Endovascular management of acute ischemic stroke

A review

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The management of stroke has progressed significantly over the past 2 decades due to successful treatment protocols including intravenous and intraarterial options. The intravenous administration of tissue plasminogen activator within an established treatment window has been proven in large, well-designed studies. The evolution of endovascular strategies for acute stroke has been prompted by the limits of the intravenous treatment, as well as by the desire to demonstrate improved recanalization rates and improved long-term outcomes. The interventional treatment options available today are the intraarterial administration of tissue plasminogen activator and newer antplatelet agents, mechanical thrombectomy with the MERCI device and the Penumbra system, and intracranial angioplasty and stent placement. In this review the authors outline the major studies that have defined the current field of acute stroke management and discuss the basic treatment paradigms that are commonly used today. (DOI: 10.3171/2009.1.FOCUS08275)

**Abbreviations used in this paper:** ATLANTIS = Ateplase Thrombolysis for Acute Non-Interventional Therapy in Stroke; ICA = internal carotid artery; ICH = intracranial hemorrhage; IMS = Interventional Management of Stroke; MCA = middle cerebral artery; MERCI = Mechanical Embolus Removal in Cerebral Ischemia; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; PROACT = Prolyse in Acute Cerebral Thromboembolism; PTA = percutaneous transluminal angioplasty; r-proUK = recombinant prourokinase; rt-PA = recombinant tissue plasminogen activator; TIMI = Thrombolysis in Myocardial Infarction.
The only intravenous thrombolysis trials that have shown a benefit for acute stroke patients have been the NINDS trials. The main difference from previous stroke trials was the early time to treatment of < 3 hours from symptom onset. Intravenous rt-PA was given as 0.9 mg/kg of body weight with a maximum dose of 90 mg. Compared with the placebo study arm, patients in the treatment arm were 30% more likely to have minimal or no disability at 90 days. The symptomatic ICH rate within 24–36 hours was higher in those receiving treatment compared with the controls (6.4 and 0.6%, respectively). However, despite this elevated rate of hemorrhage, the mortality rate at 90 days was similar between the treatment and control groups. Based on this two-part clinical trial that established a 3-hour therapeutic window, the FDA approved the use of intravenous rt-PA in 1996.

Since the approval of intravenous rt-PA, multiple studies have attempted to stratify subgroups of patients who would benefit from intravenous thrombolysis alone and those who might require further endovascular treatment. In a recent review of 54 patients with proximal MCA occlusion receiving intravenous rt-PA within 3 hours, Labiche et al. found that 75% of patients who had early recanalization and a significant clinical recovery within 2 hours of drug administration had sustained clinical benefit at 3 months. This particular analysis was not performed as primary endpoints during the NINDS trials, but post hoc analysis of the NINDS data parallels this conclusion.

In another study, Felberg et al. demonstrated that the restoration of flow at the end of intravenous rt-PA infusion was a significant factor in differentiating patients who would make a dramatic recovery from those who would not. Normal restoration of flow was seen in 58% of patients who experienced a dramatic recovery and in 14% of those who did not experience a dramatic recovery. One of the potential treatment applications of this concept could be that patients with persistent proximal occlusion without signs of early recovery may be candidates for further interventional management. In the subset of patients who do not improve after intravenous thrombolysis, prompt MR imaging, with particular attention to large mismatches between diffusion and perfusion sequences, has become routine at many institutions. If there is a salvageable ischemic penumbra, without ICH, endovascular therapy should be considered the next step in treatment and has been described by some as a “rescue” procedure.

**Intraarterial Thrombolysis**

One of the main limitations to intravenous rt-PA has been the strict 3-hour time window for initiating therapy. This window, combined with a limited public health awareness of stroke, has limited the use of intravenous thrombolysis to < 5% of eligible candidates. Intraarterial thrombolysis was first studied as an alternative to intravenous thrombolysis to address this time limit. The idea behind intraarterial thrombolysis is rapid local delivery of drug with a greater concentration of thrombolytic agent at the site of occlusion and lower concentrations systemically. Theoretically this should lead to improved recanalization and reduced hemorrhagic complications, but because of the differences in stroke severity, time to treatment, and increased rates of MCA recanalization with intraarterial treatment, direct comparisons have been difficult and currently no controlled studies exist.

The pretreatment evaluation for intraarterial treatment is similar to that for intravenous treatment: Once an acute stroke is diagnosed, baseline CT scanning or, more recently, MR imaging is commonly performed to exclude ICH, identify a point of occlusion, and define the region of salvageable brain parenchyma. A catheter cerebral angiogram is then performed to confirm the point of occlusion and assess the degree of collateral circulation. A microcatheter is advanced either to the base of the clot, into the clot, or distal to the clot, and a thrombolytic agent is injected. A variety of agents exist for intraarterial thrombolysis, and at our institution rt-PA is most commonly used. The thrombolytic agent is infused over 60–120 minutes while intermittent angiographic studies are obtained. Additionally, mechanical disruption of the clot with a guidewire or balloon may be used to effectively evacuate clot. The efficacy and safety of intraarterial rt-PA–based thrombolysis was established in the PROACT I and II studies, which were randomized, multicenter, controlled trials. Intraarterial thrombolysis in patients with MCA occlusion was at least as equally effective as intravenous thrombolysis in improving outcome and more effective in reopening the occluded artery (in approximately two-thirds of the cases). This was true even with a longer 6-hour window from symptom onset to treatment. Recanalization rates for intraarterial thrombolysis have been shown to be superior to those for intravenous thrombolysis for major cerebrovascular occlusions (70% vs 34%). The differences in recanalization are most apparent with large-vessel occlusion such as proximal MCA, ICA, and intracranial carotid artery “T” occlusion.

Figure 1 provides a cerebral angiogram of a patient in whom intravenous rt-PA was contraindicated. There is a thromboembolic clot at the left ICA terminus (“T” occlusion) resulting in significant occlusion of the left ICA, and no perfusion of the distal vessels. A microcatheter was embedded in the ICA clot, and intraarterial rt-PA (retaplase) was injected into the clot. As clot lysis was visualized on serial angiograms the microcatheter was advanced into the clot, which extended into the M1 segment of the MCA. Figure 2 demonstrates complete recanalization of the left ICA and MCA after injection of 3 mg of intraarterial rt-PA.

**Combined Intravenous and Intraarterial rt-PA Thrombolysis**

Although intraarterial thrombolysis has been shown to be effective, the time delay required for cerebral angiography and microcatheter positioning is a shortcoming. Because of this shortcoming, more recent investigations have combined both intravenous and intraarterial thrombolysis, allowing for the immediate initiation of intravenous thrombolysis within the 3-hour window followed by an intraarterial thrombolysis treatment within the 6-hour window.
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The largest prospective trial to date to study combined therapy was the recent IMS trial that was released in 2004.11 Eighty patients with a medial baseline NIHSS score of 18 received intravenous rt-PA within 3 hours of onset followed by a 2-hour infusion of intraarterial rt-PA. The primary comparisons were with a similar subset of placebo- and intravenous rt-PA–treated patients from the NINDS rt-PA Stroke trial. The 3-month mortality rate of 16% was not statistically different from that in the placebo (24%) and rt-PA treatment (21%) groups from the NINDS trial. The rate of symptomatic ICH (6.3%) was also similar to the rt-PA–treated group (6.6%) but higher than that in the placebo group (1%). The individuals in the IMS trial had significantly better outcomes at 3 months (56%) than the NINDS placebo group for all outcome measures.

A follow-up study by the IMS investigators further compared symptomatic and asymptomatic ICH rates in IMS with other large clinical trials including NINDS, ATLANTIS, European Cooperative Acute Stroke Study, Emergency Management of Stroke Bridging trial, and PROACT.12 Symptomatic ICH occurred in 6% and asymptomatic ICH in 43% of patients. The rate of symptomatic hemorrhage was similar to that in the intravenous rt-PA–only arm of the NINDS study. The rate of asymptomatic hemorrhages was higher than in the NINDS trial but similar to other more recent combined intraarterial-intravenous rt-PA trials. The only 2 factors that were independent risks for any hemorrhage were location (ICA) and atrial fibrillation.

Currently, the results from the IMS II study, a larger follow-up trial for efficacy, are still pending. Enrollment is now underway for the IMS III study to compare intravenous rt-PA with intraarterial intervention, including the adjuvant use of mechanical thrombolysis. The patients will be randomized into intravenous rt-PA–alone or intravenous/intraarterial treatment groups. The patients in the intravenous/intraarterial treatment arm will receive intravenous rt-PA and then undergo immediate angiography. If a clot is still visualized, 1 of 3 intraarterial treatment modalities will be used: the Merci retrieval device, EKOS microinfusion catheter, or intraarterial rt-PA injected at the site of the clot.

**Abciximab Trials**

There has been a recent interest in the use of abciximab for acute stroke. Abciximab is a monoclonal antibody that inhibits platelet aggregation by binding to the platelet fibrinogen receptor glycoprotein IIb/IIIa. Platelet aggregation is one of the first events to occur in the arterial thrombosis occlusion cascade, and if that initial accumulation of platelets could be inhibited, perhaps recanalization rates could be improved. Additionally, rt-PA itself promotes thrombus formation by stimulating plasmin production, thereby activating platelets. Blocking platelet activity may therefore also reduce reoclusion rates after intravenous rt-PA administration. Lee et al.18 have studied 16 patients who were given intraarterial UK alone and 20 patients who were given intravenous abciximab (0.25-mg/kg bolus) followed by a maintenance dose (0.125 ug/kg/min). These patients also received UK until complete or near-complete vessel patency was restored or until 1,000,000 U of UK had been administered. All patients underwent CT scanning immediately after treatment. In the combined urokinase/abciximab group 90%...
exhibited recanalization compared with 44% in the UK group alone. A lower dose of UK was required for recanalization when used with abciximab. There was no significant difference in the rate of hemorrhage, but there was a trend toward better outcomes in the combination group (80 vs 50%).

The findings of the study by Lee et al. support the possibility that the addition of abciximab improved the outcomes of a subgroup of intravenous rt-PA-treated patients who initially responded but experienced early failures due to vessel reocclusion. A recent study looked at 142 consecutive stroke patients with documented MCA occlusion that was treated with intravenous rt-PA. Initial recanalization occurred in 61% of patients, but 12% had documented reocclusion on transcranial Doppler ultrasonography at a mean time of 65 ± 55 minutes after recanalization. One of the independent predictors of reocclusion was severe ipsilateral carotid artery disease. The authors suggested that platelet-rich emboli most commonly found at the carotid artery bifurcation may create a thrombus that could be more resistant to lysis by rt-PA and more prone to reocclusion. The presence of a severe stenosis or occlusion in the carotid artery may also represent a marker of diffuse atherosclerotic disease. In this case the presence of simultaneous thrombus formation at the site of an underlying MCA plaque may lead to incomplete recanalization and early reocclusion. These types of cases may be ideal for the use of a combination of rt-PA and abciximab, but this premise still requires further study.

Although the use of abciximab has not been well established in the management of acute stroke, there exists a growing body of literature suggesting that it may be of significant benefit in the treatment of intraprocedural thromboembolic complications. A majority of these are small case reports, but the authors of the largest series reviewed 29 patients in whom cerebral arterial thromboembolic occlusions developed intraoperatively and in whom abciximab was administered within 60 minutes. Angiographic improvement was seen in 81% of the cases. There were 3 ICHs that occurred when abciximab was administered with mechanical clot disruption. Two of these hemorrhages also received rt-PA. At follow-up, 83% of the patients were independent, 10% were dependent, and 7% had died. In the hyperacute period of a thromboembolic event, platelet aggregation is known to play a large role in the formation of the initial thrombus plug. Abciximab is believed to disrupt this initial process and is ideal in intraprocedural complications because treatment can be administered while in the hyperacute state. Because of the increased rate of ICH with mechanical clot disruption, some interventionists do not recommend using these devices with abciximab.

Recent publications have raised the concern that abciximab causes ICH. One of the reasons cited has been the relatively long half-life of the drug that can cause low-
level blockade of platelet receptors up to 15 days after administration. Numerous prospective studies have detailed the safety and efficacy of abciximab. A randomized, double-blinded, placebo-controlled dose-escalation study conducted by the Abciximab in Stroke Investigators showed no difference in the risk of asymptomatic ICH (7%) detected on 3-month poststudy CT scans compared with controls (5%) and illustrated a trend toward better outcomes in the abciximab treatment arm. Another study showed that abciximab was safe and posed no increased risk of ICH during carotid artery stent placement in 151 consecutive patients when used in combination with heparin or aspirin. The newer glycoprotein IIb/IIIa receptor agonists eptifibatide and tirofiban have shorter half-lives (2.5 and 2 hours, respectively) and are thought to be potentially safer.

**Mechanical Embolectomy: the Merci Device**

Given the risk of ICH and limited time constraints associated with thrombolytic agents, alternate means of removing a clot are in the forefront of stroke research. The MERCI Stroke trial was designed to test an intravascular mechanical thromboembolic retrieval device that was developed to address some of the shortcomings of intravenous rt-PA therapy. The Merci device (Concentric Medical), approved by the FDA in 2004, consists of a flexible tapered nitinol wire with 5 helical loops that can be embedded within the thrombus for retrieval. Figure 3 demonstrates the Merci retrieval device. The FDA-approved Phase I and II trials were performed at 25 participating hospitals in the US. The primary endpoint was successful revascularization in all treatable vessels and major device-related complications. Revascularization criteria were based on the TIMI Scale score and defined as either TIMI 2 or 3. The inclusion criteria were patients with an acute stroke whose NIHSS score was > 8, who were treated within 8 hours of symptom onset, were ineligible for intravenous rt-PA, and who had an angiogram documenting the point of occlusion. Patients with an international normalized ratio < 3.0 were included in Part II of the study, which broadens the potential treatment group compared with previous studies.

Of the 1809 patients screened, 151 were enrolled, and of these, 141 patients had the Merci device used. In the overall group, 48% of occluded vessels were recanalized with a 7.1% rate of clinically significant procedural complications, a 7.8% rate of symptomatic ICH, and a 44% mortality rate. The baseline control arm was the spontaneous recanalization rate of 18% from the PROACT II study. Device complication included vascular perforation, intramural arterial dissection, or embolization of a previously unaffected territory. In addition, patients in whom recanalization was successful were more likely to experience a good neurological outcome (modified Rankin Scale score of 0–2) at 90 days (46 vs 10%, respectively) and the mortality rate was lower (32 vs 54%, respectively).

Figure 4 shows an anterior cerebral angiogram obtained in a patient who presented outside of the 3-hour window for intravenous rt-PA. She was taken to the angiography suite where a thromboembolic clot was noted in the cavernous ICA (Fig. 4). A microcatheter was passed distal to the clot, which indicated that the clot extended well into the MCA M2 segment. The Merci device was deployed within the clot and retracted; the corkscrew-like appearance of the deployed device is demonstrated in Fig. 5. A large clot was noted within the aspirate when the ICA clot was engaged with the L5 Merci device, and a smaller MCA clot was noted to be embedded within this device (Fig. 6). The subsequent cerebral angiogram (Fig. 7) demonstrated recanalization of the left ICA with perfusion of the distal intracranial vessels.

Most recently, the Multi-MERCI Stroke trial results were published. This multicenter, prospective, single-arm trial is similar to the previous MERCI trials; however, this study included patients receiving intravenous rt-PA...
Mechanical Embolectomy: The Penumbra System

The Penumbra system (Penumbra, Inc. (Fig. 8)) is a device by which a thromboembolic clot can be removed from large intracranial vessels. The device removes thrombus via aspiration, mechanical disruption, and extraction. Once the catheter is positioned just proximal to the clot, the aspiration pump is connected to the catheter. The aspiration pump generates a vacuum of ~20 in of Hg, which reduces the clot burden. The separator is then advanced through the catheter into the distal clot, aiding in the aspirating-debulking process. If thrombus persists, direct mechanical removal of thrombus may be performed with the aid of the thrombus removal ring. The thrombus removal ring works by engaging the clot proximally and extracting underflow arrest with the assistance of a proximal balloon guide catheter.

Phase I findings of the Penumbra system were recently published and demonstrate exciting results. A multicenter, prospective, single-arm trial was designed to evaluate the safety and efficacy of the Penumbra system. The primary endpoint was revascularization of the target vessel defined by a TIMI score of 2 or 3. The secondary endpoints were improving the NIHSS score by 4 points or achieving a modified Rankin Scale score of ≤2, and evaluating all-cause death. Twenty-three patients were enrolled in the study and 21 vessels were treated with the Penumbra system. Three patients were not treated due to vessel tortuosity and failure of access, resulting in an access rate of 87%. Recanalization to a TIMI score of 2 or 3 was achieved in all 21 vessels in which the device was deployed. The secondary endpoint of modified Rankin Scale score of ≤2 or improvement of NIHSS score by ≥4 points was achieved in 45% of the patients.

The adverse events were within the limits of previous acute stroke studies. Nine (45%) of the enrolled 20 patients died within the 30-day follow-up period. Given the severity of the stroke cases treated, a mean NIHSS score of 20, and the 9 (43%) basilar artery occlusions, the mortality rate was lower than expected; none of the deaths were related to the study device. There were 2 procedural complications: a groin hematoma and a subarachnoid hemorrhage that resolved spontaneously and did not result in neurological deterioration. In 8 cases an ICH was reported, 2 of which were classified as symptomatic. In 7 of the 8 patients with ICH, intraarterial rt-PA was used after the Penumbra system to treat vessel occlusion distal to the recanalized target vessel.

Based on the Phase I trial results, the Penumbra system has been shown to have significant potential for mechanical embolectomy in the treatment of acute stroke in large intracranial vessels. In 100% of the cases in which the device was deployed, recanalization of the target vessel was achieved. Adjunctive therapy with intraarterial rt-PA, however, was associated with a higher incidence of ICH. The Penumbra device has recently received FDA approval.

No other mechanical embolectomy device is currently approved by the FDA for use in acute stroke. Two unapproved devices are the Neuronet Endovascular Snare (Guidant Corp.) and the Amplatz Goose Neck Snare (Microvena Corp.). These have only been successfully used with persistent arterial occlusion. The primary endpoints evaluated were recanalization rates of intracranial occluded vessels and procedural complications.

Of the 1088 patients screened for the Multi MERCI Stroke trial, 177 patients were enrolled, and in 164 patients the Merci retractor device was used. In the overall group, 68% of the occluded vessels were recanalized with a 5.5% rate of clinically significant procedural complications, a 9.8% symptomatic ICH, and a 34% mortality rate at 90 days. Additionally, despite the inclusion of patients receiving intravenous rt-PA, there was no statistical difference in the ICH rate or procedure-related complications compared with earlier MERCI trials, indicating that preprocedural intravenous rt-PA is safe. Much like earlier MERCI trials, Multi MERCI demonstrated that patients with successful recanalization were more likely to have a good neurological outcome (modified Rankin Scale score of 0–2) at 90 days (49 vs 10%, respectively) and the mortality was lower (25 vs 52%, respectively).

The Merci device has been shown to be useful, especially in large-vessel occlusions, and the safety profile of the device is comparable to previous acute stroke interventions. Additionally, this device has proven that recanalization is significantly associated with better neurological outcomes and lower mortality rates. It has not yet, however, been proven to be effective in a prospective randomized controlled trial for improving clinical outcomes.

There are 2 ongoing trials using the device, the MR and Recanalization of Stroke Clots Using Embolecotmy and the IMS III trial. The former investigation is an NIH-sponsored trial to determine if diffusion-perfusion MR imaging prior to stroke intervention can identify patients who might benefit from mechanical embolectomy with the MERCI device. Finally, the IMS III trial will study intravenous rt-PA versus intraarterial multimodality treatments. The patients will be randomized into intravenous rt-PA alone or intravenous/intraarterial treatment groups. The patients in the intravenous/intraarterial treatment arm will receive intravenous rt-PA and then undergo immediate angiography. If a clot is still observed, 1 of 3 intraarterial treatment modalities will be used: the Merci retrieval device, EKOS microinfusion catheter, or intraarterial rt-PA injection at the site of the clot.

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Fig. 8. The Penumbra system: the catheter is positioned just proximal to the clot, the aspiration pump is connected to the catheter, and the separator is advanced through the catheter into the distal clot, aiding in the aspirating-debulking process. Image used with the permission of Penumbra, Inc.
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in a limited number of patients without any larger-scale demonstration of efficacy or safety.\textsuperscript{14}

\textit{Angioplasty and Stent Placement}

Concerns remain about the limited treatment window and associated hemorrhage risk of intravenous and intraarterial thrombolytics and the disappointing rates of recanalization reported with mechanical embolectomy. This concern has prompted the application of other techniques including intracranial angioplasty and stenting, used so successfully in the cardiac literature; the direct application of techniques described in the cardiac literature, however, must be considered conservatively given that the vasculature and circulation of the cardiac system differ significantly from that of the cerebrovascular system.

The largest study of angioplasty for acute stroke was conducted by Nakano et al.\textsuperscript{21} Thirty-six patients presenting with acute strokes underwent thrombolytic therapy alone, and 34 other patients were treated first with PTA and subsequent thrombolytic therapy was added if needed for distal embolization. The rate of partial or complete recanalization based on TIMI scores was 91.2\% with PTA and 63.9\% with thrombolytic therapy only. The incidence of ICH was 2.9\% and 19.4\%, respectively. This risk difference highlights one of the potential benefits of PTA. Independent outcome was also better in the PTA group than the thrombolytic-only group (73.5 vs 50\%, respectively).

Other smaller studies have also reported improvement in NIHSS score for patients who underwent angioplasty in addition to intravenous rt-PA.\textsuperscript{25,34} One of the important conclusions of these studies was the development of a protocol to ensure that angioplasty is not significantly delayed while evaluating the efficacy of already initiated thrombolytic therapy. In the most recent study, the authors conducted a retrospective review of 9 patients with acute strokes and MCA or intracranial ICA occlusion who underwent PTA.\textsuperscript{20} All patients underwent head CT scanning to assess the location of the occlusion and CT perfusion scanning to assess tissue salvageability. Patients available within the intravenous rt-PA window received the medi- to assess the location of the occlusion and CT perfusion scan. The mean minimal luminal diameter was larger with stent therapy than with angioplasty alone.\textsuperscript{7} In addition, the need for target-vessel revascularization because of ischemia, as well as death and reinfarction, were lower with stenting. The trial concluded that in patients with acute myocardial infarction, implantation of a stent has clinical benefits beyond those of angioplasty alone.

Reports on the intracranial application of stent technology are limited in the current stroke literature. The largest and most current study retrospectively analyzed 19 patients with acute stroke who underwent intracranial stent placement after failure of pharmacological and/or mechanical thrombolysis.\textsuperscript{19} All patients had an NIHSS score > 16 with 8 occlusions in the ICA terminus, 7 in the MCA, and 4 in the basilar artery. The overall recanalization rate was 79\% with only 1 asymptomatic ICH. Lesions at the ICA bifurcation and older age were associated with poor outcomes. These results suggest that intracranial stent insertion may be a viable option for recalcitrant arterial occlusions. This study also highlights some of the limitations of intracranial stents, which include the risk of vessel rupture or dissection and the long-term risks of restenosis. In addition, until recently, stents that were appropriately sized and trackable to intracranial vessels did not exist. Small coronary stents are now available that can be placed in the intracranial vasculature, but with the variety of stents now available it may be difficult to standardize the stents used in clinical studies, as was the problem in the report by Levy et al.\textsuperscript{19} In 2005 the first FDA-approved intracranial stent (WingSpan; Boston Scientific) was released. To date its applications are for intracranial atherosclerotic disease and not acute stroke, but as experience with the device grows, so perhaps will the applications.

\textbf{Conclusions}

The prompt and aggressive management of acute stroke has been shown to directly affect clinical outcomes. The 3-hour window remains a critical time period in which intravenous rt-PA needs to be administered to be of benefit. However, additional stroke studies have demonstrated that most patients do not receive intravenous thrombolysis and many others simply do not qualify. Newer endovascular technologies have greatly expanded the treatment armamentarium of stroke clinicians with catheter-based thrombolytic and antiplatelet administration, mechanical embolectomy, and angioplasty with stent placement. Many of these approaches have yet to prove their benefits in controlled clinical trials, but they offer new hope for a very large population of patients.

\textbf{Disclosure}

Dr. Prestigiacomo reports being a consultant for Boston Scientific, Thermopeutix, Micrus Endovascular, and Aesculap as well as a stockholder in Thermopeutics.

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