Ischemic stroke in the elderly: an overview of evidence

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Abstract | Stroke mostly occurs in elderly people and patient outcomes after stroke are highly influenced by age. A better understanding of the causes of stroke in the elderly might have important practical implications not only for clinical management, but also for preventive strategies and future health-care policies. In this Review, we explore the evidence from both human and animal studies relating to the effect of old age—in terms of susceptibility, patient outcomes and response to treatment—on ischemic stroke. Several aging-related changes in the brain have been identified that are associated with an increase in vulnerability to ischemic stroke in the elderly. Furthermore, risk factor profiles for stroke and mechanisms of ischemic injury differ between young and elderly patients. Elderly patients with ischemic stroke often receive less-effective treatment and have poorer outcomes than younger individuals who develop this condition. Neuroprotective agents for ischemic stroke have been sought for decades but none has proved effective in humans. One contributing factor for this translational failure is that most preclinical studies have used young animals. Future research on ischemic stroke should consider age as a factor that influences stroke prevention and treatment, and should focus on the management of acute stroke in the elderly to reduce the incidence and improve outcomes in this vulnerable group.

Chen, R.-L. *et al. Nat. Rev. Neurol.* **6**, 256–265 (2010); published online 6 April 2010; doi:10.1038/nrneurol.2010.36

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Introduction

Approximately 16 million first-ever strokes occur worldwide annually, with a death toll of ≈5.7 million people per year.[1] Stroke is ranked as the second most common single cause of death in the developed world after ischemic heart disease, or the third largest killer when neoplastic diseases are considered as a group.[2] In addition, stroke is the largest cause of adult disability,[3] with up to half of all patients who survive a stroke failing to regain independence and needing long-term health care.[4] According to a review that examined eight developed countries, 0.27% of gross domestic product is spent on stroke expenses, with stroke care accounting for ≈3% of total health-care expenditure.[5] Stroke and coronary heart disease cost the European Union economy €38 billion and €49 billion a year, respectively, which together account for nearly half the total cost of cardiovascular disease.[6]

Stroke can affect individuals of any age, although the incidence and prevalence of this condition increase sharply with age.[7] Indeed, age is the most important nonmodifiable risk factor for all stroke types, including ischemic stroke.[8] For each successive decade after the age of 55 years, the stroke rate doubles in both men and women.[9] Reports indicate that 75–89% of strokes occur in individuals aged >65 years.[10,11] Of these strokes, 50% occur in people who are aged ≥70 years and nearly 25% occur in individuals who are aged >85 years (Figure 1).[10,11]

By 2025, the global population aged >60 years is estimated to rise to 1.2 billion—double the number of people above this age in 1995.[12] Furthermore, by 2050, the global number of old people (aged ≥65 years) will exceed the number of young people (aged <65 years) for the first time since formal records began.[13] This growth in the aged population, together with the influence of

Competing interests
The authors, the Journal Editor H. Wood and the CME questions author C. P. Vega declare no competing interests.

aging on stroke, suggests that the incidence and economic cost of this disease will rise.[14] One report estimates that the global occurrence of first-ever strokes will increase to 18 million by 2015, and to 23 million by 2030.[15] Moreover, this study estimates that the death toll from stroke will reach 6.5 million per year by 2015 and 7.8 million per year by 2030.[15]

The objectives of this Review are to examine the causes of the high occurrence and poor outcomes of ischemic stroke in elderly patients, explore specific treatments for stroke in the elderly, and advocate more stroke research on older animals and humans. In this article, we use the terms 'elderly' or 'older people' to encompass those individuals aged 65–79 years,[16] while 'very old' or 'oldest old' is used for people aged ≥80 years.[13] Since ischemic stroke accounts for about 87% of all cases of this disease,[11] this Review will focus on this stroke subtype.

Key points

- Over 80% of strokes occur in the elderly (people aged ≥65 years), and patient outcomes after stroke are highly influenced by age
- The increased vulnerability of elderly people to ischemic stroke is associated with several changes that occur in the aged brain
- Risk factor profiles and mechanisms of ischemic injury vary between young and old patients with stroke
- Elderly patients often receive less-effective treatment and have poorer outcomes following a stroke than younger individuals
- Most preclinical studies of neuroprotective agents have used young animals, which might partly explain the translational failure of these drugs in humans
- Future stroke research should place more focus on aged animals and the elderly

Aging-related changes in the CNS

The brain changes during aging.[17,18] Human postmortem studies indicate that brain weight decreases by ≈0.1% per year between the ages of 20 and 60 years, with more-rapid loss thereafter.[19] Such studies reveal that most of this weight loss occurs in the cerebral cortex and hippocampus.[18] In agreement with brain weight studies, MRI shows that brain volume decreases by 0.1–0.2% per year from 30 to 50 years of age, and by 0.3–0.5% per year in people aged >70 years.[20] This decrease is relatively diffuse and uniform in cerebral white matter but shows some regional differences in gray matter, with the frontal and parietal cortices being more affected than temporal and occipital cortices, and the striatum also being affected.[21,22] Gray matter volume decreases steadily after adolescence, whereas white matter volume peaks at ≈40 years of age and decreases thereafter.[23,24] The ventricular system expands to fill the space vacated by the brain parenchyma.[18] In addition, during normal aging, the leptomeninges tend to thicken slightly (Figure 2) and the choroid plexuses in the lateral ventricles double in weight.[25] The main controversy relating to the aged brain has concerned the presence and extent of neuronal loss.[18] Some studies found that the elderly brain exhibited a marked loss of neurons,[26] but studies using stereological techniques[27,28] indicated that in normal brains (as opposed to brains from people with Alzheimer disease), the neocortex did not have large neuronal losses.[29] Instead, the cognitive declines that occur with normal aging might be a result of subtle changes, such as neuronal atrophy, which manifests as dendritic and perikaryal atrophy and reductions in the levels of neurotransmitters and receptors (for example, dopamine receptors).[30]

The neuronal atrophic changes that begin during midlife are accompanied by glial cell changes, which include white matter degeneration as well as astrocytic and microglial hyperactivity. White matter mostly consists of myelinated axons, through which messages pass between various areas of gray matter. Moderate to severe changes in white matter occur in up to one-third of people aged 65–84 years[31] and are termed leukoaraiosis.[32] On CT, leukoaraiosis is characterized by patchy or confluent

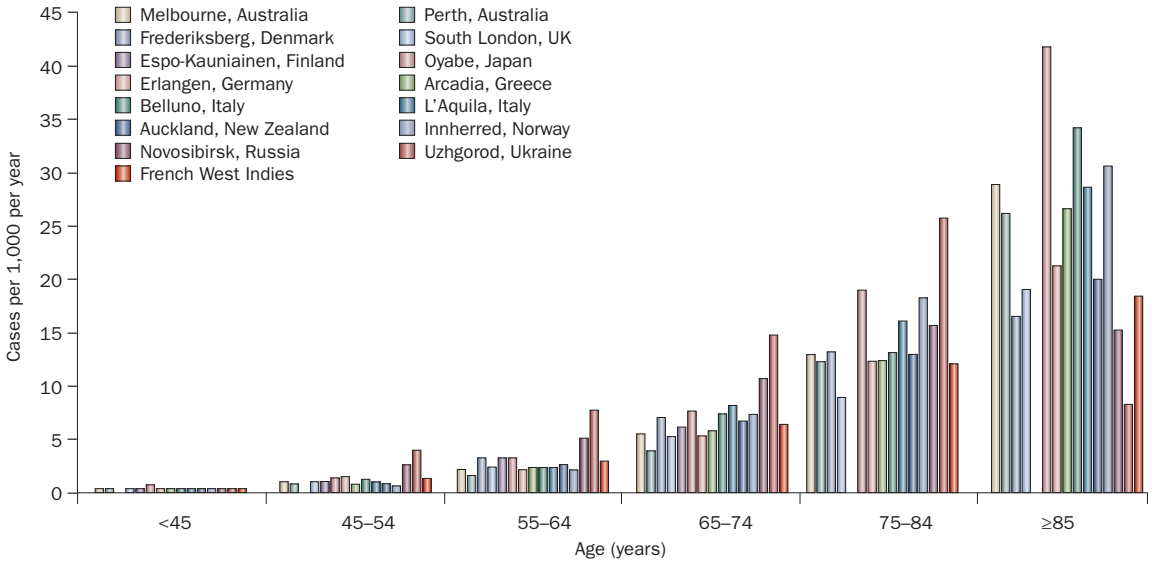

Figure 1 | Stroke incidence rates in various age groups at selected locations. Reprinted from *The Lancet Neurology*, **2**, Feigin, V. L., Lawes, C. M., Bennett, D. A. & Anderson, C. S., Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century, 43–53 © 2003, with permission from Elsevier.

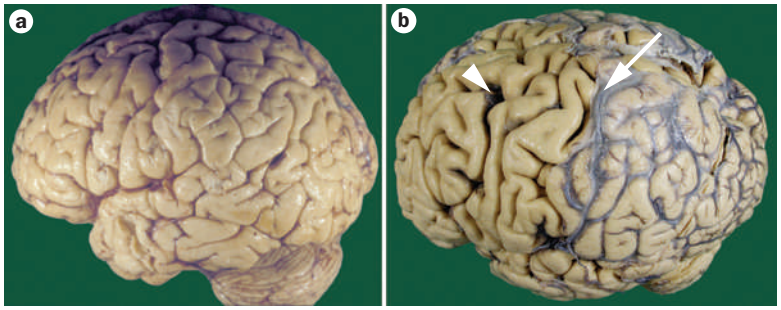

Figure 2 | Human brains at different ages. Brains from **a** | a middle-aged man and **b** | an elderly man. The front half of the elderly brain has had the meninges (arrow) removed for comparison of the cortex with the younger brain, which has the meninges completely removed. The elderly brain shows slightly wider gaps (arrowhead) between the folds of cerebral cortex at the surface (with the folds themselves being slightly narrower) than in the middle-aged brain.

periventricular and subcortical areas of low density, while on MRI areas of leukoaraiosis have high signal intensities.[33] Leukoaraiosis often affects the frontal ventricular caps[34,35] and is associated with particular manifestations of cognitive dysfunction during aging.[36,37] Specifically, periventricular white matter injury has been demonstrated to correlate with cognitive deficits,[38] whereas subcortical lesions have been shown to correspond to depressive symptoms.[36] In elderly people, leukoaraiosis has been shown to predict decline in motor performance, the onset of dementia, and rapid global functional decline.[39,40] Furthermore, leukoaraiosis has been seen in up to 44% of patients with stroke or transient ischaemic attack (TIA),[41] and the degree of leukoaraiosis correlates with the risk of recurrent stroke.[42]

Several age-related changes in white matter might contribute to the increase in vulnerability of axons to ischemia.[43] A drop in Na^+–K^+-ATPase performance in the brains of old rats compromised the ability of aging axons to maintain membrane properties and, as a result, caused white matter to be highly vulnerable to ischemia.[44] In old mice, white matter showed a twofold increase in GLT1 (the main transporter that removes glutamate from the extracellular space) gene expression and protein levels, which indicated an increase in glutamatergic signaling.[45] Indeed, the level of glutamate release was shown to increase in the striatum and hippocampus of old rats.[46] High levels of glutamate can cause excitotoxicity (and, hence, cell death) by triggering an influx of calcium ions into cells.[47] Calcium ion blockage led to an improvement in white matter function in young adult mice but did not ameliorate injury in old animals,[48] suggesting a calcium-independent mechanism of excitotoxicity in aged white matter.

The brain microvasculature that forms the blood–brain barrier (BBB) changes during aging. Studies in healthy individuals have reported that between 50 and 70 years of age capillary surface area decreases, while capillary diameter, volume and total length increase.[35,49,50] Such age-related degeneration of brain vasculature structure and function might lead to the disruption of local perfusion.[51,52] Modest 20% reductions in cerebral blood flow (CBF) are associated with diminished cerebral protein synthesis,[53] while more-severe reductions in CBF result in shifts in intracellular pH and water content, and accumulation of glutamate and lactate in brain interstitial fluid.[54] CBF reductions >50% impair ATP synthesis and decrease the ability of neurons to fire action potentials,[55] and severe reductions (>80%)—similar to the decrease in blood flow observed in ischemic stroke—lead to electrolyte imbalance and ischemic neuronal death.[56] Cerebral hypoperfusion might not necessarily cause ischemic injury as severe as in stroke, but does lead to oligemia and subsequent disruption of the microcirculation and damage to the cerebral endothelium.[56,57] Considerable evidence has accumulated suggesting that aging-related changes in brain microvasculature, particularly in the white matter, cause the aforementioned leukoaraiosis.[35,49,50]

The BBB might be able to accommodate subtle aging-related damage without showing any measurable functional changes under basal conditions, as the density of endothelial vesicles and numbers of gap junctions do not markedly change during aging.[58] A systematic review has shown, however, that BBB permeability increases with normal aging.[59] In more than two-thirds of the publications selected for this review, BBB hyperpermeability equated with an increase in the cerebrospinal fluid (CSF) to plasma albumin ratio.[59] An increase in this ratio might not be explained by BBB hyperpermeability alone, as the ratio might be affected by other factors, such as the decline in CSF secretion rate during aging.[60]

Aging-related alterations in cerebral vessels might eventually reduce cerebrovascular reserves and increase the susceptibility of the brain to vascular insufficiency and ischemic injury.[57] Such changes could underlie the increase in morbidity and mortality rates following ischemic stroke in older individuals and the high level of vascular cognitive impairment in this age group.[8] Table 1 lists these and other aging-related changes in the brain that are related to the increased vulnerability of the aged brain.

Aging-related risk factors

The incidence of stroke, and its associated morbidity and mortality, all of which rise markedly with increasing age, can be reduced by identifying and modifying risk factors (except age and sex) for this condition in older people (Box 1).[61]

Risk factor profiles have been found to differ between patients with stroke aged ≥80 years and younger individuals.[9] For example, one study showed that the incidence of ischemic stroke in patients <80 years of age was higher in men than in women.[9] Most very old patients with stroke (aged >80 years), however, are women.[62] This finding is probably explained by the survival difference between the sexes or the fact that at-risk women tend to have their stroke later in life than do men.[9]

Atrial fibrillation and congestive heart disease, both of which dramatically increase in prevalence with age,[63] have been clearly associated with cardioembolic ischemic stroke—the most frequent ischemic stroke subtype in very old patients.[64] In the Framingham study, atrial fibrillation was most prevalent among the elderly,[65] and the risk of stroke attributable to atrial fibrillation was determined to increase substantially with age, rising from

1.5% for individuals aged 50–59 years to 23.5% for people aged 80–89 years.[65] Furthermore, this study showed that the incidence of stroke increases more than fourfold in individuals with cardiac failure and nearly fivefold in patients with atrial fibrillation.[65] Similarly, as a result of an increase in cardiovascular dysfunction with age, 'watershed' infarction is more common in the elderly than in younger groups.[66]

Carotid artery stenosis is another major risk factor for ischemic stroke.[67] Despite good evidence of a high incidence of carotid artery stenosis in the elderly,[68] such stenosis is substantially underinvestigated in routine clinical practice in patients with stroke or TIA who are aged ≥80 years.[69] Moreover, very old patients can safely and successfully undergo carotid angioplasty and stenting.[70,71] Indeed, such patients have similar stroke and mortality rates to those found in young (aged <65 years) and older patients (aged 65–79 years).[72,73] The CaRESS (Carotid Revascularization using Endarterectomy or Stenting Systems) study showed that the risk of death, stroke or myocardial infarction in patients aged <80 years seemed to be higher following carotid endarterectomy than after carotid angioplasty and stenting.[74] By contrast, no relationships could be found among octogenarians between these procedures and death, stroke or myocardial infarction.[74]

Clinical manifestations

Clinical studies

Older patients with stroke not only have more-severe stroke deficits at presentation than do younger patients,[8,62,75] but they also recover more slowly.[7,75] Moreover, an older person who survives a stroke is more likely to need assistance in daily living or to require placement in an institution than a younger patient with stroke.[76] The dramatic clinical effect of stroke on older patients can be explained by changes in the vascular response to stress and injury with increasing age, which can result from factors such as prestroke medical and functional status, multiple organ dysfunction, consumption of multiple medications, and stroke severity.[62,63,77,78] In addition, older people who develop stroke often have comorbid illnesses that cause an increase in disability and needs.[62,77–79] Following a first-ever stroke or a TIA, individuals aged >65 years have a threefold increased risk of stroke recurrence within the next 10 years compared with younger individuals.[80] Furthermore, advancing age has been shown to be an independent risk factor that influences short-term, intermediate-term and long-term mortality after acute ischemic stroke.[8,75,81–85] Indeed, the stroke mortality rate is highest in people aged ≥75 years,[84–86] but the reason for this high mortality rate is not known. Several factors might be important, such as stroke severity, the occurrence of atrial fibrillation associated with cardioembolic stroke (which has a higher mortality than penetrating-artery or large-artery atherosclerotic infarcts)[62,87] and the presence of medical comorbidities.[77–79] In addition, older patients with stroke often receive a lower quality of care than younger patients and are less likely to be treated with guideline-recommended stroke therapies.[83]

Table 1 | Neuropathological causes of vulnerability in the aged brain

Age-related changes	Brain region affected	Associated outcomes
Reduction in brain weight[165]	Cerebral cortex	Cognitive impairment; dementia
Small-vessel disease[166,167]	Cerebrum and basal ganglia	Major or minor cerebral infarcts; leukoaraiosis; stroke; cogntive impairment; dementia
Congophilic angiopathy[168,169]	Leptomeningeal and cortical arteries and aterioles	Cognitive impairment; dementia; subarachnoid and intracerebral hemorrhage
Tortuosity[170]	White matter arterioles	Decrease in cerebral blood flow; leukoaraiosis; dementia (Alzheimer disease)
Multiple brain pathologies[171]	Various	Cognitive impairment; dementia
Advanced glycation end products[172,173]	Cortical neurons	Cognitive impairment; dementia
Intraneuronal tau inclusions[174]	Cerebral cortex, hippocampus, basal ganglia and brain stem	Cognitive impairment; dementia (Alzheimer disease); progressive supranuclear palsy
Intraneuronal α-synuclein inclusions[175]	Cerebral cortex, amygdalae and brain stem	Cognitive impairment; dementia (dementia with Lewy bodies); Parkinson disease; ataxia and autonomic failure (multiple system atrophy)
Expanded ventricles and increase in choroid plexus weight[25]	Ventricles and choroid plexus	Reduction in cerebrospinal fluid flow rate; dementia (Alzheimer disease)

Animal models

Studies on aged animals (for example, rodents) can closely mimic the clinical features of older patients with stroke.[88,89] Aged animals shown greater infarction volumes and a higher mortality rate than young animals following middle cerebral artery occlusion (MCAO).[88–92] Furthermore, while animals of all ages have shown neurological deficits after MCAO, old animals exhibited poorer performances than young animals in functional tests.[89,91] In one study, young animals showed a marked improvement in their neurological deficits as soon as 24 h after MCAO, whereas old animals continued to show substantial deficits.[92] The mean arterial blood pressure rose markedly during MCAO in young rats; however, aged rats exhibited a notable decrease.[91] Aged mice of both sexes showed considerably reduced stroke-induced edema compared with young animals.[92] This finding is consistent with the clinical observation that young patients with stroke are more likely to develop fatal brain edema than older patients.[93] Functional recoveries are reported to diminish in aged animals after cerebral ischemia.[94] This result reflects the effect seen in older patients, who often experience severe functional disabilities following a stroke.[76]

Treatment

The fundamental approaches to acute ischemic stroke therapy are reperfusion and neuroprotection, with early reperfusion being the most effective therapy in humans.[95] Early clot lysis with recombinant tissue plasminogen activator (rtPA) up to 3 h after ischemic stroke improves patients outcomes.[96,97] Indeed, rtPA treatment remains

Box 1 | Risk factors for first-ever stroke in the elderly

Sex
Stroke is most common in elderly (individuals aged 65–79 years) men (level 1A evidence),[157] although women comprise the largest proportion of very old (>80 years) patients with stroke (level 1A evidence)[158]

Atrial fibrillation
The risk of stroke from atrial fibrillation rises with advancing age, even in people aged >80 years (level 1B evidence)[65]

Other cardiovascular diseases, such as ischemic heart disease and heart failure
Cardiovascular disease remains a risk factor for stroke in the elderly, even in very old individuals (level 2A evidence)[159]

Carotid stenosis
Carotid stenosis is a risk factor for stroke in the elderly, even in octogenarians (level 1A evidence)[160]

High blood pressure
Hypertension is an important risk factor for stroke in patients <80 years but is less important for patients >80 years (level 1B evidence)[161]

High blood cholesterol
High blood cholesterol remains a risk factor for stroke in the elderly, but not in the very old (level 2A evidence)[162]

Metabolic syndrome
Metabolic syndrome is a strong independent risk factor for acute nonembolic ischemic stroke in older people (level 3B evidence)[163]

Adiponectin
Adiponectin has a modest role in the etiology of ischemic stroke in older people (level 3B evidence)[164]

Levels of evidence defined by the Centre for Evidence-based Medicine, Oxford, UK (http://www.cebm.net/)

the only approved therapy for acute ischemic stroke.[98] Nevertheless, elderly patients, and very old individuals in particular, have been underrepresented in or excluded from some of the largest studies of rtPA; thus, a major gap remains in our knowledge relating to this treatment. For example, part two of the National Institute of Neurological Disorders and Stroke (NINDS) rtPA trial included only 42 patients aged ≥80 years (624 patients in total).[96] Despite the underrepresention of very old patients, this monumental study showed that a beneficial effect of rtPA was apparent across all age groups.[96] Moreover, the results from the *post hoc* subgroup analysis did not support subselection of patients for thrombolytic therapy on the basis of age alone but, rather, suggested that patient selection for rtPA treatment should follow existing guidelines.[99]

Despite the positive results from the NINDS trial, the European Cooperative Acute Stroke Study (ECASS-3)[100] and the Safe Implementation of Thrombolysis in Stroke-Monitory Study (SITS-MOST)[101] excluded patients aged ≥80 years. The exclusion of such patients was in response to concerns regarding the risk of intracerebral hemorrhage (ICH),[102] as some older people are predisposed to symptomatic ICH after thrombolysis. Factors that predispose individuals to ICH include an impaired ability to clear tPA, age-associated microangiopathy (either cerebral amyloid angiopathy or hypertensive microangiopathy), and leukoaraiosis.[103–105] A systematic review of patients with stroke aged ≥80 years who were treated with intravenous rtPA showed that these individuals had a threefold higher mortality risk and less favorable outcomes at 3 months than younger patients receiving such therapy.[106] The risk of symptomatic ICH, however, was similar in both age groups. Similarly, other studies have suggested that the risk of ICH from thrombolytics is not increased by age, and that older patients tend to benefit from such treatments, despite the low rate of administration of thrombolytic therapy to the elderly.[102,104,107–109] To fill in the major gap in our knowledge relating to rtPA, more elderly patients with stroke need to be included in randomized controlled trials. The ongoing Third International Stroke Trial (IST-3), which has no upper age limit on participants, might provide better evidence than previous studies for the effectiveness of rtPA in very old patients with stroke.[110]

Intra-arterial fibrinolysis has potential for the treatment of acute ischemic stroke; however, as with intravenous rtPA studies, limited data exist regarding the safety and efficacy of intra-arterial fibrinolytics in elderly patients. Indeed, patients aged ≥85 years were excluded from the Prolyse in Acute Cerebral Thromboembolism (PROACT) randomized clinical trials of intra-arterial prourokinase.[111,112] Other studies have shown that independent predictors for hemorrhagic transformation after intra-arterial fibrinolysis include the NIH Stroke Scale score, platelet count, time to recanalization and serum glucose level, but not age.[113,114] In a comparative study of ischemic stroke patients who received intra-arterial treatment, the recanalization and hemorrhagic rates were similar between patients aged ≥80 years and younger individuals, although the mortality rate was higher and the functional outcomes were poorer in the older group.[115]

Endovascular treatments, such as combined intravenous and intra-arterial thrombolysis (the 'bridging approach'),[116] mechanical thrombectomy devices (as are being tested in the MERCI trial),[117] the penumbra technique,[118] and angioplasty with balloon-expandable or self-expandable stents,[119] are all promising alternative treatments for patients who are ineligible for standard intravenous thrombolytic therapy. These endovascular techniques have overcome some of the limitations of systemic intravenous thrombolysis, including the narrow therapeutic window, poor recanalization rate, high hemorrhagic rate, and inability to visualize the immediate effectiveness of treatment.[120] Moreover, in carefully selected patients, such techniques have been shown to be safe and effective.[121] Perhaps not surprisingly, limited data exist regarding the benefits of endovascular therapies in the oldest old people, as patients aged >80 years were excluded from the Interventional Management of Stroke (IMS) II study.[122]

Neuroprotection strategies aim to protect neurons from ischemia–reperfusion injury and to amplify the time window for thrombolytic treatment.[123] More than 1,000 drugs have been investigated for use in neuroprotection; however, only around 100 of these agents have reached clinical trials,[124] and none has proved successful in humans.[95] One contributing factor for this translational failure is that most of the preclinical studies

of these drugs were conducted on young animals, which do not truly mimic the clinical effects of stroke in older humans.[88,89] The Stroke Therapy Academic Industry Roundtable now recommends that aged animals be considered in preclinical studies.[125]

Since the use of acute interventional stroke therapies in the elderly is limited and prognosis following stroke is often poor in this vulnerable group, the treatment of other factors (for example, routine hydration, as well as active treatment of fever and hyperglycemia) might improve patient outcome. Effective acute stroke therapy can go beyond thrombolysis. Early mobilization and correction of abnormal physiological variables after stroke not only improve stroke care, reduce disability and complications, and improve long-term survival, but also lower the risk of recurrence.[126–128] Admission to a stroke unit has been shown to have marked potential benefits across all age ranges.[129,130] Performance measure-based treatment rates improve substantially over time for ischemic stroke patients in all age groups, resulting in smaller age-related treatment gaps.[81] Elderly patients who survive stroke often need long-term rehabilitation and supportive care, which are beyond the scope of this Review.

Antihypertensive therapy forms the cornerstone for both primary and secondary prevention of stroke. Studies of blood pressure reduction have demonstrated a 30–40% reduction of stroke incidence across all age groups.[131,132] The results of the Hypertension in the Very Elderly Trial (HYVET), which examined people aged ≥80 years, suggested that treating hypertension using indapamide, with or without the addition of perindopril, was associated with a 30% reduction in the rate of fatal or nonfatal stroke, a 39% reduction in the rate of death from stroke, a 23% reduction in the rate of death from cardiovascular causes, and a 21% reduction in the rate of death from any cause.[133] Hypertensive treatment has also been shown to decrease the risk of recurrent stroke by ≈ 30%.[134,135] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial—the first large-scale prospective blood pressure study in secondary prophylaxis after stroke—showed that active treatment with the angiotensin-converting enzyme inhibitor perindopril, with or without the diuretic indapamide, led to a 28% reduction in the risk of recurrent stroke in patients with a mean age of 64 years.[136] The Morbidity and Mortality After Stroke—Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study, which included older people (mean age 68 years), showed that in patients with previous cerebrovascular disorders, eprosartan-based therapy was more effective than calcium channel blocker (nitrendipine)–based therapy in reducing the incidence of cardiovascular and cerebrovascular events.[137]

No single well-established blood pressure level has been set in very old individuals. The target blood pressure used in HYVET was 150/80 mmHg.[133] Similarly, the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial, which was designed for elderly patients with high-risk hypertension, set a similar target of 150/85 mmHg.[138] The recommendation from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure was 140/90 mmHg.[139] However, blood pressure lowering to below 140/90 mmHg must be done cautiously in elderly patients.[140] The maintenance of systolic blood pressure at 140–150 mmHg and diastolic blood pressure at 80–90 mmHg has been found to be safe in older individuals and to reduce the risk of orthostatic reactions or cerebral hypofusion.[133,138,140]

Antiplatelet drugs, which inhibit platelet adhesion and aggregation, have an important role in acute ischemic stroke treatment and in both primary and secondary prevention. Aspirin decreases early mortality in patients with acute ischemic stroke when administered within 48 h of symptom onset. Moreover, in such patients, aspirin lowers the risk of all vascular events (including stroke) by ≈22%.[141–143] Similarly, low-dose aspirin has been shown to markedly reduce the risk of ischemic stroke among healthy women aged ≥65 years.[144] Very old patients are recommended to be treated with an antiplatelet drug if they have symptomatic atherosclerosis or are at a high risk of cardiovascular events.[7] Aspirin, clopidogrel, and the combination of aspirin and modified-release dipyridamole are all acceptable options for initial secondary stroke prevention, according to national guidelines based on evidence from clinical trials.[145] Limited evidence is available, however, for the risk–benefit profiles of combination therapy in the very old.

In patients with atrial fibrillation (who are at a high risk of stroke), warfarin-based anticoagulant therapy (to prevent the formation and growth of cardiac thrombus) led to a 68% decrease in the risk of stroke, with virtually no increase in the frequency of major bleeding.[146] Subgroup analysis suggested that warfarin reduced stroke risk in patients aged >75 years, and that the efficacy of warfarin was consistent across all studies and subgroups of patients.[146] The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial enrolled 973 patients with atrial fibrillation who were aged >75 years. These patients were followed up 3 months after randomization and then every 6 months for an average of 2.7 years.[147] The trial demonstrated that anticoagulation with warfarin was associated with a >50% reduction of ischemic and hemorrhagic events and a similar rate of extracranial hemorrhage to aspirin.[147] The results from this trial, together with data from another study, suggested that anticoagulation treatment in people with atrial fibrillation who are aged >75 years is safe and effective (reducing both recurrent thromboembolism and mortality).[147,148] The anticoagulant effect of warfarin might vary over time as a result of multiple food and drug interactions, thereby necessitating dose adjustments according to the international normalized ratio of antithrombin time.[149]

Incidental findings indicate that statins, the most widely used therapeutic agents for the control of plasma cholesterol, reduce the risk of ischemic stroke in patients with or without coronary disease.[150] A meta-analysis by the Cholesterol Treatment Trialists' Collaboration demonstrated the benefit of statins in prevention of major vascular events in both young and older patients,

with a 22% reduction in relative risk in patients aged ≤65 years and a 19% reduction in patients >65 years.[151] The JUPITER (Justification for the Use of Statins in Primary Prevention—an Intervention Trial Evaluating Rosuvastatin) trial showed that rosuvastatin prevented cardiovascular events, including ischemic stroke, in patients with normal lipid levels but with elevated levels of high-sensitivity C-reactive protein.[152] This study included few elderly patients, despite not setting an upper age limit in the inclusion criteria.[152] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial found that treatment with atorvastatin reduced the risk of recurrent stroke in both the elderly and young patient groups compared with controls.[153] The results from this study support the use of atorvastatin in elderly patients with recent stroke or TIA.[153] A meta-analysis has confirmed the benefit of statins in secondary stroke prevention in the elderly (patients aged 65–82 years).[154] In this study, statin therapy led to a 25% reduction in all-cause mortality and stroke.[154] The mechanisms whereby statins provide benefit against stroke are probably beyond lipid lowering and are likely to be multifactorial. Indeed, statins might have anti-inflammatory, anti-thrombotic, plaque stabilizing and/or antioxidant effects.[155] Prospective statin trials should measure initial stroke severity to determine whether these drugs also have a neuroprotective effect.[156]

Conclusions

The incidence of stroke and level of poor outcome after stroke (in terms of disability and mortality rate) both increase with age. With the growth of the global elderly population, the prevalence of stroke will also rise. As a consequence, the cost of stroke-related health care will escalate and exert a major pressure on medical resources. A vital need exists to identify and modify risk factors for stroke in the elderly, as well as to increase the awareness of the importance of stroke therapy in this age group. The reasons for the increase in vulnerability of the aged brain to stroke have only been systematically investigated in the recent past. The aims of future research should be to dissect the interaction between stroke and age-related CNS compromise to understand why old age imposes this great vulnerability, and to improve our ability to discern which therapeutics can be translated from the bench to the bedside. As age seems to be the most important risk factor for stroke, the prevention, evaluation and management of elderly patients needs particular attention.

Review criteria

Relevant evidence was found by searches of MEDLINE, Embase and the Cochrane Library using the following terms: "stroke", "cerebrovascular accident", "ischemic stroke", "ischaemic stroke", "cerebral ischemia", "cerebral ischaemia", "epidemiology", "older people", "elderly", "aging", "ageing", "aged", "aged brain", "risk factors", "management", "treatment" and "outcome". The searches were limited to studies published in English before February 2010. The articles retrieved included both human and animal studies. Articles were also identified from reference lists of the retrieved articles, cross-referencing and the content pages of the most prominent stroke journals. The final reference list was selected on the basis of each article's relevance to the topics covered in this Review.

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Acknowledgments

We are grateful for funding received from the Dunhill Medical Trust, the Medical Research Council, the Fondation Leducq, the Biomedical Research Center, the National Institute for Health Research, and the Oxford Radcliffe Hospitals National Health Service Trust. Charles P. Vega, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the MedscapeCME-accredited continuing medical education activity associated with this article.