Therapeutic Interventions for Prevention of Recurrent Ischemic Stroke

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Abstract

Patients who suffer ischemic stroke or transient ischemic attack (TIA) are at increased risk for subsequent cerebrovascular events. Secondary prevention is essential to reduce risks of recurrence and should include lifestyle modification to improve cardiovascular health, along with strict control of blood pressure, glucose, and lipids. Recurrent stroke in ischemic stroke patients is likely to be the same subtype as the initial stroke, and treatment should be unique to the stroke subtype and patient risk factors.

This article presents an overview of the recommendations for the secondary prevention of ischemic stroke or TIA and a review of the evidence supporting the role of antiplatelet therapy in managing the risk of recurrent noncardioembolic stroke. Although anticoagulants are recommended preventive treatment for cardioembolic stroke, they can increase the patient's risk of bleeding complications and are not recommended for all subtypes of ischemic stroke. The American Heart Association/American Stroke Association guidelines recommend 3 antiplatelet regimens for the secondary prevention of noncardioembolic ischemic stroke: aspirin (ASA), clopidogrel, and combined ASA + extended-release (ER) dipyridamole (DP). ASA + ER-DP is recommended over ASA alone.

Several studies have established the effectiveness of these 3 antiplatelet regimens as first-line options in the secondary prevention of noncardioembolic ischemic stroke. Clopidogrel monotherapy is a reasonable alternative for patients who cannot tolerate ASA. ASA + ER-DP has been shown to be more effective than ASA alone and does not increase the risk of bleeding. Effective secondary prevention must also address modifiable risk factors, such as obesity, smoking, and excessive alcohol consumption.

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Patients who experience a stroke or transient ischemic attack (TIA) face an increased risk of having another stroke[1-3] or other vascular event.[3,4] Approximately one quarter of the 780,000 strokes that occur in the United States each year are recurrent.[2,5] Therefore, a principal goal in managing stroke or TIA patients is to prevent another cerebrovascular event. Recommended management for the secondary prevention of stroke includes addressing modifiable risk factors, initiating long-term antithrombotic therapy, and intervening surgically, when indicated.[1]

Considerations for Secondary Prevention of Vascular Events

General Considerations

When considering the secondary prevention of vascular events, it is critical to recognize that ischemic events tend to recur in the same vascular beds; 75% to 79% of vascular events after a stroke are strokes,[5,6] and 76% to 84% of events after myocardial infarction (MI) are MI.[5] Thus, primary poststroke prevention efforts should be geared toward preventing a recurrent stroke.[5] Antithrombotic therapies should be selected according to their demonstrated efficacy in secondary stroke prevention, rather than myocardial protection.[5]

Stroke and TIA patients also bear an increased risk of suffering ischemic events in other vascular beds (eg, MI, ischemic limb),[3,4] and their risk of cardiovascular events should not be discounted. In poststroke years 1 through 10, the most common cause of death for stroke patients is cardiovascular disease (CVD).[3,7-10] In a recent study on secondary prevention of stroke in patients without known coronary heart disease (CHD), major coronary events exceeded recurrent strokes.[11] This suggests that many stroke patients have unrecognized CHD.[12] Although the primary concern when treating stroke patients should be preventing recurrent stroke, treatment plans should also consider the prevention of coronary events, especially for stroke patients who have a history of MI or peripheral arterial disease (PAD).

Cerebral vasculature appears to differ from that in other vascular beds, and stroke pathogenesis likely differs from the pathogenesis of CHD or PAD.[5] For example, the association between stroke and dyslipidemia is not as well established as dyslipidemia's association with CHD.[1,13] Stroke patients constitute a unique vascular disease population[5]; they may therefore require different preventive treatments than CHD or PAD patients. For example, certain antithrombotic agents are more likely to cause bleeding in stroke patients than in MI or

PAD patients.[5] The administration of warfarin at an anticoagulation intensity well tolerated by patients with CHD has been known to cause severe bleeding in stroke patients.[5] The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) trial found that patients with a history of stroke or TIA were more prone to episodes of major bleeding.[14] The choice of an antithrombotic therapy, therefore, should consider any adverse event risks specific to stroke patients.

Additional Considerations Unique to Ischemic Stroke Patients

If a patient's initial stroke is ischemic, another level of complexity is added to treatment decisions. Ischemic stroke comprises several pathogenic subtypes. The main etiologic subtypes are large vessel disease (LVD), small vessel disease (SVD, also called lacunar), cardioembolic, other known cause (eg, hypercoagulable state, arterial dissection), and cryptogenic (unknown cause).[1] Some risk factors vary according to ischemic stroke subtype. Risk factors more commonly associated with SVD are smoking,[15-17] diabetes,[15,18] an elevated white blood cell count,[15] and possibly hypertension (evidence of this is not conclusive).[19] Strong risk factors for LVD include smoking,[16,17,20,21] abdominal obesity,[15,22] dyslipidemia,[20,21,23,24] infection/inflammation,[25,26] and hyperhomocysteinemia.[27] Infection/inflammation[25,26] and von Willebrand factor[15] are strong risk factors for cardioembolic stroke.[25,26] Effective secondary prevention depends heavily on addressing modifiable risk factors.

Ischemic stroke subtypes differ in severity and cause varying degrees of impairment; for example, SVD is associated with a lower 5-year mortality rate and better functional outcomes,[28] whereas cardioembolic stroke has the highest 5-year mortality rate (>80%).[28] The risk of stroke recurrence also varies according to ischemic stroke subtype. SVD is associated with a lower 30-day risk of recurrence, and LVD stroke conveys the highest 30-day risk of recurrence.[28] Approximately 60% to 70% of first recurrent strokes are the same subtype as the initial stroke.[28,29]

The stroke-patient population is heterogeneous, and treatment strategies may need to be uniquely tailored not only to the ischemic stroke subtype but also to the patient. Some LVD stroke patients with severe carotid artery stenosis, extracranial vertebral artery stenosis, or hemodynamically significant intracranial stenosis will benefit from surgical or endovascular interventions.[1] Anticoagulant agents are recommended for cardioembolic stroke patients with a high-risk source of embolism, whereas antiplatelet agents are preferred for other stroke subtypes.[1] Treatment decisions should always consider the subtype of the initial ischemic stroke, and they should be individualized with regard to the patient's modifiable risk factors.

AHA/American Stroke Association Guidelines for Secondary Prevention of Stroke

Together, the American Heart Association (AHA) and American Stroke Association have established evidence-based guidelines for preventing stroke in patients who have a history of ischemic stroke or TIA.[1,12] A brief summary of these guidelines follows.

Recommendations Regarding Modifiable Risk Factors

Smoking.[1] Clinicians should urge ischemic stroke/TIA patients not to smoke and to avoid environmental smoke; counseling, nicotine products, and medications can help facilitate cessation.

Alcohol.[1] Light to moderate levels (≤2 alcoholic drinks/day for men and 1 drink/day for women) may be permitted, but heavier drinking should be discouraged.

Obesity.[1] Weight management through caloric limitation, physical activity, and behavioral counseling should be encouraged; the patient's goals should include a body mass index of 18.5 to 24.9 kg/m^2 and a waist circumference of <35 inches for women and <40 inches for men.

Physical Activity.[1] Ischemic stroke/TIA patients able to engage in physical activity are encouraged to perform ≥30 minutes of moderate exercise on most days. A supervised therapeutic regimen is recommended for patients who have poststroke disability.

Diabetes.[1] Strict control of lipid levels and blood pressure is recommended for diabetic patients;

angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) are preferred as first-line antihypertensives. Glycemic control must be strict and should target near-normal glucose levels and a hemoglobin A1C ≤7%. Note that excessively tight glucose control could result in hypoglycemia and an increased risk of mortality.

Hypertension. Antihypertensive treatment is recommended for all ischemic stroke/TIA patients past the hyperacute period, even for patients with no hypertensive history.[1] Reductions of ~10/5 mm Hg have proven beneficial.[1] Encourage lifestyle modifications known to reduce blood pressure.[1] Blood pressure targets and specific drug choices should be individualized, but evidence supports using diuretics, with or without ACE inhibitors or ARBs.[1,30]

Cholesterol and Lipid Levels. Clinicians should follow National Cholesterol Education Panel III guidelines for lifestyle modification, diet, and medications for ischemic stroke/TIA patients with elevated cholesterol, comorbid CHD, or evidence of atherosclerotic origin.[1,12] Lipid-lowering statin therapy is recommended, with a goal of reducing low-density lipoprotein cholesterol (LDL-C) levels to <100 mg/dL and <70 mg/dL in very high-risk patients.[1,12] Patients with a low level of high-density lipoprotein cholesterol can be treated with niacin or gemfibrozil.[1,12] Although the relationship between lipid levels and ischemic stroke has not been as clearly established as the relationship between lipids and cardiac disease,[1,13] evidence supports lowering lipid levels to reduce the risks of initial[31-35] and recurrent stroke.[7]

Post-hoc analysis of the 4S (Scandinavian Simvastatin Survival Study) trial showed that patients with CHD who received simvastatin trended toward fewer strokes.[13] This led to the analysis of stroke as a specified end point in the LIPID (Long-term Intervention with Pravastatin in Ischemic Disease), CARE (Cholesterol and Recurrent Events), and MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trials.[31-33] These 3 studies, along with the Heart Protection Study, found that statins were associated with a reduced risk of stroke in patients with MI, unstable angina, or other vascular disease.[31-35]

The recent SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial showed that statin therapy can reduce the risk of recurrent stroke in patients with a history of stroke or TIA.[7] This study included 4731 patients who experienced stroke or TIA within the previous 1 to 6 months, had LDL-C levels between 100 mg/dL and 190 mg/dL, and no known CHD. Patients were randomized to 80 mg of atorvastatin per day or placebo.[11] Median follow-up was 4.9 years; 11.2% of statin-treated patients and 13.1% of placebo-treated patients suffered fatal or nonfatal strokes (5-year absolute risk reduction [ARR], 2.2%; adjusted hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.71-0.99; $P = 0.03$; unadjusted $P = .05$).[7] SPARCL also observed a 3.5% ARR for major cardiovascular events (HR, 0.80; 95% CI, 0.69-0.92; $P = .002$).[11] A prespecified analysis of 4162 patients found a relative risk reduction (RRR) of 18% in stroke risk for patients receiving atorvastatin compared with placebo (HR, 0.82; 95% CI, 0.90-0.98; $P = .03$).[11] Based on the findings of the SPARCL trial, AHA/American Stroke Association updated the lipid management section of the guidelines in 2008. To reduce risks of stroke and cardiovascular events, the guidelines now recommend statin therapy for all atherosclerotic ischemic stroke or TIA patients with an LDL-C level >100 and no known CHD.[12]

Recommendations for Surgical Management in Certain LVD Patients

Extracranial Carotid Disease.[1] Carotid endarterectomy (CEA) is recommended for patients with severe ipsilateral (≥70%) carotid artery stenosis who have experienced ischemic stroke or TIA within the previous 6 months; surgery should be performed within 2 weeks of findings. CEA is also recommended in patients with moderate ipsilateral carotid artery stenosis (50%-69%), depending on age, sex, comorbidities, and the severity of initial symptoms. For patients with symptomatic severe carotid artery stenosis, carotid artery balloon angioplasty and stenting should be considered if stenosis would be difficult to access by CEA or is radiation-induced, if comorbid conditions make CEA high-risk, and if restenosis follows a prior CEA.

Extracranial Vertebrobasilar Disease.[1] Endovascular therapy (eg, angioplasty, stenting) can be performed in patients with symptomatic extracranial vertebral stenosis who demonstrate stroke or TIA

Table 1. Summary of AHA/American Stroke Association Guidelines for Antithrombotic Therapy to Prevent Stroke in Patients With Cardioembolism

Risk Factor	Recommendation
AF	Long-term oral anticoagulant treatment should be initiated in ischemic stroke/TIA patients with persistent or intermittent AF within 2 weeks of the ischemic stroke/TIA. Treatment may be delayed for patients with large infarcts or uncontrolled hypertension. Warfarin targeted to an INR of 2.5 (range, 2.0-3.0) is recommended. ASA (325 mg/day) is recommended for patients who cannot tolerate oral anticoagulants.
Acute MI and left ventricular mural thrombus	If ischemic stroke/TIA is caused by an acute MI and cardiac imaging identifies a left ventricular mural thrombus, treating with oral anticoagulants for 3 months to 1 year is reasonable, with a target INR of 2.0-3.0. Concurrent use of aspirin (≤162 mg/day, preferably enteric-coated) is recommended for patients with ischemic CHD.
Cardiomyopathy	Consider warfarin (INR, 2.0-3.0) or antiplatelet therapy to prevent recurrent stroke in ischemic stroke/TIA patients with dilated cardiomyopathy.
Rheumatic mitral valve disease	Long-term oral anticoagulants are recommended for ischemic stroke/TIA patients with rheumatic mitral valve disease, regardless of whether AF is present. Target warfarin to an INR of 2.5 (range, 2.0-3.0). To avoid increased bleeding risk, antiplatelet agents should not be added routinely. Adding ASA (81 mg/day) is suggested if embolism recurs while taking warfarin.
Mitral valve prolapse	Long-term antiplatelet therapy is reasonable for ischemic stroke/TIA patients with mitral valve prolapse.
MAC	Antiplatelet therapy may be considered for ischemic stroke/TIA patients who have MAC that has not been documented as calcific. Consider antiplatelet agents or warfarin for patients without AF who have mitral regurgitation due to MAC.
Aortic valve disease	Antiplatelet therapy may be considered for ischemic stroke/TIA patients with aortic valve disease who do not have AF.
Prosthetic heart valves	Oral anticoagulants targeted to an INR of 3.0 (range, 2.5-3.5) are recommended for ischemic stroke/TIA patients with modern mechanical prosthetic heart valves. If ischemic stroke or systemic embolism occurs despite adequate oral anticoagulant therapy, it is reasonable to add ASA (75-100 mg/day), maintaining the same target INR. For ischemic stroke/TIA patients with bioprosthetic heart valves and no other source of thromboembolism, consider warfarin, targeted to an INR of 2.0-3.0.

AF indicates atrial fibrillation; AHA, American Heart Association; ASA, aspirin; INR, international normalized ratio; MAC, mitral annular calcification; MI, myocardial infarction; TIA, transient ischemic attack.
Source: reference 1.

symptoms despite treatment with antithrombotics, statins, and other medical therapies.

Intracranial Atherosclerosis.[1] Endovascular therapy in patients with hemodynamically significant intracranial stenosis who experience symptoms despite medical treatment is considered investigational.

Recommendations for Antithrombotic Therapy in Cardioembolism

In patients with cardioembolic stroke, the primary focus is on anticoagulation (Table 1).[1] Absent a clear contraindication, atrial fibrillation (AF) patients who recently experienced stroke or TIA should be treated with oral anticoagulants, not antiplatelet therapy.[1] Ordinarily, AF patients should be initiated on oral anticoagulant therapy within 2 weeks of experiencing ischemic stroke or TIA.[1] An overall stroke RRR of 68% (95% CI, 50%-79%) has been demonstrated for patients with nonvalvular AF who receive adjusted-dose warfarin[1,36]; the optimal international normalized ratio intensity is between 2.0 and 3.0.[1] If patients with AF suffer ischemic stroke or TIA while taking anticoagulants,

current evidence does not support increasing the intensity of the anticoagulate regimen or adding antiplatelet agents.[1]

Treatment with oral anticoagulants is also recommended for patients with acute MI and left ventricular thrombus, rheumatic mitral valve disease, and prosthetic heart valves.[1] In patients with valvular heart disease, anticoagulants reduce—but do not eliminate—the likelihood of stroke[1]; therefore, recommendations vary according to the heart valves affected. Concurrent use of oral anticoagulants and lower-dose aspirin (ASA) is recommended for patients with ischemic heart disease and for stroke and TIA patients with rheumatic mitral valve disease or mechanical prosthetic heart valves who develop an embolism while taking warfarin.[1] Evidence also supports concurrent use of anticoagulants and dipyridamole (DP), alone or in combination with ASA for secondary prevention of stroke in patients with prosthetic heart valves.[1] For some patients, including those with dilated cardiomyopathy and mitral annular calcification, warfarin or antiplatelet therapy can be considered.[1] Warfarin can reduce the risk of stroke for patients with MI by 40% to 55%.[1] Warfarin has demonstrated similar stroke-preventive effects in patients with nonischemic cardiomyopathy and ischemic heart disease.[1] Ischemic stroke and TIA patients with mitral valve prolapse have not been studied in randomized trials, but AHA/American Stroke Association guidelines indicate that antiplatelet therapy is reasonable for these patients.[1]

Recommendations for Antithrombotic Therapy in TIA or Noncardioembolic Stroke (Atherosclerotic, Lacunar, or Cryptogenic Infarcts)

For all patients who suffer noncardioembolic ischemic stroke or TIA, the primary focus is antiplatelet therapy (**Table 2**).[1,12] AHA/American Stroke Association guidelines recommend antiplatelet agents rather than oral anticoagulants to reduce the risks of stroke recurrence and other cardiovascular events.[1,12] Oral anticoagulants are generally not recommended over antiplatelet agents for patients with noncardioembolic stroke,[1,12] because they have failed to demonstrate superior efficacy and they increase the patient's risk of bleeding.[1]

Antiplatelet therapy is associated with significant risk reductions (RRs) of 28% for nonfatal stroke and 16% for fatal stroke.[1,37] The US Food and Drug Administration (FDA) has approved 4 antiplatelet regimens for secondary ischemic stroke prevention: ASA, ticlopidine, clopidogrel, and combination ASA + DP.[1] Of these 4 regimens, 3 are considered acceptable options for initial therapy.[1] One study associated ticlopidine with a 21% RRR of stroke, but evidence is mixed regarding the reduction of composite outcomes; adverse events such as bleeding, neutropenia, and thrombotic thrombocytopenic purpura have been reported.[1] Clopidogrel monotherapy is comparable in efficacy and safety to ASA for secondary prevention of stroke, and it is recommended over ticlopidine because it is associated with fewer gastrointestinal symptoms and fewer incidents of hemorrhage.[1] The combination of ASA + extended-release (ER) DP is recommended over ASA monotherapy.[1,12]

Evidence from the recent ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial) trial and a meta-analysis of previous data motivated the AHA/American Stroke Association Writing Committee for the Prevention of Stroke in Patients with Stroke and Transient Ischemic Attack to upgrade this recommendation to Class I, supported by grade B evidence.[12] The recently reported PRoFESS (Prevention Regimen for Effectively Avoiding Second Stroke) trial found no significant difference in efficacy between ASA + ER-DP and clopidogrel.[38]

AHA/American Stroke Association guidelines state that there is not yet sufficient data regarding antiplatelet therapies other than ASA to make evidence-based recommendations of one over another, and choices should be individualized for each patient, taking into consideration patient allergies and comorbidities, possible side effects and costs of the medication, and rates of adherence.[1,12] New AHA/American Stroke Association guidelines are expected to be released by the end of 2008.

Use of Antiplatelet Agents in Secondary Prevention of Noncardioembolic Stroke

Aspirin

Many studies attest to the effectiveness of ASA,[1,37] which has a recurrent-event RR of approximately 13%-22%.[37,39-43] This relatively limited effi-

Table 2. Summary of AHA/American Stroke Association Guidelines for Antithrombotic Therapy to Prevent Stroke in Patients With Noncardioembolic Stroke or TIA (Specifically, Atherosclerosis, Lacunar, or Cryptogenic Infarcts)

Agent	Type	Recommendation
ASA	Antiplatelet approved by the FDA for secondary prevention of ischemic stroke	ASA (50-325 mg/day) is an acceptable option for initial therapy. For patients who experience ischemic stroke while using ASA, there is no evidence to support increasing the ASA dose; switching to another antiplatelet agent or using a combination of ASA/antiplatelet agent in this circumstance has not been carefully studied.
Ticlopidine	Antiplatelet approved by the FDA for secondary prevention of ischemic stroke	There are no specific recommendations for using ticlopidine as initial antiplatelet therapy.
CLO	Antiplatelet monotherapy approved by the FDA for secondary prevention of ischemic stroke	CLO is an acceptable option for initial therapy. CLO may be considered instead of ASA monotherapy, especially for patients who cannot tolerate ASA. Insufficient data exist to make an evidence-based recommendation of any non-ASA antiplatelet agent over another; antiplatelet choices should be individualized for each patient.
ASA + ER-DP	Antiplatelet combination approved by the FDA for secondary prevention of ischemic stroke	ASA + ER-DP is an acceptable option for initial therapy. Using a combination of ASA + ER-DP is preferred over ASA alone. Insufficient data exist to make evidence-based recommendations of any non-ASA antiplatelet agent over another; antiplatelet choices should be individualized for each patient.
ASA + CLO	Antiplatelet combination	ASA + CLO increases the risk of hemorrhage and is not routinely recommended for ischemic stroke/TIA patients unless a specific indication exists, such as acute coronary syndrome or a coronary stent.
Warfarin and other oral anticoagulants	Oral anticoagulants	Warfarin and other oral anticoagulants increase bleeding risks and monitoring costs and are not recommended.

AHA indicates American Heart Association; ASA, aspirin; CLO, clopidogrel; ER-DP, extended-release dipyridamole; FDA, US Food and Drug Administration; TIA, transient ischemic attack.
Sources: references 1, 12.

cacy indicates that treatment with ASA alone may not be aggressive enough, which has justified investigating therapy with other antiplatelet agents.

A meta-analysis of 195 randomized controlled trials conducted through 1997 (N = 135,640) found that most of the studies included ASA in at least one arm.[37] Trials compared ASA versus placebo, low- versus high-dose ASA, ASA versus another antiplatelet drug (monotherapy), and ASA versus a combination of ASA + another antiplatelet agent.[37] Antiplatelet therapy reduced the risks of nonfatal stroke by one quarter and vascular death by one sixth.[37] In patients with previous stroke or TIA, ARR of a vascular event was 36 (standard error, 6) per 1000 patients treated for 2 years.[37] No clear difference was observed in effects or serious vascular events between ASA and the other antiplatelet drugs studied.[37] In the placebo-controlled ASA trials, all ASA doses <325 mg produced a similar risk of major extracranial bleeding.[37] In 2 trials comparing different ASA dosing regimens, higher doses provided no additional benefit and increased the risk of nonfatal major gastrointestinal hemorrhage (Table 3).[44,45]

In the UK-TIA (United Kingdom Transient Ischaemic Attack) trial, 2435 patients who suffered

minor ischemic stroke or TIA were randomized to 600 mg of ASA twice daily, 300 mg of ASA once daily, or placebo; patients were followed from 1 to 7 years.[44] Risk of major stroke, MI, or vascular death was 15% lower in patients receiving ASA versus placebo, but a 1200-mg daily dose was no more effective than a 300-mg dose.[44] Intracranial hemorrhage occurred in 7 high-dose patients (6 fatalities) and 7 low-dose patients (4 fatalities); only 2 patients receiving placebo experienced an intracranial hemorrhage (1 fatality).[44] There were 39 incidents of gastrointestinal hemorrhage in patients receiving 1200 mg of ASA per day, 25 with 300 mg of ASA per day, and 9 with placebo.[44] The risks of other minor bleeding events were similarly higher in patients receiving ASA.[44]

The Dutch TIA trial randomized 3131 patients who suffered TIA or nondisabling stroke to either 30 mg or 283 mg of ASA daily and compared outcomes of vascular death, nonfatal stroke, or nonfatal MI (mean follow-up, 2.6 years).[45] The composite outcome risk was 14.7% for patients using the 30-mg dose and 15.2% for those taking 283 mg; the trial concluded that the lower dose was no less effective.[45] Compared with the 283-mg group, the 30-mg group noted fewer incidents of minor bleeding (84 vs 49, respectively) and major bleeding (53 vs 40, respectively).[45]

No evidence supports increasing the ASA dose for patients who suffer a stroke while being treated with ASA, and alternative antiplatelet agents have not been studied relative to this circumstance.[1] A subgroup analysis of the WARSS (Warfarin-Aspirin Recurrent Stroke Study) trial showed that continuing ASA therapy in patients whose treatment was initiated prior to suffering stroke was less effective than initiating ASA therapy after the incident event. For those patients who had a stroke despite receiving ASA at baseline, treatment with either ASA or warfarin resulted in similar recurrence rates at 2 years.[46]

Clopidogrel

Clopidogrel has a different mechanism of action than ASA; clopidogrel inhibits platelet aggregation induced by adenosine diphosphate.[39] Monotherapy with either clopidogrel or ASA reduces ischemic events in patients with disease in other vascular beds; thus, clopidogrel is well-suited to patients whose medical history includes CHD or PAD.[5,37,39] The pivotal CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial demonstrated that clopidogrel monotherapy was more effective than ASA monotherapy in reducing overall risk in a heterogeneous population; the difference in efficacy did not reach statistical significance in the subgroup of stroke patients studied, however.[1,5,39] CAPRIE randomized 19,185 patients with symptomatic vascular disease (including MI, PAD, or ischemic stroke) to clopidogrel (75 mg/day) or ASA (325 mg/day), with a mean follow-up of 1.91 years and a composite outcome of ischemic stroke, MI, or vascular death.[39] Intention-to-treat analysis demonstrated an 8.7% overall RRR for patients receiving clopidogrel versus ASA (P = .043).[39] The RRR in the PAD subgroup was 23.8% (P = .0028) versus 7.3% in the stroke subgroup (no significance, P = .26),[5,39] suggesting that the overall benefit derived mainly from patients with PAD.[5]

Dual therapy of clopidogrel + ASA for up to 12 months is more effective than ASA monotherapy in patients with acute coronary syndromes (ACS)[1,47-49] and is recommended for patients with coronary stents.[12] The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial enrolled 12,562 patients with ACS who presented within 24 hours of symptom onset and had no ST-segment elevation.[47] Patients were allocated randomly to clopidogrel (300-mg loading dose, 75 mg/day thereafter) or placebo, combined with ASA (75-325 mg/day), for a mean of 9 months.[47] The primary composite outcome (cardiovascular death, nonfatal MI, or stroke) occurred in 9.3% of the clopidogrel + ASA group versus 11.4% of the placebo + ASA group (RR, 0.80; P <.001).[47] Significantly more patients receiving clopidogrel versus placebo experienced major bleeding (3.7% vs 2.7%, respectively; RR, 1.38; P = .001).[47]

The CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction) trial included 3491 patients with ST-segment elevation who presented to the hospital within 12 hours of MI onset.[48] Patients were randomly allocated to clopidogrel (300-mg loading dose, 75 mg/day thereafter) or placebo, combined with ASA (150-325 mg first day, 75-162 mg/day thereafter); all patients had been scheduled to undergo angiography within 48 to 92 hours.[48] Clopidogrel conferred an ARR of 6.7% and

Table 3. Evidence for ASA Use in Secondary Prevention of Stroke From United Kingdom and Dutch TIA Trials

Trial Parameters	Inclusion Criteria	Comparisons	Outcome	Adverse Events
UK-TIA Randomized, double-blind, PLB-controlled N = 2345 Mean follow-up, 4 years (range, 1-7 years)	Experienced TIA/minor ischemic stroke ≤3 months prior	ASA 300 mg/day vs ASA 1200 mg/day vs PLB	ASA vs PLB yielded a 15% RRR for composite outcome.[a] No significant difference noted between ASA doses.	**GI hemorrhage, %:** PLB = 1 ASA 300 mg/day = 3 ASA 1200 mg/day = 5 **Upper GI symptoms, %:** PLB = 26 ASA 300 mg/day = 31 ASA 1200 mg/day = 41
Dutch TIA Randomized, double-blind N = 3131 Mean follow-up, 2-6 years	Experienced TIA/minor ischemic stroke ≤3 months prior	ASA 30 mg/day vs ASA 283 mg/day	Both ASA doses yielded similar incidences of composite outcome.[a]	**Major bleeding episodes, n:** ASA 30 mg/day, n = 40 ASA 30 mg/day, n = 49 ASA 283 mg/day, n = 53 **Minor bleeding episodes, n:** ASA 283 mg/day, n = 84

ASA indicates aspirin; GI, gastrointestinal; MI, myocardial infarction; PLB, placebo; RRR, relative risk reduction; TIA, transient ischemic attack.
[a] Nonfatal MI, nonfatal stroke, and vascular death.
Sources: references 44, 45.

an RRR of 36% (P <.001) in the primary composite end point (occluded infarct-related artery on angiography, death or recurrent MI before angiography).[48] Clopidogrel reduced the odds of recurrent MI by 30% (P = .08); there was no significant difference in the incidence of bleeding between the 2 groups.[48]

The COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) study enrolled 45,892 patients with acute MI hospitalized within 24 hours of symptom onset; 93% demonstrated ST-segment elevation.[49] Patients were randomized to clopidogrel (75 mg/day) or placebo, along with ASA (162 mg/day), until discharge or for up to 4 weeks of hospitalization (mean, 15 days in survivors).[49] The clopidogrel group saw a 9% proportional reduction in composite outcome of death, reinfarction, or stroke (P = .002).[49] The incidence of major bleeding did not increase significantly with clopidogrel versus placebo, but the incidence of minor bleeding was slightly higher (3.6% vs 3.1%, respectively; P = .005).[49] Taken together, these data suggest that combination therapy with clopidogrel + ASA has a net benefit for secondary prevention of vascular events in patients with ACS.

Patients with stroke appear to have a different response to antiplatelet agents than patients with ACS. In comparison to monotherapy using clopidogrel or ASA, the dual antiplatelet regimen of clopidogrel + ASA has not demonstrated incremental protective benefit against recurrent stroke or TIA.[50-52] Furthermore, clopidogrel + ASA may increase the risk of bleeding in patients with stroke, possibly because their cerebral vessels have increased vulnerability.[1,5,8] In the TRITON-TIMI 38 study, major bleeding occurred in more patients with a history of stroke or TIA (prasugrel, 5.0%; clopidogrel, 2.9%) than in those without this cerebrovascular history (prasugrel, 2.3%; clopidogrel, 1.8%).[14] The rate of bleeding associated with prasugrel was enough to nullify any benefit it might offer in preventing further coronary ischemia in patients with stroke.[14]

Two studies compared combination clopidogrel + ASA versus monotherapy with ASA or clopidogrel in preventing vascular events in stroke or TIA patients without ACS (Table 4). The MATCH (Management of Atherothrombosis with Clopidogrel in High-risk Patients with Recent Transient

Table 4. Evidence for Combination CLO + ASA in Secondary Prevention of Stroke From MATCH and CHARISMA Trials

Study Parameters	Inclusion Criteria	Comparisons	Outcome	Adverse Events
MATCH				
(Management of Atherothrombosis with Clopidogrel in High-risk Patients) with Recent Transient Ischemic Attack or Ischemic Stroke Randomized, double-blind, PLB-controlled N = 7599 18-month duration	Experienced ischemic stroke/TIA ≤3 months prior and a previous ischemic stroke, MI, angina pectoris, diabetes, or symptomatic PAD within 3 years prior	CLO 75 mg/day + PLB vs CLO 75 mg/day + ASA 75 mg/day	CLO + ASA was not significantly more effective than CLO + PLB in reducing primary composite outcome[a] or secondary outcome.[b] **Primary composite outcome, %:** CLO + PLB = 16.7 CLO + ASA = 15.7 (ARR, 1.0%; RRR, 6.4%; *P* = .244) **Secondary outcome, %:** CLO + PLB = 8.76 CLO + ASA = 8.14 (ARR, 0.62%; RRR, 7.1%; *P* = .353)	Incidence of major and life-threatening bleeding episodes doubled using combination therapy. **Life-threatening bleeding, %:** CLO + PLB = 1 CLO + ASA = 3 (Relative difference, 1.26%; *P* <.0001) **Major bleeding, %:** CLO + PLB = 1 CLO + ASA = 2 (Relative difference, 1.36%; *P* <.0001)
CHARISMA				
(Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) Randomized, double-blind, PLB-controlled Initial cohort: N = 15,603 Median follow-up, 28 months Post-hoc subgroup: n = 9478 Median follow-up, 27.6 months	**Initial Cohort** Patients with clinically evident CVD or multiple risk factors	ASA 75-162 mg/day + PLB vs ASA 75-162 mg/day + CLO 75 mg/day	Overall, CLO + ASA was not significantly more effective than ASA + PLB in reducing primary composite outcome[c] or secondary outcome.[d] **Primary composite outcome, %:** *All patients* ASA + CLO = 6.8 ASA + PLB = 7.3 (RR, 0.93; *P* = .22) *Patients with clinically evident CVD* ASA + CLO = 6.9 ASA + PLB = 7.9 (RR, 0.88; *P* = .046) **Secondary outcome, %:** ASA + CLO = 1.7 ASA + PLB = 2.1 (RR, 0.81; *P* = .07)	**Severe bleeding, %:** *All patients* ASA + CLO = 1.7 ASA + PLB = 1.3 (RR 1.25, *P* = .09) *Patients with clinically evident CVD* ASA + CLO = 1.6 ASA + PLB = 1.4 (*P* = .39) **Moderate bleeding, %:** ASA + CLO = 2.1 ASA + PLB = 1.3 (RR, 1.62; *P* <.001)
	Post-hoc Subgroup Analysis Prior MI, ischemic stroke, or symptomatic PAD	ASA 75-162 mg/day + PLB vs ASA 75-162 mg/day + CLO 75 mg/day	Rate of primary composite outcome was significantly lower with ASA + CLO. **Primary composite outcome, %:** ASA + CLO = 7.3 ASA + PLB = 8.8 (HR, 0.83; 95% CI, 0.72-0.96; *P* = .01)	There was no significant difference in severe bleeding. **Moderate bleeding, %:** ASA + CLO = 2.0 ASA + PLB = 1.3 (HR, 1.60; 95% CI, 1.16-2.20; *P* = .004)

ARR indicates absolute risk reduction; ASA, aspirin; CI, confidence interval; CLO, clopidogrel; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; PAD, peripheral arterial disease; PLB, placebo; RR, relative risk; RRR, relative risk reduction; TIA, transient ischemic attack.
[a]Ischemic stroke, MI, vascular death, or hospitalization for ischemic event.
[b]Fatal or nonfatal ischemic stroke.
[c]MI, stroke, or cardiovascular death.
[d]Nonfatal ischemic stroke.
Sources: references 1, 5, 12, 50-52.

Ischemic Attack or Ischemic Stroke) trial evaluated clopidogrel + ASA versus clopidogrel + placebo,[50] and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) studied clopidogrel + ASA versus ASA + placebo.[51,52]

The MATCH trial enrolled 7599 patients who recently experienced ischemic stroke or TIA, had at least 1 other risk factor for recurrence, and were already being treated with clopidogrel (75 mg/day).[50] Subjects were randomized to ASA (75 mg/day) or placebo, while continuing clopidogrel, for 18 months.[50] The clopidogrel + ASA combination did not demonstrate significantly greater efficacy than clopidogrel monotherapy (RRR, 6.4%; *P* = .244) in preventing the primary composite end point (ischemic stroke, MI, vascular death, or rehospitalization secondary to an ischemic event).[1,5,50] The incidence of life-threatening bleeding was double in the combination therapy group (2.6% vs 1.3%; *P* <.0001), and there was a significant increase in episodes of major bleeding.[5,50] The difference between the 2 regimens in the number of life-threatening bleeding episodes (47) was greater than the difference in the number of primary outcome events (40),[5,50] suggesting a poor risk-to-benefit ratio.[1] More than 50% of enrolled subjects were SVD patients, who possibly derive less benefit from antiatherothrombotic therapy and might be more susceptible to bleeding.[50] The effect this has on study results, however, is unclear.

The 28-month CHARISMA trial randomly allocated 15,603 patients to clopidogrel (75 mg/day) or placebo, in addition to ASA (75-162 mg/day). Patients had CVD or multiple risk factors for atherothrombotic events, although not all patients had an index vascular event.[4,12,51] Overall, ASA + clopidogrel did not prove to be significantly more effective than ASA + placebo in reducing the incidence of the primary composite end point (ischemic stroke, MI, or cardiovascular death).[5,51] In a prespecified subgroup analysis of 12,153 patients with documented coronary disease, PAD, ischemic stroke, or TIA within the previous 5 years, the combination of ASA + clopidogrel was slightly more effective than ASA alone in reducing risk for the primary end point (6.9% vs 7.9%, respectively; RR, 0.88; *P* = .046).[5,12,51] In patients who experienced previous cerebrovascular events, the benefit of combination therapy as secondary prevention did not reach statistical significance.[12,51] In patients using combination therapy, moderate bleeding increased significantly (2.1% vs 1.3%; RR, 1.62; *P* <.001).[5,51] A post-hoc secondary prevention analysis of 9478 CHARISMA patients with previous MI, ischemic stroke, or symptomatic PAD determined a composite end point rate of 7.3% with clopidogrel + ASA versus 8.8% with placebo + ASA (HR, 0.83; *P* = .01).[52] It was again noted that moderate bleeding increased significantly in patients using the combination regimen (2.0% vs 1.3%; *P* = .004).[52] Another post-hoc analysis of 593 CHARISMA subjects with a history of AF found that their risk of stroke increased with clopidogrel + ASA use (HR, 1.03; 95% CI, 0.49-2.10).[53] The authors concluded that this combination is not superior to ASA alone in treating patients with AF.[53]

Aspirin + Extended-release Dipyridamole

DP, a phosphodiesterase inhibitor, has a different mechanism of action than the other antiplatelet therapies. Whereas ASA inhibits thromboxane formation, DP raises intracellular levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate (cGMP), for an antiaggregation effect.[42] By increasing cGMP, DP may augment downstream signaling pathways of nitric oxide, which aids in endothelial protection.[5] ER-DP has advantages over an immediate-release formulation. Immediate-release DP has a half-life of 40 minutes, and plasma concentration would decline rapidly.[5] ER-DP also produces better gastrointestinal absorption in patients.[5]

A pivotal study showed that ASA + ER-DP was significantly more effective than ASA alone in secondary prevention of stroke and conveyed a similarly low risk of severe bleeding (**Table 5**).[42] ESPS-2 (European Stroke Prevention Study) randomized 6602 patients who recently experienced ischemic stroke or TIA to 1 of 4 therapies: ASA (25 mg twice daily), ER-DP (200 mg twice daily), ASA + ER-DP, or placebo. Patients were followed for 2 years[42] and monitored for primary end points (stroke, death) or a combined end point of stroke and death together.[42] Compared with placebo, stroke risk was reduced 18.1% with ASA

Table 5. Evidence for Combination ER-DP + ASA in Secondary Prevention of Stroke From the ESPS-2 and ESPRIT Trials

Study Parameters	Inclusion Criteria	Comparisons	Outcome	Adverse Events
ESPS-2				
(European Stroke Prevention Study) Randomized, double-blind, PLB-controlled N = 6602 2-year duration	Experienced ischemic stroke/TIA ≤3 months prior	PLB vs ASA 25 mg bid vs ER-DP 200 mg bid vs ASA 25 mg bid + ER-DP 200 mg bid	ASA + ER-DP significantly reduced risk of stroke/TIA vs placebo; combination was significantly more effective than either agent alone. **Primary outcome,[a] %:** PLB = 15.8 ASA = 12.9 ER-DP = 13.2 ASA + ER-DP = 9.9 (ASA vs PLB: RRR, 18.1%; *P* = .013) (ER-DP vs PLB: RRR, 16.3%; *P* = .039) (ASA + ER-DP vs PLB: RRR, 37%; *P* <.001) (ASA + ER-DP vs ASA: RRR, 23.1%; *P* = .006) (ASA + ER-DP vs ER-DP: RRR, 24.7%; *P* = .002) **Secondary outcome,[b] %:** PLB = 16.46 ASA = 12.63 ER-DP = 13.21 ASA + ER-DP = 10.55 (ASA vs PLB: RRR, 21.9%; *P* <.01) (ER-DP vs PLB: RRR, 18.3%; *P* <.01) (ASA + ER-DP vs PLB: RRR, 35.9%; *P* <.001)	Bleeding was significantly more frequent and more often severe with ASA-containing regimens. **Any bleeding, %:** PLB = 4.5 ASA = 8.2 ER-DP = 4.7 ASA + ER-DP = 8.7 **Moderate or severe bleeds, %:** PLB = 29.7 ASA = 39.3 ER-DP = 31.2 ASA + ER-DP = 41.7 Headache was significantly more frequent and more often a cause for discontinuation with ER-DP–containing regimens.

(Continued)

monotherapy (*P* = .013), 16.3% with ER-DP monotherapy (*P* = .039), and 37% with ASA + ER-DP (*P* <.001).[42] RRR of stroke was 23.1% with combination therapy versus ASA alone (*P* = .006) and 24.7% versus ER-DP alone (*P* = .002).[5,42] ASA + ER-DP therapy also reduced risk of the combined end point of stroke or death by 24% (*P* <.001) and the risk of TIA by 35.9% (*P* <.001).[42] The most common adverse event associated with ER-DP was headache, reported by 37% of the ER-DP cohort and 38% of the ASA + ER-DP cohort, versus 33% of patients receiving ASA monotherapy and 32% of patients receiving placebo.[42] All-site bleeding and gastrointestinal bleeding were significantly more common in patients who received ASA as monotherapy or in combination with ER-DP (*P* <.001).[42] DP did not significantly increase bleeding over ASA.[1,42] Patients receiving combination therapy and patients receiving ASA alone had similar incidence rates of severe or fatal bleeding (1.6% vs 1.2%, respectively).[5,42] Total incidence of bleeding was 8.2% in patients receiving ASA versus 8.7% in patients receiving ASA + ER-DP.[42] A post-hoc analysis of ESPS-2 data for cardiac patients who received ER-DP showed no increase in risk for MI, angina, or mortality.[1,5]

■ **Table 5.** Evidence for Combination ER-DP + ASA in Secondary Prevention of Stroke From the ESPS-2 and ESPRIT Trials *(Continued)*

Study Parameters	Inclusion Criteria	Comparisons	Outcome	Adverse Events
ESPRIT				
(European/ Australasian Stroke Prevention in Reversible Ischemia Trial) Randomized, open-label with blinded outcome assessment N = 2739 Mean follow-up, 3.5 years	Experienced ischemic stroke/TIA ≤6 months prior	ASA 30-325 mg/day vs ASA + DP 200 mg bid (fixed dose or free combination; 83% used ER-DP)	ARR was 1%/year in primary composite outcome[c] with ASA + DP vs ASA (95% CI, 0.1-1.8) **Primary composite, %:** ASA + DP = 12.7 ASA = 15.7 (HR, 0.80; 95% CI, 0.66-0.98) **Ischemic stroke, %:** ASA + DP = 7.0 ASA = 8.4 (HR, 0.84; 95% CI, 0.64-1.10) **Cardiac events, %:** ASA + DP = 3.2 ASA = 4.4 (HR, 0.73; 95% CI, 0.49-1.08)	**Major bleeding, %:** ASA + DP = 2.6 ASA = 3.9 (HR, 0.67; 95% CI, 0.44-1.02) In the ASA + DP group 26% discontinued therapy because of headaches. Most who discontinued ASA therapy offered medical reasons (eg, new stroke/TIA or indications for anticoagulant therapy). **Discontinued therapy, %:** ASA + DP = 34 ASA = 13

ARR indicates absolute risk reduction; ASA, aspirin; DP, dipyridamole; ER-DP, extended-release dipyridamole; PLB, placebo; RR, relative risk; RRR, relative risk reduction; TIA, transient ischemic attack.
[a]Fatal or nonfatal stroke.
[b]TIA.
[c]Vascular death, nonfatal stroke, nonfatal MI, and major bleeding.
Sources: references 5, 12, 42, 43.

A recent open-label study confirmed the findings of ESPS-2.[5,8,43] ESPRIT (European/Australasian Stroke Prevention in Reversible Ischemia Trial) randomized 2739 patients with recent TIA or minor ischemic stroke to ASA or ASA + DP (separately or as a fixed-dose combination).[43] Each patient's physician determined the daily dose of ASA, which ranged from 30 to 325 mg (median, 75 mg/day); DP was administered at a dose of 200 mg twice daily.[43] Of patients randomized to ASA + DP, 83% received ER-DP.[43] Mean follow-up was 3.5 years.[43] Although treatment allocation was not blinded, outcome assessment was blinded.[43]

On intention-to-treat analysis, the incidence rate of the composite primary outcome (nonfatal MI, nonfatal stroke, vascular death, or major bleeding complication) was significantly lower in patients receiving ASA + DP than in those using ASA alone (12.7% vs 15.7%, respectively; HR, 0.80; 95% CI, 0.66-0.98).[43] The ASA + DP group noted 35 major bleeding complications versus 53 for the ASA cohort (HR, 0.67; 95% CI, 0.44-1.02).[43] More patients on combination ASA + DP discontinued therapy than those receiving ASA alone; this was primarily because of adverse effects, most notably headache.[43]

The investigators also conducted a meta-analysis that included the ESPRIT trial data and findings from 5 previous studies comparing ASA with ASA + DP; 4 of the 6 studies evaluated only the immediate-release formulation of DP. The meta-analysis demonstrated an overall RR of 0.82 for composite stroke, MI, or vascular death in patients receiving combination therapy (95% CI, 0.74-0.91), and an RRR of 18% compared with ASA monotherapy.[43]

Results of the PRoFESS trial were presented in May 2008 at the XVII European Stroke Conference.[38] This randomized, double-blind trial (N = 20,332) compared the efficacy of 2 antiplatelet therapies in secondary prevention of recurrent stroke.[38] Recurrent stroke rates were similar in patients receiving ER-DP

+ ASA and clopidogrel therapy (9.0% vs 8.8%, respectively); no significant differences were observed in the incidence of the composite end point (stroke, MI, or vascular death) between ER-DP + ASA and ASA monotherapy (13.1% vs 13.1%, respectively).[38] Ischemic strokes occurred less often in patients receiving ER-DP + ASA compared with ASA (7.7% vs 7.9%, respectively), whereas hemorrhagic strokes occurred more often (0.8% vs 0.4%, respectively).[38] More major hemorrhagic events occurred in the ER-DP + ASA cohort than in the ASA group (4.1% vs 3.6%, respectively; HR, 1.15; 95% CI, 1.00-1.32), but no significant difference was found in the benefit-to-risk ratio expressed as combined recurrent stroke and major hemorrhage (11.7% vs 11.4%, respectively; HR, 1.03; 95% CI, 0.95-1.11).[38]

Evidence to date does not support differential effectiveness of antiplatelet therapies[1] among the different noncardioembolic subtypes. Ongoing trials, including SPS3 (Secondary Prevention of Small Subcortical Strokes) and ARCH (Aortic Arch Related Cerebral Hazard), should seek further understanding in this area.

Conclusion

In ischemic stroke and TIA patients, preventing subsequent cerebrovascular events is a primary goal of treatment. An individual's risk factors for recurrent stroke should be addressed, implementing lifestyle modifications and controlling blood pressure and levels of glucose and lipids.[1]

Other secondary prevention treatments for ischemic stroke patients should be geared toward preventing recurrence of a stroke that is the same subtype as the initial event. Patients who experience LVD stroke—particularly with carotid bifurcation area stenosis—can benefit from surgical or endovascular interventions.[1] Anticoagulants are recommended for most cardioembolic stroke types.[1] For other ischemic stroke subtypes, FDA-approved antiplatelet agents are recommended and preferred over anticoagulants,[1,12] which can increase the risk of bleeding complications.[1]

ASA, clopidogrel, and ASA + ER-DP are recognized as accepted first-line options for secondary prevention of noncardioembolic ischemic stroke.[1,8] For patients who cannot tolerate regimens containing ASA, clopidogrel monotherapy is a reasonable alternative.[1,12] Although dual antiplatelet therapy with ASA + clopidogrel has been shown to benefit patients with ACS,[1,12] it is not recommended as secondary prevention therapy in stroke or TIA patients because of the incrementally increased risk of hemorrhage without benefit of additional protection.[1] Growing evidence supports using combination ASA + ER-DP over ASA monotherapy in the ischemic stroke population because it provides additional benefit and has a similar safety profile,[1,12] although the PRoFESS trial did not confirm a clear advantage to using this agent rather than clopidogrel.

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