Prevention and Treatment of Acute Stroke in the Nonagenarians and Beyond: Medical & Ethical Issues

Tiberiu A Pana; Jesus A Perdomo-Lampignano, BSc; Phyo K Myint, MD

Ageing Clinical and Experimental Research Team, Institute of Applied Health Sciences, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, Aberdeen, UK.

Correspondence to:
Professor Phyo Kyaw Myint
Room 4:013, Polwarth Building
School of Medicine, Medical Sciences and Nutrition
Foresterhill, Aberdeen
AB25 2ZD,
Scotland, UK.
Tel: +44 (0) 1224 437841,
Fax: +44 (0) 1224 43791
Mail to: phyo.myint@abdn.ac.uk

Total word count: 4386

Keywords: *Stroke; Cerebrovascular Disease; Nonagenarian; Oldest old; Prevention; Management*

PURPOSE OF REVIEW

As one of the fastest growing portions of the population, nonagenarians will constitute a significant percentage of the stroke patient population in the near future. Nonagenarians are nevertheless not specifically targeted by most clinical guidelines. In this review we aimed to summarize the available evidence guiding stroke prevention and treatment in this age group.

RECENT FINDINGS

Several recent observational studies have shown that the benefits of anticoagulation for the oldest old patients with atrial fibrillation may outweigh the bleeding risk. A sub-analysis of the IST-3 trial has shown for the first time that thrombolysis treatment in acute ischaemic stroke may be beneficial and safe even in octogenarian patients and older. Several recent observational studies have assessed thrombolysis in nonagenarians. The latest of these has shown better disability outcomes without increased rates of symptomatic intracerebral haemorrhage with thrombolysis.

SUMMARY

Nonagenarian stroke patients may benefit from similar preventative and therapeutic strategies as their younger counterparts. A few important exceptions include primary prevention using aspirin or statins. Patient selection is nevertheless essential given the increased adverse event rates. Patient preference should play a key role in the decision-making process. Clinical trials including more nonagenarian patients are required to yield more robust evidence

INTRODUCTION

In Europe alone, the population older than 90 years is expected to increase from 6.5 to 16.3 million by 2050 (1). These demographic shifts are expected to be accompanied by concordant changes in the epidemiology of chronic diseases (2,3). Cerebrovascular disorders in particular exhibit such a pattern: over 20 cases in 1000 patient-years occur over the age of 85 (4), accounting for 17% of all strokes (5).

Stroke in the very old is associated with a poor prognosis: patients older than 80 years are twice more likely to die within 30 days, with a 50% increased risk of dependency (4). Those older than 85 are 3 times more likely to die at 5 years (6). Whilst these differences may be attributable to factors such a decreased life expectancy, high co-morbidity burden or decreased compensatory reserve in the very elderly (7,8), evidence suggests that older stroke patients may receive poorer care than their younger counterparts (8). Given that the evidence for the prevention and management of stroke in the very elderly is scarce (9), clinicians may often be reluctant to offer treatments that may be perceived as 'high-risk', such as anticoagulation for atrial fibrillation or thrombolysis in the setting of acute ischaemic stroke (9).

In this review, we aim to summarise the latest evidence regarding the use of preventative and curative therapies in acute stroke patients older than 90 years of age. We also highlight the ethical aspects of management in this patient group.

PREVENTION

The mainstay of stroke primary prevention is the management of modifiable risk factors (10). The INTERSTROKE study (11) evaluated the effects of modifiable risk factors on stroke incidence in 32 countries and reported that 10 risk factors are implicated in up to 90% of

strokes in all ages. These risk factors include hypertension, smoking, cardiovascular disease, obesity and dyslipidaemia. Despite extensive literature regarding the management of these risk factors and the benefits of treatment (10), there is limited evidence for those over 80 years of age. The following strategies outline the current evidence in regards to these risk factors as applied to nonagenarians.

Lifestyle Modification

Physical inactivity has been shown to be associated with a 60% increase in the risk of incident stroke in patients older than 80 years (12). Furthermore, the relationship between smoking and adverse cardiovascular events has also been confirmed in older adults (13).

The adoption of an active lifestyle along with a balanced diet and smoking cessation may be as effective for the primary prevention of stroke in the oldest old as in the general population (5,14). More importantly, such approaches are especially advantageous in the oldest old since they do not contribute to increasing polypharmacy.

Hypertension Control

Hypertension is the most important risk factor for stroke (15). Nevertheless, the management of hypertension is more complex in the oldest old patients. The classic paradigm of blood pressure control "*the lower the better*" may not apply to the very elderly and frail, who may be predisposed to cognitive dysfunction, hypotension, and falls (16). Furthermore, the issue of polypharmacy is vitally important in a population especially vulnerable to the adverse effects of pharmacotherapy and drug-drug interactions (17,18).

A few studies have reported the outcomes of antihypertensive therapy in octogenarians and above. A meta-analysis of the INDANA intervention trials (19) showed that blood pressure

management reduces the stroke risk by up to 33% in those older than 80. The HYVET trial (20) showed that blood pressure reduction using indapamide ± perindopril in octogenarians reduced the risk both overall mortality and stroke incidence by 21% and 30%, respectively. It is worth noting that the blood pressure target in the HYVET study was 150/80 mmHg, slightly higher than those recommended in current guidelines for younger age groups. Nevertheless, it is important to note that these studies have limited their evidence base to the healthiest and less frail individuals by excluding those with certain co-morbidities and care home residents.

Expert opinion statements regarding the management of hypertension in old and frail patients have emphasised that based on currently available evidence, hypertensive patients older than 80 years of age should be treated to a target systolic blood pressure between 130 and 150 mmHg (21,22). It has been recommended that therapy should always be initiated as low-dose monotherapy only after a frailty assessment (21).

Dyslipidaemia Control

Whilst the evidence supporting the use of statins in the primary and secondary prevention of cardiovascular and cerebrovascular disease is robust (10), most studies have only provided evidence for patients with a mean age of 75 years (23,24). Whilst current guidelines recommend the use of statins in all patients irrespective of age, the evidence base is very scarce for the very elderly. The largest observational study to date including 8307 patients older than 85 years has concluded that statin use was not associated with any benefit in incident stroke or death in these patients (25). Data from clinical practice suggest that the oldest old patients are nevertheless prescribed statin therapy, albeit less frequently (26).

Statin use in the very elderly may be associated with myopathy (27), sarcopenia (28) and ultimately falls and fractures. Furthermore, it has been suggested that statin use may be

associated with an increased risk of incident haemorrhagic stroke in patients with a previous transient ischaemic attack or stroke (29,30). Despite the fact that the most recent meta-analysis have failed to support this claim in either primary or secondary stroke prevention, no age-dependent sub-analyses have been performed in these studies (31-34). Given that age may play an important role in the statin-associated haemorrhagic stroke risk, further studies are required to elucidate this relationship for the oldest old.

Nevertheless, given the other adverse effects that may be associated with statin use in nonagenarians, it would be sensible to suggest thattheir usage should be discouraged in this age group.

Antiplatelet agents

Primary Prevention

The use of aspirin in the primary prevention of cardiovascular disease remains a common practice amongst older people (35,36), despite doubts of whether the risk-benefit ratio of aspirin therapy warrants its use (37,38). Given that the aspirin-associated bleeding risk increases significantly in older ages (39), this therapy should not be recommended in the very old solely for stroke primary prevention.

Secondary Prevention

It has been established that patients with stroke or transient ischaemic attack (TIA) have better outcomes with low-dose aspirin monotherapy (40). The risk-benefit ratio in older patients is likely to be different than in younger populations, given their higher propensity to suffer haemorrhagic complications (41). Nevertheless, in the absence of clinical trials evaluating this outcome specifically in the oldest old, it has been suggested that the benefits

of aspirin secondary stroke prevention may not be age-dependent (42). The adjunctive usage of proton pump inhibitors may be associated with a reduction in gastrointestinal haemorrhage rates and may potentially lead to more acceptable outcomes (41), but this needs to be weighed against increasing polypharmacy.

Short-term dual antiplatelet therapy (low-dose aspirin and clopidogrel within the first 21 days after stroke) has been recently proposed as a better preventative strategy than aspirin monotherapy in patients with minor strokes or TIAs (43). The clinical trials focused mainly on younger populations, and therefore their findings may not be necessarily applicable to the very old. A careful consideration of the risk-benefit ratio should guide the decision-making process until further clinical trial evidence emerges for secondary stroke prevention in nonagenarian patients.

Carotid Endarterectomy and Stenting

The presence of carotid stenosis is a risk factor for the development of ischaemic stroke (44). For asymptomatic patients with carotid stenosis, a comprehensive systematic review has shown that surgical endarterectomy (CEA) was associated with both lower mortality and incident ipsilateral stroke compared with best medical therapy (45). Nevertheless the CEA-associated morbidity and mortality were also increased compared to medical therapy (45). Nevertheless, given that recent advancements in best medical therapy may decrease the risk of ipsilateral stroke to levels comparable to CEA, most recent guidelines only offer a Class IIa recommendation for CEA in patients a low perioperative risk (10). Thus, given that nonagenarian patients are more likely to be at a higher perioperative risk and that the ACST trial failed to show a CEA-associated reduction in the stroke risk in the subgroup of patients older than 75 years of age (47), it would be advisable that aspirin and statin therapy be

employed for stroke prevention in nonagenarian patients with asymptomatic carotid stenosis (10).

In the case of symptomatic moderate-to-severe carotid stenosis, current guidelines recommend CEA for secondary stroke prevention, provided that the perioperative risk is less than 6% (48). Conflicting reports exist regarding the safety of CEA in patients older than 80 years. Whilst some reports suggest that CEA was not associated with a higher peri-operative risk in the very elderly compared to younger patients (49-53), others draw the opposite conclusion (54-57). A recent meta-analysis of randomised trials has concluded that age greater than 75 years was not associated with worse CEA outcomes (58). Nevertheless, another meta-analysis of observational studies has concluded that despite similar rates of adverse cerebrovascular events with CEA between patients older and younger than 80 years, the former were at a higher mortality risk (59).

Carotid Artery Stenting (CAS) is a percutaneous alternative to CEA for carotid revascularisation. The studies evaluating the use of CAS versus CEA in the very elderly have yielded more homogenous conclusions, suggesting that CAS should be avoided in this age group due to the high peri-operative stroke risk (56,58-62).(63) The ongoing CREST-2 trial is aiming to compare the outcomes of best medical therapy, CEA and CAS in the management of asymptomatic carotid stenosis. Subgroup analyses from CREST-2 will hopefully provide evidence on the best management strategy in the very elderly (64). In the meantime, appropriate medical therapy should be mainstay of treatment in those patients regardless of whether an interventional approach is also considered. Optimal patient selection for carotid revascularisation is essential in the very elderly, and adjunctive tools such as frailty scores may prove useful for this purpose (65).

Prevention of stroke in patients with Atrial Fibrillation

Oral anticoagulation

Oral anticoagulation (OAC) is the mainstay of the prevention of atrial fibrillation-related stroke (66). Despite being at a higher risk of stroke (67), a significant proportion of older patients with atrial fibrillation (up to 60%) are either not routinely anticoagulated (68-74) or receive suboptimal therapy compared to younger patients (68). Older patients are more likely to have significant contra-indications to anticoagulant therapy or an unacceptably high bleeding risk (75). Nevertheless, a review of the treatment regimens of 3378 care home residents with atrial fibrillation (mean age 85 years) has shown that only 56% of those who were not anticoagulated were deemed to have clear contraindications (76).Whilst the data regarding the quality of anticoagulation specifically in patients older than 90 years is scarce, those are even less likely to receive OAC (77,78). Less dramatic differences in the quality and quantity of anticoagulation between patients older and younger than 80 years have also been reported (79,80).

Whilst the evidence supporting the use of OAC for primary stroke prevention is robust (81), very low numbers of nonagenarians are randomised in those clinical trials, leading to an important evidence gap in this age group. Nevertheless, several observational studies (68,69,69,77,77,82,82,83,83) and two small clinical trials (84,85) suggest that despite increased risks of both ischaemic stroke and major haemorrhage in octogenarians and nonagenarians with AF, the efficacy of OAC not only remains superior to anti-platelet regimens, but also the benefits of OAC may exceed the risks of major haemorrhage. A further consideration specific to the elderly patients receiving OAC is the increased falls risk, which may potentially increase the bleeding risk. Nevertheless, recent evidence fails to support this hypothesis (86,87). Given that a patient receiving vitamin K antagonist (VKA) therapy would need to fall 295 times per year to increase their risk of haemorrhage beyond the benefits of

stroke prevention, it has been suggested that a high risk of falling in itself should not constitute an absolute contraindication for OAC (88).

Furthermore, the adoption of Direct OACs (DOAC) represents an important milestone in stroke prevention in this age group. The lack of monitoring requirements in DOAC treatment has led to the more extensive adoption of OAC in very old patient groups, particularly given the higher burden of co-morbid dementia and cognitive decline in this group (77,79). Recent evidence suggest that DOACs are at least as effective as VKAs, with comparable rates of major haemorrhage (89,90). They currently represent a very attractive alternative for OAC in nonagenarian patients due to the ease of administration, the decreased incidence of intracranial bleeding events, comparable rates of extracranial haemorrhage with certain agents, such apixaban, edoxaban and reduced-dose dabigatran (91) and the emergence of specific reversal agents (92). Furthermore, in the context of polypharmacy in older patients, DOACs may be associated with fewer, but nevertheless not ignorable, drug interactions than VKAs (89,93). Nevertheless, certain cautionary points need to be taken in consideration with the usage of DOACs in extreme old age. The very high prevalence of renal impairment amongst nonagenarians compared to the general population (94) proves particularly problematic in the usage of DOACs, since in this very high-risk patient subgroup there has not been an observed reduction in the incidence of ischaemic stroke with DOAC use (95). Furthermore, DOACs are contra-indicated in AF related to valvular heart disease, the incidence of which may be higher in nonagenarian patients (96).

Despite the scarcity of available evidence regarding the adoption of OAC in nonagenarian patients with AF, certain conclusions may be extrapolated from the rather modest body of evidence concerning those over 75-80 years. It is sensible to suggest that the benefit derived from OAC is not age-dependent and may still exceed the risks of major bleeding even in nonagenarians. This should guide the decision to offer OAC in this group, taking into account

the individual patient phenotype, such as those determined to be at a high bleeding risk (75), or those with clear contraindications to OAC. Magnetic resonance imaging techniques that are able to detect the presence of cerebral microbleeds (CMB) as a marker of cerebral amyloid angiopathy may be useful in delineating patient groups in whom OAC may be associated with an unacceptably high risk of intracranial haemorrhage (97,98). More recently, it has been suggested that the presence of five CMBs may represent an adequate threshold for identifying such high-risk subgroups amongst ischaemic stroke patients with AF (99).

Once the decision to offer OAC has been made, a choice of between VKA or DOAC regimens should be performed on a case-by-case basis, taking into the account patient preference as well as the co-morbid profile. Conditions such as renal impairment, dementia and valvular aetiology of AF along with concomitant pharmacotherapy should be considered.

Left Atrial Appendage Closure devices

Percutaneous left atrial appendage (LAA) closure is an emerging alternative to OAC in patients in whom OAC is either contraindicated or the risks of long-term therapy are unacceptably high. LAA closure devices have been shown to be non-inferior to VKAs for stroke prevention both in the short-term (100-102) and the long-term (103). Recent evidence has shown that LAA closure devices may be suitable in patients with advanced renal dysfunction for whom OAC would either involve an unacceptable bleeding risk or would not be effective (104). Furthermore, AF patients with a very high co-morbidity burden and in whom the OAC-related risk reduction of ischaemic stroke may not be satisfactory, the usage of LAA closure devices may improve their outcomes (105). Nevertheless, this procedure is not without complications, as it is performed under general anaesthesia and requires peri-procedural anticoagulation as well as long-term post-procedural anti-platelet therapy (106).

Other complications include post-implantation leak or thrombosis (106). Despite the current lack of specific evidence for LAA closure in the very elderly, such devices seem to be amenable to patient phenotypes commonly seen amongst the elderly.

TREATMENT

Intravenous Thrombolysis

The adoption of thrombolytic therapy using recombinant tissue-type plasmin activation (rtPA) has represented a revolutionary milestone in the acute treatment of ischaemic stroke. Nevertheless those agents are only licensed in the European Union for patients younger than 80 years (107). The Third International Stroke Trial (IST-3) was the first trial to show that intravenous (IV) rtPA treatment is as beneficial and safe in patients older than 80 years as in younger patients, having included 1617 patients over the age of 80 (53% of the total number randomised) and 209 patients older than 90 years (108,109). Furthermore, IST-3 patients older than 80 years who received IV rtPA had a lower 3-year post-stroke mortality than those who did not (110).(109)

A few systematic reviews exist to date evaluating this patient group. The most recent of those concluded as part of a subgroup analysis that patients older than 80 years who received IV rtPA within 6 hours had similar stroke disability and mortality outcomes as those younger than 80 years (111). Nevertheless, the very low proportion of such patients having been randomised in the trials included in this review (other than IST-3) led to the IST-3 being the primary driver of the results. A further meta-analysis of individual clinical trial patient data suggested that IV rtPA ischaemic stroke onset offered a favourable stroke disability outcome in both patients older and younger than 80 years (112). Nevertheless, there was no improvement in this outcome with IV rtPA in octogenarians if the treatment delay exceeded

3h (112). The other two meta-analyses that were published before the completion of the IST-3 trial concluded that IV rtPA treatment was associated with overall less favourable outcomes in patients over 80 years of age, including higher mortality. Nevertheless, octogenarians did not have a higher incidence of symptomatic intracranial haemorrhage events in either reports (113,114). Both studies have concluded that the observed poorer outcomes in the over 80 group may be related to residual confounding. Observational studies have shown that IV rtPA was associated with lower post-stroke disability rates in octogenarians(115-121). Furthermore, the rates of post-rtPA symptomatic intracerebral haemorrhage (sICH) were similar between octogenarians and younger patients (115-118,122-126). Finally, it has been suggested that treatment decisions facilitated by Stroke Telemedicine in octogenarian patients receiving IV rtPA achieve similar outcomes as cases where a stroke physician is present on-site (127).

The evidence concerning rtPA in the oldest old stroke patients is scarce. Given that only 209 (7%) of the participants randomised in IST-3 were older than 90 years (109), a sub-analysis of this age group has not been performed. A prospective study concluded that stroke patients older than 85 years experienced worse mortality outcomes compared to younger age groups, without a significantly increased rise in the rate of sICH (128). Observational studies have shown that amongst patients receiving rtPA, nonagenarians had higher rates of both mortality(122,129) and adverse events(129). Other observational studies have assessed the outcomes of nonagenarian stroke patients receiving thrombolysis (130-133), but have yielded contradicting results. Whilst most of those suggested that nonagenarians did not benefit from IV rtPA (131-133), a recent study including concluded that thrombolysis was associated with a better disability outcome without a significantly increased rate of sICH in this age group (130).

Overall, whilst it seems that increasing age is associated with worse mortality outcomes with IV rtPA treatment, it may be the case that residual confounders such as the increasing co-morbidity burden may be responsible for this effect. Unfortunately, the studies assessing the outcomes of nonagenarian patients receiving IV rtPA failed to yield a single conclusion regarding the benefit – risk balance, unlike in octogenarians. This is most likely due to the high risk of bias inherent from the underpowered, retrospective nature of these studies. Current evidence suggests that stroke patients older than 80 years should not be refused IV thrombolytic treatment based on age alone, although the therapeutic window in this patient group may be limited to 3h. Unfortunately, clear recommendations cannot be made for nonagenarians at this point. Further clinical trials of IV rtPA including higher proportions of nonagenarians are required.

Mechanical thrombectomy

Mechanical thrombectomy in conjunction with IV rtPA treatment has been shown to be associated with better long-term stroke outcomes (134,135). Out of the five clinical trials that included patients older than 80 years of age (136-140), four performed subgroup analyses by age. Three of them concluded that patients older than 80 years of age derive the same benefit in terms of 90-day disability from mechanical thrombectomy as younger patients (136,138,140). This has been further confirmed by a subgroup analysis in a meta-analysis of individual patient data including 5 controlled trials (141). Another meta-analysis of 8 observational studies including a total of 1711 patients concluded that in patients older than 80 years of age mechanical thrombectomy was as likely to be associated with recanalization as in younger patients, without an elevated risk of sICH. Nevertheless, octogenarians had poorer 3 month outcomes (142).

Similarly to IV rtPA, the body of evidence evaluating this treatment in nonagenarian patients is severely limited. Two retrospective studies exist, including 18 and 19 nonagenarian patients with stroke, respectively. Whilst one of them has concluded that the acute outcomes do not differ based on the age divide alone (143), the other has suggested that nonagenarian patients may have lower rates of recanalization post-thrombectomy(144). The latter therefore suggests that certain technical difficulties may exist, such as a more complex vascular approach. Nevertheless, given that better patient selection may improve the outcomes of this procedure, it would be reasonable to suggest that acute stroke patients should not be denied mechanical thrombectomy based on age alone. Other more important factors, such as pre-stroke functional status, co-morbidity burden and stroke severity should be taken into consideration when deciding on a therapeutic route in nonagenarians.

HAEMORRHAGIC STROKE

The data regarding the epidemiology, risk factors or outcomes of haemorrhagic strokes in the very elderly are extremely limited, with no studies focusing solely on nonagenarians. However, it has been shown that the clinical characteristics of intracerebral haemorrhage may be significantly different between patients older and younger than 80 years, respectively (145-147). Thus, very elderly patients may be more likely to have subcortical haemorrhages, higher bleed volumes (146) and intra-ventricular extension (145). Poorer outcomes have also been reported in the very elderly (146,147). Despite these suggestions, it is worth noting that these results originated from small observational studies and hence may not necessarily be generalizable to other populations. In the absence of more specific and robust evidence, an individualised approach with reasonable goals should be adopted. In addition, considering the high risks of intracerebral haemorrhage associated with pre-existing CMB (97,98,148), patients with CMB evidence on blood-sensitive MRI should be managed more intensively, focusing particularly on primary and secondary prevention.

ETHICAL CONSIDERATIONS

Besides the medical aspects of stroke treatment in nonagenarian patients, certain ethical elements require consideration. Regardless of age, clinical decisions should be in line with the four ethical principles governing medical practice, namely, respect for autonomy, nonmaleficence, beneficence, and justice. In terms of beneficence, the growing body of evidence evaluating the management of stroke in nonagenarian patients is likely to lead to an increase in the available therapies for this age group. Clinicians should be aware of such advances and not refuse treatment inappropriately. It is also essential that clinical practice minimise iatrogenic harm: high-risk subgroups should be identified through prognostic research and caution should be exerted whenever the risk-benefit ratio may not be favourable. It is also essential to respect the wishes of the patient and ensure that the necessary information about the risk and expected outcomes of non-treatment have been appropriately communicated. Nevertheless, given the nature of cerebrovascular events and the relatively high prevalence of dementia and cognitive impairment amongst the oldest old, communication may not be straightforward. Many nonagenarian patients presenting with a cerebrovascular event may not have the capacity to take such a complex decision. Thus, in the view of a rapidly growing nonagenarian population, healthcare providers should encourage their elderly patients to prepare for such unfortunate eventualities by completing Advanced Directives.

Finally, in a very rapidly ageing population with an increasing co-morbidity burden, the healthcare resources that need to be allocated to the prevention and treatment of cerebrovascular disease will also increase. According to a recent study in the United Kingdom (149), the cost of combined health and social care for stroke sufferers older than 90

years of age over 5 years after the index event varied sharply with stroke severity and was significantly higher than in younger ages. Thus, the estimated cost for a nonagenarian patient with a severe stroke would be £75,000 ($100,000), whilst moderate and severe strokes in this age group have been estimated to cost approximately £60,000 ($80,000) and £45,000 ($60,000), respectively. Regardless of the estimated life expectancy of nonagenarian patients, it is likely that the healthcare costs will vary with stroke severity proportionally. Thus, efforts to prevent stroke and minimise the stroke-associated disability may be associated with an overall decrease in healthcare expenditure.

Thus, healthcare providers will need to plan resource allocation accordingly, emphasising on the importance of prompt and effective preventative and treatment strategies to minimise disability and promote independence after stroke. It is only by meeting the increased demand in acute geriatric care that fairness can be ensured when deciding the clinical management of such complex patients.

CONCLUSION

Given the rapidly growing segment of population over 90 years and the age-dependent incidence of cerebrovascular disease, it is reasonable to expect that the number of nonagenarian patients suffering a stroke will also increase dramatically in the coming years. Despite the relative paucity of studies evaluating stroke prevention and treatment in this patient group, recent years have seen a dramatic increase in such trials. In this review, we have assessed the relevant literature covering those topics. We have found that some primary stroke prevention therapies may still be recommended in nonagenarians, such as anticoagulation for patients with AF, careful management of hypertension and lifestyle modifications, whilst aspirin and statin therapy have not proven efficacious. In terms of acute

management, we have found that intravenous thrombolysis and mechanical thrombectomy may be beneficial even in this age group, but at the cost of higher complication rates. Such treatments should be prescribed in a carefully selected nonagenarian population, taking into account other factors such as patient preference. Further research that is inclusive of this population stratum is encouraged to elucidate current gaps in evidence and to provide evidence-based recommendations for clinical practice.

REFERENCES

1. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2017 Revision. Vol. I: Comprehensive Tables : World Population Prospects: The 2017 Revision;2018 IIS 3080-S22.1;ST/ESA/SER.A/399 2018.

2. Yazdanyar A and Newman AB. The Burden of Cardiovascular Disease in the Elderly: Morbidity, Mortality, and Costs. Clinics in Geriatric Medicine 2009:25:563-577. Doi:10.1016/j.cger.2009.07.007.

3. Prince MJ, Wu F, Guo Y, Gutierrez-Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet 2015:385:549-562. Doi:10.1016/S0140-6736(14)61347-7.

4. Russo T, Felzani G and Marini C. Stroke in the Very Old: A Systematic Review of Studies on Incidence, Outcome, and Resource Use. Journal of Aging Research 2011:2011:108785-6. Doi:10.4061/2011/108785.

5. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation 2018:137:e67. Doi:10.1161/CIR.0000000000000558.

6. Kammersgaard LP, Jørgensen HS, Reith J, Nakayama H, Pedersen PM and Olsen TS. Short- and long-term prognosis for very old stroke patients. The Copenhagen Stroke Study. Age and Ageing 2004:33:149-154. Doi:10.1093/ageing/afh052.

7. Luker JA, Wall K, Bernhardt J, Edwards I and Grimmer-Somers KA. Patients' age as a determinant of care received following acute stroke: a systematic review. BMC Health Services Research 2011:11:161. Doi:10.1186/1472-6963-11-161.

8. Fonarow GC, Reeves MJ, Zhao X, Olson DM, Smith EE, Saver JL, et al. Age-related differences in characteristics, performance measures, treatment trends, and outcomes in patients with ischemic stroke. Circulation 2010:121:879-891. Doi:10.1161/CIRCULATIONAHA.109.892497.

9. Sanossian N and Ovbiagele B. Prevention and management of stroke in very elderly patients. Lancet Neurol 2009:8:1031-1041. Doi:10.1016/S1474-4422(09)70259-5.

10. Meschia JF, Cheryl B, Boden-Albala B, Braun LT, Bravata DM, Seemant C, et al. Guidelines for the Primary Prevention of Stroke. Stroke 2014:45:3754-3832. Doi:10.1161/STR.0000000000000046.

11. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. The Lancet 2016:388:761-775. Doi:10.1016/S0140-6736(16)30506-2.

12. Willey JZ, Moon YP, Sacco RL, Greenlee H, Diaz KM, Wright CB, et al. Physical inactivity is a strong risk factor for stroke in the oldest old: Findings from a multi-ethnic population (the Northern Manhattan Study). Int J Stroke 2017:12:197-200. Doi:10.1177/1747493016676614.

13. Mons U, Müezzinler A, Gellert C, Schöttker B, Abnet CC, Bobak M, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. BMJ : British Medical Journal 2015:350:h1551. Doi:10.1136/bmj.h1551.

14. Sarikaya H, Ferro J and Arnold M. Stroke Prevention - Medical and Lifestyle Measures. Eur Neurol 2015:73:150-157. Doi:10.1159/000367652.

15. Hauer AJ, Ruigrok YM, Algra A, van Dijk EJ, Koudstaal PJ, Luijckx G, et al. Age-Specific Vascular Risk Factor Profiles According to Stroke Subtype. Journal of the American Heart Association 2017:6:11-21. Doi:10.1161/JAHA.116.005090.

16. Odden MC, Beilby PR and Peralta CA. Blood Pressure in Older Adults: the Importance of Frailty. Curr Hypertens Rep 2015:17:55. Doi:10.1007/s11906-015-0564-y.

17. Ferri C, Ferri L and Desideri G. Management of Hypertension in the Elderly and Frail Elderly. High Blood Press Cardiovasc Prev 2017:24:1-11. Doi:10.1007/s40292-017-0185-4.

18. Benetos A, Rossignol P, Cherubini A, Joly L, Grodzicki T, Rajkumar C, et al. Polypharmacy in the Aging Patient: Management of Hypertension in Octogenarians. JAMA 2015:314:170-180. Doi:10.1001/jama.2015.7517.

19. Gueyffier F, Boutitie F, Boissel JP, Pocock S, Coope J, Cutler J, et al. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men. A meta-analysis of individual patient data from randomized, controlled trials. The INDANA Investigators. Ann Intern Med 1997:126:761-767. Doi:10.7326/0003-4819-126-10-199705150-00002.

20. Mukhtar O and Jackson SH. The Hypertension in the Very Elderly Trial - latest data. Br J Clin Pharmacol 2013:75:951-954. Doi:10.1111/j.1365-2125.2012.04427.x.

21. Benetos A, Bulpitt C, Petrovic M, Ungar A, Agabiti Rosei E, Cherubini A, et al. An Expert Opinion From the European Society of Hypertension–European Union Geriatric Medicine Society Working Group on the Management of Hypertension in Very Old, Frail Subjects. Hypertension 2016:67:820-825. Doi:10.1161/HYPERTENSIONAHA.115.07020.

22. Potter JF and Myint PK. Hypertension. In: Fillit HM, Rockwood K, Young J, et al (eds) *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*. Eighth edition ed. Philadelphia, PA: Elsevier, 2017, p.295.

23. Savarese G, Gotto AM,Jr, Paolillo S, D'Amore C, Losco T, Musella F, et al. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. J Am Coll Cardiol 2013:62:2090-2099. Doi:10.1016/j.jacc.2013.07.069.

24. Teng M, Lin L, Zhao YJ, Khoo AL, Davis BR, Yong QW, et al. Statins for Primary Prevention of Cardiovascular Disease in Elderly Patients: Systematic Review and Meta-Analysis. Drugs Aging 2015:32:649-661. Doi:10.1007/s40266-015-0290-9.

25. Ramos R, Comas-Cufí M, Martí-Lluch R, Balló E, Ponjoan A, Alves-Cabratosa L, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. BMJ 2018:362:k3359. Doi:10.1136/bmj.k3359.

26. Sundvall H, Fastbom J, Wallerstedt SM and Vitols S. Use of statins in the elderly according to age and indication-a cross-sectional population-based register study. Eur J Clin Pharmacol 2019. Doi:10.1007/s00228-019-02645-w [doi].

27. Meador BM and Huey KA. Statin-associated myopathy and its exacerbation with exercise. Muscle Nerve 2010:42:469-479. Doi:10.1002/mus.21817.

28. Campins L, Camps M, Riera A, Pleguezuelos E, Yebenes JC and Serra-Prat M. Oral Drugs Related with Muscle Wasting and Sarcopenia. A Review. Pharmacology 2017:99:1-8. Doi:10.1159/000448247.

29. Goldstein LB, Amarenco P, Szarek M, Callahan A,3rd, Hennerici M, Sillesen H, et al. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology 2008:70:2364-2370. Doi:01.wnl.0000296277.63350.77 [pii].

30. Manktelow BN and Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. Cochrane Database Syst Rev 2009:(3):CD002091. doi:CD002091. Doi:10.1002/14651858.CD002091.pub2 [doi].

31. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010:376:1670-1681. Doi:10.1016/S0140-6736(10)61350-5 [doi].

32. Hackam DG, Woodward M, Newby LK, Bhatt DL, Shao M, Smith EE, et al. Statins and intracerebral hemorrhage: collaborative systematic review and meta-analysis. Circulation 2011:124:2233-2242. Doi:10.1161/CIRCULATIONAHA.111.055269 [doi].

33. McKinney JS and Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. Stroke 2012:43:2149-2156. Doi:10.1161/STROKEAHA.112.655894.

34. Ziff OJ, Banerjee G, Ambler G and Werring DJ. Statins and the risk of intracerebral haemorrhage in patients with stroke: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2019:90:75-83. Doi:10.1136/jnnp-2018-318483 [doi].

35. Elwood P, Morgan G, White J, Dunstan F, Pickering J, Mitchell C, et al. Aspirin taking in a South Wales county. British Journal of Cardiology 2011:18. Doi:10.5837/bjc.2011.006.

36. Mostaza JM, Lahoz C, Salinero-Fort MA and Cardenas J. Cardiovascular disease in nonagenarians: Prevalence and utilization of preventive therapies. European Journal of Preventive Cardiology 2018:204748731881372. Doi:10.1177/2047487318813723.

37. Montalescot G. A farewell to aspirin in primary prevention?. Nature Reviews - Cardiology 2019:16:76-77. Doi:10.1038/s41569-018-0148-z.

38. Ridker PM. Should Aspirin Be Used for Primary Prevention in the Post-Statin Era?. N Engl J Med 2018:379:1572-1574. Doi:10.1056/NEJMe1812000.

39. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. N Engl J Med 2018:379:1509-1518. Doi:10.1056/NEJMoa1805819.

40. Hankey GJ. The benefits of aspirin in early secondary stroke prevention. The Lancet 2016:388:312-314. Doi:10.1016/S0140-6736(16)30511-6.

41. Li L, Geraghty OC, Mehta Z, Rothwell PM and Oxford Vascular Study. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017:390:490-499. Doi:10.1016/S0140-6736(17)30770-5.

42. Chen Z, Sandercock P, Pan H, Counsell C, Collins R, Liu L, et al. Indications for Early Aspirin Use in Acute Ischemic Stroke. Stroke 2000:31:1240-1249. Doi:10.1161/01.STR.31.6.1240.

43. Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RAC and Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. BMJ 2018:363:k5108. Doi:10.1136/bmj.k5108.

44. Spagnoli L, Mauriello A, Sangiorgi G, Fratoni S, Bonanno E, Schwartz RS, et al. Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke. JAMA 2004:292:1845-1852. Doi:10.1001/jama.292.15.1845.

45. Barkat M, Roy I, Antoniou SA, Torella F and Antoniou GA. Systematic review and network meta-analysis of treatment strategies for asymptomatic carotid disease. Scientific Reports 2018:8:4458-13. Doi:10.1038/s41598-018-22356-z.

46. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004:363:1491-1502. Doi:10.1016/S0140-6736(04)16146-1 [doi].

47. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014:45:2160-2236. Doi:10.1161/STR.0000000000000024 [doi].

48. Meschia J, Bushnell C, Boden-Albala B, Braun L, Bravata D, Chaturvedi S, et al. Guidelines for the Primary Prevention of Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2014:45:3754-3832. Doi:10.1161/STR.0000000000000046.

49. Schneider JR, Jackson CR, Helenowski IB, Verta MJ, Wilkinson JB, Kim S, et al. A comparison of results of carotid endarterectomy in octogenarians and nonagenarians to younger patients from the Mid-America Vascular Study Group and the Society for Vascular Surgery Vascular Quality Initiative. J Vasc Surg 2017:65:1643-1652. Doi:10.1016/j.jvs.2016.12.118.

50. Ballotta E, Toniato A, Farina F and Baracchini C. The perioperative outcomes of eversion carotid endarterectomy in diabetic patients aged 80 years or older. J Vasc Surg 2016:64:348-353. Doi:10.1016/j.jvs.2016.01.052.

51. Ballotta E, Toniato A, Da Roit A, Lorenzetti R, Piatto G and Baracchini C. Carotid endarterectomy for asymptomatic carotid stenosis in the very elderly. J Vasc Surg 2015:61:382-388. Doi:10.1016/j.jvs.2014.07.090.

52. Okawa M, Ogata T, Abe H, Fukuda K, Higashi T and Inoue T. Do octogenarians still have a high risk of adverse outcomes after carotid endarterectomy in the era of a super-aged society? A single-center study in Japan. J Stroke Cerebrovasc Dis 2015:24:370-373. Doi:10.1016/j.jstrokecerebrovasdis.2014.09.011.

53. Sadideen H, Thomson DR, Lewis RR, Padayachee TS and Taylor PR. Carotid endarterectomy in the elderly: risk factors, intraoperative carotid hemodynamics and short-term complications: a UK tertiary center retrospective analysis. Vascular 2013:21:273-277. Doi:10.1177/1708538113478740.

54. Rajamani K, Kennedy KF, Ruggiero NJ, Rosenfield K, Spertus J and Chaturvedi S. Outcomes of carotid endarterectomy in the elderly: report from the National Cardiovascular Data Registry. Stroke 2013:44:1172-1174. Doi:10.1161/STROKEAHA.111.000513.

55. De Rango P, Lenti M, Simonte G, Cieri E, Giordano G, Caso V, et al. No benefit from carotid intervention in fatal stroke prevention for >80-year-old patients. Eur J Vasc Endovasc Surg 2012:44:252-259. Doi:10.1016/j.ejvs.2012.06.006.

56. Voeks JH, Howard G, Roubin GS, Malas MB, Cohen DJ, Sternbergh 3, W Charles, et al. Age and outcomes after carotid stenting and endarterectomy: The carotid revascularization

endarterectomy versus stenting trial. Stroke 2011:42:3484-3490. Doi:10.1161/STROKEAHA.111.624155.

57. Schmidt M, Ulrichsen SP, Pedersen L, Botker HE, Nielsen JC and Sorensen HT. 30-year nationwide trends in incidence of atrial fibrillation in Denmark and associated 5-year risk of heart failure, stroke, and death. Int J Cardiol 2016:225:30-36. Doi:10.1016/j.ijcard.2016.09.071.

58. Howard G, Roubin GS, Jansen O, Hendrikse J, Halliday A, Fraedrich G, et al. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from four randomised trials. Lancet 2016:387:1305-1311. Doi:10.1016/S0140-6736(15)01309-4.

·59. Antoniou GA, Georgiadis GS, Georgakarakos EI, Antoniou SA, Bessias N, Smyth JV, et al. Meta-analysis and Meta-Regression Analysis of Outcomes of Carotid Endarterectomy and Stenting in the Elderly. JAMA Surgery 2013:148:1140-1152. Doi:10.1001/jamasurg.2013.4135.

60. Wach MM, Dumont TM, Shakir HJ, Snyder KV, Hopkins LN, Levy EI, et al. Carotid artery stenting in nonagenarians: are there benefits in surgically treating this high risk population?. Journal of Neurointerventional Surgery 2015:7:182-187. Doi:10.1136/neurintsurg-2013-011052.

61. Bonati LH, Fraedrich G and Carotid Stenting Trialists' Collaboration. Age modifies the relative risk of stenting versus endarterectomy for symptomatic carotid stenosis--a pooled analysis of EVA-3S, SPACE and ICSS. Eur J Vasc Endovasc Surg 2011:41:153-158. Doi:10.1016/j.ejvs.2011.01.001.

62. Bonati LH, Dobson J, Algra A, Branchereau A, Chatellier G, Fraedrich G, et al. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. The Lancet 2010:376:1062-1073. Doi:10.1016/S0140-6736(10)61009-4.

·63. Heo SH and Bushnell CD. Factors Influencing Decision Making for Carotid Endarterectomy versus Stenting in the Very Elderly. Frontiers in Neurology 2017:8:220. Doi:10.3389/fneur.2017.00220.

·64. Mott M, Koroshetz W and Wright CB. CREST-2: Identifying the Best Method of Stroke Prevention for Carotid Artery Stenosis: National Institute of Neurological Disorders and Stroke Organizational Update. Stroke 2017:48:e130. Doi:10.1161/STROKEAHA.117.016051.

CREST-2 trial: sub-analysis of upcoming results may provide more robust data on the issue of carotid intervention in the very elderly

65. Melin AA, Schmid KK, Lynch TG, Pipinos II, Kappes S, Longo GM, et al. Preoperative frailty Risk Analysis Index to stratify patients undergoing carotid endarterectomy. J Vasc Surg 2015:61:683-689. Doi:10.1016/j.jvs.2014.10.009.

66. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal 2016:37:2893-2962. Doi:10.1093/eurheartj/ehw210.

67. Lip GY, Nieuwlaat R, Pisters R, Lane DA and Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010:137:263-272. Doi:10.1378/chest.09-1584.

68. Alnsasra H, Haim M, Senderey AB, Reges O, Leventer-Roberts M, Arnson Y, et al. Net clinical benefit of anticoagulant treatments in elderly patients with nonvalvular atrial fibrillation: Experience from the real world. Heart Rhythm 2019:16:31-37. Doi:10.1016/j.hrthm.2018.08.016.

69. Ekerstad N, Karlsson T, Soderqvist S and Karlson BW. Hospitalized frail elderly patients - atrial fibrillation, anticoagulation and 12 months' outcomes. Clin Interv Aging 2018:13:749-756. Doi:10.2147/CIA.S159373.

70. Biteker M, Basaran O, Dogan V, Beton O, Tekinalp M, Cagri Aykan A, et al. Real-life use of digoxin in patients with non-valvular atrial fibrillation: data from the RAMSES study. J Clin Pharm Ther 2016:41:711-717. Doi:10.1111/jcpt.12460.

71. Shurrab M, Crystal E, O'Donnell D, Navare H, Neves P, Khatib R, et al. The gap between indicated and prescribed stroke prevention therapies in a high-risk geriatric population. J Interv Card Electrophysiol 2017:48:261-266. Doi:10.1007/s10840-017-0223-0.

72. McGrath ER, Go AS, Chang Y, Borowsky LH, Fang MC, Reynolds K, et al. Use of Oral Anticoagulant Therapy in Older Adults with Atrial Fibrillation After Acute Ischemic Stroke. J Am Geriatr Soc 2017:65:241-248. Doi:10.1111/jgs.14688.

73. Oqab Z, McIntyre WF, Quinn KL, Lamb T, Quadros K, Yazdan-Ashoori P, et al. Resident Physicians Choices of Anticoagulation for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation. Can J Cardiol 2016:32:824-828. Doi:10.1016/j.cjca.2015.08.004.

74. Yamashita Y, Hamatani Y, Esato M, Chun Y, Tsuji H, Wada H, et al. Clinical characteristics and outcomes in extreme elderly (age >/= 85 years) Japanese patients with atrial fibrillation: the Fushimi AF registry. Chest 2016:149:401. Doi:10.1378/chest.15-1095.

75. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal 2016:37:2893-2962. Doi:10.1093/eurheartj/ehw210.

76. Shurrab M, Crystal E, O'Donnell D, Navare H, Neves P, Khatib R, et al. The gap between indicated and prescribed stroke prevention therapies in a high-risk geriatric population. J Interv Card Electrophysiol 2017:48:261-266. Doi:10.1007/s10840-017-0223-0.

·77. Chao T, Liu C, Lin Y, Chang S, Lo L, Hu Y, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. Circulation 2018:138:37-47. Doi:10.1161/CIRCULATIONAHA.117.031658.

Large observational study showing OAC benefit in nonagenarians

78. Proietti M, Mairesse GH, Goethals P, Scavee C, Vijgen J, Blankoff I, et al. A population screening programme for atrial fibrillation: a report from the Belgian Heart Rhythm Week screening programme. Europace 2016:18:1779-1786. Doi:10.1093/europace/euw069.

79. Hugo GS, Figueiras-Graillet LM, Anguita M, Marin F, Bertomeu V, Roldan I, et al. Oral anticoagulation in octogenarians with atrial fibrillation. Int J Cardiol 2016:223:87-90. Doi:10.1016/j.ijcard.2016.08.004.

80. Lefebvre MC, St-Onge M, Glazer-Cavanagh M, Bell L, Kha Nguyen JN, Viet-Quoc Nguyen P, et al. The Effect of Bleeding Risk and Frailty Status on Anticoagulation Patterns in Octogenarians With Atrial Fibrillation: The FRAIL-AF Study. Can J Cardiol 2016:32:169-176. Doi:10.1016/j.cjca.2015.05.012.

81. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Journal of Cardio-Thoracic Surgery 2016:50:E88. Doi:10.1093/ejcts/ezw313.

·82. Patti G, Lucerna M, Pecen L, Siller-Matula JM, Cavallari I, Kirchhof P, et al. Thromboembolic Risk, Bleeding Outcomes and Effect of Different Antithrombotic Strategies in Very Elderly Patients With Atrial Fibrillation: A Sub-Analysis From the PREFER in AF (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation). J Am Heart Assoc 2017:6:10.1161/JAHA.117.005657. Doi:10.1161/JAHA.117.005657.

Large observational study showing OAC benefit in over 85s

83. Lip G, Clementy N, Pericart L, Banerjee A and Fauchier L. Stroke and Major Bleeding Risk in Elderly Patients Aged ≥75 Years With Atrial Fibrillation: The Loire Valley Atrial Fibrillation Project. Stroke 2015:46:143-150. Doi:10.1161/STROKEAHA.114.007199.

·84. Rash A, Downes T, Portner R, Yeo WW, Morgan N and Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). Age and Ageing 2007:36:151-156. Doi:10.1093/ageing/afl129.

Clinical Trial showing OAC benefit in >80s

·85. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007:370:493-503. Doi:10.1016/S0140-6736(07)61233-1.

Clinical Trial showing OAC benefit in >80s

86. Hagerty T and Rich MW. Fall risk and anticoagulation for atrial fibrillation in the elderly: A delicate balance. Cleve Clin J Med 2017:84:35-40. Doi:10.3949/ccjm.84a.16016.

87. Sellers MB and Newby KL. Atrial fibrillation, anticoagulation, fall risk, and outcomes in elderly patients. American Heart Journal 2011:161:241-246. Doi:10.1016/j.ahj.2010.11.002.

88. Man-Son-Hing M, Nichol G, Lau A and Laupacis A. Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls. Archives of Internal Medicine 1999:159:677-685. Doi:10.1001/archinte.159.7.677.

89. Oertel LB and Fogerty AE. Use of direct oral anticoagulants for stroke prevention in elderly patients with nonvalvular atrial fibrillation. J Am Assoc Nurse Pract 2017:29:551-561. Doi:10.1002/2327-6924.12494.

90. Giustozzi M, Vedovati MC, Verso M, Scrucca L, Conti S, Verdecchia P, et al. Patients aged 90years or older with atrial fibrillation treated with oral anticoagulants: A multicentre observational study. Int J Cardiol 2019:281:56-61. Doi:S0167-5273(18)37162-6 [pii].

91. Lauw MN, Eikelboom JW, Coppens M, Wallentin L, Yusuf S, Ezekowitz M, et al. Effects of dabigatran according to age in atrial fibrillation. Heart 2017:103:1015-1023. Doi:10.1136/heartjnl-2016-310358.

92. Levy JH, Douketis J and Weitz JI. Reversal agents for non-vitamin K antagonist oral anticoagulants. Nature Reviews - Cardiology 2018:15:273-281. Doi:10.1038/nrcardio.2017.223.

93. Forbes HL and Polasek TM. Potential drug-drug interactions with direct oral anticoagulants in elderly hospitalized patients. Therapeutic Advances in Drug Safety 2017:8:319-328. Doi:10.1177/2042098617719815.

94. Tonelli M and Riella M. Chronic kidney disease and the aging population. American Journal of Physiology - Renal Physiology 2014:306:469-472. Doi:10.1152/ajprenal.00063.2014.

95. Keskar V, McArthur E, Wald R, Harel Z, Zimmerman D, Molnar AO, et al. The association of anticoagulation, ischemic stroke, and hemorrhage in elderly adults with chronic kidney disease and atrial fibrillation. Kidney Int 2017:91:928-936. Doi:10.1016/j.kint.2016.10.017.

96. van Bemmel T, Delgado V, Bax JJ, Gussekloo J, Blauw GJ, Westendorp RG, et al. Impact of valvular heart disease on activities of daily living of nonagenarians: the leiden 85-plus study a population based study. BMC Geriatrics 2010:10:17. Doi:10.1186/1471-2318-10-17.

97. Charidimou A, Shakeshaft C and Werring DJ. Cerebral microbleeds on magnetic resonance imaging and anticoagulant-associated intracerebral hemorrhage risk. Front Neurol 2012:3:133. Doi:10.3389/fneur.2012.00133 [doi].

98. Wilson D, Ambler G, Shakeshaft C, Brown MM, Charidimou A, Al-Shahi Salman R, et al. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. Lancet Neurol 2018:17:539-547. Doi:S1474-4422(18)30145-5 [pii].

99. Charidimou A, Karayiannis C, Song TJ, Orken DN, Thijs V, Lemmens R, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: Meta-analysis in stroke patients with AF. Neurology 2017:89:2317-2326. Doi:10.1212/WNL.0000000000004704 [doi].

100. Aonuma K, Yamasaki H, Nakamura M, Ootomo T, Takayama M, Ando K, et al. Percutaneous WATCHMAN Left Atrial Appendage Closure for Japanese Patients With Nonvalvular Atrial Fibrillation at Increased Risk of Thromboembolism — First Results From the SALUTE Trial. Circulation Journal 2018:82:2946-2953. Doi:10.1253/circj.CJ-18-0222.

101. Holmes J, David R, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: The PREVAIL trial. Journal of the American College of Cardiology 2014:64:1. Doi:10.1016/j.jacc.2014.04.029.

102. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 2009:374:534-542. Doi:10.1016/S0140-6736(09)61343-X.

103. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, et al. 5-Year Outcomes After Left Atrial Appendage Closure. Journal of the American College of Cardiology 2017:70:2964-2975. Doi:10.1016/j.jacc.2017.10.021.

104. Ronco F, Mazzone P, Hosseinian L and Genovesi S. Recent Advances in Stroke Prevention in Patients with Atrial Fibrillation and End-Stage Renal Disease. Cardiorenal Medicine 2017:7:207-217. Doi:10.1159/000470856.

105. Davtyan KV, Kalemberg AA, Topchyan AH, Simonyan GY, Bazaeva EV and Shatahtsyan VS. Left atrial appendage occluder implantation for stroke prevention in elderly patients with atrial fibrillation: acute and long-term results. J Geriatr Cardiol 2017:14:590-592. Doi:10.11909/j.issn.1671-5411.2017.09.006.

106. Piccini JP, Sievert H and Patel MR. Left atrial appendage occlusion: rationale, evidence, devices, and patient selection. European Heart Journal 2017:38:869. Doi:10.1093/eurheartj/ehw330.

107. Ford GA. Thrombolysis for stroke in the over 80s. Age and Ageing 2004:33:95-97. Doi:10.1093/ageing/afh060.

··108. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. The Lancet 2012:379:2352-2363. Doi:10.1016/S0140-6736(12)60768-5.

IST-3 trial; First trial to show no difference in thrombolysis outcomes between >80s and <80s (subgroup analysis)

109. Wardlaw JM, Sandercock P, Cohen G, Farrall A, Lindley RI, Von Kummer R, et al. Association between brain imaging signs, early and late outcomes, and response to

intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a randomised controlled trial. The Lancet Neurology 2015:14:485-496. Doi:10.1016/S1474-4422(15)00012-5.

··110. Berge E, Cohen G, Roaldsen MB, Lundstrom E, Isaksson E, Rudberg AS, et al. Effects of alteplase on survival after ischaemic stroke (IST-3): 3 year follow-up of a randomised, controlled, open-label trial. Lancet Neurol 2016:15:1028-1034. Doi:10.1016/S1474-4422(16)30139-9 [doi].

IST-3 post-hoc analysis showing thrombolysis-related decreases in 3 year mortality in octogenarians

··111. Wardlaw JM, Murray V, Berge E and del Zoppo GJ. Thrombolysis for acute ischaemic stroke. The Cochrane Database of Systematic Reviews 2014:CD000213. Doi:10.1002/14651858.CD000213.pub3.

Cochrane review showing good disability and mortality outcomes with thrombolysis in >80s (subgroup analysis)

··112. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. The Lancet 2014:384:1929-1935. Doi:10.1016/S0140-6736(14)60584-5.

Meta-analysis showing no benefit with thrombolysis in octogenarians with a treatment delay longer than 3h

113. Engelter ST, Bonati LH and Lyrer PA. Intravenous thrombolysis in stroke patients of >80 versus <80 years of age - a systematic review across cohort studies. Age and Ageing 2006:35:572-580. Doi:10.1093/ageing/afl104.

114. Bhatnagar P, Sinha D, Parker RA, Guyler P and O'Brien A. Intravenous thrombolysis in acute ischaemic stroke: a systematic review and meta-analysis to aid decision making in patients over 80 years of age. Journal of Neurology, Neurosurgery, and Psychiatry 2011:82:712-717. Doi:10.1136/jnnp.2010.223149.

115. Pego PM, Nunes AP, Ferreira P, Sousa C and Amaral-Silva A. Thrombolysis in Patients Aged over 80 Years Is Equally Effective and Safe. J Stroke Cerebrovasc Dis 2016:25:1532-1538. Doi:10.1016/j.jstrokecerebrovasdis.2016.03.007.

116. Matsuo R, Kamouchi M, Fukuda H, Hata J, Wakisaka Y, Kuroda J, et al. Intravenous Thrombolysis with Recombinant Tissue Plasminogen Activator for Ischemic Stroke Patients over 80 Years Old: The Fukuoka Stroke Registry. PLoS One 2014:9:e110444. Doi:10.1371/journal.pone.0110444.

117. Takayanagi S, Ochi T, Hanakita S, Suzuki Y and Maeda K. The Safety and Effectiveness of Low-Dose Recombinant Tissue Plasminogen Activator (0.6 mg/kg) Therapy for Elderly Acute Ischemic Stroke Patients (≥ 80 Years Old) in the Pre-endovascular Era. Neurologia Medico-Chirurgica 2014:54:435-440. Doi:10.2176/nmc.oa.2013-0264.

118. Manawadu D, Bodla S, Keep J and Kalra L. Influence of age on thrombolysis outcome in wake-up stroke. Stroke 2013:44:2898-2900. Doi:10.1161/STROKEAHA.113.002273.

119. Pornpatr DA, Sombat M, Junya P and Permphan D. Stroke Outcomes in Thai Elderly Patients Treated with and without Intravenous Thrombolysis. Neurology International 2013:5:e15. Doi:10.4081/ni.2013.e15.

120. Busl KM, Nogueira RG, Yoo AJ, Hirsch JA, Schwamm LH and Rost NS. Prestroke dementia is associated with poor outcomes after reperfusion therapy among elderly stroke patients. J Stroke Cerebrovasc Dis 2013:22:718-724. Doi:10.1016/j.jstrokecerebrovasdis.2011.11.005.

121. Mishra NK, Ahmed N, Andersen G, Egido JA, Lindsberg PJ, Ringleb PA, et al. Thrombolysis in very elderly people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. BMJ 2010:341:1144. Doi:10.1136/bmj.c6046.

122. Bray BD, Campbell J, Hoffman A, Tyrrell PJ, Wolfe CDA and Rudd AG. Stroke thrombolysis in England: an age stratified analysis of practice and outcome. Age and Ageing 2013:42:240-245. Doi:10.1093/ageing/afs167.

123. Pundik S, McWilliams-Dunnigan L, Blackham KL, Kirchner HL, Sundararajan S, Sunshine JL, et al. Older age does not increase risk of hemorrhagic complications after intravenous and/or intra-arterial thrombolysis for acute stroke. J Stroke Cerebrovasc Dis 2008:17:266-272. Doi:10.1016/j.jstrokecerebrovasdis.2008.03.003.

124. Ringleb PA, Schwark C, Köhrmann M, Külkens S, Jüttler E, Hacke W, et al. Thrombolytic therapy for acute ischaemic stroke in octogenarians: selection by magnetic resonance imaging improves safety but does not improve outcome. Journal of Neurology, Neurosurgery, and Psychiatry 2007:78:690-693. Doi:10.1136/jnnp.2006.105890.

125. Berrouschot J, Rother J, Glahn J, Kucinski T, Fiehler J and Thomalla G. Outcome and Severe Hemorrhagic Complications of Intravenous Thrombolysis With Tissue Plasminogen Activator in Very Old (>=80 Years) Stroke Patients. Stroke 2005:36:2421-2425. Doi:10.1161/01.STR.0000185696.73938.e0.

126. Simon JE, Sandler DL, Warwick-Pexman JH, Hill MD and Buchan AM. Is intravenous recombinant tissue plasminogen activator (rt-PA) safe for use in patients over 80 years old with acute ischaemic stroke? - The Calgary experience. Age and Ageing 2004:33:143-149. Doi:10.1093/ageing/afh031.

127. Girotra T, Almallouhi E, Al Kasab S, Banerjee C, Turner NL, Debenham E, et al. Functional Outcomes of Intravenous Thrombolysis in Octogenarians and Nonagenarians Through Telestroke: Single-Center Experience. Telemed J E Health 2019. Doi:10.1089/tmj.2018.0305 [doi].

128. García-Caldentey J, Alonso de Leciñana M, Simal P, Fuentes B, Reig G, Díaz-Otero F, et al. Intravenous Thrombolytic Treatment in the Oldest Old. Stroke Research and Treatment 2012:2012:923676-7. Doi:10.1155/2012/923676.

·129. Sarikaya H, Arnold M, Engelter ST, Lyrer PA, Michel P, Odier C, et al. Intravenous thrombolysis in nonagenarians with ischemic stroke. Stroke 2011:42:1967-1970. Doi:10.1161/STROKEAHA.110.601252.

·130. Behrouz R, Masjuán-Vallejo J, Vera R, Willey JZ, Zedet M, Moulin S, et al. Outcomes of Nonagenarians with Acute Ischemic Stroke Treated with Intravenous Thrombolytics. Journal of Stroke and Cerebrovascular Diseases 2018:27:246-256. Doi:10.1016/j.jstrokecerebrovasdis.2017.08.031.

Observational study assessing thrombolysis outcomes in nonagenarians

·131. Sagnier S, Galli P, Poli M, Debruxelles S, Renou P, Olindo S, et al. The impact of intravenous thrombolysis on outcome of patients with acute ischemic stroke after 90 years old. BMC geriatrics 2016:16:156. Doi:10.1186/s12877-016-0331-1.

Observational study assessing thrombolysis outcomes in nonagenarians

·132. Mateen FJ, Nasser M, Spencer BR, Freeman WD, Shuaib A, Demaerschalk BM, et al. Outcomes of Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke in Patients Aged 90 Years or Older. Mayo Clinic Proceedings 2009:84:334-338. Doi:10.1016/S0025-6196(11)60542-9.

Observational study assessing thrombolysis outcomes in nonagenarians

·133. Montero-Ruiz-de-Gamboa V, Suazo-Vacarezza C, Ramírez-Méndez I, Bastías-Barra P, Hoppe-Wiegering A and Barrueto A. Intravenous thrombolysis in acute ischemic stroke of nonagenarian patients: a single center experience in Chile. J Neurol Sci 2015:357:e397. Doi:10.1016/j.jns.2015.08.1406.

Observational study assessing thrombolysis outcomes in nonagenarians

134. Falk-Delgado A, Kuntze-Söderqvist Å, Fransén J and Falk-Delgado A. Improved clinical outcome 3 months after endovascular treatment, including thrombectomy, in patients with acute ischemic stroke: a meta-analysis. Journal of Neurointerventional Surgery 2016:8:665-670. Doi:10.1136/neurintsurg-2015-011835.

135. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol 2016:15:1138-1147. Doi:10.1016/S1474-4422(16)30177-6.

136. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. The New England Journal of Medicine 2018:378:11-21. Doi:10.1056/NEJMoa1706442.

137. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. The New England Journal of Medicine 2015:372:2296-2306. Doi:10.1056/NEJMoa1503780.

138. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. The New England Journal of Medicine 2015:372:1019-1030. Doi:10.1056/NEJMoa1414905.

139. Campbell BCV, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. The New England Journal of Medicine 2015:372:1009-1018. Doi:10.1056/NEJMoa1414792.

140. Berkhemer OA, Fransen PSS, Beumer D, van den Berg, Lucie A, van den Berg R, van den Berg, Jan S.P, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. The New England Journal of Medicine 2015:372:11-20. Doi:10.1056/NEJMoa1411587.

··141. Goyal M, Menon BK, van Zwam W,H., Dippel DWJ, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. The Lancet 2016:387:1723-1731. Doi:10.1016/S0140-6736(16)00163-X.

Meta-analysis showing the same benefit derived from thrombectomy in patients >80s as in other age groups (subgroup analysis)

·142. Jeon JP, Kim S and Kim CH. Endovascular treatment of acute ischemic stroke in octogenarians: A meta-analysis of observational studies. Clinical Neurology and Neurosurgery 2017:161:70-77. Doi:10.1016/j.clineuro.2017.08.015.

Meta-analysis of observational studies showing similar recanalization rates with thrombectomy between >80s and younger patients.

143. Khan MA, Baird GL, Miller D, Patel A, Tsekhan S, Yaghi S, et al. Endovascular treatment of acute ischemic stroke in nonagenarians compared with younger patients in a multicenter cohort. Journal of NeuroInterventional Surgery 2017:9:727-731. Doi:10.1136/neurintsurg-2016-012427.

144. Möhlenbruch M, Pfaff J, Schönenberger S, Nagel S, Bösel J, Herweh C, et al. Endovascular Stroke Treatment of Nonagenarians. AJNR. American journal of neuroradiology 2017:38:299-303. Doi:10.3174/ajnr.A4976.

145. Chiquete E, Ruiz-Sandoval MC, Álvarez-Palazuelos LE, Padilla-Martínez JJ, González-Cornejo S and Ruiz-Sandoval JL. Hypertensive Intracerebral Hemorrhage in the Very Elderly. Cerebrovascular Diseases 2007:24:196-201. Doi:10.1159/000104477.

146. Inoue Y, Miyashita F, Minematsu K and Toyoda K. Clinical Characteristics and Outcomes of Intracerebral Hemorrhage in Very Elderly. Journal of Stroke and Cerebrovascular Diseases 2018:27:97-102. Doi:10.1016/j.jstrokecerebrovasdis.2017.08.006.

147. Guo R, Chen R, Yu Z, Tian R, Ren Y, You C, et al. Clinical Features and Prognosis of Primary Intraventricular Hemorrhage in Elderly: Single-Center Experience. World Neurosurgery 2019. Doi:10.1016/j.wneu.2018.12.114.

148. Charidimou A, Imaizumi T, Moulin S, Biffi A, Samarasekera N, Yakushiji Y, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis. Neurology 2017:89:820-829. Doi:10.1212/WNL.0000000000004259.

149. Xu X, Vestesson E, Paley L, Desikan A, Wonderling D, Hoffman A, et al. The economic burden of stroke care in England, Wales and Northern Ireland: Using a national

stroke register to estimate and report patient-level health economic outcomes in stroke. European Stroke Journal 2018:3:82-91. Doi:10.1177/2396987317746516.