Secondary Prevention of Stroke in the Very Elderly Patient

Tony Rudd
Emeritus Professor Stroke, Kings College London
Former National Clinical Director for Stroke NHS England
What are the issues?

- The older stroke patient group (over 80) is not homogenous. In fact very diverse - more so than the younger population.
- Very little good epidemiological data on the patients in terms of risk factors, natural history stroke type and recurrence rates of different stroke types.
- Many trials exclude older patients and especially those with significant comorbidities.
- Estimation of benefit using relative benefit may be misleading - relative risk benefit may decline with age but absolute risks increase often leading to similar absolute benefits for old and young.
What are the issues?

- Some treatments may **take longer to show benefit** than life expectancy e.g. statins, carotid endarterectomy
- Risks and side effects of treatment **may increase with age** and comorbidities therefore shifting the balance of risk and benefit
- Issues of **polypharmacy**
- **Lifestyle changes** – exercise, dietary adjustments, cessation of smoking **may be more difficult**
- Importance of considering **impact on all outcomes**, not just stroke
Cumulative incidence of any cerebrovascular event over 5 years after stroke or TIA (all ages)

Registry of TIA clinics in 21 countries that enrolled 4789 patients with a TIA or minor ischemic stroke from 2009 to 2011. 30% have a cerebrovascular event by 5 years, of which about half TIA.

Is the risk of stroke recurrence greater in older patients?
Population-based stroke surveillance study that began in 1985; 15,438 residents living in a township in Tianjin, China,

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Age-adjusted rates of recurrent stroke by subtypes [% (95% CI)].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>Recurrence rate within 1 year</td>
</tr>
<tr>
<td><strong>SEX:</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>6.9 (5.1, 8.8)</td>
</tr>
<tr>
<td>Women</td>
<td>4.6 (2.7, 6.5)</td>
</tr>
<tr>
<td>Total</td>
<td>5.7 (4.4, 6.9)</td>
</tr>
<tr>
<td><strong>SUBTYPES OF FIRST-EVER STROKE:</strong></td>
<td></td>
</tr>
<tr>
<td>IS</td>
<td>6.2 (4.7, 7.8)</td>
</tr>
<tr>
<td>ICH</td>
<td>6.1 (3.0, 9.2)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td><strong>AGE GROUPS:</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;45 years</td>
<td>0</td>
</tr>
<tr>
<td>45–64 years</td>
<td>4.9 (3.0, 6.8)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>7.4 (5.3, 9.4)</td>
</tr>
</tbody>
</table>

In this cohort recurrence rates greater in those over 65 years

Han J, Mao W, Ni J, et al. Rate and Determinants of Recurrence at 1 Year and 5 Years After Stroke in a Low-Income Population in Rural China. *Front Neurol.* 2020;11:2
**Prevalence of modifiable risk factors in stroke patients under 75 years and 75 years and older (Diabetic Chinese population)**

<table>
<thead>
<tr>
<th>Previous history of diseases and risk factors</th>
<th>Younger group</th>
<th>Elderly group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2,298 (78.6)</td>
<td>515 (74.4)</td>
<td>0.017</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>144 (4.9)</td>
<td>94 (13.6)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Artery stenosis</td>
<td>804 (27.5)</td>
<td>186 (26.9)</td>
<td>0.739</td>
</tr>
<tr>
<td>Dyslipidemias</td>
<td>1,135 (38.8)</td>
<td>202 (29.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>487 (16.7)</td>
<td>130 (18.8)</td>
<td>0.182</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1,078 (36.9)</td>
<td>110 (15.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>522 (17.9)</td>
<td>32 (4.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Long X et al Mortality, Recurrence, and Dependency Rates Are Higher after Acute Ischemic Stroke in Elderly Patients with Diabetes Compared to Younger Patients. Front Aging Neurosci. 2016 Jun 16;8:142..
Outcomes at 12 and 24 months after ischaemic stroke (<75 years and 75 years and over)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Younger group</th>
<th>Elderly group</th>
<th>Unadjusted</th>
<th>P</th>
<th>Adjusted†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>2.95 (2.30–3.79)</td>
<td>2.18 (1.64–2.89)</td>
<td>&lt;0.001</td>
<td></td>
<td>2.18 (1.64–2.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dependency</td>
<td>2.13 (1.78–2.55)</td>
<td>1.81 (1.49–2.20)</td>
<td>&lt;0.001</td>
<td></td>
<td>1.81 (1.49–2.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1.45 (1.14–1.86)</td>
<td>1.37 (1.06–1.76)</td>
<td>0.003</td>
<td></td>
<td>1.37 (1.06–1.76)</td>
<td>0.016</td>
</tr>
<tr>
<td>36 months:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>3.44 (2.70–4.36)</td>
<td>3.10 (2.35–4.08)</td>
<td>&lt;0.001</td>
<td></td>
<td>3.10 (2.35–4.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dependency</td>
<td>2.30 (1.79–2.95)</td>
<td>2.04 (1.57–2.64)</td>
<td>&lt;0.001</td>
<td></td>
<td>2.04 (1.57–2.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1.54 (1.19–2.01)</td>
<td>1.40 (1.07–1.85)</td>
<td>&lt;0.001</td>
<td></td>
<td>1.40 (1.07–1.85)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

*OR indicated the risks in elderly group reference as younger group. †Indicated adjusted by gender, stroke subtype, severity, and risk factors.

Higher levels of death, dependency and recurrence in the older cohort

Long X et al Mortality, Recurrence, and Dependency Rates Are Higher after Acute Ischemic Stroke in Elderly Patients with Diabetes Compared to Younger Patients. Front Aging Neurosci. 2016 Jun 16;8:142..

Fig. 4 Proportion of the population alive 31st of December 2014 with a history of stroke up to 7 years back in time, for different age groups. Men and women.

Case 1

- 89 year old man admitted with left hemisphere infarct leaving him with severe right hemiplegia, dysphasia and some cognitive impairment (MMSE 20)
- Previously living independently. Previous peptic ulcer but no other known comorbidities
- Stroke risk factors identified
  - Hypertension
  - Hyperlipidaemia (total cholesterol 5.5mmol/l)
  - Smoker since teenager of approx. 10/day

What are the risks and benefits of antiplatelets?
Do we treat the hypertension?
Do we give a statin?
What are the benefits of stopping smoking?
Aspirin is remarkably effective at reducing ischaemic events.

No evidence of interaction with age (data from CAST and IST)
Benefits of early aspirin (all ages)

15,778 participants from 12 trials of aspirin vs control in secondary prevention. Aspirin reduced the 6 week risk of recurrent ischaemic stroke by about 60% and disabling or fatal ischaemic stroke by about 70% with greatest benefit noted in patients presenting with TIA or minor stroke.

Age specific annual rate of bleeding events by age

- 3166 patients  50% aged ≥75 years.
- 405 first bleeding events (218 gastrointestinal, 45 intracranial, and 142 other) during 13 509 patient-years of follow-up.

Aspirin complications after vascular events in older patients

- Risk of non-major bleeding unrelated to age.
- Major bleeding increased steeply with age (≥75 years hazard ratio [HR] 3.10, particularly for fatal bleeds HR 5.53)
- The estimated NNT for routine PPI use to prevent one disabling or fatal upper gastrointestinal bleed over 5 years fell from 338 for people <65 years, to 25 for individuals aged 85 years or older.
- Routine PPI use to prevent such bleeds should be encouraged.

Figure 1 Continuous relationship between usual blood pressure and the risk of stroke in 2435 individuals with a history of transient ischaemic attack (TIA) or minor stroke during 4 years' follow-up in the UK-TIA aspirin trial.
PROGRESS Collaborative Group Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack Lancet 2001;358:1033-1041
Comparison of placebo vs perindopril or indapamide plus perindopril after stroke or TIA regardless of whether hypertensive or not

PROGRESS Collaborative Group Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack Lancet 2001;358:1033-1041
PROGRESS Collaborative Group Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack Lancet 2001;358:1033-1041
### PROGRESS Trial Hypertensive and non-hypertensive patient subgroups

<table>
<thead>
<tr>
<th>Strokes</th>
<th>Favours active</th>
<th>Favours placebo</th>
<th>Risk reduction (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td>163 235</td>
<td></td>
<td>32% (17 to 44%)</td>
</tr>
<tr>
<td>Non-hypertensive</td>
<td>144 185</td>
<td></td>
<td>27% (8 to 42%)</td>
</tr>
<tr>
<td>Total</td>
<td>307 420</td>
<td></td>
<td>28% (17 to 38%)</td>
</tr>
</tbody>
</table>

**Stroke**

- Hypertensive
  - Strokes: 163
  - Placebo: 235
  - Risk reduction: 32% (17 to 44%)
- Non-hypertensive
  - Strokes: 144
  - Placebo: 185
  - Risk reduction: 27% (8 to 42%)
- Total
  - Strokes: 307
  - Placebo: 420
  - Risk reduction: 28% (17 to 38%)

**Standardised hazard ratio**

- Hypertensive: 0.5
- Non-hypertensive: 1.0
- Total: 2.0
Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual participant-level data meta-analysis

The Blood Pressure Lowering Treatment Trialists’ Collaboration

Summary

Background. The effects of pharmacological blood-pressure-lowering on cardiovascular outcomes in individuals aged 70 years and older, particularly when blood pressure is not substantially increased, is uncertain. We compared the effects of blood-pressure-lowering treatment on the risk of major cardiovascular events in groups of patients stratified by age and blood pressure at baseline.

Methods. We did a meta-analysis using individual participant-level data from randomised controlled trials of pharmacological blood-pressure-lowering versus placebo or other classes of blood-pressure-lowering medications, or between more versus less intensive treatment strategies, which had at least 1000 persons-years of follow-up in each treatment group. Participants with previous history of heart failure were excluded. Data were obtained from the Blood Pressure Lowering Treatment Trialists’ Collaboration. We pooled the data and categorised participants into baseline age groups (<55 years, 55–64 years, 65–74 years, 75–84 years, and ≥85 years) and blood pressure categories (in 10 mm Hg increments from <120 mm Hg to ≥170 mm Hg systolic blood pressure and from <70 mm Hg to ≥110 mm Hg diastolic). We used a fixed effects one-stage approach and applied Cox proportional hazard models, stratified by trial, to analyse the data. The primary outcome was defined as either a composite of fatal or non-fatal stroke, fatal or non-fatal myocardial infarction or ischaemic heart disease, or heart failure causing death or requiring hospital admission.
Rate of major cardiovascular events per 5 mm Hg reduction in systolic blood pressure, stratified by treatment allocation and age categories at baseline

The Blood Pressure Lowering Treatment Trialists’ Collaboration Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual participant-level data meta-analysis The Lancet 2021;398:1053-1064
Age-stratified relative risk and absolute risk difference of systolic blood pressure reduction on primary and secondary outcomes

Relative risk reductions are presented with hazard ratios and 95% CIs per 5 mm Hg reduction in systolic blood pressure, separately for each outcome. The absolute risk difference reflects the mean blood pressure reduction for each age category.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparator</th>
<th>Hazard ratio (95% CI) per 5 mm Hg reduction in systolic blood pressure</th>
<th>Absolute risk difference (95% CI) between treatment and comparator group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Major cardiovascular events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55 years</td>
<td>1485</td>
<td>21,594</td>
<td>2142</td>
</tr>
<tr>
<td>55-64 years</td>
<td>5936</td>
<td>59,649</td>
<td>7080</td>
</tr>
<tr>
<td>65-74 years</td>
<td>7413</td>
<td>59,560</td>
<td>9551</td>
</tr>
<tr>
<td>75-84 years</td>
<td>3825</td>
<td>24,747</td>
<td>574</td>
</tr>
<tr>
<td>≥85 years</td>
<td>459</td>
<td>22,47</td>
<td>582</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55 years</td>
<td>476</td>
<td>21,599</td>
<td>640</td>
</tr>
<tr>
<td>55-64 years</td>
<td>1763</td>
<td>59,649</td>
<td>2200</td>
</tr>
<tr>
<td>65-74 years</td>
<td>2584</td>
<td>59,640</td>
<td>3313</td>
</tr>
<tr>
<td>75-84 years</td>
<td>1595</td>
<td>24,78</td>
<td>1954</td>
</tr>
<tr>
<td>≥85 years</td>
<td>139</td>
<td>22,47</td>
<td>195</td>
</tr>
</tbody>
</table>

Interpretation: Pharmacological blood pressure reduction is effective into old age, with no evidence that relative risk reductions for prevention of major cardiovascular events vary by systolic or diastolic blood pressure levels at randomisation, down to less than 120/70 mm Hg. Pharmacological blood pressure reduction should, therefore, be considered an important treatment option regardless of age, with the removal of age-related blood-pressure thresholds from international guidelines.
Lipid Lowering after Ischaemic events: Heart Protection Study

10,000 patients receiving simvastatin 40mg and 10,000 placebo after vascular ischaemic event

Heart Protection Study Collaborative Group MRC/BHF
Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo controlled trial. Lancet 2002;360:7-22
Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study


Mean age at randomisation 63
Kaplan Meier survival curves for older patients after stroke treated with statin for more or less than two years

- 5910 patients >65 yrs included in retrospective cohort study; 3157 aged over 80
- Two years of statin prescription in patients aged 80 years and older resulted in both a lower risk of the composite end point (adjusted hazard ratio, 0.80 [95% CI, 0.62–1.02]) and all-cause mortality (adjusted hazard ratio, 0.67 [95% CI, 0.57–0.80]).

Lefeber GJ et al Statins after ischemic stroke in the oldest. Stroke 2021;52:1244-1252
Is it worth advising quitting smoking after stroke?

- One year after quitting, the added risk of coronary heart disease is half that of a smoker’s. Five to 15 years after quitting, a former smoker’s stroke risk is reduced to that of a nonsmoker’s. *2004 Surgeon General’s Report, The Health Consequences of Smoking*

- Two-thirds of older adults said that a healthcare provider advised them to quit smoking, but just over one-third who tried to quit used evidence-based tobacco cessation treatments and only one in 20 successfully quit in the past year *The 2015 National Health Interview Survey:*
How Would I Manage Case 1?

- Ask the question, is preventing another stroke relevant? Probably yes.
- Antiplatelets: Yes, despite previous bleed, clear benefit especially in the early weeks after stroke. I would use clopidogrel with a PPI.
- Antihypertensives: Yes to maintain BP below 140/80 and preferably 130.
- Cholesterol lowering: ask the question is the patient likely to still be alive after 2 years. If yes then treat with a statin.
- Smoking: advise quitting and provide support to do so – pharmacological and psychosocial support. Chances of success low.
- Don’t forget diet, exercise advice and support.
Case 2

- 88 year old woman with partial left anterior circulation infarct – moderate aphasia and reduced mobility – unsteady gait, susceptible to falling
- Previously known hypertensive. Mild cognitive impairment
- Atrial fibrillation identified as likely cause for the stroke

Do we anticoagulate?
Prevalence AF by Age

Figure 1. Summary of estimated atrial fibrillation prevalence in England, 2014

Unpublished report PHE 2015
Data from National Audit UK – Proportion of people Anticoagulated with known AF when admitted with stroke

Age

AF: Not anticoagulated
AF: Anticoagulated

SSNAP April 2017-March 2018
Risk assessment scores for AF treatment

<table>
<thead>
<tr>
<th>Annual risk of stroke based on CHADS₂ or CHA₂DS₂-VASc score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
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<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
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<tr>
<td>8</td>
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<tr>
<td>9</td>
</tr>
</tbody>
</table>

CHADS₂: 1 point each for congestive heart failure, hypertension, age ≥ 75, diabetes mellitus; 2 points for prior stroke or transient ischemic attack.

CHA₂DS₂-VASc: 1 point each for congestive heart failure, hypertension, age 65–74, diabetes mellitus, vascular disease (coronary artery disease, peripheral arterial disease, aortic aneurysm), sex category female; 2 points for age ≥ 75 and for prior stroke or transient ischemic attack.

<table>
<thead>
<tr>
<th>HAS-BLED¹⁴</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding history</td>
<td>1</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (age &gt; 65)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1</td>
</tr>
</tbody>
</table>

**Maximum score** 9

Hagerty et al Cleveland J Med 2017;85:35-40
Use and complications associated with anticoagulation for elderly patients with AF

Study of 33,539 patients with AF in Taiwan

Anticoagulant complications
between 2009 and 2015 in
people >85 years

- Lower mortality
- Fewer ischaemic stroke
- Fewer bleeding complications including ICH
- Overall fewer adverse events

Changes in anticoagulant usage between 2009 and 2015 in people >85 years

FIGURE 2. Temporal trends of the initiation rates of oral anticoagulants (OACs) among the elderly newly diagnosed atrial fibrillation (AF) patients. The initiation rates of OACs after AF was newly diagnosed in the elderly significantly increased from 9.5% to 34.3%, and is mainly due to the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) (from 0% to 26.2%).

Balancing the risks of falls and bleeding against the benefits of anticoagulation of patients with AF

- Incidence of falls in community living over 65 yrs 30% in previous year and 50% for nursing home residents

- Older adults with nonvalvular AF and a history of falls 1.9 increased risk of intracranial haemorrhage but no difference between those on antiplatelets, anticoagulants and no treatment. In this analysis, patients with a CHADS2 score of 2 or higher benefited from anticoagulation. Deandrea S, et al Arch Gerontol Geriatr 2013; 56:407–4

- In another study it was estimated that an individual would have to fall 295 times in 1 year for the risk of fall-related major bleeding to outweigh the benefit of warfarin in reducing the risk of stroke. Gage BF et al Am J Med 2005; 118:612–617.
How Would I Manage Case 2?

- Each patient needs an individual assessment; there can be no blanket rule including patient preference
- If severe impairment following previous stroke probably not advise anticoagulation
- I would not anticoagulate if major recent bleed
- Everyone else I would anticoagulate using direct oral anticoagulants regardless of age and falls risk. If high HAS-BLED score I would monitor anticoagulation more carefully but wouldn’t withhold
Case 3

- 90 year old woman with living in a nursing home. Moderate cognitive impairment, frail but mobile with a zimmer frame. Frequent faller
- Transient weakness of right side and dysarthria
- Carotid bruit, hypertensive, total cholesterol 5.0mmol/l

Do we investigate with brain imaging, carotid imaging?

Do we treat with antiplatelets?
Two major trials of carotid surgery for symptomatic disease

NASCET trial: Cumulative risk of ipsilateral stroke at two years was 26% in medically treated patients and 9% in surgical patients - absolute risk reduction 17%

ECST: Risk of disabling or fatal stroke was reduced in patients treated with CEA


Carotid endarterectomy or stenting

- The annual risk of stroke in individuals with symptomatic carotid stenosis about 4-12% without carotid intervention.
- Trials of carotid intervention in patients over 70 for symptomatic carotid stenosis consistently show better results for surgery vs stenting
- But risks of surgery high and numerous contraindications
- Carotid surgery trials done before introduction of high intensity medical interventions e.g. high intensity statins so benefits seen in earlier trials maybe attenuated
How Would I Manage Case 3?

- I would not do carotid endarterectomy or stenting. There are very few patients over the age 85 years that I would treat with surgery.
- I would image the carotids if I wanted to treat hypertension.
- No reason to do brain imaging – history clear and very unlikely to show haemorrhage.
- I would treat with a statin and an antiplatelet.
- I would treat hypertension very cautiously if carotid stenosis.
Summary

- Patients need individual assessment preferably by neurologist working in collaboration with a geriatrician
- Little evidence to suggest that any of the major secondary prevention treatments are less effective in the very elderly
- We do need more evidence to guide management of frail, multimorbid very elderly patients
An excellent summary of the evidence

Stroke
Volume 49, Issue 3, March 2018; Pages 796-802
https://doi.org/10.1161/STROKEAHA.117.017952

TOPICAL REVIEWS

Stroke Prevention in the Very Elderly

Richard I. Lindley, MD

Stroke remains a common cause of death and disability in the very elderly (here defined as those aged 80 years and older), with about a third of all stroke occurring in this age bracket in high-income countries.\(^1\) There is uncertainty on the exact pattern of stroke type in extreme old age, because of potential poor ascertainment of very frail and institutionalized older people in prior studies.