

Stroke in old age

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Abstract

Strokes are more common in old age, and with an increasingly ageing population, Sri Lanka is likely to witness a dramatic increase in older patients with stroke. Strokes are different, are more severe and lead to more deaths and disability in old age, requiring different approaches to management. However, decision making on treatment and prevention of stroke in old age is hampered by a lack of robust evidence, as clinical trial data on stroke in old age is limited. Available data suggest that effective treatment and prevention options are underutilized due to a sense of therapeutic nihilism and concerns over safety of medications. More research is clearly needed to define the optimal treatment and preventive strategies.

Key words: stroke, old age, elderly, geriatric, management

Stroke is a problem in old age

People worldwide are living longer. It is estimated that the number of old people (aged ≥ 65 years) worldwide will exceed the number of young people (aged < 65 years) by 2050.¹ Importantly, by 2050, 80% of these older people are expected to be living in low- and middle-income countries like Sri Lanka.²

Stroke is a global health problem and is the second leading cause of death and the third leading cause of death and disability combined worldwide.³ The incidence of stroke increases markedly with age, with a doubling of incidence seen in each decade over the age of 55 years.⁴ One-third of all strokes in high income

countries are seen in those over the age of 80 years.⁵ Stroke outcomes are poorer in old age due to many overlapping factors. Older people have more severe strokes,⁶ more severe physical, psychological and social consequences of stroke,⁷ and higher mortality after stroke.^{1,7} They are also more likely to show a lower response to rehabilitation and have higher residual disability among survivors.⁸


Strokes are different in old age

Older adults have different strokes, different stroke mechanisms and different stroke risk factors. The typical stroke presentations are not seen in older age groups, and 'atypical' syndromic presentations such as delirium, falls, immobility, incontinence, pain and sepsis are more likely.⁵ As a result, stroke symptoms are often under recognized as due to stroke by patients, families, caregivers, ambulance staff and hospital staff, leading to delays in reaching hospital and receiving appropriate care, and sometimes mismanagement.

Underlying aetiological mechanisms of stroke are different in old age. Ischaemic strokes are more likely to be related to cardiogenic embolism, and intracerebral haemorrhages are more likely to be lobar haemorrhages related to amyloid angiopathy rather than hypertension-related deep subcortical haemorrhages.^{5,6} The incidence of atrial fibrillation (AF) doubles with each successive decade after the age of 55 years,⁷ and AF becomes an increasingly important risk factor for ischaemic stroke in older people.^{1,5,9} In a large population study of people aged > 65 years in northern England, the main stroke risk factors identified were previous TIA, AF, smoking, hypertension, and a composite of cardiovascular disease (ischaemic heart

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disease, peripheral vascular disease or heart failure). Diabetes and obesity were not important risk factors.⁴ The relative importance of hypertension and dyslipidaemia as stroke risk factors decline with increasing age, especially in the very old (>80 years).^{1,4}

There are several good reasons for the differences in stroke seen in old age. Ageing is associated with changes in both the macrocirculation (large vessels supplying the brain) and the microcirculation that forms the blood-brain barrier. Microcirculatory changes include endothelial dysfunction, impaired cerebral autoregulation and impaired neurovascular coupling leading to inflammation and microvascular injury.¹⁰ These changes are clearly evident on neuroimaging as silent infarcts, white matter hyperintensities and microbleeds.¹⁰

Old age is associated with several conditions that have a direct impact on stroke risk, presentation and outcomes. Frailty, which is a common companion in old age, has a bi-directional relationship with stroke; it increases stroke risk and hinders post-stroke recovery, and stroke in turn is associated with increased frailty.¹¹ Multiple co-morbidities and multiorgan dysfunction are commonly seen in old age, and interact with other cardiovascular risk factors to increase stroke risk, and adversely affect stroke recovery.¹⁰

Stroke in old age needs different treatment – or does it?

Older adults are frequently denied appropriate stroke care due to widespread therapeutic nihilism. This is further compounded by a relative paucity of evidence to guide therapeutic decision making as most clinical trials exclude older adults, especially those over 80 years of age. This is particularly true regarding randomized trials on acute treatments such as thrombolysis and mechanical thrombectomy.^{4,7,10}

Intravenous thrombolysis is inadequately used, especially in the very old (>80 years). This may partly be related to concerns regarding excessive bleeding complications, and to conflicting recommendations in international guidelines. The American Heart Association/American Stroke Association guidelines do not recommend the use of intravenous t-PA in the 3-4.5-hour time window in patients >80 years of age,¹² whereas the European Stroke Organisation and Canadian guidelines have no different recommendations based on age.^{13,14} Older patients were shown to have higher rates of intracranial bleeding and excess mortality following t-PA treatment in several studies.^{1,6,15} However, in the large 3rd International Stroke Trial (IST-3), almost 80% of those randomized

were over the age of 80 years, and there was no difference in outcomes (mortality, disability, ICH) with age.¹⁶ A meta-analysis of nine randomised trials by the Stroke Thrombolysis Trialists' Collaborative Group showed that proportional treatment benefits with tPA were similar irrespective of age.¹⁷ Data on endovascular treatment (EVT) in old age is even more limited as very few older adults have been randomized in EVT trials. A meta-analysis of seven randomized trials by the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) collaboration showed that EVT was beneficial even in the very old, but the benefits were smaller compared to younger patients.¹⁸ Importantly, stroke unit care, which is effective in both ischaemic and haemorrhagic stroke, is known to produce significant benefits irrespective of age.¹⁹

Stroke prevention has to be different in old age

Stroke prevention is even more important in older individuals due to several reasons. As noted earlier, old age is the most important risk factor for stroke. Risk of recurrent stroke following a stroke or TIA is 3 times higher in those aged over 65 years. Strokes lead to vascular cognitive impairment and increase the risk of Alzheimer disease, and stroke prevention is considered the best way to minimise cognitive decline in old age.⁹ As in younger individuals, lifestyle modification, control of risk factors, and antiplatelet or anticoagulant treatment in ischaemic stroke remain the cornerstones in primary and secondary stroke prevention in old age, but these approaches may need to be modified due to special considerations in older people.

Blood pressure (BP) reduction is associated with a 30-40% stroke risk reduction across all age groups,¹ and lowering systolic BP by 5-10 mmHg reduces risk of stroke by 1/3rd.²⁰ However, lowering BP can lead to postural hypotension, falls and renal impairment in the elderly, and there is no consensus on an ideal target BP in older people.²⁰ Several large randomized trials such as HYVET (Hypertension in the Very Elderly; age ≥80 years, target BP 150/80 mm Hg), SPRINT (Systolic Blood Pressure Intervention Trial; age ≥50 years with high CVD risk, SBP target 120 mm Hg) and SPS3 (Secondary Prevention of Small Subcortical Strokes; mean age 63 years; target SBP <130 mm Hg) did not show reductions in stroke risk or mortality with intensive BP lowering.^{16,21,22} In contrast, the STEP trial (Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients; age 60-80 y, SBP target 110 mm Hg) showed a stroke risk reduction of 33% with intensive treatment, but this did not include those over 80 years of age.²³ Older people with stiff arteries

have a higher risk of brain ischaemia with diastolic blood pressure (DBP) <60 mm Hg and pulse pressure (PP) >60 mm Hg, and a systolic BP (SBP) of <120 mm Hg is best avoided.⁹

Lipid-lowering therapy is clearly indicated for stroke prevention in all age groups.^{1,5,9} A meta-analysis of 28 RCTs of statin therapy by the Cholesterol Treatment Trialists Collaboration showed stroke risk reduction with statin therapy irrespective of age.²⁴ Older patients are thought to benefit even more from lipid-lowering therapy than younger patients.^{9,25} The number needed to treat (NNT) to prevent one cardiovascular event with lipid lowering therapy is estimated to be 200 at 40 years, 38 at 60 years and 14 at 79 years.²⁶ A subgroup analysis of the IMPROVE-IT trial showed that the NNT to prevent one cardiovascular event with intensive lipid lowering therapy was 11 in patients ≥ 75 years, compared to 125 in those <75 years.²⁷

Antiplatelet drugs are effective in secondary prevention following ischaemic stroke, and the benefits in old age are similar to younger age groups.^{5,28} Current guideline recommendations regarding choice of antiplatelet agent (aspirin alone, clopidogrel alone or aspirin/dipyridamole combination) do not differ in old age. Aspirin or other antiplatelet agents are, however, not recommended for primary stroke prevention, similar to recommendations for younger individuals.^{5,9,29} Data from several recent RCTs such as ASCEND [A Study of Cardiovascular Events in Diabetes], ASPREE [Aspirin in Reducing Events in the Elderly] and ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events] have highlighted major concerns regarding the safety of aspirin in primary prevention of cardiovascular disease.⁹ A systematic review by the US Preventive Services Task Force showed increased risks of ICH and gastrointestinal bleeding with the use of aspirin for primary prevention, especially in old age.³⁰

Older adults have higher rates of cardioembolic stroke, especially due to atrial fibrillation, and are therefore more likely to benefit from anticoagulation for secondary prevention. However, they are less likely to receive anticoagulants due to concerns regarding falls and bleeding risk.⁹ In the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial, warfarin use was associated with >50% reduction of ischaemic and haemorrhagic stroke, compared to aspirin, in older people (aged ≥ 75 y) with AF, with no increase in bleeding.³¹ Treatment with direct acting oral anticoagulants (DOACs) is preferred in older patients.⁹ A meta-analysis of four RCTs showed that

benefits of DOACs in stroke prevention in AF, compared to warfarin, were similar between patients above and below 75 years, with DOACs associated with fewer intracranial bleeding but more gastrointestinal bleeding.³² Commencing anticoagulation in older people requires careful evaluation of falls risk, including assessment of functional capacity, neurological deficits, visual impairments, home hazards, comorbidities, current medications, and cognitive capacity for managing anticoagulant treatment.⁵ Risk scoring, such as CHA₂DS₂-VASc scoring, to determine the risk of stroke in AF is not needed in those over 80 years as they already are in a very high stroke risk category.⁵

Lifestyle changes are important in stroke prevention in old age, similar to younger individuals, with emphasis on smoking cessation, healthy diet, regular physical activity and maintaining an ideal body weight. Recent recognition of an intriguing interaction between the diet, intestinal microbiome and renal function may require modifications to the dietary recommendations in old age.⁹ Red meat and egg yolk contain dietary constituents which are converted by the gut microbiome to TMAO (trimethylamine N-oxide) which has been associated with endothelial dysfunction, atherosclerosis and cardiovascular disease. TMAO is renally eliminated and may be an important factor in stroke pathogenesis, especially when renal function declines in old age.^{9,33}

End piece – “*Primum non nocere*” (First, do no harm)

Strokes are different in old age and may require different treatment and preventive strategies. Optimal use of many available treatments and preventive measures is, however, hindered by a lack of robust data from older populations. Acute treatments and preventive interventions may lead to serious adverse events in older people with stroke, and the age-old concept of “First, do no harm” may be especially relevant in old age. Both overtreatment and undertreatment are common prescribing problems in these patients, and every clinical encounter should be a time for re-evaluation of all treatment options, cautious escalation of treatment where required and deprescription of all non-essential medications. Careful decision-making with due attention to many potential confounding factors such as drug adverse effects, drug interactions, co-morbidities, frailty, activity limitation and falls risk would minimise potential harm and lead to better outcomes. The ultimate goal in stroke care in old age should be ensuring a good quality of life, rather than trying to control the values in blood pressure charts or laboratory reports.

References

1. Chen RL, Balami JS, Esiri MM, Chen LK, Buchan AM. Ischemic stroke in the elderly: an overview of evidence. *Nat Rev Neurol*. 2010; **6**(5): 256-65. doi: 10.1038/nrneurol.2010.36
2. UN Decade of Healthy Ageing (2021-2030). Available from: <https://www.who.int/news-room/fact-sheets/detail/ageing-and-health>
3. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021; **20**(10): 795-820. DOI: 10.1016/S1474-4422(21)00252-0.
4. Rodgers H, Greenaway J, Davies T, Wood R, Steen N, Thomson R. Risk factors for first-ever stroke in older people in the northeast of England: a population-based study. *Stroke*. 2004; **35**(1): 7-11. DOI: 10.1161/01.STR.0000106914.60740.78
5. Lindley RI. Stroke Prevention in the Very Elderly. *Stroke*. 2018; **49**(3): 796-802. DOI: 10.1161/STROKEAHA.117.017952.
6. Chen CI, Iguchi Y, Grotta JC, et al. Intravenous TPA for very old stroke patients. *Eur Neurol*. 2005; **54**(3): 140-4. DOI: 10.1159/000089086.
7. Michael KM, Shaughnessy M. Stroke prevention and management in older adults. *J Cardiovasc Nurs*. 2006; **21**(5 Suppl 1): S21-6. DOI: 10.1097/00005082-200609001-00006.
8. Paolucci S, Antonucci G, Troisi E, et al. Aging and stroke rehabilitation. a case-comparison study. *Cerebrovasc Dis*. 2003; **15**(1-2): 98-105. DOI: 10.1159/000067137
9. Spence JD, Azarpazhooh MR, Larsson SC, Bogiatzi C, Hankey GJ. Stroke Prevention in Older Adults: Recent Advances. *Stroke*. 2020; **51**(12): 3770-77. DOI: 10.1161/STROKEAHA.120.031707.
10. Yousufuddin M, Young N. Aging and ischemic stroke. *Aging (Albany NY)*. 2019; **11**(9): 2542-44. DOI: 10.18632/aging.101931
11. Bushnell CD, Chaturvedi S, Gage KR, et al. Sex differences in stroke: Challenges and opportunities. *J Cereb Blood Flow Metab*. 2018; **38**(12): 2179-91. DOI: 10.1177/0271678X18793324.
12. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2019; **50**(12): e344-e418. DOI: 10.1161/STR.0000000000000211.
13. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J*. 2021; **6**(1): I-LXII. DOI: 10.1177/2396987321989865.
14. Boulanger JM, Lindsay MP, Gubitz G, et al. Canadian Stroke Best Practice Recommendations for Acute Stroke Management: Prehospital, Emergency Department, and Acute Inpatient Stroke Care, 6th Edition, Update 2018. *Int J Stroke*. 2018; **13**(9): 949-84. DOI: 10.1177/1747493018786616.
15. Engelter ST, Bonati LH, Lyrer PA. Intravenous thrombolysis in stroke patients of > or = 80 versus < 80 years of age – a systematic review across cohort studies. *Age Ageing*. 2006; **35**(6): 572-80. DOI: 10.1093/ageing/af1104.
16. Lindley RI, Wardlaw JM, Whiteley WN, Cohen G, Blackwell L, Murray GD, Sandercock PA; IST-3 Collaborative Group. Alteplase for acute ischemic stroke: outcomes by clinically important subgroups in the Third International Stroke Trial. *Stroke*. 2015; **46**(3): 746-56. DOI: 10.1161/STROKEAHA.114.006573.
17. Emberson J, Lees KR, Lyden P, et al. Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet*. 2014; **384**(9958): 1929-35. DOI: 10.1016/S0140-6736(14)60584-5.
18. McDonough RV, Ospel JM, Campbell BCV, et al; HERMES Collaborators. Functional Outcomes of Patients ?85 Years With Acute Ischemic Stroke Following EVT: A HERMES Substudy. *Stroke*. 2022; **53**(7): 2220-26. DOI: 10.1161/STROKEAHA.121.037770.
19. Langhorne P, Ramachandra S. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke: network meta-analysis. *Cochrane Database Syst Rev*. 2020; **4**(4): CD000197. DOI: 10.1002/14651858.CD000197.pub4.
20. Silver B, Anderson CS. Review of the Systolic Blood Pressure Intervention Trial for Hypertension Management: How Low to Go for Patients With Stroke? *Stroke*. 2016; **47**(6): 1692-4. DOI: 10.1161/STROKEAHA.116.012402.
21. Beckett NS, Peters R, Fletcher AE, Staessen JA, et al.; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008; **358**(18): 1887-98. DOI: 10.1056/NEJMoa0801369.
22. SPS3 Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet*. 2013; **382**:507-515. DOI: 10.1016/S0140-6736(13)60852-1
23. Zhang W, Zhang S, Deng Y, et al; STEP Study Group. Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension. *N Engl J Med*. 2021; **385**(14): 1268-79. DOI: 10.1056/NEJMoa2111437.
24. Cholesterol Treatment Trialists Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet*. 2019; **393**: 407-15. DOI: 10.1016/S0140-6736(18)31942-1
25. Gotto AM Jr. Intensive Lipid Lowering in Elderly Patients. *JAMA Cardiol*. 2019; **4**(9): 855-6. DOI: 10.1001/jamacardio.2019.2333.

26. Mortensen MB, Falk E. Primary Prevention With Statins in the Elderly. *J Am Coll Cardiol*. 2018; **71**(1): 85-94. DOI: 10.1016/j.jacc.2017.10.080
27. Bach RG, Cannon CP, Giugliano RP, et al. Effect of Simvastatin-Ezetimibe Compared With Simvastatin Monotherapy After Acute Coronary Syndrome Among Patients 75 Years or Older: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol*. 2019; **4**(9): 846-54. DOI: 10.1001/jamacardio.2019.2306.
28. Chen ZM, Sandercock P, Pan HC, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40 000 randomized patients from the Chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. *Stroke*. 2000; **31**: 1240-9.
29. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019; **140**: e563-e595. DOI: 10.1161/CIR.0000000000000677
30. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016; **164**: 826-35. DOI: 10.7326/M15-2112
31. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007; **370**(9586): 493-503. DOI: 10.1016/S0140-6736(07)61233-1.
32. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014; **383**: 955-962. DOI: 10.1016/S0140-6736(13)62343-0
33. Roncal C, Martínez-Aguila, E, Orbe J. et al. Trimethylamine-N-Oxide (TMAO) Predicts Cardiovascular Mortality in Peripheral Artery Disease. *Sci Rep*. 2019; **9** (1): 15580. DOI: 10.1038/s41598-019-52082-z