Personalising secondary prevention: different treatments for different strokes

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ABSTRACT

Stroke is a syndrome caused by many different disease mechanisms rather than being a single disease. It is important to identify the underlying mechanism accurately in individual patients in order to choose the best treatment approach. This article provides practical tips to diagnose the underlying subtype of stroke, and in particular discusses non-lacunar pathologies that can present with a clinical lacunar syndrome. It also reviews the recent advances in recurrent stroke prevention, including using more intensive antiplatelet regimens in the acute phase, and the concept that undetected cardiac arrhythmias may be important in apparently cryptogenic stroke.

ARTICLE

The risk of recurrent stroke is increased following ischaemic stroke and transient ischaemic attack (TIA), particularly in the first few weeks.¹ This offers an opportunity to implement secondary prevention measures to reduce this risk. Effective prevention depends on both an accurate diagnosis of the stroke subtype, and an appreciation that different stroke subtypes may respond differently to secondary preventative treatments.

Ischaemic stroke represents a syndrome caused by several diverse pathologies that all result in disruption of blood supply and secondary ischaemic damage. The three main subtypes are: large artery stroke, cardioembolic stroke and lacunar stroke. Stroke due to large artery stenosis—from atherosclerosis in the carotid, vertebral or intracranial vessels—is probably primarily thromboembolic secondary to thrombosis at the site of stenosis, rather than haemodynamic. Stroke secondary to cardioembolism also has a thromboembolic basis, although from thrombosis occurring in the heart. The exact mechanisms underlying lacunar stroke are uncertain, and

there is debate about the role of thrombosis as a final mediating mechanism causing ischaemia. Genetic data suggest that risk factors relating to altered coagulation are important for both cardioembolic and large artery stroke, but less so for small vessel stroke.²

Accurate diagnosis is essential

Tailored secondary prevention approaches require accurate diagnosis of the stroke subtype. This requires application of a pathophysiological subtyping algorithm such as the Trial of Org 10172 in Acute Stroke Treatment algorithm.³ Classification systems that record clinical syndromes rather than underlying pathophysiological mechanisms, such as in the Oxfordshire Community Stroke Project, are less useful. Frequently the diagnosis is clear; for example, in a patient with a territorial infarct, finding atrial fibrillation suggests a cardioembolic cause, or finding a ipsilateral carotid stenosis suggests a large artery stroke. However, often the underlying cause is not immediately apparent, and patients require further investigations. Review of the brain imaging is important, particularly using diffusion-weighted imaging (DWI), which identifies recent infarcts occurring in the previous 3 weeks. For example, the finding of infarcts in multiple arterial territories with normal large artery imaging suggests a cardioembolic source (figure 1); this needs investigating with prolonged cardiac monitoring, even if a single 24-hour tape is negative. Unilateral infarction in the watershed regions, and particularly the internal border zone region, raises the possibility of ipsilateral carotid or middle cerebral artery stenosis (figure 2). If the carotid duplex is negative, imaging of the more distal carotid artery with CT angiography or MR angiography may identify a stenosis.

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Figure 1 The contribution of DWI MRI to the diagnosis of the stroke mechanism a 43-year-old man with hypertension, diabetes and raised serum cholesterol developed sudden-onset left hemiparesis with face, arm and leg weakness, consistent with a pure motor lacunar syndrome. CT scan of head showed extensive leucoaraiosis consistent with small vessel disease, and T2-weighted MR scan showed confluent white matter hyperintensities also consistent with small vessel disease (A). The provisional diagnosis was a lacunar infarct due to small vessel disease. DWI showed multiple small acute infarcts in both hemispheres (B, C and D). This led to a more extensive search for cardioembolic sources and atrial fibrillation was identified. (copyright Hugh Markus). DWI, diffusion-weighted imaging.

Lacunar stroke is perhaps the subtype most often misdiagnosed. Clinical radiological studies have shown that only half of lacunar syndromes, when diagnosed using a syndromic system such as in the Oxfordshire Community Stroke Project, are caused by the small-vessel disease, that is, a lacunar syndrome is not always caused by a lacunar infarct.⁴ It is important to remember that lacunar infarcts almost always

Figure 2 Carotid stenosis presenting with a lacunar syndrome a 50-year-old man presented with left-sided weakness and numbness. CT scan of head was normal. This would usually be diagnosed as a lacunar syndrome and presumed lacunar infarct. DWI MR scan of brain showed scattered small acute infarcts, including a 'string of pearls' in the internal watershed region. This pattern suggests a tight carotid stenosis. A carotid Doppler was normal but a CT angiogram showed a tight distal carotid stenosis. (Copyright Hugh Markus). DWI, diffusion-weighted imaging.

Figure 3 Weakness affecting one body part (eg, the arm) is usually due to a cortical infarct rather than a lacunar infarct. These cortical infarcts are usually due to embolism. In this case, a patient with no previous strokes developed sudden-onset left arm weakness with greater weakness of the distal arm, and especially hand. CT scan of head showed no acute infarct. On DWI MR imaging, there was a small recent infarct in the right motor strip (A). The apparent diffusion coefficient map showed a corresponding area of low density (B). (copyright Hugh Markus). DWI, diffusion-weighted imaging.

involve at least two body parts. If only one body part is affected, and particularly part of one body part (eg, isolated hand weakness), the infarct is almost always cortical in the motor strip, and usually has an embolic pathogenesis (from cardioembolic or large artery disease).⁵ In such cases, the infarct is often not seen on a CT scan, but can be seen on DWI MRI (figure 3). DWI in a patient with a lacunar syndrome may also identify multiple small infarcts consistent with an embolic source, whereas the CT scan might show only a single or no infarcts. Larger striatal infarcts—often comma shaped and >2 cm in diameter (the upper limit of lacunar infarcts)—are referred to as striato-capsular infarcts (figure 4). These classically result from occlusion of the middle cerebral artery with rapid recanalisation. During the period of ischaemia, infarction occurs in the territory of the lenticulostriate perforating arteries, which come off the middle cerebral artery. These are end arteries with a poor collateral supply, and therefore, the tissue supplied by them infarcts, while ischaemic cortex survives owing to its better collateral supply. This subtype suggests that an embolus has transiently occluded the middle cerebral artery; therefore, such patients require a search for cardioembolic and large artery sources.

Antiplatelet therapy and stroke

Large secondary prevention stroke trials have shown that monotherapy with either aspirin or clopidogrel is effective in preventing stroke, although clopidogrel is slightly more effective.⁶ The combination of aspirin and dipyridamole has an effectiveness similar to clopidogrel monotherapy.⁷ However, clopidogrel is usually used as first-line therapy, partly because dipyridamole has a poorer side effect profile and is less well tolerated. However, these trials were in long-term secondary prevention, with most cases being recruited

during the subacute or chronic phase after stroke and TIA.

Epidemiological data arising after these trials demonstrated that the risk of recurrent stroke following TIA and minor stroke was particularly high in the first few weeks, with the highest risk over the first few days.¹ This raises the question as to whether to use more intensive antiplatelet regimens in the first few weeks, similar to those used in cardiology where more intensive secondary preventative regimens are used acutely than in the long term.

Phase II randomised controlled trials showed that the combination of clopidogrel and aspirin was more effective than aspirin alone in preventing cerebral embolisation (detected using transcranial Doppler ultrasound) in patients with both extracranial and intracranial large artery stenosis.⁸ The recent Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial⁹ and Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) trial¹⁰ randomised patients with minor stroke and high-risk TIA (selected on the basis of the ABCD2 score) to clopidogrel and aspirin, vs aspirin alone, within the first 24 hours (in CHANCE) or within the first 12 hours (in POINT) of symptom onset; these studies showed 32% and 25% reduction in recurrent events, respectively. Treatment was given for 1 month. These results suggest that we should use more intensive regimens in acute secondary prevention. However, POINT reported major haemorrhage in 23 patients (0.9%) receiving clopidogrel plus aspirin, and in 10 patients (0.4%) receiving aspirin plus placebo

(HR, 2.32; 95% CI 1.10 to 4.87; $p=0.02$). Thus, some patients may suffer harm and so we need better ways to identify those who might benefit.

It is important to start these intensive regimens as soon as possible after presentation. However, dual therapy with aspirin and clopidogrel is probably not advisable in patients with larger strokes because of their greater risk of haemorrhagic transformation. The Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial randomised patients with acute ischaemic stroke recruited up to 48 hours after stroke onset to the combination of aspirin clopidogrel and dipyridamole, versus clopidogrel alone or aspirin and dipyridamole.¹¹ Patients with all severity of stroke were included. Intensive therapy was associated with an increased risk of intracerebral haemorrhage, and subgroup analysis suggested an increased risk of haemorrhagic transformation in patients with larger infarcts, and also when treatment was started after the first 24 hours.

A further question is whether all stroke subtypes presenting with TIA or minor stroke should receive dual antiplatelet therapy, or whether it is more effective in particular stroke subtypes. Epidemiological data have shown that the risk of early recurrent stroke is much higher for large artery stroke than for other stroke subtypes.¹ A subgroup analysis in the CHANCE trial—looking at people who had CT angiography to detect the presence or absence of intracranial stenosis (most cases of large artery stenosis were intracranial in this Chinese population)—showed an apparently greater effectiveness of dual antiplatelet therapy in people with intracranial stenosis than those without stenosis.¹² In the SOCRATES trial, another antiplatelet agent, ticagrelor, was similarly effective to aspirin alone in early secondary prevention, but was more effective than aspirin in a subgroup analysis in patients with large artery stroke.¹³ This does suggest that more intensive antiplatelet regimens are particularly effective in patients whose TIA and stroke are due to large artery stenosis.

It remains uncertain whether aspirin and clopidogrel should be given acutely to patients with lacunar stroke. These patients were included in the CHANCE and POINT trials supporting their use. However, the secondary prevention of small subcortical strokes (SPS3) study showed that in longer term prevention after lacunar stroke, dual antiplatelet therapy was associated with no additional reduction in ischaemic events, but a significantly increased risk of bleeding.¹⁴ It is now appreciated that the same small artery pathology that causes multiple small lacunar infarcts and white matter hyperintensities is also a risk factor for intracerebral haemorrhage. These patients are particularly susceptible to intracerebral haemorrhage in the presence of anticoagulants. Therefore, in patients with evidence of extensive small vessel disease on brain imaging (leukoaraiosis or white matter hyperintensities and/or

Figure 4 A striatocapsular infarct. A man presented with right-sided hemiparesis, that is, a lacunar syndrome. He had multiple white matter hyperintensities on T2 MR brain scan suggesting cerebral small vessel disease (A). However, the DWI MR scan shows a comma-shaped striatocapsular infarct. (B) These non-lacunar infarcts are usually due to transient middle cerebral occlusion by an embolus. Infarction occurs in the territory of the perforating arteries supplying the striatal region as these are end arteries with no collateral supply. However, the cortex is spared because it has a better collateral supply and so does not infarct before recanalisation occurs. Therefore, in people with this pattern, one should search hard for an embolic source. In this case prolonged telemetry identified paroxysmal atrial fibrillation enabled a diagnosis of presumed cardioembolic stroke and anticoagulation was started. (copyright Hugh Markus). DWI, diffusion-weighted imaging.

multiple lacunar infarcts) I would treat acutely with aspirin alone. We need more data from secondary prevention studies in well phenotyped lacunar stroke.

Anticoagulation, cardioembolic stroke and embolic stroke of undetermined cause

Anticoagulation with warfarin or a direct oral anticoagulant (DOAC) is one of the most effective secondary preventative treatments for stroke, with a relative risk reduction of recurrent stroke of 60%. However, there are still several questions about when to start anticoagulation, and how widely to give it to patients with suspected but not proven cardioembolic sources.

In the first 2 weeks after ischaemic stroke, there is a risk of haemorrhagic transformation. Concern that this could be increased by anticoagulation has led to a reluctance in starting anticoagulation in patients with proven cardioembolic sources, primarily atrial fibrillation, within the first 2 weeks after stroke. Based on current evidence, some experts recommend starting anticoagulation early in people with small infarcts, and waiting 2–3 weeks in those with larger infarcts.¹⁵ However, the delay in starting anticoagulation may be excessively cautious, while exposing patients to an unnecessary risk of early recurrent ischaemic stroke. The correct approach can only be determined in randomised clinical trials comparing treatment with immediate and delayed initiation of anticoagulation, and several of these using DOACs are currently underway.¹⁵

A further question is whether anticoagulation should be used more widely in patients who have no identified cause of stroke, but who have a possible underlying arrhythmia. This hypothesis led to the construct of ‘Embolic Strokes of Undetermined cause’ (ESUS). The criteria for this diagnosis are: stroke detected by CT or MRI that is not lacunar, absence of extracranial or intracranial stenosis of >50%, no major risk of cardioembolic source of embolism, and no other specific cause of stroke (eg, dissection).¹⁶ Interestingly, thrombectomy specimens from patients with cryptogenic stroke showed thrombi similar to those from patients with a definite cardioembolic source, and different from those extracted from patients with large artery stroke.¹⁷ However, two large recent trials of DOACs in patients with ESUS have shown no benefit over antiplatelets alone, questioning whether patients with ESUS really are likely to harbour an undiagnosed cardioembolic source.^{18 19} It is possible that the diagnostic criteria applied in these trials were not strict enough, and those patients with other stroke subtypes were also included. However, based on current evidence, there is no indication for using DOACs in patients with ESUS without proven cardioembolic source.

Nevertheless, studies have shown that many patients with apparently cryptogenic stroke do have atrial fibrillation when they undergo prolonged ECG monitoring. Studies using both repeated Holter monitoring,

and implantable monitoring devices such as the Reveal device, have shown that the proportion of patients with atrial fibrillation rises progressively from about 10% at 4 weeks to 6 months, to 30% at 3 years.^{20 21} Frequently very short bursts of atrial fibrillation are detected, and it is often uncertain whether these relate to the pathogenesis of stroke. One study suggested that episodes lasting longer than 24 hours were strongly associated with stroke while episodes lasting 6 hours or less were not.²² We need further studies to determine how frequent such brief episodes are in the normal population, and whether they do indeed relate to stroke pathogenesis.

Based on the current evidence, we routinely record with bedside telemetry all patients admitted to the Stroke Unit with both TIA and stroke. If atrial fibrillation is detected during the acute phase, we would start anticoagulation. If we detect prolonged episodes within the first few weeks of longer term monitoring we would start anticoagulation. However, when only very brief episodes are detected on longer term monitoring months after the acute event, we are more cautious about anticoagulation. It is also important to take the results of other investigations into account when determining the significance of a brief episode of atrial fibrillation. For example, if there are multiple territorial infarcts in different vascular territories, and large artery imaging has shown no evidence of intracranial or extracranial stenosis, then the underlying pathology is likely to be cardioembolic and the episode of atrial fibrillation likely to be significant.

CONCLUSIONS

There are huge opportunities to reduce stroke by effective secondary prevention. Implementing this depends on early and accurate diagnosis. This should include assessing the size of any acute infarct, as well as determining the underlying pathophysiological cause where possible.

Speed is of the essence in implementing antiplatelet therapy, particularly for TIA and minor stroke—these should be treated as the medical emergencies. This calls into question whether the outpatient TIA clinic, in which treatment is not started within the first 48 hours, is the best model of care; perhaps systems, such as ambulatory care attached to an emergency department, would be more effective. Based on the results of POINT and CHANCE, patients should be considered for dual antiplatelet therapy with clopidogrel and aspirin if these can be given within the first 12–24 hours. However, in those with larger strokes, where the risk of haemorrhagic transformation is greater, we would advise aspirin therapy alone based on current evidence.

Longer term secondary prevention should be tailored according to the stroke subtype; careful review of brain imaging can help to determine the underlying

Key points

- ▶ Optimal management of stroke requires an accurate diagnosis of the cause of stroke.
- ▶ Clinicians should use a pathophysiological stroke classification system such as the Trial of Org 10172 in Acute Stroke Treatment system.
- ▶ The pattern of infarction on diffusion-weighted MR imaging can give useful clues to the stroke mechanism.
- ▶ Large artery stenosis is associated with a higher early recurrent stroke risk, and many physicians would treat such patients routinely with aspirin and clopidogrel dual therapy during the acute phase.

mechanisms. Clinicians must be cautious in diagnosing lacunar stroke, and should be aware of common misdiagnoses such as cortical infarcts causing weakness of one body part, or striatocapsular infarcts secondary to embolic sources.

Atrial fibrillation is underdiagnosed, and anticoagulation to prevent recurrent stroke in atrial fibrillation is one of the most effective secondary preventative treatments we have. Patients admitted with stroke and patients with TIA should undergo routine telemetry to detect atrial fibrillation. Prolonged monitoring should be considered after discharge, particularly in those where the imaging pattern fits with suspected cardio-embolic stroke.

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