

**MACKRAM
ELEID:**

Hi, I'm Mack Eleid, and I'm here with Michael Cullen. We're both cardiovascular fellows at Mayo Clinic, and we'd like to present to you prosthetic valve thrombosis. We'd like to thank Dr. Fletcher Miller for providing us guidance on preparing this presentation. We have no disclosures. Our learning objectives today on prosthetic mechanical valve thrombosis include, choosing and appropriate anticoagulation regimen for different prostheses, assessing clot burden and degree of obstruction in prosthetic valve thrombosis, applying guideline recommended therapy for prosthetic valve thrombosis, and safely administering thrombolytic therapy in selected cases of prosthetic valve thrombosis.

The incidence of prosthetic valve thrombosis ranges from 0.1% to 0.3% per year in patients with St. Jude mechanical, aortic, or mitral prosthesis. With some studies showing a slightly higher incidence of thrombosis in mechanical valves in the mitral position. I'd like to start with the case of a 37-year-old woman with a 31 millimeter mechanical St. Jude prosthesis in the tricuspid position. Two months, previously, she'd had an epicardial pacemaker implanted, and received vitamin K for supratherapeutic INR. Since that time she had noticed the lack of clicks, increasing abdominal fullness, and progressive New York Heart Association class three dyspnea.

She was taking aspirin, 81 milligrams a day, and warfarin for a goal INR of 2.5 to 3.5. A transesophageal echocardiogram was performed to further evaluate her mechanical prosthesis. This is a short axis view with the aortic valve on the right side of the screen. You can see the mechanical tricuspid valve has essentially frozen leaflets on the left, and on the right hand side you, again, see the frozen leaflets, and color flow shows significant tricuspid regurgitation. The Doppler evaluation of the prosthesis showed a prolonged pressure at half-time, and an increase mean gradient of 8 millimeters mercury. Her INR at that time was 3.8. Here are additional 3D TEE views of the tricuspid prosthesis looking down from the right atrium, you can appreciate that the side orifices are persistently open, consistent with frozen leaflets.

The ACC/AHA guidelines for right sided prosthetic valve thrombosis are based on patient symptoms and clot burden. The majority of patients, assuming that there are no contraindications to thrombolytics benefit from thrombolytic therapy. If patients have minimal symptoms and a small thrombus burden, IV unfractionated heparin is considered reasonable. These are all class two recommendations based on limited evidence. The patient was treated with alteplase bolus at 10 milligrams, followed by an infusion for five hours. Towards the end of the infusion she had a return of her closing clicks, and a bedside echocardiogram showed a reduction of her mean gradient to 3 millimeters mercury, with a return of normal leaflet motion.

IV heparin was continued once her alteplase infusion was complete. And the patient's target INR range was increased from 3 to 3.5, and she was discharged from the hospital once her INR reached 3.0. She's been followed closely in our valve clinic for the last year and a half since, and has not had recurrent prosthetics valve thrombosis. I just wanted to talk about the ACC/AHA guidelines for adjusting anticoagulation therapy after a successful resolution of thrombosis. And they recommend that the INR range should be increased for prosthetic aortic valves to 3 to 4.0, and for prosthetic mitral valves, 3.5 to 4.5. There's limited data on tricuspid valves, however, we tend to use the same guidelines for mitral valves for the tricuspid valves. Heparin should be continued until target INR is achieved, and importantly, all patients should receive low dose aspirin, unless contraindicated. And for patients who were not already on aspirin, who have a prosthetic valve thrombosis, it's reasonable to start aspirin instead of adjusting their warfarin target INR range.

Additionally, when patients require a reversal of anticoagulation for emergency procedures, fresh frozen plasma is recommended due to its quick onset, and relatively short duration of action. In patients who have more elective procedures, a low-dose vitamin K may be a reasonable alternative. However, the guidelines recommend against high-dose vitamin K, as it may be associated with an increased hypercoagulable condition. I'd like to transition now to Dr. Michael Cullen, who will be discussing left sided prosthetic valve thrombosis.

**MICHAEL
CULLEN:**

Thank you. My name is Mike Cullen. I'd like to thank Dr. Eleid for presenting the first case on the right sided prosthetic valve thrombosis. We're now going to discuss the case of an 80-year-old male, who had a bileaflet mechanical aortic valve replacement 12 years ago. He had normal left ventricular function, no atrial fibrillation, no prior thromboembolic events, and no prior stroke or bleeding history. When the patient first presented, there was a question about the appropriate anticoagulation regimen for him. Now, as Dr. Eleid alluded to the recommendations in the ACC/AHA guidelines, stipulate that all patients with prosthetic valves, we got a list of whether or not they are bioprosthetic or mechanical, require at least low-dose aspirin.

Furthermore, all patients with mechanical valves require warfarin. And then the level of anticoagulation will then depend on the valve location, the time since the operation, and other risk factors, such as atrial fibrillation, prior thromboembolic events, left ventricular dysfunction, or hypercoagulable conditions. When we look at the table from the ACC/AHA guidelines, and apply this to our particular patient, we see that he had an aortic valve replacement greater than three months ago, it was a mechanical aortic valve, and he had no other risk factors. So therefore, his anticoagulation regimen should have been warfarin to a goal INR of 2 to 3, and aspirin, 81 milligrams daily. One of the key points I'd like to make on this table is the fact that all patients with prosthetic valves, again, whether or not they're mechanical or bioprosthetic, require aspirin.

I think that's something providers frequently miss, and oftentimes other health care professionals will tell patients that if they are taking warfarin, they shouldn't take aspirin. However, when we look back at the data for aspirin, it's quite compelling. This is a randomized controlled trial of approximately 370 Canadian patients, the new old patients in the late '80s and early '90s, all of these patients had either mechanical valves, or high-risk bioprosthetic valves. The patients were randomized to receive either warfarin alone, or aspirin plus warfarin.

They were followed for four years, and you can see that the results are quite compelling. So this study resulted in approximately a 63% decrease in all cause mortality, and a 77% decrease in embolic events, and vascular death, in the patients randomized to receive aspirin. There was no increase in major bleeding in the patients receiving aspirin. Therefore, the guidelines are pretty clear that all patients with mechanical valves and bioprosthetic valves should be receiving aspirin in addition to warfarin, if they otherwise meet the criteria for anticoagulation with warfarin.

Now, if we go back to our case, he was actually only receiving warfarin alone, despite the guideline recommendations. But his INR was typically well controlled, it was almost always within the middle of his range, at around 2.5. However, he presented with six weeks of persistent dyspnea. He had a diminished closing click to his prosthetic aortic valve on examination, and he also had a prolonged systolic ejection murmur at the left sternal border. He underwent the transthoracic echocardiogram, you can see [INAUDIBLE] long axis images here, show relatively preserved left ventricular function, and the valve motion is difficult to detect. However, on CW Doppler imaging his mean gradient was elevated at 47 millimeters of mercury.

The question then becomes, what is the next step in this patient? And again, looking at the ACC/AHA guidelines, additional imaging is typically necessary. So the only class one recommendations in the prosthetic valve thrombosis section of the ACC/AHA guidelines address the need for, both, transthoracic and Doppler echocardiography, in the patients with a suspected prosthetic valve thrombosis to assess hemodynamic severity. And then transesophageal echocardiography, or fluoroscopy to assess valve motion, and clot burden. In our particular case, the patient went on to a transesophageal echocardiogram, where you can see a transgastric view of the prosthetic aortic valve, and you can see that one of the leaflets is not moving. And there also appears to be a small thrombus, a mobile mass, on the ventricular surface of the prosthetic valve.

So when we think about the next steps in assessing this patient, it's helpful to recall data from the PRO-TEE Registry. This was an international study of 14 centers that enrolled 107 patients who presented with prosthetic valve obstruction. And then underwent a transesophageal echocardiogram, followed by thrombolysis. Most of the patients had prosthetic valves in the mitral position, but some also had aortic, or tricuspid valves. The patients were eventually treated with thrombolytics. There was a complication rate of approximately 18%, and a mortality rate of approximately 5% to 6%. The results from the PRO-TEE Registry really helped develop some of the guideline recommendations regarding the assessment and the management of patients with prosthetic valve thrombosis. You can see here that the complication rates and mortality rates were significantly higher in patients with a higher clot burden, defined as a thrombus size greater than 0.8 centimeters squared, regardless of whether or not they had significant functional limitations.

So based on this data, the guidelines recommend surgery as first line therapy, and lytics as either backup therapy, or as an alternative to surgery, if surgery is unavailable in patients with left sided obstructive prosthetic valve thrombosis. If they are in either, New York Heart Association functional class 3 or 4 dyspnoea, or they have a large clot burden. Now, if we think back to our particular case, the transesophageal echocardiogram was very helpful, because that patient had a small clot burden. His thrombus area was less than 0.8 centimeters squared, and he was not in significant heart failure, even though he had a large gradient, he was hemodynamically stable. So in his particular situation, he would have qualified for lytics based on a class two B recommendation from the ACC/AHA guidelines.

The next question then becomes, how to give lytics. Traditional lytic dosing regimens have come from data regarding pulmonary embolism, and acute myocardial infarction [INAUDIBLE]. They have generally given lytics with a bolus, and then a relatively high dose infusion over a short amount of time. There have never been any randomized trials assessing the appropriate lytic dosing regimen for prosthetic valve thrombosis. This trial, which was published in *Journal of Intensive Care Medicine* in January of 2013, attempted to define the most appropriate and safest lytic regimen in cases of mechanical valve thrombosis. This study, called the TROIA Trial, enrolled patients with mechanical valve thrombosis over a period of about 15 years, between the early 1990s and late 2000s, they gave patients a series of different lytic regimens, including streptokinase, bolus, followed by a high dose infusion of TPA, or TPA at a relatively low infusion dose without a bolus.

And then they followed patients to determine, both, the success rates, and complication rates of those regimens. And you can see that the patients with the highest success rates, and the lowest complication rates, were actually those who received a relatively long infusion of TPA with a relatively low dose. This was actually the lowest dose infusion of TPA. So it would suggest that patients can be safely treated with thrombolytics, a little bit differently than we typically administer thrombolytics in the acute myocardial infarction setting. We may be able to, in cases of prosthetic valve thrombosis that qualify for lytics, administer a lower dose of TPA without a bolus to provide our patients with similar outcomes, and a lower complication rate.

So to summarize, from the guidelines, the data is pretty clear that all patients with prosthetic valves require aspirin. And then all patients with mechanical prosthetic valves require warfarin. We saw from the PRO-TEE Registry that a thrombus burden of greater than 0.8 centimeters squared has been associated with a higher risk of complications. Dr. Eleid mentioned that thrombolytics are indicated in cases of right sided prosthetic valve thrombosis with a large clot burden, or significant heart failure. For cases of left sided thrombosis, thrombolytics are indicated as an alternative to surgery in cases of small clot burden and stable symptoms.

Lower-dosed thrombolytic regimens may reduce complication rates as we saw in the recent Turkish data published earlier in 2013, and patients with successful resolution of a prosthetic valve thrombosis require an increase in their goal INR. And I'd like to thank you for your time. If you have any questions, you may contact either, Dr. Eleid, or myself. Thank you very much.