

# Stroke and TIA

## Crucial knowledge for a critical event

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**Rapid and accurate recognition of acute stroke symptoms is essential for the timely referral of patients with acute stroke or TIA to hospital for reperfusion therapy, including endovascular clot retrieval. GPs are well placed to implement and monitor secondary prevention strategies for these patients.**

**S**troke is a massive global health issue, and it is estimated that one in six people worldwide will have a stroke during their lifetime. In the past two decades, there have been significant advances in treatment options available for patients with acute stroke, especially those with ischaemic stroke. The most significant recent advance, endovascular clot retrieval (also known as mechanical thrombectomy) has been shown to be associated with a dramatic improvement in survival with reduced disability in patients with ischaemic stroke and large vessel occlusion.<sup>1-6</sup>

### KEY POINTS

- Accurate diagnosis of stroke relies on the identification of acute onset focal neurological syndromes.
- Rapid assessment, triage and management are essential in patients with acute stroke.
- Patients with a transient ischaemic attack should be rapidly assessed and investigated, especially for symptomatic carotid stenosis and atrial fibrillation.
- When an acute stroke is recognised in the community, the patient should be transferred by ambulance to the nearest hospital with the appropriate stroke services.
- Premedication with aspirin is not appropriate as it is impossible to confidently distinguish ischaemic stroke from intracerebral haemorrhage without a CT scan of the brain.
- The GP plays a crucial role in the secondary prevention of stroke, both lifestyle and pharmacological interventions.

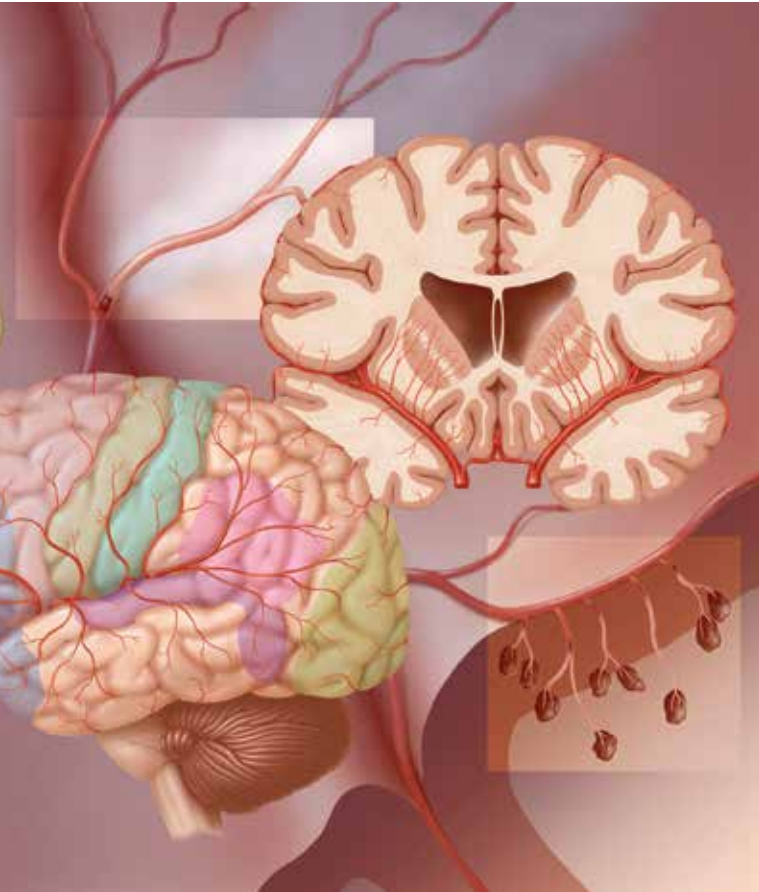
Failure or delay in the recognition of stroke symptoms precludes many patients from evidence-based therapies, most of which are crucially time-dependent.<sup>7</sup> Furthermore, secondary prevention after ischaemic stroke or transient ischaemic attack (TIA) is an ever-expanding field with novel pharmacological agents and approaches available. Primary care remains a critical cog in the care of patients with stroke, from the recognition and triage of those with acute stroke to their ongoing long-term medical management.

This review provides an update on the latest evidence in acute stroke management, an area that has undergone a major revolution in recent years, as well as reviewing secondary prevention strategies. It also presents strategies for the accurate recognition of acute stroke symptoms to allow patients to be rapidly triaged and directed towards definitive therapy. For the purposes of this article, stroke is defined as ischaemic stroke or intracerebral haemorrhage.

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## Recognising a stroke

The first question to ask when faced with a potential stroke presentation – ‘Is it a stroke?’ – dictates subsequent assessment and treatment. The features of acute onset and focal signs can be used to reliably distinguish a stroke or TIA from the many potential mimics, including seizures, migraine, hypoglycaemia and functional disorders.

The first crucial clinical clue that a person is having a stroke is the rapidity of onset of the symptoms. Stroke symptoms classically present very suddenly compared with other brain pathologies, which may evolve over minutes, hours or days. Typically, the patient or a family member will recall the exact time of symptom onset or the activity the patient was involved in when the symptoms began (such as making a cup of tea or watching the 6 o’clock news). Important exceptions to this are the so-called ‘wake-up stroke’, which occurs in about 15% of cases and in which a patient wakes with their symptoms, and cases where the patient is unable to describe the onset for other reasons (e.g. he/she is noticed to be aphasic but has not been seen for several hours prior to this). In these cases, it is important to identify the time when the patient was last known to be well as this is assumed to be the stroke onset time for the purpose of determining eligibility for thrombolysis/endovascular clot retrieval.

As well as acute onset, stroke typically affects specific vascular territories of the brain, leading to commonly recognisable stroke syndromes (Table 1). The vast majority of patients with stroke will present with one of these recognised syndromes. Patients who present atypically require careful assessment for a potential stroke mimic.

Importantly, when an acute stroke is recognised in the community, urgent ambulance transfer should be arranged to

the nearest hospital with the appropriate stroke services. In contrast with myocardial infarction, premedication with aspirin in the field for stroke is not appropriate as it is impossible to confidently distinguish ischaemic stroke from intracerebral haemorrhage without a CT scan of the brain.

## Atypical stroke presentations

Differentiating an atypical stroke presentation from a stroke mimic can be challenging, even for a seasoned clinician. It is useful to keep a framework in mind for potential atypical presentations, including certain red flag features that should trigger alarm bells for potential mimics or concurrent problems. It is important to remember that even with the benefit of experience, brain imaging is required to confirm the clinical suspicion.

## Vertigo and dizziness

The symptom complex of dizziness can be a difficult experience for patients to communicate accurately. Considerable effort is often required to ascertain whether the patient is experiencing vertigo (a perception of motion) or any one of a group of symptoms that are often described as dizziness, including light-headedness, headache, blurred vision, fatigue, or even anxiety and dissociative states.

**TABLE 1. COMMON ISCHAEMIC STROKE SYNDROMES\***

Vascular territory	Clinical presentation
Left middle cerebral artery	Aphasia, right hemiparesis (face/arm affected most), right inattention, right homonymous hemianopia
Right middle cerebral artery	Left hemiparesis (face/arm affected most), left inattention, left hemianopia, apraxia (e.g. dressing apraxia), dysarthria
Anterior cerebral artery	Contralateral leg weakness
Posterior cerebral artery	Hemianopia
Lacunar stroke	Pure motor stroke (hemiparesis), pure sensory stroke, ataxic hemiparesis, clumsy hand/dysarthria
Posterior inferior cerebellar artery	Lateral medullary syndrome (i.e. dysarthria, ipsilateral Horner’s syndrome, facial sensory loss, palatal weakness and limb ataxia) Contralateral trunk/limb sensory loss
Other posterior circulation syndromes	Eye movement abnormalities, nystagmus, cranial nerve signs, cerebellar ataxia, depressed conscious state

\* Stroke syndromes listed according to vascular distribution.

Although sudden onset isolated vertigo can be a feature of posterior circulation stroke, benign paroxysmal positional vertigo (BPPV) is far more common and vestibular neuronitis may also be possible. In BPPV, careful history taking may reveal that the episodes of vertigo are very brief (seconds) and are typically precipitated by movement; confirmation of the condition requires the absence of central features (see below) and a positive Hallpike test. In vestibular neuronitis, the patient typically has spontaneous horizontal nystagmus with the fast phase directed away from the side of the lesion, in conjunction with a positive head impulse test (and, again, an absence of central features).

It is important to look carefully for any signs of central (brainstem) pathology, which if present, should overrule any clinical suspicion that the pathology may have a peripheral vestibular origin. These signs include limb weakness or sensory loss, cranial nerve abnormalities, eye movement abnormalities or ataxia. Nystagmus is a feature of both central and peripheral lesions, but nystagmus that has a vertical component or that changes direction is indicative of a central lesion.

### Confusion

Patients presenting with confusion are more likely to have delirium than a stroke. Nonetheless, it can be difficult to distinguish confusion, agitation or lack of compliance with the examiner from a more focal neurological problem such as aphasia, hemianopia or visual inattention. A neurological screening examination is a valuable tool to identify subtle hints that a confused patient may have a central problem such as stroke (Table 2). It is important to note that this screening examination does not replace a more formal neurological examination, which may be required to further evaluate any positive findings.

### Loss of consciousness

An 'unconscious collapse' is rarely the result of a stroke or TIA, and is more likely to result from a seizure, cardiac abnormality

or syncope. The important exception to this is patients with vertebrobasilar ischaemia who may present with transient and recurrent episodes of loss of consciousness. In such cases, there are usually other focal signs of brainstem dysfunction before or after the loss of consciousness, such as focal weakness, eye movement abnormalities, dysarthria or ataxia.

### Headache

Severe headache is unusual in acute stroke. Even in patients with primary intracerebral haemorrhage, headache is generally not a significant feature of the presentation. Therefore, patients presenting with severe acute headache should be assessed for alternative pathology such as subarachnoid haemorrhage (especially in the case of 'thunderclap' headache) or migraine.

### Hypotension

It is common for patients with stroke to have hypertension at presentation. Significant hypotension, however, is a red flag in patients with a possible stroke. Patients with severe hypotension due to sepsis or hypovolaemia may present with generalised weakness or drowsiness, and it is important to distinguish these signs from the focal signs of a stroke. In addition, patients with stroke and significant hypotension should be assessed for other possible concurrent conditions such as myocardial infarction or aortic dissection. These particular conditions are especially important to recognise when making decisions regarding thrombolysis or endovascular therapy.

### TIA: a medical emergency

The features of acute onset and focal signs apply equally to ischaemic stroke and TIA and should be confirmed in both conditions. The important clinical difference between TIA and stroke is that patients with TIA will, by definition, have no ongoing signs on clinical examination. Despite this, patients with TIA still require urgent evaluation to identify potentially treatable causes of recurrent TIA or disabling stroke. In general, this evaluation should

be performed in hospital and in consultation with a stroke physician. However, local practices may vary depending on resource availability. GPs are more likely to investigate patients who present very late after symptoms of TIA.

The crucial aspects of TIA work-up, which are much the same as those for stroke work up, are outlined in Table 3.

### Update on acute in-hospital stroke management

The axiom of 'time is brain' remains as true as ever in modern stroke care. Public awareness and education campaigns focusing on this are important given that the effectiveness of the primary acute stroke therapy (reperfusion) is crucially time dependent.

### Ischaemic stroke

Intravenous thrombolysis with alteplase has been shown in multiple large randomised controlled trials and important pooled meta-analyses to improve functional outcome when given within 4.5 hours of ischaemic stroke onset. Even within this 4.5-hour time window, the benefit of the therapy rapidly diminishes over time.

More recently, endovascular clot retrieval has also been shown to improve functional outcomes in patients with large vessel occlusion (internal carotid artery and/or proximal middle cerebral artery) who present within six hours of onset and who do not have evidence of extensive established infarction on baseline imaging. Ongoing trials and post-hoc analyses are addressing important questions regarding the optimal brain imaging protocol, as well as whether selected patients beyond six hours post-stroke onset may also benefit. In addition, statewide referral protocols are being devised to allow patients with large vessel occlusion to be rapidly identified and transferred to designated centres that can perform endovascular clot retrieval on a round-the-clock basis.

### Intracerebral haemorrhage

In patients with intracerebral haemorrhage, major recent interest has revolved around



**TABLE 2. NEUROLOGICAL SCREENING EXAMINATION FOR SUSPECTED STROKE**

Component	Examination method	Significance of findings
Gait	Observe the patient's gait, including heel-toe walking	Look for a wide-based (ataxic) gait suggesting a cerebellar lesion, or a tendency to fall towards one direction, which can occur with motor weakness as well as cerebellar lesions Patients with a hemiplegic or 'spastic' gait generally have other obvious signs on bedside testing
Visual fields and visual inattention	While facing the patient, ask them to look at the examiner's nose. Move the outstretched fingers on either side in the upper and lower portions of the visual fields, first independently and then simultaneously	Look for hemianopia Failure to appreciate simultaneous visual stimuli while correctly appreciating movement on one side only suggests visual inattention
Eye movements	Ask the patient to follow the examiner's finger in an H-shaped pattern while keeping their head still, to assess both vertical and horizontal eye movements Avoid moving the finger into the extremes of the visual field as this may cause a degree of physiological nystagmus or diplopia	Patients with severe carotid territory stroke often have forced gaze deviation towards the side of the lesion Patients with less severe stroke may have a gaze preference towards the side of the lesion, but are still able to look in the opposite direction Look for eye movement abnormalities such as a third, fourth or sixth cranial nerve palsy, internuclear ophthalmoplegia or failure of vertical gaze Look for nystagmus
Facial weakness	Ask the patient to smile Ask the patient to close the eyes tightly Ask the patient to raise the eyebrows	Observe for any asymmetry. Patients with very mild stroke may have minor asymmetry of the nasolabial fold. If uncertain, compare with an old picture (e.g. driver's licence) Weakness affecting both the upper half and lower half of the face suggests a lower motor neuron lesion (Bell's palsy)
Upper limb	Ask the patient to hold the arms horizontally with the palms facing the ceiling, and to close the eyes While the arms are in this position, touch each hand individually and ask the patient which hand is being touched. Subsequently touch both hands simultaneously to assess for sensory inattention Ask the patient to open the eyes. Check for finger–nose ataxia on each side by asking the patient to touch the examiner's finger and then touch their own nose Test individual muscle groups in more detail as required Confirm sensory findings with a neurological examination pin or ice as required	Patients with mild pyramidal weakness show drift of the weak arm with an element of pronation of the wrist ('pronator drift')
Lower limb	With the patient lying on the bed, ask them to raise each leg to 45 degrees and hold it in that position for 5 seconds Test for sensory inattention with both legs on the bed and with the eyes closed as for the upper limb Test for heel–shin ataxia by asking the patient to place the heel of one foot on the opposite knee and run the heel up and down the shin as quickly and accurately as possible Check the plantar responses	The weak leg may drift towards the bed. Note: patients with significant musculoskeletal or joint problems may show a drift in the absence of a neurological problem. A more focused examination may be required in such cases
Speech/language assessment	Assess the patient's speech in normal conversation Check for aphasia by asking the patient to describe the room and to name some objects (e.g. watch, pen, shirt) Ask the patient to follow commands of increasing complexity (e.g. close your eyes; clap your hands twice then point to the ceiling; touch your left ear with your right thumb) Ask the patient to repeat some simple phrases	Is the speech dysarthric (slurred)? Is there aphasia? Subtle aphasia may manifest as a semantic error (e.g. calling a knife a fork) or a phonemic error (e.g. calling a knife a 'nife') Alternatively the patient may clearly present with a nonfluent aphasia and may be obviously frustrated by the inability to find the words to say Patients with fluent ('receptive') aphasia are often misdiagnosed with delirium given the fluent but nonsensical nature of their speech

**TABLE 3. WORK UP FOR SUSPECTED TRANSIENT ISCHAEMIC ATTACK (TIA)**

Type of test	Investigation	Purpose
Brain imaging	Usually CT of the brain MRI in some cases where stroke or alternative pathology may be suspected rather than TIA	To exclude alternative pathology such as intracerebral haemorrhage or brain tumour Antiplatelet or anticoagulant medication should not be commenced prior to brain imaging
Vascular imaging	Traditionally carotid doppler ultrasound for carotid territory TIA CT angiography (aortic arch to vertex) becoming routine in many centres	To identify patients with symptomatic carotid stenosis (50 to 99%); these patients should be referred for urgent vascular surgical assessment for potential endarterectomy CT angiography is particularly useful for evaluation of the posterior and intracranial circulations, as well as in the diagnosis of arterial dissection
Cardiac rhythm monitoring	12-lead ECG 24-hour Holter monitor (usually as outpatient)	To detect paroxysmal atrial fibrillation
Other cardiac investigations	Echocardiography may be considered	Transthoracic echocardiography can be performed to screen for significant valvular disease or left ventricular dysfunction In young patients without clear alternative pathology, transoesophageal echocardiography is recommended to look for more subtle valve pathology, septal defects, patent foramen ovale or other less common cardiac pathologies (e.g. atrial myxoma)
Blood tests	Fasting lipid and glucose levels Thrombophilia/vasculitis screen	To identify patients with diabetes and/or dyslipidaemia Younger patients with no alternative aetiologies should also be investigated for thrombophilic states such as the antiphospholipid syndrome, as well as for systemic/cerebral vasculitis (generally through specialist consultation)

acute blood pressure reduction to a systolic target of 140 mmHg. In the INTERACT-2 (second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial) study, this was shown to be associated with improved outcomes compared with standard care, without an increase in adverse events, particularly renal impairment and significant hypotension.<sup>8</sup> However, another similar trial, ATACH-II (Antihypertensive Treatment of Acute Cerebral Hemorrhage), has recently been suspended for futility on the primary endpoint, although the final trial results have not been published at this stage.

Surgical evacuation of intracerebral haemorrhage may also play an increasing role in future management protocols. In particular, minimally invasive surgery involving catheter aspiration followed by intermittent direct instillation of thrombolytic agents into the haematoma to facilitate clot dissolution is a promising method that may avoid the morbidity of more invasive craniotomies.

## Secondary prevention – the role of the GP

### Lifestyle modification

As with other cardiovascular conditions, one of the most important aspects of the continuing management of patients with stroke and TIA is the long-term implementation and reinforcement of positive lifestyle changes, most notably smoking cessation, moderation of alcohol intake, weight loss, healthy diet and regular exercise. These implementations require the type of long-term and regular follow up that is ideally suited to the primary care setting, allowing the GP to play a central role in the patient's overall health status. Given that many of the risk factors overlap, most lifestyle modifications are applicable to both ischaemic stroke and intracerebral haemorrhage.

A full review of specific lifestyle recommendations is beyond the scope of this article, and readers are directed to guidelines available from the NHMRC and other services for detailed information relating

to alcohol intake, exercise, smoking and diet. These include the following:

- Clinical Guidelines for Stroke Management 2010 (<http://www.nhmrc.gov.au/guidelines-publications/cp126>)
- Australian Guidelines to Reduce Health Risks from Drinking Alcohol 2009 (<https://www.nhmrc.gov.au/health-topics/alcohol-guidelines>)
- Australia's Physical Activity and Sedentary Behaviour Guidelines (<http://www.health.gov.au/internet/main/publishing.nsf/content/health-pubhlth-strateg-phys-act-guidelines>)
- Australian Dietary Guidelines 2013 (<https://www.nhmrc.gov.au/guidelines-publications/n55>).

### Antithrombotic agents

Patients with ischaemic stroke or TIA will universally be commenced on an antithrombotic agent in hospital unless there is a major contraindication.

### **Antiplatelet agents**

In general, low-dose (100 mg) aspirin is the initial antithrombotic agent of choice. In many instances, patients who have further events on aspirin may be 'upgraded' to clopidogrel or alternatively aspirin plus dipyridamole, although the evidence that this is a true 'upgrade' is not particularly strong.

Trials examining dual antiplatelet therapy (aspirin plus clopidogrel) for long-term stroke secondary prevention failed because of excessive bleeding complications. A single randomised controlled trial in China showed reduced stroke recurrence with short-term (21 days) dual antiplatelet therapy (aspirin plus clopidogrel) followed by clopidogrel alone.<sup>9</sup> However the benefit was predominantly in patients with intracranial atherosclerosis, which is uncommon in Western populations.

Results of the ongoing USA-led POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial will further inform therapy.

Nonetheless, in patients with mild stroke or TIA who are deemed at high risk for further early events, dual antiplatelet therapy for approximately one month may be reasonable, after which a single agent should be continued.

### **Anticoagulants**

The nonvitamin K antagonist oral anticoagulants (NOACs; apixaban, dabigatran and rivaroxaban) are now widely used for prevention of further stroke in the specific setting of nonvalvular atrial fibrillation (AF). Although the definition of 'valvular' AF varies to some extent, the term generally refers to patients with mechanical heart valves or a history of rheumatic valve

disease or mitral stenosis. Patients with bioprosthetic heart valves can still be considered for therapy with NOACs.

NOACs are considered overall to be at least as effective as warfarin for non-valvular AF, cause less intracerebral haemorrhage and are clearly more practical to use. There are no head to head trials comparing safety and efficacy between the individual agents, and thus the choice of agent should be individualised. It is important to note that NOACs should be used cautiously in patients with renal impairment where the creatinine clearance needs to be calculated using the Cockcroft-Gault formula rather than relying on estimated glomerular filtration rate. NOACs are contraindicated in patients with severe renal impairment (creatinine clearance below 25 to 30 mL/min).

In the context of secondary stroke prevention, all patients should receive anti-coagulation therapies based on usual CHADS2 and CHA2DS2-VASc criteria as the previous stroke or TIA event places them in a moderate-to high-risk category.

Aspirin is not effective for stroke prevention in patients with AF.

### **Antiplatelet therapy plus anticoagulant**

There is generally no need to add aspirin to an anticoagulant for patients with AF and ischaemic heart disease unless a coronary stent has been recently implanted as additional antiplatelet medication increases the bleeding risk.

### **Antihypertensive agents**

Long-term management of hypertension is an important aspect of secondary prevention after either ischaemic stroke or intracerebral haemorrhage. There is no clear lower threshold of blood pressure where benefit ceases. Therefore, anti-hypertensive medications should be used in most patients unless there are significant issues with postural hypotension. ACE inhibitors, angiotensin receptor blockers, calcium channel antagonists and diuretics are all reasonable options. Beta-blockers are not recommended as first-line agents and may increase blood pressure variability, although patients who are taking a  $\beta$ -blocker for an alternative indication (e.g. coronary disease) should continue the medication.<sup>10</sup>

Management of hypertension is arguably more important in patients with intracerebral haemorrhage than in those with ischaemic stroke given that hypertension is one of the most important treatable causes of this type of stroke.

### **Lipid-lowering agents**

There is evidence that lowering lipid levels by the use of statins reduces the risk of recurrent ischaemic stroke regardless of baseline lipid levels.<sup>11,12</sup> Although the strongest evidence is for prevention of recurrent stroke in the setting of large artery atherosclerosis, patients with other

stroke subtypes (e.g. cardioembolic or small vessel disease) are usually also considered for statin therapy unless contraindicated. In younger patients with clear alternative pathology (e.g. thrombophilia or arterial dissection) and in whom the lipid profile is normal, it is reasonable not to commence lipid-lowering therapy.

In patients with serious adverse reactions to statins (usually severe muscular aches and weakness, often with an increased level of creatine kinase or severe liver function abnormalities), a lower dosage or an alternative statin can be considered. Patients who are statin intolerant (or in whom full-dose statins have not achieved lipid targets) should be considered for treatment with an alternative lipid-lowering agent such as ezetimibe or a fibrate.

There is some evidence suggesting that statin therapy is associated with an increased risk of intracerebral haemorrhage, although it is important to note that this generally comes from retrospective studies, and the evidence is somewhat varied. Therefore, the specific indications for statin therapy should be reviewed in patients with intracerebral haemorrhage and an individual decision should be made depending on the patient's comorbidities. In general, if there is an indication for statin therapy, it is still reasonable to use statins in patients with a history of intracerebral haemorrhage.

### **Conclusion**

Stroke medicine has been transformed in the past two decades, with the development of reperfusion therapies, including intravenous thrombolysis and endovascular clot retrieval, that reduce disability after ischaemic stroke. New therapies for intracerebral haemorrhage, including rapid blood pressure lowering and the potential promise of novel surgical techniques, also raise the possibility of improved outcomes for patients with this subtype of stroke. Importantly, in the context of reperfusion therapy, earlier time to treatment is directly associated with

improved treatment efficacy. Rapid identification of stroke symptoms is therefore crucial. As well as recognising patients with stroke symptoms in the clinic, GPs have a key role in reinforcing community education regarding the recognition of stroke and early activation of emergency services to allow patients to access appropriate therapies.

There have also been significant advances in the field of secondary stroke prevention, including the recent introduction of the NOACs for nonvalvular AF. GPs continue to play a key role in secondary stroke prevention using pharmacological interventions as well as through the implementation of positive lifestyle modifications. MT

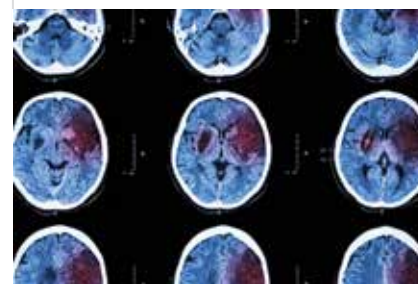
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A list of references is included in the website version of this article ([www.medicinetoday.com.au](http://www.medicinetoday.com.au)).

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