

Stroke

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Stroke is the second most common cause of death and major cause of disability worldwide. Because of the ageing population, the burden will increase greatly during the next 20 years, especially in developing countries. Advances have occurred in the prevention and treatment of stroke during the past decade. For patients with acute stroke, management in a stroke care unit, intravenous tissue plasminogen activator within 3 h or aspirin within 48 h of stroke onset, and decompressive surgery for supratentorial malignant hemispheric cerebral infarction are interventions of proven benefit; several other interventions are being assessed. Proven secondary prevention strategies are warfarin for patients with atrial fibrillation, endarterectomy for symptomatic carotid stenosis, antiplatelet agents, and cholesterol reduction. The most important intervention is the management of patients in stroke care units because these provide a framework within which further study might be undertaken. These advances have exposed a worldwide shortage of stroke health-care workers, especially in developing countries.

Epidemiology

Stroke causes 9% of all deaths around the world and is the second most common cause of death after ischaemic heart disease.¹ The proportion of deaths caused by stroke is 10–12% in western countries, and 12% of these deaths are in people less than 65 years of age.² In 2002, stroke-related disability was judged to be the sixth most common cause of reduced disability-adjusted life-years (DALYs—the sum of life-years lost as a result of premature death and years lived with disability adjusted for severity).³ However, because of the burgeoning elderly population in western societies, the estimation is that by 2030 stroke-related disability in western societies will be ranked as the fourth most important cause of DALYs.⁴

Worldwide, stroke consumes about 2–4% of total health-care costs, and in industrialised countries stroke accounts for more than 4% of direct health-care costs. The total costs to society have been variously estimated at £7·6 billion in the UK at 1995 prices, AUS\$1·3 billion in Australia, and US\$40·9 billion in the USA at 1997 prices,^{5,6} which represents about US\$100 per head of population per year. Nevertheless, the proportion of research funds directed towards stroke remains disproportionately and disappointingly low.⁷

Although, the average age-adjusted stroke mortality for developed countries is about 50–100 per 100 000 people per year, there are differences between countries. For example, projections for 2005 based on age-standardised death rates for ages 30–69 years in the Russian Federation were greater than 180 per 100 000 people, whereas for Canada they were less than 15 per 100 000 people (figure 1).⁸ Such strong geographical variations might suggest a role for differences in the prevalence of risk factors and genetic factors and differences in the management of stroke. Even though there has been a constant reduction in stroke mortality in developed countries during the past 50 years (a relative reduction of about 1% per year until the late 1960s followed by a more steep fall of as much as 5% per year),⁹ we are less certain about trends in developing countries. The most plausible explanation for the reduction in mortality in western countries is improved control of

stroke risk factors (especially high blood pressure and cigarette smoking) combined with a parallel improvement in living standards.^{9,10} The lessons for the developing world are obvious.

In a community-based study, the incidence of cerebrovascular events (transient ischaemic attack [TIA] and ischaemic stroke) was higher than that of ischaemic heart disease or peripheral vascular disease (table 1).¹¹ Apparent differences in reported stroke incidence might result from methodological weaknesses in individual studies. Even in studies of the highest quality, stroke incidence ranges from 240 per 100 000 people in Dijon, France (standardised to the European population aged 45–84 years), to about 600 per 100 000 people in Novosibirsk, Russia,¹² again suggesting important roles for both environmental and genetic factors. However, for the first time, substantial reductions in the incidence of stroke have been reported, although less is known about changes in stroke severity or incidence of TIAs. For instance—between 1989 and 1995—a 25% reduction in stroke incidence was seen in Perth, Australia, and—between 1981 and 2002—a 29% reduction was seen in Oxfordshire, UK; these reductions imply that improved risk-factor management can have a substantial effect in some societies (figure 2). By contrast, in Novosibirsk—between 1987 and 1994—stroke incidence in people aged 35–69 years actually rose. Less attention has been paid to

Search strategy and selection criteria

We searched Medline for English language manuscripts. We used the search terms “stroke prognosis”, “secondary prevention”, “primary prevention”, “intracerebral haemorrhage”, and “acute stroke therapies” in combination with the term “review”. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by the search strategy and selected those we judged relevant. Review articles are cited to provide readers with details, and major studies or trials are cited to support level 1 evidence.

stroke prevalence (ie, the burden of patients living with the consequences of stroke), mainly because the identification of such individuals is a daunting task. Typical estimates, largely drawn from knowledge of stroke incidence and mortality, are that about 500 people per 100 000 population live with the consequences of stroke. Because stroke mortality is probably decreasing more rapidly than stroke incidence, the proportion of stroke survivors is likely to increase, which will place increased demands on health-care and social-care systems.

Risk factors for stroke can be broadly classified as modifiable or fixed. Some modifiable risk factors (such as hypertension, diabetes, and smoking) are common and affect health in several ways, providing opportunities to modify risk in large numbers of people. Other risk factors, such as atrial fibrillation and TIAs, are less prevalent and more specific than the common risk factors for stroke. Risk factors that have been identified explain only about 60% of the attributable risk, whereas more than 90% of ischaemic heart disease is explained by identifiable risk factors.^{13,14} Investigation is needed to identify the risk factors that account for the 40% gap, some of which might be genetic.

Subtypes and pathophysiology

Strokes are either ischaemic or haemorrhagic. Because the management of these subtypes is so different, the clinical distinction between the subtypes is one of the most important and urgent steps in stroke management. This distinction has been revolutionised by the introduction of CT and MRI. Although CT has been the workhorse of stroke diagnosis during the past 20 years, MRI is now as useful as, if not more so than, CT.¹⁵

Further systems for stroke classification have been driven by the needs of both clinical trials (that have led to the introduction of the Trial of Org 10172 in Acute Stroke Treatment [TOAST] criteria; panel) and epidemiological studies (that have led to the Oxfordshire Community Stroke Project [OCSP] classification).^{16–19} The TOAST criteria identify the most probable pathophysiological mechanism on the basis of clinical findings and results of investigations,¹⁶ whereas the OCSP classification relies exclusively on clinical findings and is therefore broadly applicable in any number of different settings in which access to investigations might be restricted.¹⁹ In view of the rapid advances made in imaging and other investigations, TOAST criteria and OCSP classifications will need to be updated in the near future.

Haemorrhagic stroke (intracerebral haemorrhage)

The most common mechanism is hypertensive small-vessel disease, which causes small lipohyalinotic aneurysms that subsequently rupture.²⁰ Whether other contributing factors—such as haemorrhage into a previous infarction—are important needs to be clearly established.²¹ About two-thirds of patients with primary

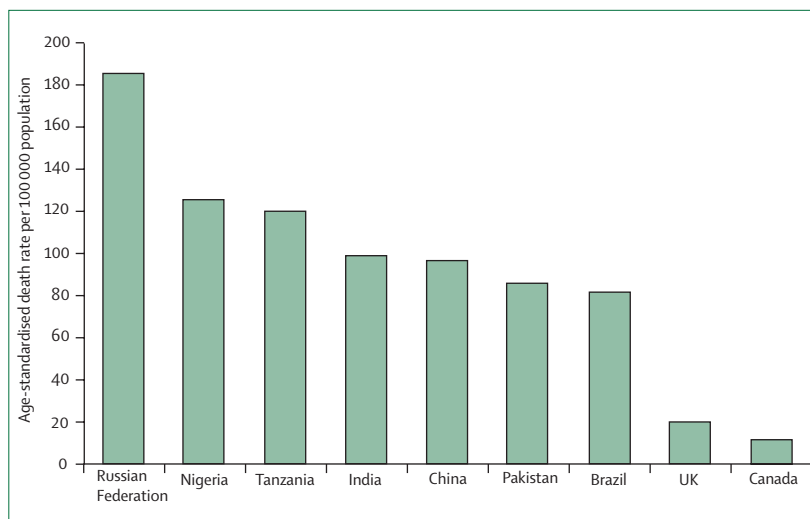


Figure 1: Age-standardised death rates from stroke per 100 000 for ages 30–69 years in selected countries, projections for 2005

Reproduced from Strong and colleagues⁸ with permission.

	Total number*	Rate† (95% CI)
Cerebrovascular events		
Ischaemic stroke	550	2.01 (1.85–2.19)
Intracerebral haemorrhage	41	0.15 (0.11–0.20)
Subarachnoid haemorrhage	27	0.10 (0.07–0.14)
Transient ischaemic attack	300	1.10 (0.98–1.23)
All cerebrovascular events	918	3.36 (3.14–3.58)
Coronary vascular events		
Sudden cardiac death	163	0.60 (0.51–0.7)
STEMI	159	0.58 (0.49–0.68)
N-STEMI	316	1.16 (1.03–1.29)
Unstable angina	218	0.80 (0.70–0.91)
All coronary vascular events	856	3.13 (2.93–3.35)
Peripheral vascular events		
All events	188	0.69 (0.59–0.79)

Stroke incidence was greater than ischaemic heart disease or peripheral vascular disease, which emphasised the need for greater resource allocation for the first and last event (modified from Rothwell and colleagues²¹ with permission).
 STEMI=ST-segment elevation acute myocardial infarction.
 N-STEMI=non-ST-segment elevation acute myocardial infarction. *Number of events during 3 years. †Number of events per 1000 population per year.

Table 1: The incidence of cerebrovascular, coronary, and peripheral vascular events (first and recurrent) in the Oxford vascular study

cerebral haemorrhage have either pre-existing or newly diagnosed hypertension.²² The remaining patients might be seen, on more detailed investigation, to have intracranial vascular malformations (cavernous angiomas or arteriovenous malformations), cerebral amyloid angiopathy, or infarcts into which secondary haemorrhage has occurred.

Subarachnoid haemorrhage is classified as a type of stroke, and accounts for about 5% of all strokes. Most subarachnoid haemorrhages are caused by rupture of saccular aneurysms within the subarachnoid space.

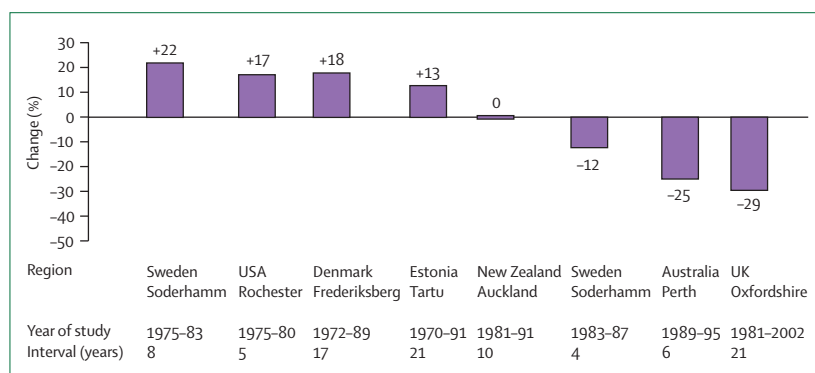


Figure 2: Trends in stroke incidence in eight ideal stroke incidence studies

Note that the trends in later decades are toward reductions in incidence in developed countries in which the effect of risk factor modification may be becoming evident.

Panel: Classification of subtypes of acute ischaemic stroke

TOAST* (Trial of Org 10172 in Acute Stroke Treatment) criteria¹⁶

- Large-artery atherosclerosis (embolus or thrombosis)*
- Cardioembolism (high-risk or medium-risk)*
- Small-vessel occlusion (lacune)*
- Stroke of other determined cause*
- Stroke of undetermined cause
 - Two or more causes identified
 - Negative evaluation
 - Incomplete evaluation

*Possible or probable depending on results of ancillary studies.

Perimesencephalic haemorrhages are thought to be caused by rupture of intracranial veins; they are less severe, have a better prognosis, and generally no aneurysm is seen on angiography.²³

Ischaemic stroke and transient ischaemic attacks

About 80% of all strokes are ischaemic.²⁴ Classification based on the OCSF system can be done in the emergency room and conveys important prognostic information. Classification based on the TOAST system identifies the mechanism that leads to vessel occlusion (cardioembolic, artery to artery embolism, or in-situ small-vessel [lacunar] disease) and is important in everyday management because such information should influence both acute treatments and secondary prevention strategies.

The distinction between symptomatic cerebral ischaemic events that last 24 h or less (TIAs) and events of longer duration (stroke) is entirely arbitrary. Permanent tissue damage can be seen with MRI in at least 25% of patients with TIAs^{25,26} and some have argued that a new definition of TIAs incorporating such imaging findings is needed.²⁷ We believe that the diagnosis of symptomatic cerebral ischaemic events remains essentially clinical and should trigger an appropriate emergency response

in the community, from primary care physicians through to those in emergency departments. Response should be based on the clinical features of an individual case (for instance, the ABCD² score based on age [A], blood pressure [B], clinical features [C], and duration of symptoms [D], table 2), and the role of imaging is to eliminate other causes and help to stratify the risk of early recurrence.

Ischaemic penumbra and cascade

Once vessel occlusion has occurred, a volume of functionally impaired, but structurally intact, tissue surrounds the ischaemic core.²⁹ This tissue is known as the ischaemic penumbra and is the target for therapeutic interventions since its salvage is associated with neurological improvement and recovery.³⁰ The state of functional impairment with structural integrity has been seen with magnetic resonance scanning in some patients up to 24 h after stroke onset; mismatch between the volume of brain with reduced perfusion is shown on perfusion-weighted imaging, and the volume of brain showing cellular swelling, the ischaemic core, is shown on diffusion weighted imaging (figure 3). The penumbra is seen up to 48 h after stroke onset by use of PET.^{31,32}

Within the ischaemic penumbra, a cascade of neurochemical events begins with energy depletion followed by disruption of ion homeostasis, release of glutamate, calcium channel dysfunction, release of free radicals, membrane disruption, inflammatory changes, and necrotic and apoptotic cell death triggering.³³ In animal models of stroke, these cascades can be arrested at various points, which forms the basis of neuroprotective therapies that are discussed subsequently.³⁴ The infarct core contains tissue that is unsalvageable and represents the terminal events of the ischaemic cascade.

Stroke prognosis

About a quarter of stroke patients are dead within a month, about a third by 6 months, and a half by 1 year.^{35,36} Prognosis is even worse for those with intracerebral and subarachnoid haemorrhage because the 1-month mortality approaches 50%. The major cause of early mortality is neurological deterioration with contributions from other causes such as infections secondary to aspiration (if not managed aggressively), but later deaths are more commonly caused by cardiac disease or complications of stroke.³⁶ In the OCSF classification, the 1-year mortality for patients with total anterior circulation syndromes (about 60%) is substantially higher than that for those with partial anterior circulation and posterior circulation syndromes (about 15–20%), which in turn is higher than that for patients with lacunar syndromes (10%).^{37,38} The best predictors of stroke recovery at 3 months are the initial neurological deficit and age; other factors include high blood glucose concentrations, body temperature, and previous stroke.³⁹

Feature	Points
Age 60 years or older	1
Blood pressure elevation on first assessment (≥140 mm Hg systolic, ≥90 mm Hg diastolic)	1
Clinical features of transient ischaemic stroke	
Unilateral weakness	2
Speech impairment without weakness	1
Duration of transient ischaemic attack	
≥60 min	2
10–59 min	1
Diabetes	1

A score of 4 points or more might justify admission to hospital or urgent evaluation, treatment, and observation since 30-day stroke risk is in the order of 5–15%. Reproduced from Johnston and colleagues.²⁸

Table 2: ABCD² score

A third of patients with primary intracerebral haemorrhage have a rapid expansion of the haematoma within the first few hours after presentation, which is an independent predictor of poor outcome at 3 months alongside other factors such as age and initial neurological deficit (figure 4).⁴⁰

After TIA or minor stroke, the risk of further stroke is substantially higher than previously thought, reaching as high as 30% within the first month in some subgroups.^{41–44} Patients at very high risk (>30%) of recurrence within 7 days can be identified on the basis of their age, blood pressure, and the characteristics and duration of their symptoms; simple scores have been developed, on the basis of these factors, to predict those patients at greatest risk who might benefit most from early risk-factor modification (table 2).^{28,45} Additionally, imaging strategies—for instance the presence of diffusion-weighted image lesions on magnetic resonance scanning or of occluded vessels on magnetic resonance angiography—can identify patients at increased risk of recurrence.⁴⁶

Acute interventions

Stroke care units (SCUs)

Remarkable advances in the management of acute stroke seen in the past 10–15 years consist of four proven interventions supported by level 1 evidence and various promising interventions under investigation (table 3). Without doubt the most substantial advance in stroke has been the routine management of patients in SCUs, which is effective and appropriate for all stroke subtypes, and provides a focus for professionals in stroke care. Management of patients within an SCU reduces mortality by about 20% and improves functional outcome by about the same amount.⁴⁷ A physical space identified as an SCU is associated with better outcomes than seen with a dedicated stroke team visiting patients on general medical wards.⁷² Although the precise components of SCU management responsible for the

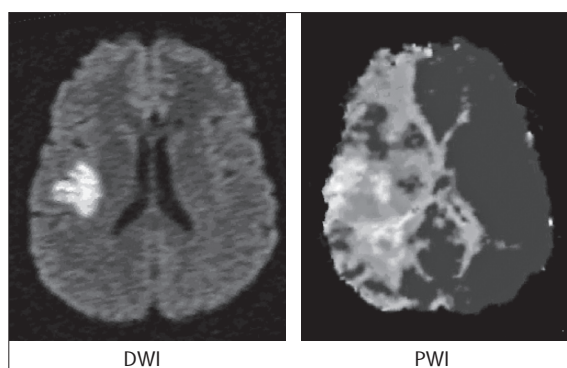


Figure 3: MRI of the ischaemic penumbra

Mismatch between large perfusion deficit seen on perfusion-weighted image (PWI) and infarct core seen on small-diffusion-weighted image (DWI) represents penumbral target for therapy. DWI/PWI mismatch is increasingly being used to identify patients who are most likely to benefit from new interventions in acute ischaemic stroke.

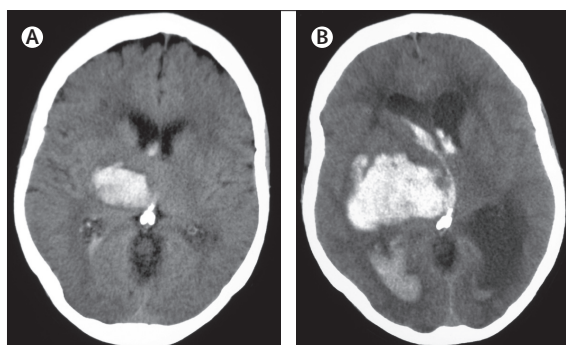


Figure 4:

Haematoma growth seen during 24 h from the initial presentation at 3.5 h (A) to 27.5 h (B) in a 74-year-old man with right hemiparesis

Haematoma growth is an independent predictor of outcome and is the target for the haemostatic therapy recombinant factor VII in phase 3 clinical trials.

effectiveness of SCUs are unclear, improved blood pressure control, early mobilisation, and general adherence to best practice have been identified as some of the components.^{73,74} In a community-based epidemiological study, in which all patients eligible for possible acute stroke interventions were considered, SCU management had the potential to prevent death or disability for around 50 patients for every 1000 strokes, compared with about six per 1000 with tissue plasminogen activator (tPA) and four per 1000 with aspirin.⁷⁵ The mechanisms by which SCU management improves outcomes are uncertain. However, evidence-based advances, such as results from the prevention of venous thromboembolism after acute ischaemic stroke with low-molecular-weight heparin enoxaparin (PREVAIL) trial,⁷⁶ have established the superiority of enoxaparin compared with unfractionated low-dose heparin for prevention of deep vein thrombosis after stroke. The widespread introduction of SCUs should be a priority in planning health systems, especially in developing countries with high rates of death.

Thrombolysis: recombinant tPA

Recombinant tPA is one of the most biologically effective treatments for acute ischaemic stroke; the number needed to treat to improve outcome to minimum or no neurological deficit in one person is about seven or about 18 people when avoidance of death or disability is considered (table 3).^{48,77} However, these numbers relate to treatment within 3 h of stroke onset. Because of the short therapeutic time window, the number of patients who might receive treatment and therefore potentially benefit is small; prevention of disability is seen in only six patients per 1000 ischaemic strokes.⁷⁵ tPA—although very effective in reducing disability—does not improve mortality.⁷⁷ Indeed, most stroke centres use tPA in only about 5% of stroke patients.⁷⁸ Even in developed countries, many hospitals treating acute stroke do not offer thrombolysis, largely because of a worldwide shortage of physicians who are experts in acute stroke management. In some countries, such as the USA, reimbursement might also be an issue.

The major adverse effect of thrombolysis is symptomatic intracerebral haemorrhage, seen in about 6–7% of cases. This value was somewhat lower in a Europe-wide registry (SITS-MOST), although the definition of symptomatic haemorrhage differed from that in the original trials.⁷⁹ Risk of symptomatic intracerebral haemorrhage increases with age, high blood pressure, very severe neurological deficits, severe hyperglycaemia, and, possibly, with early ischaemic changes on CT.^{80,81} Data supporting an increased risk of haemorrhage with early ischaemic change on CT come largely from trials of therapy initiated up to 6 h after symptom onset, and therefore might not be relevant to therapy initiated within a 3 h time window.⁸² However, most, but not all, physicians regard CT evidence of early ischaemic change that affects more than a third of middle-cerebral-arterial territory as a contraindication to therapy.⁸³ One phase III trial suggested that prourokinase given intra-arterially within 6 h of symptom onset can improve outcome, and various centres routinely use this approach with results similar to those from trials of intravenously administered tPA (although not approved by the US Food and Drug Administration [FDA]).^{84,85}

Because of the substantial effectiveness of tPA, efforts to increase the number of patients who are eligible for thrombolytic therapy are underway. First, some effectiveness of tPA is likely to remain beyond 3 h, and this theory is being tested in the European cooperative acute stroke III (ECASS III) trial and the international stroke trial 3 (IST3).^{86,87} The alteplase thrombolysis for acute noninterventional therapy in ischaemic stroke (ATLANTIS) study, which was done before ECASS III and IST3 studies, did not show benefit in the 3–5 h time window.⁸⁸ Second, stroke-to-hospital times are reduced by identification of factors associated with delay, such as failure to immediately call an ambulance.⁸⁹ Third, door-to-needle times are reduced by the use of efficient triage pathways.⁹⁰ Finally, efforts are being made to extend the time window for therapy in individual patients by detection of persistent ischaemic penumbra, for instance, by use of MRI.^{91–93}

Aspirin

Evidence from about 40 000 randomised patients shows that the administration of oral aspirin within 48 h of onset of ischaemic stroke reduces 14-day morbidity and mortality.^{49,94} However, the benefit is quite small, with only about nine patients saved from death or disability per 1000 treated, and prevention of death or disability is seen in only four per 1000 ischaemic strokes after exclusion factors are taken into account.⁷⁵ The advantages of aspirin use are low cost, ease of administration, and low toxic effects, leading to widespread early use.⁷⁵ The effectiveness of aspirin probably stems from early secondary prevention, but penumbral salvage is also possible.⁹⁵

	Initial or important study, year	RRR (95% CI)	ARR	NNT ₁
Acute stroke				
Proven				
Stroke unit ⁴⁷	Langhorne and colleagues, 1993	6.5%	3.8%	26
Thrombolysis (tPA) ⁴⁸	NINDS, 1995	9.8%	5.5%	18
Aspirin ⁴⁹	IST, 1997	2.6%	1.2%	83
Decompressive surgery for IS ⁵⁰	Vahedi and colleagues, 2007	48.8%	23%	4*
Under investigation				
Recombinant factor VII ICH ⁵¹	Mayer and colleagues, 2005	..	..	..
Surgery for ICH ⁵²	Mendelow and colleagues, 2005 ⁸⁵	..	..	..
Extending time window for thrombolysis ⁵³	DIAS, 2005	..	..	..
Sonothrombolysis ⁵⁴	Alexandrov and colleagues, 2004	..	..	..
Thrombectomy ⁵⁵	MERCI, 2005	..	..	..
Blood pressure lowering ⁵⁶	ENOS, 2007	..	..	..
Neuroprotection ⁵⁷	SAINT, 2006	..	..	..
Secondary prevention				
Proven				
Aspirin ⁵⁸	Canadian Co-op Study Group, 1978	13.0%	1.0%	100
Aspirin plus dipyridamole ⁵⁹	Diener, 1996	15.0%	1.9%	53
Clopidogrel ⁶⁰	CAPRIE, 1996	10.0%	1.6%	62
Anticoagulants ⁶¹	EAFIT, 1993	66.0%	8.0%	11
Carotid endarterectomy ^{62,63}	NASCET, 1991, ECST 1991	44.0%	3.8%	26
Blood pressure lowering ⁶⁴	PROGRESS, 2001	28.0%	4.0%	97†
Cholesterol lowering ⁶⁵	SPARCL, 2006	16.0%	2.2%	220†
Under investigation				
Angioplasty ⁶⁶	Yadav and colleagues, 2004	..	..	..
Thrombin inhibitors ⁶⁷	SPORTIF, 2003	..	..	..

The number needed to treat (NNT₁) to prevent one stroke patient dying or becoming dependent (acute stroke) or to prevent one fatal or non-fatal stroke (secondary prevention) per year is given. All values are approximate and derived from previous analyses, Cochrane database, or individual trials if these are the only data available.^{48–75} RRR=relative risk reduction. ARR=absolute risk reduction. tPA=tissue plasminogen activator. IS=ischaemic stroke. ICH=intracerebral haemorrhage. *NNT for survival with modified Rankin scale ≤3. †Calculations based on mean follow-up of 3.9 years in PROGRESS (NNT_{3.9}=25) and median 4.9 years in SPARCL (NNT_{4.9}=45).

Table 3: Acute interventions and secondary prevention strategies of proven benefit based on level I evidence

Decompressive surgery for ischaemic stroke

Hemispheric decompression in young patients with malignant middle-cerebral-artery-territory infarction and space-occupying brain oedema is supported by evidence. This combination occurs in about 1–10% of patients with supratentorial hemispheric infarcts and might arise between 2 and 5 days after stroke.⁹⁶ The natural history of ischaemic stroke is poor, with about 80% mortality rates usually reported.⁹⁷ Identification of early predictors of fatal brain oedema has been difficult, although early CT hypodensity of more than 50% of the supratentorial hemisphere has been consistently noted.⁹⁸ Evidence for effectiveness of decompressive surgery comes from a prospective individual-patient meta-analysis of three randomised control trials.⁵⁰ These trials were hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial (HAMLET; interval to treatment up to 99 h), decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL; interval to treatment up to 30 h), and decompressive surgery for the treatment of malignant Infarction of the middle cerebral artery (DESTINY; interval to treatment up to 36 h).⁵⁰ For the purposes of the individual-patient analysis, a cutoff time to surgery of 48 h was adopted; other inclusion and exclusion criteria of the three trials were largely similar.

In the pooled analysis of 93 patients, more patients in the decompressive surgery group than in the control group had a modified Rankin scale (mRS) of 4 or less (75% vs 24%; pooled absolute risk reduction 51% [95% CI 34–69]), an mRS of 3 or less (43% vs 21%; 23% [5–41]), and survived (78% vs 29%; 50% [33–67]); number needed to treat was two patients for survival with an mRS of 4 or less, four for survival with an mRS of 3 or less, and two for survival irrespective of functional outcome.⁵⁰ The effect of surgery was highly consistent across the three trials. Although decompressive surgery is appropriate for only a very small proportion of patients who present with ischaemic stroke, the benefits of surgery have now been so clearly established that it should form part of routine clinical practice.

Interventions under evaluation

Various interventions that are presently under investigation in phase II proof-of-concept trials show great promise—ie, recombinant factor VII for acute intracerebral haemorrhage, surgery for intracerebral haemorrhage, extension of the time window for thrombolysis, sonothrombolysis (combination of ultrasound and thrombolysis), thrombectomy devices, blood pressure reduction, and neuroprotection. Haematoma growth within the first few hours of stroke onset is a key independent prognostic factor for poor clinical outcome.^{40,99} Recombinant factor VII, which is usually given to patients with haemophilia or to reduce haemorrhagic complications of major surgical procedures (such as, for example, prostatectomy) was shown to attenuate haematoma

growth, with secondary clinical benefits, in a phase II trial.⁵¹ The findings of a phase III study were negative for the primary endpoint and functional outcome, although attenuation of haematoma growth was confirmed (not yet published).

The surgical trial in intracerebral haemorrhage (STICH) trial provided little support for early surgical drainage of haematomas after primary haemorrhage.⁵² Purpose of the STICH II trial was to investigate the efficacy of surgery in patients with lobar haemorrhage because uncertainty remains about how to treat these patients.⁵² Posterior-fossa decompressive surgery is generally done to avoid clinical deterioration and death when cerebellar haematoma or infarction causes brainstem compression or raised intracranial pressure, or both, with obstruction of cerebrospinal-fluid flow.³⁸

Various trials are investigating extension of the time window for thrombolysis: (1) standard tPA therapy with expanded entry criteria with therapeutic time windows of up to 6 h; (2) imaging techniques to assess the presence of penumbra with time windows of up to 6 h or even 9 h; (3) use of alternative thrombolytic agents such as desmoteplase; (4) combined (bridging) approach with intravenous therapy followed by intra-arterial therapy;^{53,100–102} and (5) combination therapies using, for example, glycoprotein (GP) IIb/IIIa antagonists with tPA, tested with time windows of up to 24 h (ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation [ROSIE]).¹⁰³

Low-frequency ultrasound—might enhance thrombolysis by mobilisation of endogenous tPA, which increases the surface area that is available to exogenous tPA and causes mechanical disruption of the clot. Results of a phase II trial in which patients received transcranial Doppler ultrasound (with a 2 MHz probe focused on the symptomatic middle-cerebral artery) and intravenous tPA showed improved recanalisation rates and a trend towards better functional outcomes;⁵⁴ a phase III trial is about to begin. A similar phase II trial of sonothrombolysis (with a 5 MHz probe) led to unacceptably high intracerebral haemorrhage rates.¹⁰⁴

Thrombectomy devices are mechanical devices that have been developed to allow the direct removal of a blood clot from major vessels such as middle-cerebral or basilar arteries. The device that has received the most attention is the mechanical embolus removal in cerebral ischemia (MERCi) retrieval catheter (Concentric Medical, Mountain View, CA, USA) which has a corkscrew shape. In a phase II trial, investigators showed that this catheter could be used to remove the clot in a timely fashion with a complication rate similar to that seen with intravenous tPA.⁵⁵ Subsequently, the FDA approved the device for clot removal, but not as a stroke therapy, an action which evoked some controversy among stroke physicians who were accustomed to the rigorous regulatory requirements for pharmaceutical agents.^{105,106} Various other devices have been developed, but are less well studied.¹⁰⁷

Uncertainty exists about how to manage high blood pressure in the early stages of stroke.¹⁰⁸ About 70% of patients with ischaemic stroke have high blood pressure at onset, which might improve with bed rest.¹⁰⁹ Concern about perfusion pressure reduction to the critically vulnerable ischaemic penumbra has led to the practice of non-intervention unless systolic blood pressure is greater than 200 mm Hg or diastolic blood pressure is greater than 120 mm Hg. A similarly conservative approach holds for treatment of primary intracerebral haemorrhage, although the recorded blood pressure is generally higher than for ischaemic stroke, and some guidelines suggest aggressive blood pressure control.¹¹⁰

Improved evidence for the optimum management of blood pressure after stroke should come from trials that are presently in progress: the efficacy of nitric oxide in stroke (ENOS) trial for the study of blood pressure reduction with a nitroglycerin patch in patients with ischaemic or haemorrhagic stroke⁶⁶ and the intensive blood pressure reduction in acute cerebral haemorrhage (INTERACT) trial for the study of intravenous blood pressure reduction in patients with haemorrhagic stroke.¹¹¹ Evidence to support the view that the risk of delayed cerebral ischaemia in patients with subarachnoid haemorrhage is reduced by the maintenance of blood pressure and blood volume (triple-H therapy) is insufficient.¹¹²

Use of drugs that interfere with the pathophysiological cascades that cause much of the brain injury in stroke is an appealing idea because of the potential for low-toxic effects, ease of administration, and for early administration in an ambulance setting. However, translation of therapeutic interventions from animal models to clinical practice is very difficult,^{113,114} despite the biological plausibility of attenuation of the ischaemic cascade and substantial evidence that various classes of neuroprotectants reduce infarct volumes and improve neurological outcomes in models of focal cerebral ischaemia.^{33,106} The spin trap agent disulfenon sodium (NXY-059), for which there was substantial evidence for effectiveness in animals,¹¹⁵ showed a modest reduction in disability in a phase III study (stroke-acute ischemic NXY-059 treatment [SAINT] I) of about 1700 patients;⁵⁷ however, a second study (SAINT II)¹¹⁶ with a sample size larger than 1700 patients showed no efficacy, suggesting that SAINT I was falsely positive.

Repeated failures of translational research in neuroprotection show the need for a new approach based on a consensus of opinions of academic and industry leaders.¹⁰⁶ Evidence that neuroprotectants work in human brain tissue is absent. Any continued translational research in neuroprotection should include a rigorous experimental technique in animals, and should then confirm neuroprotection in cell cultures of human brain tissue or brain slices exposed to the effects of hypoxia or glucose deprivation, or both.¹¹⁷ The next logical step would be to show that the putative neuroprotectants reach their

therapeutic target—ie, the ischaemic penumbra—with PET or single-photon-emission CT.¹¹⁸ A proof-of-principle approach, perhaps with a preloading dose of neuroprotectant in high-risk patients (such as early after TIA or minor stroke, or those undergoing cardiac surgery, carotid endarterectomy, or angioplasty), would provide reassurance that the compound was effective in people.^{28,119,120} Phase II trials to study treatment effects on ischaemic lesion formation should only begin after identification of a proof-of-principle approach and should include patients with penumbra confirmed by use of imaging techniques, and then phase III trials with a clinical endpoint should be done.^{121,122}

Prevention

Primary prevention

The steadily reducing mortality from stroke is largely attributable to improved control of risk factors,¹²³ especially for hypertension, in which waves of blood-pressure-lowering agents, each more effective than the previous one, have permeated western societies from the 1950s onward.¹²⁴ Modification of other risk factors such as socioeconomic status, cholesterol, diabetes, atrial fibrillation, and reduction in smoking rates might also have had some effect.^{10,125} Level I evidence for the treatment of hypertension in patients without previous stroke or TIA suggests the use of warfarin for patients with atrial fibrillation, lipid reduction with statins in patients with pre-existing ischaemic heart disease, and use of aspirin in women 45 years or older but not men.^{126–130} Implementation of stroke prevention strategies is urgently needed in developing countries because these countries account for about two-thirds of nearly 5 million stroke-induced deaths per year.¹

Secondary prevention

The prevention of recurrent stroke has been one of the major therapeutic advances in stroke management in the past 30 years. In 1977, there was no proven secondary prevention strategy for stroke. Aspirin was introduced in 1978,⁵⁸ aspirin plus dipyridamole in 1987,¹³¹ warfarin for patients with atrial fibrillation in 1993,¹³² carotid endarterectomy for symptomatic carotid-artery stenosis of greater than 70% in 1991,^{62,63} clopidogrel in 1996,⁶⁰ blood pressure reduction with perindopril and indapamide or ramipril in 2001,^{64,133} and cholesterol reduction with atorvastatin in 2006.⁶⁵ Hence, a formidable array of secondary prevention strategies is now available, with most patients qualifying for at least one, and many for up to three or more interventions at hospital discharge.

Antiplatelet agents

The various antiplatelet agents assessed in clinical trials for secondary stroke prevention provide about 22% (SE 4) reduction in relative risk (RR) of further vascular events.¹³⁴ For patients with TIA or minor stroke, the RR reduction

with aspirin alone (at any dose) might be as low as 13% (95% CI 4.0–21.0), but this protection is almost doubled by the addition of extended-release dipyridamole.^{59,135,136} Clopidogrel monotherapy is slightly better than aspirin monotherapy (RR reduction 8.7%, 0.3–16.5) and possibly more effective than aspirin against vascular disease affecting the heart and the peripheral circulation; however, the absolute improvement in outcome is small and needs 108 patients to be treated in 2 years to prevent one major vascular event (stroke, myocardial infarction, or vascular death).⁶⁰ A reasonable consideration is combination treatment with aspirin plus extended-release dipyridamole as the standard treatment, with clopidogrel used when there is aspirin allergy or concurrent symptomatic coronary artery disease, and aspirin monotherapy used when cost considerations are paramount. Combination treatment with aspirin plus clopidogrel is associated with increased risk of major bleeding that is not offset, at least in unselected patients, by improved effectiveness.^{137,138} Treatment with GPIIb/IIIa antagonists is associated with increased mortality.¹³⁹ A ceiling effect to the beneficial effects of platelet inhibition might exist, beyond which adverse effects, predominantly major haemorrhage, offset any additional effectiveness.^{137–140}

Anticoagulants

Warfarin remains one of the most biologically effective secondary prevention strategies for patients with atrial fibrillation and reduces RR of recurrent stroke in patients with TIA or minor stroke by about 70% (hazard ratio 0.34, 95% CI 0.20–0.57).⁶¹ This effect of warfarin is partly offset by a small risk of major bleeding, especially intracerebral haemorrhage (0.3–0.6% per year), which rises with age, high blood pressure, use of warfarin in combination with antiplatelet agents, and increasing intensity of anticoagulation.¹⁴¹ Evidence suggests that the combination of warfarin and aspirin might also be associated with an increased risk of bleeding without evidence of benefit.¹⁴² In patients without atrial fibrillation, presenting with TIA or minor stroke, warfarin is not better than aspirin as a secondary prevention agent.¹⁴³

Carotid endarterectomy

In patients with TIA or minor stroke who have at least 70% stenosis of the symptomatic carotid artery, carotid endarterectomy is an effective secondary prevention strategy.^{62,63} Relative reduction in the risk of ipsilateral fatal or non-fatal stroke is about 60% during 3 years,¹⁴⁴ which should be balanced with a surgical risk of stroke or death, in expert hands, of around 5%.¹¹⁹ Importantly, the interval between TIA or stroke and endarterectomy is inversely proportional to the benefit, with uncertainty as to whether any benefit remains beyond 12 weeks.¹¹⁹

A relative reduction in the risk of stroke or death is also seen in patients with asymptomatic carotid stenosis.¹⁴⁵ However, because the absolute risk in these

patients is low, the absolute benefit is only 1% per year, set against an operative risk in patients with asymptomatic carotid stenosis of around 3%; the clinical usefulness of carotid endarterectomy is not clear. The strong epidemiological evidence of a direct association between blood pressure and stroke recurrence led to trials of blood pressure reduction in unselected patients (ie, including those without hypertension) following TIA or minor stroke.^{146,147} Results of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), which tested perindopril and indapamide, showed a reduction in recurrent stroke of around 30% during 5 years that was independent of baseline blood pressure.⁶⁴ This effect was broadly similar to that seen for ramipril in the Heart Outcomes Prevention Evaluation (HOPE) study in a subset of patients with cerebral vascular disease.^{133,148}

Although cholesterol is a weak risk factor for ischaemic stroke, evidence suggests that both fatal and non-fatal stroke is reduced in patients with coronary artery disease who are given statins.^{147,149,150} This effect seems to be independent of the baseline cholesterol concentration, which raises the possibility that efficacy might be caused by anti-inflammatory, rheological-plaque-stabilising, or neuroprotective attributes of statins.¹⁵⁰ The heart protection study (HPS)¹⁵¹ showed that treatment with simvastatin (40 mg) in patients with TIA or stroke led to reductions in the risk of cardiac events but not of recurrent stroke. The stroke prevention by aggressive reduction in cholesterol levels (SPARCL)⁶⁵ study showed that intensive cholesterol reduction (atorvastatin 80 mg) in patients with TIA or minor stroke and no history of ischaemic heart disease reduced the risk of both fatal and non-fatal stroke.

Surgical clipping of intracerebral aneurysms has been an established practice for the avoidance of recurrent haemorrhage after subarachnoid haemorrhage.²³ Endovascular approaches (coiling) have been compared with surgery, and have been shown to have improved clinical outcomes at 1 year and reduced complication rates at the expense of a small increase in the risk of late rebleeding.¹⁵²

Treatments under investigation

Carotid angioplasty with stenting, which is now generally combined with distal protection devices, is a minimally invasive procedure that will probably replace carotid endarterectomy as the treatment of choice in most patients. Initial trials suggested that the perioperative risks associated with the procedure are similar to carotid endarterectomy,^{153,154} but the risks might be increased in less skilled hands;¹²⁰ further randomised controlled trials are underway to explore the procedural risks and long-term effectiveness of stenting. In view of the complexities of warfarin use, simpler and safer alternatives would provide a major advance in stroke treatment. The direct-thrombin inhibitor ximelagatran

showed promise in early trials, but resulted in an unacceptably high frequency of liver enzyme abnormalities (about 6%);⁶⁷ other direct-thrombin inhibitors are being developed. Prevention of stroke recurrence by modification of risk factors such as blood sugar reduction in diabetics,¹⁵⁵ smoking cessation, reduced alcohol consumption (although moderate consumption can be protective), or increased exercise is not substantiated by evidence from clinical trials. However, on the basis of observational studies, which show many potential benefits, modest costs, and small risks of adverse effects, patients should be advised to stop smoking, to drink in moderation, to eat a well-balanced diet, and to exercise regularly.^{156–159}

Conclusions

Although there have been advances in our understanding of the epidemiology and pathophysiology of stroke during the past decade, the most striking changes have been in the increasing array of therapeutic interventions. The greatest advance is the recognition that SCU management reduces mortality and improves clinical outcomes. The importance of this finding is emphasised as networks of SCUs become established across many countries and form a framework for the propagation of knowledge of stroke management. Much of the translational research described in this seminar has taken place within such frameworks. However, despite the advances in management, stroke continues to pose major therapeutic challenges, both to neuroscientists and to clinicians, partly because of the low priority accorded to stroke research.

Effective introduction of many therapeutic strategies for stroke has served, paradoxically, to highlight a worldwide shortage of health-care professionals who are able to facilitate implementation of the strategies. This imbalance, especially in the developing world where the health-care burden during the coming decades is likely to be most keenly felt, needs to be urgently addressed.

Conflict of interest statement

We declare that we have no conflict of interest.

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