

JAMES S. On that note, as a surgeon I never get to talk about happy topics. We talk about bad-- aneurysms, cancer. And **WALDRON, MD:** this topic's similar to all those topics. We're talking now, for the most part, which is the most destructive form of stroke that we see here in our Comprehensive Stroke Center.

And we spend a lot time on the value of IV tPA, and a lot of the things that will allow us to potentially, in a subset of people, make people better, and at least hopefully, diminish the amount of disability they have when they leave the hospital. And IV tPA and the other endovascular therapies for ischemic stroke have moved the ball a long ways down that court.

Unfortunately, with intracerebral hemorrhage, we're not nearly as far. OK. And with our growth as a comprehensive stroke center, we're seeing more of these patients in transfers. Those of you who are with HIA or internal medicine groups are seeing these patients, both in the ICU and on the floor. Our nursing staff in the ICU, on the floor, are seeing a lot more these patients. And obviously, all the therapy staff as well.

And so my goal tonight is simply to kind of go over the disease and tell you kind of where we are and kind of what the current avenues for investigation, with the goal bringing this field up to where ischemic stroke is now. And unfortunately, I have no disclosures.

In terms of a learning objectives today-- so today we're going to go over and we're going to understand kind of the prevalence and impact of cerebral hemorrhage. We're going to go over the pathophysiology and why it causes so many problems. And like all good programs, we're going to spend a lot time looking at the guidelines, and trying to evidence base medicine.

And then we're also in depth going to discuss the role of surgery. Because I frequently get asked the question, this guy has a big hemorrhage in his brain. Why don't you take it out? And we'll go through that in exhaustive detail.

I always like to start with this slide for any stroke talk. And this simply demonstrates the stroke belt in the United States and the fact that the Texas is the Western-most anchor of the stroke belt. Austin is a little oasis, but you go 15 miles in any direction, we're in the heart of the stroke belt. And so we see a lot of patients here who have strokes at younger ages due to a wide variance of reasons. But the good thing about younger stroke patients is they tend to do better than 80-year-old with strokes in terms of the recovery, if there is a good thing.

As Joanna mentioned in her talk, there's about 700, 000, to 800,000 strokes a year in the United States. 87% are ischemic. About 13% are hemorrhagic. About 500,000 are first strokes, and the other 200,000 are recurrence.

Ischemic strokes, pretty self-explanatory. You have a blood vessel, it gets shut down for whatever reason. Brain beyond it doesn't get blood supply. You get an ischemic stroke.

Hemorrhagic strokes is more defined by the presentation. You're bleeding. The bleeding can either be in the brain with intracerebral hemorrhage, or it can be outside the brain with subarachnoid hemorrhage. We're not going to talk about subarachnoid hemorrhage today because we did that last year.

This screen shows two kinds of hemorrhages that we very commonly see in the ICU. The one on the left is simply a subdural hematoma, and it's basically a neurosurgical disease. If you see this, if the patient isn't already too foregone, you take it out.

In this case here, the blood is between the surface of the brain and the bone. As you can see on this, it's having significant mass effect on the underlying brain, and the center of the brain is pushed over. This is one of those things that, if you take it out early enough, the patient can do very well. If not, they will go on and die.

The image over on the over on the right side is the classic presentation of a subarachnoid hemorrhage patient. And the key thing with this image is that, all this blood-- the white stuff that looks like a crab in the middle the field-- it's not in the brain. It's in the spaces around the blood vessels that take blood to the brain. And so it's, to a certain extent, it's a very different beast.

There's an initial ICP spike when you have hemorrhaging in this space, but the patient makes it through that. There's not necessarily a huge amount of underlying damage to the brain. And so, a fair percentage of these patients can go on to recover.

And now we have intracerebral hemorrhage. Of these three pictures, which would you rather have? And it's not going to be this one, OK? And this picture basically looks like a classic hypertensive hemorrhage that's large. You have a large blood clot that's in the middle of the brain disrupting the surrounding fibers. You have blood that's gone into the ventricle just because the clot's so large. And you have significant mass effect. And it's pretty obvious that this patient is devastated by this.

In terms of epidemiology, about 8% to 15% of strokes in the United States are intracerebral hemorrhage. It occurs more frequently in Asian and African-American populations. And overall, the most important number of the stroke is, if you present to the hospital with an intracerebral hemorrhage, there's an overall 40% mortality rate. That's higher than any other type of stroke. And like everything else, with our aging population and the advent of comprehensive stroke centers, the rate of hospital admissions of these patients has actually gone up 18% over the last 10 years.

Another dense slide, and I've got a bunch of these. The point of this is to demonstrate the intracerebral hemorrhage is very closely associated with age. If you're in the zero to 44 age group, you have a little less than two per hundred thousand incidences of intracerebral hemorrhage. Once you hit 65 to 74, goes up to 98. At 75 to 84, it's 175 per hundred thousand. And over 85, it's 300 per hundred thousand.

And to a certain extent, this skewed towards the elderly also explains its mortality. If you're over 85 years old and you have a brain hemorrhage, chances are that's your life-ending event. And it's not something, regardless of medical care, that you're likely to recover from.

In terms of mortality, again this slide demonstrates that in most groups, the mortality rate is over 40%. The one with the vertical bar here is the rate in people whose clot is large enough that it actually hemorrhages into the ventricles. And the ventricles are those spaces in the middle of the brain where your cerebral spinal fluid is made. And in that group, the mortality rate is actually 60%. And so that's a huge marker for bad outcome.

The other thing that's most important in doing prognosis for someone is the overall size of the hemorrhage. I drew a red box on the screen which basically has no black dots in it. And this red box is directly over the numbers one through three on this disability score. One through three are moderate disability or less. Four, five, and dead are pretty self-explanatory. That means you're very bad off. And if you note, the volume of the hemorrhage, no one who had a hemorrhage, except for the one patient who had a hemorrhage over 30 cc was in this low disability group. So there's a huge correlation between the size of the hemorrhage and your overall disability after experiencing this.

So what your risk factors? What drives intracerebral hemorrhage? And because it's a disease that has multiple causes, there's one condition that causes still the vast majority of them, and that's high blood pressure. So by far, high blood pressure is a risk factor for intracerebral hemorrhage.

Age is another major risk factor, one that's come about a lot more with the use of antiplatelet agents, the use of Coumadin, and now the use of the newer Pradaxa and Xarelto, and other anticoagulant agents, as we're seeing it more that are, at least in part, related to these anticoagulant medicines.

There's other factors, such as ethnicity and drug use. This slide just demonstrates the difference in rates between African-American and Caucasian-American patients. Once you get to 75, they basically equal out. And this is pretty much wholly attributed to the fact that there is a much higher rate of high blood pressure in young African-Americans that is often not treated. And it is set up for these hemorrhages, unfortunately.

So what are the overall causes? And like I said, we define intracerebral hemorrhage as more of what the head CT looks like, rather than it's a specific cause related to the presence of the hemorrhage. The most common causes are hypertensive hemorrhage and amyloid angiopathy. The two of these cause probably 85% of the intracerebral hemorrhages. Hypertensive hemorrhages account for probably 60% of those.

You also have a percentage of patients who have ischemic infarcts that go on to develop hemorrhage within their infarct. Then as I mentioned earlier, medication n-related ones.

Less common ones are the vascular malformations-- aneurysms, AVMs. And then you can get hemorrhagic tumors. And as in Joanna's talk, there's always a laundry list of more rare things that could contribute as well.

Again, I come back to this picture just because I want to drive home kind of the magnitude of what a large intracerebral hemorrhage does to the surrounding brain. And like I said, that picture was a classic picture of a hypertensive hemorrhage. The location for the hemorrhage is what we consider deep. Its origin is an area called the basal ganglia, which has a lot of functional characteristics for the brain. A lot of your motor fibers go through those areas. Consciousness is close to that. And so when you have something like this, in this case, the cat's probably already out of the bag. No matter what you do for this patient, this is going to be in that vegetative to dead group.

Why do people get hypertensive intracerebral hemorrhages? And basically what happens, and this schematic helps demonstrate this, is when you have prolonged hypertension, you have a lot of perforating arteries that come off the major blood vessels that take blood to the brain. And these perforating blood vessels-- and it's thought to be because they arise directly from a major artery-- are susceptible to high blood pressure in the sense that, over time, it causes injury to the blood vessel wall.

You get degradation of that wall, and then you also get dissection. And to a certain extent, you can get formation of the pseudo aneurysms in these regions. And these pseudo aneurysms are the set up for potential intracerebral hemorrhages.

So this is an MRI of someone with severe hypertension, has never had an intracerebral hemorrhage. But what this does show, as you can see, these little microbleeds on it. And so what these microbleeds represent, they represent these little aneurysms that have ruptured. The body's just done a good job of controlling the initial hemorrhage, so it never became clinical. All right. But this is-- if you have an MRI like this, you're at extremely high risk to go on and have intracerebral hemorrhage.

So the next most common diagnosis is cerebral amyloid angiopathy. And the way to think about this is the mechanism is actually fairly similar to hypertensive, where you get damage to the blood vessel walls. That leads to the degradation of integrity of that wall. It's just a completely different cause. You get the deposition, this A beta peptide, which is actually the same protein that causes Alzheimer's disease, in the blood vessel walls.

And it's usually associated with age. In general, people who have bleeds from this are in old age cohort, 70 and greater. As it says on this slide, greater than 50% of people over 80 have evidence of amyloid angiopathy, not necessarily a hemorrhage. And the other difference between this and hypertensive bleeds is amyloid angiopathy actually tends to be more cortically based, or what we call a low bar hemorrhages.

If you look at the top left of this image here where you're more on the cortex, that's the region that amyloid angiopathy-related hemorrhages tend to occur. The deeper ones more often are hypertensive in origin.

So the next thing we're going to talk about is the path of physiology. So how does this hemorrhage cause injury? Some of them are pretty evident. You get primary injury at the time of hemorrhage. This is just a simple, mechanical injury to cell destruction, cell stretch that leads to cell death. And also ischemia and their surrounding tissues because there's so much pressure just from the new blood clot that's there. Nothing about that right now it's fixable. That's the kind of injury that's done at the time of hemorrhage.

Then there goes on to the secondary injury that's due to inflammation, this both from the breakdown of that blood clot and also some of the clotting factors that are associated with the presence of blood in the brain. These go on to activate microglia, which are like the macrophage of the brain. They set in motion another inflammatory response that can lead to cell death and what we would consider secondary injury.

In addition to the direct injury caused by the clot and inflammatory process it starts, you also get this perihematomal edema. And this is, basically, the cells in the area around the clot aren't very happy. They've just been through this horrific experience, and the way the body reacts to that is you get fluid that comes out of the cells. And you get this extra-cellular edema. And it's been demonstrated that you get up to a 75% increase in edema in the first 24 hours. It goes on to continuously swell for up to five to six days. And then slowly over the following two weeks, you go back down to a pre-hemorrhage state.

This can lead to secondary injury directly around the clot, again, just from the high level of pressure preventing those cells from getting adequate nutrition. And also, if it's large enough, it can cause global ICP elevation so that-- the way you think about it is, your skull is fixed. You've got a brain in your skull. If that brain has a reason to swell, it doesn't have anywhere to go to expand. So all it can do is increase the pressure. And if those pressures get high enough, that can cause global ischemia and death.

Another issue that we encounter with intracerebral hemorrhage is the issue of hematoma expansion. So this slide does a very good job of illustrating this. So the image on the far left here is a thalamic hemorrhage that came in, and this was their initial head CT. So not a bad scan. This is definitely a survivable scan. We'll probably have a deficit because this is in some of the motor areas.

Then look at the subsequent CTs that were obtained over the next seven hours. This corresponded with the patient declining. And this is expansion of the hematoma from continued bleeding within the initial hemorrhage bed. Some sort of hematoma expansion is actually seen in about 73% percent of patients. Significant hematoma expansion, say, more than a third increase in the size of clot, occurs in about a third of patients. And as you can imagine, hematoma growth doesn't do good things for mortality or disability.

But this also offers a potential target for treatment. Is the way we can stop hematoma growth and prevent people from moving from a small hemorrhage into a big hemorrhage and the mortality associated with that?

So based on that quick overview of pathophysiology behind these hemorrhages, so what are our options for therapy? We just talked about reduction in hematoma expansion. In the mid-2000s, there was a trial done with an agent called Factor VII, which is a clotting agent. And it's actually used for hemophilia and it's very good at stopping bleeding. You can use it in trauma and other situations.

And for a while, it was thought to be very hopeful for using this to prevent further clot expansion. In a big trial that was published in the *New England Journal of Medicine* that basically demonstrate, yes, you do slow down hematoma extension, but in that trial, it actually did not improve outcomes. Part that was thought to be related to an increase in instances of thrombotic events. So that basically kind of fell off the table and recommendations are not to use it for just intracerebral hemorrhage.

The other factor in blood pressure expansion that's still being studied is just blood pressure management. So a lot of these patients come in with extremely elevated blood pressures, and the question is, how low do you take that blood pressure, and how quickly do you do it? We'll talk about that a little bit more.

The next thing, and this is another obvious one for most people, is what about decreasing the mass effect from the clot from either taking it out or finding some other way to drain it. And people have tried surgery for that. There are paradigms out there where you stick a little catheter in the clot so it's much more minimally invasive, and then try to drain the clot out. And then people also, with patients with intraventricular hemorrhage put catheters into the brain and then use tPA to try and help clear that clot out. So those are other things we'll talk about.

And then lastly, there's this whole secondary injury where you get down that cascade of cell death, where inflammatory signals basically start to signal the cells to undergo apoptosis, which is programmed cell death. There's been multiple studies on neuroprotectants, trying to mitigate that process. They've all been negative, so it's not really a viable area right now. Basically, it's because drug companies won't fund it anymore because there have been too many failures.

So a patient shows up in the emergency room. They've got a diminished level of consciousness. What do they do? Initially, you do everything, all the stuff you normally do in ER. The patient very frequently will have a very diminished level of consciousness, and need innovation simply for airway protection. They can't send them to a CT scanner if they're gurgling on their own secretions.

Once you get beyond that, it's very important to get a timely CT scan of the head. And depending on your institution and its capability, it can also include a CT angiogram to look at the blood vessels. This allows differentiation from an ischemic stroke. Then you want to look at other factors. What's their blood pressure? Do they have any evidence of antiplatelet agents or anticoagulation? And also, how sick are they? Because how sick they are, to a certain extent, will also drive prognostication and the aggressiveness of therapy.

One of the scores that's out there that's been widely circulated over the last decade as a way to try and communicate severity of intracerebral hemorrhage is the ICH score. It basically has five different components to it. One is the GCF. The next is the size of the ICH, whether or not that blood got into the ventricle. And also, where did it originate? Is it in the hemispheres of the brain, or is it what we call infratentorial, which means in the brain stem or in the cerebellum.

You get different points. More points is bad. Low points is good. If you look at the table here on the right, it's basically 30-day mortality plotted against the number of points you have. The maximum number of points is six. Everyone was dead. If you look at zero to two, there's actually a reasonable mortality rate. Once she's getting into the three to four to five, the rates of death climb rapidly.

So the American Heart Association has published guidelines about the initial neuroimaging for intracerebral hemorrhage. Just to go through them quickly, they want a rapid CT or MRI to, like we said, determine between ischemic stroke and hemorrhagic stroke. You can do angiography if you want to look for indicators of risk for hematoma progression.

And then, based on clot position-- you know, we spent a lot of time talking about amyloid and hypertension-related strokes, but some do come from aneurysms or AVM or other sources. So based on clinician's suspicion, you can order other tests to rule out other sources.

So this is what your traditional non-contrast CT scan will look like. And what I put together here is a compilation of the most common locations that hypertensive hemorrhages occur. On the first one is a basal ganglia hemorrhage, followed by a thalamic hemorrhage, followed by a lobar hemorrhage, followed by the two posterior fossa hemorrhages, which are cerebellar, and then a devastating hemorrhage in the brain stem. And the importance of this is it helps you determine therapy and also outcome.

This patient with the bottom right image has got the big clot in the brain stem. Its effect will be, if not already brain dead, will be brain dead shortly, and there's nothing to do about it.

This is the reason that we sometimes get angiograms in patients with cerebral hemorrhage. This is a CTA. And if you look at the top two images here, you can look for something called the spot sign. The image on the left demonstrates a lobar hemorrhage of medium to small size. If you look at the angiogram directly next to it, you can see a few different speckles. And what these speckles represent is actually areas of contrast extravasation. It's sign. And if you see this, it's actually are a strong predictor of further hemorrhage expansion. If you look down at Image D here, this is what that patient went on to evolve to.

The next issue is this treatment of blood pressure. When you read the American Heart Association guidelines, the first thing they start off with is a disclaimer basically saying that the clinical trials aren't done. All these are recommendations. There's really not good evidence behind it, OK. And they basically say that lowering blood pressure down to 140 is probably safe, based on what we know.

Then they do go out and put some recommendations out there, I think more just to have some uniformity of treatment and some guidance. Basically, what these recommendations say is if you're come in, your blood pressure is greater than 180 systolic or your MAP's greater than 130, it's very reasonable to try and get that systolic down to less than 160 or a MAP of 110. And you can do anything you want for this. Then they go on to say if your blood pressure is really high, say, over 200 or 150, you should aggressively lower this, typically with like IV nicardipine or another IV medication.

Lastly, they have a caveat that if your blood pressure's high, and you think you have high intracerebral pressures, maybe you don't want to lower it too much for reasons of cerebral perfusion, let's be honest and accurate for patients-- you know, that's that the cat's already out of the bag group. And so I wouldn't worry too much about lowering blood pressure on someone who's already got high ICPs.

Since the publication of those guidelines, there has been one major blood pressure trial published called the INTERACT 2. And it actually came out this past summer. This was a very large, international trial. Actually, a large component was done in China.

And basically, what they were looking at was aggressive lowering of the systolic blood pressure, less than 140, versus kind of doing whatever you want, gradually lowering it over six hours. They had two endpoints. One was simply primary death and disability in 90 days. And the second area, they looked at physical disability by modified Rankin breakdowns.

And it was kind of a mixed trial. It showed no-- the primary outcome was not significant, did not show that there was a significant difference in death or disability at 90 days. However, in that secondary endpoint, when they break people out by modified Rankin scores. And again, modified Rankin-- it's typically, in most of these studies-- if your a zero, one, or two, your considered a success with moderate or less disability. Three and above, you're pretty disabled or dead.

When you look at it-- when you do the analysis this way, it was statistically significant, and they saw a 30% reduction in the odds of serious disability. And so, again, they haven't redone the recommendations, but this will probably slant people into being more aggressive towards blood pressure reduction.

There's also a study ongoing called ATACH-II that's being done 100% in the US. And it's dictated that they use IV Nicardipine with the same endpoints. And once that comes out, that should provide a lot more guidance around blood pressure management.

So the next thing that comes up, whether you're in the ER, or you're in the ICU, and you've just received one these patients. Nowadays lot of patients are on Coumadin, Plavix, Xarelto, Pradaxa, what do you do? The Heart Association guidelines, they give good guidelines for Coumadin, but they don't address any of the newer agents.

And so, for Coumadin, their guidelines are basically, yes, you should reverse it. And patients should get vitamin K. And then you can reverse it, either with FFP, which is basically fresh frozen plasma, in a type of transfusion. Or you can use something called Prothrombin Concentrate Complex, which is essentially a cocktail of factors.

You can get to the same place with both different treatments. The PCC works in minutes. You have to give a large volume of FFP to fully correct someone. And so that can take two, three, four hours. And so, all things equal, PCC works very quickly. It's a little more expensive, but it's not that much more expensive than a lot of FFP in transfusion-related costs. It's what we use a lot here at St. David's.

In the last issue, they point out is that if someone comes on aspirin or Plavix, there is essentially no data that really supports giving someone platelet transfusions right now.

So here's just an overview of kind of the coagulation cascade and where all the current anticoagulants fall in. So the classic one, warfarin, hits all the vitamin K dependent factors. And this is the one we're all familiar with and that there are good antidotes for. Heparin, which also is short acting, has good antidotes, hits certain factors down here.

So there are two new classes of anticoagulants that are now on the market. These top two here, rivaroxaban and apixaban, are the factor Xa inhibitors. The commercial name for rivaroxaban is Xarelto. It's been approved for use in AFib. The other one we see a lot of is this dabigatran, which is Pradaxa. And it's a direct thrombin inhibitor.

And as a neurosurgeon, I don't like these drugs because I could have somebody that comes in with a headbleed, it's much harder for me to do something with them. But if you look at the data in the trials that brought these drugs to market, in addition to them just being simply much easier to take. You don't have to check INRs. They're not-- what your liver is doing. What food you're eating. Don't change your therapeutic levels. They actually all had lower rates of intracranial hemorrhage than patients on warfarin. So to a certain extent, they're good, but when they show up in your emergency room, they're not good.

So what are our current strategies here? And so for Coumadin, it's pretty straightforward. PCC is a great drug for someone with intracranial hemorrhage. We have it in our pharmacy here, and like I said, it reverses in minutes. It's important to remember whether you use PCC or FFP. You also need to give some IV vitamin K because the first two will expire, and the vitamin K will ramp up the production of normal factors.

For Pradaxa or dagibatran, you're really in a tough spot. There are basically no proven reversal agents whatsoever. So your options are stop the drug. Half life's 12 to 14 hours. Because a lot of it is not protein-bound, you can dialyze a lot of it off. And normally, it takes about three hours of dialysis to get it out of your system.

Beyond that, there are case reports of people trying PCC or Factor VII. Some people claim it worked. There has been no series that actually says it works. And currently the manufacturers are working on a monoclonal antibody to actually serve as an antidote.

So the second group, the Factor X inhibitors, are in a similar boat in the sense that there's not a large study that says this is the way to reverse them. There is some limited series in human trials that PCC, because it has Factor X in it will, to some extent, reverse these agents. So I've had a couple people I know who have actually switched from dabigatran over to Xarelto just because in the event that they have something like a hemorrhage in their brain. At least currently, my sense is that I could potentially give them PCC with some hope that it might have some efficacy, although that's not proven yet.

So with regards to antiplatelet agents-- so the patient that comes on and asks for an aspirin, Plavix, Effient, treatment right now is 100% physician driven. There's no evidence that says we should do this or we should not do this. Your options are basically to give someone desmopressin, which kind of counteracts aspirin to a certain extent, or a platelet transfusion. You know, in my mind, I have someone that comes on aspirin, to a certain extent Plavix, kind of is what it is.

If someone comes in on one of the newer-- Effient or-- and depending on if I'm going to take them to the OR or something like that, I'll consider giving them platelet transfusions. There's definitely-- right now, any use of it's considered investigational. There's no real recommendations. They have launched a patch trial, which is looking at the use of platelet transfusions in hemorrhage in these patients. But that's a long way off.

Now let's talk about the issue of surgery, which is something that I've done on a lot of these cases. And I do a lot less now that a lot of trial data has come out. Basically, the current 2010 AHA guidelines state that simply for patients with ICH, the usefulness of surgery is uncertain, meaning there's no recommendation for surgery currently.

Patients who have cerebellar hemorrhage, so infratentorial blood clots that are localized in the cerebellum, if they have any evidence of neurologic deterioration, any evidence of brain stem compromise, or any evidence of hydrocephalus, there is actually a recommendation those patients go to surgery for decompression. Because those patients tend to deteriorate dramatically, and some of them you can actually get really good saves from.

They also have a third recommendation that it's not suitable just to put an EVD in these patients for their hydrocephalus and manage them that way.

They go on to have a couple other kind of smaller guidelines. They're just basically in response to different things people are trying out there. Right now, based on some of the study data, they go into a lobar clot, so those ones that are near the surface that are within one centimeter of the surface, you can consider doing it if you really want to. Like if you have an awake patient who then becomes unawake, and they've got a superficial clot.

They also want on-- there are, at some places there's been a lot of enthusiasm for what's called minimally invasive approaches, which means basically, instead of doing a big craniotomy, you make a small burr hole, and you use a catheter, a little dilator, and you go down into the clot itself to suck it out. All those therapies-- there's one trial that I'll talk about in a little while that's going on looking at that. But no current trial data supports doing that routinely for intracerebral hemorrhage that it makes a difference. It's considered investigational at this time.

And then they went out of their way to actually point out that, and it's something that I think a lot of neurosurgeons struggle with, when you see someone who just shows up in your ER and they got a good clot, if I take it out right now, will I make this patient better? And right now, the recommendation is simply that, no, you shouldn't. And often you'll hurt people more, because you'll get more leading just drummed up from the surgery itself.

So where did this strong antisurgical bias come from? Well, they did a STICH trial in Europe which was actually extremely difficult to do because these are not that common. They actually got 83 centers involved in this trial and were able to randomize over 1,000 patients.

And they see-- what they did is they looked at surgery within the first 24 hours or presentation. So not, oh, the patient's awake. Let's wait to see if they do bad, and then we'll chase the clot, the hemorrhage. If they were enrolled in the trial, and they ended up in the surgery arm, they got surgery in the first 24 hours, regardless of location, although they didn't operate on brain stem hemorrhages. And the primary outcomes were death or disability at six months.

And basically, if you look at the table over here on the right, you see how closely those red and blue lines are overlaid? Basically, there was no difference in outcomes for patients with surgery or not surgery. And this is why, when you see the guy who shows up in the ICU with a big clot, this is why they're not going to the operating room, because there's very good trial data that, actually, you shouldn't do that. OK.

The only thing that came out of this trial is that, again, in that superficial group of patients who have clots within a centimeter, there is maybe a trend toward significant if they'd been able to enroll another 3,000 or 4,000 patients. OK, and so that was kind of the one little silver lining. That was not a significant trend based on the number of patients in that trial.

But because of that, they actually did a Stitch 2 trial, which basically just got published this past summer. In this trial, they tried to cherry pick the patients they thought would do best with surgery, and see if we should do surgery in this subset. What they looked at was surgical evacuation now within 12 hours only for these lobar superficial hemorrhages. And not only that, you had to be conscious. And the way they defined conscious was a GCF of nine or greater. So you couldn't be in a deep coma.

And again, they looked at death or disability and other disability numbers. And basically there was some separation. It wasn't significant. And again, they had a fairly large trial size for this space. It was like 600 or 700 patients. It did show that, in general, operating on these lobar hemorrhages, you didn't tend to hurt people. But again, it didn't make a significant impact on outcomes.

There was one question. Like in that first one, there is a suggestion that maybe superficial lobar hemorrhage would be a different subset you should operate on. And the same type of analysis in this trial. They said, maybe in the superficial lobar patients now who have GCS of 9 to 12, but not 13 to 15, maybe those are the ones you would consider.

My attitude towards this is, in general I don't operate on supratentorial hematomas. The only patients I'll consider is someone that comes in with a reasonably high GCS and goes on to decline in front of you and doesn't have a catastrophic hemorrhage. Other than that, I think that the trial data is very, very strong that routine craniotomy for these is not indicated.

So MISTIE II. I wanted to go over this because this is kind of one of the still ongoing surgical investigations. And the only way I could get a copy of this picture is I actually had to do a screen shot from their presentation from the last stroke. They have it so secure because they don't want people using these pictures in presentations. And what it shows-- and the only reason I did this is that I wanted-- because it's much easier to explain pictures than words.

And basically, the goal here is to take a group of patients who have a hemorrhage such as this one, a fairly sizable hemorrhage, even in a deep location. You wait six or so hours till you're positive that there's no further expansion of the hematoma, so you're beyond that window where hematoma expansion occurs.

And then you use a stereotactic placement of the catheter into the hemorrhage, and you try to drain the hemorrhage out just through this tube. And the whole premise is that part of the problem with open craniotomy, and particularly with deep lesions like this is that, because those fibers in that area are very important, surgery itself is causing damage.

And so in this small kind of pilot phase two study, they put this catheter in, tried to drain it out. They also infused some IV tPA to help loosen things up basically. And their whole focus on this is clot reduction in size, hoping to prevent further secondary hemorrhage.

And this is kind of what they did. 83 patients. In this trial, they found, yes, you could make the clot smaller. And in their sub-analysis, they found a trend towards increased functional independent, and that the cost of treatment was less because these patients got out of the ICU quicker and got basically out of the hospital quicker. It wasn't powered to do any type of significance about whether this actually makes a difference as the other surgical trials were done. There's a larger MISTIE III one being planned to answer that.

And the last surgical trial that I'm aware of that's undergoing right now is called CLEAR-- it's actually going to be CLEAR III. What CLEAR II was is-- this goes back to that subset of patients that have an extra high mortality rate of 60% that have hemorrhage into their ventricles. And a lot of those patients will get EVDs placed because they'll also develop hydrocephalus.

And if they come in and they have hydrocephalus, and they're not already a GCS four, five, six patient who is already morbidly injured, you can potentially put in EVDs to reduce that hydrocephalus. And so someone came up with the idea of what if we put tPA into the EVD in order to help clear out clot. And obviously, these all came out right when tPA started getting used for ischemic stroke because it's the new drug on the market and everyone wants to figure out a way to use it against blood clots.

And so what they did in this trial is they were able to show that, yes, if you put IV tPA into an EVD catheter, you have a slightly higher rate of hemorrhage, but it's not dramatically higher. And they also showed that if you do this for several days, you'll be able to get that EVD out in a much higher rate of patients who won't require permanent shunting. And you also get that EVD out much sooner, OK, which is what this graph here on the left is. If you're on the light gray on the bottom, that was your clearance with the tPA. And the one on top was just having an EVD in.

Then they went on to extrapolate what's here on the right side. They did the mathematical exercise where they linked improvement in Glasgow coma score with the rate of clearance of ventricular hemorrhage. And they came up with a really cool graph. But you have to be very careful when you start doing projections like that on very small patient populations because you get a lot of interesting data. You just can't really believe it. So that's another trial that's ongoing.

And lastly, I just want to go back to that cerebellar hemorrhage, just so we kind of go over it again. This is your classic cerebellar hemorrhage. Notice the clot is not in the brain stem. The clot's in the brain stem, you don't take it out. That's not something you can fix. But this image actually shows all the things that lead towards deterioration. Cursor come up here.

So you have a clot here. This is black area here is called the fourth ventricle. And it's one of the major drainage pathways for CSF out of the ventricles where they're made. And you get compression with hemorrhage. And you see how-- these are the temporal tips here. And they're much larger than they should be.

So this patient has hydrocephalus from compression of their fourth ventricle. In addition, you see compression of the brain stem here. And so this is the logic behind taking these out, is by taking this clot out you're able to relieve that compression of the fourth ventricle in the brain stem. And in patients who aren't already morbidly comatose or mortally ill, this can often improve outcome. And so this is the group of patients that we operate on.

And so in summary for the role of surgery in intracerebral hemorrhage, currently there is no evidence supporting routine craniotomy for any supratentorial lesions. It is recommended for patients to undergo surgery if you have a cerebellar hemorrhage with neurologic deterioration, brain stem compression, or hydrocephalus. There's a subset of very small ones you can watch. But if compression or a neurological deterioration occur, those need surgery.

And then the two outstanding surgical trials are this MISTIE III with the catheter to see if that will improve outcome, and also the CLEAR II or CLEAR III, which is looking at clearing intraventricular hemorrhage. So those are the major efforts we have right now to try to address what we think are the big levers for improving outcome, which is decreasing that clot burden, and reducing this hematoma expansion.

There are a bunch of other guidelines around medical and ICU management. So the question is, so you have someone with a big blood clot in their head, should you put an EVD in? Should you measure their ICPs? Then should you hit them with Mannitol and everything else you do when someone has an ICP of 25, 35, 40. And the AHA guidelines basically say you can do whatever you want. There's no evidence that shows that that makes a difference or improves outcomes.

But at the same time when these guidelines were put forward in 2010, there was also realization that a lot of those really high mortality numbers were driven by just physician pessimism. And patients would come in and then be DNR in comfort care within six hours of arrival. And so with these guidelines, they're trying to open the door for neurointensivists to use their own decision-making processes in some select patients to go on and try and try intensive therapy in an attempt to shift another 10% of that mortality rate into moderately disabled or less.

And they go on and say ventricular drainage for hydrocephalus is reasonable. And the last one simply says that they don't recommend routine tPA into your EVD until those trial results come out.

With regard to seizures, treat patients that have seizures. Don't recommend routine seizure prophylaxis. If someone's exam is a lot worse than you think it should be, based on the size of the hemorrhage, it's reasonable to get an EEG to rule out subclinical seizures.

And then lastly, with medical management, all the standard things. ICU is recommended. Recommendation is an ICU with neurointensively trained staff, and staff that see a lot of these patients. Hence, a comprehensive stroke program.

To treat high glucose levels, you should treat DVTs initially with SCDs. And once you get two to three days out, it's OK to do subcu heparin. And again, they specifically went out of their way to do a guideline about withdrawal support. And their recommendation is, unless someone already comes in with a DNR comfort care order, you should at least give them into the second day before you have that conversation with the family.

To a certain extent, if someone comes in, their 87, they've got a huge hemorrhage, you don't necessarily need to wait. But for a lot of patients, there is a goal to try and get physicians beyond that pessimism to at least give the patient 24 hours to declare themselves.

Again, in terms of areas of ongoing research, we have the ATACH-II blood pressure trial. We've got the MISTIE III clot reduction. We've got the CLEAR III for IVH. We've got the patch trial looking at platelet transfusions. And then there are new agents coming on, or hopefully coming on the market for the new anticoagulants.

And in conclusion, this is a very tough problem. I just want you look at this picture, and if you know of a way to fix it, please, please tell me how to do it. So when someone comes in like this, you're probably not going to fix them.

When they come in with a hemorrhage a third of the size of this, that hasn't expanded in size, hopefully we'll get to the point where we can take a lot of those patients who would have ended up severely disabled or dead and bring them back to moderate disability are less. Are there any questions?