CME CREDIT | ***EDUCATIONAL OBJECTIVE:*** The reader will understand the current indications and rationale for aspirin, dipyridamole, and clopidogrel to prevent recurrent stroke

ATIZAZUL H. MANSOOR, MD
Department of Cardiovascular Services, PinnacleHealth Cardiac and Vascular Institute, PinnacleHealth Hospitals, Harrisburg, PA

MOHAMMAD T. MUJTABA, MD
Department of Cardiology, Hartford Hospital, Hartford, CT

BRIAN SILVER, MD
Associate Professor of Neurology, Department of Neurology, Rhode Island Hospital, Brown Alpert Medical School, Providence, RI

Antiplatelet therapy to prevent recurrent stroke: Three good options

ABSTRACT

Drugs that prevent platelets from sticking together—ie, aspirin, dipyridamole, and clopidogrel—are an important part of therapy to prevent recurrence of ischemic stroke of atherosclerotic origin. We discuss current indications for these drugs and review the evidence behind our current use of aspirin, dipyridamole, and clopidogrel.

KEY POINTS

After a stroke, antiplatelet therapy lowers the rate of recurrent nonfatal stroke by about 25%.

Aspirin is the most established, best tolerated, and least expensive of the three approved drugs.

Adding dipyridamole to aspirin increases the efficacy, with a 22% reduction in relative risk, but only a 1% reduction in absolute risk.

Clopidogrel is similar in efficacy to aspirin and to dipyridamole.

All three agents are regarded as equal and appropriate for secondary prevention of stroke; the choice is based on individual patient characteristics.

A small number of strokes result from atherosclerotic disease of the common carotid bifurcation, and patients with symptomatic carotid disease can be treated with the combination of surgery or stenting and drug therapy, or with drug therapy alone.

AFTER A STROKE, an important goal is to prevent another one.[1,2] And for patients who have had an ischemic stroke or transient ischemic attack (TIA) due to atherosclerosis, an important part of secondary preventive therapy is a drug that inhibits platelets—ie, aspirin, extended-release dipyridamole, or clopidogrel. This has taken years to establish.

In the following pages, we discuss the antiplatelet agents that have been shown to be beneficial after stroke of atherosclerotic origin, and we briefly review the indications for surgery and stenting for the subset of patients whose strokes are caused by symptomatic carotid disease.

(Although managing modifiable risk factors such as smoking, hypertension, diabetes, and dyslipidemia is also important, we will not cover this topic here, nor will we talk about hemorrhagic stroke or stroke due to atrial fibrillation. Also not discussed here is cilostazol, which, although shown to be effective in preventing recurrent stroke when compared with placebo and aspirin,[3,4] has not been approved for this use by the US Food and Drug Administration, as of this writing.)

HOW WE REVIEWED THE LITERATURE

We searched PubMed using the terms aspirin, acetylsalicylic acid, clopidogrel, and/or dipyridamole, in combination with stroke, cerebral ische(ae)mia, transient ische(ae)mic attacks, or retinal artery occlusion. We reviewed only clinical trials or meta-analyses of these drugs for either primary or secondary prevention of cerebrovascular disease.

As our aim was to review the topic and not to perform a meta-analysis, no cutoffs were

used to exclude trials. The references in the selected papers were also reviewed to expand the articles. Finally, the references in the current American Heart Association and American Stroke Association secondary stroke prevention guideline were also reviewed.

For a summary of the trials included in our review, see the Data Supplement as an appendix to the online version of this article at www.ccjm.org.

■ ASPIRIN: THE GOLD STANDARD

Prescribed by Hippocrates in the form of willow bark extract, aspirin has long been known for its antipyretic and anti-inflammatory properties. Its antiplatelet and antithrombotic properties, first described in 1967 by Weiss and Aledort,[5] are mediated by irreversible inhibition of cyclooxygenase, leading to decreased thromboxane A2, a platelet-aggregation activator.

Fields et al,[6,7] in 1977 and 1978, reported that in a controlled trial in patients with TIA or monocular blindness, fewer subsequent TIAs occurred in patients who received aspirin, although the difference was not statistically significant, with lower rates of events only in nonsurgical patients. Over the next 20 years, the results remained mixed.

The Danish Cooperative study[8] (1983) found no significant difference in the rate of recurrent stroke with aspirin vs placebo.

AICLA.[9] The *Accidents Ischémiques Cérébraux Liés à l'Athérosclérose* study of 1983 did find a difference. However, both the Danish Cooperative study and the AICLA were limited by lacking standardized computed tomographic imaging to rule out hemorrhagic stroke and by being relatively small.

The Swedish Cooperative Study[10] (1987) found no statistical difference between high-dose aspirin and placebo in preventing recurrent vascular events (stroke, TIA, or myocardial infarction [MI]) 1 to 3 weeks after a stroke. However, it had several limitations: the aspirin group contained more patients with ischemic heart disease (who are more likely to die of cardiac causes), there were significantly more men in the aspirin group, and nearly one-fourth of the deaths were a result of the initial stroke, potentially masking the

effect of aspirin in secondary prevention.

Later studies began to show a consistently favorable effect of aspirin.

Boysen et al[11] in 1988 reported a nonsignificant trend toward fewer adverse events with aspirin.

UK-TIA.[12] The United Kingdom Transient Ischaemic Attack trial in 1991 found a similar trend.

SALT.[13] The Swedish Aspirin Low-dose Trial, also in 1991, showed a significant 18% lower rate of stroke or death in patients with recent TIA, minor stroke, or retinal occlusion treated with low-dose aspirin. The inclusion of patients with TIA helped broaden the population that might benefit. However, the study may have favored the aspirin group by having a run-in period in which patients were nonrandomly treated either with aspirin or with anticoagulation at the discretion of the patient's physician and, if they suffered "several" TIAs, a stroke, retinal artery occlusion, or MI, were removed from the study.

ESPS-2.[14] The second European Stroke Prevention Study in 1996 added to the evidence that aspirin prevents recurrent stroke. Patients with a history of TIA or stroke were randomized in double-blind fashion to four treatment groups: placebo, low-dose aspirin, dipyridamole, or aspirin plus dipyridamole. At 2 years, strokes had occurred in 18% fewer patients in the aspirin group than in the placebo group, and TIAs had occurred in 21.9% fewer. However, aspirin was associated with an absolute 0.5% increase in severe and fatal bleeding. The power of the study was limited because patients from one center were excluded because of "serious inconsistencies in patient case record forms and compliance assay determinations."[14]

Comment. The mixed results with aspirin in studies predating ESPS-2 were partly because the study populations were too small to show benefit.

ATT.[15] The Antithrombotic Trialists' Collaboration performed a meta-analysis that conclusively confirmed the benefit of aspirin after stroke or TIA. The investigators analyzed individual patient data pooled from randomized controlled trials published before 1997 that compared antiplatelet regimens (mostly aspirin) against placebo and against

Prescribed by Hippocrates in the form of willow bark extract, aspirin has long been known for its antipyretic and anti-inflammatory properties

each other. The rates of vascular events were 10.7% with treatment vs 13.2% with placebo ($P < .0001$). Antiplatelet therapy was particularly effective in preventing ischemic stroke, with a 25% reduction in the rate of nonfatal stroke, and with an overall absolute benefit in stroke prevention across all high-risk patient groups. This translated to 25 fewer nonfatal strokes per 1,000 patients treated with antiplatelet therapy.

What is the optimal aspirin dose?
Studies of aspirin have used different daily doses—the earliest studies used large doses of 1,000 to 1,500 mg.[6–10]

Boysen et al[11] in 1988 found a trend toward benefit (not statistically significant) with doses ranging from 50 mg to 100 mg.

In 1991, three separate studies found that higher doses of aspirin were no more effective than lower doses.

The UK-TIA trial[12] compared aspirin 300 mg vs 1,200 mg and found a higher risk of gastrointestinal bleeding with the higher dose.

The SALT Collaborative Group[13] found 75 mg to be effective.

The Dutch TIA trial[16] compared 30 mg vs 283 mg; end point outcomes were similar but the rate of adverse events was higher with 283 mg.

ESPS-2 was able to show efficacy at a dose of only 50 mg.[14]

Taylor et al[17] compared lower doses (81 or 325 mg) vs higher doses (650 or 1,300 mg) for patients undergoing carotid endarterectomy and found that the risk of adverse events was twice as high with the higher doses.

The ATT Collaboration[15] found that efficacy was 40% lower with the highest dose of aspirin than with the lowest doses.

Algra and van Gijn[18] performed a meta-analysis of all these studies and found no difference in risk reduction between low-dose and high-dose aspirin, with an overall relative risk reduction of 13% at any dose above 30 mg.

Campbell et al,[19] in a 2007 review, found that doses greater than 300 mg conferred no benefit, and that rapid and maximum suppression of thromboxane A2 can be achieved by chewing or ingesting dissolved forms of aspirin 162 mg.

Conclusion. Aspirin doses higher than 81 mg (the US standard) confer no greater benefit and may even decrease the efficacy of aspirin. In an emergency, rapid suppression of thromboxane A2 can be achieved by chewing a minimum dose of 162 mg.

■ DIPYRIDAMOLE CAN BE ADDED TO ASPIRIN

In 1967, Weiss and Aledort[5] found that aspirin's antiplatelet effect could be blocked by adenosine diphosphate, which is released by activated platelet cells and is an essential part of thrombus formation. Adjacent platelets are then activated, leading to up-regulation of thromboxane A2 and glycoprotein IIb/IIIa receptors and resulting in a cascade of platelet activation and clot formation.[20] Dipyridamole inhibits aggregation of platelets by inhibiting their ability to take up adenosine diphosphate.

Studies of dipyridamole
AICLA.[9] Bousser et al[9] randomized patients who suffered one or more cerebral or retinal infarctions to receive placebo, aspirin 1 g, or aspirin 1 g plus dipyridamole 225 mg. Aspirin was significantly better than placebo in preventing a recurrence of stroke. The event rate with aspirin plus dipyridamole was similar to the rate with aspirin alone, although on 2-by-2 analysis, the difference between placebo and aspirin plus dipyridamole did not reach statistical significance. However, the rate of carotid-origin stroke was 17% with aspirin alone and 6% with aspirin plus dipyridamole, a statistically significant difference.

Thus, this study confirmed the benefit of aspirin in preventing ischemic events but did not fully support the addition of dipyridamole, except in preventing stroke of carotid origin. The study had a number of limitations: the sample size was small, TIA was not included as an end point, computed tomography was not required for entry, and many patients were lost to follow-up, decreasing the statistical power of the trial.

The ESPS study[21] was also a randomized controlled trial of aspirin plus dipyridamole vs placebo. But unlike AICLA, ESPS included patients with TIA.

ESPS found a 38.1% relative risk reduction in stroke with aspirin plus dipyridamole

Aspirin doses > 81 mg confer no greater benefit and may even decrease the efficacy

compared with placebo, and a 30.6% reduction in death from all causes. Interestingly, patients who had a TIA as the qualifying event had a lower end-point incidence and larger end-point reduction than those who had a stroke as the qualifying event. However, ESPS did not resolve the question of whether adding dipyridamole to aspirin affords any benefit over aspirin alone.

ESPS-2[14] hoped to answer this question. Patients were randomized to placebo, aspirin, dipyridamole, or aspirin plus dipyridamole. On 2 x 2 analysis, the dipyridamole group had a 16% lower rate of recurrent stroke than the placebo group, and patients on aspirin plus dipyridamole had a 37% lower rate. Aspirin plus dipyridamole yielded a 23.1% reduction compared with aspirin alone, and a 24.7% reduction compared with dipyridamole alone. Similar benefit was reported for the end point of TIA with combination therapy compared with either agent alone.

However, nearly 25% of patients had to withdraw because of side effects, particularly in the dipyridamole-alone and aspirin-dipyridamole groups, and, as mentioned above, verification of compliance in the aspirin group was an issue.[14,22] Nevertheless, ESPS-2 clearly showed that aspirin plus dipyridamole was better than either drug alone in preventing recurrent stroke. It also showed the effectiveness of dipyridamole, which AICLA and ESPS could not do, because it had a larger study population, used a lower dose of aspirin, and perhaps because it used an extended-release form of dipyridamole.[23]

The ATT meta-analysis[15] showed a clear benefit of antiplatelet therapy. However, much of this benefit was derived from aspirin therapy, with the addition of dipyridamole resulting in a nonsignificant 6% reduction of vascular events. Most of the patients on dipyridamole were from the ESPS-2 study. In effect, the ATT was a meta-analysis of aspirin, as aspirin studies dominated at that time.

A Cochrane review[24] publsihed in 2003 attempted to rectify this by analyzing randomized controlled trials of dipyridamole vs placebo.[24] Like the ATT meta-analysis, it did not bear out the benefits of dipyridamole: compared with placebo, there was no effect on the rate of vascular death, and only a minimal

benefit in reduction of vascular events—and this latter point is only because of the inclusion of ESPS-2.

Directly comparing aspirin plus dipyridamole vs aspirin alone, the reviewers found no effect on the rate of vascular death, and with the exclusion of ESPS-2, no effect on vascular events.

The Cochrane review had the same limitation as the ATT meta-analysis, ie, dependence on a single trial (ESPS-2) to show benefit, and perhaps the fact that ESPS-2 was the only study that used an extended-release form of dipyridamole.

Leonardi-Bee et al[25] performed a meta-analysis that overcame the limitation of ESPS-2 being the only study at the time with positive findings: they used pooled individual patient data from randomized trials and analyzed them en masse. Patients on aspirin plus dipyridamole had a 39% lower risk than with placebo and a 22% lower risk than with aspirin alone. Unlike the ATT and the Cochrane review, excluding ESPS-2 did not alter the statistically significant lower stroke rate with aspirin plus dipyridamole compared with controls. This meta-analysis helped to confirm ESPS-2's finding of the additive effect of aspirin plus dipyridamole compared with aspirin and placebo control.

ESPRIT.[26,27] The European/Australasian Stroke Prevention in Reversible Ischaemia Trial confirmed these findings. This randomized controlled trial compared aspirin plus dipyridamole against aspirin alone in patients with a TIA or minor ischemic stroke of arterial origin within the past 6 months. For the primary end point (death from all vascular causes, nonfatal stroke, nonfatal MI, nonfatal major bleeding complication), the hazard ratio was 0.80 favoring aspirin plus dipyridamole, with a number needed to treat of 104 over a mean of 3.5 years (absolute risk reduction of 1% per year). Importantly, twice as many patients taking aspirin plus dipyridamole discontinued the medication.

Caveats to interpreting this study are that it was not blinded, the aspirin doses varied (although the median aspirin dose—75 mg—was the same between the two groups), and not all patients received the extended-release form of dipyridamole.

> **Unfortunately, many patients stop taking dipyridamole because of side effects, primarily headache**

Conclusions about dipyridamole

ESPS-2, ESPRIT, and the meta-analysis by Leonardi-Bee et al showed that aspirin plus dipyridamole is more effective than placebo or aspirin alone in secondary prevention of vascular events, including stroke. Also, extended-release dipyridamole appears to be more effective.

Unfortunately, many patients stop taking dipyridamole because of side effects (primarily headache).

Based on the results of ESPRIT, the absolute benefit of dipyridamole used alone may be small.

■ CLOPIDOGREL: SIMILAR TO ASPIRIN IN EFFICACY?

Like dipyridamole, clopidogrel targets adenosine diphosphate to prevent clot formation, blocking its ability to bind to its receptor on platelets. It is a thienopyridine and, unlike its sister drug ticlopidine, does not seem to be associated with the potentially serious side effects of neutropenia. However, a few cases of thrombotic thrombocytopenic purpura have been reported.[28] The other drugs in this class have not been evaluated in clinical trials for secondary stroke prophylaxis.

Trials of clopidogrel

CAPRIE.[29] The Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events trial, in 1996, was one of the first to compare the clinical use of clopidogrel against aspirin. It was a randomized controlled noninferiority trial in patients over age 21 (inclusion criteria: ischemic stroke, MI, or peripheral arterial disease) randomized to aspirin 325 mg once daily or clopidogrel 75 mg once daily. Patients were followed for 1 to 3 years.

Patients on clopidogrel had a relative risk reduction of 8.7% in primary events (ischemic stroke, MI, or vascular death); patients on aspirin were at significantly higher risk of gastrointestinal hemorrhage. Patients with peripheral arterial disease as the qualifying event did particularly well on clopidogrel, with a significant relative risk reduction of 23.8%.

Limitations of the CAPRIE trial included its inability to measure the effect of treatment on individual outcomes, particularly stroke,

and the fact that the relative risk reduction for patients with stroke as the qualifying event was not significant (P = .66). Another limitation was that it did not use TIA as an entry criterion or as part of the composite outcome. Also, the relative risk reduction had a wide confidence interval, and a large number of patients discontinued therapy for reasons other than the defined outcomes.

Nevertheless, the CAPRIE trial showed clopidogrel to be an effective antiplatelet prophylactic, particularly in patients with peripheral artery disease, but with no discernible difference from aspirin for those patients with MI or stroke as a qualifying event.

MATCH.[30] The Management of Atherothrombosis With Clopidogrel in High-risk Patients trial hoped to better assess clopidogrel's efficacy, particularly in patients with ischemic cerebral events. Cardiac studies leading up to MATCH suggested that adding a thienopyridine to aspirin might offer additive benefit in reducing the rate of vascular outcomes.[15,31] MATCH randomized high-risk patients (inclusion criteria were ischemic stroke or TIA and a history of vascular disease) to clopidogrel or to aspirin plus clopidogrel.

There was a nonsignificant 6.4% relative risk reduction in the combined primary outcome of MI, ischemic stroke, vascular death, other vascular death, and re-hospitalization for acute ischemic events in the aspirin-plus-clopidogrel group compared with clopidogrel alone. However, this came at the cost of double the number of bleeding events in the combination group, mitigating most of the benefit of combination therapy.

An important caveat in interpreting the results of MATCH, as compared with the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, is that aspirin was being added to clopidogrel, not vice versa. CURE, which looked at the addition of clopidogrel to aspirin vs aspirin alone in cardiac patients, found a significant reduction of ischemic events taken as a group (relative risk 0.8), and a trend toward a lower rate of stroke (relative risk 0.86, but 95% confidence interval encompassing 1) for aspirin plus clopidogrel vs aspirin alone.[31] However, patients in the CURE trial did not have high-risk vasculopathy per se but rather non-ST-elevation MI, perhaps skewing

Like dipyridamole, clopidogrel targets adenosine diphosphate to prevent clot formation

the benefit of combination therapy and lessening the risk of intracranial bleeding.

CHARISMA.[32] The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial, like the CURE trial, compared aspirin plus clopidogrel vs aspirin in patients with established cardiovascular, cerebrovascular, or peripheral arterial disease, or who were at high risk of events. As in the MATCH study, the findings for combination therapy were a nonsignificant relative risk of 0.93 for primary events (MI, stroke, or death from cardiovascular causes), and a significant reduction of secondary end points (primary end point event plus TIA or hospitalization for unstable angina) (relative risk 0.92, P = .04).

Importantly, combination therapy significantly increased the rate of bleeding events. In asymptomatic patients (those without documented vascular disease but with multiple atherothrombotic risk factors), there was actually harm with combined treatment. Conversely, for symptomatic patients (those with documented vascular disease), there was a negligible, but significant reduction in primary end points.

The result was that in patients with documented vascular disease, aspirin plus clopidogrel combination therapy provided little or no benefit over aspirin alone. For patients with elevated risk factors but no documented vascular burden, there may actually be harm from combination therapy.

PRoFESS.[33] Logically following is the question of whether aspirin plus dipyridamole offers any benefit over clopidogrel as a stroke prophylactic. The Prevention Regimen for Effectively Avoiding Second Strokes trial hoped to answer this by comparing clopidogrel against aspirin plus dipyridamole, both with and without telmisartan, in patients with recent stroke.

The rate of recurrent stroke was similar in the two groups, but there were 25 fewer ischemic strokes in patients on aspirin plus dipyridamole, offset by an increase in hemorrhagic strokes. Rates of secondary outcomes of stroke, death, or MI were nearly identical between the groups. Early discontinuation of treatment was significantly more frequent in those patients taking aspirin plus dipyridamole, meaning better compliance for those taking clopidogrel.

Initially, patients were to be randomized to either aspirin plus dipyridamole or aspirin plus clopidogrel. However, after MATCH[30] demonstrated a significantly higher bleeding risk with aspirin plus clopidogrel, patients were changed to clopidogrel alone. But despite this, the bleeding risk was still higher with aspirin plus dipyridamole.

During the trial, the entry criteria were expanded, allowing for the inclusion of younger patients and those with less recent strokes; but despite this change, the study remained underpowered to demonstrate its goal of noninferiority. Thus, it showed only a trend of noninferiority of clopidogrel vs aspirin plus dipyridamole.

What the clopidogrel trials tell us

Clopidogrel confers a benefit similar to that of aspirin (as shown in the CAPRIE study).[29] Although aspirin plus dipyridamole confers greater benefit than aspirin alone (as shown in the ESPS-2,[14] Leonardi-Bee,[25] and ESPRIT[26] studies), aspirin plus dipyridamole is not superior to clopidogrel, and may even be inferior.[34]

■ WARFARIN FOR ATRIAL FIBRILLATION ONLY

Warfarin acts by disrupting the coagulation cascade rather than acting at the site of platelet plug formation. In theory, warfarin should be as effective as the antiplatelet drugs in preventing clot formation, and so it was thought to possibly be effective in preventing stroke of arterial origin.

However, in at least three studies, warfarin increased the risk of death, MI, and hemorrhage, with perhaps a slight decrease in the risk of recurrent stroke in patients with suspected stroke or TIA.[35–37] This should be differentiated from stroke originating from cardiac dysrhythmias, for which warfarin has clearly been shown to be beneficial.[28]

■ THREE GOOD MEDICAL OPTIONS FOR PREVENTING STROKE RECURRENCE

Antiplatelet therapy offers benefit in the primary and secondary prevention of stroke, with a 25% reduction in the rate of nonfatal stroke and a 17% reduction in the rate of death due to vascular causes.[15]

Regardless of the etiology, antiplatelet drug therapy is the standard of care for preventing a second stroke in all cases of atherosclerotic stroke

Aspirin is the best established

Aspirin is the best established, best tolerated, and least expensive of the three contemporary agents. Further, it is also the agent of choice for acute stroke care, to be given within 48 hours of a stroke to mitigate the risk of death and morbidity. The data for other agents in acute stroke management remain limited.[38]

Aspirin plus dipyridamole

Aspirin plus dipyridamole is slightly more efficacious than aspirin alone, and it is an alternative when aspirin is ineffective and when the patient can afford the additional cost. Aspirin plus dipyridamole offers up to a 22% relative risk reduction (but a small reduction in absolute risk) of stroke compared with aspirin alone, as demonstrated by ESPS-2,[14] Leonardi-Bee et al,[25] and ESPRIT.[26]

When is clopidogrel appropriate?

Up to one-third of patients may not tolerate aspirin plus dipyridamole because of side effects. Clopidogrel is an option for these patients. The CAPRIE study[29] showed clopidogrel similar in efficacy to aspirin.

In contrast to aspirin plus dipyridamole, there is clearly no benefit to combining aspirin and clopidogrel for ischemic stroke prophylaxis. And data from PRoFESS[33] suggested the combination was qualitatively inferior to aspirin plus dipyridamole. However, the PRoFESS trial was underpowered to fully bear this out.

Therefore, current guidelines consider all three agents as appropriate for secondary prevention of stroke. One is not preferred over another, and the selection should be based on individual patient characteristics and affordability.[28]

■ CAROTID SURGERY OR STENTING: BENEFITS AND LIMITATIONS

Atherosclerosis is the most common cause of stroke, and atherosclerosis of the common carotid bifurcation accounts for a small but significant percentage of all strokes.[39–41]

The degree of carotid stenosis and whether it is producing symptoms influence how it should be managed. For patients with symptomatic carotid stenosis of more than 70%, multicenter randomized trials have shown that surgery (ie, carotid endarterectomy) added to medical therapy decreases the rate of recurrent stroke by up to 17% and the rate of combined stroke and death by 10% to 12% over a 2- to 3-year follow-up period (level of evidence A).[42–44] No study has proven the efficacy of surgery in patients with symptomatic stenosis of less than 50%.[43,44]

Similarly, in asymptomatic carotid disease, preventive surgery is a beneficial adjunct to medical therapy in certain patients. An approximate 6% reduction in the rate of stroke or death over 5 years has been shown in patients with moderate stenosis (> 60%), with men younger than age 75 and with greater than 70% stenosis deriving the most benefit.[45–47]

However, these robust, positive results with surgical intervention should not overshadow the importance of intensive and guided medical therapy, which has been shown to mitigate the risk of stroke.[48,49]

Is stenting as good as surgery? In the multicenter randomized Carotid Revascularization Endarterectomy vs Stenting Trial (CREST), stenting resulted in similar rates of stroke and MI in patients with symptomatic and asymptomatic disease.[50] However, stenting carried a greater risk of perioperative stroke, and endarterectomy carried a greater risk of MI. Those under age 70 benefited more from stenting, and those over age 70 benefited more from endarterectomy.

But another fact to keep in mind is that the relationship between carotid narrowing and an ipsilateral stroke is not necessarily direct. Two follow-up studies in patients from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) found that up to 45% of strokes that occurred after intervention in the distribution of the asymptomatic stenosed carotid artery were unrelated to the stenosis.[51,52] Moreover, up to 20% of subsequent strokes in the distribution of the symptomatic artery were not of large-artery origin, increasing up to 35% for those with stenosis of less than 70%.[51] Clearly, thorough screening of those with presumed symptomatic stenosis is needed to eliminate other possible causes. ■

The choice of antiplatelet regimen should be based on individual patient characteristics and affordability

REFERENCES

1. **Zivin JA**. Approach to cerebrovascular diseases. In: Goldman L, Schafer AI, editors. Goldman's Cecil Medicine. 24th ed. Philadelphia, PA: Elsevier, 2012:2304–2309.
2. **Samsa GP, Bian J, Lipscomb J, Matchar DB**. Epidemiology of recurrent cerebral infarction: a Medicare claims-based comparison of first and recurrent strokes on 2-year survival and cost. Stroke 1999; 30:338–349.
3. **Gotoh F, Tohgi H, Hirai S, et al**. Cilostazol Stroke Prevention Study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction. J Stroke Cerebrovasc Dis 2000; 9:147–157.
4. **Shinohara Y, Katayama Y, Uchiyama S, et al; CSPS 2 group**. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. Lancet Neurol 2010; 9:959–968.
5. **Weiss HJ, Aledort LM**. Impaired platelet-connective-tissue reaction in man after aspirin ingestion. Lancet 1967; 2:495–497.
6. **Fields WS, Lemak NA, Frankowski RF, Hardy RJ**. Controlled trial of aspirin in cerebral ischemia. Stroke 1977; 8:301–314.
7. **Fields WS, Lemak NA, Frankowski RF, Hardy RJ**. Controlled trial of aspirin in cerebral ischemia. Part II: surgical group. Stroke 1978; 9:309–319.
8. **Sorensen PS, Pedersen H, Marquardsen J, et al**. Acetylsalicylic acid in the prevention of stroke in patients with reversible cerebral ischemic attacks. A Danish cooperative study. Stroke 1983; 14:15–22.
9. **Bousser MG, Eschwege E, Haguenau M, et al**. "AICLA" controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia. Stroke 1983; 14:5–14.
10. High-dose acetylsalicylic acid after cerebral infarction. A Swedish Cooperative Study. Stroke 1987; 18:325–334.
11. **Boysen G, Sørensen PS, Juhler M, et al**. Danish very-low-dose aspirin after carotid endarterectomy trial. Stroke 1988; 19:1211–1215.
12. **Farrell B, Godwin J, Richards S, Warlow C**. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991; 54:1044–1054.
13. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. The SALT Collaborative Group. Lancet 1991; 338:1345–1349.
14. **Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A**. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143:1–13.
15. **Antithrombotic Trialists' Collaboration**. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, MI, and stroke in high risk patients. BMJ 2002; 324:71–86.
16. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. The Dutch TIA Trial Study Group. N Engl J Med 1991; 325:1261–1266.
17. **Taylor DW, Barnett HJ, Haynes RB, et al**. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. Lancet 1999; 353:2179–2184.
18. **Algra A, van Gijn J**. Aspirin at any dose above 30 mg offers only modest protection after cerebral ischaemia. J Neurol Neurosurg Psychiatry 1996; 60:197–199.
19. **Campbell CL, Smyth S, Montalescot G, Steinhubl SR**. Aspirin dose for the prevention of cardiovascular disease: a systematic review. JAMA 2007; 297:2018–2024.
20. **Weiss HJ, Aledort LM, Kochwa S**. The effect of salicylates on the hemostatic properties of platelets in man. J Clin Invest 1968; 47:2169–2180.
21. European Stroke Prevention Study. ESPS Group. Stroke 1990; 21:1122–1130.
22. **Davis SM, Donnan GA**. Secondary prevention for stroke after CAPRIE and ESPS-2. Opinion 1. Cerebrovasc Dis 1998; 8:73–77.
23. **Diener HC**. Dipyridamole trials in stroke prevention. Neurology 1998; 51(suppl 3):S17–S19.
24. **De Schryver EL, Algra A, van Gijn J**. Cochrane review: dipyridamole for preventing major vascular events in patients with vascular disease. Stroke 2003; 34:2072–2080.
25. **Leonardi-Bee J, Bath PM, Bousser MG, et al; Dipyridamole in Stroke Collaboration (DISC)**. Dipyridamole for preventing recurrent ischemic stroke and other vascular events: a meta-analysis of individual patient data from randomized controlled trials. Stroke 2005; 36:162–168.
26. **ESPRIT Study Group, Halkes PH; van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A**. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006; 367:1665–1673.
27. **Tirschwell D**. Aspirin plus dipyridamole was more effective than aspirin alone for preventing vascular events after minor cerebral ischemia. ACP J Club 2006; 145:57.
28. **Furie KL, Kasner SE, Adams RJ, et al; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research**. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011; 42:227–276.
29. **CAPRIE Steering Committee**. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996; 348:1329–1339.
30. **Diener HC, Bogousslavsky J, Brass LM, et al; MATCH investigators**. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004; 364:331–337.
31. **Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators**. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345:494–502.
32. **Bhatt DL, Fox KA, Hacke W, et al; CHARISMA Investigators**. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006; 354:1706–1717.
33. **Sacco RL, Diener HC, Yusuf S, et al; PRoFESS Study Group**. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med 2008; 359:1238–1251.
34. **Kent DM, Thaler DE**. Stroke prevention—insights from incoherence. N Engl J Med 2008; 359:1287–1289.
35. **Chimowitz MI, Lynn MJ, Howlett-Smith H, et al; Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators**. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005; 352:1305–1316.
36. **ESPRIT Study Group; Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A**. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurol 2007; 6:115–124.
37. **Mohr JP, Thompson JL, Lazar RM, et al; Warfarin-Aspirin Recurrent Stroke Study Group**. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001; 345:1444–1451.
38. **Jauch EC, Saver JL, Adams HP Jr, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology**. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44:870–947.
39. **Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU**. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke 2001; 32:2735–2740.
40. **Zivin JA**. Ischemic cerebrovascular disease. In: Goldman L, Schafer AI, editors. Goldman's Cecil Medicine 24th ed. Philadelphia, PA: Elsevier; 2012: chap 414. www.mdconsult.com. Accessed November 7, 2013.
41. **Smith WS, Johnston C, Easton D**. Cerebrovascular diseases. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison's Principles of Internal Medicine. 16th ed. New York, NY: McGraw Hill; 2005: chap 349. www.accessmedicine.com.

42. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991; 325:445–453.
43. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998; 351:1379–1387.
44. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998; 339:1415–1425.
45. Hobson RW 2nd, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. N Engl J Med 1993; 328:221–227.
46. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995; 273:1421–1428.
47. Halliday A, Mansfield A, Marro J, et al; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004; 363:1491–1502.
48. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. Stroke 2010; 41:e11–e17.
49. Spence JD, Coates V, Li H, et al. Effects of intensive medical therapy on microemboli and cardiovascular risk in asymptomatic carotid stenosis. Arch Neurol 2010; 67:180–186.
50. Brott TG, Hobson RW 2nd, Howard G, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010; 363:11–23.
51. Barnett HJ, Gunton RW, Eliasziw M, et al. Causes and severity of ischemic stroke in patients with internal carotid artery stenosis. JAMA 2000; 283:1429–1436.
52. Inzitari D, Eliasziw M, Gates P, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 2000; 342:1693–1700.

ADDRESS: Atizazul H. Mansoor, MD, PinnacleHealth Cardiac & Vascular Institute, 1000 North Front Street, Wormleysburg, PA 17043; e-mail: atizaz@yahoo.com