Chapter 9
Stroke in the Elderly Population

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Abstract Stroke incidence and mortality increase with advancing age. Age is a nonmodifiable risk factor for stroke. Moreover, cardiovascular risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation, are more prevalent in older people than in younger ones. Poststroke neurological deficits often impair activities of daily living in stroke patients; thus, stroke is a main cause of disability worldwide. Effective and efficient measures against stroke are urgently required, especially in aging societies, to prolong the healthy life expectancy of the population. Recent epidemiological studies and clinical trials have accumulated evidence regarding the effects of preventive treatment against stroke in the elderly population, as well as the risks and benefits of stroke treatment in older patients. However, there remain a number of issues regarding how to reduce the stroke incidence among elderly populations and improve clinical outcomes after stroke without increasing adverse events in elderly patients. In this chapter, we will discuss the current understanding of risk factor management to prevent stroke and the optimal treatment for stroke in the elderly population.

Keywords Risk factor · Stroke prevention · Stroke care · Older adults

Stroke is one of the leading causes of death and disability globally. The incidence of stroke increases with advancing age; therefore, stroke is a major health problem, especially in an aging society. Poststroke disability often impairs not only activities of daily living but also quality of life in patients. The reduction of stroke incidence and mortality and the alleviation of poststroke symptoms are critical issues to reduce the burden of stroke and prolong healthy life expectancy worldwide.

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9.1 Epidemiology

9.1.1 Stroke Incidence

Age is a nonmodifiable but significant risk factor for stroke (Fig. 9.1). The incidence of ischemic and hemorrhagic stroke increases with age in men and women, irrespective of ethnic origin. However, the trends in age-specific incidence of stroke differ according to stroke subtypes and region or country. In the Hisayama study, which began in 1961 and established five cohorts consisting of residents in a Japanese community aged ≥40 years, stroke incidence consistently decreased, even in the elderly group [1]. However, the incidence rate of brain hemorrhage continuously increased over time in participants aged ≥80 years, although that of ischemic stroke decreased [2]. The Global Burden of Disease Study 2010 estimated regional and country-specific incidence of stroke in 1990, 2005, and 2010 [3]. In the past two decades, the incidence of ischemic stroke among people aged ≥75 years decreased in high-income countries but not in low-income counties. Incidence of hemorrhagic stroke decreased in both high- and low-income countries, whereas the incidence rates among people aged 20–64 years significantly increased in low- and middle-income countries [3].

Older patients with stroke are at high risk for recurrent stroke. We previously developed risk scores for stroke recurrence in Japanese patients with ischemic stroke, and age was identified as a factor in the score [4]. Similarly, the risk of stroke

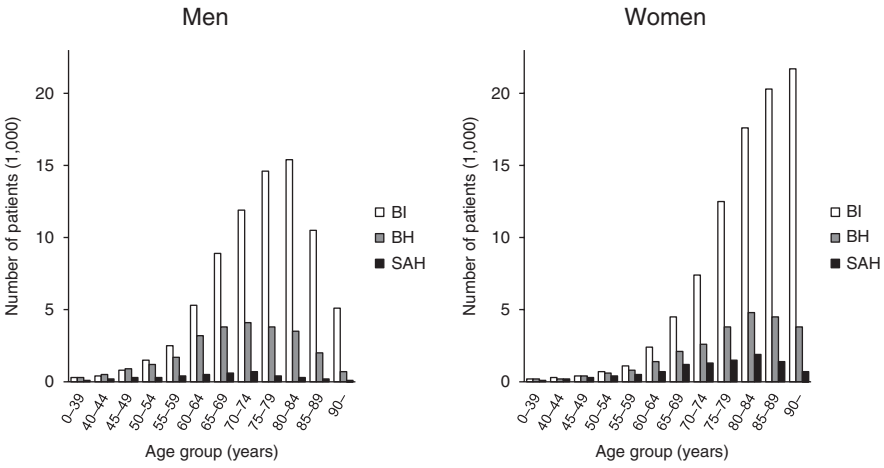

Fig. 9.1 Estimated number of patients with stroke in Japan, according to age. Estimated number of patients (inpatients and outpatients) with brain infarction (BI, white bars), brain hemorrhage (BH, shaded bars), and subarachnoid hemorrhage (SAH, black bars), shown according to each age group for men and women (Patient Survey 2014, Ministry of Health, Labour and Welfare)

after transient ischemic attack (TIA) increases with advancing age. In patients with TIA, age is a significant factor comprising risk scores to predict future stroke, such as ABCD score [5], ABCD2 score [6], and other related scores [7].

9.1.2 Stroke Mortality

Stroke mortality is declining in all countries [3, 8]. Nevertheless, stroke mortality remains high in people aged ≥75 years (Fig. 9.2). In high-income countries, age-standardized mortality rates have significantly decreased by a similar proportion in both younger and older people. However, in low- and middle-income countries, the reduction was less striking in people >75 years compared with younger people [8].

Case fatalities among stroke patients increase with advancing age. Among the Get With the Guidelines-Stroke population in the United States, the in-hospital case fatality was more than threefold higher in participants ≥80 years of age (10.3%) compared with those aged <50 years (3.0%) [9]. The adjusted odds ratio for in-hospital mortality has been reported as 1.27 (95% confidence interval [CI] 1.25–1.29) per 10-year increase [10]. Between 1990 and 2010, mortality-to-incidence rates were reduced in people <75 years compared with older people across all countries [8].

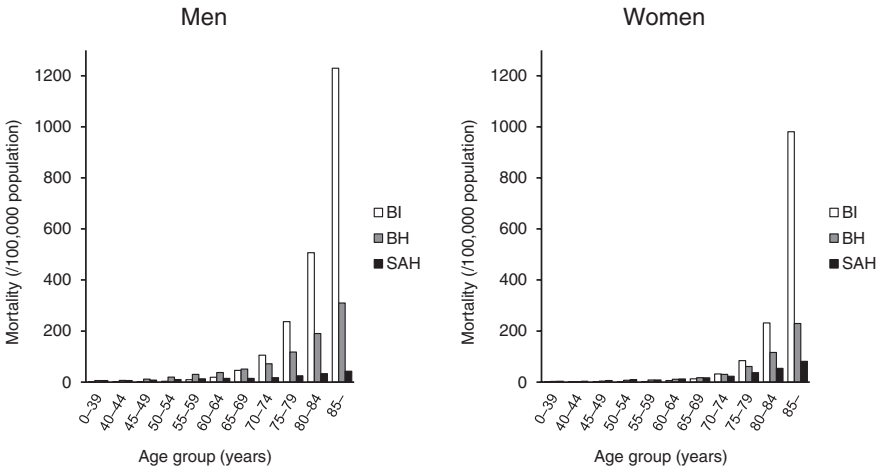

Fig. 9.2 Mortality of stroke in Japan according to age. Deaths (per 100,000 population) caused by brain infarction (BI, white bars), brain hemorrhage (BH, shaded bars), and subarachnoid hemorrhage (SAH, black bars), shown according to each age group for men and women (Vital Statistics 2010, Ministry of Health, Labour and Welfare)

9.2 Stroke Risk Factors and Prevention in the Elderly Population

9.2.1 Hypertension

High blood pressure is the most influential risk factor for the development of stroke. Prospective cohort studies have shown that the association between high blood pressure and stroke risk is present in all ages, even in people aged ≥80 years [11]. However, the cutoff value of systolic hypertension in relation to mortality may differ by age [12]. The increase in stroke risk per blood pressure change is less remarkable in old age than in middle age [11].

9.2.1.1 Antihypertensive Treatment

The question arises as to whether antihypertensive treatment can reduce stroke risk or mortality, even in elderly patients. In a meta-analysis of nine randomized controlled trials of antihypertensive treatment among patients aged ≥60 years, antihypertensive treatment reduced stroke morbidity and mortality by 35% and 36%, respectively [13]. In a meta-analysis of eight trials among patients aged ≥60 years who had isolated systolic hypertension ≥160 mmHg and diastolic blood pressure <95 mmHg, active treatment reduced total mortality by 13% and stroke by 30%; the absolute benefit was larger in patients aged ≥70 years [14]. To elucidate the benefits and risks of antihypertensive treatment in very old patients, the Hypertension in the Very Elderly Trial (HYVET) was performed among patients aged ≥80 years with sustained systolic blood pressure ≥160 mmHg. Consequently, active treatment with indapamide (and perindopril if necessary), targeting blood pressure of 150/80 mmHg, reduced the rate of fatal or nonfatal stroke and death from stroke by 30% and 39%, respectively [15]. Therefore, antihypertensive treatment seems to be beneficial, even in older patients.

9.2.1.2 Target Blood Pressure Levels

The optimal blood pressure level to reduce cardiovascular events without increasing adverse events remains uncertain in elderly patients. The presence of a J-shaped curve relationship between blood pressure and cardiovascular events remains a subject of debate [16]. Post hoc analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) among patients with cerebrovascular disease reported that intensive blood pressure lowering, even below 120 mmHg, produced a greater reduction of stroke risk [17]. In contrast, a post hoc observational analysis of the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial for patients with recent noncardioembolic ischemic stroke

revealed a J-shaped relationship between systolic blood pressure levels and recurrent stroke [18].

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [19] and the Systolic Blood Pressure Intervention Trial (SPRINT) [20], the rates of cardiovascular events were lower, but those of serious adverse events were higher under intensive therapy (systolic blood pressure <120 mmHg) than under standard therapy (<140 mmHg) for participants with high cardiovascular risk. Currently, the optimal level of blood pressure should be determined after individualized assessment in aged patients [21].

9.2.2 Diabetes Mellitus

Diabetes mellitus is another well-known risk factor for stroke, the prevalence of which increases with advancing age. In patients with diabetes, adjusted hazard ratios increased to 2.27 (95% CI 1.95–2.65) for ischemic stroke and 1.56 (95% CI 1.19–2.05) for hemorrhagic stroke in a meta-analysis by the Emerging Risk Factors Collaboration [22]. In the Hisayama study, the risk of ischemic stroke increased with both fasting (7.0 mmol/L) and 2-h postload (11.1 mmol/L) glucose levels [23]. As the prevalence of diabetes is increasing in all countries [24], preventive measures against diabetes are needed to reduce the global stroke burden.

9.2.2.1 Glycemic Control

Recent trials failed to provide evidence that intensive glycemic control reduces stroke risk in diabetic patients. In the UK Prospective Diabetes Study (UKPDS) 33, intensive glucose control did not decrease the risk of cardiovascular diseases in patients with type 2 diabetes [25]. Thereafter, randomized clinical trials, such as the Action in Diabetes and Vascular Disease, Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [26], Action to Control Cardiovascular Risk in Diabetes (ACCORD) [27], and Veterans Affairs Diabetes Trial (VADT) [28], have been performed to determine whether further intensive glucose control can reduce cardiovascular events. However, intensive control could not significantly reduce major cardiovascular events, including stroke. In meta-analyses of 5 randomized controlled trials [29] and 13 additional trials [30], intensive treatment was not associated with a reduction in the risk of nonfatal stroke or all strokes.

Appropriate glycemic control is essential to avoid microvascular diabetic complications or acute diabetic complications, such as dehydration, poor wound healing, and hyperglycemic hyperosmolar coma. However, intensive glycemic control may not necessarily result in a reduction of stroke risk in diabetic patients. Because elderly patients are at higher risk of hypoglycemia, glycemic goals might be relaxed for these patients [31, 32].

9.2.2.2 Multifactorial Intervention

To prevent stroke during remaining life expectancy, control of concomitant cardiovascular risk factors by use of antihypertensive, lipid-lowering, and antithrombotic treatments is important for older patients with diabetes. In older adults, these risk factors are treated in consideration of the life expectancy of each individual patient. In older adults with diabetes, targets and therapeutic approaches should be chosen after assessment of coexisting chronic illnesses as well as cognitive and functional status [31, 32].

9.2.3 Atrial Fibrillation

Atrial fibrillation could generate thrombus in the left atrium or appendage, which occasionally causes cardioembolic stroke. The incidence of atrial fibrillation increases with advancing age [33]; for instance, the age-specific prevalence in people aged 60–69, 70–79, and ≥80 years in Japan has been reported as 1.9, 3.4, and 4.4 in men and 0.4, 1.1, and 2.2 in women, respectively [34]. Additionally, stroke events significantly increase in older patients with atrial fibrillation. The Framingham study revealed that the attributable risk of stroke for atrial fibrillation was 1.5%, 2.8%, 9.9%, and 23.5% in people aged 50–59, 60–69, 70–79, and 80–89 years, respectively [35].

Risk stratification for stroke or systemic embolisms in patients with nonvalvular atrial fibrillation has been attempted, and risk scores have been developed. Among these, the $CHADS_2$ score (0–6 points) assigns 1 point for ages ≥75 years [36], and the CHA_2DS_2-VASc score (0–9 points) assigns 1 point for ages 64–74 years and 2 points for ages ≥75 years [37]. As underdiagnosis of atrial fibrillation appears to be a predominant cause of cardioembolic stroke [38], awareness, pulse palpitation, or electrocardiogram may be more necessary for the detection of atrial fibrillation in older populations.

9.2.3.1 Anticoagulation Therapy

Anticoagulation therapy is highly effective to reduce the risk of stroke in patients with atrial fibrillation. In people with atrial fibrillation aged >75 years, the event rate per 100 person-years is 3.22 in patients not taking warfarin but 1.43 in those taking warfarin [39]. Meta-analysis of 29 trials showed that adjusted-dose warfarin reduced stroke by 64% compared with controls [40]. As a result, according to the Framingham Heart study [41], the risk of stroke in the 20 years after onset of atrial fibrillation was reduced by 74% between 1958–1967 and 1998–2007.

Direct oral anticoagulants (DOACs; dabigatran [42], rivaroxaban [43], apixaban [44], edoxaban [45]) have been developed as alternatives for vitamin K antagonists in the prevention of stroke or systemic embolism in patients with atrial fibrillation. Subanalyses of trials investigating the risks of ischemic stroke and intracranial

bleeding during treatment with DOACs in older patients have been conducted. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, intracranial bleeding risk was lower, but extracranial bleeding risk was similar or higher in patients aged ≥75 years treated with dabigatran compared with those taking warfarin [46]. In the trial entitled Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), the risk of major bleeding increased with age, but there were no apparent differences in the risk of major bleeding between rivaroxaban and warfarin in each age category (<65, 65–74, ≥75 years) [47]. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, the rates of stroke or systemic embolism and major bleeding were lower in the apixaban group than in the warfarin group, regardless of age [44, 48]. The net clinical benefit for older patients should be compared between DOACs and vitamin K antagonists in the real-world setting.

9.2.3.2 Hemorrhagic Risk During Anticoagulation Therapy

Old age is an important risk factor for major bleeding during anticoagulation therapy. Age (years of age, ABC score [49]; age >65 years, HAS-BLED score [50]; age ≥75 years, HEMORR$_2$HAGES score [51], ATRIA score [52], and ORBIT score [53]) is included as an item in the risk scores for bleeding during anticoagulation.

The incidence of hemorrhagic stroke has been reported as high in Asian people [3]. The reported incidence of intracerebral hemorrhage per 100,000 person-years is 24.2 (95% CI 20.9–28.0) in white people, 22.9 (95% CI 14.8–35.6) in blacks, 19.6 (95% CI 15.7–24.5) in Hispanic populations, and 51.8 (95% CI 38.8–69.3) in Asians [54]. Similarly, the hazard ratio of intracranial hemorrhage during warfarin therapy for atrial fibrillation increased to 4.06 (95% CI 2.47–6.65) in Asians compared with whites as referent [55]. Previous studies in Japanese patients with atrial fibrillation revealed that the optimal prothrombin time (PT)-international normalized ratio (INR) to reduce the risk of major ischemic or hemorrhagic events may be lower in older patients than in younger ones [56, 57]. Based on these findings, Japanese guidelines for pharmacotherapy for atrial fibrillation recommend warfarin therapy with a target PT-INR range of 1.6–2.6 for patients aged ≥70 years and a target of 2.0–3.0 for patients aged <70 years [58]. In older patients, careful monitoring of the intensity of anticoagulation is crucial to extend the time maintained in the therapeutic range to as long as possible.

9.2.4 Hypercholesterolemia

Hypercholesterolemia is known as a risk factor for major coronary events; however, the association between cholesterol levels and stroke is inconsistent or weak. The association may be evident if we investigate the relationship of LDL cholesterol

levels with ischemic stroke caused by thrombotic mechanisms. In the Hisayama study, the age- and sex-adjusted incidences were significantly elevated for atherothrombotic and lacunar infarctions with increasing LDL cholesterol level [59].

9.2.4.1 Lipid-Lowering Treatment

Lipid-lowering treatment with statins is considered effective in reducing both initial and recurrent stroke. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial revealed that 80 mg of atorvastatin reduced the overall incidence of stroke in patients with a recent stroke or TIA [60]. Meta-analysis of randomized trials of statins showed that each 1-mmol/L decrease in LDL cholesterol equates to a reduction in relative risk for stroke of 21.1% (95% CI 6.3–33.5). In secondary prevention of noncardioembolic stroke, intense reduction of LDL cholesterol by statins also reduced the risk of recurrent stroke (relative risk [RR] 0.84, 95% CI 0.71–0.99) [61].

A meta-analysis of individual data from 61 prospective studies suggested that total cholesterol was negatively related to hemorrhagic and total stroke mortality, particularly in patients with older ages (70–89 years) and systolic blood pressure >145 mmHg [62]. However, other meta-analyses of randomized trials did not show a significant increase in the risk of hemorrhagic stroke by intense lipid lowering [61, 63]. Recently, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) demonstrated that the risk of cardiovascular events was further lowered by the addition of ezetimibe to simvastatin therapy, with a nonsignificantly high risk of hemorrhagic stroke in stable patients with an acute coronary syndrome [64]. In elderly patients without established cardiovascular disease, statins reduced the incidence of myocardial infarction and stroke, but did not significantly prolong their survival in the short term.[65] Further studies are still needed to clarify the benefit of lipid-lowering therapy in older people, especially those without diabetes or cardiovascular risk factors.

9.3 Stroke Treatment for Elderly Patients

9.3.1 Stroke Care Unit

Poststroke functional outcome becomes worse with increasing age. We previously showed that women had higher risk of poor outcome after stroke than men, among patients aged ≥70 years [66]. To improve poststroke functional outcome in elderly patients, stroke care units may be beneficial. Randomized trials have been conducted on the efficacy of stroke units, and meta-analysis revealed that organized stroke unit care results in reductions in death, dependency, and the need for institutional care [67, 68]. In older patients aged ≥70 years with acute stroke and concomitant cardiac disease, the risk of death or institutional care was reduced after 3 months

among patients in the stroke unit compared with those receiving conventional care [69]. A quasi-randomized, controlled study among patients ≥60 years old with stroke within 24 h of onset revealed that treatment in the stroke unit increased survival at 12 and 18 months after stroke onset and patients with intracerebral hemorrhage benefitted the most [70]. Benefits of the stroke unit likely exist for elderly patients, but the effects on clinically reliable outcomes are modest and insignificant [71].

9.3.2 Intravenous Thrombolytic Therapy

Intravenous recombinant tissue plasminogen activator (rt-PA) is highly effective in improving functional outcome after acute ischemic stroke. However, there are a number of clinical, radiological, and laboratory-related exclusion criteria for rt-PA because of the potential risk of hemorrhagic events [72]. In a post hoc subgroup analysis of the National Institute of Neurological Disorders and Stroke (NINDS) t-PA stroke trial for stroke patients within 3 h of symptom onset, there was no favorable response to treatment in patients aged >75 years [73]. Therefore, advanced age is recognized as a factor related to increased hemorrhagic risk with little benefit of rt-PA.

However, recent analysis of the Safe Implementation of Treatments in Stroke, a prospective internet-based audit of the International Stroke Thrombolysis Registry (SITS-ISTR) and the Virtual International Stroke Trials Archive (VISTA), demonstrated that the association between thrombolysis treatment and improved outcome was maintained in very elderly people [74]. Furthermore, the third International Stroke Trial (IST-3) indicated greater benefit in patients >80 years of age, contrary to expectations [75]. Systematic review and meta-analysis showed that the effect of rt-PA treatment was similar between patients aged ≤80 years and those >80 years [76, 77]. We also investigated the efficacy and safety of intravenous rt-PA in elderly Japanese patients by propensity score (PS)-matched case-control analysis. Consequently, intravenous rt-PA therapy was associated with improved clinical outcomes without a significant increase in risk of hemorrhagic complications in elderly patients aged >80 years with acute ischemic stroke [78]. Thus, age alone may not be a contraindication to the treatment. Nevertheless, use of intravenous rt-PA should be cautiously considered after estimating the balance between benefits and risks of therapy for elderly patients.

9.3.3 Carotid Endarterectomy and Stenting

Carotid endarterectomy (CEA) and endovascular carotid artery stenting (CAS) reduce the risk of ischemic stroke in patients with carotid stenosis. However, the benefit and safety of these procedures may differ depending on the patient's age. In

the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the risk of ipsilateral ischemic stroke at 2 years was decreased by CEA in three age categories (<65, 65–74, and ≥75 years) for patients with 70–99% stenosis [79]. Further analysis of pooled data from the European Carotid Surgery Trial (ECST) and NASCET showed that the benefit from surgery was greatest in patients aged ≥75 years [80]. Moreover, in patients with 50–69% stenosis, the absolute risk reduction was significant only in those aged ≥75 years [79].

Many studies have been done to compare the benefit and safety of CEA and CAS in elderly patients. In post hoc analyses of data in the Stent-Protected Angioplasty versus Carotid Endarterectomy in Symptomatic Patients (SPACE) trial, the risk of ipsilateral stroke or death significantly increased with age in the CAS group but not in the CEA group [81]. The pooled data from the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), SPACE, and the International Carotid Stenting Study (ICSS) favored CEA more strongly with increasing age, although risk ratios of any stroke or death within 120 days of randomization increased linearly with age [82]. CAS tended to show greater efficacy at younger ages, and CEA at older ages, with a crossover at age approximately 70 years [83]. In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), risk for the primary end point, including stroke, increased with age by 1.77 (95% CI 1.38–2.28) per 10-year increment for CAS, whereas there was no evidence of increased risk for CEA-treated patients [84]. In the meta-analysis of individual patient-level data from the Carotid Stenosis Trialists' Collaboration (CSTC), the periprocedural risk for stroke and death in patients receiving CAS was roughly 4.0 for age ≥70 years compared with age <60 years, although there was no evidence of an increased periprocedural risk by age group in the CEA group [85].

Recently, embolic protection devices have been developed, which reduce the stroke risk during the procedure. Moreover, the best medical treatment in recent years is more effective than before to decrease stroke risk, possibly via stabilization and regression of plaque with carotid stenosis. Carotid stenosis should be treated based on up-to-date evidence in elderly patients.

9.4 Conclusions

A number of studies have revealed the benefits and risks of stroke prevention and stroke care in the elderly population. To effectively prevent stroke and improve poststroke outcomes in older patients, appropriate health care should be provided that is based on the latest evidence, in consideration of each person's age, disability, frailty, comorbidity, and cardiovascular risk.

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