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Preventing ischemic stroke: Choosing the best strategy

■ ABSTRACT

Many questions remain about specific strategies to
prevent first or subsequent stroke: Do statins prevent
stroke? Which antithrombotic drugs are best? What is the
best way to treat carotid stenosis? We review current
evidence on drug therapy and surgical options,
addressing key stroke risk factors: ie, hypertension,
atherosclerosis, atrial fibrillation, patent foramen ovale,
aortic stenosis, and carotid stenosis.

■ KEY POINTS

Aggressive lowering of blood pressure and low-density
lipoprotein cholesterol levels reduces the risk of stroke.

If the patient has a stroke while taking aspirin, switch to
clopidogrel or extended-release dipyridamole plus aspirin
and consider platelet aggregation studies to determine if
the patient is "aspirin-resistant."

Patients with cardioembolic stroke should undergo
extended Holter monitoring for paroxysmal atrial
fibrillation, since they may benefit from warfarin as
secondary prevention.

Patients with stroke related to a patent foramen ovale
can be treated initially with aspirin if they were not
already taking aspirin before the event. If the event
occurs while a patient is on aspirin therapy, consider
percutaneous closure or warfarin, preferably in the setting
of a clinical trial.

WE CAN OFTEN PREVENT stroke—be it a
first ischemic stroke (ie, primary preven-
tion) or a subsequent stroke (secondary pre-
vention). Current preventive strategies, if
properly implemented, can reduce stroke inci-
dence by as much as 50% to 80%.[1]

Nevertheless, many questions remain and
require further study. For example, is one drug
better than another for preventing a second
stroke? In which patients is surgical therapy to
prevent subsequent stroke appropriate?

In this article, we examine the rationale
for current preventive strategies and recom-
mend how to put them into practice.

■ STROKE SUBTYPE CAN DIRECT TREATMENT

Stroke is a heterogeneous disorder, and one
therapy does not fit all strokes. Besides the tra-
ditional distinction of ischemic vs hemorrhag-
ic stroke, several subtypes reflect unique
pathogenesis or underlying conditions that
affect the response to treatment. Strokes have
been classified into five subtypes for the pur-
poses of therapeutic trials[2]:
- Large-artery atherosclerosis: a moderate-
to-severe stenosis of a major vessel to the brain
associated with the appropriate cortical signs
such as aphasia, neglect, or cerebellar signs
- Cardioembolism: directly referable to the
heart, eg, due to atrial fibrillation or a
mechanical heart valve
- Small-vessel occlusion: usually with no
clinical signs of cortical involvement, and
usually occurring in patients with diabetes
mellitus or hypertension, or both[3]
- Stroke due to nonatherosclerotic conditions
(eg, arterial dissection or hypercoagulable state)

- Stroke with no identifiable cause.

■ MRI AND STROKE PREVENTION

In patients who have had a stroke, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) can help determine the stroke subtype and the most likely cause of the stroke. MRI has proven much more sensitive and specific than computed tomography in the acute and chronic settings.

Determining the stroke subtype is important, since stroke subtype and cause have the most bearing on the intervention chosen to prevent future strokes in an individual patient. For example, certain patterns of infarction on MRI may aid the clinician in identifying patients with embolic stroke, prompting further investigation of the heart. Patients with strokes involving the cortex, the cortical-subcortical areas, the subcortex (> 15 mm involvement), or both hemispheres have an increased likelihood of an embolic source. Smaller subcortical strokes (< 15 mm) are likely to be due to small-vessel occlusion.[4] The appearance of multiple infarcts in a linear pattern on diffusion-weighted MRI suggests large-artery thromboembolism (ie, carotid stenosis).[5]

■ GENERAL PRINCIPLES OF PREVENTION

All patients who have had a stroke should receive aspirin therapy and should be carefully monitored. But risk factor reduction goes beyond prescribing aspirin. Prevention of a subsequent stroke requires the identification and aggressive management of any risk factor: eg, hypertension, atherosclerosis, atrial fibrillation, patent foramen ovale, aortic stenosis, and carotid stenosis (**FIGURE 1**). Patients also should be encouraged to participate in exercise programs, alter their diet, and stop smoking.

The choice of antithrombotic agent in addition to aspirin depends largely on the cause of the stroke, risk factors, and on past failures of other drug regimens. As we will discuss later, questions remain about how to make best use of current drugs: eg, whether one agent is more effective than another in preventing subsequent stroke of a specific subtype, or whether certain combinations are better than monotherapy.

Covering all risk factors

Wald and Law[6] proposed a single pill that would comprise three antihypertensives, aspirin, and a statin, in the hope of reducing the risk of first stroke by 80%. This "polypill" concept is controversial, but it emphasizes that reduction of blood pressure and low-density lipoprotein cholesterol should be part of any plan to reduce the incidence of stroke.

Current prevention strategies are effective when thoroughly applied, but they are often not used as effectively as they could be, as evidenced by a recent audit in the United Kingdom, in which 41% of patients remained hypertensive 6 months after hospitalization for a stroke.[7]

Lowering blood pressure

Numerous studies have shown that controlling hypertension with antihypertensive drugs prevents ischemic stroke. Yet debate persists over which is more important, the class of antihypertensive used or the target blood pressure.[8]
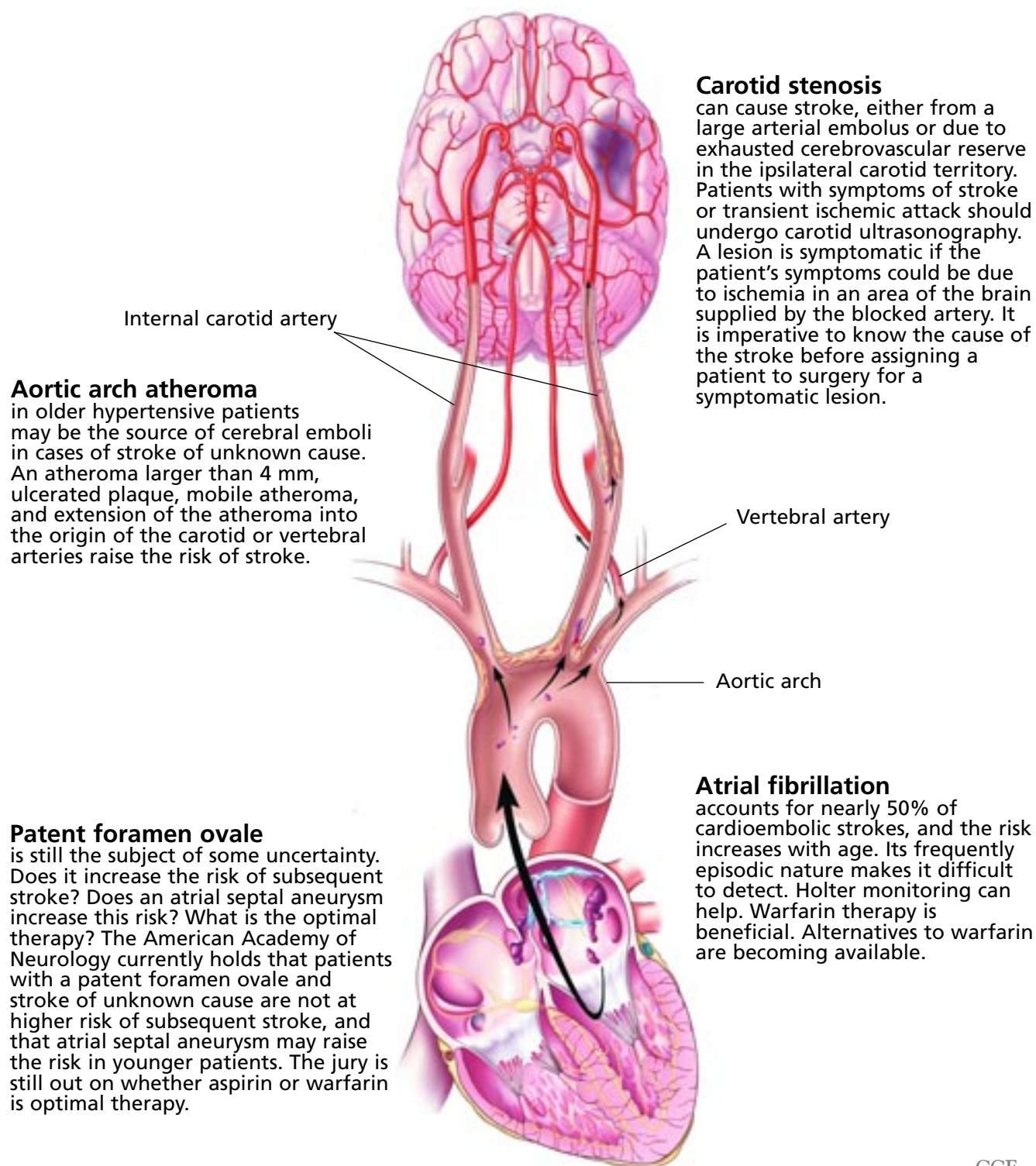
Most of the evidence on antihypertensive therapy and ischemic stroke is from trials of secondary prevention of cardiovascular events; it was found that as a by-product strokes were reduced as well.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[9] measured the occurrence of first heart attack in more than 42,000 patients with mild to moderate hypertension who received chlorthalidone, amlodipine, lisinopril, or doxazosin. The investigators found no difference among these drugs in preventing the primary end point of fatal or nonfatal myocardial infarction. Stroke, a secondary end point of the study, occurred more often in the lisinopril group. The authors believed this was because patients receiving chlorthalidone achieved lower systolic blood pressures than those receiving lisinopril.

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[10] randomized patients to receive either perindopril or perindopril and indapamide for secondary prevention of stroke. Reducing the blood pressure reduced the risk of subsequent stroke, regardless of stroke subtype.[10] This reiterates the importance of blood pressure reduc-

Risk factor reduction goes beyond prescribing aspirin

■ Sources of risk for ischemic stroke

Carotid stenosis
can cause stroke, either from a large arterial embolus or due to exhausted cerebrovascular reserve in the ipsilateral carotid territory. Patients with symptoms of stroke or transient ischemic attack should undergo carotid ultrasonography. A lesion is symptomatic if the patient's symptoms could be due to ischemia in an area of the brain supplied by the blocked artery. It is imperative to know the cause of the stroke before assigning a patient to surgery for a symptomatic lesion.

Internal carotid artery

Aortic arch atheroma
in older hypertensive patients may be the source of cerebral emboli in cases of stroke of unknown cause. An atheroma larger than 4 mm, ulcerated plaque, mobile atheroma, and extension of the atheroma into the origin of the carotid or vertebral arteries raise the risk of stroke.

Vertebral artery

Aortic arch

Atrial fibrillation
accounts for nearly 50% of cardioembolic strokes, and the risk increases with age. Its frequently episodic nature makes it difficult to detect. Holter monitoring can help. Warfarin therapy is beneficial. Alternatives to warfarin are becoming available.

Patent foramen ovale
is still the subject of some uncertainty. Does it increase the risk of subsequent stroke? Does an atrial septal aneurysm increase this risk? What is the optimal therapy? The American Academy of Neurology currently holds that patients with a patent foramen ovale and stroke of unknown cause are not at higher risk of subsequent stroke, and that atrial septal aneurysm may raise the risk in younger patients. The jury is still out on whether aspirin or warfarin is optimal therapy.

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FIGURE 1

tion in stroke prevention.

Is one antihypertensive drug better? At this time, there is no evidence that one antihypertensive drug is superior to another in stroke prevention. The angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may have intrinsic properties[11–13] that confer benefits beyond lowering blood pressure, but this hypothesis is still being tested in clinical trials.[14] The advantage of ACE inhibitors and ARBs is largely theoretical at this point.

Statins to lower cholesterol

The ability of statins (HMG-CoA reductase inhibitors) to stabilize atherosclerotic plaque has been studied extensively in cardiology,[15] but evidence has recently surfaced that statins may also provide neuroprotective effects in acute stroke.[16] Still, the evidence linking hypercholesterolemia to stroke has not been convincing.[17]

A recent meta-analysis of nearly 80,000 patients with vascular risk factors showed an absolute risk reduction of 0.7% in stroke with statins (21% relative risk reduction).[18]

This benefit was confirmed by a recent randomized controlled trial[19] showing an absolute risk reduction of 1.4% and a relative risk reduction of 30% for primary prevention of ischemic stroke favoring simvastatin over placebo. Interestingly, there was no statistical difference in secondary prevention of stroke, but patients with prior strokes did have a lower risk of other major vascular events if they took simvastatin, with a 5.1% absolute risk reduction and 20% relative risk reduction.[19] These results suggest that patients with vascular disease benefit from statins in preventing a first stroke. In addition, patients with a history of stroke may benefit from statins for preventing other vascular events such as myocardial infarction.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial now under way may help answer whether statins are beneficial in secondary prevention of stroke and whether they reduce the severity of the neurologic deficit if a stroke occurs.[20] This second question is interesting, since others have observed that patients who have taken statins before a stroke may have shorter hospi-

tal stays[21] and, possibly, better functional outcomes at longer time intervals.[22]

Aspirin

A large meta-analysis showed that aspirin reduces the incidence of stroke, myocardial infarction, or vascular death by 25%.[23]

Primary prevention. The Physicians' Health Study reviewed data on primary prevention of stroke in patients taking aspirin[24] and found a benefit in prevention of myocardial infarction. However, there was a trend toward an increase in stroke, owing to an increase in hemorrhagic stroke.

In the Women's Health Study, a trial of primary prevention in women, aspirin lowered the risk of stroke without affecting the risk of myocardial infarction or death from cardiovascular causes.[25] On the basis of the Women's Health Study, it could be argued that low-dose aspirin to prevent coronary disease in women under age 65 is to be avoided unless the global risk score is very high. But what about the prevention of stroke? We feel that the prescription of aspirin for the primary prevention of stroke and other vascular events should be decided on an individual basis.

Secondary prevention. Numerous clinical trials and meta-analyses have shown that aspirin is efficacious in reducing the risk of a secondary stroke when compared with placebo. Two major trials[26,27] have shown that giving aspirin within 48 hours of an acute stroke has a small but statistically significant benefit in reducing the occurrence of a second ischemic stroke. In the International Stroke Trial (IST), patients who received aspirin were less likely to have another stroke within 14 days of the first stroke (absolute risk reduction 0.9%, relative risk reduction 23%).[26] In the Chinese Acute Stroke Trial (CAST), patients receiving aspirin were less likely to have a recurrent stroke at 30-day follow-up (absolute risk reduction 0.5%, relative risk reduction 23%).[27]

The debate has been over the optimal dosing of aspirin. The Dutch Transient Ischemic Attack Trial compared 30 mg of aspirin with 283 mg of aspirin and showed no difference in stroke reduction rates.[28] A more recent trial compared low-dose aspirin (81 mg

We have no proof yet that one antihypertensive drug is best in preventing stroke

or 325 mg) vs high-dose aspirin (650 mg or 1,300 mg) in patients undergoing carotid endarterectomy. No difference was found for stroke, myocardial infarction, or death at 30 days.[29] A meta-analysis of these trials showed no difference in stroke reduction rates on the basis of aspirin dosage, with doses ranging from 30 to 1,300 mg daily.[30]

The US Food and Drug Administration (FDA) has since recommended that a daily dose between 50 and 325 mg is acceptable in the secondary prevention of stroke.[31] We recommend 81 mg and consideration of platelet aggregation studies if there is any doubt about efficacy, eg, due to noncompliance or recurrent clinical events.

Despite these results, aspirin is still underprescribed for patients being discharged from the hospital after stroke.

Aspirin resistance

Some patients still have a vascular event even if they are taking aspirin. Researchers have found that some patients are predisposed to biochemical aspirin resistance, as measured by platelet aggregation studies. A study of 326 patients with stable coronary artery disease found that 5.2% had resistance to aspirin at a dose of 325 mg, and that this resistance increased the risk of a vascular event fourfold in a multivariate model.[32] Another group considered stroke patients only and found that 37% of 129 patients had normal platelet function despite taking aspirin in doses ranging from 81 to 325 mg daily. Interestingly, they found a twofold increase in resistance in patients taking a lower dose of aspirin.[33]

These findings have prompted consideration of other antiplatelet drugs for stroke prevention, in addition to checking for platelet aggregation in patients in whom aspirin therapy fails.

Clopidogrel

Clopidogrel is an irreversible inhibitor of platelet function that blocks the adenosine diphosphate receptor, thereby preventing the aggregation of platelets. There are no published trials of clopidogrel in the primary prevention of stroke, but there are two major trials of clopidogrel in secondary prevention.

The Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study[34] was a controlled trial of about 20,000 patients, randomized to take aspirin 325 mg or clopidogrel 75 mg daily. This study showed a 0.5% absolute risk reduction and an 8.7% relative risk reduction favoring the clopidogrel group for the combined primary end point (myocardial infarction, stroke, or vascular death). In the subgroup with previous stroke, there was a 7.3% relative risk reduction favoring clopidogrel, but the difference was not statistically significant.

The results of CAPRIE have prompted numerous studies to determine if clopidogrel is superior to aspirin in vascular disease. The recently completed Management of Atherothrombosis with Clopidogrel in High-risk Patients with Recent TIA or Ischemic Stroke (MATCH) trial[35] compared clopidogrel 75 mg plus low-dose aspirin against aspirin alone for the prevention of the primary end point of vascular death, myocardial infarction, or stroke. The results revealed an absolute risk reduction of 1% and a relative risk reduction of 6.4% for the primary end point with combination therapy, but these findings were not statistically significant. The incidence of major bleeding events was also higher with combination therapy (1.94% vs 0.58%, $P <$ .001).

More data are needed to determine if clopidogrel is superior to aspirin in preventing ischemic stroke in high-risk patients, but it appears to be beneficial with regard to secondary prevention of vascular events.

Limitations of clopidogrel

Limitations of clopidogrel include a delay in onset of action of several hours, irreversibility of action, and possible resistance. Third-generation thienopyridines are under evaluation in clinical studies, and preliminary data suggest that prasugrel may address some of these shortcomings.

Clopidogrel resistance. Although less well known than aspirin resistance, resistance to clopidogrel is probably caused mostly by inefficient metabolism of the prodrug clopidogrel to its active metabolite. In a recent study by Alberts et al,[36] clopidogrel resistance was shown in more than 30% of patients taking one or two antiplatelet therapies.

We recommend aspirin 81 mg for secondary prevention of stroke

Dipyridamole

Dipyridamole is a platelet phosphodiesterase inhibitor that allows cyclic adenosine monophosphate to remain elevated, thereby preventing platelet aggregation. It also acts as a vasodilator and prevents platelet adhesion to the vessel wall.[37] Of note, the gene encoding phosphodiesterase-4D has recently been shown to confer a risk of ischemic stroke: in particular, large-artery atherosclerosis and cardiogenic subtypes.[38]

So far, dipyridamole has only been studied in the secondary prevention of stroke.

One controlled study in 1983 failed to show any effectiveness of dipyridamole in combination with aspirin in reducing the risk of stroke when compared with aspirin alone.[39] The first European Stroke Prevention Study[40] compared dipyridamole plus aspirin against placebo and found a 38% relative risk reduction in stroke with combination therapy. This was felt to be an additive effect of dipyridamole and prompted the second European Stroke Prevention Study.[41] This was a factorial study with one arm comparing extended-release dipyridamole and aspirin vs aspirin alone in 6,600 patients. This study found that extended-release dipyridamole 200 mg twice a day along with aspirin 50 mg a day was superior to aspirin monotherapy (50 mg), with an absolute risk reduction of 2.9% and a relative risk reduction of 23%. It was also more effective than placebo, with an absolute risk reduction of 5.6% and a relative risk reduction of 37%. Headaches were commonly noted by patients who discontinued the medications, and bleeding rates were not significantly higher than with aspirin monotherapy.

Another ongoing clinical trial[42] has been enrolling patients in Europe and Australia to determine if the combination of aspirin and dipyridamole is superior to aspirin alone or anticoagulants in preventing secondary strokes and other vascular events, including myocardial infarction and death.

Warfarin for secondary prevention: Indications narrowing

The indications for warfarin in the secondary prevention of stroke have been gradually narrowing.[43,44] The Warfarin-Aspirin Symptomatic Intracranial Disease study[43] compared high-dose aspirin (1,300 mg/day) with warfarin in patients with intracranial atherosclerosis. The study was stopped prematurely because patients in the warfarin group had a higher rate of hemorrhage, and because no difference was noted in the two groups with regards to stroke prevention.

The Warfarin-Aspirin Recurrent Stroke Study[44] compared aspirin 325 mg daily vs warfarin and excluded patients with symptomatic carotid stenosis and atrial fibrillation. No difference in rates of stroke recurrence, hemorrhage, or death was noted between the two groups.

Warfarin, heart failure, and stroke. No randomized controlled trial has yet been published that tested warfarin in the primary or secondary prevention of stroke in patients with heart failure or reduced ejection fraction. However, two trials are under way to test warfarin and antiplatelet agents in patients with low ejection fraction.[45]

■ ATRIAL FIBRILLATION

Atrial fibrillation accounts for nearly 50% of cardioembolic strokes and confers a risk of recurrent stroke of roughly 5% a year,[46] increasing with age.[47]

Warfarin is beneficial

The relative risk reduction in prevention of stroke ranges from 27% to 48% with warfarin vs aspirin,[48–50] and 47% to 86% with warfarin vs placebo.[48,51] A meta-analysis of the five major trials showed that warfarin was superior to placebo, conferring an absolute risk reduction of 3.1% and a relative risk reduction of 68% in the primary prevention of stroke.[46] There is an increased risk of major bleeding with warfarin, but the number of strokes prevented (23 per 100 patient-years) is greater than the number of bleeding complications (9 per 100 patient-years).[52] In addition, warfarin has been found to be effective in the secondary prevention of stroke when compared with aspirin or placebo.[48]

Holter monitoring aids detection

Unfortunately, atrial fibrillation may be missed because it can be episodic in up to 30% of patients.[53] This often poses a problem for the clinician who suspects a cardioembolic

Atrial fibrillation accounts for nearly 50% of cardioembolic strokes

source of the stroke. The diagnosis is often missed because the length of the recording of a patient's rhythm is inadequate.

Holter monitoring may increase detection in an additional 6.1% of patients with paroxysmal atrial fibrillation.[54,55] A recent report studied 149 consecutive patients admitted for acute stroke and found that a routine electrocardiogram (ECG) showed atrial fibrillation in 2.7% of patients. When a 24-hour Holter monitor was placed on patients with a normal ECG, an additional 5% of patients were found to have atrial fibrillation. The most interesting part of this study was that a 7-day event-loop recorder documented this rhythm disturbance in 5.7% of patients with a negative ECG and negative 24-hour Holter monitoring.[56]

Alternatives to warfarin

An exciting new alternative to warfarin that showed promise in patients with atrial fibrillation was Ximelagatran, an oral anticoagulant and a direct thrombin inhibitor that does not require coagulation monitoring and has no interactions with food or other medications.[58] It was compared with warfarin in a multicenter trial, which found no statistical difference in safety or efficacy between the two groups. However, Ximelagatran was found to be toxic to the liver, with a fatality rate in the order of 1 per 5,000 patients. In September 2004, an FDA panel turned down approval of the drug due to these concerns, so its future availability in the United States is in doubt.

Another intriguing development is an experimental device implanted via catheterization to occlude the percutaneous left atrial appendage.[58] This could be an option for patients with contraindications to warfarin. In this procedure, a self-expanding cage covered with a polymeric membrane could be implanted to occlude the left atrial appendage, the location of thrombus in patients with atrial fibrillation nearly 90% of the time.[59] Early experience has shown that this procedure is technically feasible,[60] but it is unclear if these devices reduce the risk of stroke.

■ PATENT FORAMEN OVALE

Although patent foramen ovale has long been recognized as a cause of paradoxical embolism and stroke, the elusive nature of the clot makes this a challenging diagnosis. An exception is if a young patient who is known to have a venous clot has an embolic stroke after performing a Valsalva maneuver.

Three major questions remain:
- Does patent foramen ovale confer an increased risk of subsequent stroke?
- Does an atrial septal aneurysm increase this risk?
- What is the optimal therapy?

Two prospective randomized control studies help answer the first question and give insights into the other two questions.

Patent foramen ovale and stroke risk

Mas et al[61] reported 581 patients under age 55 with cryptogenic stroke, who were followed for 4 years. In those receiving aspirin, they found no difference in stroke recurrence rates in patients without an atrial defect compared with those with a patent foramen ovale or atrial septal aneurysm. They did note an increase in the yearly rate of recurrent stroke or transient ischemic attack in patients with both patent foramen ovale and atrial septal aneurysm compared with patients without an atrial septal defect (4.8% vs 1.6%, hazard ratio 3.91, 95% confidence interval 1.59–9.59).

The Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS)[62] is particularly valuable because of its large cohort and prospective design. Patients with a recent ischemic stroke enrolled in the Warfarin-Aspirin Recurrent Stroke study were randomized to treatment with warfarin or aspirin. A subgroup of these patients underwent transesophageal echocardiography after exclusion of an alternative cardiogenic source and severe carotid stenosis. The prevalence of patent foramen ovale was greater among those with stroke of unknown cause (39.2%) than among those in whom a potential cause of stroke could be identified (29.9%; $P < .02$); this was particularly true with respect to patients with a large patent foramen ovale (20.0% vs 9.7%, $P < .001$). However, no significant difference was found in the rate of recurrent stroke or death over 2 years between those with a patent foramen ovale of any size and those without a patent foramen ovale. Furthermore, there were no significant differences in primary event

Holter monitoring may help detect atrial fibrillation in patients with acute stroke

rates between patients randomized to warfarin or aspirin (325 mg/day), regardless of whether the cause of the index stroke was identifiable or unidentifiable.

Drug vs surgical therapy

Endovascular closure to treat patent foramen ovale is becoming an increasingly used option.[63] The FDA has published guidelines regarding which patients may qualify for percutaneous closure via the humanitarian device exemption.[64] Patients can meet the exemption criteria if they have a recurrent cryptogenic stroke despite being on therapeutic doses of warfarin. This is confusing, since we still do not have enough evidence that warfarin is superior to aspirin in this patient population. A recently initiated trial will compare medical therapy (any antithrombotic) with endovascular closure of patent foramen ovale in preventing recurrent stroke.[65]

American Academy of Neurology guidelines

Based on the above findings, the American Academy of Neurology stated that patients with a patent foramen ovale and stroke of unidentifiable cause are not at higher risk of a subsequent stroke when compared with patients without patent foramen ovale and with stroke of unidentifiable cause.[66] The presence of an atrial septal aneurysm along with a patent foramen ovale may pose a higher risk in younger patients.

The Academy also felt there was insufficient evidence to determine optimal therapy in comparing aspirin vs warfarin for this group of patients, and even less evidence with regard to the effectiveness of percutaneous closure.[66]

■ AORTIC ARCH ATHEROMA

Patients who are older and have hypertension are at increased risk of developing atheromatous disease of the aortic arch.[67] These atheromas may be responsible for cerebral emboli in patients with stroke of unidentifiable cause. Patients with an atheroma larger than 4 mm, ulcerated plaque, mobile atheroma, or extension of atheroma into the origin of the carotid or vertebral arteries are at increased risk of future stroke.[68–70]

At this time it is unclear which antithrombotic agents should be used to prevent stroke in these patients. A trial now under way is comparing clopidogrel and aspirin vs aspirin monotherapy to determine if intensified antiplatelet therapy can reduce stroke risk.[71]

Surgery. The role of surgical intervention such as aortic arch replacement is unknown. However, the presence of clot or atheroma in the aortic arch increases the chance of perioperative stroke at least fourfold.[72] Surgical procedures to address this risk have been devised[73,74] and may one day become acceptable options for secondary stroke prevention in patients with aortic arch atherosclerosis.

■ CAROTID STENOSIS

Patients with symptoms of stroke or transient ischemic attack should undergo ultrasonography of the carotid artery as part of the etiologic workup. A carotid lesion is considered symptomatic if the patient has a stroke or transient ischemic attack with symptoms that could be due to ischemia in the part of the brain supplied by the blocked artery. Stroke associated with carotid stenosis can be due to a large arterial embolus or, less frequently, to exhausted cerebrovascular reserve in the ipsilateral carotid territory.

Key management issues

Two issues need consideration when managing patients with carotid stenosis. First, mild stenosis (< 50%) or moderate stenosis (51%–69%) often progresses, and the further narrowing increases the risk of stroke or transient ischemic attack.[75] Second, in patients with carotid stenosis of 60% to 69%, stroke is more likely to have been due to cardioembolism than it is in patients with a higher degree of stenosis.[76] It is imperative to understand the cause of the stroke before assigning a patient to surgery for a symptomatic lesion.

Preventing a first stroke in carotid artery stenosis

Two studies examined the primary prevention of ischemic stroke in patients with carotid artery stenosis.[77,78]

Several antiplatelet drug options are available in aortic arch atheroma

Endarterectomy vs medical therapy. The Asymptomatic Carotid Atherosclerosis study[77] included only patients with asymptomatic carotid stenosis of 60% to 99%. These patients were randomized to endarterectomy or medical therapy. The rate of stroke or death at 5-year follow-up favored surgery (5.1% vs 11%, $P < .004$).[77] However, the results may not be generalizable to the community at large because the surgeons in this study had lower complication rates than those in other trials.

The Asymptomatic Carotid Surgery trial[78] also found that endarterectomy reduced the risk of ipsilateral stroke, and the results are consistent with the 5-year results of the Asymptomatic Carotid Atherosclerosis study.

The North American Symptomatic Carotid Endarterectomy trial, a secondary stroke prevention trial, showed that patients with a symptomatic stenosis of greater than 70% had a nearly threefold decrease (9% vs 26%, $P < .001$) in ipsilateral stroke with surgery vs drug therapy at 2-year follow-up.[79]

Stenting. Recently, the advent of carotid stenting has increased treatment options for patients with carotid artery stenosis. But it is not yet known which patients who have had no previous stroke will benefit the most, because most data on stenting are for secondary prevention, although some trials have included asymptomatic carotid stenosis.

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial[80] compared stenting with endarterectomy in high-risk surgical patients. All patients in this study had carotid disease; some were asymptomatic, and others had already had a transient ischemic attack or stroke. Patients who underwent stenting had a significantly lower rate of myocardial infarction, stroke, or death at 30-day follow-up (5.8% vs 12.6%, $P < .047$). At 1 year, the rate of ipsilateral stroke was 3.8% in the stent group vs 5.3% in the endarterectomy group.

In contrast, an earlier, methodologically less stringent study comparing carotid endarterectomy and carotid artery stenting with a self-expanding endoprosthesis[81] was stopped early because patients undergoing stenting had a stroke rate of 12.1% at 30 days, compared with 4.5% in the endarterectomy group. It is now felt that these results were related to operator inexperience rather than to the angioplasty and stenting procedure.

The Carotid Revascularization Endarterectomy vs Stenting Trial (CREST)[82] is randomizing patients to endarterectomy or stenting and, we hope, will determine which procedure is superior in a more generalizable group of patients.

At our institution, if a patient has a symptomatic carotid stenosis greater than 70%, we offer carotid endarterectomy or randomization into one of our carotid stenting trials. Patients with severe asymptomatic carotid stenosis are offered revascularization on a case-by-case basis. At this time, patients should be offered carotid stenting as an option only as part of a clinical trial.

■ SERUM MARKERS

Recently, there has been interest in serum markers such as homocysteine and C-reactive protein to identify patients who might benefit from treatment to prevent ischemic stroke.

Homocysteine

Reduction of homocysteine levels with pyridoxine, vitamin B_{12}, and folic acid was found to reduce the risk of coronary restenosis after revascularization procedures.[83] Furthermore, homocysteine levels greater than 15 μmol/L (normal 5–15) have been shown to be an independent risk factor for recurrent stroke in multivariate regression models.[84] However, the only randomized controlled study to date did not show a reduction in recurrent stroke after initiation of vitamin therapy to reduce moderately elevated levels of serum homocysteine.[85] The major criticism of this study was that the mean levels of homocysteine for the cohort were lower than levels reported elsewhere as putting patients at a higher risk of stroke. Another concern was that the follow-up period was too short, and possible benefits could have been missed.

For now, routine measurement of homocysteine levels has no role in stroke prevention.

C-reactive protein

C-reactive protein is a marker of inflammation. It is associated with atherosclerosis and is a pre-

In mild or moderate carotid stenosis, narrowing can progress, raising stroke risk

dictor of acute coronary events.[86] Elevations have also been associated with an increased risk of recurrent ischemic stroke in patients with large-artery atherosclerosis.[87] Angiotensin-converting enzyme inhibitors and statins reduce levels of C-reactive protein.[88,89]

Further research is needed to define the role of C-reactive protein elevations in stroke patients. Until we know more, routine screening for this marker is not indicated.

Lipoprotein-associated phospholipase A_2

Given the prominent role of inflammation in coronary artery disease, there is growing evidence to suggest that many strokes manifest from the same process. Lipoprotein-associated phospholipase A_2 is a novel inflammatory marker which has been shown to be associated with inflammation and which may actively promote inflammation.[90,91]

■ LIFESTYLE MODIFICATIONS

Each patient should be counseled on lifestyle modifications. These should include smoking cessation, 30 minutes of exercise on most days of the week, a balanced diet, and avoidance of large quantities of alcohol. All of these modifications have been recommended by the American Heart Association's Scientific Committee for primary and secondary stroke prevention.[92]

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