A  s we read through the medical literature, we are always looking for the “hottest” new advances (jumping right into the smoke/fire analogy thing): basic science that gives us new mechanistic insights, clinical trials that confirm or reject our so-called insights, major new diagnostic and therapeutic options, and breakthrough technology. We are a lot like forest rangers, sitting up on a platform, way above the trees, looking out over the forest, and seeing something in the distance that looks like smoke. Then we have to decide what we are seeing is really smoke coming from some forest-threatening fire, or if it is just fog in the trees.

The Study
The study by Payne et al involved 100 patients undergoing elective CEA, all of whom received 150 mg of aspirin for 4 weeks before surgery. Patients were randomized to clopidogrel (75 mg given 12 hours before surgery; n=46) or placebo (n=54). Four of the patients undergoing staged procedures had the same therapy for both procedures.

The operations were done with systemic heparinization (5000 U). TCD monitoring was performed during the operation and for 3 hours afterward. Patients with very high rates of embolization (>25 emboli in any given 10-minute period) were treated with low-molecular-weight dextran (LMD). An arbitrary criterion of 20 emboli during the postoperative monitoring period was used to categorize patients as “high-grade” and “low-grade” embolizers.

No patient taking clopidogrel had >25 emboli detected over 3 hours of postoperative monitoring. Very high embolic rates necessitated LMD in 2 placebo patients. There were significantly fewer high-grade embolizers in the clopidogrel group compared with the placebo group (1 of 46 versus 10 of 54). There was a small but significant decrease in fibrinogen binding in response to ADP in the clopidogrel group. There were no differences between groups in major bleeding complications (including neck hematomas, transfusion, and return to the operating room for reexploration) or wound drainage, but postoperative closure times were significantly longer in the clopidogrel group (exact numbers not given).

So what specific trial-related issues need to be considered, and in what larger context do the trial results need to be interpreted?

Trial-Related Issues
One of the key aspects of any clinical trial is the end point—in this case, TCD “microembolii.” The technique of transcranial Doppler is exquisitely sensitive, and some issues still remain as to whether all of the “events” are truly particulate emboli or may also involve gaseous microbubbles.6,7 More recently, however, it has been possible to demonstrate that microembolic events were completely abolished with the use of a glycoprotein IIb/IIIa antagonist,8 which suggests a primary platelet role. In modern-day practice, TCD is used for postprocedural monitoring, and as in the present study, additional therapy is given when very high frequencies of microemboli are detected. However, a microembolic event does not mean that there is neurological damage. It is not the neurological equivalent of cardiac enzymes as indicators of myocardial damage. It is a marker for a physiological process—platelet microaggregates—that may be an indicator of worse things to come. It is not even really analogous to the Folts cyclic flow model,9 which monitors changes in flow in stenosed medium-sized vessels as an indicator of platelet aggregation and dislodgement. Rather, TCD-detected microemboli are an indicator of nonocclusive aggregatory events, probably platelet mediated.
Payne et al\(^1\) have somewhat arbitrarily chosen a cut point of 20 events in the 3-hour monitoring period. This is far below their own threshold of clinically meaningful emboli (\(>25\) in 15 minutes) for adding therapy with LMD. Another small study examining the relationship between microembolic events after CEA and postoperative MRI studies has suggested that only microembolic event rates of \(>5\) per 15 minutes are associated with postoperative MRI ischemic changes.\(^10\) Unfortunately (again, back to the smoke and fire thing) there is no “smoking” gun linking microembolic events as assessed by TCD to postoperative macroembolic events such as stroke. Yes, there probably is a threshold, but it is much higher than the cutoff point used in this study. So what we are left with is observational: More intense antiplatelet therapy reduces the frequency of microembolic events. There is, as yet, no evidence to suggest whether this means anything clinically.

It is interesting to note that the authors use a postoperative algorithm incorporating LMD, a drug largely abandoned in the cardiology community, where it was used in the primeval days of coronary intervention, before the use of warfarin or the emergence of thienopyridines. The present observations with clopidogrel suggest that perhaps such a more potent thienopyridine might be the preferred initial addition to aspirin instead of the very weak antiplatelet actions of LMD. Extending the authors’ current postoperative algorithm, if TCD embolic event rate rises above a certain threshold, one could rapidly load with a thienopyridine. As secondary backup in the face of even higher embolic event rates, or if thienopyridine loading is not possible, a glycoprotein IIb/IIIa antagonist could be used.

What we arrive at is a layered therapeutic algorithm, with our various layers of therapy based on how active the presumptive platelet aggregatory response is (as reflected in TCD microemboli). It makes physiological sense but is completely unproven and needs to be prospectively tested. Does reducing the incidence of lower-level microembolic events improve outcomes? Is this going to be like reducing postoperative anginal events (and myocardial infarction), or is it going to be like reducing asymptomatic premature ventricular contractions (and having more complications with no benefit)? Is a tiered approach going to be safe and effective? Only a prospective study will say.

And what about bleeding complications? The current study involving the preoperative use of a single oral 75-mg dose of clopidogrel did not result in a significant increase in major bleeding, as assessed by blood loss and transfusion. There was, however, a significant increase in closure time, presumably as a result of more bleeding in the operative field. One has to question whether the benefit (fewer patients with lowish-to-medium microembolic event rates) is worth the risk (longer, more difficult procedures, perhaps with more bleeding). More rapid postoperative loading, or even the use of other forthcoming ADP receptor antagonists with more rapid onset of action,\(^11\) may help shift use from preoperative to postoperative dosing strategies.

The Study in a Larger Context

The technique of surgical CEA is being challenged by percutaneous techniques, especially with the advent of distal protection devices. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial showed that carotid stenting (with distal protection) was significantly better than CEA, with the composite of death, myocardial infarction, and stroke reduced by \(>50\%\) at 30 days in the stent group.\(^12\) The real downside of CEA has not necessarily been the long-term results, but rather the immediate surgical complications. In a recently published meta-analysis of the European Carotid Surgery Trial (ECST), North American Symptomatic Carotid Endarterectomy Trial (NASCET), and Veterans Affairs trial 309 (VA 309) (all of which were randomized trials of CEA versus medical therapy), the 30-day incidence of stroke or death was 7.1\%, and the 30-day mortality rate was 1.1\% in a total of 6092 surgical patients.\(^13\) This meta-analysis also suggested that although there was benefit of surgery over medical therapy in patients with lesions \(>50\%\), that benefit was limited in patients with lesions between 50\% and 69\% and was substantially greater in patients with lesions \(>70\%\) but without near-occlusion. In patients with near-occlusion (\(n=262\)), the benefits of CEA were “marginal in the short term, and uncertain in the long term.”

So if we have ways to improve the outcome of surgery, do we need to do the stent-versus-surgery comparisons all over again? I would say “no,” for the simple reason that we don’t yet know if we can improve surgical outcomes. And in much the same way as “a rising tide floats all boats,” I suspect that the more aggressive use of thienopyridines (and other potent antiplatelet agents, perhaps physiologically guided as with TCD) will provide benefit both for surgery and stenting—perhaps even more for stenting because pretreatment doesn’t make the surgical procedure more difficult with more bleeding.

We also need to expand our perspective to encompass other situations in which TCD microembolic signals (and presumed platelet microaggregatory events) have been shown to be important: recent stroke or transient ischemic attack, symptomatic carotid disease, cardiopulmonary bypass, and carotid stenting.\(^14\)-\(^17\) In all of these circumstances, antiplatelet therapy is an issue. Will the use of a super-sensitive technique help us in bettering adjusting antiplatelet therapy? Aspirin given acutely reduces microembolic events.\(^18\) Adding a thienopyridine to aspirin appears to reduce it more.\(^1\) Adding a IIb/IIIa antagonist may abolish it completely.\(^8\) But when should we reach for the bigger guns, if the bigger guns are going to produce more bleeding?

Directions for the Future

Where do we go from here? A couple of issues really need to be addressed before we can move ahead with a large-scale clinical trial. First, if we are to use a surrogate marker (such as TCD), we need to establish a threshold that is clinically meaningful. As noted above, we do have data suggesting that TCD microembolic rates \(>5\) in 15 minutes are associated with postoperative ischemic changes on MRI.\(^10\) Perhaps MRI, as recently used in a study of distal protection\(^9\) for carotid stenting, might be a more acceptable surrogate. However, in this study, the incidence of focal ischemia on MRI was 25\% with carotid stenting, even with the use of distal protection.
And, as pointed out by Yadav in an accompanying editorial, MRI ischemia does not always represent infarction, and “the gold standard for measuring ischemic brain injury, either spontaneously or postprocedural, remains a careful neurologic examination.”

Second, the safety issues are far from addressed. A single 75-mg oral dose of clopidogrel significantly increases the time for surgical closure. Approximately 30% of clopidogrel-treated patients had closure times >40 minutes, compared with 8% of placebo patients. This is probably not acceptable in the real world. Are lower doses going to be as efficacious? If the active compound is a metabolite, perhaps even a longer dosing interval after the 75-mg dose might be helpful. There are two additional alternatives: either dosing with a rapid load immediately postoperatively (or shortly thereafter), or else using a deferred approach where clopidogrel is used as an adjunct when needed (perhaps as indicated by TCD monitoring). Simply stated, if you are going to use more potent antiplatelet therapy, you are going to have more bleeding. Because we can’t seem to get around that, maybe we can use it more judiciously.

The final message is one of optimism. There is room for improvement. We have better antiplatelet agents. We can reduce TCD-detected microemboli. What we really have is an opportunity to improve patient care and perioperative outcomes. We just need to be able to do the studies, with acceptable end points and with less-than-prohibitive increases in bleeding (if possible), to see whether this opportunity is going to be realized or not.

Even through all this fog, there is some legitimate smoke and, probably, some fire. But having found a possible fire, now we have to do something about it.

After all, only you can prevent forest fires.

References


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