Secondary stroke prevention

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See Online for appendix

For the **recurrence risk estimator** see http://www.nmr.mgh.harvard.edu/RRE/

Survivors of stroke and transient ischaemic attacks are at risk of a recurrent stroke, which is often more severe and disabling than the index event. Optimum secondary prevention of recurrent stroke needs rapid diagnosis and treatment and prompt identification of the underlying cardiovascular cause. Effective treatments include organised acute assessment and intervention with antithrombotic therapy, carotid revascularisation, and control of causal risk factors, as appropriate. However, effective treatments are not implemented optimally in clinical practice. Recurrent strokes continue to account for 25–30% of all strokes and represent unsuccessful secondary prevention. Immediate and sustained implementation of effective and appropriate secondary prevention strategies in patients with first-ever stroke or transient ischaemic attack has the potential to reduce the burden of stroke by up to a quarter.

Introduction

The world is facing a stroke epidemic: between 1990 and 2010, the number of stroke-related deaths increased by 26% (95% CI 14–32) and disability-adjusted life-years by 19% (5–26%), to make stroke the second leading cause of death and third leading contributor to disability-adjusted life-years in the world.[1,2] Complementary strategies to reduce the increasing global burden of stroke include the so-called population/mass and high-risk approaches to prevent first-ever and recurrent stroke, and the treatment and rehabilitation of acute stroke to improve disability-free survival.[3] The most relevant of these approaches for stroke physicians are the treatment and rehabilitation of acute stroke and the secondary prevention of recurrent stroke.

This Review summarises evidence for optimum secondary prevention of recurrent ischaemic stroke. The rationale for this report is that recurrent strokes constitute a notable proportion (25–30%) of all preventable strokes;[4] they are frequently ischaemic and more disabling, fatal, and costly than the first stroke;[4,5] and their rates could be reduced by improved translation of evidence-based advances in secondary stroke prevention into clinical practice.[6]

Since the rate of recurrent stroke and the potential benefits and risks of secondary prevention strategies are higher earlier rather than later after ischaemic stroke, I will describe separately the prognosis and predictors for early and long-term recurrent ischaemic stroke and the strategies to prevent both types of stroke.

Panel 1: The ABCD2 and ABCD3–I scores to predict early recurrent stroke

ABCD2

The ABCD2 score (appendix pp 4–5) is a simple scoring system that can be used in primary care and by emergency department clinicians to stratify patients with transient ischaemic attack (TIA) into low, moderate, and high risk of early recurrent stroke.[10] The score has been validated in several independent datasets to have good power to predict the rate and severity of recurrent stroke at 7 days.[11,12] A limitation of the ABCD2 score is that it was not derived from datasets with information about the cardiovascular lesion(s) causing the ischaemic stroke or TIA, such as carotid stenosis and atrial fibrillation, which also determine early prognosis. Most early recurrent strokes are caused by recurrent thromboembolism from an unstable atherosclerotic plaque that is still unstable (*vs* recurrent cardiogenic embolism or small vessel occlusion).[13–16] Another limitation of the score is that 10% of strokes at 7 days after TIA occur in patients judged to be at low risk (ABCD2 score 0–3), and 50% of strokes occur in patients classed as moderate risk (ABCD2 score 4–5).[17,18] Hence, patients with TIA should be assessed immediately, irrespective of ABCD2 score, because some with lower scores have treatable causes, such as carotid stenosis and atrial fibrillation, that might be associated with raised short-term risks of stroke.

ABCD3–I

The ABCD3–I score has been developed for use in secondary care settings that have access to carotid and brain imaging (appendix pp 4–5).[19] It uses the prognostic significance of the cardiovascular lesion causing the ischaemic stroke or TIA, and the presence of recent focal brain ischaemia detected by magnetic resonance diffusion-weighted imaging.[20,21] It has been validated externally as having a higher predictive value than the ABCD2 score for assessing risk of early stroke.[19,22] Limitations of the ABCD3–I score are that the yield of magnetic resonance diffusion-weighted imaging varies according to the timing of the scan after the TIA; if the procedure is undertaken more than 24 h after symptom onset, the odds of finding a diffusion-weighted imaging lesion could be increased by up to threefold.[23]

Early recurrent stroke

Prognosis and predictors

The risk of a recurrent stroke is highest early after an ischaemic stroke or transient ischaemic attack (TIA)—about 1% at 6 h, 2% at 12 h, 3% at 2 days, 5% at 7 days, and 10% at 14 days.[7–9] Therefore, ischaemic stroke or TIA is a medical emergency that demands immediate diagnosis and treatment.

Some clinical features, such as sudden-onset unilateral weakness and speech disturbance lasting for longer than 10 min, predict a high risk of stroke soon after TIA, probably because they distinguish TIA from a myriad of TIA mimics that have a more benign prognosis.[10] These, and other, clinical features have been used to derive a prognostic index: the ABCD2 score (panel 1; appendix pp 4–5).[10–12] Additional prognostic information from carotid and brain imaging about the cause of the ischaemic event has been incorporated into the ABCD3–I score[19] (panel 1; appendix pp 4–5) and the recurrence risk estimator.[14,24]

However, low scores on these prognostic indices should not preclude appropriate assessment and management because some patients with a low predicted risk of stroke have treatable causes, such as carotid stenosis and atrial fibrillation, that might warrant urgent intervention.[17,18]

Secondary prevention

Effective strategies to prevent early recurrent ischaemic stroke include assessment and management in an acute

specialist unit, immediate antiplatelet therapy, and early carotid revascularisation, as appropriate (table 1, panel 2).

Antiplatelet and anticoagulation therapies

As a single antiplatelet therapy, aspirin 160–300 mg daily, started within 48 h of onset of ischaemic stroke in 40 000 patients, and continued for 2–4 weeks, reduced the odds of recurrent ischaemic stroke by 23% (2·4% aspirin *vs* 3·1% control; odds ratio [OR] 0·77, 95% CI 0·69–0·87), increased the odds of symptomatic intracranial haemorrhage by 22% (1·0% *vs* 0·8%; OR 1·22, 95% CI 1·00–1·50), and reduced the odds of any recurrent stroke by 12% (3·4% *vs* 3·9%; OR 0·88, 95% CI 0·79–0·97) compared with control (table 1).[25]

A meta-analysis of 14 randomised controlled trials comparing dual antiplatelet therapy with antiplatelet monotherapy, both started within 3 days of onset of ischaemic stroke or TIA, in 9102 adults showed that dual antiplatelet therapy significantly reduced early recurrent stroke by a third (6·21% dual therapy *vs* 8·95% monotherapy; risk ratio [RR] 0·69, 95% CI 0·60–0·80, absolute risk reduction 2·74%) at about 3 months' follow-up (range 7 days–18 months), compared with monotherapy, and non-significantly increased the risk of major bleeding (0·52% dual therapy *vs* 0·36% monotherapy; RR 1·35, 95% CI 0·70–2·59, absolute risk increase 0·16%).[26] The results of trials comparing different dual combinations of antiplatelet drugs with different single antiplatelet drugs were consistent with the overall result for all trials (table 1).[26] However, the results might not apply to patients with major ischaemic stroke (eg, those with a score on the National Institutes of Stroke Scale >4) who were excluded from many trials because of the risk of haemorrhagic transformation of new brain infarction.[51]

The results of the CHANCE trial of aspirin and clopidogrel compared with aspirin in Chinese patients[9] are consistent with previous similar smaller trials undertaken

	Outcome	Stroke rate		RRR (95% CI)	ARR	NNT and time period
		Control	Inter-vention			
Early recurrent stroke						
Aspirin (*vs* no aspirin)[25]	Stroke at 2–4 weeks	3·9%	3·4%	12% (3 to 21)	0·5%	200 over 2–4 weeks
Clopidogrel plus aspirin (*vs* aspirin)[9,26]	Stroke at roughly 3 months	11·1%	7·8%	30% (18 to 41)	3·3%	30 over roughly 3 months
Aspirin plus dipyridamole (*vs* aspirin)[26]	Stroke at 3–28 months	7·9%	5·3%	36% (–10 to 63)	2·6%	38 over 3–28 months
Aspirin plus dipyridamole (*vs* clopidogrel)[26]	Stroke at 3 months	2·9%	1·6%	44% (–17 to 73)	1·8%	56 over 3 months
Clopidogrel plus aspirin (*vs* clopidogrel)[26]	Stroke at 18 months	4·7%	3·9%	17% (–93 to 64)	0·8%	125 over 18 months
Carotid endarterectomy or stent (*vs* no carotid revascularisation)[27,28]						
70–99% stenosis, symptomatic	Stroke at 5 years	33%	17%	48% (38 to 60)	16%	6 over 5 years
50–69% stenosis, symptomatic	Stroke at 5 years	27%	19%	28% (14 to 42)	8%	12 over 5 years
Acute specialty units (*vs* outpatient clinics)[29]	Stroke at 90 days	10·3%	2·1%	80% (51 to 92)	8·2%	12 over 90 days
Longer-term recurrent stroke						
Aspirin (*vs* no aspirin)[30,31]	Stroke, MI, or VD, per year	7·0%	6·1%	13% (6 to 19)	0·9%	111 over 1 year
Clopidogrel (*vs* aspirin)[32,33]	Stroke, MI, or VD, per year					
All high-vascular-risk patients		5·8%	5·3%	9% (0·3 to 16)	0·5%	200 over 1 year
Ischaemic stroke patients		7·7%	7·1%	7% (–6 to 19)	0·6%	167 over 1 year
Aspirin and extended-release dipyridamole (*vs* aspirin)[34]	Recurrent stroke, per 2·6 years (mean)	11·3%	9·0%	22% (10 to 32)	2·3%	43 over 2·6 years, or 113 over 1 year
	Stroke, MI, or VD, per 2·6 years (mean)	15·2%	12·5%	18% (8 to 28)	2·7%	37 over 2·6 years, or 100 over 1 year
Aspirin and extended-release dipyridamole (*vs* clopidogrel)[35]	Recurrent stroke, per 2·5 years (mean)	8·8%	9·0%	–1% (–11 to 8)	0·2% (NS)	NA
	Stroke, MI, or VD per 2·5 years (mean)	13·1%	13·1%	1% (–7 to 8)	0% (NS)	NA
Cilostazol (*vs* aspirin)[36]	Stroke, MI, or VD, per 1·25 years (mean)	8·8%	6·3%	28% (11 to 43)	2·5%	40 over 1·25 years, or 50 over 1 year
Warfarin for atrial fibrillation (*vs* no warfarin)[37,38]	Recurrent stroke, per year	12%	4%	61% (37 to 75)	8%	12 over 1 year
New direct oral anticoagulants for atrial fibrillation (*vs* warfarin)[39]	Stroke and systemic embolism, per 1·9 years	5·3%	4·5%	14% (0 to 26)	0·8%	134 over 1·9 years, or 255 over 1 year
Lowering of blood pressure (*vs* no lowering of blood pressure)[40,41]	Recurrent stroke, per 3 years (roughly)	9·9%	8·6%	22% (10 to 32)	1·3%	75 over roughly 3 years, or 225 over roughly 1 year
Statins to reduce low-density-lipoprotein cholesterol (*vs* no statin)[42]	Recurrent stroke, per 5 years	11·9%	10·5%	12% (1 to 22)	1·4%	74 over 5 years, or 370 over roughly 1 year

See appendix pp 1–3 for explanations of statistical terms. RRR=relative risk reduction (risk ratio). ARR=absolute risk reduction. NNT=number needed to treat. NS=not significant. MI=myocardial infarction. VD=vascular death. NA=not applicable.

Table 1: **Summary of effective strategies to prevent recurrent stroke**