

International Perspectives on Stroke Triage, Diagnosis and  
Treatment

A Webinar Series Presented by the American Stroke Association and  
the Society of Vascular and Interventional Neurology

Episode 3:

Treatment with IV Lytics

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>> Welcome everyone! Thank you for joining us for our four-part webinar series. This is the third episode in the series, Treatment With IV Lytics. My name is Aurora.

I will start today's program by going over a few important items. This webinar is jointly presented by the ASA and SVIN. There are no CE's available for any of the webinars. However, there are certificates of completion available. This webinar is being recorded. If you experience any technology issues, most can be resolved by refreshing your browser. If your issue is still not resolved, please contact the GoToWebinar customer service team.

You will have the opportunity to submit questions by typing them into the questions pane of the control panel. You may send in your questions at any time during the presentation. We will collect these and address them at the end of today's presentation.

Our moderators are Dr. Lyden, and Dr Jadhav. Dr. Lyden is a professor at the USC School of Medicine. He's been active in the study of treatments for stroke patients. He's been researching for over 35 years.

Dr. Jadhav is a vascular neurologist. He went to Harvard. He then trained in neurology in Massachusetts, and at the University of Pittsburgh. He serves on the AHA's stroke council.

Dr. Jadhav is moderating the audience questions. You may receive a message from him from the control panel.

Now, Dr, Lyden.

>> Thank you. I want to thank the AHA, American Stroke Association, and everyone else who could put this webinar together. I am honored to be here. The panel is outstanding. We tried to keep the presentations brief. There will be time for questions at the end. I will introduce our panelists before. I will give you an

overview. Dr. Khatri is from Cincinnati. Dr. Czap is from Houston. Dr. Liu is from Beijing. Dr. Mansour is from Alexandria.

We will move to our first talk. I will introduce Dr. Khatri. She's a professor of neurology at the University of Cincinnati. She is a secretary of the World Stroke Organization.

>> Thank you. I hope everyone can hear me okay.

>> Yes.

>> Great. It's a pleasure to speak to all of you on this topic. I will try to give you updates, and touch on international considerations.

My brief overview will be about who we should treat, who we should not treat, patients we should probably treat, and those we should debate about treating. I mirrored my talk directly out of the 2019 AHA essay update, the clinical management for patients with acute stroke.

It's important to use the framework that the AHA uses. It's very useful. There are classes of recommendations. That's related to the strength in which we believe that this recommendation is class I.

hemorrhage. We don't need to worry if they have single or double anti platelets on board. We don't need to worry about renal insufficiency, or end stage renal deficiency.

Microbleeds are an area I bring up because the question has come up, as we get MRIs more and more, whether microbleeds should stop us from treating this. We know we shouldn't waste the time to get the MRI if we don't have a well-oiled machine. If we waste the time to get the MRI, the rate of microbleeds in the overall population is low enough for most patients on average, we've done more harm than good.

There is emerging data in patients who have a high burden of microbleeds, more than 10, there's an increased risk of hemorrhages. There's been a study that came out since the guidelines were published, from Germany. They did an analysis with real data. They argued that TPA is associated with higher mortality with patients that are older with more strokes. There is more harm. Screening is appropriate in our older patients, with severe strokes, and a history of dementia. That remains to be seen.

Contraindications. In the interest of time, I will not go over the evidence of each. They all have bearing levels of evidence. Some are based on precedent, some are based on early trials, some are more clear-cut. The first one, mild, nondisabling stroke. That's based on the prism trial. The study showed no evidence of treatment benefit in patients who have mild strokes. That study was stopped low. Blood pressure that cannot be safely lowered is uncommon in settings where you have antihypertensive drips available.

Severe head trauma within three months. Previous intracranial hemorrhage. [On screen.] [Reading: Alteplase Contradictions.]

Patients that we are generally treating based on guidelines in clinical practice are those who show early improvement, but still

have defects. Seizures are likely to be stroke symptoms.

If you have corrected low glucose . . .

[On screen.]

These can be treated more often than you think if you are less experienced. Those are grey areas for many of us. We will treat these patients anyway.

We are more and more clear that this is beneficial.

I am purposefully going to tease you with the grey areas in the interest of time. As far as lumbar punctions within the previous seven days, there's a judgment. Major trauma. We have to weigh that. We have to weigh the risk of injury and trauma for what the injuries are, and the severity of the stroke. We have to think about that for surgical settings.

Intracranial arterial dissection. We have no idea if we are safe treating in that. It's less common. Also, giant unruptured aneurysms is a place where people would pause, but also could treat.

The second slide of the grey areas are those with patients who have mild disabilities from their stroke. Acute pericarditis. The thrombus is a tough one. We worry about clotting. To date, most experts think it's reasonable to treat patients in this setting. Weighing the level of disability. Generally, for all of these, we are thinking about life expectancy. If their life expectancy is greater than six months, that's something to be considered.

Pregnancy. Usually, the benefits outweigh the risk. It gets tougher when we are in the early postpartum period. It's important to work with your specialist.

With preexisting dementia, these patients need to be treated as well. It's appropriate to treat them, especially if their dementia is mild, and can bring them to their previous baseline.

Moving on to the next slide, there are some additional exclusion criteria in the 3-4.5 hour time window. I won't get into them now. We can talk about them if you have questions.

Finally, there is the extended time window. I won't get into details, but I'm happy to talk about it. Go to the next slide after that.

The wake up time gave us evidence that we can treat patients and provide benefit within 3-4.5 hours. The extend trial has opened up that possibility as well.

I will end by saying there are guidelines coming out of great interest soon. Stay tuned for the European stroke guidelines on thrombolysis. We are excited the World Health Organization has put into place essential evidence that it's been there for a long time. We deal with the reality that we don't have all the resources we'd like all around the world, like access to CT scans, or emergency hospital medications. I think there's much t

In this individual patient data metaanalysis of the five trials, we saw among every 1,000 patients achieving substantial endovascular reperfusion, every 15 minute faster emergency department door to reperfusion, 39 patients would have a less disabled outcome at 3 months.

In over 13% of patients, LVO opens the vessel. It's important to note that the authorization is often incomplete. These numbers of 13% and 6% are higher than the previous reported numbers. [On screen.]

We know about recanalization. For m2, you had to treat only six patients.

They saw recanalization breaks were lower in other patients. Only 3.8% of patients had early rate recanalization. A higher rate of recanalization, are due to the longer exposure. We know that early recanalization is related to a favorable outcome.

It's not affective for many patients. It's dependent on exposure time.

The next relevant or logical question is whether or not tPA is beneficial. This is a study of data. What they found was there were no differences in successful recanalization rates.

[On screen.]

The available clinical evidence of several studies demonstrates that immediate recanalization is effective. If patients are immediately treated in a hospital focused on strokes.

Not all strokes are the same. We can see large differences large vessel occlusion strokes. Patient one has an ischemic core of 163. However, patient two has an ischemic core of less than 10. What

accounts for this difference?

It's accounted for the patients who have poor collaterals.

It's been previously reported that with a large vessel occlusion we lose over one million neurons per minute. However, the rate of neuron loss per minute can range greatly.

We know that the time is critical. Patients should be moved quickly to endovascular units.

The authors found that the time for patients was 22 minutes longer.

This can mean that delays can be penalizing for our fast progressive population.

The arguments can be made for the cost associated with TPA. A 100 milligram is very expensive.

With increased costs with TPA, is this good use for limited resourced centers?

Why not skip TPA? We had two randomized control studies published. Is it inferior to bridging? [On screen.] The first of which is a SKIP study.

It was across 23 different sites in Japan. After meeting their inclusion criteria, age, symptom onset, and etcetera, they were randomized in 1:1, or bridging therapy.

It's important to note that the trials were used to reduce notes of TPA.

The results were presented at the international stroke conference this year. Even though there was no significant difference at the primary endpoint, the noninferiority was not met. It's important to



note that there were similar rates of 90-day mortality rates. Incidents of ICH was higher with bridging therapy.

The next trial is direct MT. [On screen.]

Direct MT included over 656 acute stroke patients. They had coronated artery. One was treated with the full dose.

After meeting the inclusion criteria, they were randomized. The infusion was created before the thrombectomy. [On screen.]

A thrombectomy was permitted if perfusion failed. It was done as a rescue therapy.

For direct MT, primary thrombectomy was not inferior to combined thrombectomy. The primary outcome was 90-day mRS.

There were multiple subgroups for analysis. These did not have any significant differences. There are four additional ongoing trials that compare primary versus bridging. [On screen.]

I've looked at the current enrollments for each trial.

In conclusion, there are arguments for bypassing alteplase. Should this be skipped? There's no effort for patients primarily in stroke centers, even if they are thrombectomy candidates. Should they be referred to the next stroke center, bypassing a stroke unit? The results of these ongo-



You can see that the graph shows the different group from this from I to III. Next slide please.

If we put IV rtPA, the number of patients for this therapy, we can see the percentage here. The highest percentage is 3. We can see the therapy situation around the 2005-2009. The highest percentage use here is if the patient can get in 3.5 hours after onsite, the TPA therapy is around 7%.

We are trying to figure out the reason for the impact of the therapy at different periods. I recalled, the first paper I mentioned from CNSR I, we were trying to figure out the reason. We found that it's pretty much the hospital delay in China. We compare the door to needle period. We found the same period from door to imaging, we have pretty much delayed from the imaging to needle. I think there's a huge difference for the workflow, and also the insurance, and something like that, in China.

There are older families and relatives. After admission to the hospital, not at the emergency room.

>> Thank you. That was terrific. Very useful information about China for us. Our final speaker is Dr. Mansour. He is a professor at Alexandria University, the director of the stroke unit. He's a board member, a president, and a cochair of different committees. We are looking forward to your talk. Hopefully we will finish early so there's time for questions.

>> Thank you for the introduction. It's a great pleasure for me to speak in front of on this topic, thrombolysis and treatment of AIS.

I will talk about strokes in developing countries. One example is Egypt. The official national statistics show that strokes are the primary cause of death in Egypt. Egypt is a very populous country in the middle east. They have about 1.2 million in the population. [On screen.] Many strokes occur per year.

I think we have such a high burden of stroke and mortality in Egypt because it's complicated. We can device it into two measures. One of them is inadequate primary prevention programs. Also, a weak healthcare system setup. There is lack of recognizing stroke providers in our region.

This graph is one of the formal graphs, coming from the states. We have a high mortality rate. The mortality rate is increasing over the past few years. We have about 1% of our population die every year.

The majority of NCDI services are financed by household, out of pocket payment. The contribution of the state in this regard is less than 30%.

We have a high rate of poverty in Egypt. About 33% of the population is living under the poverty line. The mid income of families per year is about \$2,005 dollars.

In Egypt, less than 6% utilize emergency service. In other countries, we can imagine how it is.

We have a huge problem regarding the triage, especially the extra hospital pathway. Also, regarding the interhospital pathway.

This is a survey that was done two years ago on the causes or reasons behind futile transfers. About 40% of the causes are related to the hospital problems. They over circulate the patient before they reach the stroke hospital. Also, the ambulance driver may not take the patient to the right hospital.

We can summarize challenges facing Egypt in the stroke business. There are four causes. Equality, and stability.

This is very interesting. Even in between physicians, the awareness of the stroke information is very minimal. Sometimes, the physician lacks information about intravenous, stroke warning signs, stroke disease, and etcetera.

A huge amount of effort was done in the country by different groups to increase stability and improve interfusion therapy. One of them is training for certification, and so on.

I think different models, innovative models, have been developed in different parts of the world, to increase stability for interfusion therapy. Most of them are acting on different parts. Either hospital or stroke unit.

One of these innovative models are in the end year, who are working on establishing more stroke units. Sometimes, they work with the government to provide it free of charge.

Regarding our effort in Alexandria, I think we tried to use a concept of the Thinly Effect. What seems impossible at a larger scale can be possible at a smaller scale.

Alexandria is working as a hub for about 12 million population in Egypt.

We realize we have a problem with the prehospital and intrahospital. We decided to impose these pillars through different tools. The first one is identification of surface providers through recognition. This one is based on something established two years ago.

This is the application for stroke Egyptian clinical registry.

This is a different type of registry. One of them is hospital based for stroke care. This part of the registry is aimed to recognize the surface provider into different capabilities to serve the stroke patient. There's a color-coded levels. The green level is the most advanced level.

At the end, we have recognition of the hospital. The hospital will be recognized on the system as a stroke ready hospital.

The other tool is a smartphone application. It can control the prehospital and interhospital stage. It has a lot of functions. There's a model to connect the stroke service providers. Also, there's a calculator to judge the patient, if he has a large vessel occlusion or not. It has a platform to telling medicine communication. Some can file communication through different hospitals.

We decided to examine the effect of this project based on data for one year. This is the study. We collected information from several hospitals in the Alexandria network. It was very interesting. Regarding the patient that has been managing through this system, the functional independence and avoidance of intracranial hemorrhage was better.

There was an improvement for stroke patients who managed it by this system. I think this is our model in Egypt. We are trying to increase access for reperfusion therapy. We need more for our region. Thank you!

>> That was fantastic! Especially knowing the barriers you've overcome to build the infrastructure in Egypt. Very fascinating talk.

We are going to turn to questions. We are running late. I want everyone to know we will stay a little past the hour. We will go five or ten minutes long. That way, we can get some questions in. Please use the question tab in the software to offer your questions.

The first one, I will ask Dr. Liu and Dr. Khatri. When you think about

doctors. Can you help us with studies looking at the EMS severity scales, using the rating scales in the field, or using telemedicine in the field, to determine patient destination and select a bypass, or closest facility? A quick rundown of stroke resources to use in the field?

>> There are currently a number of different scales. They are used by EMS providers around the world. One of the trials talked about bypassing the scales, and going to a stroke hospital. Is going to a capable hospital better? Those are currently being looked at. We use these scales in the field for the mobile stroke unit. Can they go to a stroke center? I discussed that in great detail on one of the first lectures, episode one.

>> Great. Episode one may be available. Maybe at the end, Aurora can tell everyone how to access that. Doctor, what is your perspective?

>> I think from my point of view, regarding our culture and hospitals in my region, I think using these scales can help a lot to avoid the prehospital loss of the patient. They can be triaged to the proper stroke area. One problem in my region is delay of the patient circulating between different hospitals, and how long it takes to reach the target hospital. I think using medicine and the scales is very beneficial to avoid such problems. It can help stroke victims be triaged to the right hospital at the right time.

>> The next question I can direct to a doctor and to myself. Is there any evidence that TPA works better with certain things? Are there locations that TPA acts better, with or without thrombectomy? This questioner speaks for everyone. Direct thrombectomy is not standard. Most centers still are combining TPA with thrombectomy. The basic science perspective is a fresh clot tends to have more embedded enzymes. The TPA can access them. Fresher clots, not decalcified, may do better with TPA and thrombectomy. Do you have a perspective on that?





advantageous. It's not superior. All of these trials, looking at whether or not to go directly to thrombectomy, or using alteplase. It may be outdated at this point. It's a great question for a neurologist. What about bridging with Alteplase? I'm looking at patients in the prehospital setting. Should we give them a one time drug?

>> In one minute, Dr. Liu, because we are just about out of time, what about China? What is the future for this in China?

Are you still with us? I think you are on mute.

>> Sorry for the delay of the internet. In China, we are considering a clinical trial. It should arrive extending the time window. Some instances, like a minor stroke, we discussed. Probably compare the bridging and the right thrombectomy. We are working on an agreement. We are still discussing.

>> What I'd like to do now is give every panelist one last minute to answer the following question. If our participants are going to take

the value of TPA bridging at thrombectomy centers, we need to acknowledge there are many different variables that may not be captured in the clinical trials, like clinical trials. There are some individuals that should not be treated.

>> Outstanding.

>> I would say I think it's important to remember that thrombolysis is an effective treatment we have. Everything we can do to bring this to our patients worldwide will improve lives.

>> Thank you. That's it for the panel. I'll turn it over to Aurora.

>> Thank you. That's all the time we have for questions. Thank you to our panelists and moderators for sharing their time and expertise. This webinar was recorded. It will be available before the next episode. You can access it from the link. There's one remaining webinar in this series. On World Stroke Day, we encourage you to join us for One Cycle Nation. Also, follow their social media accounts for discount codes for other educational opportunities.