Preventing Stroke
Is Preventing Microemboli Enough?

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Prevention of stroke shares much in common with prevention of other vascular events because the underlying pathological process, namely, atherosclerosis, is the same. Attesting to this is the recent demonstration that statins,1 ACE inhibitors,2 and more well-known measures, such as control of hypertension and smoking, are as effective in preventing stroke3 as they are in preventing other cardiovascular events.

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However, there is a pathological process, namely, embolization, that leads to arterial occlusion in the cerebral circulation much more frequently than in the coronary bed. Consequently, the detection and prevention of embolic events is critical to reducing the burden of stroke. Emboli may cause either large disabling strokes or small subclinical events, depending on the size and eventual location of the embolus. Emboli generated from the chambers or valves of the heart or from atherosclerotic plaques in the arteries of the neck are variable in their size and consistency. When the cardiac chambers are dyskinetic or fibrillating, leading to stasis and the formation of thrombus, distal emboli are usually large, they lodge in the initial branches of the circle of Willis, and the resultant strokes are devastating. The posterior wall of the most proximal portion of the internal carotid artery just distal to the bifurcation is a common site of atherothrombosis because of the unique hemodynamic effects caused by the flow divider. Emboli from such large-artery atheroma may consist of a thrombus or pieces of calcified plaque, but they may also be microscopic if composed only of fibrin-platelet material. If such “microemboli” are <0.1 mm in diameter, they might pass into the small arteriolar branches. There they may be lysed by endogenous protective hemostatic defenses, or they may cause areas of microinfarction.

Much has been learned about the clinical consequences and prevention of large emboli. Because such strokes are the leading cause of disability among US adults, multicenter, randomized, clinical stroke prevention trials have been organized to reduce clinically apparent strokes as the primary end point. These have conclusively demonstrated that antplatelet therapy reduces the incidence of recurrent stroke by ≈20% to 25%4 and that anticoagulation in patients with atrial fibrillation5 and surgical endarterectomy in patients with severe carotid stenosis6 are also highly effective. However, there is still much room for improved therapy. Many embolic strokes are still not prevented by existing antplatelet regimens, and even in the best surgical series, carotid endarterectomy is associated with a 2% to 5% perioperative rate of stroke or transient ischemic attack (TIA).6 In the study by Kaposzta et al7 reported in this issue of Circulation, the perioperative rate of stroke or TIA after carotid endarterectomy was 5 (12%) of 42 patients. Therefore, new therapies to prevent these clinically evident and mostly embolic strokes are certainly needed.

Although the clinical consequences and prevention of large emboli are reasonably well understood, the same cannot be said of microemboli. Microemboli are common, at least in some high-risk patients with carotid stenosis or in patients undergoing carotid or cardiac surgery, but clinically apparent embolic strokes resulting from them are much less frequent.8 Subcortical ischemic changes are frequently seen on CT or MRI scanning in association with increasing age and atherosclerotic risk factors, and it has long been suspected that they may be due in part to the accumulated impact of microemboli occurring over years.9,10 The penetrating arterioles supplying the basal ganglia, internal capsule, and deep white matter are end arteries with little collateral flow. Theoretically, microemboli lodging in such vessels might lead to microinfarcts. This hypothesis remains to be proven. The best supporting evidence is correlative, showing an association between such subcortical abnormalities on postoperative CT or magnetic resonance images and transcranial ultrasonic detection of microembolic signals during carotid endarterectomy.10

Transcranial Doppler (TCD) ultrasound is a rapidly evolving technology with many unique advantages. It is portable, noninvasive, repeatable, and relatively inexpensive. Clinical TCD applications11 are effective in the reduction of ischemic stroke in children with sickle cell disease, because TCD identifies those in need of prophylactic blood transfusion. TCD is also well established in the detection of intracranial arterial stenosis and occlusion, in monitoring clot lysis in acute ischemic stroke, in the detection and monitoring of cerebral vasospasm after subarachnoid hemorrhage, and in documenting cerebral circulatory arrest in suspected brain death.11 Relevant to the article by Kaposzta et al,7 TCD helps to detect, quantify, and localize cerebral embolism, because it topographically detects transient high-intensity embolic signals in real time. TCD is extremely sensitive to moving gaseous or solid embolic particles of variable size ranging from millimeters to <240 μm.12 Because these particles reflect or scatter more ultrasound energy than does the

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surrounding blood, these embolic events can be documented during various procedures and studied offline. In the study of Kaposzta et al, detection with TCD was limited to a single arterial segment (distal M1 middle cerebral artery). Embolization to proximal perforating arteries and other carotid branches was not detected. This conventional method of TCD embolus detection also cannot differentiate between gaseous and solid emboli and cannot determine the composition of a solid embolus (i.e., a fibrin-rich clot or a piece of atheromatous plaque).

Kaposzta et al describe the use of embolus detection by TCD as a surrogate end point in the evaluation of 2 agents that contribute to the formation of NO and are known to reduce platelet aggregation in vitro and ex vivo. The authors, who are recognized leaders in the field of embolus detection, have carried out the study with careful attention to avoiding the technical pitfalls and interpretation bias of the procedure. It appears certain that inhibiting platelet aggregation by modulating the NO system is an exciting new approach that might be useful in stroke prevention. It is especially encouraging that a possible additive effect of these drugs, i.e., reduction of the number of embolic signals, occurred in patients who were already on aspirin.

However, what is the value of prevention of microemboli as measured by TCD as a surrogate marker for clinical stroke prevention? It is certainly true that a valid surrogate outcome measure would be a useful tool in stroke prevention studies. Because the yearly stroke incidence in high-risk populations is only 2% to 5%, the number of patients needed to show superiority over existing therapies but also the validity of reduced microembolic signals as a surrogate marker for preventing clinical embolic strokes.

Finally, however, we must show that the desired clinical outcome (reduced stroke incidence) is based on the drug effect on the surrogate. Here, we may have a problem. Although the dramatic reduction in embolic events as detected by TCD in patients treated with either l-arginine or S-nitroso glutathione is striking and encouraging, the fact that 5 (12%) of 42 patients still experienced postoperative TIAs or strokes is discouraging. Unless all these events occurred in the placebo group, which is not stated but is unlikely, the results bring into question not only the clinical efficacy of these therapies but also the validity of reduced microembolic signals as a surrogate marker for preventing clinical embolic strokes.

References

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