the illusion of motion, mostly rotation, and is commonly associated with nausea or vomiting. It is a common presentation, especially among elderly patients.

The most common cause of vertigo is benign paroxysmal positional vertigo, which can be diagnosed and mostly cured by the Hallpike positioning test.[13] Patients with vestibular neuritis often present with spontaneous unilateral nystagmus and severe nausea and vomiting. The head impulse test might help to differentiate between patients with cerebellar infarcts and those with vestibular neuritis.[14] Cerebellar infarcts can produce very few symptoms and affected patients will, in most cases, also present with ipsilateral ataxia, which can be difficult to detect. The nystagmus is mostly bidirectional and gaze-evoked. However, even life-threatening cerebellar infarcts may occasionally present with vertigo predominantly, and not many other signs.[15]

If the history and clinical examination does not allow a clear identification of the aetiology of the symptoms and the symptoms have an acute onset, MRI or computed tomography (CT) of the brain should rule out a serious condition.

Nerve or nerve root damage

Sensory and motor deficits as a result of nerve or root damage can be determined by the history and pattern of the symptoms. In most cases of peripheral nerve

Table 4. ABCD2 score for early stroke risk after TIA[17]

ABCD2	Points
A: Age 60 years or older	1
B: Blood pressure equal to or greater than 140 mmHg systolic or 90 mmHg diastolic	1
C: Clinical features:	
– unilateral weakness	2
– speech impairment without weakness	1
D: Duration	
– 60 minutes or longer	2
– 10 to 59 minutes	1
D: Diabetes mellitus	1

Sum score predicts risk of having a stroke within two days:

- score 0 to 3 = low risk (1.0%)
- score 4 to 5 = moderate risk (4.1%)
- score 5 to 6 = high risk (8.1%)

damage, symptoms will persist for at least several days. Nerve or root compressions are generally painful. However, if the compression occurs after the taking of a medication or drug that reduces the pain threshold or intensifies sleep (for example, compression of the radial nerve after heavy drinking) then the symptoms might be painless and therefore possibly confused with a TIA.

Clinical examination

To rule out a persistent neurological deficit in a patient, it is important to conduct a complete neurological examination, especially when there are symptoms that are often overlooked by patients, such as hemianopia or ataxia.

Certain clinical findings and medical history predict a high risk condition requiring immediate action. The risk of a recurrent vascular event or death after an initial TIA seems to be independently associated with age greater than 60 years, diabetes mellitus, symptom duration longer than 10 minutes, weakness, speech impairment and blood pressure equal to or greater than 140/90 mmHg on the first measurement after TIA symptoms.[6]

Rothwell and colleagues have developed and validated a simple clinical score that allows identification of patients with a high risk of recurrent vascular events after a TIA or minor stroke.[16,17] Using the refined and unified ABCD2 score, patients who have suffered a TIA can be stratified into a low risk group with a two-day risk of a stroke of 1.0%, a moderate risk group with a two-day stroke risk of 4.1% or a high risk group with a two-day stroke risk of 8.1%, as shown in Table 4.[17]

Patients assessed as being at moderate or high risk of a stroke on the basis of their ABCD2 score need an immediate assessment of risk factors and urgent treatment, either as an inpatient or within a well-organised outpatient management system. Those at low risk should be evaluated carefully for other underlying risk factors, such as atrial fibrillation or carotid artery stenosis. Internal carotid artery stenosis and atrial fibrillation are high-risk conditions despite affected patients possibly having low ABCD2 scores.

Table 5. Investigations in patients with TIA

- Brain imaging: CT or MRI
  – for ischaemic versus haemorrhagic stroke, and for intracranial vessel disease
- Neurovascular investigations: Doppler sonography, CT or MRI angiography, digital subtraction angiography
  – for stenosis of the internal carotid artery, pathology in the flow of the vertebral arteries
- Electrocardiogram (ECG)
  – for atrial fibrillation
- Holter ECG
  – for intermittent atrial fibrillation
- Echocardiogram
  – for cardiomyopathy, ischaemic heart disease, dilatation of the atrium, septum defects, and more
- Blood pressure
  – for arterial hypertension
- Laboratory investigations: lipids (especially LDL and HDL cholesterol), fasting glucose or glucose tolerance test, full blood cell count, electrolytes, renal and liver function tests, homocysteine, thrombophilia screen (in selected patients without any other evident cause of stroke, e.g. protein S and C deficiency, factor V Leiden mutation, antiphospholipid antibodies, antinuclear antibodies [ANA], antineutrophil cytoplasmic antibodies [ANCA], erythrocyte sedimentation rate, etc.)

Investigation of TIA

The most important investigations in patients with TIA are summarised in Table 5. These investigations serve to define the pathophysiological mechanisms of the event and to assist with further risk stratification.

Table 6. CHADS2 criteria and stroke risk stratification in patients with atrial fibrillation[24]

CHADS2 criteria	Points
C: Congestive heart failure	1
H: Hypertension	1
A: Age 75 years or older	1
D: Diabetes mellitus	1
S: Prior TIA or stroke	2

Stroke risk stratification

CHADS2 score	Annual stroke risk	Treatment
0	Low (2%)	Aspirin
1	Moderate (3%)	Warfarin or aspirin
2 to 6	High (4 to 18%)	Warfarin (INR target, 2.0 to 3.0)

Brain imaging – CT or MRI

The objectives of neuroimaging studies are to verify the vascular nature of the symptoms and exclude any nonvascular causes, investigate the underlying vascular mechanism (embolic, large vessel or lacunar–small vessel disease) and identify prognostic outcome categories.[8]

All patients with TIA require brain imaging with CT or, if possible, with MRI; MRI should include diffusion-weighted sequences. Patients in moderate- or high-risk ABCD2 groups need this examination as early as possible after the TIA, ideally on the same day. Those in the low-risk group should ideally undergo brain imaging within 48 hours. The imaging will:

- identify patients with ischaemic lesions
- provide evidence of whether the patient suffers from small vessel disease with multiple lacunar infarcts or large vessel disease with embolic infarcts, or even a watershed infarct (which is suggestive of high-grade internal carotid stenosis)
- allow identification of those patients with a higher risk of recurrence of stroke.

MRI has many advantages over CT in diagnosing stroke :

- MRI detects small strokes, which are commonly missed in CT scans
- white matter changes are much more evident in MRI than in CT scans, thus allowing differentiation of aetiology in most cases
- diffusion-weighted MRI will highlight an acute ischaemic event
- MRI allows noncontrast MR-angiography, which will reveal any large artery stenosis.

Neurovascular investigations – Doppler sonography and angiography

According to two large randomised trials, endarterectomy in symptomatic high-grade internal carotid artery stenosis can prevent stroke in selected patients (see later, under 'Carotid stenosis treatment'). The North American Symptomatic Carotid Endarterectomy Trial (NASCET) showed a net benefit of endarterectomy over medical management in symptomatic stenosis that is greater than 50% in the long-term analysis.[18,19] The European Carotid Surgery Trial (ECST), a randomised trial of endarterectomy, demonstrated a clear net benefit of the intervention for greater than 80% stenosis.[20] Both these trials were based on digital subtraction angiographic rating of the stenosis; however, they used different stenosis grading methods, which explains the discrepancy to some degree.

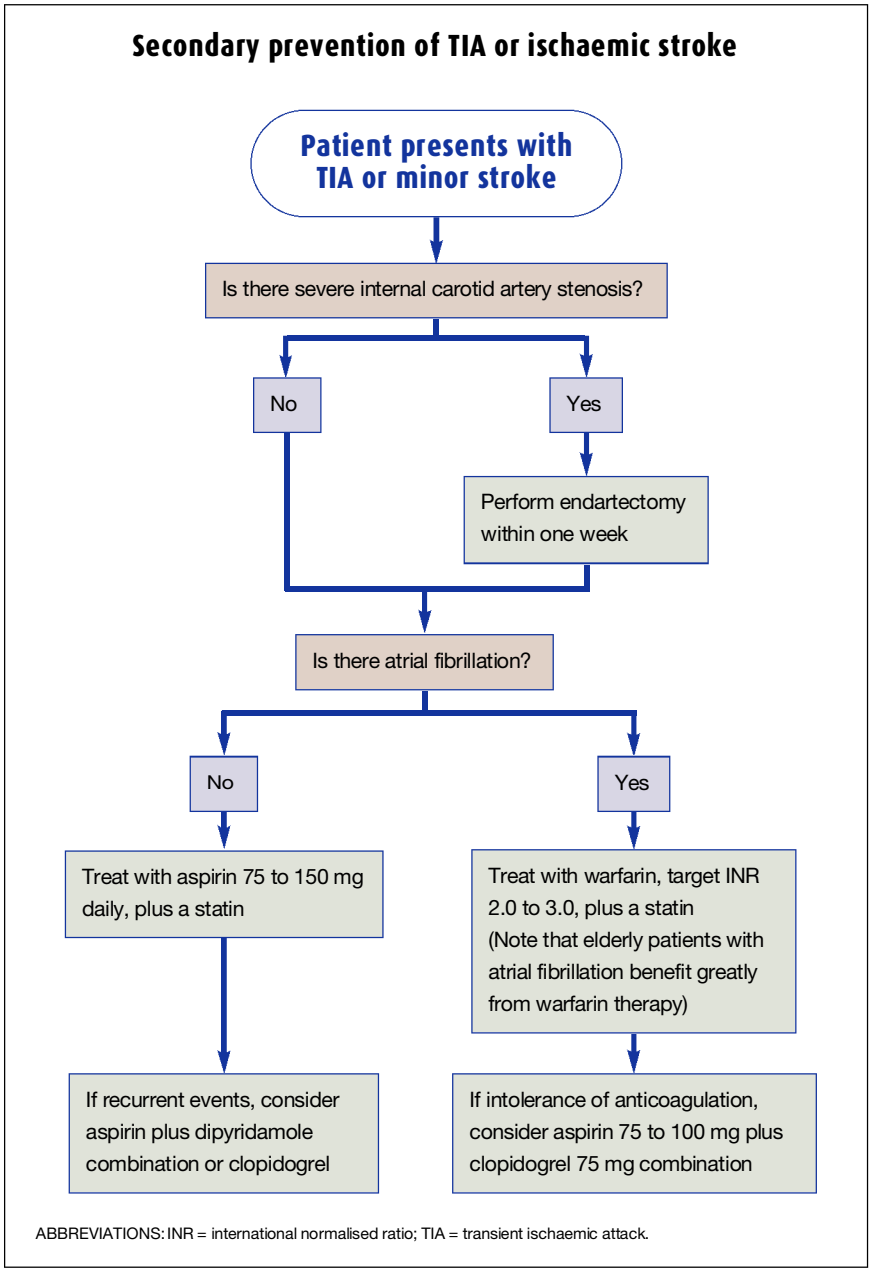
Doppler duplex sonography of cervical and intracranial arteries is a cost-effective and noninvasive method of identifying 'surgical' stenosis in the common and internal carotid arteries. However, the reliability of the investigation depends to a great extent on the experience and skill of the sonographer.

Advances in MRI and CT angiography have enabled these imaging modalities to largely replace conventional catheter angiography. In broad terms, these modalities have equivalent or superior sensitivity and specificity compared with duplex sonography for the detection of moderate to high-grade carotid stenosis.[21] However, duplex sonography is mostly favoured as a screening tool for carotid stenosis because of its wider availability and lower costs.

Electrocardiogram and Holter ECG

Nonvalvular atrial fibrillation increases the risk of an ischaemic stroke fivefold.[22] Such cardioembolic strokes are more severe than other strokes. The electrocardiogram (ECG) at the first visit will identify these patients in most cases, but a 24-hour Holter ECG may be necessary to rule out intermittent atrial fibrillation because this might not be evident at the initial consult. A recent study suggested that the stroke risk is significantly increased in patients with intermittent atrial fibrillation of even short duration (5.5 hours or more on one single day).[23] On the background of this finding it is sensible to repeat a Holter ECG on one or two occasions if there is any clinical suspicion of atrial fibrillation.

The CHAD2 score allows for an easy stroke risk stratification of patients with atrial fibrillation (see Table 6).[24] Those patients with a previous TIA or stroke



already score two points and therefore have at least double the risk of an embolic event and require anticoagulation.

Echocardiogram

Transthoracic and transoesophageal echocardiograms will provide information on cardiac function and most likely detect cardiomyopathy, valvulopathy and septum defects. Echocardiograms also allow assessment of atrium size and detection of clots in the atrium in patients with atrial fibrillation.

The transoesophageal echocardiogram will also detect atheromas in the aortic arch, and is the examination of choice although it requires the patient to fast and be sedated.

Laboratory investigations

Serum lipids have been associated with ischaemic vascular diseases such as coronary heart disease and stroke. Screening for lipids is a routine workup for all stroke patients.

Diabetes mellitus is one of the most important risk factors for stroke. The vascular risk is increased long before diabetes is diagnosed, in the prediabetes stage, when impaired fasting glucose and/or impaired glucose tolerance develop.[25]

The evidence that thrombophilic syndromes are related to ischaemic stroke is insufficient to allow recommendation for routine screening. However, conditions such as antiphospholipid antibody syndrome have been associated with arterial thrombosis.[26] It might therefore be useful to screen young patients without any other evident risk factors after an ischaemic cerebrovascular insult. Haematological diseases such as essential thrombocythaemia, polycythaemia vera and thrombotic thrombocytopenic purpura are related to ischaemic stroke,[27] and will be evident in the blood count in most cases.

Hyperhomocysteinaemia has been considered as an independent risk factor for stroke.[28,29] However, both interventional trials have failed to demonstrate a benefit from homocysteine lowering therapy.[30-32]

Interventions in TIA

All patients with TIA or stroke should be treated as soon as is feasible with antithrombotic therapy, either platelet inhibition or, for those with atrial fibrillation, anticoagulation. In addition, all underlying modifiable vascular risk factors should be addressed as soon as possible. A guide to the use of antithrombotic therapies is provided in the flowchart on this page.

Anticoagulation

Atrial fibrillation is one of the most important risk factors for stroke and, as mentioned earlier, increases by fivefold the risk of ischaemic stroke.[22] Oral anticoagulation

with the vitamin K antagonist warfarin reduces the stroke risk to a third of that seen without antithrombotic therapy.[33] Warfarin is underutilised for many reasons. This is especially so in the elderly, a group of patients who have a higher risk of stroke from atrial fibrillation and who are therefore likely to benefit most from warfarin therapy.[34] The Birmingham Atrial Fibrillation Treatment of the Aged Study compared aspirin to warfarin treatment in an elderly and frail population with atrial fibrillation.[35] The study showed a clear benefit of warfarin therapy comparable with warfarin therapy in a younger population.

Platelet inhibition with aspirin or clopidogrel plus aspirin proved to be inferior to warfarin therapy in all patients, even in those with low-risk atrial fibrillation, as shown in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W).[36] A recent Cochrane analysis has shown that anticoagulation with warfarin reduces stroke, disabling stroke and other major vascular events in patients with nonvalvular atrial fibrillation by about one-third when compared with antiplatelet therapy.[37] The recommended target international normalised ratio (INR) is 2.0 to 3.0. It has been shown that warfarin therapy with a target INR of 2.0 or greater reduced not only the risk of an ischaemic event but also the severity of a stroke and the risk of death within three months; no benefit was seen with an INR below 2.0.[38] The risk of intracranial haemorrhage correlates with the INR, with a moderately elevated risk for an INR below 3.0.[39] If the INR is 4.0 or greater, the risk of a major haemorrhage increases much more.

If anticoagulation is absolutely contraindicated in patients with atrial fibrillation, there is a small benefit for the combination of low-dose aspirin (75 to 100 mg) with clopidogrel 75 mg as compared with aspirin alone, as shown in the ACTIVE-A trial.[40] In this trial, the combination of clopidogrel and aspirin reduced the risk of ischaemic strokes in patients with atrial fibrillation significantly but increased the risk of major haemorrhage; the dual platelet inhibition did not have any survival benefit, not even on vascular death.

The presence of a prosthetic heart valve demands anticoagulation as well. According to a recent meta-analysis, after implantation of new generation prosthetic mechanical mitral valves, patients should receive warfarin to a target INR of 2.5 to 3.5; for older types of valve, the target INR should be 3.5 to 4.5.[41] The combination of low-dose aspirin and anticoagulation for patients with prosthetic heart valves seems to yield a small but significant advantage according to a Cochrane analysis from 2003, especially after presentation with a TIA under sufficient anticoagulation.[42]

Platelet inhibition

Patients who do not undergo anticoagulation therapy should receive immediate antiplatelet treatment with low-dose aspirin (75 to 150 mg daily), low-dose aspirin plus dipyridamole, or

clopidogrel. The combination of low-dose aspirin and clopidogrel is not superior to clopidogrel alone in the treatment of stroke or TIA.[43]

A recent Cochrane review highlighted that immediate antiplatelet treatment after stroke reduced death or dependency, all-cause mortality, pulmonary embolism, and recurrent stroke.[44] Current evidence indicates that both clopidogrel and the combination of aspirin plus dipyridamole are superior to aspirin in the prevention of recurrent vascular events.

The CAPRIE study (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events study) compared the uses of aspirin 325 mg daily and clopidogrel 75 mg daily in 19,185 patients after an ischaemic cerebral vascular event or myocardial infarction, or with peripheral arterial disease.[45] Overall, clopidogrel was significantly better than aspirin in preventing the primary endpoint of ischaemic stroke, myocardial infarction or vascular death, with an overall relative risk reduction of 8.7% and an annual event rate of 5.32% in the clopidogrel group and 5.83% in the aspirin group.

The ESPRIT trial (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) compared aspirin plus dipyridamole with aspirin alone in patients after cerebral ischaemia.[46] The trial included more than 2600 patients assigned to aspirin 30 to 325 mg daily with or without dipyridamole 200 mg twice daily. The mean follow up was 3.5 years and the median aspirin dose was 75 mg in both treatment groups. The combination of aspirin plus dipyridamole was significantly better in preventing the primary endpoint of death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction or major bleeding complication, with an absolute risk reduction of 1.0% per year. The combination of aspirin and dipyridamole, however, was significantly less well tolerated: significantly more patients discontinued the aspirin and dipyridamole combination than aspirin alone (470 versus 184), mainly because of headache.

The PRoFESS trial (Prevention Regimen for Effectively Avoiding Second Strokes trial) compared clopidogrel 75 mg with the combination therapy of aspirin 25 mg plus dipyridamole 200 mg in the prevention of recurrent stroke in patients with recent ischaemic stroke.[47] The trial was designed as a noninferiority trial and enrolled more than 20,000 patients. Although the trial did not meet the predefined criteria for noninferiority, there was no significant difference between the two agents in the primary endpoint of recurrence of stroke or a composite of all vascular events including vascular death. There were more patients discontinuing aspirin plus dipyridamole than clopidogrel, predominately due to headaches. The rate of headaches was, however, much lower compared with the ESPRIT trial, probably reflecting dose titration in the initial treatment period.

Failure of antiplatelet therapy

Recurrent vascular events can occur in patients on antiplatelet therapy, and such events should not necessarily be regarded as indicating therapy 'resistance'. However, the use of NSAIDs or proton pump inhibitors, and genetic polymorphism are associated with failure of antiplatelet therapy.

NSAIDs such as ibuprofen seem to reduce or abolish aspirin's capacity to inhibit platelet aggregation.[48] The concomitant use of a proton pump inhibitor seems to attenuate the efficacy of clopidogrel and leads to an increased risk of recurrent ischaemic events or death.[49] Intestinal absorption of clopidogrel is limited by an intestinal efflux pump P-glycoprotein coded by the *ABCB1* gene. The prodrug clopidogrel requires the P450 2C19 isoenzyme to convert into the active compound. Polymorphism in the *ABCB1* and *CYP2C19* genes was associated with diminished clopidogrel response and increased rate of ischaemic events and death under therapy with clopidogrel.[50,51]

Carotid stenosis treatments

Patients with severe internal carotid artery stenosis (70% or greater, according to the NASCET stenosis grading) will clearly benefit from early endarterectomy after TIA or nondisabling stroke. This benefit is greater in men and patients older than 75 years, and wears off with time. The greatest risk reduction is achieved if endarterectomy is performed within two weeks after an ischaemic event.

Stent protected angioplasty of an internal carotid artery stenosis was inferior to endarterectomy in two large randomised trials.[52,53] The inferiority of stenting is mainly attributed to a significantly higher procedural risk, whereas the four-year stroke risks of the two procedures seem to be equivalent.[54] Recurrence of stenosis seems to be slightly higher after stenting compared with after endarterectomy.[55] As long as the procedural risk of stenting is significantly higher than endarterectomy, stenting is not a valid alternative to endarterectomy.

Persistent foramen ovale – possible interventions

Prospective cohort studies have shown that the presence of a patent foramen ovale without any other septal abnormality does not increase the risk of recurrent stroke after a recent stroke or TIA.[56,57]

However, the combination of patent foramen ovale and atrial septal aneurysms has been shown to be associated with an increased risk of recurrent stroke, with a hazard ratio of 4.17.[56] Whether these patients benefit from therapy with vitamin K antagonists or from interventional treatment remains unclear. Randomised trials of patent foramen ovale closure are under way.

Statins

Statins have been shown to be beneficial in patients with ischaemic cerebrovascular events, and this benefit exceeds the pure cholesterol lowering effect of statins. A recent Cochrane review recommends all patients receive statins after an ischaemic event.[58] All patients with TIA or ischaemic

stroke should, therefore, receive a statin regardless of their cholesterol level.

Antihypertensive agents

Hypertension is common and clearly an important risk factor for first and recurrent stroke. In patients with TIA or vascular risk factors, the ACE inhibitors perindopril and ramipril reduce the risk of recurrent stroke.[59,60] However, the combination of telmisartan and ramipril was associated with more adverse events without an increase in benefit, according to the recently published large randomised study ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial).[61]

Diabetes mellitus treatments

The benefits of good glycaemic control (target glycosylated haemoglobin [HbA_{1c}] level below 7%) has been demonstrated conclusively for type 1 and type 2 diabetes in several studies with regard to microvascular and macrovascular complications.[62-68] There seems to be no benefit for a more rigid glycaemic control with respect to prevention of macrovascular events such as stroke or death.

The ACCORD study (Action to Control Cardiovascular Risk in Diabetes study) investigated the benefits of an intensified glycaemic control in type 2 diabetes in more than 10,000 patients randomised to either normal glycaemic control with an HbA_{1c} target between 7.0 and 7.9% or intensified glycaemic control with an HbA_{1c} target below 6.0%.[69] This trial was terminated early due to a significant increase in death in the group with the intensified treatment, which was mainly caused by fatal cardiovascular events.

A similar study comparing an intensified antidiabetic therapy with a target HbA_{1c} of 6.5% or less with standard treatment – the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial) – in more than 11,000 patients, did not find an increase in mortality.[70] However, this trial failed to demonstrate any benefit of intensified therapy with regard to macrovascular events such as myocardial infarction or stroke, but improved microvascular complications such as nephropathy or retinopathy.

Conclusion

Patients with TIAs may present with a great variety of neurological symptoms but most commonly present with weakness or clumsiness, reduced sensation, speaking difficulties or confusion. The onset is usually prompt and the episode generally lasts only minutes but may last hours. Up to half of the patients who present with transient neurological symptoms lasting over one hour will have suffered brain infarction and immediate imaging of the brain with CT or MRI is necessary.

Assessment of the stroke risk factors atrial fibrillation, diabetes, hypertension and age in a patient with a TIA allows rapid identification of the patient's risk of subsequent vascular events.[17] Those patients with a moderate- or high-risk profile need immediate referral to a TIA clinic or a hospital with the capacity to treat acute stroke, because immediate treatment of a TIA reduces the risk of early major stroke by 80%, leading to a significant reduction in disability and hospital costs.[71,72]

Treatment as soon as possible after the TIA with a statin and platelet inhibitor, or an anticoagulant for patients with atrial fibrillation or prosthetic heart valves, significantly reduces the risk of early disabling stroke. For patients with atrial fibrillation, anticoagulation with maintenance of the INR in the target range of 2.0 to 3.0 is the main predictor of a good long-term outcome on warfarin. Elderly and frail patients with atrial fibrillation have the greatest risk of severe stroke and benefit most from therapy with warfarin despite their increased risk of major haemorrhage. First-line antiplatelet therapy remains aspirin 75 to 150 mg daily. For recurrent ischaemic events, second-line treatment is clopidogrel alone or aspirin plus dipyridamole, of which the latter seems to be most cost-effective but causes more headaches.

Blood pressure lowering in the acute phase of a stroke does not seem to be beneficial in patients with TIA unless the blood pressure is excessively high (above 200 mmHg) or the patient has been thrombolysed. Long-term control of blood pressure and glycaemia (target HbA_{1c} of 7.0 to 7.9%) is beneficial to prevent further strokes. Intensified glycaemic control is not beneficial to these patients.

Patients with TIA who have symptomatic moderate- or high-grade internal carotid artery stenosis benefit from immediate endarterectomy. This benefit wears off with time and is greatest in the first 14 days after an ischaemic event. Men and older patients (aged 75 years or older) benefit from endarterectomy much more than women or younger patients. Stenting is inferior to surgery. MT

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A list of references is available on request to the editorial office.

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MARTIN KRAUSE FRACP

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