Published in final edited form as:

*Ann N Y Acad Sci*. 2015 March ; 1338: 1–15. doi:10.1111/nyas.12723.

# Advances in stroke prevention

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## Abstract

Stroke remains to be a leading cause of disability. However, optimal strategies can prevent up to 80% of strokes. A large body of evidence supports many strategies for primary and secondary prevention of stroke. The purpose of this paper is to highlight recent major advances for management of modifiable medical and behavioral risk factors of stroke. Specific studies are highlighted, including those related to atrial fibrillation (AF), hypertension, revascularization, hyperlipidemia, antiplatelets, smoking, diet, and physical activity. Effective strategies include the use of novel oral anticoagulants for AF, antiplatelet therapy, and intensive lowering of atherosclerosis risk factors.

### Keywords

stroke; risk factors; prevention; epidemiology

## Introduction

Stroke is the fourth leading cause of death in the United States and one of the leading causes of serious disability.[1] According to the Global Burden of Disease, Injuries, and Risk Factors Study (GDB 2010), stroke was ranked as the most common cause of death after ischemic heart disease, with a 26% increase in stroke mortality since 1990.[2] Even though the most recent report showed a decrease in stroke-related mortality, the global burden of stroke based on disability-adjusted life years lost and the absolute number of people affected every year is still on the rise, with the highest burden seen in low-income and middle-income countries.[3] It has been suggested that up to 80% of recurrent stroke may be prevented by addressing the modifiable risk factors.[4,5] Applying a mass stroke prevention approach can serve as complementary strategy to reduce the increasing global burden of stroke and subsequent disability.[6] This paper reviews major advances in stroke prevention in the last few years, pertaining to the modifiable medical and behavioral stroke risk factors.

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Conflicts of interest

The authors declare no conflicts of interest.

## Atrial fibrillation

While atrial fibrillation (AF) has long been recognized as a major cause of stroke, and the role of anticoagulants to prevent stroke in patients with AF is well established, there have been several recent developments in our understanding of the importance of AF in stroke risk and in our treatment of it. These advances include the development of new anticoagulants, evidence of the benefits of long-term monitoring, and appreciation of the potential role of atrial disease in cryptogenic stroke, even in the absence of AF.

AF is a common cause of disabling stroke, resulting from embolism of stasis-precipitated thrombi formed in the left atrium, left atrial appendage, or both.[7] The first randomized controlled trial (RCT) of anticoagulant therapy in AF, conducted in 1989, demonstrated that warfarin markedly decreased the incidence of stroke.[8] Warfarin and other vitamin K antagonists are effective treatments, both for primary and secondary stroke prevention, but their use is limited owing to a narrow therapeutic range, drug and food interactions, the need for consistent coagulation monitoring, and the risk of bleeding.[8] In the past decade, a major advance in stroke prevention owing to AF has been the use of new oral anticoagulants.[9–12] These can be broadly divided into the direct factor Xa inhibitors, such as rivaroxaban, edoxaban, and apixaban, and the direct thrombin inhibitors, particularly dabigatran. Collectively, these agents are commonly known as novel oral anticoagulants (NOAC). The NOAC were compared with warfarin for stroke prevention among patients with AF in four pivotal randomized trials.

RE-LY (Randomized Evaluation of Longterm Anticoagulant Therapy) was a randomized phase III clinical trial that compared fixed, blinded doses of dabigatran with open-label–adjusted dose warfarin.[13] A total of 18,113 patients with nonvalvular AF within the last 6 months before randomization and at least one additional risk factor were randomized. For patients with AF, the main predictors of an increased risk of stroke are assessed using the $CHADS_2$ (congestive heart failure, hypertension, age, diabetes, prior stroke, or transient ischemic attack (TIA)) score, which is a clinical risk stratification scheme that predicts stroke and thromboembolism in patients with AF (Tables 1 and 2).[14–16] A total of 31.9% of the patients had a $CHADS_2$ score of 0 or 1, 35.6% had a score of 2, and 32.5% had a score of 3–6; stroke patients within 14 days of randomization were excluded. The study demonstrated that dabigatran at a dose of 150 mg twice daily (BID) was superior to warfarin treatment for the prevention of stroke and systemic embolism. The primary outcome of stroke or systemic embolism occurred at a higher rate among those in the warfarin group, followed by those in the 110 mg BID dabigatran group, and least in the 150 mg BID dabigatran group (Table 3). Similarly, major bleeding occurred at a higher rate in warfarin-treated patients. The rate of hemorrhagic stroke was reduced with both doses of dabigatran compared to warfarin treatment. A subgroup analysis of patients with TIA or prior strokes did not demonstrate superiority of dabigatran compared to warfarin in preventing strokes, but at the same time dabigatran was noninferior to warfarin at both doses.[17] A network meta-analysis and indirect comparison of dabigatran with aspirin or the combination of aspirin and clopidogrel suggested that dabigatran is also very effective compared to antiplatelet therapy, without a significant increase in intra- or extracranial hemorrhage.[18]

In ROCKET-AF (rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation), patients with AF were randomized in a double-blind, double-dummy manner to receive either the factor Xa inhibitor rivaroxaban, or dose-adjusted warfarin.[16] Inclusion criteria included two or more stroke risk factors and documented AF within 6 months of randomization. Most of the patients (87%) had a $CHADS_2$ score of ≥3. Stroke, the primary end point, occurred at a higher rate among patients treated with warfarin compared to those treated with rivaroxaban, which was found to be noninferior to warfarin. Major bleeding was seen more in the rivaroxaban group compared to those taking warfarin. The rate of intracranial hemorrhage was significantly lower with rivaroxaban treatment compared to warfarin treatment (Table 3).[19]

In the ARISTOTLE (apixaban for reduction in stroke and other thromboembolic events) in AF trial, apixaban was compared with adjusted-dose warfarin for the prevention of stroke or systemic embolism in patients with AF and at least one additional risk factor for stroke. The rate of the primary outcome (stroke or systemic embolism) was significantly reduced by apixaban compared with warfarin, as were the rates of major bleeding and death from any cause. The rate of hemorrhagic stroke in the apixaban group was about half the rate in the warfarin group (Table 3).[20] The absolute benefit of apixaban may be higher among patients with stroke or TIA, since stroke rates are higher among those with prior stroke or TIA.[21]

The AVERROES (apixaban versus acetylsalicylic acid to prevent strokes) trial compared apixaban and aspirin (acetylsalicylic acid) in AF patients who were considered unsuitable for treatment with warfarin. Patients were randomized to receive either apixaban or aspirin.[22] After an interim analysis that showed a 50% reduction in stroke and systemic embolism in patients in the apixaban treatment arm, the study was terminated before completion. Compared to aspirin, patients had better tolerance for apixaban and there was no significant difference in hemorrhagic stroke in both treatment groups.[22]

The use of NOAC is a major stride toward stroke prevention in patients with AF with a prior TIA or stroke who are at an increased risk of recurrent stroke. However, the safety and efficacy of these agents have not been determined for early strokes and TIAs (less than 2 weeks old), as those patients were excluded from the randomized trials. Several of the trials, however, do provide evidence that the novel anticoagulants have a lower risk of intracranial bleeding compared to warfarin.

Aspirin has not proven to be an effective agent in preventing recurrent stroke in patients with ischemic stroke or TIA with AF.[23] The combination of clopidogrel and aspirin is more effective in stroke prevention than aspirin alone in patients who are not candidates for anticoagulation (RR 0.72, 95% CI 0.62–0.83). However, this combination may cause an increase in major bleeding (RR 1.57, 95% CI 1.29–1.92), and the combination was not as effective as warfarin in preventing recurrent stroke in patients with AF (6.22% vs. 2.99% per year; RR 2.13, 95% CI 1.23–3.69).[24]

One of the challenges in care of patients with cryptogenic strokes and TIA is the detection of covert paroxysmal AF, which constitutes about 30% of all ischemic strokes.[25] Extended

cardiac rhythm monitoring of such patients has revealed evidence of AF in a significant proportion of patients, with longer periods of monitoring increasing the yield.[26] In a retrospective analysis of patients within 6 months of cryptogenic stroke, paroxysmal AF was detected among 17.3% of patients using mobile cardiac outpatient telemetry up to 30 days.[27] The length of monitoring was associated with detection of paroxysmal AF, such that the rate of detection increased from 3.9% in the first 48 h to 9.2% at 7 days, 15.1% at 14 days, and 19.5% at 21 days.[27] In the recently reported cryptogenic stroke and underlying atrial fibrillation (CRYSTAL-AF) study, an insertable cardiac monitor (ICM, REVEAL XT) had a higher rate of AF detection compared to standard care. In the ICM arm, AF was detected in 8.9%, 12.4%, and 30% of patients at 6, 12, and 36 months, respectively. More than 6 min of AF was detected in 92.3% of AF patients in the ICM arm. This change in detection increased the use of anticoagulation in 97% of the patients.[28] There is no convincing evidence that anticoagulation protects against recurrent stroke among patients without a definite source of cardiac embolism. In a secondary analysis of the Warfarin–Aspirin Recurrent Stroke Study (WARSS), in which patients were randomly allocated to warfarin or aspirin treatment, warfarin did not reduce the risk of stroke when compared to aspirin therapy among patients with a cryptogenic stroke and aortic arch atheroma identified by transesophageal echocardiography.[29] Large aortic arch atheroma and complex plaques were, however, associated with a higher risk of stroke over a period of 2 years.[29]

N-terminal pro-B-type natriuretic peptide (NTproBNP) is a serum biomarker associated with cardiac dysfunction that predicts the development of AF[30,31] A subgroup analysis of WARSS provided evidence that patients whose NTproBNP levels were above the 95th percentile and who were randomized to warfarin had a reduction in their risk of stroke or death compared to patients allocated to aspirin.[32] Further trials of the use of NTproBNP and other biomarkers associated with AF in the risk stratification of patients with cryptogenic stroke are needed.

## Hypertension

Hypertension is the most important modifiable risk factor for both cerebral infarction and intracerebral hemorrhage (ICH). Studies have consistently demonstrated a strong, continuous and independent positive relationship between blood pressure (BP) and stroke, such that the higher the BP, the greater the risk of stroke, throughout the usual range of BP, including the nonhypertensive range.[33,34] There are several recent advances in our understanding of hypertension in relation to primary and secondary stroke prevention.

### Primary stroke prevention

Owing to increased awareness of hypertension in the United States over the past 25 years, treatment of BP has improved from 54% in 1988–1994, to 73% in 2007–2008, and BP control has improved, though prevalence of hypertension has remained stable at 29%.[35] According to the Eight Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high BP (JNC-8), there is strong evidence that supports treatment of hypertension to a goal of less than 150/90 mmHg in those aged ≥60 years, and to a goal of diastolic BP less than 90 mmHg in those aged 30–59 (Table 4).[36] The JNC-8

report provides a more lenient BP target than the previous JNC-7, which recommended a treatment threshold of 140/90, regardless of age of the patient. Unlike the JNC-7, the recommendation in JNC-8 is based on RCTs as opposed to observational studies, with explicit delineation of expert opinions. The choice of antihypertensives is expanded to two classes for blacks, and four classes for non-blacks (Table 5). In addition, lifestyle choices such as diet and exercise are strongly emphasized. Recent meta-analyses have explored the need for antihypertensive agents to treat prehypertension, and their relationship with stroke risk. Among 16 trials of over 70,000 patients with prehypertension, pharmacologic treatment had a statistically significant reduction in the risk of stroke compared with placebo.[37] Other studies have provided evidence that intensive control of BP reduces risk of stroke more than less intensive control. In a recent meta-analysis, the relative risk of stroke was found to be 20% lower for patients with systolic BP (SBP) < 130 mmHg, compared to 130–139 mmHg. The effect was greater among those with cardiovascular risk factors than without cardiovascular disease (Table 6).[38] The benefit of intensive BP control may be specific to certain subgroups of patients. In the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial, more intensive control of SBP <120 mmHg among diabetic patients led to a reduction in risk of stroke and other vascular events (composite score) in patients with diabetes, as compared to standard control (<140 mmHg). However, mortality and the primary composite outcome were unaffected (Table 6).[39] In a secondary analysis of the Losartan Intervention For Endpoint (LIFE) reduction in hypertension trial, however, intensive BP control to ≤130 mmHg was not associated with a reduction in stroke after multivariable adjustment, and an increase in all-cause mortality was detected (Table 6).[40] Therefore, the goal BP should be tailored according to patient characteristics and the comorbidity burden (see Box 1).

A number of trials have tested antihypertensive treatment for patients with cardiovascular disease without hypertension. Among 80,594 patients with atherosclerotic disease or risk factors for atherosclerosis, treatment with either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker decreased the risk for cardiovascular outcome, including stroke (Table 6).[41] In a meta-analysis of cardiovascular disease patients without hypertension, those who received antihypertensive medication had a reduced risk of stroke compared to controls (Table 6).[42] Clinical trials have demonstrated that in most patients, more than one drug is needed to control BP effectively.[43–45] There is no definitive evidence supporting specific classes of antihypertensive therapy over others as a means to prevent stroke. Therefore, current guidelines support most antihypertensive agents for primary prevention of stroke, although specific subpopulations may benefit from certain medication class. Further hypothesis-driven trials are needed to delineate the efficacy of individual agents in specific subpopulations.

Since the benefit of BP reduction is documented across the range of BP measured in the population, it may be appropriate to recommend antihypertensive medication after a certain age, for patients with or without cardiovascular diseases.[46] Other complimentary strategies such as population-wide approaches to reduce BP have also been endorsed as more effective than individual approaches for the detection and treatment of high BP, that is, the high-risk approach.[47] SBP should be treated to a target of <150/90 mmHg, as these levels are

associated with a lower risk of stroke and cardiovascular events. The same goal is recommended for patients with hypertension with diabetes or renal disease.

### Secondary prevention

The management of hypertension for secondary stroke prevention is probably the most important intervention, and has been studied repeatedly in the past. The recent 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke[48] recommends that, under specific circumstances, antihypertensive medication may be initiated or resumed after an acute ischemic stroke within the first 24 h for patients who have pre-existing hypertension, and who are neurologically stable.[48]

There are limited data on the optimal BP target for secondary stroke prevention. In the recent Secondary Prevention of Small Subcortical Strokes (SPS3) trial, lowering BP below a target of 130 mmHg 2 weeks after a lacunar stroke lowered the risk of recurrent stroke compared with the target being a SBP of 130–149 mmHg, but the result was not statistically significant (Table 6).[49] Observational studies among patients with recent ischemic stroke suggest that aggressive reduction of SBP <120 mmHg may increase the risk of recurrent stroke.[50] In the recent observational subgroup analysis of the International Verapamil SR–Trandolapril Study (INVEST), a tight control of SBP of <130 mmHg was not associated with improved cardiovascular outcomes among hypertensive patients with coronary artery disease and diabetes, compared to those with less stringent SPB range of 130–140 mmHg, or higher.[51]

## Revascularization

Atherosclerosis of the large arteries causes up to 15% of ischemic strokes.[52] A systematic review of 16 trials comparing CEA with CAS in 7572 patients with symptomatic carotid stenosis revealed that CAS was associated with lower risk of periprocedural complications, such as access site hematoma, cranial nerve injury, and myocardial infarction (MI). However, compared to CEA, periprocedural stroke (between randomization and 30 days after treatment) was higher after CAS (OR 1.81, 95% CI 1.40–2.34), as were death, any stroke, or myocardial infarction (OR 1.44, 95% CI 1.15–1.80).[53] Based on a Cochrane database review, CEA is more appropriate for patients with symptomatic carotid stenosis resulting in a TIA or a nondisabling stroke, with stenosis ranging between 50% and 99%. The timing of CEA remains controversial and has been the subject of much debate, with suggestions ranging from 2 to 6 weeks. Pooled analyses from CEA trials have demonstrated that early surgery (<3 weeks) can be performed in low-risk patients, that is, those with minor stroke and without intracerebral hemmorhage.[54] The absolute risk reduction of stroke is 18.5% if CEA is performed with 2 weeks of stroke. However, this absolute risk reduction declines if there is delay between the stroke and CEA.[54] The rate of complication associated with CEA is lower if the surgeon has an audited perioperative stroke rate and mortality rate of <7%.[55] CEA is more appropriate for elderly patients (aged ≥70 years) owing to high risk of perioperative complications associated with stenting.[56] CAS may be offered to patients who are not candidates for CEA, either owing to anatomical limitations, or owing to their comorbidities (see Box 1).[56]

Intracranial atherosclerosis (ICAS) is a common cause of stroke and is associated with a high risk of recurrent stroke, especially in patients with a recent stroke or TIA and severe arterial stenosis. The Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial was designed to assess whether percutaneous transluminal angioplasty and stenting (PTAS) plus aggressive medical treatment is more effective than aggressive medical treatment alone in high-risk patients with this disease. Patients with 70–99% ICAS who had a stroke or TIA within the preceding 30 days were randomly assigned to aggressive medical management plus PTAS, or aggressive medical management alone, which included the combination of aspirin (325 mg/day) and clopidogrel (75 mg/day) for 90 days followed by aspirin (325 mg/day) alone for the remainder of the trial, intensive BP and LDL level management, with target levels of less than 140 mmHg (<130 mmHg in patients with diabetes) for SBP and LDL lower than 70 mg/dL, and adherence to a lifestyle modification program. However, the trial was stopped early in 2011 because of the high rate of periprocedural stroke in the stenting arm.[57] After a median of 32.4 months, 15% of patients in the medical group and 23% patients in the stenting group had a primary end point event (stroke or death within 30 days after enrollment, ischemic stroke beyond 30 days of enrollment, or stroke or death within 30 days after a revascularization procedure during follow-up). Beyond 30 days, the absolute differences in the primary end point rates between the two groups were 7.1% at year 1 (95% CI 0.2–13.8%; $P = 0.0428$), 6.5% at year 2 (0.5–13.5%; $P = 0.07$), and 9.0% at year 3 (1.5–16.5%; $P = 0.0193$). Adverse events occurred at a higher rate in the PTAS group than in the medical group (stroke 26% vs. 19%; $P = 0.0468$; major hemorrhage 13% vs. 4%; $P = 0.0009$). A key finding in the study was the high success rates of management of vascular risk factors, particularly achieving target levels for SBP and low-density lipoprotein cholesterol throughout the duration of the trial.[57] This, in combination with the use of aspirin and clopidogrel for 90 days followed by aspirin alone, probably contributed to the much lower than expected risk of stroke in the medical group. These results support the use of aggressive medical management rather than PTAS with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis (see Box 1).[58]

## Hyperlipidemia and elevated high-sensitivity C-reactive protein (hs-CRP)

Lowering blood cholesterol in patients at elevated cardiovascular risk has been a significant strategy in stroke prevention. In addition to several older studies showing lower risks of stroke with HMG-CoA reductase inhibitors,[59] the JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) confirmed the benefits of statins on stroke in a primary prevention population at elevated risk.[60] JUPITER evaluated a cohort of men 50 years of age or older, and women 60 years of age or older, without cardiovascular disease, with LDL level <130 mg/dL and triglyceride level of <500 mg/dL, but hs-CRP level ≥2.0 mg/L. Patients were randomly assigned to rosuvastatin or placebo. The results showed a 51% reduction in ischemic stroke ($P = 0.004$). The authors suggested that a healthy patient population at high risk and previously ineligible for statin therapy may benefit from rosuvastatin treatment if hs-CRP is elevated, even if LDL-C is within acceptable levels. There was no evidence of an interaction of statin therapy with hs-

CRP levels, however, meaning that the level of hs-CRP itself did not predict a response to statin therapy.[60]

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial studied the effect of high dose atorvastatin and the risk of secondary stroke in patients with a previous stroke or TIA, but without known heart disease.[61] Compared to placebo, daily treatment of 80 mg of atorvastatin resulted in a 16% relative risk reduction of fatal and nonfatal stroke among patients with a recent stroke or TIA. Several post hoc analyses revealed similar reduction in stroke and cardiovascular events when stratified by age, sex, presence of carotid disease, and type of stroke, suggesting that statin treatment reduces the likelihood of stroke and other cardiovascular events in the mentioned subgroups.[62–64]

In addition to well-documented vascular risk factors, inflammatory mechanisms have been associated with subcortical or lacunar strokes.[65–67] Few studies have examined the association of hs-CRP with ischemic stroke. In the prospective Northern Manhattan Study (NOMAS), hs-CRP predicted MI and death, but not first ischemic stroke, after adjusting for potential confounders.[68] In a large meta-analysis of 54 prospective cohort studies ($n$ = 160,309), the risk ratio of ischemic stroke per standard deviation of increase in log CRP was 1.44 (95% CI, 1.32–1.57) after adjusting for age and sex, but was reduced to 1.27 (95% CI, 1.15–1.40) when further adjusting for other risk factors.[69] Recently, in the Levels of inflammatory Markers in the Treatment of Stroke (LIMITS) study, a nested study within the SPS3 study, high hs-CRP level was associated with increased risk of recurrent ischemic and total stroke, and other major vascular events among patients with recent lacunar stroke (top quartile of hs-CRP (>4.86 mg/L) adjusted HR 2.23, 95% CI 1.15–4.68).[70] The risk of stroke and other vascular events were similar using clinically recommended hs-CRP threshold of 3 mg/L. Compared to those with hs-CRP of <1 mg/L, those with >3 mg/L had approximately twofold increase in the risk of ischemic stroke (adjusted HR 2.16, 95% CI 1.13–4.11) and high risk for major vascular events (adjusted HR 1.72, 95% CI 1.02–2.90). No interaction was detected between antiplatelet treatment and stroke risk for high hs-CRP. The effect of hs-CRP on the risk of recurrent stroke persisted after adjusting for statin use and was not influenced by the use of statin at baseline. Therefore, it remains unclear whether treatment of elevated hs-CRP at the time of stroke can reduce the risk for recurrent stroke. The results may indicate that among patients with small infarcts in whom the level of hs-CRP are not confounded by the severity of stroke, hs-CRP could serve as a potential prognostic biomarker for recurrent vascular events. Further studies are needed to determine if other specific therapies can be used in stroke patients with elevated hs-CRP.

## Antiplatelet therapies

Current guidelines recommend antiplatelet therapy for noncardioembolic ischemic stroke or TIA, with aspirin, clopidogrel, or their combination for prevention of stroke recurrence.[71] Beyond 90 days, aspirin, ticlopidine, and the combination of aspirin and dipyridamole are each effective for secondary stroke prevention (see Box 1).[71] Clopidogrel appears to be safer than the aspirin/dipyridamole combination. The combination of aspirin and clopidogrel may be considered as initial therapy within 24 h of TIA or minor ischemic stroke, and be continued for 90 days.[71] Clopidogrel may be used as an alternative to aspirin–dypiridamole

for secondary stroke prevention. For patients with an ischemic stroke or TIA while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been adequately studied in patients who have had an event while receiving aspirin. For patients with ischemic stroke or TIA and AF, the efficacy of adding aspirin to their anticoagulant regimen to reduce the risk of ischemic stroke remains unknown.[71]

Recently, the safety and efficacy of dual antiplatelet therapy in the acute phase of stroke have been examined, when the risk of recurrence is the highest, and may require more intensive therapy. In the Clopidogrel in High-risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, the safety and efficacy of aspirin and clopidogrel were compared to aspirin alone in the prevention of recurrent stroke in Chinese patients with acute minor stroke or TIA.[72] Patients were randomized to two groups: group 1 received a loading dose of clopidogrel (300 mg) and aspirin (75–300 mg) on day 1, followed by daily dose of 75 mg of clopidogrel and 75 mg of aspirin for a total of 21 days. Group 2 received a loading dose of aspirin alone (75–300 mg) followed by 75 mg daily for 21 days. The results indicated that dual antiplatelet therapy was more effective in reducing stroke risk at 3 months (HR 0.68; 95% CI, 0.57–0.81) without an increase in risks of moderate to severe bleeding ($P = 0.73$) during that time.[72] These results are consistent with other smaller trials conducted in other patient populations. In a recent meta-analysis of 14 trials ($n = 9012$) among patients with acute noncardioembolic ischemic stroke and TIA within 3 days of symptom onset, dual antiplatelet therapy significantly reduced risk of stroke recurrence (RR 0.69; 95% Cl, 0.60–0.80), as well as the composite outcome of stroke, TIA, acute coronary syndrome, and all death (RR 0.71; 95% CI 0.63–0.81) compared to monotherapy. Dual therapy nonsignificantly increased risk of major bleeding (RR 1.35; 95% CI 0.70–2.59).[73]

In the SPS3 trial, among patients with lacunar strokes, long-term dual antiplatelet therapy with combined clopidogrel plus aspirin did not significantly reduce the risk of recurrent stroke (HR 0.92; 95% CI, 0.72–1.16), but did significantly increase major bleeding (HR 1.97; 95% CI, 1.41–2.71) when compared to aspirin alone. All-cause mortality was increased among patients receiving dual antiplatelet therapy (HR 1.52; 95% CI, 1.14–2.04), therefore leading to the conclusion that in patients with lacunar stroke, the addition of clopidogrel to aspirin did not reduce the risk of recurrent stroke significantly, and significantly increased the risk of bleeding and death.[74]

The ongoing Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial, will examine the short term efficacy of more aggressive dual antiplatelet therapy in high-risk patients in the prevention of major vascular events (ischemic stroke, myocardial infarction, and ischemic vascular death) at 90 days.[75]

## Smoking

Smoking has been strongly associated with increased risk of stroke.[4] The long-term effect of smoking on risk of death and vascular events in stroke patients was examined in a 10-year survival study ($n = 1589$ cases of stroke) (see Box 1).[76] Patients who were current smokers at the time of their ischemic stroke (first or recurrent) had worse outcome (HR 1.30; 95% CI

1.06–1.60) compared to nonsmokers. Among the 28-day survivors, current smokers and ex-smokers at baseline had worse outcome compared to never smokers. The risk of recurrent vascular events was also higher among current smokers than ex-smokers (HR, 1.23; 95% CI 1.00–1.50; $P = 0.050$). This relationship has not been established for ICH, perhaps owing to the small sample size of patients in that group.[76] Exposure to environmental tobacco smoke (passive cigarette smoke, or "secondhand" tobacco smoke) is an established risk factor for heart disease. Recent observational studies provide evidence that smoking bans in communities can reduce the risk of stroke. After Arizona enacted a statewide ban on smoking, for example, there was a 14% reduction in strokes in countiesthathadnotpreviouslyhadabaninplace.[77]

## Diet

There is an increasing interest in the relationship between diet and stroke. Several observational studies have been conducted examining individual micronutrients, such as potassium or sodium.[78,79] In the Northern Manhattan Study, participants who consumed ≥4000 mg/day sodium had an increased risk of stroke (HR 2.59; 95% CI 1.27–5.28) versus those who consumed ≤1500 mg/day with a 17% increased risk of stroke for each 500 mg/day increase (95% CI, 1.07–1.27).[79] There is ample evidence that a diet high in fruits and vegetables is associated with reduced stroke risk in a dose–response manner.[80–83] However, owing to intrinsic methodological limitations of diet research, there is a trend to study dietary patterns as opposed to single macro- or micronutrients. The Mediterranean diet has been touted for its health benefits. It is consistent with the American Heart Association's dietary guidelines, as it is high in fruits, vegetables, monounsaturated fat, fish, whole grains, legumes, and nuts, and recommends moderate alcohol consumption and a low intake of red meat, saturated fat, and refined grains. A few studies have examined the relation between Mediterranean diet and stroke risk.[84–86] In the Northern Manhattan Study, Gardener *et al.* found an inverse association between Mediterranean diet and vascular deaths and myocardial infarction, but did not find any association for stroke.[85] This lack of association could have been owing to the low power in NOMAS, or the fact that stroke cases include both large and small vessel disease, as opposed to cases of myocardial infarction, which are primarily large vessel atherosclerotic diseases. In a recent multicenter trial in Spain ($n = 7447$), the Mediterranean diet reduced cardiovascular events (MI, stroke, or death from cardiovascular cause) compared to a low-fat diet. This study randomized patients with diabetes mellitus or other vascular risk factors to one of three diets: (1) Mediterranean diet supplemented with nuts, (2) Mediterranean diet with extra virgin olive oil, or (3) a control low-fat diet. Compared to controls, a significant difference was observed in the composite outcome of stroke, myocardial infarction, and cardiovascular death with the Mediterranean diet (HR 0.70), and for the secondary end point of stroke alone (HR 0.61), and the trial was stopped after an interim analysis.[86] Currently, there are no data on the role of dietary patterns for secondary stroke prevention. Thus, current recommendations on dietary choices after a TIA or stroke rely on primary prevention trial data (see Box 1).

## Physical activity

Physical activity is known to improve cardiovascular disease risk factors as well as stroke (see Box 1).[87–89] Multiple trials have been able to demonstrate the protective effects of physical activity for both men and women. In the Northern Manhattan Study, individuals in the upper quartile of increased level of physical activity had lower risk of silent brain infarcts (OR 0.6, 95% CI 0.4–0.9), compared to those who did not exercise.[90] A preliminary study of the California Teachers Study Cohort, postmenopausal women on hormone therapy who exercised moderately to strenuously in the 3 years before enrollment had 20% reduced risk of stroke (HR 0.79, 95% CI 0.71–0.98); physical activity appeared to counteract the high risk of stroke associated with hormone therapy.[91] So far, physical activity has not been tested adequately in clinical trials. In particular, no randomized clinical trials have examined the effectiveness of exercise for secondary prevention of stroke. Two trials that a reusing multimodal approaches, with physical activity as one of the variables, are in progress.[92,93]

## Conclusions

Over the last few years, changing demographics have increased the demand for health services for acute stroke and the long-term disability associated with it. With most stroke risk factors being modifiable, it is important to improve stroke awareness and provide more rigorous education to those who are at high risk. Specifically, the latest data show that novel anticoagulants offer greater convenience than warfarin for stroke prevention owing to AF, but antiplatelet therapy and intensive lowering of atherosclerosis risk factors remain key components of stroke prevention from artery-to-artery embolus and intracranial disease. Extracranial internal CAS and surgical endarterectomy offer similar outcomes in suitable patients at high risk of stroke and low periprocedural/perioperative risk. Future research focused on early risk profile development is urgently needed to tailor prevention strategies.

## Acknowledgments

This research was made possible by Grant T32NS07153 from the National Institute of Neurological Disorders and Stroke (NINDS).

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**Box 1.**

## Latest recommendations for stroke prevention

**Atrial Fibrillation**

- Apixaban (Level of Evidence A), dabigatran (Level of Evidence B), or rivaroxaban (Class IIa; Level of Evidence B) are indicated for the prevention of recurrent stroke in patients with nonvalvular AF.
- The combination of oral anticoagulation (either warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA (Class IIb; Level of Evidence C).
- Aspirin alone can be used for patients with ischemic stroke or TIA and AF, who are unable to take oral anticoagulants (Class I; Level of Evidence A). The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone may be reasonable (Class IIb; Level of Evidence B).
- For patients with cryptogenic acute ischemic stroke or TIA, extended cardiac rhythm monitoring up to 30 days for AF is reasonable within 6 months of the index event (Class IIa; Level of Evidence C).

**Hypertension**

- As stated in the JNC-8 report, treatment of hypertension for primary stroke prevention may be started for those aged ≥60 years, to lower BP at SBP ≥ 150 or diastolic blood pressure ≥90, to a BP target of <150/90 (Level of Evidence A).
- For those aged 30–59, treatment of hypertension may be started at SBP ≥ 140, to a BP target of SBP <140 (Level of Evidence E).
- There is insufficient evidence in hypertensive persons <60 years for a systolic goal, or in those <30 years for a diastolic goal. Therefore, a BP of less than 140/90 mmHg is recommended for those groups (Level of Evidence E).
- For secondary stroke prevention, antihypertensives may be resumed in patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA within the first 24 h of the stroke (Level of Evidence B) or beyond several days (Level of Evidence A).
- The goals for target BP level for secondary stroke prevention are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mmHg and a diastolic pressure <90 mmHg (Class IIa; Level of Evidence B).

**Revascularization**

- Carotid endarterectomy (CEA) is more appropriate for elderly patients (aged ≥70 years) owing to high risk of perioperative complications associated with stenting (Class IIa; Level of Evidence B).
- CEA is more appropriate for patients with symptomatic carotid stenosis resulting in a TIA or a nondisabling stroke, with stenosis ranging between 50% and 99%.
- Carotid artery stenting (CAS) may be indicated instead of CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the stenosis is >70% by noninvasive imaging or >50% by catheter-based imaging (Class IIa; Level of Evidence B).
- CAS may be offered to patients who are not candidates for CEA, either owing to anatomical limitations, or owing to their comorbidities (Class IIa; Level of Evidence B).

**Intracranial Atherosclerosis**

- Based on the results of the SAMMPRIS trial, medical therapy was superior to intracranial stenting for stroke prevention. Therefore, in patients with recent stroke or TIA (within 30 days) owing to severe stenosis (70–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days in addition to aggressive LDL and BP management, is recommended (Class IIb; Level of Evidence B).
- Antiplatelet therapy, rather than anticoagulation, in addition to strict BP control and hyperlipidemia control is recommended for those with intracranial atherosclerosis (Class I; Level of Evidence B).

**Hyperlipidemia**

- Treatment with a statin is recommended for the primary prevention of ischemic stroke in patients estimated to have a high risk for cardiovascular events (Class I; Level of Evidence A).

**Antiplatelet Therapies**

- The combination of aspirin and clopidogrel may be considered as initial therapy within 24 h of TIA or minor ischemic stroke, and be continued for 90 days (Class IIb; Level of Evidence B).
- In Chinese population with acute (<24 h) minor stroke or TIA, a loading dose of aspirin and clopidogrel, followed by long-term dual antiplatelet therapy was more effective in preventing stroke recurrence (Level of evidence B).
- For patients with ischemic stroke or TIA and AF, the efficacy of adding aspirin to their anticoagulant regimen to reduce the risk of ischemic stroke remains unknown (Class IIb; Level of Evidence C).

**Smoking**

- Abstaining from cigarette smoking is recommended for patients who have never smoked owing to a consistently strong association between smoking and both ischemic stroke and hemorrhagic strokes (Class I; Level of Evidence B).
- Counseling and drug therapy is recommended for active smokers to assist in quitting smoking (Class I; Level of Evidence A).

**Diet**

- Reduced intake of sodium and increased intake of potassium are recommended to lower BP, and subsequent stroke (Class I; Level of Evidence A).
- A diet that is rich in fruits and vegetables may lower the risk of stroke (Class I; Level of Evidence B).
- A Mediterranean diet may be considered in lowering the risk of stroke (Class IIa; Level of Evidence B).

**Physical Activity**

- Physical activity is recommended as it is associated with a reduction in the risk of stroke (Class I; Level of Evidence B).
- Healthy adults should perform at least moderate to strenuous aerobic physical activity at least 40 min/day 3–4 days per week (Class I; Level of Evidence B).

**Table 1.**

$CHADS_2$: risk stratification to predict thromboembolism in atrial fibrillation[14]

| | Comorbidities | Points |
|---|---|---|
| C | Congestive heart failure | 1 |
| H | Hypertension: blood pressure > 140/90 mmHg (or treated with medication) | 1 |
| A | Age ≥75 years | 1 |
| D | Diabetes mellitus | 1 |
| $S_2$ | Prior stroke or TIA or thromboembolism | 2 |

*Ann N Y Acad Sci*. Author manuscript; available in PMC 2020 February 10.

**Table 2.**

Annual stroke risk in patients with atrial fibrillation using the $CHADS_2$ score[15]

| $CHADS_2$ score | Stroke risk % | 95% CI |
|---|---|---|
| 0 | 1.9 | 1.2–3.0 |
| 1 | 2.8 | 2.0–3.8 |
| 2 | 4.0 | 3.1–5.1 |
| 3 | 5.9 | 4.6–7.3 |
| 4 | 8.5 | 6.3–11.1 |
| 5 | 12.5 | 8.2–17.5 |
| 6 | 18.2 | 10.5–27.4 |

CI, confidence interval.

**Table 3.**

Summary of recent clinical trials on novel oral anticoagulants

| Atrial fibrillation | Drug | Comparison | Primary end point: stroke and systemic embolism | ICH rate (% per year) | Major bleeding event (% per year) |
|---|---|---|---|---|---|
| RE-LY[14] | Dabigatran 150 mg BID or 110mg BID | Dose-adjusted warfarin | 1.71% warfarin 1.54% dabigatran 110mg (P = 0.34) 1.11% dabigatran 150 mg (P< 0.001) | 0.74% warfarin 0.23% dabigatran 110mg (P< 0.001) 0.3% dabigatran 150 mg (P< 0.001) | 3.57% warfarin 2.87% dabigatran 110mg (P = 0.003) 3.32% dabigatran 150 mg (P=0.31) |
| ROCKET AF[9] | Rivaroxaban 20 mg once a day | Dose-adjusted warfarin | 2.42% warfarin 2.12% rivaroxaban (P=0.117) | 0.74% warfarin 0.49% rivaroxaban (P= 0.019) | 3.45% warfarin 3.6% rivaroxaban (P= 0.576) |
| ARISTOTLE[16] | Apixaban 5 mg BID | Dose-adjusted warfarin | 1.60 warfarin 1.27% apixaban (P< 0.001) | 0.47% warfarin 0.24% apixaban | 3.09% warfarin 2.13% apixaban (P< 0.001) |
| AVERROES[19] | Apixaban 5 mg BID | Aspirin (81–324 mg daily) | 3.9% aspirin 1.7% apixaban (P< 0.001) | 0.3% aspirin 0.4% apixaban (P=0.83) | 1.2% aspirin 1.4% apixaban (P=0.33) |

RE-LY, Randomized Evaluation of Longterm Anticoagulant Therapy; ROCKET-AF, Rivaroxaban Once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES, Apixaban versus aspirin to reduce the risk of stroke; mg, milligram; BID, twice a day.

**Table 4.**

The Eighth Joint National Committee (JNC-8) Panel's Definitions of Threshold and Goal for Pharmacologic Treatment of Hypertension[36]

| Hypertensive population | BP to start pharmacologic treatment (mmHg) | BP treatment goal (mmHg) | Level of evidence |
|---|---|---|---|
| ≥60 years old | SBP ≥ 150 DBP ≥ 90 | SBP < 150 DBP < 90 | Grade A: Strong recommendation |
| 30–59 years old | DBP ≥ 90 | DBP < 90 | Grade A: Strong recommendation |
| 18–29 years old | DBP ≥ 90 | DBP < 90 | Grade E: Expert opinion |
| <69 years old | SBP ≥ 140 | SBP < 140 | Grade E: Expert opinion |
| ≥ 18 years old with CKD | SBP ≥ 140 or DBP ≥ 90 | SBP < 140 DBP < 90 | Grade E: Expert opinion |
| ≥ 18 years old with diabetes | SBP ≥ 140 or DBP ≥ 90 | SBP < 140 DBP < 90 | Grade E: Expert opinion |

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Table 5.**

Pharmacologic recommendations for management of hypertension by the eighth joint national committee panel[36]

| Hypertensive population | Initial pharmacologic agents | Level of evidence |
|---|---|---|
| Non-African Americans (including those with diabetes) | •Thiazide-type diuretics<br>•Calcium channel blockers<br>•ACE inhibitors<br>•Angiotensin receptor blockers<br>•Thiazide-type diuretics<br>•Calcium channel blockers | Grade B: Moderate recommendation |
| African Americans (including those with diabetes) | | Grade B: Moderate recommendation for African Americans with diabetes, Grade C: Weak recommendation |

**Table 6.**

Summary of the meta-analyses and trials on treatment of hypertension and stroke outcome

| Author | Study type | *N* | Primary versus secondary stroke prevention | Treatment group; blood pressure target | Comparison group | Stroke outcome |
|---|---|---|---|---|---|---|
| Sipahi *et al.*[37] | Meta-analysis | 70,664 | Primary | <140/90 | Placebo | RR 0.78 (95% CI 0.71–0.86) |
| Lee *et al.*[38] | Meta-analysis | 42,572 | Primary | SBP < 130 mmHg compared to 130–139 mmHg | Placebo | RR 0.80 (0.70–0.92) |
| Cushman *et al.*[39] (ACCORD trial) | RCT | 4733 | Primary | Diabetic patients, SBP < 120 mmHg | SBP target < 140 mmHg | HR 0.59, 95% CI 0.39–0.89 |
| Okin *et al.*[40] (LIFE trial) | RCT | 9193 | Primary | SBP target < 130 mmHg and SBP target 131–141 mmHg | SBP target ≥ 142 mmHg | SBP < 130 mgHg: OR 1.08, 95% CI 0.79–1.47 SBP 131–141 mmHg: OR 1.06, 95% CI 0.47–0.79 |
| McAllister *et al.*[41] | Meta-analysis | 80,594 | Primary | Patients with CVD, no HTN | Placebo | OR 0.91, 95% CI 0.86–0.97 |
| Thompson *et al.*[42] | Meta-analysis | 21,872 | Primary | Patients with CVD, no HTN | Placebo | 0.77, 95% CI 0.61–0.98 |
| Benavente *et al.*[49] (SPS3 trial) | RCT | 3020 | Secondary | SBP target <130 mmHg 2 weeks after lacunar stroke | SBP 130–149 mmHg | HR0.81,95%CI 0.6–1.03 |

RCT, randomized clinical trial; SBP, systolic blood pressure; RR, relative risk; HR, hazard ratio; OR, odds ration; CVD, cardiovascular disease; HTN, hypertension; ACCORD, Action to Control Cardiovascular Risk in Diabetes; LIFE, Losartan Intervention For Endpoint reduction in hypertension; SPS3 trial, Secondary Prevention of Small Subcortical Strokes trial.