



The case for an elderly targeted stroke management

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Stroke is a leading cause of death and disability worldwide. The elderly, in whom atrial fibrillation (AF) is most prevalent, carry the greatest risk, undergoing more recurrent, deadlier strokes, with bigger deficits, slower recoveries, and more comorbidities. Evidence-based data on advanced age stroke management are scarce. Age-related cerebral changes might undermine the benefit of established stroke treatments. Nevertheless, the elderly should probably also undergo thrombolysis for ischemic stroke: they do not bleed more, and die not because of hemorrhage but of concomitant illnesses. Beyond natural bleeding risks, AF in advanced age has a high embolic potential if not anticoagulated. Standard or lower intensity warfarin anticoagulation prevents embolic stroke in the elderly with a hemorrhage risk even lower than aspirin. In fact, adverse effects seem to occur more often with aspirin. Excess anticoagulation hazards are prevented with lower starting doses, stricter corrections, more frequent International Normalized Ratio monitoring, and longer adjustment intervals. Validated prognostic scores such as CHADS₂ help minimize bleeds. Direct inhibitors have recently shown a benefit similar to warfarin with fewer hemorrhages. Carefully tailoring antithrombotics to this age group is therefore useful. Antihypertensives probably help 80-plus stroke patients as well, but the risk/benefit of lowering blood pressure in secondary stroke prevention at that age is uncertain. Evidence-based data on diabetes management and use of lipid-lowering drugs are still lacking in this age group. In summary, emerging data suggest that stroke management should be specifically targeted to the elderly to better prevent its devastating consequences in the population at the highest risk.

Keywords: stroke management, elderly population, antithrombotics

THE CASE FOR AN ELDERLY TARGETED STROKE MANAGEMENT

Stroke is one of the leading causes of death and the main cause of disability worldwide. The stroke rate increases with age: beyond 55, it doubles each successive decade, and by 2050 the 65-plus world population will outnumber the rest (Wolf et al., 1992; Brown et al., 1996; Chen et al., 2010). The elderly are therefore at greater cerebrovascular risk than anyone, and stroke will probably acquire epidemiological proportions in the near future.

Thrombolysis, anticoagulation, antihypertensive, antiplatelet, and antilipemic agents have all been proven of benefit in stroke treatment and prevention in the population at large. However, management strategies useful in younger adults may not be equally effective in the elderly, who undergo age-related cerebral changes that might undermine that benefit, or entail further clinical risk.

Brain weight decreases 0.1–0.2% yearly between the ages of 20 and 50, and 0.3–0.5% yearly beyond 70 (Anderson et al., 1983; Pfefferbaum et al., 1994). Leukoaraiosis, a patchy or confluent subcortical/periventricular hypointensity on CT (or high signal intensity on MRI), occurs in up to one-third of people aged 65–84, and in up to 44% of patients with stroke and transient ischemic attack (TIA). It predicts gait disturbances and cognitive decline in the very elderly, and its degree correlates with the risk of recurrent stroke (Breteler et al., 1994; Pfefferbaum et al., 1994; de Groot et al., 2000; Dettmer et al., 2007; Smith, 2010). With aging, blood brain

barrier permeability and plasma albumin ratio in the cerebrospinal fluid increase. Capillaries enlarge, elongate, and disrupt perfusion. Cerebral blood flow reductions diminish protein synthesis, induce changes in intracellular pH and water content, cause glutamate/lactate accumulation, impair ATP synthesis, decrease neuron excitability, and bring on electrolyte imbalance and ultimately ischemic neuronal death (Farrall and Wardlaw, 2009).

In various “very old” populations (beyond 80 years of age), stroke predominates in women (Rojas et al., 2007; Andersen et al., 2010). Atrial fibrillation (AF) is most prevalent in the elderly, with up to 23.5% of associated stroke risk at 80–89 years (Wolf et al., 1991; Fuster et al., 2001; Adams et al., 2008), and the highest hazard ratio beyond 65 (Rodgers et al., 2004). Contrary to younger populations, hypertension and hyperlipidemia are less significant risk factors in the very old (Weverling-Rijnsburger et al., 2003; Rodgers et al., 2004; Milionis et al., 2005; Babatsikou and Zavatsanou, 2010).

Stroke in patients beyond 85 is deadlier, entails longer hospital stays, and results in bigger deficits and slower recoveries that require assistance in daily living and ultimately institutionalization (Arboix et al., 2000). Older stroke patients have a substantially higher risk of stroke recurrence (Johnston et al., 2000; Kaplan et al., 2005), and comorbidities that increase disability (Hickenbottom et al., 2002).

Old age is therefore associated with specific cerebral structural changes, risk factors, and clinical features that may all impair

or delay stroke recovery. Unfortunately, because very few old patients were included in the large stroke clinical trials, reliable data on elderly stroke management are scarce and have only recently started to emerge. As a result, the population most in need of clear stroke treatment recommendations has been neglected.

INTRAVENOUS THROMBOLYSIS

Intravenous thrombolysis with rt-PA reduces stroke disability. However, breakthrough trials demonstrating this benefit have either excluded very elderly patients, or randomized very few (The National Institute of Neurological Disorders, 1995; Hacke et al., 2008). These restrictions do not seem warranted, since patients over 80 have not shown a higher bleeding risk, both in small cohort studies and in larger databases (Tanne et al., 2000; Berrouschot et al., 2005; Mouradian et al., 2005; Engelter et al., 2006; Sylaja et al., 2006; Ford et al., 2010; Mishra et al., 2010; **Table 1**). This may depend on how bleeding is defined (The National Institute of Neurological Disorders, 1995; Wahlgren et al., 2007), but in any case, elderly stroke patients do not seem to die as a consequence of hemorrhage or thrombolysis, but of concomitant illnesses (Schwark and Schelling, 2006; Alshekhlee et al., 2010). So, if the ultimate goal is to reduce death and disability, present data suggest the elderly should undergo thrombolysis under the same criteria as the general population.

ATRIAL FIBRILLATION, ANTICOAGULATION, AND ANTIPLATELET THERAPY

Atrial fibrillation leads to left atrial thrombi, carries a sixfold annual stroke risk (Wolf et al., 1991), and is most prevalent in the elderly. An estimated 5.6 million people will have it by 2050 in the USA, of which 50% will be over 80 (Go et al., 2001). Cardioembolic stroke due to AF is consequently a very high risk in this group. From several clinical trials we know that oral anticoagulation reduces relative stroke risk by about 68% and mortality by 33%, and hence is the best means to prevent cardioembolic stroke in the general population (Lip and Lowe, 1996). However, old patients, anticoagulated or not, may also be at high bleeding risk, due to factors such as amyloid angiopathy (Rosand et al.,

2000), ischemia of arterial (rather than cardioembolic) mechanism and concomitant medication (Gorter, 1999), or brain microbleeds (Roob et al., 1999). Those with AF may in fact have both the highest spontaneous ischemic stroke risk and, when anticoagulated, the highest bleeding risk (Warfarin versus aspirin, 1994).

Prescribing anticoagulation is therefore a critical challenge in the elderly (Hylek et al., 2006). Beyond conventional contraindications, such as stomach ulcer, physicians often avoid anticoagulation in elderly patients, for fear of intracerebral hemorrhage, falls, and faulty compliance (with or without cognitive decline), choosing to leave the patient at higher embolic risk as a result (Lew and Lim, 2002; van Walraven et al., 2009). Nevertheless, using conventional optimal anticoagulation intensity (International normalized ratio, INR 2.0–3.0; The European Atrial Fibrillation Trial Study Group, 1995; Hylek et al., 1996; Stroke prevention in atrial fibrillation III, 1996), one trial has shown the benefit of warfarin over aspirin in preventing embolic stroke in the elderly, with a 46% relative risk reduction, and low major extracranial hemorrhage rates, not significantly different from those with aspirin: 1.4 vs. 1.6% per year (Mant et al., 2007). With the same standard anticoagulation intensity, a smaller trial looked at specific adverse events (death, thromboembolism, severe hemorrhage, withdrawal from the study), which turned out to be very significantly more frequent with aspirin (33%) than with warfarin: 6%, $p = 0.002$ (Rash et al., 2007; **Table 2**). These are sobering results, as antiplatelet agents are not felt to be dangerous and usually prescribed quite freely in the elderly, on the basis of general population trials.

Excess anticoagulation and INR variability seem to be, more than anything, the main risk factors for bleeding in all patients (Ansell et al., 2008). These may be prevented in the elderly with a lower warfarin starting dose (4 mg), more frequent INR monitoring (with a maximum interval of 3 weeks), longer intervals between two dose adjustments (at least 4 days apart, especially with higher doses), and, if necessary, stricter or even 1 mg step dose adjustments, as shown in computer-assisted warfarin management systems (Harrison et al., 1997; Gage et al., 2000; Ansell et al., 2008; Gouin-Thibault et al., 2010). The American Geriatrics Society recommends daily INR testing until stable, followed by two to three times/week testing for 1–2 weeks, weekly testing for 1 month, and monthly testing thereafter (American Geriatrics Society Clinical Practice Committee, 2002). Lower intensity anticoagulation regimens, which have included the elderly, with target INRs <2, can provide the same prevention efficacy than standard intensity treatments, with significantly lower bleeding risk (Yamaguchi, 2000; Pengo et al., 2010).

Table 1 | Thrombolysis in general and advanced age populations.

	General population	Advanced age population
THROMBOLYSIS		
Symptomatic ICH (%)	6 (The National Institute of Neurological Disorders, 1995), 2.4 (Hacke et al., 2008), 6 (Tanne et al., 2000), 2.6 (Berrouschot et al., 2005)	3 (Tanne et al., 2000), 6 (Berrouschot et al., 2005)
Outcome (modified ranking scale)	OR 1.6 (95% CI 1.5–1.7) (Ford et al., 2010)	1.4 (95% CI 1.3–1.6) (Ford et al., 2010)

Symptomatic intracerebral hemorrhage (ICH) and outcome (The National Institute of Neurological Disorders, 1995; Tanne et al., 2000; Berrouschot et al., 2005; Hacke et al., 2008; Ford et al., 2010).

Table 2 | Anticoagulation (warfarin) vs. antiplatelet therapy (aspirin) for stroke prevention in atrial fibrillation in the elderly^{49, 50}.

	Warfarin (INR 2.0–3.0)	Aspirin
Major extracranial hemorrhage (%)	1.4/year (Mant et al., 2007)	1.6/year (Mant et al., 2007)
Adverse events (%)	6 (Rash et al., 2007)	33 (Rash et al., 2007)

Dabigatran etexilate, approved by the FDA in October 2010 for stroke prevention in AF, inhibits coagulation by specifically and reversibly binding thrombin (Hussar and Zimmerman, 2011). At a dose of 110 mg twice daily, it showed similar embolic stroke and systemic embolism rates (non-inferior $p < 0.001$), but significantly lower major bleeding rates than warfarin in a large trial (Connolly et al., 2009). However, in patients ≥ 75 years, intracranial bleeding risk was lower but extracranial bleeding risk was similar or higher with dabigatran (Eikelboom et al., 2011). Apixaban, a novel oral direct factor Xa inhibitor, at a dose of 5 mg twice daily compared to warfarin (at a target INR of 2.0–3.0), was superior in preventing stroke or systemic embolism ($p < 0.001$ for non-inferiority, $p = 0.01$ for superiority), caused less bleeding ($p < 0.001$), and resulted in lower mortality ($p = 0.047$), in a study of 18201 patients with a mean age of 70 years, of which $> 31\%$ were at least 75, a welcome older stroke risk population trial (Granger et al., 2011). Rivaroxaban, another oral factor Xa inhibitor, was approved by the FDA in November 2011. At a daily dose of 20 mg, vs. dose-adjusted warfarin, it was non-inferior to warfarin for the prevention of stroke or systemic embolism ($p < 0.001$), and showed less intracranial and fatal bleeding ($p = 0.003$), but no difference in the risk of major bleeding (Patel et al., 2011), in a population of patients with a mean age of 73 years. While with these newer direct inhibitors we may be at the brink of a breakthrough allowing us, at long last, to forget about INRs, it is still uncertain whether these agents will truly result in a lower hemorrhagic risk in everyday practice. Other compounds are under investigation.

Finally, validated risk stratification schemes for better decision-making are other useful tools to minimize bleeding risk. For instance, the validated CHADS₂ score allocates points to the presence of five clinical risk factors: congestive heart failure, hypertension, age > 75 years, diabetes mellitus (1 point each), and prior stroke/TIA (2 points; Gage et al., 2001). For patients with a CHADS₂ score of 0 (annual stroke risk 1%), the absolute benefit of warfarin is not substantially greater than that of aspirin. For patients with a CHADS₂ score of 2 or more (annual stroke risk 4%), warfarin is both beneficial and cost-effective. Patients with a CHADS₂ score of 1 may have a choice of either, but most AF patients over 75 have a CHADS₂ score of 2 or higher, and are therefore appropriate candidates for warfarin (Gage et al., 2004).

The HAS–BLED score (uncontrolled Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly over 65 years, concomitant Drugs/alcohol) targets AF patients under anticoagulation. One point is given for each risk factor, with a maximum of 9. A score of 3 or more suggests high risk bleeding (Lip et al., 2011).

It is clear that to avoid both embolic stroke and bleeding risk in elderly AF patients, the choice of antithrombotic drug, dosage, treatment regimen, and appropriate evaluation of cost/benefit should be carefully tailored to the specific characteristics of this age group.

HYPERTENSION AND ANTIHYPERTENSIVE TREATMENT

Arterial hypertension is recognized as one of the most prevalent modifiable stroke risk factors. Several trials have shown the benefit

of antihypertensive drugs for primary and secondary stroke prevention in the general population. Some of these trials or meta analyses have shown similar results in primary prevention in the elderly (Gueyffier et al., 1999; Beckett et al., 2008), but there are not enough data on secondary stroke prevention. In one of the elderly targeted trials of hypertension treatment, only 7% of participants had a history of previous stroke (Gueyffier et al., 1999). The heart outcomes prevention evaluation (HOPE) trial included about 11% stroke survivors, but patients beyond 80 were excluded (Bosch et al., 2002). In the study on cognition and prognosis in the elderly (SCOPE), a trial involving almost 5000 elderly patients, only 4% had had a prior stroke (Lithell et al., 2003). Secondary prevention stroke trials, such as PROGRESS, PATS, and MOSES were not specifically addressed to the elderly, and the mean age of the populations studied was < 70 (PATS Collaborating Group, 1995; PROGRESS Collaborative Group, 2001; Schrader et al., 2005). Antihypertensives would probably benefit 80-plus stroke patients as well, but aren't there any risks in lowering the blood pressure in the elderly? Is not cerebral blood flow compromised as a consequence? In one meta analysis addressing antihypertensives in old people, no treatment benefit was seen for cardiovascular death, and there was a non-significant 6% relative excess death from all causes (Gage et al., 2004). How can this be explained? Shouldn't such a result be investigated further?

DIABETES, CHOLESTEROL, AND LIPID-LOWERING TREATMENTS

Although diabetes is considered a stroke risk factor in the elderly, intensive HbA_{1c}-lowering treatment ($< 6.5\%$) has been discouraged by the American Heart – American Stroke Association guidelines because of the higher death risks involved, a recommendation issued on the basis of data obtained from general and not from advanced age populations (Action to Control Cardiovascular Risk in Diabetes Study Group et al., 2008; Furie et al., 2011).

Epidemiological studies demonstrate a relationship between high cholesterol and vascular disease in the elderly (Prospective Studies Collaboration, 2007), and the benefit of statins in preventing vascular disease and stroke, despite the lack of association of cholesterol levels with ischemic stroke risk (Cholesterol Treatment Trialists' Collaboration, 2005). Again most of the evidence on statin efficacy in primary and secondary stroke prevention comes from subgroup analyses from general population trials, despite a large study reporting a 25% relative risk reduction in secondary stroke (Afilalo et al., 2008). There is only one secondary prevention trial with stroke as a primary end-point, but with very few patients over 80 (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels Investigators, 2006). So even when the available evidence supports statins as effective in primary and secondary vascular prevention in the very old, the data are just not enough to make evidence-based decisions in stroke patients.

In summary, present available evidence shows that some stroke management schemes may reasonably be applied to the elderly as safely as to the population at large, but not others. Emerging data suggest that, because the risk/benefit ratio is still uncertain, stroke management in old patients should be addressed separately. Better evidence could help the elderly, the population at highest stroke risk, prevent the devastating consequences of stroke.

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