[MUSIC PLAYING]

BRADLEY GROSS: Good afternoon. My name is Brad Gross. I'm a cerebrovascular neurosurgeon at the University of Pittsburgh. This afternoon, I'm here to talk about evidence-based management of intracerebral hemorrhage. So when we think about stroke-- and as a cerebrovascular neurosurgeon, this is what I primarily deal with-- we think about the ischemic stroke, which refers to a blockage of a blood vessel in the brain. Or we think about hemorrhagic stroke, which essentially refers to a bleed in the brain.

Ischemic stroke has had a lot of exciting developments where we're able to get the vessel open faster, more efficiently, and in a larger proportion of patients, and certainly comprised the majority of strokes. But today, we're going to focus on a specific type of hemorrhagic stroke that is intraparenchymal hemorrhage, or intracerebral hemorrhage, as it can also be referred to.

Other forms of hemorrhagic stroke include subarachnoid hemorrhage and intraventricular hemorrhage. [INAUDIBLE] subarachnoid hemorrhage is the most common source of that besides trauma in the form of stroke is an aneurysm rupture. Intraventricular hemorrhage is usually contingent in either subarachnoid or intraparenchymal hemorrhage.

So the topic of this discussion this afternoon, intracerebral hemorrhage or intraparenchymal hemorrhage, is going to be broken up into four pieces. We're going to look at some background information, assessment and diagnosis of the problem, medical management, and surgical management. And all of this is provided in the nice recent review that we had in the *Journal of the American Medical Society* published in April. And all this can be found in there, essentially.

So, some background information about intracerebral hemorrhage. It accounts for 20% of all forms of stroke. It is the most common form of hemorrhagic stroke. In a meta-analysis of 36 studies, the overall incidence of intracerebral or intraparenchymal hemorrhage was 24.6 out of 100,000 person years. There was no sex correlation. And as many know, the preponderance of it increases with age. Median 1:1 fatality of intraparenchymal hemorrhage is 40%.

You can stratify intraparenchymal hemorrhage into essentially two types-- primary intraparenchymal hemorrhage, which refers to a hemorrhage presumably due to hypertensive event, or Cerebral Amyloid Angiopathy, abbreviated as CAA. Secondary intraparenchymal hemorrhage refers to a bleed secondary to an underlying source, such as an AVM, a dural arteriovenous fistula, cavernous malformation of mycotic aneurysm, thrombosis, the venous sinus system, moyamoya disease, vasculitis, hemorrhagic tumors or perhaps hemorrhagic inversion of an ischemic stroke.

So in this study in *Lancet* in 2010 where they looked at risk factors for ischemic and intracerebral will hemorrhage across 22 countries in a case-control study, they had overall 3,000 cases, 663 with intracerebral hemorrhage, compared to control patients. And they found that the most strong risk factor for intracerebral hemorrhage was a self-reported history of hypertension or a documented systolic blood pressure greater than 160 over 90.

Other statistically significant risk factors in this case-control study included being a smoker, drinking, and there is actually proportionality to patients who were binge drinkers who were drinking more than 30 drinks per month. And paradoxically, there was an association with increased HDL-- or sorry, decreased HDL cholesterol or increased non-HDL cholesterol.

Another source of intracerebral hemorrhage is a diagnosis of cerebral amyloid angiopathy, which, as we all know, increases with age. Now, this is a little bit more of a difficult diagnosis to formally garner. The most rigorous criteria for the diagnosis of cerebral amyloid angiopathy, the Boston criteria-- really, the only effective way to garner a diagnosis of cerebral amyloid angiopathy is a full post-mortem examination.

Now, there are other ways to diagnose a probable or a possible diagnosis of cerebral amyloid angiopathy. But again, with even more rigorous criteria, it can be challenging to garner that diagnosis. In fact, really the only diagnosis that you can obtain without a formal surgical piece of tissue is really a possible diagnosis that you can see down here. And that's based on clinical data and MRI or CT demonstrating either a single lobar cortical or cortical/subcortical ICH, age greater than or equal to 55, and the absence of another cause of hemorrhage.

So when we look at the significance of identifying whether a bleed is secondary to hypertension or cerebral amyloid angiopathy, there is, in fact, a significant clinical relevance to this. So if you look here at this meta-analysis evaluating the risk of recurrent hemorrhage in patients with either hypertensive or cerebral amyloid angiopathy, that you can see that the risk of rehemorrhage in a patient with a hypertensive bleed is about 1% per year, which contrasts to a rebleed rate of about 7.4% per year in patients cerebral amyloid angiopathy.

This is actually quite relevant in counseling patients prospectively in terms of whether they need to be restarted on anticoagulation or other factors as well and also underscores the importance of distinguishing a cerebral amyloid angiopathy bleed versus a non-cerebral amyloid angiopathy bleed.

As I previously mentioned, the diagnosis of cerebral amyloid angiopathy can be quite challenging and often dependent on, in fact, a tissue diagnosis, which is based on surgery, which a lot of those patients don't need. Recently in *Lancet Neurology,* the Edinburgh CT and genetic diagnostic criteria were published that demonstrate a fairly substantial sensitivity and specificity for cerebral amyloid angiopathy.

So this was based on an autopsy study of 110 patients. And what they found was that if you did not have subarachnoid hemorrhage, ApoE4 allele possession, or finger-like projections, which are these little, basically, finger-like things you can see in the bottom right of the screen, the rule-out sensitivity was essentially 100% to not have cerebral amyloid angiopathy. Whereas if you had two of these three factors-- that is, subarachnoid hemorrhage, ApoE4 possession, or finger-like projections-- the rule-in specificity was 96%.

So having reviewed some background information about sources of intracerebral or intraparenchymal hemorrhage, we're now going to look at the assessment and diagnosis of the problem.

So interestingly, on presentation, about a quarter of patients with intraparenchymal or intracerebral hemorrhage will deteriorate in transport. And another quarter with good GCS in the emergency department will deteriorate by at least two points on a GCS scale in the emergency department. This has been recently recapitulated in a recent study about a year or two ago. But again, these quarter/quarter factors are important numbers to remember.

Now, predictors of deterioration in the emergency department in this study that I cite from 2012 include antiplatelet usage, onset to arrival less than three hours, temperature of at least 37.5 degrees, intraventricular hemorrhage, or 2 millimeters or more of midline shift on a CT scan.

Now, in the emergency department, the initial evaluation of patients suspected of intracerebral hemorrhage, it's important to garner the type of onset, relevant past medical history, including history of hypertension and particularly anticoagulant use, and of course, an examination. And patients initially presenting with intracerebral hemorrhage can mimic patients presenting with ischemic events.

And so some factors to consider to contrast an acute ischemic stroke or hemorrhagic stroke include the presence of a headache, which can often indicate a hemorrhagic stroke in contrast with ischemic stroke, the presence of nausea, vomit, or depressed mental status. Whereas both ischemic and hemorrhagic strokes will present acutely with a focal deficit and potentially with blood pressure lability that will be managed in differing ways based on the type of stroke. Patient with ischemic stroke will often be allowed to have permissive hypertension, whereas a patient with a hemorrhagic stroke will often be managed with acute lowering of their blood pressure.

For the remainder of the discussion, we're going to be discussing evidence. And it's important. This slide I extracted from the 2015 AHA guidelines-- describes-- so when I describe a class I treatment effect, that is a procedure treatment that should be performed. Class IIa refers to a reasonable performance of a procedure. IIb is a consideration of it. Class III refers to no benefit, or even harm, OK?

When we talk about the level of evidence-- level A is based on multiple populations evaluated. And this is from multiple randomized clinical trials or meta-analyses. Level B is data derived from a single randomized trial or non-randomized study. And level C is based on limited populations. This is consensus opinion. Our case studies are considered just standards of care. This is important to keep in mind as we go through this.

So garnering a diagnosis of an intracerebral hemorrhage is based on rapid imaging. That's a class I, level A recommendation. That can be done in the form of CT, which is my personal preference, or MRI. I prefer CT because it's more timely. And then advanced imaging-- the value for an underlying lesion, a secondary etiologic cause of intracerebral hemorrhage, is a class IIa, level B recommendation. This can be done in the form of CT angiogram, which, again, is more expedient than the other options, MRI or DSA.

Positive predictors of an underlying lesion in a study in the*Journal of Neurosurgery* from 2012 included age less than 65, female sex, non-smoker, IVH presence, a lack of a history of hypertension is an extremely strong factor, whereas patients that were hypertensive and older than 65 with basal ganglia cerebellar bleeds ubiquitously had negative CTAs or underlying sources in this study.

One of the most important things to manage and avoid in the case with acute intracerebral hemorrhage is hematoma growth. That's what we're trying to avoid after a patient presents with a hemorrhage. And when we look at this study from *Lancet Neurology* in 2012 that evaluated predictors of hematoma growth and outcomes in patients, this looked at the spot sign, which is a little contrast deposit within the hemorrhage. And the spot sign was a significant predictor of hematoma growth.

So what this study defined as hematoma growth was either a increase in 6 cc or 33% growth of the hemorrhage on a subsequent CT scan. Patients that had a spot sign across the cohort had a 60% chance of having an increase in hematoma growth on an interval scan, in contrast to a 21.6% occurrence of this in patients that did not have a spot sign.

And when they looked at all of these factors-- absolute ICH growth, IVH growth, all these factors-- they were all significantly increased with patients that had a spot sign. And in fact, a spot sign was also a significant predictor of outcome. So at the bottom where we look at secondary clinical outcomes, the likelihood of a 4-point worsening in NIHSS score at 24 hours was significantly more common in patients with spot sign.

Worst outcome, mRS score of 90 days-- the mean mRS score was 5 in patients spot signs compared to 3 with patients without a spot sign. And even mortality was significantly increased, 43% versus 20% in the study.

Now, that being said, when we're evaluating for secondary cause, if we are quite suspicious that there is a secondary cause of the hemorrhage that is not a hypertensive or cerebral amyloid cause of the intracerebral hemorrhage, digital subtraction angiography remains the gold standard to evaluate for an underlying lesion, a vascular lesion that would be in the form of an AVM or a dural fistula, or perhaps a venous sinus thrombosis.

This is a patient. It was a 63-year-old female. Presented with a history of hypertension, hyperlipidemia, diabetes, and is a smoker, with a lobar position of her hemorrhage, and given a suspicion for a possible underlying lesion. Although the CT angiogram was negative, we performed a catheter angiogram that demonstrated a very small arteriovenous malformation supplied by small thalamic perforators of the PCA.

Interestingly, these tiny AVMs with deep venous drainage have a very high risk of rehemorrhage. This table on this slide that I extracted from the New York Island data report a 34% risk of rehemorrhage for small-- or correction, for these deep hemorrhagic AVMs that had exclusive deep venous drainage like this AVM, underscoring the importance of rendering this diagnosis.

Now, this was an AVM that I was able to treat through a transvenous approach through embolization, which is a nice and growing approach for selected AVMs. And this was a well-suited AVM to avoid having the patient undergo a craniotomy to find this very small AVM.

It's a class I, level B recommendation to obtain a baseline severity score for patients with intraparenchymal hemorrhage. This is perhaps the most commonly used score. This is the Hemphill score that is almost 20 years old at this point, published in *Stroke* in 2001-- a fairly useful predictor of mortality.

The Hemphill score is comprised of the GCS score presentation-- you give 2 points if it's 3 to 4. You give 1 point of it's 5 to 12-- age of at least 80, which is 1 point, an infratentorial hemorrhage origin, which is 1 point, a volume of the hemorrhage being at least 30 cc, and the intraventricular blood is also worth a point.

You can see that when you go from 2 to 3 points on this score, there is a massive uptick from 26% mortality rate to 72%, which is fairly substantial. We use this regularly at the University of Pittsburgh.

So moving on from the assessment and diagnosis of intracerebral or intraparenchymal hemorrhage, we're now going to look at the medical management. So in the patient presenting with an acute intracerebral or intraparenchymal hemorrhage, the first things to do-- secure the airway, as indicated, avoid hyper- or hypoglycemia. That's a class I, level C recommendation.

If a patient has a seizure, they should be administered an antiepileptic. That's a class I, level A recommendation. If they do not have seizures, it is not recommended to place the patients on prophylactic antiepileptic. A screening EKG and troponin is a class IIa, level C recommendation, as a substantial portion of these patients can have troponin release.

We're going to focus on these areas in blue here-- blood pressure control-- a systolic blood pressure goal of less than 140 is advised-- coagulopathy management, the admission to an ICU or stroke unit, which is a class I, level B level of evidence.

Now, what has been studied in studies formally is, again, as I already mentioned, the use of prophylactic ADs, which is not recommended, the empiric administration of recombinant factor VIIa-- this is non-patients that are coagulopathic. This is across the board. This was evaluated about 10 years ago in a randomized study that compared patients, all comers with intracerebral hemorrhage, that randomized either receive recombinant factor VIIa or not receive it. And based on those studies, it is not recommended.

In a similar, more recent study in *The Lancet,* the empiric administration of tranexamic acid is not recommended this time. And furthermore, the empiric administration of steroids is not recommended. Overall, in patients presenting with intraparenchymal hemorrhage, the goal is to limit hematoma growth in order to improve outcomes.

Now, in terms of predicting hematoma expansion, we already discussed the clinical significance of the spot signs as both a predictor of hematoma expansion, as well as a predictor of even outcome. In this study from Harvard in *JAMA Neurology* 2014 that looked at 817 patients with intraparenchymal hemorrhage and tried to evaluate significant risk factors for hematoma expansion.

First and foremost, they found that the overall probability of hematoma expansion was 19% in this cohort. Significant predictors of hematoma expansion-- this goes beyond simply the spot sign, which was identified as significant in the study-- were also the usage of anticoagulation in the form of warfarin, an early time to the initial CT less than or equal to 6 hours, and a baseline ICH volume.

And they actually derived the score based on four factors-- the spot sign, baseline ICH volume, time to the initial CT, and warfarin usage, and were able to garner a predicting system that, if the score was 0, the prevalence of expansion of the core was 5%, whereas the score was at least 4, the prevalence of hematoma expansion was 36%.

In this study, age, sex, antiplatelet usage, presenting GCS, amyloid etiology of the hemorrhage, ICH location, the presence of IVH were not significant predictors of hematoma expansion.

So moving on, looking at ways to mitigate hematoma growth. One of the first factors I'd like to really review in depth is blood pressure control. There were two important studies the INTERACT and the ATACH study, which we'll look at separately.

We're first going to look at INTERACT2, published in *The New England Journal of Medicine* in 2013. This was a follow-up study after INTERACT1. The randomized controlled trial *The Lancet Neurology* in 2008 found that in 500 patients, a systolic blood pressure goal of 140 was associated with less hematoma growth.

So in this randomized control study, patients with spontaneous non-massive ICH with a GCS score of at least 6 were included. There were 1,382 patients that were randomized to the group of blood pressure control from 110 to 139 versus 1,412 patients that were randomized to a cohort where blood pressure control was a systolic goal of 140 to 179. This was initiated within six hours after the hemorrhage, and was sustained for seven days, which contrasted the ATACH study.

What this study found was that the odds of a poor outcome-- that is, mRS of 3 to 6-- the prevalence, rather-- was 52% in the patients with tighter blood pressure control-- that is 110 to 139-- versus 55.6% in patients with blood pressure goals of 140 to 179. This nearly met statistical significance in the order of p equals 0.06 and did meet statistical significance in subsequent ordinal analyses.

The rates of serious adverse events did not significantly differ between the two cohorts. But if you could look in this extracted table of health-related quality of life, several factors, for example, problems with health care, problems with the usual activities, problems with pain or discomfort, problems with anxiety or depression, and an overall health utility score, were all better in the cohort with tighter blood pressure control.

When we look at the ATACH-2 study-- this is the Antihypertensive Treatment of Acute Cerebral Hemorrhage data that was published subsequently in *The New England Journal* in 2016. This study included patients with spontaneous supratentorial ICH less than 60 cc and a GCS score of at least 5.

500 patients were randomized with systolic goal of 110 to 139 versus 500 that were randomized to a goal of 140 to 179. This was specifically managed by usage of a Cardene drip. This was initiated within 4 and 1/2 hours after symptom onset, but only maintained for the next 24 hours, OK? What this study found was that the odds of a poor outcome-- and in this study, they define that as an mRS of 4 to 6 in contrast to the INTERACT study, which was 3 to 6-- did not significantly differ between the two groups.

Overall treatment-related serious adverse events did not significantly differ between the two groups. Hematoma expansion was slightly less common in the group with tighter blood pressure control, although this did not meet statistical significance with a p-value of 0.08. Renal adverse events were more common in the group with tighter blood pressure control-- was found to be 9% versus 4%.

But it's important to emphasize that in this study, if you actually look at the actual mean systolic blood pressure in the two cohorts, in the patients with the blood pressure goal of 110 to 139, the mean systolic blood pressure was 128.9, whereas in patients with a systolic blood pressure goal of 140 to 179, the mean systolic blood pressure was in fact 141.

This contrasted the INTERACT study where these respective mean blood pressure values were 150 in the tight blood pressure group and 164 in the tight blood pressure group. Taking this into account, I think it's pretty clear that patients with a systolic goal of 140 are probably more likely to do well than those with a systolic blood pressure goal of less than 180.

A second important factor is the management of coagulopathy in these patients presenting to the emergency department. Obviously, patients with coagulation factor deficiency or thrombocytopenia-- repletion is recommended. This is a class I, level C recommendation. Reversal of anticoagulation is also a class I, level C recommendation with the usage of vitamin K or the use of prothrombin complex concentrate if they're taking a Vitamin K Antagonist, abbreviated as VKA in the slide.

Hematoma growth was 19% in a study of prothrombin complex concentrate was used versus 33% of fresh frozen plasma is removed. And thus, it's recommended to use prothrombin complex concentrate in patients taking vitamin K antagonists in contrast to FFP. These patients would essentially be administered prothrombin complex concentrate and vitamin K. FFP was associated with fluid overload and an overall similar thromboembolic complication profile. If patients are taking heparin, they should [INAUDIBLE] protamine sulfate-- that's a class IIb, level C recommendation.

Now, one question that often comes up is the reversal of antiplatelet agents. And that was addressed in a recent study, the PATCH trial. In this study, patients with spontaneous supratentorial ICH within six hours of symptom onset were randomized either platelet transfusion for antiplatelet usage or standard of care. Patients had a GCS of less than 8, and they had to use an antiplatelet agent for at least seven days prior.

Now, it's very important to carefully scrutinize the antiplatelet agents that these patients were taking in this trial. The vast majority, 78%, were taking simply COX inhibitors, that is, aspirin. A smaller proportion were taking a combination of 16% of a COX inhibitor, dipyridamole and a very small proportion were taking ATP inhibitors, that is, in the form of clopidogrel, prasugrel. So this study primarily evaluates the effect of platelet transfusions on patients taking aspirin or a COX inhibitor. 97 patients were randomized to the transfusion group, and 93 to standard of care.

What this study found was that patients that were alive at three months, the rate of being alive three months was nearly statistically significantly higher in patients that did not receive a platelet transfusion. That was 68% versus 77%. Whereas if you looked at the odds of the poor outcome-- that is an mRS of 4 to 6 in three months-- this did meet statistical significance. It was significantly worse in patients that were administered a transfusion. So that was 72% versus 56%.

Median ICH growth in 24 hours did not significantly differ between the two groups. And the rate of serious adverse events were higher in the group of patients receiving platelet transfusion. That was 42% to 29%. And that's based on the study.

Personally, I do not transfuse platelets to patients simply taking aspirin. However, I do not think you can really make any definitive conclusions from the study for patients that are taking something like prasugrel or clopidogrel or an ADP inhibitor like that.

Admission of the patients to an ICU or stroke unit is a class I, level B recommendation for patients with intraparenchymal hemorrhage. In a study in the *Journal of Neurology, Neurosurgery, and Psychiatry* in 2009, it was found the patients admitted to an ICU or stroke unit had significantly greater chance of independence, actually, in three months. So the rate of three-month death or dependence was only 59% in patients admitted to an ICU or stroke unit versus 75% of patients not admitted to one of these wards.

Other earlier recommendations-- an early dysphagia screen in these patients is a class I, level B recommendation. Intermittent pneumatic compression-- that is for DVT prophylaxis-- is a class I, level A recommendation. This was evaluated in the CLOTS study. So this was the Clots in Legs Or sTockings after Stroke study published in *Lancet* 2013. The DVT rate was significantly reduced in these patients that were placed on intermittent pneumatic compressions. It was 8.5% versus 12.1%.

We're going to look more carefully at the administration of subdued heparin or low molecular weight heparin 1 to 4 days after stability of the bleed. This is overall a class IIb, level B recommendation. So this was a meta-analysis of controlled studies that evaluated res-- starting, rather, patients on DVT prophylaxis in the form of either UnFractionated Heparin, UFH, or low molecular weight heparin within 24 to 96 hours of their hemorrhage.

What this meta-analysis found was that the DVT rate was less, although not statistically significantly so, in patients that were started on these agents within 24 to 96 hours, with 3.2% versus 4.2%. The PE rate, however, was statistically significantly less in patients started on prophylactic unfractionated heparin or low molecular weight heparin. This was 1.7% versus 2.9%.

Hematoma enlargement rate was slightly higher, albeit not statistically significantly so in patients started on these agents. And mortality, interestingly, was nearly statistically significantly less in patients that were started on DVT prophylaxis, 16% versus 21%. The confidence interval does cross 1 for the relative risk for this number, however.

So we discussed the background information, assessment and diagnosis, and the medical measurement of intracerebral hemorrhage or intraparenchymal hemorrhage. We're now going to move on to discuss the surgical management of this problem.

Patients with intraparenchymal hemorrhage should be managed with early neurosurgical consultation. As neurosurgeons, one of the early things we look for or are concerned about is hydrocephalus. In a randomized trial of surgical management of intracerebral hemorrhage, it was found the 23% of all comers had hydrocephalus with intracerebral hemorrhaging. This rate increased to 55% if patients had intraventricular hemorrhage associated with it. And indeed, intraventricular hemorrhage is something that keeps us more alert for the risk of developing hydrocephalus.

An external ventricular drain is placed. And this can be placed also in patients with a decreased level of consciousness. That's a class IIa, level B recommendation, or in general, with a GCS less than 9. That's a class IIb, level C recommendation that is sort of extrapolated from trauma literature.

Surgical evacuation is recommended in patients with posterior fossa cerebellar hemorrhages that are at least 3 centimeters in size. It's a class I, level B recommendation, particularly if they're deteriorating, have brain [INAUDIBLE] compression or hydrocephalus. In patients with a supratentorial hemorrhage, it is recommended that they undergo a surgical evacuation decompression if they have a large hematoma shift. That's a class IIb, level C recommendation.

Here's some examples of patients. This is a patient with a large temporal hemorrhage with midline shift and a deteriorating exam. I performed surgical evacuation. At six months, their mRS was 2.

Now, this was studied more systematically for supratentorial hemorrhaging across all comers in a STICH trial. So the STICH trial was the international Surgical Trial In intraCerebral Hemorrhage. This was first published in *Lancet* in 2005. This was a randomized trial with 1,003 patients with 83 centers in 27 countries. They had a minimum hematoma diameter of 2 centimeters and a GCS of at least 5. Patients were randomized to either early surgery-- that was 503 patients-- or conservative treatment. That was 530 patients.

Six-month favorable outcome rate did not significantly differ between these two groups. However, when they looked at particularly lobar locations in patients with more selected GCS, there was perhaps some signal. And that's what encouraged the performance of the STICH II trial, which was a subsequent randomized trial of surgical evacuation versus conservative management in patients with supratentorial lobar intracerebral hematoma.

This was published in *The Lancet* in 2013. This was based on 601 patients from 78 centers in 27 countries. This included patients with superficial hematomas that were 10 to 100 cc in size, 1 centimeter from the surface with a GCS score of at least 8. 307 patients were randomized to surgery. 294 patients were randomized to conservative treatment. Interestingly, however, the six-month rate favorable outcome, again, in this study, did not significantly differ between the two groups.

So in terms of other potential approaches to managing surgically intracerebral hemorrhage, particularly in the supratentorial compartment, there have been several evaluations of the uses of less invasive approaches rather than a full craniotomy and evacuation-- minimally invasive evacuation of supratentorial intracerebral hemorrhages. This was a meta-analysis that was published in *Stroke* in 2012 that did demonstrate some signal for better outcomes in patients treated with minimally invasive surgery for supratentorial intracerebral hemorrhage.

The MISTIE trial-- this was MISTIE II that was published in 2016, and more recently, MISTIE III that is coming out any moment now. This was a trial that evaluated the usage of catheter placement and the administration of tPA to try to break up the clot and drain it through the catheter placement.

This was a trial that looked at patients 18 to 80 years old with a spontaneous at least 20-cc hemorrhage. And they underwent-- they either randomized undergo minimally invasive placement of basically an EVD catheter into the hematoma with the use of aspiration and subsequent administration of tPA. There were 54 patients that were randomized to minimally invasive placement of this catheter versus 42 randomized to medical care. In

This study, however, there was no significant difference in the overall 30- or 7-day mortality, symptomatic bleed rate, infection rate, asymptomatic bleed rate. MISTIE III is an ongoing study evaluating 100-day functional outcomes in these patients. That should be coming out very soon.

Other potentially minimally invasive approaches-- this is the BrainPath system, which is a small tube that can be placed through a sulcus to evaluate the hemorrhage. This was simply a one-arm study published in *Neurosurgery* in 2017 that looked at 39 cases. And interestingly, they had a very nice clinical outcome rate in the single-arm study-- 52% mRS 2 or less and no mortality. There's certainly some promise to these minimally invasive studies.

The ongoing ENRICH study, which UPMC is a part of, the early minimally invasive removal of intracerebral hemorrhage study, which is involving patients age 18 to 80, GCS 5 to 14, and 30 to 80 cc intraparenchymal hemorrhage, evaluating the usage of the BrainPath system versus medical management and looking at the utility-weighted mRS at 180 days, is an interesting study that is ongoing. And I'm excited to see the results from the study.

These minimally invasive evaluations and surgical trial evaluations primarily for primary intracerebral hemorrhage, that is intracerebral hemorrhage secondary to hypertension or cerebral amyloid angiopathy. When we look at secondary etiologies of intracerebral hemorrhage, the demands of these are more disease- or problem-specific.

So patients with arteriovenous malformations causing the hemorrhage are typically diagnosed with the use of either a CTA or DSA. And the AVM, if hemorrhagic, is often either surgically excised, rarely can be cured through embolization means, as we demonstrated on the earlier slide. And if the patients are not surgical candidates, stereotactic radiosurgery is certainly a very reasonable option for these lesions.

Patients with hemorrhagic dural arteriovenous fistulas that can be diagnosed on either CTA or DSA-- they're often evaluated for embolization, which is, in general, a reasonable option for about 80% of these excepting those of the anterior fossa, ethmoidal fistulas, or otherwise evaluated for surgical disconnection of the cortical venous drain if that's the cause of hemorrhage.

Cavernous malformations-- these are small mulberry-like clusters of dilated sinusoids that are diagnosed on MRI-- if hemorrhagic, are often managed essentially by surgical excision. Patients with mycotic aneurysms, small distal aneurysms that are diagnosed on either CTA or more sensitively and specifically by DSA, are treated by embolization if the lesion can be reached for surgical excision.

Venous sinus thrombosis is diagnosed on CT venography or angiography. It could be treated via thrombectomy and/or anticoagulation as indicated. Moyamoya which is a source of hemorrhagic disease, can be managed to revascularization. Vasculitis is managed with medication. Tumors are managed by surgical excision or stereotactic radiosurgery as indicated.

So in summary, intraparenchymal or intracerebral hemorrhage accounts for 20% of all stroke. There's a median 1:1 fatality of 40%. ICH risk factors include a history of hypertension, smoking, alcohol abuse. HDL cholesterol being elevated is paradoxically a risk factor for intracerebral hemorrhage. It's important to underscore that patients with intracerebral hemorrhage secondary cerebral amyloid angiopathy have recurrent ICH rate of 7.4% per year versus 1.1% per year patients with non-cerebral amyloid angiopathy primary intracerebral hemorrhage.

Risk factors for cerebral amyloid angiopathy, as reviewed in that recent*Lancet* paper, include the presence of subarachnoid hemorrhage and finger-like projections on the CT scan, ApoE4 allele, which is a blood test. The Hemphill score is a useful score to help predict mortality after intraparenchymal hemorrhage. That is based on GCS, an age of at least 80, infratentorial location, IVH presence, and a greater than 30-cc bleed.

Now support in the early medical management for patients with intracerebral hemorrhage to keep blood pressure less than 140 to treat coagulopathy and admit them to an ICU or stroke unit. From a surgical perspective, patients with hydrocephalus are managed with external ventricular drain placement. it can be managed with evacuation or decompression if the lesion is cerebellar or if there's a pending herniation or a large intracerebral hemorrhage. Minimally invasive trials are ongoing in the management of supratentorial bleeds.

I thank you for your time of attention.