Ischaemic stroke

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Abstract | Stroke is the second highest cause of death globally and a leading cause of disability, with an increasing incidence in developing countries. Ischaemic stroke caused by arterial occlusion is responsible for the majority of strokes. Management focuses on rapid reperfusion with intravenous thrombolysis and endovascular thrombectomy, which both reduce disability but are time-critical. Accordingly, improving the system of care to reduce treatment delays is key to maximizing the benefits of reperfusion therapies. Intravenous thrombolysis reduces disability when administered within 4.5 h of the onset of stroke. Thrombolysis also benefits selected patients with evidence from perfusion imaging of salvageable brain tissue for up to 9 h and in patients who awake with stroke symptoms. Endovascular thrombectomy reduces disability in a broad group of patients with large vessel occlusion when performed within 6 h of stroke onset and in patients selected by perfusion imaging up to 24 h following stroke onset. Secondary prevention of ischaemic stroke shares many common elements with cardiovascular risk management in other fields, including blood pressure control, cholesterol management and antithrombotic medications. Other preventative interventions are tailored to the mechanism of stroke, such as anticoagulation for atrial fibrillation and carotid endarterectomy for severe symptomatic carotid artery stenosis.

Stroke is a leading cause of death and disability worldwide and can be broadly classified into ischaemic stroke and haemorrhagic stroke, the latter of which includes intracerebral haemorrhage and subarachnoid haemorrhage. Ischaemic stroke is defined as infarction of the brain, spinal cord or retina[1] and represents ~71% of all strokes globally[2]. Advances in brain imaging have shifted the definition of ischaemic stroke from a largely clinical determination to a tissue-based classification. Many transient events with full clinical recovery are now classed as stroke based on the identification of permanent tissue injury on MRI. Transient ischaemic attack (TIA) occurs when blood flow is temporarily interrupted and resolves before causing permanent injury. The pathogenesis is the same as ischaemic stroke, and the investigations for the underlying cause and the secondary prevention strategies are identical.

In the 1970s, pioneering experiments identified that much of the initial clinical deficit in patients with stroke is due to a hypoperfused, hibernating, electrically non-functional part of the brain termed the ischaemic penumbra[3]. This region progressively converts to irreversibly injured tissue over time (known as the ischaemic core), but at a rate that varies considerably between individuals. However, with rapid reperfusion, this penumbral brain can be salvaged and can recover normal function. This landmark discovery formed the rationale for the reperfusion therapies that have transformed outcomes for patients with ischaemic stroke since the first positive trial of stroke thrombolysis, published in 1995 (REF.[4]).

Current optimal management of patients with ischaemic stroke occurs in geographically defined stroke units with an experienced interdisciplinary team of physicians, nurses and allied health clinicians, using best-evidence stroke guidelines, which includes intravenous thrombolysis and/or endovascular thrombectomy[5]. Intravenous thrombolysis reduces disability when administered within 4.5 h of stroke onset (defined as the time from when the patient with a stroke was last known to be healthy)[6], although selected patients with favourable brain perfusion imaging benefit up to 9 h or after wake-up-onset stroke (that is, stroke symptoms upon waking that were not present before sleep)[7–9]. Endovascular thrombectomy (that is, mechanical clot retrieval via catheter angiography) reduces disability in a broad group of patients with large vessel occlusion when performed within 6 h of the time the patient with a stroke was last known to be healthy[10] and, in patients selected using brain perfusion imaging, up to 24 h after stroke onset[11,12]. However, both intravenous thrombolysis and endovascular thrombectomy are time-critical[6,13], and health system engineering to accelerate treatment remains one of the key challenges to maximizing the benefits of these therapies.

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https://doi.org/10.1038/s41572-019-0118-8

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This Primer describes the epidemiology, pathophysiology and diagnosis of ischaemic stroke and TIA. The acute reperfusion therapies are discussed in detail. Secondary prevention of ischaemic stroke is also discussed, and shares many common elements with cardiovascular risk management in other fields, but distinct differences exist and the prevention strategy must be tailored to the mechanism of stroke.

Epidemiology

Stroke (including ischaemic stroke and haemorrhagic stroke) affects 13.7 million people globally per year and is the second leading cause of death, with 5.5 million deaths per year[14,15]. An estimated 1 in 4 adults will experience a stroke in their lifetime and there are >80 million survivors of stroke globally[2,15]. These stroke survivors represent a high-risk population and are the focus of secondary prevention strategies.

The incidence and prevalence of ischaemic stroke has evolved over time. In 2016, the global incidence of ischaemic stroke events was 9.5 million[2,14]. In 2017, there were 2.7 million deaths due to ischaemic stroke[16] (FIG. 1). The global incidence, mortality and disability-adjusted life years for ischaemic stroke decreased over the 1990–2013 period[17]. Conversely, the prevalence of ischaemic stroke increased from 1990 to 2005, then decreased from 2005 to 2013 (REF.[17]), ultimately leading to a slight, although not statistically significant, increase in the worldwide prevalence from 1990 to 2013 (REF.[17]). Possible reasons for the changing prevalence include reductions in stroke mortality, improved secondary prevention and better detection of stroke.

Interestingly, trends in the epidemiology of ischaemic stroke from 1990 to 2010 vary according to the level of a country's income. For example, the incidence, mortality, disability-adjusted life years and mortality-to-incidence ratio decreased in high-income countries, although no significant differences were observed in low-income and middle-income countries over this time frame[18]. These disparities could be due to differences in population age demographics, life expectancy, health status and standards of health-care provision.

Risk factors

Non-modifiable risk factors for ischaemic stroke include age, sex and genetic factors. The influence of age on the risk of ischaemic stroke differs by the development status of a country; for example, steeper increases in incidence after 49 years of age and prevalence after 39 years of age have been observed in developed countries compared with developing countries[17]. In those between 20 and 64 years of age, the prevalence of ischaemic stroke has nearly doubled globally from 1990 to 2013, with an increase of 37.3% in associated disability-adjusted life years[19]. The incidence of ischaemic stroke was higher in men (133 cases per 100,000 person-years) than in women (99 cases per 100,000 person-years) in the 2013 Global Burden of Disease Study[20]. Although some monogenic causes of ischaemic stroke have been identified, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), most cases are sporadic. The estimated heritability of ischaemic stroke is 37.9% when calculated using genome-wide complex trait analysis[21].

Several modifiable risk factors for ischaemic stroke have been identified. In the INTERSTROKE study, 10 factors accounted for 91.5% of the population-attributable risk for ischaemic stroke worldwide and were consistently associated with ischaemic stroke across geographical regions, sex and age groups[22]. These factors were a history of hypertension or a blood pressure of ≥160/90 mmHg, low levels of regular physical activity, a high apolipoprotein B (ApoB)-to-ApoA1 ratio, diet, a high waist-to-hip ratio, psychosocial stress and depression, smoking, cardiac causes (such as atrial fibrillation and previous myocardial infarction), high alcohol consumption and diabetes mellitus. Of these factors, self-reported hypertension or a blood pressure of >160/90 mmHg carried the strongest risk (OR 3.14, 99% CI 2.67–3.71) and a population-attributable risk of 45.2% (99% CI 40.3–50.0%)[22].

Other potential risk factors include sleep apnoea, chronic inflammation, periodontal disease and chronic kidney disease[23]. In addition, some studies have demonstrated associations between transient increases in stroke incidence and exposure to air pollution[24].

Mechanisms/pathophysiology

Most ischaemic strokes are thromboembolic in origin, with common sources of embolism being large artery atherosclerosis and cardiac diseases, particularly atrial fibrillation. Other causes of ischaemic stroke include small vessel disease, which is associated with elevated blood pressure and diabetes mellitus and is particularly common in Asia. Less common overall, but proportionally more prevalent in younger patients, are arterial dissection, vasculitis, patent foramen ovale (PFO) with paradoxical embolism (that is, whereby venous thrombi enter the systemic and cerebral circulation) and haematological disorders (FIG. 2; TABLE 1). The cause of ischaemic stroke is important as it can guide therapeutic strategies for the prevention of recurrent stroke.

Arterial causes of stroke

Atherosclerosis. One common cause of ischaemic stroke is an embolus in the cerebral vasculature (FIG. 3) that originated from an ulcerated and typically stenotic atherosclerotic plaque in the aortic arch, neck or intracranial vessels. In patients with atherosclerosis, thrombi

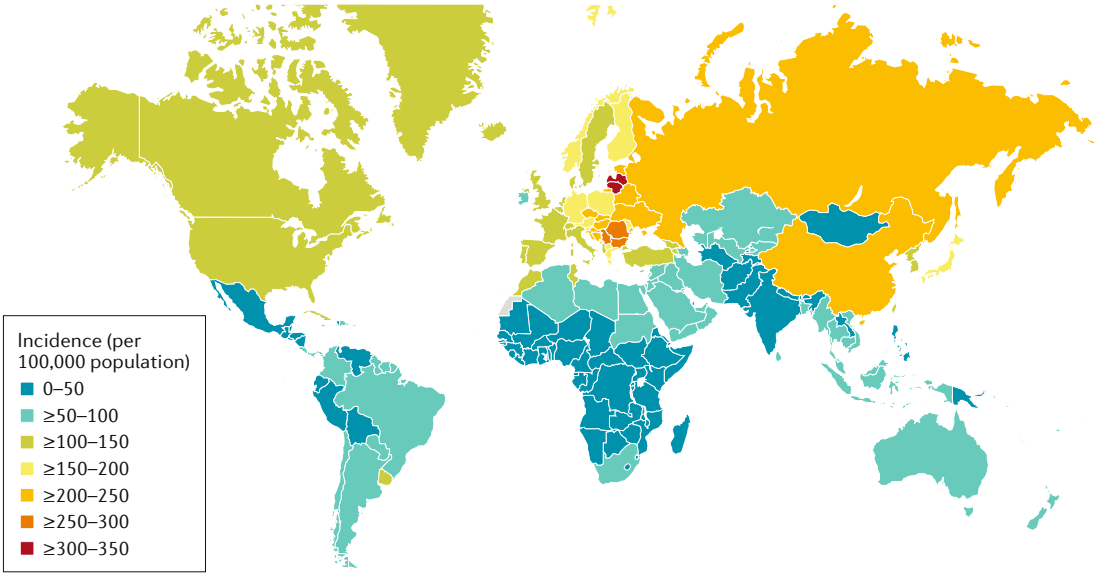

Fig. 1 | **Epidemiology of ischaemic stroke.** The global distribution of ischaemic stroke incidence by country. Data from the Global Burden of Disease Study 2017.

can form when the lipid core of atherosclerotic plaques is exposed to the bloodstream, which can be caused by inflammation and ulceration of the fibrous cap of plaques. These thrombi can occlude the atherosclerotic vessel or, more commonly in the large vessels relevant to stroke, can embolize distally.

In western populations, the most frequent location of atherosclerotic plaques that can cause ischaemic stroke is the internal carotid artery, just after its bifurcation from the common carotid artery. This is hypothesized to relate to reduced shear stress on the arterial wall at that site. Low shear stress is associated with intimal thickening and reduced nitric oxide release that are thought to mediate this susceptibility to cholesterol plaque development[25]. Although intracranial atherosclerosis is sometimes observed in patients in western countries, usually in heavy smokers and individuals with diabetes mellitus[26], it is much more common in Asia[27]. Indeed, intracranial atherosclerosis is reported to cause ~30–50% of ischaemic strokes in Asian patients compared with 5–10% of strokes in white patients[28]. This disorder presents a challenge for standard thrombectomy, as it is associated with higher reocclusion rates after thrombectomy and has an increased requirement for stenting, the latter carrying a greater risk of complications, particularly bleeding related to the use of antiplatelet medications to maintain stent patency[29].

Small vessel disease. As the name suggests, small vessel disease affects the smaller arteries and arterioles of the brain. Small vessel disease can manifest in several ways, including lacunar stroke, leukoaraiosis (white matter changes that can be observed as T2-hyperintensities on MRI or hypodensities on CT), cerebral microbleeds and intracerebral haemorrhage. Deep subcortical and brainstem structures are supplied by small-calibre perforating arteries that arise from much larger arteries of the circle of Willis, exposing the small vessels to high pressure that could predispose to lipohyalinosis (narrowing of the small cerebral vessels). Lipohyalinosis is not the only cause of small subcortical infarcts, and traditional clinical patterns defined as lacunar syndromes have limited specificity for small vessel disease-related stroke. Atherosclerosis of the parent artery with occlusion of the perforating vessel origin is another important mechanism of lacunar clinical syndromes[30]. In rare cases, monogenic disorders can cause small vessel disease, for example, CADASIL, which typically presents with migraine followed by lacunar infarcts and then dementia.

Arterial dissection. A dissection or tear in the intimal layer of an artery with intramural thrombus is an important cause of stroke, particularly in younger patients. Most dissections that cause ischaemic stroke are in the extracranial carotid and vertebral arteries and can occlude the artery at the site of dissection or cause thrombus formation and distal embolism. Although varying degrees of cervical trauma can cause dissection, it is often quite minor; for some individuals, forceful coughing or sneezing may be sufficient to cause dissection. Furthermore, dissections are often spontaneous. Some collagen and connective tissue diseases can predispose to arterial dissections, although, aside from fibromuscular dysplasia and Ehlers–Danlos syndrome, these disorders are rarely identifiable with currently available tests and limited genetic contributions to dissection risk have been discovered to date[31]. As a result, testing for an underlying connective tissue disorder is not routine.

Cerebral vasculitis. Vasculitis of the cerebral arteries is rare but can occur as a primary central nervous system (CNS) angiitis or as a manifestation of a systemic vasculitis. In these conditions, vessel wall inflammation can lead to luminal narrowing and thromboembolism causing ischaemic stroke (and sometimes intracerebral haemorrhage).

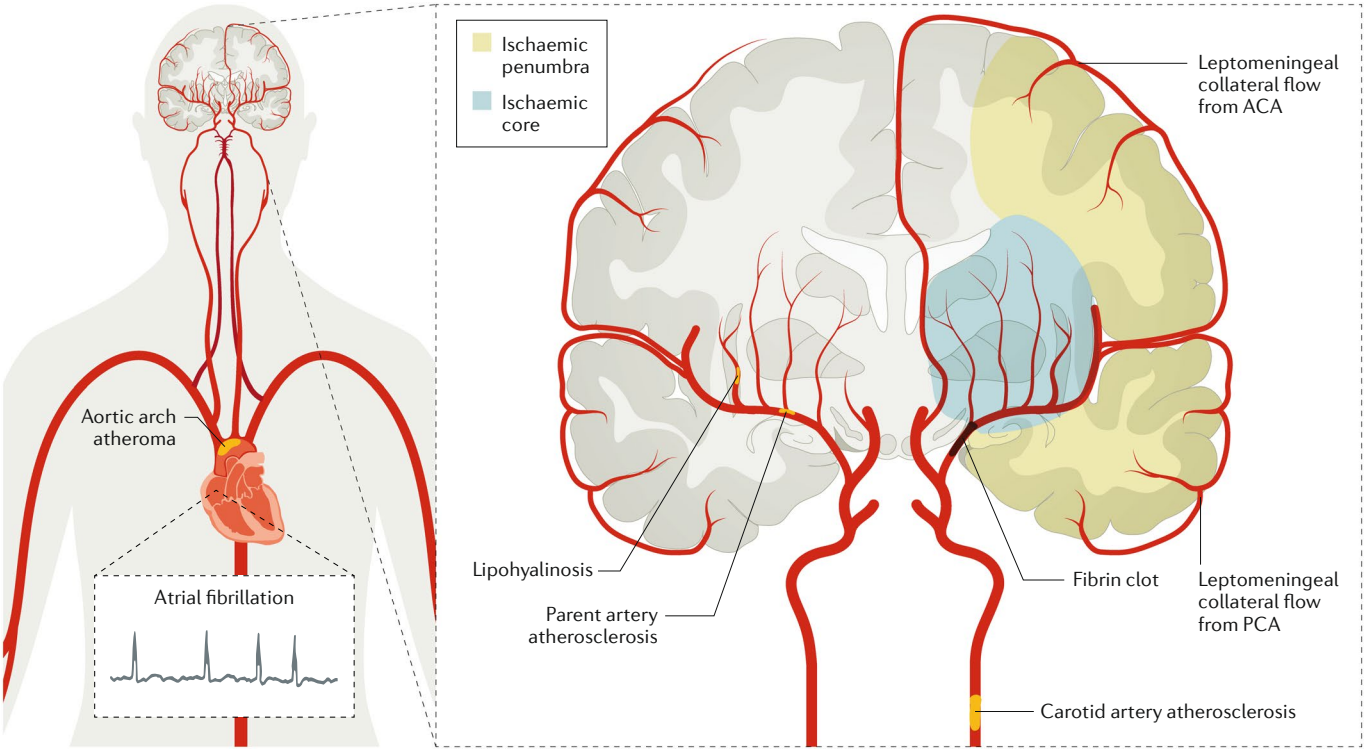

Fig. 2 | **Ischaemic stroke mechanisms.** The heart and cerebrovascular tree illustrating cardioembolic stroke from the left atrial appendage in atrial fibrillation, carotid artery atherosclerosis and small vessel disease due to lipohyalinosis and parent vessel atherosclerosis. When a thrombus occludes the middle cerebral artery distal to the circle of Willis (that is, the circulatory anastomosis that supplies blood to the brain and surrounding structures), leptomeningeal anastomoses with anterior cerebral artery (ACA) and posterior cerebral artery (PCA) branches will supply retrograde blood flow to a variable proportion of the middle cerebral artery territory. This collateral flow might be sufficient to sustain metabolic viability but not electrical activity in the ischaemic penumbra. The penumbra will contribute to the clinical deficit, but this is reversible with rapid reperfusion. Regions without adequate collateral blood flow will become irreversibly injured, termed the ischaemic core, and the extent of irreversible injury expands with time.

Reversible cerebral vasoconstriction syndrome. Reversible cerebral vasoconstriction syndrome presents with recurrent thunderclap (abrupt onset) headaches and can cause ischaemic stroke, intracerebral haemorrhage or focal subarachnoid haemorrhage through vasospasm and vascular dysregulation. The precise aetiology is unknown and vasospasm might not be present on the initial arterial imaging[32]. This is a separate entity to the vasospasm that occurs after aneurysmal subarachnoid haemorrhage that can also cause ischaemic stroke.

Cardiac causes of stroke

Atrial fibrillation. Atrial fibrillation and flutter allow blood to stagnate, particularly in the left atrial appendage, which can allow thrombosis and subsequent embolism to the cerebral or systemic circulation. Both permanent and paroxysmal atrial fibrillation increase the risk of cardioembolic ischaemic stroke[33].

The prevalence of atrial fibrillation is increasing with an ageing and increasingly obese population[34]. Other risk factors for atrial fibrillation include chronic hypertension, ischaemic heart disease, valvular disease, diabetes mellitus, hyperthyroidism, excessive alcohol consumption and obstructive sleep apnoea[35]. The risk of ischaemic stroke in patients with atrial fibrillation can be estimated using the CHA2DS2-VASc score, which takes into account age, history of stroke, sex, diabetes mellitus, hypertension, heart failure and vascular disease, and can be used to indicate patients who should be considered for prophylactic anticoagulation[36].

Patent foramen ovale. In utero, the cardiac foramen ovale allows the flow of placental oxygenated blood from the right to the left atrium. After birth, the increase in pressure in the left side of the heart closes the flap in most people but ~25% of individuals have a degree of residual patency (that is, a PFO)[37]. This patency creates a potential mechanism for paradoxical embolism, which could lead to ischaemic stroke. The importance of PFO in young adult stroke has been highlighted by the significant reduction in risk of recurrent ischaemic stroke after endovascular closure of PFO[38–40]. Various risk factors have been proposed to indicate a higher risk of stroke in individuals with PFO, including the extent of shunting and an aneurysmal (that is, hypermobile) interatrial septum.

Infective endocarditis. Bacterial endocarditis can cause septic emboli in the brain, leading to ischaemic stroke. In addition to the increased risk of stroke, bacterial endocarditis presents difficulties for stroke treatment as it is associated with an increased risk of haemorrhagic

transformation after thrombolysis owing to septic arteritis that weakens vessel walls[41]. Surveillance for mycotic aneurysms (infected aneurysms) should be considered, as they can occur after endocarditis and can rupture, causing subarachnoid or intracerebral haemorrhage.

Hypokinetic segment with mural thrombus. Regions of segmental hypokinesis within the heart can occur following myocardial infarction, which can predispose to cardioembolic stroke. In these cases, the hypokinesis can allow the formation of mural thrombi (that is, thrombi attached to the wall of a vessel or the heart) that can embolize and cause ischaemic stroke[42]. Severely reduced ejection fraction (the percentage of blood pumped from the ventricles each time the heart contracts) in individuals with dilated cardiomyopathy is also a risk for cardioembolic ischaemic stroke, as is the rare Takotsubo cardiomyopathy due to sympathetic overload[43].

Haematological disorders. Haematological disorders are a rare but important cause of ischaemic stroke[44]. They are a more common cause of clotting in the cerebral veins, termed cerebral venous thrombosis. Essential thrombocytosis (via increased platelet count), polycythaemia vera (via increased red blood cell count and blood viscosity) and antiphospholipid syndrome (via a procoagulant state) are three of the more common haematological conditions that predispose to thrombus formation. Stroke can be the presenting feature of these disorders (TABLE 1). In addition, sickle cell anaemia can cause stroke[45] and is an important cause of paediatric stroke in individuals of African descent.

Stroke pathophysiology

Collateral blood flow. When an intracranial artery is occluded, alternative blood flow pathways (called collaterals) can sustain viability in the penumbral brain regions for a period of time. The extent of collateral flow

Table 1 | **The cause of stroke determines the strategy for prevention of recurrent stroke**

Aetiology	Investigation	Secondary stroke prevention strategy
Atherosclerosis (for example, artery-to-artery embolism and intracranial atherosclerosis)	• CT angiography • Magnetic resonance angiography • Carotid Doppler ultrasonography	• Antiplatelet therapy • Blood-pressure-lowering medication • High-potency statin • Carotid endarterectomy or stent for >50% symptomatic carotid stenosis
Cardioembolism (caused by, for example, atrial fibrillation, left ventricular akinetic segment, infective endocarditis, patent foramen ovale and cardiac tumours)	• Holter/loop recorder • Echocardiography	• Anticoagulation therapy • Left atrial appendage occlusion • Antibiotics • Percutaneous closure
Small vessel disease	• Brain MRI	• Antiplatelet therapy • Blood-pressure-lowering medication • High-potency statin
Arterial dissection	• CT angiography • Magnetic resonance angiography • T1 fat saturated neck MRI	• Antiplatelet therapy • Anticoagulation therapy
Cerebral vasculitis	• CT angiography • Magnetic resonance angiography • Catheter angiography • Cerebrospinal fluid examination • Brain and leptomeningeal biopsy	• High-dose steroids • Cyclophosphamide
Reversible cerebral vasoconstriction syndrome	• CT angiography • Magnetic resonance angiography • Catheter angiography	• Calcium channel antagonists • Avoidance of corticosteroids
Moyamoya disease	• CT angiography • Magnetic resonance angiography • Catheter angiography	• Conservative or revascularization (for example, superficial temporal to middle cerebral artery bypass)
Fabry disease	• MRI • Blood spot enzyme test	• Enzyme replacement
Antiphospholipid syndrome	• Lupus inhibitor assay • Anti-cardiolipin IgG assay • Anti β_2-glycoprotein antibody assay	• Anticoagulation therapy
Sickle cell anaemia	• Blood film • Haemoglobin electrophoresis	• Transfusion
Polycythaemia vera	• Haemoglobin measurement • Haematocrit measurement • *JAK2* mutation status	• Venesection • Aspirin • Cytoreduction therapy
Essential thrombocytosis	• Platelet count • *JAK2* mutation status	• Aspirin • Cytoreduction therapy

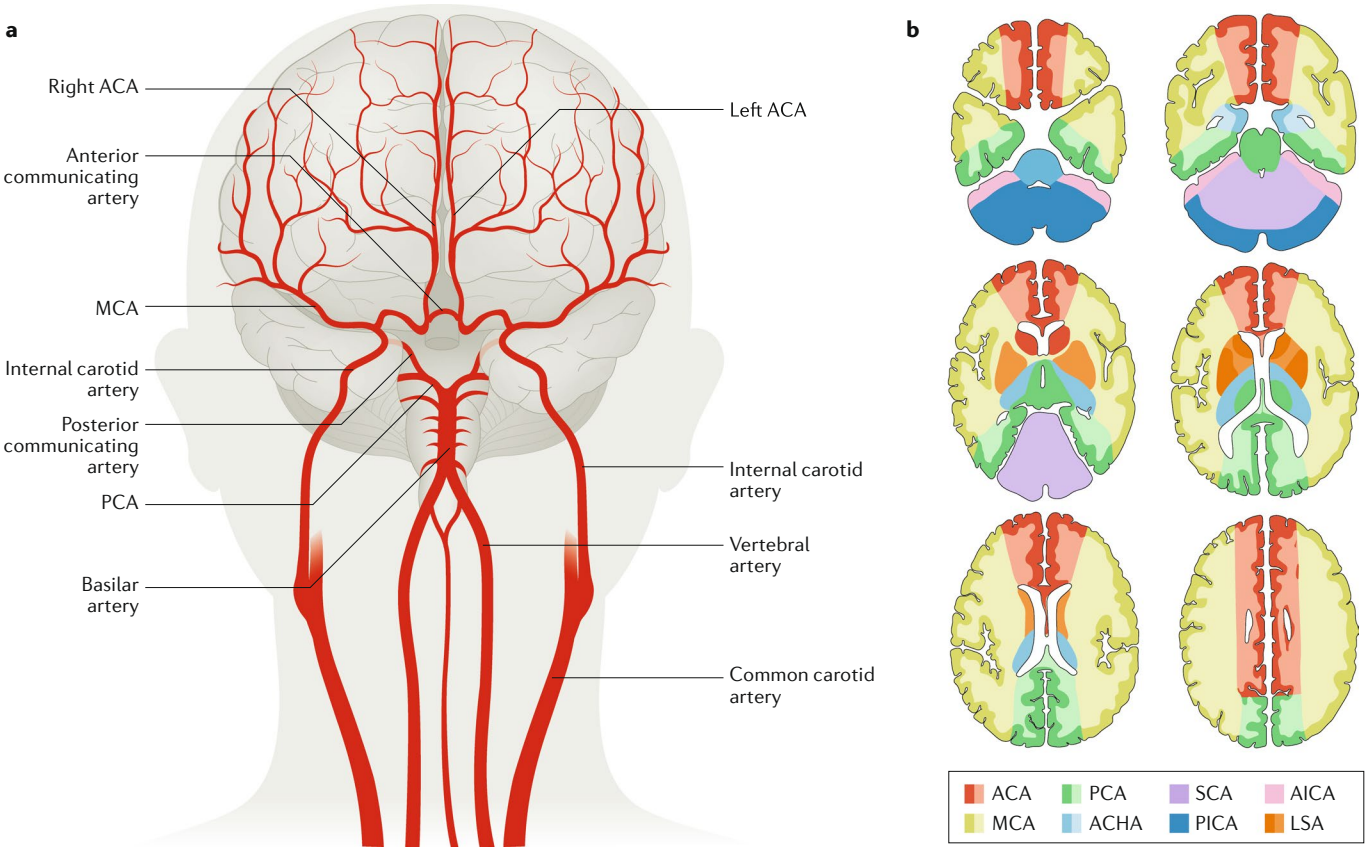

Fig. 3 | **Cerebral vasculature.** The major arteries of the brain (part **a**) and their vascular territories (part **b**). Although simplified here for illustrative purposes, an ischaemic stroke in one of these vessels could cause tissue damage in the regions highlighted. ACA, anterior cerebral artery; ACHA, anterior choroidal artery; AICA, anterior inferior cerebellar artery; LSA, lenticulostriate artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery. Part **b** adapted from REF.[197], Springer Nature Limited.

varies substantially between individuals and probably has both genetic and environmental determinants[46]. In addition, the extent of collateral flow can vary over time within the same individual[47].

The circle of Willis is one potential source of collateral flow, but it is often incomplete and occlusions are common downstream, limiting its capacity for compensatory flow. The most clinically relevant source of collateral blood flow in most patients is via leptomeningeal anastomoses. Collateral blood flow can be imaged using CT, magnetic resonance perfusion imaging or catheter angiography, and patients with good collateral blood flow have slower progression of infarct growth, allowing a benefit from reperfusion therapies in delayed time windows[48]. By contrast, poor collateral blood flow leads to rapid progression of infarction and limited response to reperfusion therapies.

Ischaemic cascade and reperfusion injury. The cellular consequences of reduced cerebral perfusion in laboratory animals are well understood[49] (FIG. 4) and have generated models of stroke pathology that are largely supported by human, in vitro, neuroimaging and post-mortem studies. However, substantial differences in brain structure, coagulation system and functional complexity between rodents and humans leave open the possibility that different pathophysiological processes have different relative contributions to human disease than in animal models. In addition, human stroke could involve additional processes that are not present in animal models.

Despite the identification of many potential target pathways and the demonstration that treatments targeting these pathways have efficacy in animal models of ischaemic stroke[50], success in resulting clinical trials has remained elusive. Several reasons could explain this failure of translation, such as an overstated efficacy in animal models, suboptimal circumstances for human studies (for instance, the drug may be unable to reach its site of action in sufficient concentration) or that animal studies might not recapitulate human disease with sufficient fidelity to be a useful guide to treatment. All of these factors could have a role in the failure of stroke trials. Thus, the failure of a clinical trial targeting a presumed pathophysiological mechanism does not, in itself, refute the importance of that mechanism in human disease.

Ischaemic stroke leads to oxygen depletion in the brain, which has several cellular and molecular consequences that affect neuronal and glial function in addition to vascular alterations and inflammation. Neuronal function relies on the continuous availability of ATP (which in turn requires a continuous supply

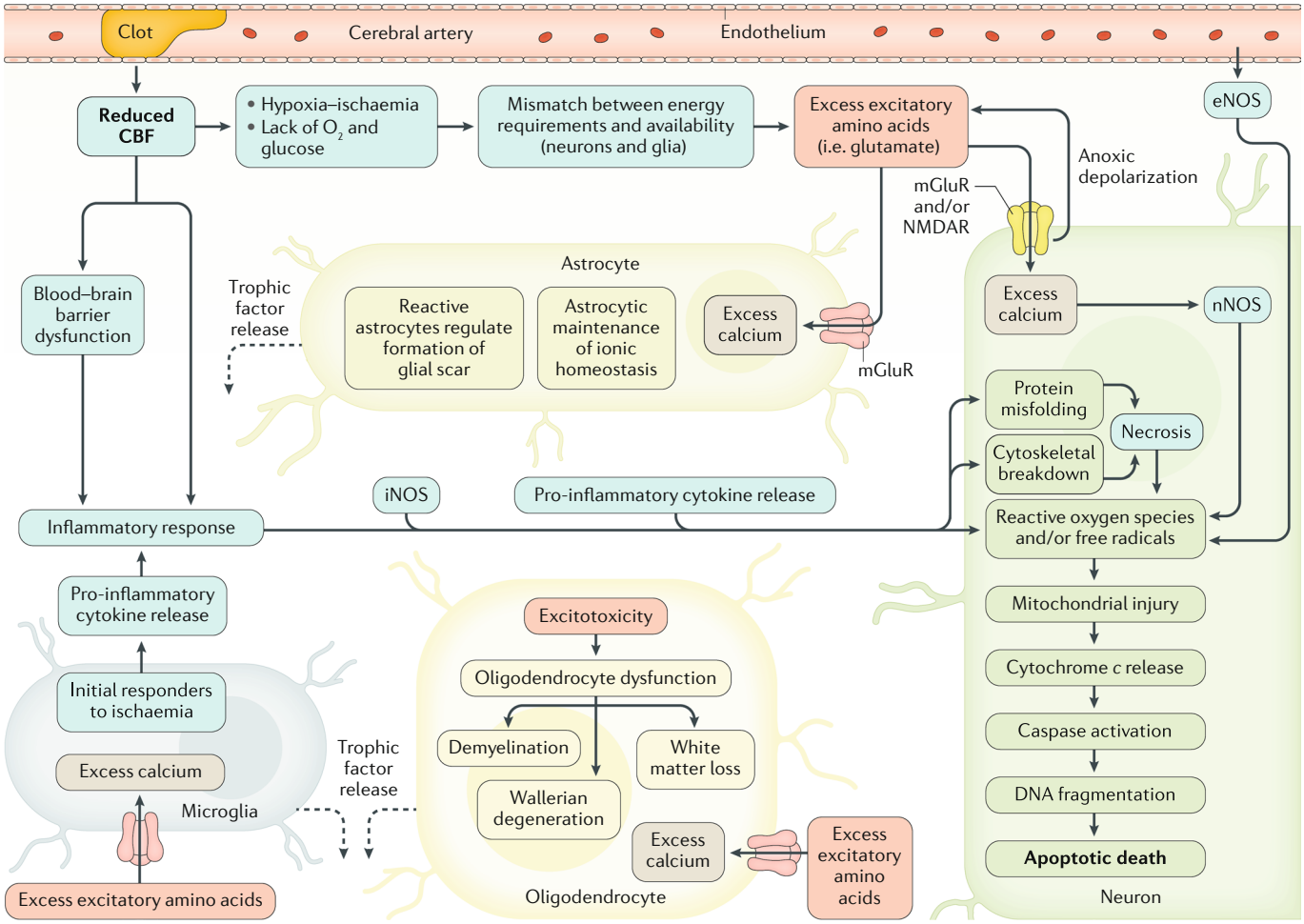

Fig. 4 | **Cellular effects of ischaemia.** Occlusion of a cerebral artery initiates a cascade of responses. Reduced cerebral blood flow (CBF) leads to reduced availability of glucose and oxygen and a mismatch in energy requirements and availability in neurons, glia and endothelial cells. Anoxic depolarization and reduced activity of glutamate reuptake leads to increased extracellular levels of glutamate. This leads to neuronal calcium influx (through the *N*-methyl-D-aspartate (NMDA) ion receptor (NMDAR)) and release of calcium from intracellular stores in neurons and glia (mediated via metabotropic glutamate receptors (mGluRs)). Blood–brain barrier dysfunction and release of signalling molecules (for example, cytokines) from astrocytes, microglia and oligodendrocytes lead to an inflammatory response. In neurons, the cumulative effect is cell death mediated through diverse pathways including necrosis and apoptosis. eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; nNOS, neuronal nitric oxide synthase. Adapted with permission from REF.[198], Elsevier.

of oxygen and glucose to the brain). When this supply is interrupted, as in stroke, neurons can no longer maintain their transmembrane gradient, leading to the impairment of neuronal signalling. In addition, anoxic depolarization (that is, sudden, progressive neuronal depolarization during states of inadequate blood supply to the brain) at presynaptic terminals leads to neurotransmitter release[51]. The clearing of excitatory neurotransmitters from the synaptic cleft is an active, energy-dependent process; thus, neurotransmitter concentrations (including glutamate) increase during ischaemic stroke.

Particular properties of the *N*-methyl-D-aspartate (NMDA) receptor cause additional problems. At typical resting membrane potentials, conductance through the open NMDA receptor is limited as the channel is blocked by extracellular magnesium. However, upon depolarization, the magnesium is removed and conduction is substantially higher[52], leading to calcium influx and the secondary release of large amounts of calcium from intracellular stores[53,54]. The resulting increased intracellular calcium concentration leads to the activation of several calcium-dependent processes such as the activation of neuronal nitric oxide synthase with consequent free radical production[55], and the initiation of cell death processes including apoptosis, necrosis, necroptosis and autophagy. Degeneration of distant nerve fibres (that is, Wallerian degeneration) in tracts that serve the infarcted brain (such as the corticospinal tract for motor weakness) occurs in animal models[56] and can be detected using diffusion tensor imaging in humans, in whom changes in early fractional anisotropy predict long-term clinical outcome[57]. These systems are well defined in rodent models of stroke, and interfering with NMDA signalling[58], neuronal nitric oxide synthase activity[59] and p53 activation following DNA damage[60]

provides powerful neuroprotection in cell culture and animal models. However, although drugs that inhibit these processes convey protection in animal models, they showed little efficacy in clinical trials[50]. This finding might reflect issues with the timing of treatment, drug concentration at the target site or the prominence of other pathophysiological processes in humans.

Spreading depolarization can occur in the healthy brain and following brain injury, and is defined as a rapid-onset, self-propagating wave of the near-complete breakdown of transmembrane ion gradients in neurons and astrocytes that spreads through grey matter[61]. In states of injury, spreading depolarization is often initiated in regions of anoxia but propagates to surrounding (less ischaemic) brain regions, whereby it increases the metabolic demand of the penumbral tissue and can lead to this tissue transitioning to infarction[62]. Although some evidence suggests that such spreading depolarization can have a preconditioning (protective) effect[63], the protective effects occur over days rather than minutes; therefore, in acute injury states, the deleterious effects of spreading depolarization are most prominent.

Throughout the CNS, neurons exist in a complex local environment with important contributions from other cell types including astrocytes, oligodendrocytes and pericytes, which are also affected in stroke. For example, activation of metabotropic glutamate receptor 5 by increased extracellular levels of glutamate leads to increased intracellular levels of calcium, reduced expression of glial glutamate transporters[64] and, therefore, to further increases in extracellular levels of glutamate. In addition, astrocytes become 'reactive', which can display pro-inflammatory (A1) or immunomodulatory (A2) phenotypes that are protective or harmful, respectively[65,66]. Reactive astrogliosis occurs 48–96 h after ischaemia, with cells expressing glial fibrillary acidic protein (an astrocyte marker) becoming hypertrophic and forming a glial scar that inhibits neuronal regeneration[67]. Neural axons in the CNS are supported by myelin sheaths formed from oligodendrocytes, with each oligodendrocyte supporting up to 50 axons. The fate of oligodendrocytes after stroke is not as well studied as the fate of astrocytes, but it has been suggested that the numbers of oligodendrocytes and oligodendrocyte progenitor cells are reduced in the ischaemic core (through processes similar to those involved in neuronal cell death)[68]. There is an increase in the number of oligodendrocyte progenitor cells in peri-infarct areas, which results in remyelination to control levels in peri-infarct areas after 2 weeks[69]. Pericytes are contractile cells that form an integral part of the blood–brain barrier and are activated following ischaemia, leading to capillary constriction. Pericyte death has also been reported, which could cause irreversible capillary constriction and breakdown of the blood–brain barrier[70]. The breakdown of this barrier could contribute to the ingress of peripheral inflammatory cells to the brain parenchyma and increased risk of haemorrhage when spontaneous or therapeutic reperfusion occurs.

Following ischaemia, neuronal ubiquitin is depleted, which may lead to a reduced clearance of oxidized proteins with subsequent formation of protein aggregates and endoplasmic reticulum stress[71]. Mitochondrial changes include increased cisternal calcium levels, protease activation, release of pro-apoptotic factors and free radicals, and decreased production of ATP[72].

Many patients with acute ischaemic stroke receive treatments to open the occluded blood vessel; however, large vessel reperfusion with no improvement — or sometimes worsening — of clinical status occurs in some patients. Numerous causes for this have been postulated, including distal capillary collapse following a period of no perfusion, responses of a damaged distal capillary endothelium to reperfusion and maladaptive responses of the neurovascular unit including breakdown of the blood–brain barrier, pericyte contraction and swelling of astrocytic endfeet[73].

Inflammation in rodent models of stroke is often characterized as an early activation of resident microglia, followed by an influx of macrophages and then neutrophil polymorphs and lymphocytes to the brain parenchyma[74]. Fewer data are available regarding the inflammatory response in humans, but it has been suggested that neutrophil accumulation in the ischaemic core, with activation and proliferation of microglia in the penumbra, occurs during the early stages of stroke (within the first 3 days). Later, both these brain-derived microglia and blood-derived macrophages adopt an amoeboid phagocytic phenotype and clear cellular debris[75]. Macrophages can manifest with predominantly pro-inflammatory or anti-inflammatory phenotypes; during the early stages of human stroke, macrophages, particularly in peri-infarct areas, express major histocompatibility complex class I molecules (involved with antigen presentation), NADPH oxidase (involved with free radical production) and inducible nitric oxide synthase[76] (a phenotype associated with increased phagocytosis)[77]. At later stages, the phenotype alters, with the expression of the mannose and haptoglobulin receptors (CD206 and CD163)[76] associated with reduced phagocytosis and reduced production of inflammatory cytokines such as interferon-γ and IL-1 (REF.[77]).

The therapeutic potential of manipulating the inflammatory response to stroke is not clear. Treatment with an IL-1 receptor antagonist appears to be protective in animal models[78], but other approaches, such as interfering with α4 integrin (CD49a) signalling using natalizumab, had no effect in a phase II clinical trial[79]. Interestingly, the animal data on which this trial was based showed variable results. However, one prospective multicentre animal study[80] demonstrated a reduction in infarct growth in a permanent distal middle cerebral artery occlusion model with natalizumab, but not in a temporary proximal occlusion model. A greater effect in the mice with small cortical infarcts was similar to a signal observed in the human trial. However, the variable effects on clinical outcomes were insufficient to justify a phase III trial.

Systemic effects. The immediate responses to a large ischaemic stroke include hypertension[81], arrhythmias including bradycardia[81,82] and pulmonary exudates[83,84], but whether these alterations are a direct result of brain injury or are secondary to other phenomena is unclear.

For instance, pulmonary oedema could be an indirect result of the cardiac consequences (myocardial 'stunning') of severe brain injury, and could contribute to secondary insult and injury by reducing the efficient perfusion of brain regions unaffected or only partially affected by the initial ischaemic insult. However, even small strokes can have systemic consequences. These include a systemic immune response[85], stress response (elevation of cortisol levels)[86], release of macrophages from the spleen[87] and stem cells from the bone marrow[88], and changes in gut permeability[89] and microbiota[90]. Although some of these adaptive changes might be at least initially beneficial, they can have negative effects. Thus, manipulation of the systemic response to stroke is a potential therapeutic target.

Mechanisms of recovery

The extent of recovery of behavioural function in animal models of stroke can be remarkable[49], and similar improvements can indeed be seen in young patients following stroke or traumatic brain injury. Much of this recovery is due to neuroplasticity (that is, the ability to leverage alternate pathways to replace those lost due to stroke). This plasticity might involve local sprouting, synaptogenesis or simply the strengthening of transmission at existing synapses. Importantly, this plasticity seems to come at some cost; it is very common for younger patients to experience very good physical recovery but be left with problems attending to simultaneous events and of fatigue[91]. Imaging studies suggest that to function normally they need to recruit much larger, more diffuse networks, and that this comes at a cost of effort and of the ability to deploy these networks in other tasks[92].

Endogenous stem cells contribute to neurogenesis in animal models of stroke, but the relative contribution of neurogenesis and neuroplasticity is not clear. Human post-mortem studies have shown the presence of endogenous stem cells in peri-infarct regions, suggesting a role for these cells in human stroke[93]. Most, if not all, of the beneficial effects of experimentally introduced exogenous stem cells observed in animal models[94–96] is probably mediated through the production of various trophic and supportive factors at the site of injury, and a subsequent alteration of the local environment to one more supportive of regeneration and repair, rather than to their direct integration into signalling pathways.

Diagnosis, screening and prevention

Diagnosis

The clinical presentation of stroke involves the sudden onset of a focal clinical deficit, referable to a specific site in the CNS. Symptoms can include hemiparesis, hemianaesthesia (numbness on one side of the body), aphasia (language disorder), homonymous hemianopia (loss of the same half of the visual field in each eye) and hemispatial inattention.

The diagnosis of stroke requires differentiation from common mimics including migraine, seizures, vestibular disturbances, metabolic disturbances and functional disorders, and is assisted by neuroimaging. In addition, ischaemic stroke needs to be differentiated from intracerebral haemorrhage. However, there is no clinical means to do this and brain imaging is the key to diagnosis. Globally, imaging usually involves CT, but MRI is the first-line imaging modality in a minority of centres worldwide. Rapid access to MRI is a common limitation, and some patients are unable to have an MRI due to metallic implants or agitation.

In addition to its use for diagnosis, brain imaging now has an important role in identifying patients with stroke who are likely to benefit from reperfusion therapies. Thrombolysis and thrombectomy have traditionally been tested within a limited time frame after the last known time the patient was healthy. This time-based approach has restricted treatment options for patients with stroke symptoms on waking or other delayed presentations, patients with aphasia who are unable to describe their symptom onset or those with inattention that makes them unaware of their deficit. However, advanced brain imaging can now be used to identify salvageable brain tissue in patients and to select those who are likely to benefit from reperfusion beyond traditional time windows[11,12].

Non-contrast CT. Non-contrast CT of the brain has close to 100% sensitivity for the detection of intraparenchymal and extra-axial (within the skull but outside the parenchyma) haemorrhage. Traditionally, a CT brain scan excluding haemorrhage in a patient with clinical signs of a stroke has formed the basis of thrombolysis treatment decision making. In some patients it is possible to make a positive diagnosis of stroke based on early ischaemic changes such as loss of grey matter–white matter differentiation (FIG. 5), which represents early ionic oedema in the irreversibly injured brain, or a hyperdense artery, which represents acute thrombus. However, these signs can be subtle, and loss of grey matter–white matter differentiation is difficult to detect in the first few hours after stroke onset[97].

CT angiography and perfusion. Intravenous injection of iodinated contrast agent can be used to assess the cerebral vasculature via either a static acquisition (CT angiography) or a time-resolved series (CT perfusion). CT angiography is highly accurate for the detection of arterial stenosis and occlusion, and, therefore, can diagnose ischaemic stroke and provide insights into the mechanism of stroke if atherosclerosis or arterial dissection are identified. CT angiography should be routinely acquired from the aortic arch to the cerebral vertex in all patients with ischaemic stroke to assess eligibility for endovascular thrombectomy if this treatment is an option on site or via a transfer elsewhere. In addition, CT angiography can be used to assess the extent of collateral flow, which provides additional prognostic information about the likely extent of tissue injury[98]. However, standard single-phase acquisitions are timed to coincide with peak arterial enhancement, which is too early to accurately characterize collateral blood flow that has a delayed arrival. CT angiography can, therefore, underestimate the extent of collaterals. If the quality of collateral blood flow is used to select patients who are suitable for thrombectomy, this underestimation could potentially exclude patients with late-arriving collateral

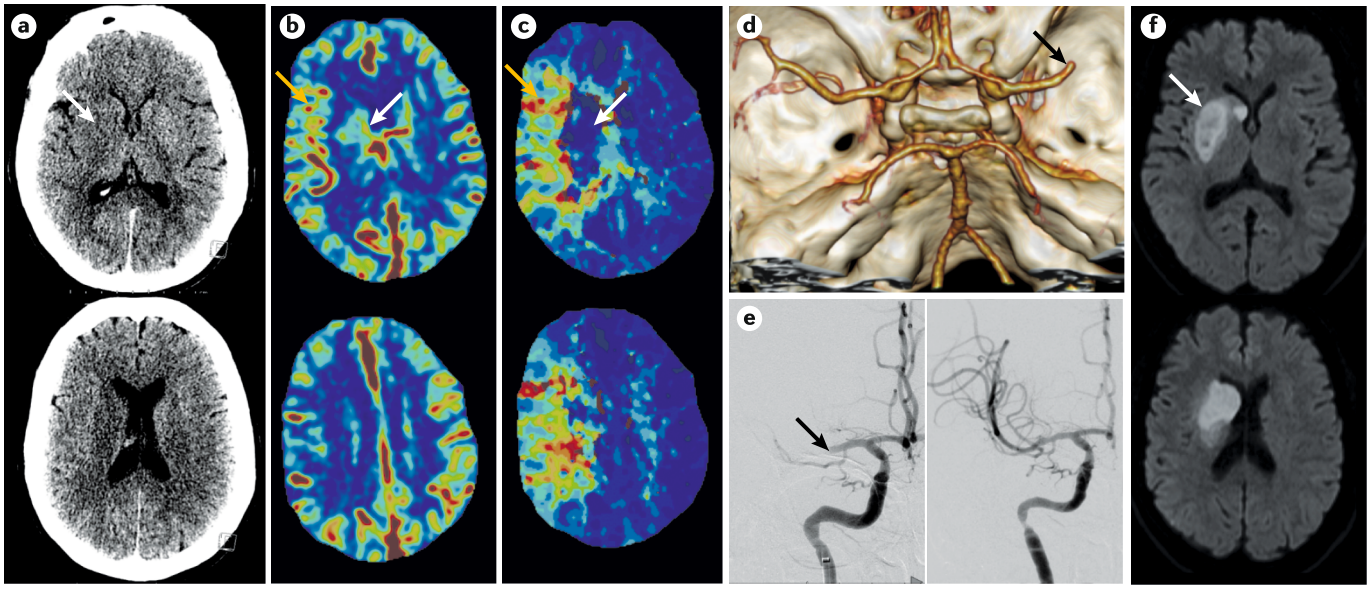

Fig. 5 | **Brain imaging to diagnose ischaemic stroke and identify salvageable brain tissue.** Imaging from a 66-year-old woman presenting with left hemiparesis, dysarthria and inattention 16 h after she was last seen to be healthy. Non-contrast CT (panel **a**) showing loss of grey–white differentiation in the right basal ganglia (white arrow) indicating proximal right middle cerebral artery occlusion at some stage. However, CT perfusion processed with RAPID (iSchemaView, Menlo Park, CA, USA) automated software (panels **b**,**c**) demonstrates reperfused basal ganglia (white arrows) with increased cerebral blood flow (panel **b**) indicating post-reperfusion hyperperfusion. In the right middle cerebral artery (MCA) territory (yellow arrows), time to maximum (T_{max}) (panel **c**) shows delayed arrival of contrast (retrograde via collateral vessels). The preservation of cerebral blood flow (panel **b**) within the region of delayed T_{max} indicates likely salvageable ischaemic penumbra. CT angiography (panel **d**) and digital subtraction catheter angiogram (panel **e**) confirm occlusion of the right MCA (at the distal M1 segment, black arrows). The patient had successful endovascular thrombectomy with reperfusion 2 h after the CT perfusion. MRI diffusion (panel **f**) the following day shows the expected infarct in the basal ganglia (white arrow) with salvage of the cortical regions. The patient recovered left-sided power and was discharged to inpatient rehabilitation.

blood flow that is adequate to maintain brain viability, and who could benefit from therapy.

CT perfusion characterizes the complete contrast bolus passage and can be processed to generate maps that indicate the degree of delay and regional reduction in blood flow within the brain (FIG. 5). Numerous automated software techniques are now available. Accordingly, CT perfusion is increasingly performed routinely as a diagnostic and prognostic tool that can also help to identify patients who could benefit from endovascular thrombectomy or thrombolysis beyond traditional time windows.

MRI. MRI offers multiple sequences that assess different structural and functional characteristics of brain tissue, including diffusion MRI, perfusion MRI and T2-based sequences. Diffusion MRI assesses the random motion of water molecules and is the most sensitive imaging modality for the detection of acute ischaemia. Diffusion is restricted in regions of cytotoxic oedema, where there is a shift in water distribution from extracellular to intracellular compartments. Diffusion MRI becomes abnormal within minutes of ischaemic stroke onset[99], and regions with diffusion restriction rarely return to an entirely normal radiological or histological appearance[100]. Over the next few hours, further blood–brain barrier injury leads to ionic and vasogenic oedema, which is visible on T2-based MRI sequences and non-contrast CT[101]. Time of flight magnetic resonance angiography uses signals from endogenous blood flow (without intravenous contrast) to visualize the arterial lumen, whereby susceptibility-weighted imaging is highly sensitive for bleeding. Perfusion MRI is similar to CT perfusion — an intravenous gadolinium contrast bolus is tracked through the cerebral circulation and images are processed to form maps of contrast arrival delay and blood flow. The mismatch between a small diffusion lesion and a larger perfusion lesion on MRI (or a severe clinical deficit) has also been used to identify patients who would benefit from reperfusion therapies beyond traditional time windows.

Primary prevention

Population-wide interventions, often through regulatory interventions (such as tobacco or sugar taxes), may have a major effect in reducing the incidence of stroke[102]. In addition, obesity and salt intake both contribute to hypertension, which is the strongest risk factor for stroke[22], and these can be effected at a population level by public policy adjustments, including public space designs that promote healthy diet and exercise.

Targeted interventions to prevent stroke in high-risk individuals are based on the assessment of absolute risk of cardiovascular events. This assessment combines the various contributions of age, sex, blood pressure, smoking, diabetes mellitus and cholesterol levels to estimate

a risk of cardiovascular events in the next 5 years. A high absolute risk (that is, >15% probability of a cardiovascular event in the next 5 years) should prompt intensive treatment of all risk factors, not just the risk factors that are abnormal. Typically, this treatment is carried out using blood-pressure-lowering and cholesterol-lowering medications, alongside diet and lifestyle interventions.

The concept of a polypill containing a low dosage of blood-pressure-lowering agents, aspirin and statins has been proposed as a means of increasing adherence and reducing cost. Polypill trials have mostly involved patients with established cardiovascular disease[103]. However, the inclusion of aspirin in a polypill for the primary prevention of stroke is questionable owing to a lack of demonstrated benefit in patients without established symptomatic cardiovascular or cerebrovascular disease in a recent trial[104]. By comparison, blood-pressure-lowering therapies and statins have a well-established role in cardiovascular prevention, and commercial combinations of various blood-pressure-lowering agents with or without statins are available.

The main stroke-specific risk factor is atrial fibrillation, the prevalence of which rises sharply with increasing age[105]. This arrhythmia is often unrecognized as it is frequently asymptomatic and intermittent, and community screening approaches have been suggested[105]. As previously mentioned, the CHA2DS2-VASc score is used to identify patients with atrial fibrillation who would benefit from prophylactic anticoagulation for the prevention of stroke[36]. Antiplatelet therapy is ineffective for stroke prevention in patients with atrial fibrillation.

Management

Stroke unit care

Management in a geographically defined stroke unit that is staffed by medical, nursing and allied health clinicians who have an interest in stroke is likely the intervention with the greatest overall benefit as care is guided by standardized protocols that reduce both morbidity and mortality for all forms and severity of stroke. The precise components that contribute to this benefit are not known, but prevention of complications (such as aspiration pneumonia, venous thromboembolism and pressure ulcers), early institution of targeted secondary prevention and rehabilitation are likely to be key. Stroke unit care is possible in resource-constrained environments and is a key component of the World Stroke Organization's global guidelines[106].

Stroke unit care is the prerequisite foundation on which more complex acute interventions are built[5]. One key aspect of stroke unit care is the targeting of secondary prevention strategies based on an understanding of stroke mechanism (TABLE 1). Indeed, although some aspects of care are generic, such as lowering blood pressure, some interventions are specific and require identification of the cause of stroke, such as anticoagulation for atrial fibrillation, carotid endarterectomy for severe symptomatic atherosclerotic stenosis and percutaneous closure of PFO. By contrast, the initial choice of reperfusion therapy is determined by the location of vessel occlusion and the presence of viable brain tissue, and is generally not influenced by the mechanism of stroke.

Antiplatelet therapy

Aspirin given acutely within 48 h reduces the risk of recurrent stroke (see Secondary prevention, below) and improves outcome[107,108]. The benefit is smaller than with reperfusion therapies, but aspirin is widely applicable and inexpensive. Aspirin–dipyridamole or clopidogrel are alternatives that are slightly more effective than aspirin in secondary prevention of stroke, but are more costly[109]. The combination of aspirin and clopidogrel started within 12 h of minor stroke and TIA and continued for ~3 weeks reduced the incidence of recurrent stroke in patients at high risk[110,111].

Reperfusion therapies

Intravenous thrombolysis. Two main drugs are available for intravenous thrombolysis: alteplase and tenecteplase. Alteplase is a recombinant form of tissue plasminogen activator (tPA), which cleaves plasminogen to plasmin. Plasmin then degrades fibrin and dissolves the thrombus. Plasmin is rapidly inactivated by antiplasmin and, therefore, has a short half-life outside the thrombus. Accordingly, alteplase is administered as an initial bolus followed by a 1 h infusion. This therapy is considered the standard thrombolytic and is globally licensed for ischaemic stroke.

The optimal time frame for alteplase administration has been evaluated in several trials. For example, the NINDS tPA part A and B trials demonstrated a clinical benefit following alteplase administration within 3 h of stroke onset (the last time the patient was known to be healthy)[4]. Subsequent trials demonstrated varying degrees of benefit with alteplase administration for up to 6 h after onset[112–116]. Individual patient data meta-analyses have demonstrated a clear clinical benefit (a significant reduction in disability and neutral mortality) with alteplase administration up to 4.5 h after symptom onset[6]. The treatment efficacy reduces over this 4.5 h time period — the number needed to treat to achieve excellent outcome for one additional patient increases from ~4.5 patients within 90 min to ~15 patients between 3 and 4.5 h (REF.[117]). This effect relates to the reduction in salvageable penumbral tissue with the passage of time. In addition, the susceptibility of the thrombus to lysis could also reduce over time, reducing the efficacy of treatment with delayed adminstration[118].

The original randomized trials of thrombolysis therapy used non-contrast CT to identify patients who were candidates for treatment. The diagnostic approach of excluding haemorrhage on CT and relying on clinical features that indicate stroke led to the inclusion of patients with stroke mimics and those without a target vessel occlusion, which probably diluted the observed treatment effect in the trials. For example, in the NOR-TEST trial, 17% of participants received a final diagnosis of a stroke mimic[119], illustrating the challenges of diagnosis when only non-contrast CT is used. Subanalyses of the efficacy of thrombolysis have consistently demonstrated a strong effect of thrombolysis in patients with a target vessel occlusion (including small distal occlusions) and very little effect in the absence of vessel occlusion[120]. However, patients with lacunar stroke with an occlusion in a tiny perforating artery beyond the

Box 1 | **The current state of clinical trials for ischaemic stroke**

The main successes in stroke trials have been in the field of reperfusion therapies for ischaemic stroke. Alteplase has been used for >20 years, but increased interest in tenecteplase as a potentially more effective intravenous thrombolytic has led to several trials, some of which are ongoing (TABLE 2). Trial design varies from broadly inclusive pragmatic trials that tend to use only non-contrast CT imaging to those using imaging selection requiring vessel occlusion or perfusion lesion on CT or magnetic resonance angiography or perfusion studies. A selection of non-contrast CT only includes many patients with mild stroke or those with stroke mimics that dilute a potential treatment effect, and studies have repeatedly found clearer treatment effects in patients with a vessel occlusion or perfusion lesion.

After decades of unsuccessful neuroprotection trials, the high rates of successful reperfusion with endovascular thrombectomy offer the potential to mimic the animal model of temporary middle cerebral artery occlusion in humans. Previous neuroprotection trials could have failed for numerous reasons, including poorly reproducible preclinical experiments, failure of the drugs to penetrate the blood–brain barrier and heterogeneous clinical trial populations with unpredictable timing and extent of reperfusion.

Patients with stroke are often not competent to consent to research studies, especially for time-critical therapies. Consent from relatives is often used but this can cause delays. In some jurisdictions, consent might be deferred or waived for certain types of research trials that have been approved by an ethics committee to have an appropriate risk–benefit profile for the potential participants.

resolution of routine non-invasive angiography do seem to benefit from thrombolysis[121].

Recent trials have extended the time window for intravenous thrombolysis using advanced brain imaging. For example, the WAKE-UP trial demonstrated an improvement in functional outcome following alteplase treatment in patients with an uncertain onset time who had radiological evidence of stroke onset within 4.5 h (indicated by the presence of a lesion on the diffusion but not the FLAIR sequence) compared with treatment with placebo[7]. In addition, the EXTEND trial demonstrated reduced disability in patients treated with alteplase compared with placebo administered up to 9 h after the time the patient was last known to be healthy or the midpoint of going to sleep and waking with stroke symptoms if perfusion imaging demonstrated the presence of salvageable brain[8]. An individual patient data meta-analysis pooled EXTEND (which predominantly used CT perfusion imaging), the European ECASS4-EXTEND trial (which had a similar protocol to EXTEND but used visual assessment of MRI perfusion–diffusion mismatch) and the earlier EPITHET MRI-based randomized trial to evaluate the time frame of alteplase administration in further detail[9]. In this meta-analysis, alteplase improved functional outcomes overall but particularly in patients with perfusion mismatch when automated perfusion processing software was used. The thresholds applied by the automated software excluded 45% of patients in the ECASS4-EXTEND trial who had visual mismatch, mostly due to small and mild perfusion lesions. Functional independence occurred in 40% of patients in the overall alteplase-treated group and increased to 51% in those patients with perfusion mismatch detected using automated software. Alteplase-treated patients were also significantly more likely to improve by at least 1 point on the modified Rankin scale (mRS; ordinal analysis), indicating net benefit, despite the 4.6% risk of symptomatic intracerebral haemorrhage. Approximately 15–20% of all patients with ischaemic stroke are eligible for thrombolysis using a 0–4.5-h treatment window[122]. The extent of the increase in this proportion with an expansion of the time window remains to be seen, but ~20% of patients have wake-up-onset stroke[8].

Tenecteplase is a genetically modified tPA that has a longer half-life than alteplase, permitting bolus infusion, and has greater fibrin specificity and resistance to inhibitors[123]. Tenecteplase has become the standard thrombolytic for myocardial infarction when percutaneous coronary intervention is not immediately available[124]. Several trials on ischaemic stroke have demonstrated the efficacy and safety of tenecteplase as being similar to or superior than alteplase[125]. In particular, patients with vessel occlusion showed improved reperfusion and clinical outcomes with tenecteplase compared with alteplase[126–128]. Accordingly, guidelines have begun to include recommendations regarding tenecteplase and it is now entering clinical practice, although the drug is currently only licensed for ischaemic stroke in India. Ongoing trials are testing tenecteplase versus alteplase in the patient population with broader ischaemic stroke (BOX 1; TABLE 2).

The main adverse effect of thrombolysis is haemorrhage, particularly haemorrhagic transformation of the stroke which, in severe cases, can worsen cerebral injury and increase mass effect. Accordingly, aside from the time window for administration or imaging evidence of salvageable brain tissue, eligibility for intravenous thrombolysis also requires the exclusion of factors that pose an increased risk of intracerebral or systemic bleeding. A past history of intracerebral haemorrhage, recent surgery, trauma or systemic bleeding, the use of anticoagulants or coagulopathy and uncontrolled hypertension are some of the reasons patients can be excluded from thrombolytic treatment[129]. The risk of symptomatic intracerebral haemorrhage varies depending on the definition used. However, using the SITS-MOST definition, a large parenchymal haematoma occupying >30% of the infarcted area with a major mass effect and associated significant clinical deterioration or death occurred in 3.7% of patients with stroke treated with alteplase in a meta-analysis of the alteplase trials[130]. The absolute risk of symptomatic intracerebral haemorrhage increased from 2% in patients with mild stroke to 5% in those with severe stroke.

Endovascular thrombectomy. The publication of five positive trials of endovascular thrombectomy in 2015 revolutionized the stroke reperfusion landscape[10]. Two years earlier, three neutral trials had questioned the value of the endovascular approach; however, the positive trials used a new generation of more effective devices, featured improved patient selection using non-invasive imaging to prove a target vessel occlusion, and used faster treatment workflows.

Initial guidelines for endovascular thrombectomy recommended treatment within 6 h of stroke onset. However, the more recent DAWN[12] and DEFUSE 3 (REF.[11]) trials demonstrated a major benefit of reperfusion up to 24 h after onset, provided advanced brain imaging indicates the presence of salvageable brain tissue.

Table 2 | **Key ongoing trials in ischaemic stroke**

Trial name	Aim	*n*	Expected completion date	Trial registration
Intravenous thrombolysis				
TASTE	Improve outcomes with tenecteplase 0.25 mg per kg versus alteplase (non-thrombectomy patients, non-inferiority)	400–1,024	2020	ACTRN12613000243718
ATTEST-2	Improve outcome with tenecteplase 0.25 mg per kg versus alteplase (superiority)	1,870	2020	NCT02814409
EXTEND-IA TNK II	Determine optimal dose of tenecteplase (0.25 mg per kg versus 0.4 mg per kg; superiority)	300–656	2020	NCT03340493
TIMELESS	Improve outcome with tenecteplase and thrombectomy; 4.5–24 h (superiority)	456	2022	NCT03785678
ETERNAL	Improve outcome with tenecteplase versus standard care (may include alteplase with or without thrombectomy); 0–24 h (superiority)	740–1,000	2025	TBC
TWIST	Improve outcome with tenecteplase 0.25 mg per kg versus alteplase in patients with wake-up-onset stroke (superiority)	500	2022	NCT03181360
NOR-TEST 2	Improve outcome with tenecteplase 0.40 mg per kg versus alteplase (superiority)	1,342	2023	NCT03854500
MOST	Improve outcome by adding eptifibatide or argatroban to alteplase	1,200	2023	NCT03735979
Omitting intravenous thrombolysis before endovascular thrombectomy in an early time window				
SWIFT DIRECT	Assess non-inferiority of omitting alteplase before endovascular thrombectomy	404	2021	NCT03192332
MR CLEAN NO IV	Assess superiority of omitting alteplase before endovascular thrombectomy	540	2022	ISRCTN80619088
DIRECT SAFE	Assess non-inferiority of omitting alteplase before endovascular thrombectomy	780	2021	NCT03494920
DIRECT-MT	Assess non-inferiority of omitting alteplase before endovascular thrombectomy	540	2021	NCT03469206
Endovascular thrombectomy or intravenous thrombolysis for mild stroke				
ENDO-LOW	Improve outcome with endovascular thrombectomy in patients with NIHSS 0–5	TBC	NA	Not yet registered
IN EXTREMIS — MOSTE	Improve outcome with endovascular thrombectomy in patients with NIHSS 0–5; 0–24 h	TBC	NA	Not yet registered; see https://www.inextremis-study.com/
TEMPO-2	Improve outcome with intravenous tenecteplase in patients with NIHSS 0–5	1,274	2021	NCT02398656
Endovascular thrombectomy for stroke with a large ischaemic core				
IN EXTREMIS — LASTE	Improve outcome with endovascular thrombectomy in patients with ASPECTS 0–5; 0–6.5 h)	TBC	NA	Not yet registered; see https://www.inextremis-study.com/
TENSION	Improve outcome with endovascular thrombectomy in patients with ASPECTS 3–5	714	2022	NCT03094715
TESLA	Improve outcome with endovascular thrombectomy in patients with ASPECTS 2–5	300	2022	NCT03805308
SELECT-2	Improve outcome with endovascular thrombectomy in patients with ischaemic cores 50–100 ml or with ASPECTS 0–5	560	2021	NCT03876457
RESCUE-Japan LIMIT	Improve outcome with endovascular thrombectomy in patients with ASPECTS 3–5	200	2021	NCT03702413
Neuroprotection				
ESCAPE-NA1	Improve outcome through neuroprotection with NA-1 in patients undergoing endovascular thrombectomy	1,120	2019	NCT02930018
Anti-oedema				
CHARM	Improve outcome through reduced oedema using intravenous glibenclamide in patients with large hemispheric infarction	680	2021	NCT02864953

ASPECTS, Alberta Stroke Programme Early CT Score; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; TBC, to be confirmed.

Indeed, the safety profile and procedural success rates for treatment in the extended time window were very similar to those for treatment within 6 h of stroke onset. However, the proportion of patients with favourable imaging reduces with passing time. With the expanded time window, ~15% of all patients with stroke could be eligible for thrombectomy[131]. The DEFUSE 3 criteria were substantially simpler (allowing a core volume up to 70 ml) than those used in DAWN, and using the DEFUSE 3 criteria led to ~60% more patients being eligible for treatment than with the use of DAWN criteria[11]. The additional patients had the same treatment benefit as those eligible for DAWN.

In general, endovascular thrombectomy has few contradictions in patients with a suitable large artery occlusion target and good premorbid function. Patients who are ineligible for intravenous thrombolysis due to a risk of systemic bleeding can be treated with endovascular thrombectomy. Proximal vascular access can complicate the procedure and reduce the probability of success but would generally not prevent an attempt at thrombectomy in an otherwise good candidate. Endovascular thrombectomy is associated with risk of haemorrhagic transformation, although symptomatic intracerebral haemorrhage occurred in a similar proportion of patients who received endovascular thrombectomy to those who received intravenous thrombolysis alone in pivotal trials[10]. Arterial perforation or dissection can occur but was relatively uncommon (~1.3%) in the experienced centres that participated in randomized trials[132].

Technical approaches to thrombectomy vary but generally involve a combination of stent retriever devices and aspiration catheters. Unlike coronary disease, where the occlusive thrombus is generally superimposed on a stenotic atherosclerotic plaque, the embolic thrombus in ischaemic stroke is most often lodged in a normal segment of the artery. Hence, clot retrieval techniques without the need for stent implantation are the usual approach unless there is intracranial atherosclerosis. The original neutral trials used the MERCI coil retriever and small-bore, early-generation aspiration catheters that showed limited effectiveness[133]. Conversely, the positive trials predominantly used stent retrievers and achieved reperfusion of >50% of the affected vascular area in ~71% of patients in the pivotal trials[10], with higher rates reported in more recent studies. Randomized comparisons of stent retrievers and newer-generation, large-bore aspiration catheters have shown similar results[134,135]. Endovascular thrombectomy for basilar artery occlusion is the subject of ongoing randomized trials but is widely accepted to be an effective intervention based on translation of the anterior circulation endovascular results. The BEST trial demonstrated improved outcomes in patients treated with thrombectomy versus medical therapy but was confounded by a high crossover to intervention that led to neutral results in an intention-to-treat analysis[136].

Percutaneous coronary intervention has largely replaced thrombolysis for ST-segment elevation myocardial infarction in metropolitan regions[124]. However, for ischaemic stroke, intravenous thrombolysis has remained the standard therapy for all eligible patients, to which thrombectomy is then added with no delay to assess response to thrombolysis. The time between intravenous thrombolysis and endovascular thrombectomy varies from a few minutes to several hours, depending on the need for interhospital transfer and the time required for transport. Trials are underway to test whether direct thrombectomy without the intravenous thrombolysis is non-inferior when thrombectomy is immediately available. However, this issue applies to only a minority of patients who are eligible for thrombectomy, as most patients require interhospital transfer for the procedure. Indeed, in the immediate future, it is likely that the majority of patients with ischaemic stroke in most countries will continue to first go to a primary stroke centre where they may receive thrombolysis before those with a large vessel occlusion are transferred to a comprehensive stroke centre capable of endovascular thrombectomy — the so-called drip and ship process. This process incurs a substantial time delay[137] that provides an opportunity for intravenous thrombolysis to achieve reperfusion. To this end, the INTERSECT study demonstrated that ~60% of large vessel occlusions can eventually be dissolved by alteplase, but this can take up to 6 h (REF.[138]). Rates of reperfusion are related to thrombus burden, and internal carotid artery occlusions are less likely to dissolve with thrombolysis than middle cerebral artery occlusions.

There are potential developments in pre-hospital triage of patients who are likely to have large vessel occlusion that could disrupt this paradigm of drip and ship. For example, clinical assessments by paramedics using the Rapid Arterial Occlusion Evaluation (RACE)[139] or Los Angeles Motor Score (LAMS)[140] are being employed in some systems to identify individuals with possible large vessel occlusion ischaemic stroke and bypass them direct to a comprehensive centre if the additional travel time is not excessive (for example, <15 min in the American Heart Association Mission Lifeline programme). RACE and LAMS have reasonable sensitivity but more modest specificity, and this, combined with the relatively low prevalence of large vessel occlusion among patients with suspected stroke, means the positive predictive value for large vessel occlusion is <50%[139]. The Ambulance Clinical Triage for Acute Stroke Treatment (ACT-FAST) algorithm[141] aims to simplify and shorten assessment time while improving specificity and is currently undergoing field testing by paramedics (BOX 2).

Mobile stroke units (MSUs) represent an exciting new approach designed to move the stroke unit to the patient. These units are specially designed ambulances equipped with CT scanners that can perform definitive triage of large vessel occlusion and initiate thrombolysis, potentially within the 'golden hour' or the first 60 min after stroke onset. In Berlin, Germany, MSU thrombolysis occurred a median 25 min earlier than in-hospital thrombolysis[142] and ongoing studies are evaluating the effectiveness of the MSU model in different health-care systems.

Global access to reperfusion therapies. Intravenous thrombolysis and endovascular thrombectomy are relatively costly therapies. Although both therapies are economically dominant in the long term[143,144], the initial cost, which often falls to the families of patients in developing countries, might be unaffordable. To meet this need, the

WHO added alteplase to its list of essential medicines in the 2019 revision[145]. In addition, the requirement to pay before treatment commences introduces delays that may reduce the effectiveness of treatment. Intravenous thrombolysis requires the capability for a CT scan and some clinical expertise in addition to a medication cost that varies widely between countries. One of the driving factors behind the use of tenecteplase in India has been the affordability (~US$407 versus US$590–1,180 for alteplase, depending on patient weight; M. Kate, personal communication). To put these values into context, the average annual wage in India is US$1,800 (REF.[146]). Similarly, one of the reasons for the use of lower-dose alteplase in Asia is that it usually corresponds to one rather than two drug vials, despite this dose not meeting liberal on-inferiority criteria compared with higher-dose alteplase in a randomized trial[147]. Endovascular thrombectomy is further limited by additional costs and the specialized expertise required to perform the procedure. Accordingly, thrombolysis is limited and there is no access to thrombectomy throughout most of Africa.

Prevention of complications

Oedema is part of the natural history of infarction and peaks ~3–5 days after stroke. Large middle cerebral artery territory infarcts can swell to an extent that causes brainstem herniation and death. In these patients, hemicraniectomy reduces mortality and disability, particularly in those <60 years of age, and is generally performed within 48 h of stroke onset when there are signs of evolving mass effect (for example, a midline shift on brain imaging) and drowsiness[148]. Similarly, large cerebellar infarcts can swell and compress the fourth ventricle causing hydrocephalus, or can directly compress the brainstem causing coma and death. Posterior fossa decompression has not been evaluated in a randomized trial, but observational data suggest that this procedure can reduce death and convey a good prognosis for recovery if brainstem compression is avoided. Reducing oedema formation might be possible using pharmacological approaches; one example is intravenous glyburide, which has strong preclinical and phase II data[149] and is being tested in a phase III clinical trial (NCT02864953).

Patients with ischaemic stroke are at particularly high risk of deep venous thrombosis and pulmonary embolism. Pharmacological prophylaxis with low-molecular-weight heparin[150] and/or intermittent pneumatic compression devices[151] reduces the risk of venous thromboembolism. Standard compression stockings are not effective. Venous thromboembolic prophylaxis is recommended in guidelines for all immobile patients with stroke[129]. In addition, aspiration pneumonia associated

Box 2 | **Examples of prehospital identification tools for suspected large vessel occlusion**

Several tools can be used to identify individuals with ischaemic stroke before they arrive in the hospital setting. The Rapid Arterial Occlusion Evaluation (RACE), Los Angeles Motor Score (LAMS) and Ambulance Clinical Triage for Acute Stroke Treatment (ACT-FAST) are used to assess motor features in those with suspected large vessel occlusion, such as arm drift (by positioning both arms at 90° and observing for unilateral drift >10 s). The RACE tests aphasia by asking the patient to 'close your eyes' and 'make a fist' and evaluates if the patient obeys. RACE also tests agnosia by asking the patient 'whose arm is this?' while they are being shown their paretic arm and evaluates whether the patient recognizes their own arm. Another assessment in RACE is the question 'can you lift both arms and clap?' to evaluate whether the patient recognizes their functional impairment.

RACE score[a]

- Facial droop
  - Absent (0 points)
  - Mild (1 point)
  - Severe (2 points)
- Arm drift
  - Absent or mild (0 points)
  - Drifts to stretcher (1 point)
  - Cannot get antigravity (2 points)
- Head and gaze
  - Absent deviation (0 points)
  - Present deviation (1 point)
- Aphasia (if the right arm is weak)
  - Both tasks okay (0 points)
  - One error (1 point)
  - Two errors (2 points)
- Agnosia (if the left arm is weak)
  - Both tasks okay (0 points)
  - One error (1 point)
  - Two errors (2 points)

LAMS[b]

- Facial droop
  - Absent (0 points)
  - Present (1 point)
- Arm drift
  - Absent (0 points)
  - Drifts to stretcher (1 point)
  - Falls rapidly (<10 s) (2 points)
- Hand grip
  - Normal grip (0 points)
  - Weak grip (1 point)
  - No grip (2 points)

ACT-FAST algorithm[c]

- Step 1: arm drift to stretcher within 10 s
  - No (ACT-FAST negative)
  - Yes (proceed to step 2)
- Step 2: if the right arm is weak, assess language
  - No deficit (ACT-FAST negative)
  - Significant deficit (proceed to step 3)
  - If the left arm is weak, assess eye deviation and shoulder tap
  - No eye deviation and appropriately localizes to a tap on the left shoulder and calling their name (ACT-FAST negative)
  - Significant deficit (proceed to step 3)
- Step 3: eligibility and mimic exclusion
  - Stroke onset (last known to be healthy) <24 h
  - Premorbid independent function
  - Not comatose; no seizure at onset
  - No known malignant brain tumour
  - Glucose level of >2.8 mmol/l

[a]RACE ≥5 indicates a high probability of large vessel occlusion. [b]LAMS ≥4 indicates a high probability of large vessel occlusion. [c]All three ACT-FAST steps being positive indicates a high probability of large vessel occlusion.

with dysphagia (difficulty swallowing) is a common complication in patients with ischaemic stroke. Carrying out a validated swallow screen is, therefore, essential before the oral administration of medications, food and drink. A package of nursing care to manage fever, blood glucose and safe swallowing reduced mortality in a cluster-randomized trial[152].

Secondary prevention

The prevention of recurrent stroke requires a combination of standard strategies and targeted interventions and, in some patients, depends on stroke aetiology. Lifestyle risk factors for stroke include smoking, excessive salt intake, obesity and physical inactivity, which are similar to the risk factors for other cardiovascular diseases. Accordingly, strategies to improve diet, increase physical activity and quit smoking through behavioural change remain challenging but are highly worthwhile when successful.

Intensive blood pressure lowering in the initial period after ischaemic stroke has not proven beneficial[153,154] and may be harmful for neurological recovery if collateral blood flow is compromised[155]. Conversely, after the acute phase of ischaemic stroke, intensive blood pressure control is critically important as the risk of recurrent stroke (both ischaemic stroke and intracerebral haemorrhage) is particularly sensitive to small changes in blood pressure; epidemiological studies have suggested no lower threshold for the benefit of blood pressure lowering[156]. The recent SPRINT trial, comparing systolic blood pressure targets of 120 mmHg and 140 mmHg, found reduced stroke in the intensive-lowering group but specifically excluded patients with previous stroke[157], providing indirect evidence for a lower target in secondary prevention of stroke. Ongoing trials are focusing on long-term blood pressure lowering in patients with ischaemic stroke.

Antiplatelet therapies (such as aspirin, clopidogrel and aspirin–dipyridamole) are the main antithrombotics used after ischaemic stroke. Clopidogrel has a small absolute risk reduction benefit compared with aspirin[158], although aspirin is still commonly prescribed as first-line therapy because it is inexpensive and widely available. Aspirin–dipyridamole and clopidogrel have very similar efficacy[109]. The use of aspirin and clopidogrel for ~3 weeks significantly reduces the risk of recurrent stroke after minor stroke and high-risk TIA[110,159]. With longer-term use, the benefits of this therapy are outweighed by the prevalence of bleeding events. Antiplatelet therapy is not effective for all patients who require anticoagulation, such as those with atrial fibrillation. Direct oral anticoagulants have largely replaced warfarin in these patients owing to convenience and reduced intracerebral haemorrhage risk, provided creatinine clearance is adequate to excrete these medications and there is no mechanical prosthetic valve or moderate–severe mitral stenosis[36]. No head-to-head comparisons of the direct oral anticoagulants dabigatran (a thrombin inhibitor), apixaban, rivaroxaban and edoxaban (all of which are factor Xa inhibitors) have been carried out. Specific reversal agents now exist, such as idarucizumab for dabigatran, which is widely available, and andexanet alfa for apixaban and rivaroxaban, which is FDA approved and increasingly available. This improves safety in the event of trauma or a requirement for emergency surgery. In patients taking dabigatran who present with ischaemic stroke, case series have shown that reversal with idarucizumab can be safely followed by thrombolysis[160,161]. A role for percutaneous left atrial appendage occlusion in patients with a genuine contraindication to anticoagulation is emerging[162]. However, anticoagulation is generally underutilized in patients with atrial fibrillation and often underdosed due to misperceptions about risk versus benefit, leading to unnecessary recurrent ischaemic strokes.

High-dose, high-potency statins have an established role in preventing recurrent stroke in patients with potential atherosclerotic mechanisms of ischaemic stroke[163]. In addition, trials of PCSK9 inhibitors have shown promise in further reducing the risk of recurrent stroke[164]. However, these drugs are expensive and are not universally available. Some patients do not tolerate statins owing to muscle or liver toxicity, and PCSK9 inhibitors could be particularly valuable for this group.

Surgical interventions for the prevention of recurrent stroke can be warranted in some patients depending on the cause of the ischaemic stroke. Patients with a symptomatic carotid stenosis of >70% (assessed compared with the distal normal artery by the NASCET criteria) benefit from carotid endarterectomy and there is a smaller but significant benefit of carotid endarterectomy in selected patients with 50–70% symptomatic stenosis. However, those with asymptomatic stenosis are probably best managed with intensive medical therapy. Early trials did report a small benefit of endarterectomy for asymptomatic high-grade stenosis. However, these trials largely preceded current intensive medical therapy including high-potency statins[165]. Ongoing trials are re-evaluating the benefit of surgery in the context of contemporary medical management. Carotid stenting has consistently been associated with a higher risk of perioperative stroke than endarterectomy, although post-hoc analyses suggest similar efficacy in patients <70 years of age[166]. In intracranial atherosclerotic stenosis, intensive medical therapy is clearly superior to stenting[167].

PFO has been a controversial stroke aetiology in the past. It is present in ~25% of the general population but over-represented in patients with ischaemic stroke who have no other apparent cause[168]. Earlier trials of percutaneous closure of PFOs failed to demonstrate a reduction in the risk of recurrent stroke. However, three subsequent trials in patients <60 years of age used more specific patient selection to exclude alternative mechanisms and longer-term follow-up, and demonstrated a clear benefit of percutaneous PFO closure over medical therapy[38–40]. The reduction in stroke recurrence is ~1% per annum and appears to continue to accumulate over time.

Rehabilitation and recovery

Clinical trials of rehabilitation strategies after ischaemic stroke to date have largely been neutral or, in some cases, harmful[169]. In rehabilitation trials, interpreting the efficacy of the intervention is confounded by the natural

recovery trajectory observed in patients. The intensity of rehabilitation interventions that has been studied to date might be inadequate; some guidelines recommend 3 h per day of therapy[170], but this is not achieved in many systems and, in large parts of the world, formal rehabilitation does not exist. To this end, one trial of family-led, home-based rehabilitation in India was neutral[171]. Nonetheless, there is general consensus that rehabilitation is an important component of reintegrating survivors of stroke into the community.

Quality of life

Stroke has a major effect on the individual, their relatives and carers, and society as a whole. The severity of disability relates to the volume and location of the infarct, and is altered by the individual's pre-stroke health and functional reserve. One key clinical decision when patients present to the emergency department is whether reperfusion therapies have the potential to give the patient a quality of life that they would deem acceptable.

The mRS, which assesses functional status after stroke, has become the standard primary outcome for phase III stroke trials. The mRS has been mapped to quality of life as rated by both patients and health-care professionals. In some cultures, an mRS score of 5 (requiring nursing home care) is regarded as having health utility or quality of life equivalent to, or even worse than, death[172]. However, this interpretation is not universal and, to further complicate decisions around the futility of treatment, patients' views on acceptable quality of life alter following a stroke. For example, although many individuals would state pre-stroke that they would not want to live with a severe disability, most survivors after hemicraniectomy state that, in retrospect, they would consent to having the procedure if they were faced with the same decision, despite substantial disability in many cases[173]. Although the mRS is a patient-reported (or carer-reported) outcome, there are also dedicated patient-reported outcomes such as the PROMIS10 (REF.[174]), neuroQOL[175] and EQ5D[176] that are becoming more widely used in stroke trials.

The definition of a successful therapy in trials has often been an mRS score between 0 and 2 (that is, regaining functional independence). However, shifts in disability that may not reach an mRS score of 2 can also be important — for instance, returning home with assistance in cleaning and cooking (an mRS score of 3) would usually be preferable to death or requirement for nursing home care (mRS score of 5). This shift in disability would also substantially reduce health-care costs. As a result, ordinal analysis of the mRS has gained in popularity as a means to capture all of the transitions in disability states.

Assessment of pre-stroke functional status can be challenging in the time-pressured environment of reperfusion treatment decisions. The mRS is not well suited to this application as categories 1 and 2 focus on differences compared with the pre-stroke state. All patients in randomized trials had independent pre-stroke function (mRS scores between 0 and 2). However, in clinical practice, patients who are living at home but who require some support services due to pre-existing illnesses may be considered for acute stroke treatment on an individual basis. Although these patients cannot be expected to improve on their baseline mRS, regardless of treatment, a strong argument can often be made on quality-of-life and cost-effectiveness grounds if the patient has a reasonable chance of returning to their baseline functional status rather than progressing to greater levels of disability. In general, the severity of cognitive dysfunction, impaired mobility and medical comorbidities are important considerations when estimating the current level of function and the likely effect of the stroke with and without treatment. For example, a young patient in a wheelchair due to a non-progressive injury could have an mRS score of 4 but have very good prospects for returning to premorbid function after thrombolysis or endovascular thrombectomy. Similarly, a patient who is cognitively intact and living at home but receiving cleaning or cooking assistance has an mRS score of 3, but is likely to have substantially better outcome with thrombolysis or endovascular thrombectomy than with conservative management. It is important to be aware of the self-fulfilling prophecy of early limitations on care, particularly when treating patients with pre-stroke disability. These complex decisions may be informed by brain imaging evidence of salvageable versus irreversibly injured brain.

Outlook

Prevention

As mentioned earlier, many strokes are due to preventable factors. Optimal long-term blood pressure targets for patients with stroke will be informed by ongoing trials. However, long-term blood pressure targets are likely to be lower than those currently achieved, based on indirect evidence from other high-risk cardiovascular disease groups[157], which creates an opportunity for improved stroke prevention. In addition, the detection of atrial fibrillation has presented a major challenge as it is often paroxysmal and asymptomatic. Longer-term monitoring (up to 3 years) using small implantable loop recorders leads to detection of atrial fibrillation in ~30% patients with cryptogenic stroke. However, these devices remain expensive, and increasingly sophisticated consumer electronic wearable devices, including electrocardiography capture, may be used in the future.

Diagnosis

Accurate stroke diagnosis requires the differentiation of ischaemia from haemorrhage and an understanding of the specific mechanism of stroke. The latter point determines acute treatment and secondary prevention strategies and requires more sophisticated brain imaging than the non-contrast CT of the brain that is routinely used in clinical practice. CT perfusion and angiography have an advantage in terms of speed and accessibility over MRI for use as the initial imaging strategy, and allow the detection of patients who are suitable for reperfusion therapies beyond standard time windows. MRI follow-up refines the understanding of infarct location and pathophysiology. In addition, MRI has great potential as the initial imaging modality if practical issues

such as safety screening for metallic implants can be overcome.

Reperfusion

The greatest advancement in stroke care has been the development of reperfusion therapies, although there is still much room for improvement in increasing the speed and quality of reperfusion with both intravenous thrombolysis and endovascular approaches.

Studies have emphasized the value of defining an imaging target for revascularization. Indeed, when brain imaging demonstrates a vessel occlusion target and evidence of salvageable brain tissue, the time elapsed since onset (which is often not precisely known) is of little additional prognostic value[177,178]. As a result, there is now the potential to treat patients with endovascular thrombectomy who have large artery occlusion and evidence of salvageable brain tissue up to 24 h after the time the patient with stroke was last known to be healthy. Previously, thrombolysis has been limited to 4.5 h after the last known time the patient with stroke was healthy, but trials have demonstrated that the same imaging paradigms used to extend the time window for thrombectomy can also be used to select patients for thrombolysis[7,8]. This shift in focus from onset time to tissue status is a major advance but does not reduce the urgency of reperfusion once the patient has started medical care as neuronal death relentlessly progresses.

Endovascular thrombectomy techniques have a high success rate using the prevailing definition of >50% restoration of blood flow to the affected area. However, the proportion of patients who achieve virtually complete reperfusion is considerably lower. Central analysis of post-thrombectomy reperfusion from the HERMES collaboration has shown clear advantages of a more stringent definition for endovascular success[179]. Ideally, given the powerful prognostic effect of time to reperfusion, this should be achieved with the first pass of the device. Device evolution is ongoing and a continued focus on increasing the quality and speed of reperfusion is required. Safe endovascular treatment in more distal vessels will require device development. Ongoing trials are testing the benefit of endovascular thrombectomy in patients with milder stroke severity and larger ischaemic core volumes.

Intravenous thrombolysis remains more widely available than endovascular thrombectomy, but the incidence of rapid, complete reperfusion, particularly in patients with large vessel occlusion, has been suboptimal. The speed of reperfusion could be improved with alternative thrombolytics (for example, tenecteplase)[126–128] and adjunctive agents (for example, eptifibatide and argatroban (NCT03735979)). A major limitation of thrombolysis therapies is poor access of the drug to the clot face, as blood flow in the occluded vessel tends to stagnate and diffusion to the clot face is a slow process. In the INTERSECT study, ~60% of patients with large vessel occlusion eventually recanalized but this process took up to 6 h, during which time stroke progression may be substantial[138]. Patients with good collateral flow are more able to tolerate this delay in reperfusion, and the collateral flow could also transport the thrombolytic drug to the clot face, increasing reperfusion[180]. Residual anterograde flow through the thrombus improves thrombolytic access and was associated with much faster recanalization (but a similar ultimate success rate) in the INTERSECT study[138]. New technologies may enable enhanced delivery of the thrombolytic to the clot face. For example, magnetically enhanced diffusion using intravenously injected iron nanoparticles and an external magnetic field is being trialled[181]. Ultrasonography-assisted thrombolysis (sonothrombolysis), which has not been shown to be successful in trials to date, remains under investigation. Adjunctive antiplatelet agents (for example, eptifibatide) are being tested in trials. Some of the non-fibrin structural components of the thrombus, including von Willebrand factor and neutrophil extracellular traps (DNA extruded from neutrophils designed to trap microorganisms), might require alternative treatments[182].

Cytoprotection

Despite cynicism induced by multiple negative trials, techniques to preserve brain tissue viability before reperfusion remain an attractive goal for ischaemic stroke. However, no strategy has yet succeeded in being translated from preclinical to human trials. Early trials were often confounded by flawed preclinical methodologies and heterogeneous clinical trial populations with inconsistent reperfusion; however, a new generation of trials is now underway using the more reliable endovascular reperfusion paradigm. For example, the ESCAPE NA-1 trial of a PSD-95 inhibitor that impairs NMDA-mediated glutamate excitotoxicity has shown benefit in several preclinical models of ischaemic stroke, including primate models[183], and in a proof-of-principle human study[184].

Other strategies to improve tissue viability include hypothermia, enhancing collateral blood flow and controlling oedema formation. Hypothermia targets multiple detrimental processes after ischaemia, but clinical implementation remains challenging as the control of shivering without sedation is difficult. One notable example, the EuroHYP trial, which initially aimed to recruit 1,500 patients, was terminated after 98 patients were recruited over 4.5 years and showed no sign of benefit[185].

Enhancing collateral blood flow is another approach to induce cytoprotection pending definitive reperfusion. Several techniques have been explored, including aortic balloon flow diversion[186], head position[187] and sphenopalatine ganglion stimulation. Sphenopalatine ganglion stimulation leads to vasodilatation and enhanced collateral blood flow in animal models[188]. Improved functional outcome was observed in a subgroup of patients with cortical infarction and optimized stimulation parameters in the ImpACT-24B trial[189], with further trials ongoing. Aortic balloon flow diversion did not demonstrate clinical benefit despite evidence of improved collateral flow in some patients[186]. Head-down positioning showed no benefit in unselected patients[187], but studies in selected patients with large vessel occlusion are ongoing.

Reducing secondary injury after reperfusion could prove to be another important strategy. Controlling oedema formation pharmacologically by preventing fluid and electrolyte influx would be highly attractive to avoid

neurosurgery. One such example is an ongoing trial that is investigating intravenous glyburide (glibenclamide) to inhibit SUR-1 receptors, with the aim of reducing malignant oedema (NCT02864953). Haemorrhagic transformation remains a major concern, despite its rarity, and preventive strategies have potential application but are still in the early stages of development.

Systems of care and prehospital management

The time-critical nature of a benefit from reperfusion therapy means that one of the most effective strategies to maximize the benefit of thrombolysis and thrombectomy is to streamline the system of care to deliver treatment faster. To date, door-to-needle and door-to-puncture times have been reduced through prenotification of the receiving emergency department that they will receive a patient with suspected stroke when the patient is in the ambulance, and via direct transport of the patient to the CT scanner on the ambulance stretcher[190,191]. However, unwarranted clinical variation remains widespread and there is much room for improvement.

With improvements in in-hospital systems, the time that elapses before the patient attends hospital has become the greatest contributor to the onset-to-reperfusion time. Community awareness of the signs of stroke and the need to call an ambulance at the first sign of symptoms is still limited in most communities. In addition, the FAST (face, arm, speech, time) stroke recognition message is widely promoted internationally but deserves even greater prominence. Severity-based triage tools that assist paramedics to identify patients who probably require endovascular thrombectomy and bypass them to an endovascular-capable hospital will increasingly be used[139–141]. MSUs equipped with CT scanners allow definitive diagnosis and triage. Cost-effectiveness studies of these units are ongoing, but the potential to administer thrombolysis to patients within the 'golden hour' after onset in MSUs is highly attractive.

Globally, acute stroke mortality is highly variable[192]. With a predicted increase in the burden of stroke in the developing world[193], there is a need for strategic organization of all health-care systems, even in resource-poor locations. Accordingly, the World Stroke Organization has produced a roadmap aiming to assist prioritization in health systems with varying resources[106].

Rehabilitation and recovery

Although more intensive interventions based on preclinical data have, as yet, been unrewarding, the dosage of intensive therapy might still be less than required. Robotics has been proposed as a solution to allow increased task practice without increasing therapist requirements. Although one recent trial was neutral[194], others are ongoing. In addition, medical interventions to enhance recovery are also being trialled. Several of these have been neutral (for example, RESTORE (NCT02877615)), but selective serotonin reuptake inhibitors[195] and stem cell therapy remain under investigation. A single-arm pilot study of stereotactic perilesional implantation of bone-marrow-derived mesenchymal stem cells in patients with chronic stroke had an acceptable safety profile and these patients with previously stable deficits showed small improvements in neurological function[196]. A phase II randomized trial of bone-marrow-derived multipotent adult progenitor cells delivered intravenously to patients with acute stroke demonstrated safety and potential signs of efficacy. Larger trials are ongoing (for example, PISCES III (NCT03629275) and MASTERS2 (NCT03545607)).

In general, the treatment of patients with stroke has made major advances in recent years. The basic principle of reducing disability through rapid reperfusion to salvage hibernating ischaemic penumbra remains central. Future developments to preserve the brain pending reperfusion and to maximize the speed and quality of reperfusion through improved devices, pharmaceuticals, systems and prehospital interventions are likely to be key to further improving patient outcomes.

Published online: 10 October 2019

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Author contributions
All authors contributed to all sections of the Primer.

Competing interests
S.M.D. reports personal fees for advisory board membership and lectures for Boehringer Ingelheim and Medtronic. G.A.D. reports personal fees from Allergan, Amgen, Bayer, Boehringer Ingelheim, Pfizer and Servier. All other authors declare no competing interests.

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