



# Current Medical Therapy for Stroke Prevention and Treatment

*Endovascular Today* engages lipid expert Richard Milani, MD, and stroke expert Roekchai Tulyapronchote, MD, in a rapid-fire Q&A session.



**Richard Milani, MD**, is Vice-Chairman, Department of Cardiology, Ochsner Clinic Foundation, New Orleans, Louisiana. Dr. Milani may be reached at (504) 842-5874; [rmilani@ochsner.org](mailto:rmilani@ochsner.org).



**Roekchai Tulyapronchote, MD**, is from the Department of Neurology, Division of Vascular Neurology, Bumrungrad Hospital, Bangkok, Thailand. Dr. Tulyapronchote may be reached at 011-662-2829320; [rotuly@hotmail.com](mailto:rotuly@hotmail.com).

**Endovascular Today:** What factors do you consider when determining whether a patient who has not suffered a stroke is at risk?

**Dr. Tulyapronchote:** I think there are quite a few factors, such as old age, dyslipidemia, diabetes, and cardiac rhythm abnormality, in particular atrial fibrillation. All of these are well-known risk factors for stroke.

**Dr. Milani:** Yes, age and hypertension, certainly, but dyslipidemia is an issue because in the Prospective Studies Collaboration, a meta-analysis of 45 prospective cohorts totaling 450,000 patients, cholesterol was not shown to have any kind of direct relationship to stroke. We know that smoking and peripheral vascular disease are both risk factors, as well as diabetes. There is some increase in patients of African American descent and a very minor increase in males over females. But the big risk factors are the ones already mentioned. And of course, previous TIA is one and a recent heart attack would be another.

**Endovascular Today:** Has the composition of the plaque ever entered into the equation?

**Dr. Milani:** It enters into the equation, but it is going to be problematic to turn that into a risk factor for stroke at this point. You have to recognize that risk factors are determined generally by large population studies in which we can look at the independence of one risk factor over another. Study of plaque composition is done in very small numbers of people using multiple techniques, and therefore cannot in large numbers be compared to other traditional risk factors for independence. What we can do from a population perspective are the things that have already been mentioned, we can monitor heart rhythm, age, and other significant comorbidities.

**Endovascular Today:** As your specialty evolves, do you consider yourself more of an endotheliologist? If so, how does that conflict with the data supporting statins and stroke prevention?

**Dr. Milani:** That's a very important question because if you look at the nonstatin trials, we have not been impressed by the impact on stroke via lipid modulation. It really wasn't until the statins came along that we found very consistent effects, and clearly, some of this must be due to lipids, but there are some other properties that statins possess that may be playing a significant role in stroke prevention. So, it is very unclear as to which of the effects are playing the primary role, but it appears to be more than just a lipid intervention.

**Endovascular Today:** How about if we include heart attack?

**Dr. Milani:** Well, heart attack is fascinating—you're absolutely right—because that is a period of time during which we have a very disturbed endothelium and, typically, beyond the culprit plaque that ruptures we will see an average of two to three other plaques that are very unstable or have ruptured as well but are not the culprit lesion. So, the milieu of heart disease suggests that there is a systemic endothelial problem, and that may in fact be the main reason why we see such a high prevalence of stroke in that period.

**Endovascular Today:** Are those other unstable plaques that you're observing only in the coronary artery?

**Dr. Milani:** Probably not. The reports have looked at just the coronary artery, and they have shown other unstable plaques within the coronary tree. No one yet, to my knowledge, has looked in the carotid or other areas of the vasculature to see what the frequency of instability would be. Our suspicion would be that it would be very similar, but that has not been studied yet.

**Dr. Tulyapronchote:** I think the size of the vessel may play some role. If you look at the carotid artery, we see 6 mm or 7 mm in size compared to the size the coronary artery. I'm sure that the structure of the plaque would affect some of the other vessels but probably not as much as in the heart.

**Endovascular Today:** Dr. Tulyapronchote, you have seen multiple strokes every day in your career for the last several years. How often do you see a plaque hemorrhage in a carotid artery as the etiology of the patient's stroke?

**Dr. Tulyapronchote:** My answer may be biased, but I think I see a fair amount, maybe 10% to 20% of our population.

**Endovascular Today:** Dr. Milani, isn't that the biochemically unstable plaque that you were mentioning?

**Dr. Milani:** Exactly. And the difference that Dr. Tulyapronchote brings up, of course, is that based on vessel size, I may not see an occluded carotid, whereas I might see an occluded coronary. The important understanding here is that most strokes, ischemic strokes at least, are due to embolization, which are likely platelet emboli. The underlying process would be in keeping with what is happening with the coronary vasculature. What we're learning, in fact, is that much of what we see with the heart is embolic as well. Again, the majority of acute coronary syndromes (ACSs) are non flow-limiting (non-ST-segment elevation MIs or unstable angina), which are typically characterized by TIMI II or III flow and peripheral embolization of platelet and other debris to the myocardium.

"The key to treating stroke patients is that we have to look at two basic things: (1) What is the etiology of the acute event; and (2) What are the coexisting factors?"



**Endovascular Today:** Dr. Tulyapronchote, if you see a patient who has had a stroke and is undergoing rehab and all the other things that you do for acute stroke patients, how do you prevent the next stroke? How do you treat that patient medically?

**Dr. Tulyapronchote:** I think the key to treating stroke patients is that we have to look at two basic things: (1) What is the etiology of the acute event; and (2) What are the coexisting factors? For example, in a patient who has a carotid stenosis plus atrial fibrillation, obviously the carotid needs to be fixed. At the same time, after the carotid is fixed, the patient needs to be on warfarin. So, to address that, you have to know the reason why they had a stroke in the first place.

**Endovascular Today:** Let's say in a patient with carotid plaque hemorrhage alone and atrial fibrillation is not an issue.

**Dr. Tulyapronchote:** In that kind of patient, if they

have acute stroke and if the size of the stroke is either moderate or large but they still have substantial risk to their brain, I would put the patient on warfarin for 4 to 6 weeks. At the very same time, obviously we have to take care of the risk factors and bring the patient back to undergo a revascularization procedure. After that, in the long run, provided the patient does not have any other risk factors, I may consider placing them on an antiplatelet drug.

**Dr. Milani:** I think we have learned a lot from our mistakes, if you will, in treating coronary disease. One of those mistakes was the lack of recognition that the primary event here is a plaque that's rupturing and the primary process that follows is initiated by platelets. So, we need therapies that stabilize plaque, that prevent rupture, and also therapies that reduce the response that occurs once a rupture does happen. These therapies include statins and of course antiplatelet therapy. An example would be a patient who, if we saw a plaque hemorrhage or evidence of rupture, would be treated much the same as we do in a coronary, which would be aggressive antiplatelet therapy and statin therapy. And, interestingly, now there are two trials, one of which was recently announced at the American Stroke Association and Stroke Conference in February, that looked at acute stroke intervention with statins, much like we do with acute MI. This was a trial called MISTICS and it showed that statin intervention within 3 to 12 hours after onset of symptoms of a stroke already demonstrated an improvement in the NIH stroke score assessed at day 3 and at day 90. Again, this suggests the importance of the plaque stabilization process.

**Endovascular Today:** So when you are on rounds over the weekend and you see a patient with acute MI, one of the first things you do is place them on a statin?

**Dr. Milani:** We do. We put them on a statin and we put them on, as we do for all ACS patients, aggressive antiplatelet therapy that would include an ADP antagonist on top of aspirin. This has been shown to be effective in the CURE trial, to have impact not only on MI and death, but also on stroke in patients with acute MI. The same process would occur in an unstable plaque in another area of the vasculature, and of course the other important area would be any area that is feeding the brain, so we treat them much the same.

**Dr. Tulyapronchote:** I couldn't agree more. That is

why I mentioned that, during the time that we are waiting for the patient to come back for revascularization, we should put them on lipid-lowering agents.

**Dr. Milani:** The only difference is that maybe we shouldn't wait until then to start it. The rationale behind it is the data from MISTICS—there might be an immediate benefit, just like with MI.

"We need therapies that stabilize plaque, that prevent rupture, and also therapies that reduce the response that occurs once a rupture does happen."



**Endovascular Today:** So with that recommendation, Dr. Milani, it sounds as though your career is really evolving in the direction of becoming an endotheliologist.

**Dr. Milani:** I couldn't agree with you more. I think what we have learned is that these therapies we thought were important in terms of the chronic management of patients, whether we were dealing with heart disease or cerebrovascular disease, are now transferring into acute management. The process of stroke, or at least ischemic stroke, as well as MI, are disorders of the endothelium and therapies that are designed to enhance endothelial function are showing benefits acutely. It is critically important that we are proactive in the hospital setting because that translates into not only short-term immediate gain, which is a period of high morbidity and mortality in the patient's hospitalization and posthospitalization phases, but also in terms of better long-term compliance.

**Endovascular Today:** You may remember a study that looked at hospital discharge; 12,000 patients were reviewed, and it was startling how infrequently PCI patients were not on all the right medications were not on optimal medical therapy.

**Dr. Milani:** That is absolutely right. There have been several data sets that have looked at this, one of which was through the National Registry of Myocardial Infarction, in which we see that really up to 50% of people up until at least March 2002 were getting statin therapy, and only 80% to 85% were on just aspirin ther-

apy following an MI. That's really something that should be closer to 95% to 100%. There is still a long way to go toward optimizing secondary prevention in patients who are being discharged with an acute event.

**Endovascular Today:** We'd like to ask each of you the same question: Say you have a patient—a physician who is 60 years old, working like crazy, high stress of course, normotensive, but already on a statin, and he has an asymptomatic 50% carotid, which disturbs him a great deal. Dr. Tulyapronchote, what medicines do you want him on?

**Dr. Tulyapronchote:** For an asymptomatic 50% carotid stenosis, obviously there is no study supporting that you need to undergo revascularization. If you take care of yourself by taking statins and antiplatelet drugs, I think I may add folic acid to the regimen. Now, whether or not clopidogrel is better than aspirin in your setting, I don't think anybody knows.

"I think that revascularization is the area that is most debatable because, as we delve more into this area, we find a lot of holes in the original NASCET and ACAS data."



**Endovascular Today:** So, what would you make him take?

**Dr. Tulyapronchote:** Plavix. I believe it is better than aspirin, but it has not been proven yet. I would prescribe Plavix and folic acid.

**Endovascular Today:** Dr. Milani?

**Dr. Milani:** Well, I have a lot to say. Unfortunately, there was a trial that was just published in JAMA in February this year called VISP (Vitamin and Intervention for Stroke Prevention). These were people with ischemic stroke who were randomized to folate to prevent a recurrent stroke, and it is unfortunate that folate therapy didn't change anything. In other words, lowering homocysteine in these individuals did not have any impact whatsoever over a 2-year period. Now, that doesn't mean that it may not potentially have an impact because if we were just to do the first

lipid-lowering trial that was ever to be done, and we were to stop at 2 years, we probably wouldn't see a whole lot of benefit. We often don't see benefits for 3, 4, or 5 years for many of the lipid trials. So, we don't have any clinical data yet that says that lowering homocysteine reduces stroke risk, although homocysteine on the front end appears to be a risk factor. We can tell you that antiplatelet therapy can reduce stroke risk and, at least in CAPRIE, an ADP antagonist was superior to aspirin monotherapy. TASS utilizing ticlopidine as monotherapy did show a similar superiority of the ADP antagonist over that of aspirin. The combination of the two is actively being studied. We can tell you the combination of the two is superior in reducing stroke as a combined endpoint in patients following an MI, in the CURE trial, but we will have to await more data to demonstrate that the combination of the two is superior in long-term management in someone like you've just described. I think that revascularization is the area that is most debatable because, as we delve more into this area, we find a lot of holes in the original NASCET and ACAS data. For instance, CEA in these trials doesn't seem to be of any benefit in women, and it appears not to offer much advantage in people even who are symptomatic unless it is done within a 2-week period following symptoms. And finally, you have to be in a center that has a very low perioperative morbidity and mortality. But, I think from a medication standpoint, this would be a person I would want to have on aspirin and clopidogrel. I would use a low dose of aspirin (81 mg), and I would certainly want to have them on ideal blood pressure control, and probably as important as anything else, I would want to have them on a statin.

**Dr. Tulyapronchote:** When we look at the data that has just been published, even in the CAPRIE study, we have to be careful because of those studies enter the secondary prevention, and we are trying to prevent primary events. We have to look into the risk versus benefit ratio. I think folic acid is benign medication and I think it may be worthwhile to drop homocysteine levels.

**Endovascular Today:** Dr. Milani, could you differentiate between ADP antagonist therapy (plus or minus aspirin) versus warfarin?

**Dr. Milani:** I would favor, at least for ischemic stroke, an antiplatelet approach versus an antithrombin approach. The most aggressive and relatively safe antiplatelet approach would be the combination of a low dose of aspirin plus clopidogrel.

**Endovascular Today:** And warfarin would be reserved for which patients?

**Dr. Milani:** Warfarin would be reserved primarily for patients with atrial fibrillation, a thromboembolic source of stroke coming from the cardiac source.

"When we look into our registry, approximately 15% to 18% of patients have more than one potential etiology."



**Endovascular Today:** Dr. Tulyapronchote, would that go along with your workup for most of your stroke patients? They do get TEEs, or do they not?

**Dr. Tulyapronchote:** Yes, they do. Now, there are a few indications in which we use warfarin in patients who have tight carotid stenosis who are waiting for surgery, or patients who have complete occlusion in whom we suspect stump emboli. Another indication for warfarin being studied is the patient who has intracranial stenosis, particularly African-American patients. So, those are the main indications for warfarin, other than what has been addressed.

**Endovascular Today:** Dr. Milani, any thoughts on statin therapy? Water-soluble? Fat-soluble? Does it make a difference? What about cytochrome P450 issues and polypharmacy in patients taking over-the-counter medications.

**Dr. Milani:** I think it is a huge issue. Of course, most patients that have cardiovascular disease, including cerebrovascular disease, typically are older, and there is a direct relationship between age and the number of medications one is taking. The higher the number of medications, the more likely it is that there will be a potential drug interaction. Those are all important factors in determining which statin to utilize. In terms of the efficacy in reducing stroke, there doesn't appear to be any difference among the statins but there does appear to be a significant difference among the statins in terms of drug interactions, and that must be taken into account. The water-soluble statin that is available is pravastatin, and it doesn't go through the cytochrome

P450 system by virtue of its water solubility. All the rest are essentially lipid-soluble to some extent, including rosuvastatin (which utilizes 2C29), simvastatin, atorvastatin, and lovastatin (which utilizes 3A4), all of which are part of the P450 pathway. With each of them, one has to be cognizant of potential interactions that could lead to myopathy or hepatotoxicity.

**Endovascular Today:** Dr. Tulyapronchote, would you like to give us parting remarks for a 60-year-old, female patient who has modified all of her risk factors? She has had an embolic stroke, has had carotid surgery, and we want to prevent her from having a recurrence. What is your optimal prescription medical therapy?

**Dr. Tulyapronchote:** After carotid surgery, I would probably put her on an antiplatelet drug. I agree with Dr. Milani and would use low-dose aspirin therapy plus Plavix. Whether or not it is actually better than a single agent I don't know but I have a feeling it is probably better.

**Endovascular Today:** Dr. Milani, CAPRIE would suggest that combined cardiovascular events in patients with peripheral vascular disease benefited tremendously with ADP antagonists.

**Dr. Milani:** Again, yes. Recognizing that both TASS and CAPRIE featured a single antiplatelet agent versus another one, and as such did not offer a combination approach. I agree with Dr. Tulyapronchote; I would use a combination ADP antagonist and aspirin over that of either the monotherapies, whether it be aspirin or an ADP antagonist.

**Endovascular Today:** In determining the source of a stroke, how confidently are you able to determine whether the embolism is coming from an atrial fibrillation problem or some other plaque along the circulation?

**Dr. Tulyapronchote:** I don't think we know. When we look into our registry, approximately 15% to 18% of patients have more than one potential etiology. For example, a patient can have atrial fibrillation with clot in the heart plus an ipsilateral carotid stenosis. But, I think both of those need to be addressed separately.

**Endovascular Today:** Gentlemen, thank you for your remarks. We have learned a great deal today and hope to invite you back in the future as better pharmacologic options are found for treating cardiovascular and cerebral vascular disease. ■