Secondary Stroke Prevention Strategies for the Oldest Patients:

Possibilities and Challenges

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Abstract

Older adults are not only at higher risk of experiencing stroke, but also have multiple co-morbidities that make treatment for secondary stroke prevention challenging. Very few clinical trials specifically related to secondary stroke prevention treatment efficacy have focused on the oldest-old (85 years) and, therefore, evidence-based recommendations for treatment specific to this population are not available. Some of the special considerations for stroke prevention treatments in older patients include careful titration of blood-pressure-lowering drugs to avoid hypotension, the risk of haemorrhagic stroke with HMG-CoA reductase inhibitors (statins) and weighing the risk of recurrent ischaemia versus bleeding in patients taking antiplatelet or anticoagulant therapy. The risk of peri-procedural complications appears to be high with both carotid angioplasty and stenting and carotid endarterectomy in older patients with carotid stenosis. Other common issues in older patients include adverse drug events, recognizing the risk of dementia, depression and osteoporosis and deciding when to discontinue secondary stroke prevention. In this review, we provide the practitioner with the evidence related to specific approaches to secondary stroke prevention in older patients, and identify the knowledge gaps that currently limit our ability to appropriately treat this vulnerable population.

1. Prevalence and Incidence of Stroke in Older Adults: the Need for Secondary Prevention

Stroke is a major cause of morbidity and mortality in older adults (figure 1), with the incidence increasing dramatically with age.[1–3] Previous occurrence of stroke is a major risk factor for recurrent ischaemic stroke,[4–7] with a cumulative 10-year risk of 43 % (95% CI 34, 51) after an initial event.[8] Survival after recurrent stroke is also significantly lower than after first stroke, especially with increasing age (figure 1).[9] The risk of secondary stroke is greatest in the first 6 months (9% ; 95% CI 5, 14) with an average annual risk of 4% thereafter. Previous occurrence of stroke is also a marker for increased risk of ischaemic events in other vascular beds.[4–7] Thus, even patients with limited life expectancies due to advanced age or co-morbidities may benefit from secondary prevention after a stroke.

Because ischaemic stroke is such a strong predictor of secondary ischaemic events, clinicians caring for older adults with a history of ischaemic stroke need to carefully

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consider secondary prevention strategies in these patients. Recent US studies suggest that older stroke patients receive less aggressive secondary prevention strategies than younger patients.[3,10] Of note, recurrent strokes are associated with higher rates of morbidity and mortality than incident events.[11] For example, in the Perth Community Stroke Study, the 30-day mortality rate for recurrent stroke was almost twice as great as that of an initial stroke (41% vs 22% ; p = 0.003).[8] Of the 637 patients enrolled in the MATCH (Management of Atherothrombosis with Clopidogrel in High Risk Patients) trial who had a recurrent event during the study period, 345 (54%) were disabled after the recurrent event; of these, only 33% were disabled prior to the event, [12] again emphasizing the need for secondary prevention. Unfortunately, although the burden of stroke is highest in the oldest subset of the population, much of the research on secondary prevention has been performed in relatively younger and healthier subjects. The purpose of this paper is to review the evidence for secondary prevention strategies after ischaemic stroke, with particular attention to its generalizability to frail, older populations.

2. Guideline Recommendations

The American Heart Association (AHA)/ American Stroke Association (ASA)[13,14] and the American College of Chest Physicians (ACCP)[15] have compiled evidence-based guidelines that contain recommendations for the secondary prevention of ischaemic stroke. The AHA/ ASA guidelines cover the full range of modifiable risk factors (table I), whereas the ACCP guidelines pertain only to antithrombotic/thrombolytic therapy (table II).

2.1 Literature Search Methods

Articles for this review were identified by searching the MEDLINE database (1950 to September 2008) using the following terms, either singly or in combination: 'adverse drug events', 'arthritis', 'dementia', 'depression', 'elderly', 'ischemic stroke', 'osteoporosis', 'quality improvement initiative', 'recurrent stroke', 'secondary prevention' and 'transient ischaemic attack'. Additional terms, which were identified using the current AHA/ASA recommendations for secondary stroke prevention as a guide, included 'anti-platelet', 'antithrombotic', 'diabetes', 'dyslipidemia', 'carotid stenosis', 'hyperhomocysteinemia', 'hypertension' and 'smoking'. Relevant articles published in the English language were identified by a review of their abstracts. Additional articles were identified by manually searching the reference lists of the initially identified articles. Articles were included in this review if they were (i) randomized controlled trials of secondary prevention of stroke; (ii) randomized controlled trials of primary prevention if focused on the elderly or those aged 75 years and stroke was a primary or secondary outcome; or (iii) cohort studies of strokes in the elderly or those aged 75 years. No other specific exclusion criteria or formal assessments of article quality were employed.

Based on the results of this search, we review the evidence for the major recommendations, highlighting results of clinical trials targeted to older adults, as well as the generalizability of the results of other trials to patients aged 75 years. Summaries of clinical trials included in this review can be found in tables III and IV.

2.2 Blood Pressure Lowering

Hypertension is one of the most prevalent modifiable risk factors for stroke. Antihypertensive treatments have been shown to reduce the relative risk of incident stroke by 28–39%.[32] Therefore, pharmacological therapy and lifestyle modifications are recommended for all patients who have had an ischaemic stroke or transient ischaemic attack (TIA) and who are beyond the hyperacute period, with a goal systolic blood pressure (BP) of <140 mmHg.[14] The Joint National Committee on Prevention, Detection,

Evaluation, and Treatment of High Blood Pressure recommends that a combination of diuretics and ACE inhibitors be used for secondary prevention of all patients, regardless of their BP levels.[33] These recommendations are primarily based on results from PROGRESS (Perindopril Protection Against Recurrent Stroke Study), in which patients with a recent stroke regardless of a history of hypertension were enrolled and randomized to perindopril or placebo (plus indapamide if additional BP control was necessary).[17,34] PROGRESS is the only trial of secondary prevention with BP-lowering medications, and it demonstrated that patients taking ACE inhibitors and diuretics in combination had a reduced risk of recurrent stroke, regardless of BP levels or a history of hypertension. However, it is important to recognize that the mean age of subjects in PROGRESS was 64 years and that older patients may be at higher risk of adverse drug reactions from these agents.

We also included primary prevention trials in this review when stroke was a primary outcome and the trial was focused on older patients. A number of trials have shown that antihypertensive treatment can lower the risk of incident stroke in older patients with known hypertension. These include the STOP-Hypertension (Swedish Trial in Old Patients with Hypertension)[18] and the SHEP (Systolic Hypertension in the Elderly Program).[19,35] Interestingly, in the per-protocol analysis of the SYST-EUR (Systolic Hypertension in Europe) trial,[36] the benefit of mortality reduction with anti-hypertensive treatment was attenuated in patients aged 75–80 years, but the protection against cardiovascular events was not. Therefore, the totality of current evidence favours control of BP in all older patients.[18,19,36–38]

Recently, results from the HYVET (Hypertension in the Very Elderly Trial) were reported.[21] In this placebo-controlled trial of 3845 patients aged 80 years, antihypertensive treatment with an indapamide-based regimen reduced the number of fatal and non-fatal strokes from 17.7 per 1000 patient-years to 12.4 per 1000 patient-years (unadjusted hazard ratio [HR], 0.70; 95% CI 0.49, 1.01; p = 0.06); the number of fatal strokes from 42 per 1000 patient-years to 27 per 1000 patient-years (HR 0.61; 95% CI 0.38, 0.99; p = 0.046); and the number of deaths from any cause from 235 per 1000 patient-years to 196 per 1000 patient-years (HR 0.79; 95% CI 0.65, 0.95; p = 0.02). This reduction in mortality is somewhat surprising because results from the HYVET pilot study reported that antihypertensive therapy increased the number of non-stroke deaths by 20 for every 1000 patients treated for 1 year.[20] A recent study of elderly veterans found a higher mortality rate among patients aged >80 years with lower BP, raising concern about the advisability of aggressive BP targets in the oldest-old, although the cohort design may have led to unmeasured confounders that influenced the result.[39] Given the preponderance of evidence from randomized trials such as SHEP, SYST-EUR, STOP-Hypertension and HYVET, which included subjects aged >80 years, we believe that current BP targets are appropriate with careful titration to avoid orthostatic hypotension.

2.3 Dyslipidaemia

Hyperlipidaemia is a stronger risk factor for coronary artery disease than for stroke. [40,41] However, treatment with HMG-CoA reductase inhibitors (statins) in patients with coronary disease significantly reduced the risk of stroke in multiple randomized controlled trials.[42–49] Current guidelines recommend that patients with cerebrovascular and/or coronary vascular events should have cholesterol levels managed according to guidelines established by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (NCEP III), with a goal low-density lipoprotein cholesterol (LDL-C) level of <100 mg/dL.[13,14,49]

Although it is very important to assess secondary prevention with statin therapy in patients with cerebrovascular disease but no evidence of coronary disease, very few trials have

directly addressed this question or that of use of statins for stroke prevention in the elderly. However, the Medical Research Council/British Heart Foundation Heart Protection Study (HPS)[42] was sufficiently large and included a suitably wide variety of patients with vascular disease to allow assessment of these issues. In the subgroup of patients with a history of cerebrovascular disease but no coronary disease in this study, there was a significant reduction in major cardiovascular events with statin treatment, although rates of stroke were unaffected. The PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease) study, conducted specifically in the 70-to 82-year-old population with a history of, or risk factors for, vascular disease, also showed no significant reduction in stroke events, although there was a modest reduction in TIAs.[24] The only trial to address secondary prevention for stroke was the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study.[23] This was a randomized, controlled trial of high-dose atorvastatin versus placebo in patients with a history of recent stroke or TIA and LDL-C levels between 100 and 190 mg/dL. A significant treatment benefit in favour of atorvastatin was observed, with an absolute risk reduction of 2.2% and an adjusted HR of 0.84 (95% CI 0.71, 0.99; $p = 0.03$) for the primary outcome of non-fatal or fatal stroke. However, similar to the results of the HPS,[42] there was even greater protection against cardiovascular events (e.g. HR for any coronary event 0.65; 95% CI 0.46, 0.73; $p < 0.001$).[23]

An additional important result of SPARCL was a haemorrhagic stroke rate of 2.3 % in the atorvastatin group versus 1.4% in the placebo group (adjusted HR 1.66; 95% CI 10.8, 2.55).[23] Aside from statin therapy, other independent predictors of haemorrhagic stroke in SPARCL included male sex, stage 2 hypertension at the last visit preceding the event and increased age (HR 1.42; 95% CI 1.16, 1.74 for 10-year increments).[50] Because the mean age of subjects in SPARCL was 63 years and there was a significant age-related risk of haemorrhagic stroke, caution is required when administering high-dose atorvastatin to the oldest population of stroke patients. Thus, the available evidence suggests that statin therapy after stroke yields only a small reduction in recurrent strokes and a small but significantly increased risk of haemorrhagic stroke in the elderly. While randomized trials are not available for the oldest-old, a matched cohort study of 2626 nursing home residents with vascular disease, 1313 of whom were taking statins, showed a 31% relative decrease in the hazard of hospitalization and mortality from secondary vascular events associated with statin use, with the number needed to treat to prevent one additional event being 5–7 patients.[51] However, it should be emphasized that this cohort was treated with conventional doses rather than the high doses of statins used in SPARCL. Although selection bias may well have impacted on these results, this study supports the use of statins in appropriately selected frail patients, including those in nursing facilities. In general, statin therapy is a reasonable strategy for reducing recurrent stroke and other cardiovascular events in this high-risk population.

Other concerns associated with statin use in older adults include cognitive decline, muscular dysfunction, myotoxicity, hepatotoxicity, rhabdomyolysis and drug-drug interactions. The evidence regarding the impact of statins on cognitive decline is inconsistent as clinical trials have shown negative,[52,53] neutral[24,54–56] and beneficial[57,58] effects, although none of these studies included patients with prior stroke. Although the incidence of severe or fatal rhabdomyolysis is rare (0.15 deaths per 1 million prescriptions), the incidence of myalgias with or without elevation of creatine kinase is poorly defined.[59] Hepatotoxicity manifested by 3-fold increases in amino-transferases occurs in approximately 1–3% of patients, although there is little evidence to suggest that mild to moderate elevations correlate with histological liver injury, and regular monitoring of liver function tests is of questionable benefit.[60] Therefore, the decision to treat older adults with statins for secondary stroke prevention should take into account the risks for coronary disease and intracerebral

haemorrhage and the possibility of myotoxicity and hepatotoxicity. There is no clear evidence to suggest that these severe adverse effects are more likely to occur with advancing age.

2.4 Hyperhomocysteinaemia

In observational studies, elevated levels of homocysteine have been shown to increase the risk of stroke by as much as 3-fold.[61–64] While hyperhomocysteinaemia can be easily treated with B vitamins, primary prevention trials[65,66] have not shown a reduced risk of cardiovascular events or stroke with vitamin supplementation. Similarly, a large secondary prevention trial in patients with prior ischaemic stroke, the VISP (Vitamin Intervention for Stroke Prevention),[64] showed no impact on stroke, coronary heart disease (CHD), severe stroke or death with high-dose compared with low-dose B vitamins over 2 years. A *post hoc* subgroup analysis reported a significant benefit on a combined stroke and CHD outcome for patients with a baseline vitamin B_{12} level above the median;[67] however, this somewhat counter-intuitive finding may be a chance result and requires further confirmation. While others have expressed concerns that the trial may have been underpowered in the setting of folic-acid fortified cereals,[68] any true treatment effect is likely to be small, and current evidence is insufficient to recommend routine vitamin supplementation after stroke.

Interestingly, a study of Japanese patients aged 65 years with residual hemiplegia at least 1 year after a stroke who were prescribed combined folate and vitamin B_{12} treatment reported a significant 7.1% absolute risk reduction in sustaining a hip fracture compared with those prescribed placebo.[69] The mechanism for this reduction is unclear, and the generalizability of the finding to non-Japanese populations needs to be established before vitamin B_{12} supplementation can be routinely advised.

2.5 Cigarette Smoking

The majority of studies linking cigarette smoking to ischaemic stroke have been focused on incident events. However, the South London Stroke Register reported that patients aged >75 years who smoked at the time of stroke were more likely than younger patients to have either tried or succeeded with smoking cessation in the first 3 years after incident stroke.[70]

2.6 Diabetes Mellitus

Only one published study has identified diabetes mellitus as an independent predictor of recurrent stroke in the elderly. In the Cardiovascular Health Study cohort, patients aged >65 years (80% were aged >75 years) were followed for death, recurrent stroke and cardiovascular disease event.[3] Diabetes was independently associated with a nearly 60% increased risk of recurrent stroke (HR 1.59; 95% CI 1.07, 2.37; p = 0.022).

2.7 Antithrombotic Therapy for Transient Ischaemic Attack and Noncardioembolic Stroke

The rationale for antithrombotic therapy in ischaemic stroke patients is predicated on the underlying atherosclerotic and atherothrombotic mechanisms that account for the majority of these events.[15] Most ischaemic stroke patients should be treated with some form of antithrombotic therapy, especially in light of the likelihood of polyvascular disease, and the overlap of treatment strategies for CHD and peripheral arterial disease. However, for ischaemic stroke, the optimal therapy differs depending on the underlying mechanism of ischaemia. For patients with noncardioembolic stroke or TIA, antiplatelet therapy is recommended rather than anticoagulants to reduce the risk of recurrent stroke and other cardiovascular events (tables I and II).[14,71] This recommendation is based on the results of the WARSS (Warfarin Aspirin Recurrent Stroke Study), which showed no increased efficacy of warfarin (adjusted dose to target international normalized ratio [INR] 1.4–2.8)

over aspirin (acetylsalicylic acid) 325 mg for non-cardioembolic stroke or TIA.[72] Currently available antiplatelet drugs include aspirin, aspirin/ extended-release (ER), dipyridamole and clopidogrel. Aspirin is the most widely studied anti-platelet therapy, and is a standard of care for secondary prevention of all atherothrombotic events. In patients with prior TIA or stroke, aspirin reduces the relative risk of major cardiovascular events by 22%.[73]

Unlike aspirin, which inhibits platelet aggregation promoted by formation of thromboxane A_2, the thienopyridine clopidogrel selectively inhibits adenosine diphosphate-induced platelet aggregation. The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial was a large, randomized, controlled trial of clopidogrel 75 mg versus aspirin 325 mg in patients with a history of ischaemic stroke, myocardial infarction (MI) or symptomatic peripheral arterial disease.[26] In the overall trial, there was a 0.5% absolute reduction in the composite endpoint of ischaemic stroke, MI or vascular death associated with clopidogrel and no significant difference in the risk of bleeding. However, subgroup analysis of patients who entered the study because of ischaemic stroke showed no significant difference between aspirin and clopidogrel. Current recommendations state that clopidogrel is acceptable for secondary prevention in patients with a history of ischaemic events, including those with stroke,[13,14,71] although its benefit over aspirin in ischaemic stroke patients may be modest. Because the mean age of subjects in the CAPRIE trial was 62.5 years, it is unclear how these results can be applied to the older population.

The effects of the combination of aspirin and clopidogrel for stroke prevention have also been studied in patients with prior stroke or TIA. The MATCH trial, which enrolled only patients with a history of ischaemic stroke or TIA, showed no benefit for the combination of aspirin and clopidogrel versus clopidogrel alone in preventing recurrent ischaemic stroke, MI, cardiovascular death or rehospitalization for acute ischaemia,[27] and the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management, and Avoidance) trial failed to show a benefit for the combination of aspirin and clopidogrel versus aspirin alone on a similar composite endpoint in the overall study population of symptomatic (documented coronary artery disease, cerebrovascular disease or peripheral arterial disease) and asymptomatic (three or more atherothrombotic risk factors) patients.[28] In addition, the MATCH trial showed a significant increase in haemorrhagic strokes with aspirin and clopidogrel compared with clopidogrel alone. [27] Based on these results, the combination of aspirin plus clopidogrel is not routinely recommended for secondary stroke prevention.[13,14]

Dipyridamole, a phosphodiesterase inhibitor and nitric oxide carrier, represents another class of antiplatelet agent which, when used in its ER form in combination with low-dose aspirin, is an acceptable option for secondary prevention.[13,14,71] Results from the ESPS-2 (Second European Stroke Prevention Study)[29] and the ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial)[30] showed that aspirin plus ER dipyridamole (ASA-ERDP) significantly reduced the absolute risk of the composite outcome (incidence of stroke or death in ESPS-2; incidence of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication in ESPRIT) by 19% and 3%, respectively, compared with aspirin alone after TIA or stroke of presumed arterial origin. Subgroup analysis showed that patients aged >65 years had a similar or greater benefit from ASA-ERDP over aspirin compared with those aged 65 years in ESPRIT.[30] The recently completed PRoFESS (Prevention Regimen For Effectively avoiding Second Strokes) trial was designed to compare the efficacy of aspirin plus ER dipyridamole with that of clopidogrel monotherapy in patients with stroke.[31] The rates of recurrent stroke were similar in both groups (ASA-ERDP 9.0% vs clopidogrel 8.8% ; HR 1.01; 95% CI 0.92, 1.11), and therefore the trial did not meet the prespecified criteria for noninferiority for ASA-ERDP. The subgroup analysis based on age revealed no benefit in favour of either

drug in patients aged 75 years. However, there was a significant increase in intracranial haemorrhages in the ASA-ERDP group (4.1 % vs 3.6% in the clopidogrel group; HR 1.15; 95% CI 1.00, 1.32). Whether the subjects with intracranial haemorrhages were older than those without was not reported.

The oldest subsets of the population appear to have a comparable relative risk reduction to that observed in younger patients and given their high risk of secondary vascular events, may derive a greater absolute risk reduction. Unfortunately, CAPRIE, ESPS-2 and ESPRIT did not provide data related to bleeding risk in this age group. However, even if we assume that the benefit of stroke risk reduction is partially offset by an increased bleeding risk in the oldest-old, the risk-benefit ratio favours antiplatelet therapy for most patients.

2.8 Antithrombotic Therapy for Cardioembolic Stroke

The most important cause of cardioembolic stroke in older adults is atrial fibrillation (AF), which accounts for about 50% of all cardioemboli.[71] AF increases the risk for stroke by about 5-fold[74] and is associated with poor outcomes[75] and higher costs;[76,77] therefore, aggressive treatment of AF is essential for both primary and secondary stroke prevention.

Clinical trials of warfarin versus aspirin for AF have determined that the risk of stroke in individuals with this condition differs depending on the presence of specific risk factors, which can be measured using several different validated scores.[78,79] Because oral anticoagulant therapy with warfarin (target INR 2.5; range 2.0–3.0) decreases the relative risk of stroke by about 62% versus 22% reduction with aspirin,[80] these risk scores can be used to determine the absolute benefit of warfarin treatment and aid the decision-making process in the setting of primary or secondary prevention.

For secondary prevention in AF patients with a history of stroke or TIA, treatment with oral anticoagulation is recommended unless major contraindications are present.[14] Most AF prevention trials have measured ischaemic stroke as a primary outcome, with the only clinical trial focusing solely on secondary prevention in AF being the EAFT (European Atrial Fibrillation Trial).[81] In this trial, there was a significant absolute risk reduction in stroke events with oral anticoagulation versus aspirin or placebo (anticoagulation 4 % vs placebo 12% ; HR 0.34; 95% CI 0.36, 0.79). Combining these results with those of other AF trials, individual patient meta-analyses have shown consistently better prevention of ischaemic stroke with oral anticoagulation over aspirin or placebo (table V). [82,83]

Once warfarin treatment is initiated, it is critical to maintain INRs in the therapeutic range to achieve the maximum benefit; in one study, patients who were receiving subtherapeutic doses of warfarin (INR 1.5–1.9) at the time of admission for stroke had a 3.4-fold higher 30-day mortality than patients who were in the therapeutic range (INR 2.0–3.0).[86] The timing of initiation or reinitiation of warfarin for secondary prevention in patients with AF and a recent stroke is difficult because of the risk of haemorrhage. Although there are no studies to guide this decision, the EAFT compared haemorrhage rates in patients with warfarin initiated within 2 weeks and after 2 weeks of the acute stroke and found no difference.[81] Therefore, the ACCP Guidelines suggest 2 weeks is safe, although it is reasonable to wait longer for patients with large strokes.[15]

Alternative anticoagulants are also currently being tested in randomized controlled trials. In the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, rivaroxaban, a direct factor Xa inhibitor is being compared with adjusted-dose warfarin for prevention of stroke and thromboembolic events in 14 000 patients with non-valvular AF.[87] In addition, the ARISTOTLE (Apixaban for Reduction in Stroke and

Other Thromboembolic Events in Atrial Fibrillation) trial is a double blind non-inferiority trial of apixaban versus adjusted dose warfarin in 15 000 patients with AF and at least one additional risk factor for stroke.[88]

For patients who are not candidates for warfarin, newer antiplatelet therapies are being tested to determine their benefit in reducing stroke risk. Although the warfarin arm of the ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) trial, ACTIVE-W, was discontinued because of the superiority of warfarin,[89] the aspirin arm (ACTIVE-A) is ongoing.[90] This trial is designed to assess whether dual antiplatelet therapy with clopidogrel 75 mg/day and aspirin 100 mg/day is superior to aspirin 100 mg/day monotherapy in preventing stroke, non-CNS systemic embolism, MI or vascular death in high-risk patients with AF during 3 years of follow-up.[89] The irbesartan arm (ACTIVE-I), in which patients from ACTIVE-W and ACTIVE-A were randomized in a factorial manner to receive either the angiotensin II type 1 receptor antagonist irbesartan or placebo, is also ongoing.[90]

While the overall AF population is under-treated with warfarin, this is especially true for older adults,[91–93] for whom therapy is often withheld because of a history or risk of falling.[92] A study of Medicare beneficiaries who were at high risk for falls and were anticoagulated for AF at hospital discharge showed that the rate of traumatic intracranial haemorrhage was more than twice as high as in those not at high risk for falls (2.0/100 patient-years; 95% CI 1.3, 3.1 vs 0.34 /100 patient-years in other patients; 95% CI 0.27, 0.45; $p < 0.0001$).[94] The $CHADS_2$ risk score was used to assess future stroke risk, which assigns 1 point each for the presence of congestive heart failure, hypertension, age >75 years, and diabetes, and 2 points for history of stroke or TIA.[78] In patients discharged on anticoagulation with a $CHADS_2$ risk score of 2–6, and therefore at high risk of stroke, there was still a protective benefit with anticoagulation for a composite outcome of hospitalization for stroke, any haemorrhage, MI or out-of-hospital death.[94] Therefore, many patients at risk for falls would benefit from warfarin therapy, and it is important for clinicians to carefully discuss the risks and benefits of anticoagulation with their older patients.

If AF is not the cause of an embolic-appearing stroke, other cardioembolic causes of stroke should also be considered, especially if no large vessel source has been identified. Causes with a high risk of recurrence include mitral stenosis, prosthetic mechanical valves, recent MI, left ventricular thrombus, infective endocarditis and dilated cardiomyopathies.[71] The risks and benefits of anticoagulation are likely to vary substantially in these settings, and the guideline recommendations cannot replace individualized clinical judgement.

2.9 Extracranial Carotid Stenosis

Symptomatic carotid stenosis carries a high rate of recurrent stroke. As shown in the NASCET (North American Symptomatic Carotid Endarterectomy Trial) study, the risk of ipsilateral ischaemic stroke in patients with symptomatic carotid stenosis >70% was 26% over 2 years, whereas surgical treatment with carotid endarterectomy (CEA) was associated with a stroke rate of 9% (absolute risk reduction, 17% ; number needed to treat to prevent one stroke = 6).[95] This trial, along with the ECST (European Carotid Surgery Trial)[96] and the Veterans Affairs Cooperative Studies Program, [97] has clearly defined our current practice of recommending CEA for patients with symptomatic, severe stenosis (70–99%).[14]

While the overall population of patients in NASCET who had moderate carotid stenosis (50–69%) did not benefit from CEA, patients aged   75 years did. Similarly, a pooled analysis of both NASCET and ECST showed that patients aged   75 years and with   50% symptomatic stenosis benefited from CEA, with an absolute risk reduction over 5 years of

19.2% (95% CI 10.2, 28.2).[98] CEA is therefore a consideration for symptomatic patients aged 75 years with moderate stenosis, provided there is an exceptionally low surgical complication rate of <4%.[95] However, an analysis of a large Medicare database from 1992 to 1993 revealed an increased 30-day mortality risk following CEA with each 5-year increase in age; 1.2% for those aged 65–69 years, 2.46% for those aged 80–84 years and 3.6% for those aged 85 years (p = 0.001).[99] These mortality rates were also lowest in the institutions that enrolled patients in NASCET and ACAS (Asymptomatic Carotid Artery Study) [100] compared with non-trial institutions, and in high-volume versus low-volume centres. In addition, rates of 30-day mortality risk following CEA were higher in trial institutions according to the 'real-world' database than rates reported in the randomized trials for these same institutions, indicating careful selection of subjects for trials.[99]

CEA for asymptomatic carotid stenosis has been a topic of intense debate. The Veterans Affairs Cooperative Study Group[101] and ACAS,[100] as well as the more recently completed European ACST (Asymptomatic Carotid Surgery Trial),[102] all showed a significant but small benefit from CEA for asymptomatic carotid stenosis. It is important to remember that to participate in these trials, surgeons must have demonstrated a very low complication rate, such that the overall benefit in reducing the rate of stroke during follow-up was not overshadowed by the risk of catheter angiography plus the perioperative complication rate. Therefore, CEA for asymptomatic carotid artery stenosis between 60% and 100% is recommended when performed by a surgeon with a complication rate of <3%.[103]

A systematic review of age- and gender-associated risks associated with CEA showed that women had a higher rate of operative stroke and death than men (odds ratio [OR] 1.31; 95% CI 1.17, 1.47). [104] Although operative mortality was increased in older patients (OR 1.50; 95% CI 1.26, 1.78), the risk of non-fatal stroke was not significantly increased. Unfortunately, this review did not include any other co-morbidities that could guide decision making for surgery. Therefore, based on well established operative risks, for the oldest subset of the population whose life expectancy, and therefore cumulative risk for stroke, is lower because of advanced age or co-morbidities, the operative risks of CEA for asymptomatic carotid stenosis may not outweigh the potential benefit.

An alternative to CEA for patients with symptomatic or asymptomatic carotid stenosis is carotid angioplasty and stenting (CAS). Unfortunately, despite its popularity, data from clinical trials concerning the efficacy and safety of CAS are lacking or contradictory. For example, two randomized clinical trials failed to demonstrate the noninferiority of CAS compared with CEA in treating patients with symptomatic carotid stenosis,[105,106] and one of these trials was stopped prematurely because of safety and futility issues associated with CAS.[105] In contrast, the SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial showed that in patients deemed to be high-risk candidates for CEA, regardless of whether or not the stenosis was symptomatic, CAS was not inferior to CEA.[107] Even though the endpoint for this trial was a combination of stroke, death or MI in 30 days, death from neurological causes or ipsilateral stroke between 31 days and 1 year, there was no evidence of any benefit for stroke as an outcome in any of the subgroups in this trial.

The results of the SAPPHIRE trial introduce a major evidence gap in the oldest-old who need treatment for carotid stenosis. Specifically, if patients are excluded from CEA because of high risk (oldest-old age groups) and are only referred for CAS, then the complication rates would be higher in this population by definition. Other studies have shown that in patients aged 75 years, CAS was associated with a significant increase in the 30-day stroke risk compared with CEA.[108] Also, in the ongoing CREST (Carotid Revascularisation

Endarterectomy vs Stent Trial), the risk of stroke or death increased significantly with increasing age, especially in those aged 80 years.[109] Several anatomical factors have been hypothesized to cause the increased number of adverse effects related to CAS procedures in the elderly, including aortic arch elongation and calcification, as well as carotid tortuosity.[110] Therefore, based on high risk for early mortality with either procedure in patients aged >80 years, there are currently no data to support CEA over CAS (or vice versa), and more studies in this population are needed.

3. Special Challenges in Elderly Patients

3.1 Adverse Drug Events

Older adults are particularly susceptible to adverse drug events because of a higher risk for drug-drug and drug-disease interactions and toxicity arising from altered pharmacokinetics. Cardiovascular medications are consistently identified as one of the leading causes of adverse drug events in older adults, and are a frequent cause of emergency department visits.[111,112] While patient-reported adverse effects of anti-hypertensive agents such as β-adrenoceptor antagonists are actually lower in older adults compared with younger patients,[113] conduction system abnormalities and use of multiple cardiovascular agents are more prevalent and can lead to symptomatic bradyarrhythmias.[114] Less well recognized is that withdrawal of cardiovascular medications is also associated with adverse drug events, occurring approximately 26% of the time.[115] Although results are inconsistent as to whether age itself increases the risk of bleeding with warfarin therapy,[116,117] older patients are more likely to be taking other medications that may interact with warfarin, or to have underlying disease processes that increase bleeding risk. Thus, it is important to adjust all medications slowly and monitor for adverse effects diligently when either initiating or stopping secondary prevention therapies.

3.2 Dementia

Stroke is a major risk factor for cognitive decline. In a prospectively followed cohort of patients with a mean age of 75 years determined to be cognitively and neurologically normal at baseline, stroke increased the odds of dementia by 5.6-fold (95% CI 2.76, 11.4) and the odds of conversion of a mild cognitive impairment to dementia by 12-fold (95% CI 1.5, 99).[118,119] Moreover, cognitive and functional outcomes are substantially worse for patients with underlying Alzheimer's type dementia who also experience a stroke.[120] Therefore, ongoing screening for worsening cognitive and functional impairment is warranted after stroke.

Cerebral amyloid angiopathy (CAA), a condition caused by deposition of β-amyloid protein in the vasculature, predisposes persons to both dementia and intracranial haemorrhage. The prevalence of this condition increases dramatically in older adults from virtually nonexistent in persons <50 years of age to >50% in persons aged >90 years.[121,122] Intracerebral haemorrhage due to CAA typically occurs in a lobar distribution, as opposed to the basal ganglia distribution that occurs with hypertensive intracerebral haemorrhage. In addition, anticoagulant and antiplatelet therapies increase haemorrhage risk in these patients[123–126] and should therefore be avoided. Detection of subclinical cerebral microbleeds is suggestive of underlying CAA, which can be diagnosed with the use of T2*-weighted gradient-refocused magnetic resonance imaging.[127] Although there is no evidence to support this approach, this type of imaging could be used to guide decision making for antithrombotic use in patients who may have evidence of microbleeds and therefore are at high risk of haemorrhagic stroke with these drugs.

3.3 Osteoporosis

Osteoporosis has been shown both to increase the risk of stroke and to become worse after stroke.[128] Loss of bone density is common after stroke, particularly on the ipsilateral side, and increases the risk of fracture, especially that of the hip.[129] Treatment of post-menopausal women with the bisphosphonate risedronic acid during the acute period following stroke reduced the odds of hip fracture in post-menopausal women by 7-fold[130] and in men aged   65 years by 5-fold,[131] and vitamin B_{12} and folate supplementation may decrease the risk of hip fracture. The results of these studies draw attention to the need to assess bone mineral density in all stroke patients and to aggressively treat osteoporosis both before and after stroke.[132,133]

3.4 Arthritis

Many older patients suffer from arthritis and require NSAIDs or cyclooxygenase (COX)-2 inhibitors to maintain their quality of life. There is evidence to suggest that ibuprofen, but not rofecoxib or diclofenac, interferes with the anti-platelet activities of aspirin, and therefore, its ability to protect against stroke and MI.[134,135] In older patients with stroke and arthritis, the choice of anti-inflammatory and antiplatelet agents should be made carefully. Caution is also required when NSAIDs and COX-2 inhibitors are used in conjunction with aspirin and warfarin because of an increased risk of gastrointestinal bleeding and with antihypertensive agents because of an increased chance of losing BP control. Overall, the relative risks and benefits of NSAIDs and COX-2 inhibitors should be carefully considered before they are prescribed to older stroke patients.

3.5 Depression

Up to 34% of stroke patients, regardless of age or sex, experience depression, a serious problem that requires treatment.[136] Although selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat post-stroke depression, their use has been linked to an excess risk of upper gastrointestinal and perioperative bleeding, especially in patients taking aspirin and SSRIs.[137] There is also a recognized interaction between SSRIs and warfarin that can prolong the effect of warfarin and increase bleeding risk.[138] When NSAIDs cannot be avoided, other options include use of non-SSRI medications for depression,[139] use of an SSRI that has a lower receptor affinity that may decrease the bleeding risk,[140] or use of proton pump inhibitors or high-dose histamine H_2 receptor antagonists to reduce the risk of NSAID-related peptic ulcer disease. [141]

3.6 Deciding When to Discontinue Secondary Prevention Strategies

Although studies suggest that older stroke patients are often not offered secondary prevention strategies when indicated,[3,10] it is also clear that secondary prevention is inappropriate for some older patients. For patients who have had a recent stroke, the very high risk of additional events in the next 6 months makes use of secondary prevention strategies reasonable, at least acutely. In addition, there is evidence that withdrawal of lipid-lowering therapy in patients with acute coronary syndromes can precipitate vascular events,[142] and withdrawal of statins in the acute stroke period significantly worsens outcome at 90 days.[143] However, for patients with a remote history of stroke, most of the studies cited in table III reported a reduction in secondary events only after   2 years of therapy, suggesting that patients with more limited life expectancies as a result of other co-morbidities or very advanced age may not benefit once they have passed the immediate post-stroke period. Although objective data are lacking, it is reasonable to withdraw secondary prevention therapies when transitioning to a palliative care approach unless there has been a recent acute vascular event or therapy cessation would cause psychological distress to the patient.[144,145] Specific clinical situations such as gastrointestinal bleeding or

frequent falls require careful, ongoing discussion about the competing risks and benefits of secondary prevention therapies.

4. Secondary Prevention Quality Improvement Initiatives

One of the greatest barriers to effective implementation of secondary preventive strategies after an atherothrombotic event appears to be related to the absence of a systemized approach to discharge planning.[146] The PROTECT (Preventing Recurrence of Thromboembolic Events through Coordinated Treatment) programme, conducted in a single academic hospital with a primary stroke service, sought to promote initiation of certain guideline-directed secondary preventive measures during acute hospitalization for an ischaemic cerebrovascular event. Compared with a pre-PROTECT patient cohort, discharge utilization and 90-day adherence rates were significantly enhanced with statin and anti-hypertensive therapies, implementation of long-term antithrombotic therapy approached 100%, and lifestyle-intervention goals were discussed with all patients.[147] A multicentre, ongoing study of secondary prevention adherence is the Adherence Evaluation After Ischemic Stroke-Longitudinal (AVAIL) registry.[148] AVAIL was designed to determine barriers to adherence following hospitalization for acute stroke, taking into account age, sex, socioeconomic status, disability, depression and quality of life. Another impediment to effective implementation is a lack of knowledge concerning the guidelines. The AHA's Get With the Guidelines (GWTG)-Stroke initiative is designed to educate in-hospital healthcare providers about available treatments and prevention guidelines and provide tools to increase and streamline their implementation.[149]

5. Conclusion

Although more direct evidence for secondary prevention after ischaemic stroke in the oldest subset of the population is needed, such patients are potential candidates for the full range of strategies recommended for younger patients. Factors such as stroke severity, functional status, competing co-morbidities and the patient's goals of care should take precedence over age when planning treatment and rehabilitation after stroke. The oldest patients are at higher risk for adverse drug events, drug-drug interactions and drug-disease interactions, and require a more thoughtful approach to prescribing and monitoring than younger stroke patients. There is substantial room for improvement in the use of medications that may improve prognosis after stroke in older adults; ongoing quality improvement initiatives such as AVAIL and GWTG-Stroke will hopefully improve treatment, and therefore outcomes, of stroke survivors.

Acknowledgments

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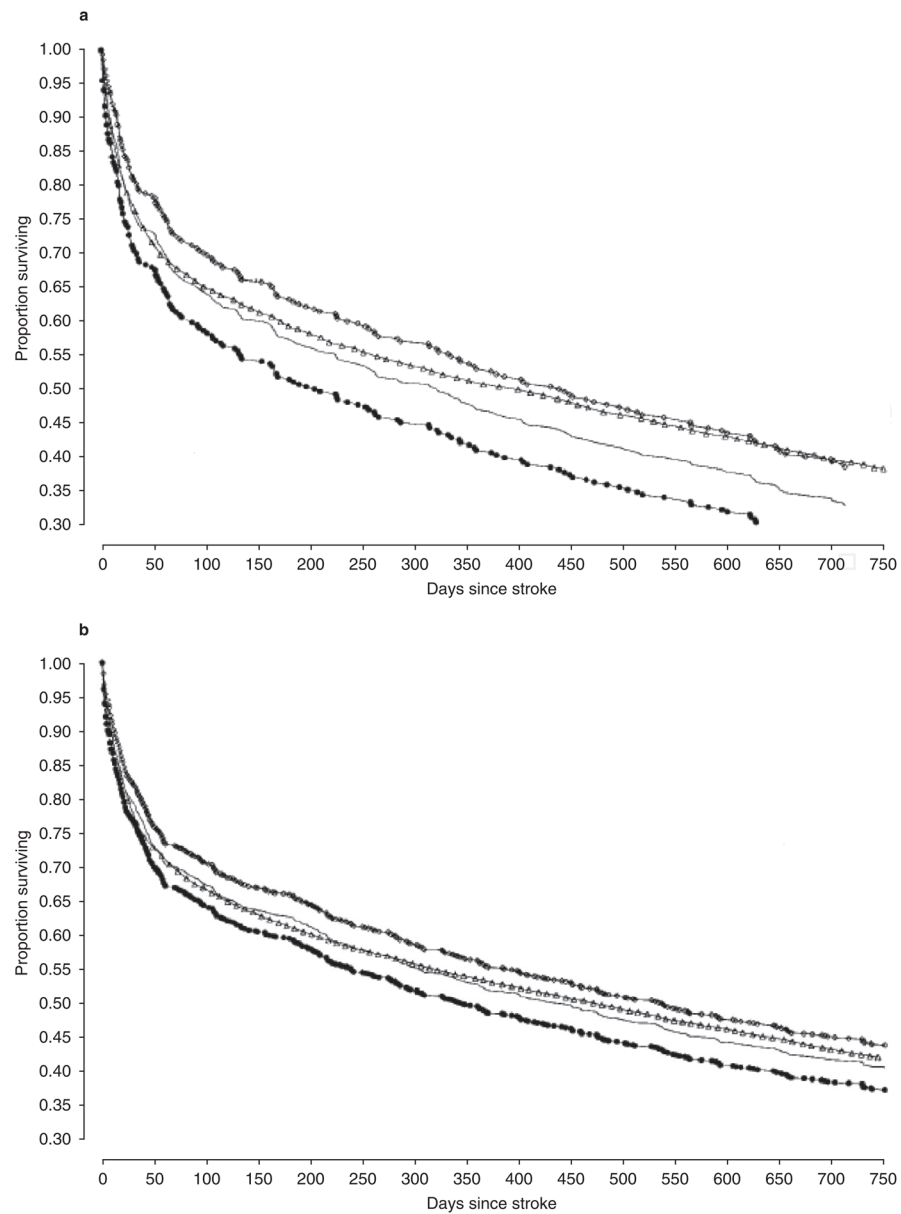
Fig. 1.
Survival in patients aged 85 years with first and recurrent stroke: (**a**) males and (**b**) females. Open triangles represent the Kaplan-Meier estimate of the survival curve in patients with first stroke; lines represent the Kaplan-Meier estimate of the survival curve for patients with recurrent stroke. Open squares and closed circles represent the upper and lower 95% confidence limits (reproduced from Samsa et al.,[9] with permission).

Table I

American Heart Association/American Stroke Association recommendations for risk factor modification in secondary stroke prevention[13,14]

Recommendation	Class/level of evidence[a]
Hypertension	
Antihypertensive treatment is recommended for all ischaemic stroke or TIA patients who are beyond the hyperacute period	I/A
Drug choices should be individualized based on the available data and specific patient characteristics	I/A
Absolute BP levels are uncertain and should be individualized	IIa/B
Comprehensive therapy should include proven lifestyle modifications	IIb/C
Diabetes mellitus	
ACE inhibitors and ARBs should be prescribed as they reduce renal disease progression	I/A
Glucose levels should be as near to normoglycaemia as possible in patients with ischaemic stroke or TIA	I/A
HbA_{1c} should be 7%	IIa/B
BP and lipids should be more rigorously controlled	IIa/B
Cholesterol	
Ischaemic stroke or TIA patients with elevated cholesterol, co-morbid CAD or evidence of an atherosclerotic origin should be managed according to NCEP III guidelines	I/A
HMG-CoA reductase inhibitors (statins) are recommended with a target LDL-C goal of <100 mg/dL (<70 mg/dL for high-risk patients)	I/A
Ischaemic stroke or TIA patients without known CHD should receive statin therapy to reduce the risk of stroke and cardiovascular events	I/B
Ischaemic stroke or TIA patients with low HDL-C may be treated with niacin or gemfibrozil	IIb/B
Smoking	
All patients who smoked in the past year should be encouraged to quit	I/C
A combination of counselling, nicotine products and oral smoking cessation products should be considered	IIa/B
Environmental smoke should be avoided	IIa/C
Alcohol	
Heavy drinkers should eliminate or reduce their alcohol consumption	I/A
2 drinks/day for men and 1 drink/day for nonpregnant women may be considered	IIb/C
Obesity	
A goal BMI of 18.5–24.9 kg /m^2 and a waist circumference <35 cm for women and <40 cm for men should be encouraged	IIb/C
Physical activity	
At least 30 minutes of moderate-intensity physical activity per day should be considered for all capable patients	IIb/C

[a]Class I: conditions for which there is evidence for and/or general agreement that it is useful and effective; class IIa: weight of evidence is in favour; class IIb: usefulness/efficacy is less well established; level of evidence A: data derived from multiple randomized clinical trials; level of evidence B: data derived from a single randomized trial or nonrandomized studies; level of evidence C: expert opinion or case studies.

ARB = angiotensin II type 1 receptor antagonist (angiotensin receptor blocker); **BMI** = body mass index; **BP** = blood pressure; **CAD** = coronary artery disease; **CHD** = coronary heart disease; **HbA$_{1c}$** = glycosylated haemoglobin; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **NCEP** = National Cholesterol Education Program; **TIA** = transient ischaemic attack.

Table II

American College of Chest Physicians recommendations for antiplatelet and anticoagulant therapy in secondary stroke prevention[15]

Therapy	Patient population	Grade[a]	Dosage
Antiplatelet	Patients who have experienced a cryptogenic stroke and have a PFO	1C+	Dependent on therapy chosen[b]
	Patients who have aortic atherosclerotic lesions or mitral valve strands or prolapse	1C+	Dependent on therapy chosen[b]
	Option for patients who have experienced a cryptogenic stroke associated with mobile aortic arch thrombi	2C	Dependent on therapy chosen[b]
Aspirin (acetylsalicylic acid)	Option for all patients who have experienced a noncardioembolic stroke or TIA	1A	50–100 mg/day
	Patients undergoing CEA (treatment should start prior to CEA and continue thereafter)	1A	50–100 mg/day
	Patients with a cardioembolic stroke who have contraindications to anticoagulant therapy	1A	75–325 mg/day
	Patients with a moderate to high risk of bleeding complications	1C+	50–100 mg/day
Aspirin + dipyridamole[c]	Option for all patients who have experienced a noncardioembolic stroke or TIA	1A	25 mg aspirin + 200 mg dipyridamole twice daily
Clopidogrel[d]	Option for all patients who have experienced a noncardioembolic stroke or TIA	1A	75 mg/day
Oral anticoagulant, vitamin K antagonists (e.g. warfarin)	Patients with AF	1A	Target INR, 2.5; INR range, 2–3
	Patients with cerebral venous sinus thrombosis	1B	Target INR, 2.5; INR range, 2–3
	Patients with well documented prothrombotic disorders	2C	Target INR, 2.5; INR range, 2–3
	Option for patients who have experienced a cryptogenic stroke associated with mobile aortic arch thrombi	2C	Target INR, 2.5; INR range, 2–3

[a]Grade 1 recommendations are strong and indicate that the ratio of benefit to risk, cost and burden is favourable. Grade 2 recommendations indicate patients' values may lead to different choices. A full description of the grading system can be found in Guyatt et al.[16]

[b]Aspirin 50–325 mg/day, aspirin 25 mg + dipyridamole 200 mg twice daily and clopidogrel 75 mg/day are equivalent.

[c]Recommended over aspirin alone (grade 2A).

[d]Recommended over aspirin alone (grade 2B).

AF = atrial fibrillation; **CEA** = carotid endarterectomy; **INR** = international normalized ratio; **PFO** = patent foramen ovale; **TIA** = transient ischaemic attack.

Table III

Clinical trials relevant to the secondary prevention of stroke at any age, or prevention of stroke in the oldest patients with cardiovascular risk factor modification

Name	Population	Treatment	Key clinical findings
Hypertension			
PROGRESS[17]	6105 hypertensive and non-hypertensive patients with a history of stroke of any cause or TIA (mean age 64 years; SD 10 years)	β-Adrenoceptor antagonist ± diuretic vs placebo	Antihypertensive therapy resulted in an ARR of 3.7% for stroke (10.1% vs 13.8% ; p < 0.0001) and 4.8% for vascular events (15.0% vs 19.8% ; p < 0.0001) compared with placebo; dual therapy with a β-adrenoceptor antagonist and diuretic was superior to monotherapy with a β-adrenoceptor antagonist
STOP-Hypertension[18]	1627 hypertensive patients aged 70–84 years	3 β-adrenoceptor antagonists + 1 diuretic vs placebo	Antihypertensive therapy reduced the number of primary endpoint events^a by 36 (58 vs 94; p = 0.0031), fatal and non-fatal strokes by 24 (29 vs 53; p = 0.0081) and total deaths by 27 (36 vs 63; p = 0.0079) compared with placebo
SHEP[19]	4736 patients aged 60 years (mean 72 years) with systolic hypertension	β-Adrenoceptor antagonist + diuretic vs placebo	Antihypertensive therapy resulted in an ARR of 2.0% (3.6% vs 5.6%)
HYVET (pilot study)[20]	1283 hypertensive patients aged 80 years (mean age 83.8 years; range 79.5–96.1 years)	Diuretic vs β-adrenoceptor antagonist vs placebo	Antihypertensive therapy prevented 19 strokes but resulted in 20 additional non-stroke deaths per 1000 patients per year
HYVET[21]	3845 hypertensive patients aged 80 years (mean age 83.6 ± 3.2 years for active treatment, 83.5 ± 3.1 years for placebo)	Indapamide vs placebo	Treating 1000 patients with indapamide for 2 years would prevent 11 strokes (95% CI 0, 21)
Dyslipidaemia			
HPS[22]	20 536 patients aged 40–80 years with a history of cerebrovascular disease (mean age 65.5 years; SD 7.8) or other arterial occlusive disease (mean age 63.7 years; SD 8.5)	Simvastatin vs placebo	In the 3280 patients with pre-existing cerebrovascular disease, simvastatin did not significantly reduce the absolute risk for stroke (10.3% vs 10.4%), but did reduce the absolute risk of having a major CVE by 5.1% (24.7% vs 29.9% ; p = 0.001)
SPARCL[23]	4731 patients aged 18 years of age with hyperlipidaemia, no known CHD and a history of stroke or TIA in the previous 1–6 months (mean age 62.5 years; SD 0.2 years)	Atorvastatin vs placebo	Treatment with atorvastatin resulted in a 2.2% ARR for stroke (p = 0.03) and a 3.5% ARR for a major CVE (p = 0.002)
PROSPER[24]	5804 patients aged 70–82 years with a history of, or risk factors for, vascular disease	Pravastatin vs placebo	Allocation to pravastatin resulted in an ARR of 2.1% (14.1% vs 16.2% ; p = 0.014) compared with placebo for the primary endpoint of CHD death, non-fatal MI, non-fatal stroke
Retrospective analysis of 50 clinical trials[25]	5924 persons aged 65 years (mean age range 71–74 years) enrolled in the Pfizer Atorvastatin Clinical Program Database	Atorvastatin vs placebo	The rate of having at least one adverse event was similar among patients taking 4 different doses of atorvastatin (10.2–16.1%) and placebo (15.0%) and the number of serious adverse events was low (1.0%)

^{a}Stroke, MI or cardiovascular death.

ARR = absolute risk reduction; **CHD** = coronary heart disease; **CVE** = cardiovascular event; **MI** = myocardial infarction; **SD** = standard deviation; **TIA** = transient ischaemic attack.

Table IV

Relevant clinical trials of antiplatelet therapy in elderly patients with ischaemic stroke

Name	Population	Treatment	Key clinical finding	Findings in subgroups by age
CAPRIE[26]	19 185 patients with a history of ischaemic stroke, MI or PAD. Mean age 62.5 years	ASA vs clopidogrel	Clopidogrel reduced the absolute risk of the primary outcome[a] by 0.51% compared with ASA (p = 0.043)	No published data
MATCH[27]	7599 patients with TIA or ischaemic stroke within 3 months. Mean age 66.3 years	Clopidogrel + placebo vs clopidogrel + ASA	Clopidogrel + ASA did not significantly reduce the absolute risk of the primary outcome[b] (1.0%, p = 0.244) but did significantly increase the risk of life-threatening, major and minor bleeding (p < 0.0001) compared with clopidogrel alone	No significant differences between age <65 (ARR 2.3% ; HR 0.86; 95% CI 0.64, 1.02) and 65 years (ARR 0.3% ; HR 1.0; 95% CI 0.86, 1.12)
CHARISMA[28]	15 603 patients with clinically evident cardiovascular disease or multiple risk factors. Mean age 64 years	ASA + placebo vs ASA + clopidogrel	Clopidogrel + ASA had no effect on the primary outcome[a] (ARR 0.5% ; RR 0.93; 95% CI 0.83, 1.05) and increased the absolute risk of moderate bleeding events by 0.8% (p < 0.001) compared with ASA alone	No difference in age <75 (HR 0.9; 95% CI 0.8, 1.05) vs 75 years (HR 0.91; 95% CI 0.75, 1.2)
ESPS-2[29]	6602 patients with TIA or ischaemic stroke within 3 months. Mean age 66.7 years	Placebo vs ASA vs dipyridamole vs ASA/ER dipyridamole	ASA/ER dipyridamole reduced the absolute risk of the primary outcome[c] by 12.9% (p = 0.056) compared with ASA alone and by 10.7% (p = 0.073) compared with dipyridamole alone	No published data
ESPRIT[30]	2739 patients with a TIA or minor stroke within 6 months. Mean age 63 years	ASA + placebo vs ASA/ER dipyridamole	ASA/ER dipyridamole resulted in an ARR of 1.0% per year in the primary outcome[d] (95% CI 0.1, 1.8) compared with ASA alone	No significant difference between age 65 (HR 0.9; 95% CI 0.7, 1.1) and >65 years (HR 0.8; 95% CI 0.65, 1.0)
PRoFESS[31]	20 332 patients with ischaemic stroke <90 days before randomization. Mean age 66.1 years	ASA/ER dipyridamole vs clopidogrel	No significant difference in primary outcome (ASA/ER dipyridamole 9%, clopidogrel 8.8%). Did not meet statistical criteria for non-inferiority for ASA/ER dipyridamole	No significant difference between treatments among age <65 years, age 65 years to < 75 years or age 75 years

[a] Ischaemic stroke, MI, cardiovascular death.

[b] Ischaemic stroke, MI, cardiovascular death, rehospitalization for acute ischaemia.

[c] Ischaemic stroke or cardiovascular death.

[d] Ischaemic stroke, MI, cardiovascular death, major bleeding.

ARR = absolute risk reduction; **ASA** = aspirin (acetylsalicylic acid); **ER** = extended-release; **HR** = hazard ratio; **MI** = myocardial infarction; **PAD** = peripheral arterial disease; **RR** = relative risk; **TIA** = transient ischaemic attack.

Table V

Meta-analyses of antithrombotic therapies in patients with atrial fibrillation: pooled data from randomized trials (reproduced from Singer et al.,[82] with permission)

Treatment comparison	RRR for ischaemic stroke (95% CI)
Adjusted-dose OAC vs no antithrombotic therapy[84]	68% (50, 79)
ASA vs no antithrombotic therapy[85]	21% (0, 38)
Adjusted-dose OAC vs ASA[83]	52% (37, 63)

ASA = aspirin (acetylsalicylic acid); **OAC** = oral anticoagulation; **RRR** = relative risk reduction.