Secondary Prevention of Ischemic Stroke: Challenging Patient Scenarios

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The risk for recurrent stroke following a stroke or transient ischemic attack (TIA) is high. Prevention of a secondary event is a priority, as the associated morbidity and mortality are great. Antiplatelet agents have been shown to reduce this risk, but the choice of treatment modality depends on a number of factors, including the underlying cause of the stroke and the patient’s comorbidities. For example, a cardioembolic stroke is best treated with anticoagulants, whereas one of noncardioembolic origin requires antiplatelet therapy. A number of challenging patient scenarios are explored in this article, and appropriate medical management is discussed, with the goal of examining the most recent trial data and information in the context of an actual case. Eight sample cases are presented: stroke prevention in a patient with recent stent placement, low ejection fraction, intracranial stenosis, carotid stenosis, atherosclerosis of the aortic arch, symptomatic coronary artery disease, antiplatelet failure, and stroke prevention in a patient already on warfarin. Journal of Hospital Medicine 2008;3(4 Suppl): S20–S28. © 2008 Society of Hospital Medicine.

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The risk of recurrent stroke is high following an ischemic stroke or transient ischemic attack (TIA). Within the first 90 days following an initial TIA, between 4.8% and 18.3% of individuals will have an ischemic stroke, with many experiencing an ischemic event within the first 2–7 days. The risk of subsequent stroke in a stroke survivor is high as well—4.2% at 6 months, 6.5% at 1 year, and 11.8% at 3 years. The management of these patients poses substantial challenges for the health care professional. Prevention of secondary stroke, with its risk for greater morbidity and mortality, is a priority. However, depending on the cause of the event, patient comorbidities, and other factors, the most effective therapeutic strategies may differ. For example, cardioembolic strokes, which constitute approximately 20% of ischemic strokes, are treated with anticoagulants, whereas strokes of noncardioembolic origin are usually treated with antiplatelet agents. Other risk factors or variables such as recent stent placement or reduced left ventricular ejection fraction (LVEF) may affect therapeutic decisions as well, although in many cases clear data are not available to direct these difficult decisions. Thus, although antiplatelet agents, including aspirin, clopidogrel, and aspirin plus extended-release dipyridamole, prevent strokes, the choice of agent depends on the individual patient risk profile. A number of challenging patient scenarios
are explored in this article with the goal of providing a context for some of the more recent trial data.

RECENT STENT PLACEMENT

In 2004, there were approximately 663,000 percutaneous coronary interventions (PCIs). Stenting after PCI is a common procedure and is used in more than 70% of coronary angioplasty procedures. The addition of stenting to the PCI procedure has improved the outcome for patients, reducing the need for revascularization. Because restenosis of the area following stent placement is common, drug-eluting stents are also used to allow slow release of antiproliferative agents such as sirolimus or paclitaxel.

Studies such as Percutaneous Coronary Intervention—Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE) and Clopidogrel for Reduction of Events During Observation (CREDO) have supported the use of up to 8 months of clopidogrel plus aspirin following coronary interventions. The European Society of Cardiology PCI guidelines state that in regard to PCI procedures, clopidogrel is superior to aspirin. The guidelines recommend 3–4 weeks of clopidogrel following stenting in patients with stable angina but up to 12 months in patients receiving brachytherapy. Among patients who have received drug-eluting stents, clopidogrel therapy should be continued for 6–12 months. In patients who have had a non–ST segment elevation myocardial infarction (MI) or who have unstable angina, these guidelines recommend the continuation of clopidogrel (75 mg/day) plus aspirin (100 mg/day) for 9–12 months after a PCI procedure. However, although clopidogrel plus aspirin reduces the incidence of major ischemic events in the period immediately following a stenting procedure, some have suggested that long-term use of clopidogrel is not supported by the evidence. It has been proposed that the sustained beneficial effect of clopidogrel given in the immediate postoperative period may account for much of the long-term benefit, as has been shown to be true of the glycoprotein IIb/IIIa antagonists. However, others caution that in the case of drug-eluting stents, inhibition of endothelialization of the stent struts by the embedded agents makes these stents more susceptible to thrombosis formation, particularly if therapy with clopidogrel plus aspirin is interrupted. It is believed that late stent thrombosis, which has a high mortality rate, is more common with drug-eluting stents than with bare-metal stents. As a result, many cardiologists recommend at least 12 months of dual antiplatelet therapy with aspirin plus clopidogrel for patients who have received drug-eluting stents. However, given the results of the recent Management of Atherothrombosis in High-risk Patients with Recent Transient Ischemic Attack or Ischemic Stroke (MATCH) and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trials, in particular, the high incidence of bleeding events in the clopidogrel plus aspirin group, there are concerns about longer-term or lifelong therapy with this combination in a population at risk for recurrent stroke.

What about the patient who has undergone a coronary stent placement in the past 12 months and experiences a subsequent ischemic stroke or TIA? The patient should be continued on clopidogrel plus aspirin for the recommended time, as premature discontinuation of antiplatelet therapy increases the risk of stent thrombosis. No data are currently available to support decision making regarding these patients. However, it has been suggested that among patients given drug-eluting stents, extended use of clopidogrel at 6, 12, and 24 months is associated with reduced risk of death or death/MI.

LOW EJECTION FRACTION

Patients who have had a stroke or TIA and have underlying left ventricular dysfunction are at increased risk of a cardioembolic stroke. The reduction in stroke volume creates a condition of stasis in the ventricle that increases the likelihood of coagulation and thromboembolic events. Evidence indicates that the risk of stroke is inversely correlated with LVEF; LVEF of 29%–35% carries a cumulative 5-year stroke risk of 7.8%, and LVEF of 28% or below carries a 5-year risk of 8.9%. Data from the Survival and Ventricular Enlargement (SAVE) study showed an 18% increase in the risk of stroke for every 5% decline in LVEF, and the Studies of Left Ventricular Dysfunction (SOLVD) trial found a 58% increase in thromboembolic events for every 10% decrease in
LVEF among women ($P = .01$). Among patients with low LVEF who have had a stroke, the 5-year recurrent stroke rate may be as high as 45%. 

Although it would appear that stroke associated with left ventricular dysfunction and a low LVEF may potentially be cardioembolic in origin, risk reduction for recurrent stroke has not been adequately investigated as a primary end point in clinical trials, particularly in the absence of atrial fibrillation. Thus, the question of whether antiplatelet or anticoagulant therapy would be more effective has not yet been answered. However, results of secondary end point analyses in the SOLVD and SAVE trials suggested that patients had a lower risk of sudden death, thromboembolism, and stroke with antiplatelet therapy. In an observational analysis of prospectively collected data on patients enrolled in the SAVE trial, use of aspirin reduced the overall risk of stroke by 66% in patients with an LVEF below 28%. Warfarin is the standard of care for stroke prevention in atrial fibrillation, and the conditions often coexist. In those patients, warfarin is the recommended therapy.

In patients with sinus rhythm and a low LVEF, the choice is less clear. The results of the Warfarin/Aspirin Study in Heart failure (WASH) failed to establish efficacy or safety for aspirin in preventing all-cause mortality, nonfatal MI, and nonfatal stroke in patients with heart failure. Patients treated with aspirin were significantly more likely to be hospitalized for cardiovascular events, especially worsening heart failure. The trial found no significant difference for the composite end point between the 3 treatment groups: aspirin, warfarin, or no antithrombotic treatment. However, this was a small trial, and the findings were far from definitive, as the study was designed primarily to be a feasibility study to aid in the design of a larger outcomes study. Because of the inconsistent results and lack of well-designed studies regarding the benefit of aspirin or anticoagulation for secondary stroke prevention in patients with LVEF in the absence of atrial fibrillation, further study is needed.

More recently, results were presented from the Warfarin and Antiplatelet Therapy in Heart Failure Trial (WATCH), which randomized patients with heart failure, sinus rhythm, and LVEF of 35% or below to either aspirin 162 mg, warfarin (target international normalized ratio [INR] 2.5–3.0), or clopidogrel. Two major comparisons were planned—warfarin versus aspirin and aspirin versus clopidogrel. Whereas warfarin therapy was open-label because of the need to check blood levels, antiplatelet therapy was given in a double-blind manner. After a mean follow-up of 23 months, no significant differences were found for the primary composite end point of all-cause mortality, nonfatal MI, and nonfatal stroke, which occurred in 20.5% of those on aspirin, 19.8% on warfarin, and 21.8% on clopidogrel. However, for the secondary end point of stroke, there was a strong trend favoring warfarin over aspirin: stroke occurred in 0.7% of patients taking warfarin versus 2.1% of those taking aspirin ($P = .06$). However, the WATCH investigators concluded that the question of warfarin’s value for patients with low LVEF and sinus rhythm remained unresolved.

In the absence of clear data, the American Heart Association (AHA)/American Stroke Association (ASA) guidelines on stroke prevention in this patient population recommend either warfarin (INR 2.0–3.0) or antiplatelet therapy, including aspirin (50–325 mg/day), aspirin plus extended-release dipyridamole (200 mg twice daily), or clopidogrel (75 mg/day). Patients with coexisting atrial fibrillation should be treated with warfarin, or if unable to tolerate that agent, aspirin 325 mg/day.

The Warfarin Versus Aspirin for Reduced Cardiac Ejection Fraction (WARCEF) trial may provide more definitive answers on the best approach for reducing the risk of recurrent stroke in patients with low LVEF. The study will compare warfarin (INR 2.5–3.0) and aspirin (325 mg/day) in the prevention of all-cause mortality and all strokes (ischemic and hemorrhagic) in patients with an LVEF of 35% or below but no atrial fibrillation. The study has a target enrollment of 2860 patients, who are being recruited at 70 North American and 70 European sites, and it will include patients with recent stroke or TIA. The results are anxiously anticipated.

**INTRACRANIAL STENOSIS**

Stroke patients with symptomatic intracranial atherosclerosis have a high risk of recurrent stroke—in the range of 10% per year—and this accounts for approximately 8% of ischemic strokes. Intracranial stenosis appears to be more common in African Americans and Hispanics than in white patients.
Recurrent stroke prevention in patients with intracranial stenosis was explored in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study, a multicenter, double-blind trial. Patients with angiographically verified 50%–99% stenosis of a major intracranial artery who had experienced either a stroke or TIA were randomized to either warfarin (target INR 2.0–3.0) or high-dose aspirin (1300 mg/day). The primary end point was ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke. Mean follow-up was 1.8 years, and enrollment was stopped after 569 patients had been randomized because of concerns about the safety of warfarin in this patient population. The primary end point occurred in 22.1% of those treated with aspirin and 21.8% of those treated with warfarin. There were no significant differences between the 2 treatment groups for any of the prespecified secondary end points, including ischemic stroke in any vascular territory and ischemic stroke in the territory of the stenotic intracranial artery.

The rate of death was significantly higher in the warfarin group (9.7%) than in the aspirin group (4.3%; P = .02). Patients in the warfarin group had higher rates of death from both vascular and nonvascular causes. Major hemorrhage was significantly more common in the warfarin group (8.3%) than in the aspirin group (3.2%; P = .01). The investigators concluded that warfarin should not be used as first-line prevention of recurrent stroke in patients with intracranial stenosis. However, there was a significant association between an INR less than 2 and increased risk of ischemic stroke and major cardiac events (P < .001) as well as a significant increase in major hemorrhages in patients with INRs greater than 3 (P < .001).

The failure of many patients in the study to remain within the therapeutic INR casts doubt on these results to some extent, although this may actually mirror a common real-world scenario. Patients were within the therapeutic INR goal only 63% of the time. Furthermore, a nonstandard high dose of aspirin (1300 mg/day) was used, which may also have affected the results. Others looking at this data have suggested that aspirin remains an imperfect therapy, with an unacceptably high risk of ischemic stroke and other vascular events, and that anticoagulation may play a role in the period immediately following ischemic stroke or TIA with transition to antiplatelet therapy. This would require additional investigation.

The current AHA/ASA guidelines recommend that for patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulants be used to reduce the risk of recurrent stroke (class I, level A). Aspirin (50–325 mg/day), the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy (class IIa, level A). The combination of aspirin and extended-release dipyridamole is suggested instead of aspirin alone (class IIa, level A), and clopidogrel may be considered instead of aspirin alone (class IIb, level B). However, data are insufficient at this point to make evidence-based recommendations between antiplatelet options other than aspirin.

In patients with significant intracranial stenosis whose symptoms persist despite medical therapy, including antithrombotics, statins, and antihypertensives, endovascular therapy with angioplasty and/or stent placement is an option, but it remains investigational and its value is uncertain.8

**CAROTID STENOSIS**

Asymptomatic carotid stenosis greater than 50% has been found in 7% of men and 5% of women older than 65 years. Among those with asymptomatic carotid stenosis greater than 50%, there is an annual risk of stroke of up to 3.4%. In such patients, the benefit of carotid endarterectomy (CEA) is highly dependent on the surgical risk, and if complication rates exceed 3.0%, benefit is eliminated. The AHA/ASA guidelines recommend that patients be given treatment for all identifiable risk factors, including statins for dyslipidemia, antihypertensives for hypertension, and aspirin as an antiplatelet agent. In select patients with high-grade asymptomatic carotid stenosis, CEA performed by a surgeon with a morbidity/mortality rate below 3% is recommended. In asymptomatic patients with greater than 70% carotid stenosis, CEA can be an effective therapy. Trial data indicate that the overall 5-year risk of any stroke or perioperative death is 11.8% for deferred surgery versus 6.4% for immediate endarterectomy (P < .0001). Unfortunately, data on the value of stents or angioplasty compared with CEA in this patient population are limited.

In patients who have had a recent TIA or stroke, carotid stenosis would be considered
symptomatic. In these patients, the benefit of CEA is strongly associated with the degree of stenosis. Data from the Carotid Endarterectomy Trialists’ Collaboration and North American Symptomatic Carotid Endarterectomy Trial (NASCET) have shown that in patients with stenosis greater than 70%, CEA reduces the absolute 5-year risk of ischemic stroke by 16.0% \( (P < .001) \), whereas in patients with 50%–69% stenosis, the 5-year absolute risk reduction is 4.6% \( (P = .04) \). In those with stenosis of 30%–49%, there is no effect, and CEA in patients with less than 30% stenosis increases the risk of stroke.\(^{38,39}\) In patients with 50%–69% stenosis, benefit is achieved only if patients at highest risk are selected.\(^{40}\) Recent data have also questioned the typical 4- to 6-week delay before performing a CEA following a nondisabling stroke. Rothwell et al. found that surgery performed within 2 weeks of such a stroke was not associated with increased operative risk.\(^{41}\) Moreover, benefit from CEA fell rapidly within the first few weeks after a TIA or stroke, particularly in women, perhaps reflecting the high risk of recurrent stroke in the period immediately following an initial event.\(^{41}\)

Angioplasty or stents have been investigated as alternatives to CEA, but the evidence to date has been disappointing. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) demonstrated preventive efficacy and major risks similar to those found for CEA after 3 years of follow-up in 504 patients with carotid stenosis.\(^{42}\) However, a more recent study was stopped prematurely after 527 patients had been enrolled because of a higher incidence of disabling stroke or death at 30 days in the stenting cohort (3.4%) compared with the CEA cohort (1.5%). The 30-day incidence of any stroke or death was 3.9% after CEA and 9.6% after stenting, yielding a relative risk of 2.5 for stenting.\(^{43}\) The Stent-Protected Angioplasty Versus Carotid Endarterectomy in Symptomatic Patients (SPACE) trial has also failed to find benefit for carotid stenting and/or angioplasty in comparison with CEA.\(^{44}\)

The AHA/ASA guidelines recommend CEA in patients with ipsilateral severe (70%–99%) stenosis and a recent TIA or ischemic stroke (within 6 months). Surgery should be performed by a surgeon with a perioperative morbidity/mortality rate less than 6%.\(^{8}\) In patients with 50%–69% stenosis, the advisability of CEA depends on patient factors such as age, sex, comorbidities, and severity of symptoms. Surgery should be performed within 2 weeks of an ischemic event. In patients with severe stenosis in whom CEA would be difficult to perform, carotid angioplasty or stenting may be recommended if performed by practitioners with a morbidity/mortality rate less than 4%–6%.\(^{8}\) The Seventh ACCP Conference also recommends that patients undergoing CEA receive aspirin 81–325 mg/day prior to and following the procedure.\(^{7}\)

**ATHEROSCLEROSIS OF THE AORTIC ARCH**

Atherosclerosis of the aortic arch contributes significantly as an independent factor to risk of embolic stroke.\(^{7}\) Such plaques can be detected using transesophageal echocardiography; those that are thicker than 4–5 mm, exhibit ulceration, or have mobile components place individuals at higher risk for stroke.\(^{7,45}\) The stroke risk associated with aortic arch plaques greater than 5 mm is as high as 33% per year.\(^{7,46}\)

However, data from large-scale randomized clinical trials on the efficacy of therapeutic interventions in this condition are lacking. Two small trials found efficacy for warfarin in patients with mobile thrombi in the thoracic aorta. In one, patients given oral anticoagulants had better outcomes than those treated with antiplatelet agents, and in the other, warfarin proved to be more effective than no treatment.\(^{47,48}\) A retrospective trial that looked at 519 patients treated with warfarin, antiplatelet agents, or statins found there was a protective effect of statins, with an absolute risk reduction in embolic events, including ischemic stroke, TIA, and peripheral embolization of 17%, and a relative risk reduction in embolic events of 59%. The odds ratio for embolic events was 0.39 for statins, 0.77 for antiplatelet agents, and 1.18 for warfarin.\(^{49}\) The French Study of Aortic Plaque in Stroke found no significant difference in risk of events between those treated with warfarin and those treated with aspirin; however, this study was not designed as a therapeutic trial, and few patients received warfarin, casting doubt on this finding.\(^{45}\)

Given the paucity of data, suggestions for treatment of patients with an aortic arch atheroma are difficult. Certainly, statin therapy, which would address general atherosclerotic risk reduction, can be initiated. Warfarin appeared to be more effective than antiplatelet agents in several of the studies; however some have expressed concern about the possibility of anticoagulation
increasing the risk of cholesterol embolism in these patients.7

SYMPTOMATIC CORONARY ARTERY DISEASE

For patients with a history of ischemic stroke or TIA who have symptomatic CAD, their condition must be managed for both stroke and CAD risks. In patients with stable or unstable angina and a history of stroke or TIA, similar risks must be managed. The acute treatment of ACS or symptomatic CAD cannot be adequately addressed here; however, it may involve a number of therapeutic modalities, including PCI, β-blocker therapy, glycoprotein IIb/IIIa inhibitors, anticoagulant therapy, angiotensin-converting enzyme (ACE) inhibitors, and clopidogrel plus aspirin, depending on the exact nature of the syndrome. The long-term management and, in particular, prevention of recurrent stroke in the setting of symptomatic CAD are the focus here. As with a patient with a history of CAD and a recent TIA or stroke (as discussed earlier), patients with symptomatic CAD and TIA or stroke must be managed for multiple risk factors. NCEP guidelines recommend aggressive cholesterol lowering with statin therapy. Hypertension must be addressed as well, and long-term therapy with β-blockers and ACE inhibitors has been shown to reduce mortality in patients with ACS and is recommended by the AHA/ASA.53–55

Once the acute ACS period has resolved, it is reasonable to address the question of the best possible antiplatelet therapy for long-term stroke prevention. Long-term use of clopidogrel plus aspirin is not advisable given the increased risk of bleeding events noted in the MATCH and CHARISMA trials.16,17 At this point, it would be reasonable to start the patient on aspirin 75–150 mg/day, which reduces risk of stroke up to 25%, aspirin plus extended-release dipyridamole, which reduces risk by about 37%, or clopidogrel 75 mg/day, which reduces the relative risk for stroke alone by 7.3% compared with aspirin.59 In patients who cannot tolerate or are allergic to aspirin, clopidogrel is a reasonable choice.8

ANTIPLATELET FAILURE

Patients who have failed antiplatelet therapy—that is, have gone on to have a recurrent stroke—are particularly difficult. It is important to remember that any therapeutic intervention only reduces stroke risk; it does not eliminate it. Keeping that in mind, it is essential to reevaluate and reconsider both the original diagnosis and the etiology of the stroke or TIA. A number of diagnostic alternatives should be considered, including sensory seizure and migraine equivalents, as well as other etiologies, such as atrial fibrillation or cerebral amyloid angiopathy. Therapy may have to be adjusted accordingly, but the patient remains at increased risk for stroke recurrence, and thus preventive therapy is critical.

Several key points should be remembered. As outlined previously in this article, if the stroke is still thought to be noncardioembolic in origin, a reduction in the risk of stroke has not been found for those patients receiving warfarin, an increased dose of aspirin, a combination of antiplatelet agents and warfarin, or clopidogrel plus aspirin. However, if atrial fibrillation has developed in the patient, the recommendation is warfarin (INR 2.0–3.0) or, if anticoagulants cannot be taken, aspirin 325 mg/day. Risk factors should be reassessed and managed, with agents and lifestyle changes to control hypertension and dyslipidemia. Antiplatelet agents should be continued in patients with noncardioembolic stroke. Acceptable antiplatelet agents include aspirin (50–325 mg/day), aspirin plus extended-release dipyridamole, and clopidogrel. The combination of aspirin plus extended-release dipyridamole is suggested over aspirin alone. If the patient cannot tolerate or is allergic to aspirin, clopidogrel is a reasonable alternative.8 The decision of which antiplatelet agent to use should be based on the individual patient's risk factor profile. The temptation to put patients on anticoagulation therapy because of a wish to “do more” should be avoided, as this is likely to expose patients to increased risk without known benefit.60,61

Consider a common case scenario—a patient with a known history of hypertension and TIA presents with a 30-minute episode of left arm numbness. The patient has been adherent to his prescribed medications, including aspirin 81 mg/day. What is the appropriate approach to acute treatment at this time? This is a common scenario in emergency departments—new-onset TIA while taking aspirin 81 mg/day. There are advocates for several different treatment regimens in these patients: increasing the aspirin dose to 325 mg/day as a new treatment; discontinuing aspirin and initiating clopidogrel 75 mg/day; discontinu-
PATIENTS ON WARFARIN

Data from the Warfarin-Aspirin Recurrent Stroke Study (WARSS), a large-scale recurrent stroke prevention trial conducted in 2206 patients, demonstrated that there was no survival benefit for noncardioembolic stroke survivors who were treated with warfarin.60,61 Yet there are patients still taking warfarin to reduce stroke risk who do not have atrial fibrillation. Unless a patient is allergic to or intolerant of antiplatelet agents such as aspirin, clopidogrel, or dipyridamole, they should not be treated with warfarin for noncardioembolic stroke risk.8 The results of other studies of anticoagulation in recurrent stroke prevention, including the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT),62 the Stroke Performance for Reporting the Improvement and Translation (SPIRIT) trial,63 and the WASID study,33 have yet to demonstrate a role for warfarin in prevention of noncardioembolic stroke.

Given these trial results, patients currently on warfarin who do not have a cardioembolic risk factor should be placed on antiplatelet therapy with aspirin, aspirin plus extended-release dipyridamole, or clopidogrel 3–5 days after discontinuing warfarin therapy. However, it would be advisable to evaluate these patients for atrial fibrillation, as patients with that risk factor should remain on warfarin.8

SUMMARY

In clinical practice, health care providers often must manage patients with complex profiles. Multiple risk factors and comorbidities complicate treatment of these individuals, and robust clinical data are often lacking as clinical trials rarely include such individuals. Guidelines offer recommendations, but these too are often based on extrapolations from clinical trial data. This is particularly true of patients at risk for ischemic stroke, as the primary underlying cause—vascular disease—has systemic implications and comorbidities that often complicate treatment.

In general, antiplatelet therapy should be used to prevent recurrent stroke in patients with TIA or noncardioembolic stroke, whereas anticoagulation therapy should be used in patients with cardioembolic stroke such as that caused by atrial fibrillation. However, therapy must be individualized to account for the patient’s full risk profile. Conditions such as dyslipidemia and hypertension must be addressed as well, as these not only give rise to stroke but also to the CAD, coronary heart disease, and ACS that may coexist with stroke. Among patients deemed suitable for antiplatelet therapy, class Ila, level A evidence supports the use of aspirin 50–325 mg/day, the combination of aspirin and extended-release dipyridamole, and clopidogrel for secondary prevention of stroke.8

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