Melanie Cole, MS (Host): Welcome to the podcast series from the specialists at Penn Medicine. I'm Melanie Cole. And today, we're discussing peripheral artery disease with Dr. Elizabeth Anne Genovese. She's a board-certified vascular surgeon, an Assistant Professor of Surgery at the University of Pennsylvania, and the Director of the Penn Advanced Limb Preservation Program at the Hospital of the University of Pennsylvania.

Dr. Genovese, thank you so much for joining us today. I'd like you to start by giving us a little bit of an overview for other providers about peripheral artery disease or PAD, P-A-D, and it's end-stage manifestation, chronic limb-threatening ischemia, or CLTI. Tell us a little bit about these conditions, who they affect, and why do they occur.

Elizabeth Anne Genovese, MD: Yeah. So, peripheral arterial disease is very common in our greater community of Philadelphia. And essentially, it's any kind of level of stenosis or full complete arterial blockage causing decreased perfusion to the lower extremities. So, it can be at the level of the arterial tree in the abdomen all the way to below the inguinal ligament, either above or below the knee. And what we see is that the patients at highest risk for peripheral arterial disease, or PAD, tends to be patients over the age of 50. And they often have comorbidities you think of with coronary artery disease or cerebrovascular disease, so hypertension, hyperlipidemia, diabetes, and particularly either some renal insufficiency or full-on end-stage renal insufficiency, renal disease, all contributing to atherosclerotic disease and progressive occlusion.

We often see that this affects men at a little bit of an earlier age and women at a little bit of an older age, but really, an equal distribution between men and women. Often women are a little bit more prominent in the older age patient population. So, the same patient population we're thinking about with coronary disease, carotid disease, patients who are at risk of stroke, same patient population.

Host: Thank you for that overview. And while we're in that realm there, the initial presentation of PAD is often prompted by claudication, pain in the legs, are there ways to detect it before this point in asymptomatic people? Is there something that would signal walking difficulties, limiting factors?

Elizabeth Anne Genovese, MD: Yeah, absolutely. When we look at PAD, there is a continuum of symptoms that we see. So, the first patient population is going to be our asymptomatic patient population. So, they'll either have some screening test or a physical exam, or maybe you can't feel the pulses in the foot. However, they have no symptoms. It doesn't hurt when they walk, they don't have any pain in their feet, they have no wounds. In those patients, it's important to actually identify PAD, because it is a cardiovascular risk factor, and it signals importance in risk factor modifications. So first and foremost, smoking cessation, diabetes control, anti-lipid and anti-platelet medications.

Then, the next step in this continuum is going to be often claudication. Not everyone is going to actually go next to claudication, but a fair majority of patients will describe claudication, which is essentially a very predictive amount of exercise, resulting in cramping in a certain muscular bed. And that muscular bed is usually the one just distal to the area of the occlusion or the stenosis. So, if people have aortoiliac occlusive disease, they may complain of cramping in their buttock or in their thighs. If they have more disease in their femoral or popliteal arteries, they'll complain of calf cramping when they walk. And people can be mixed pictures, right? You can have multi-level disease. But typically, it is a, "I start to do an exercise. Five minutes into it, I notice I have this cramping, and then it's relieved when I stop after a couple minutes. And then I start walking again, and this happens again."

Now, when people have blockages that are just below the knee and it's kind of isolated tibial disease, so we see this in patients with diabetes, renal insufficiency, sometimes they don't claudicate, because there's really not a muscular bed below those blockages to cause pain with exercise. So, sometimes people will go from asymptomatic to the next thing they complain about is just pain in their foot or tissue loss. So typically, what they'll say with regards to rest pain is, "When I'm just laying at night and my leg is at the level of my heart in bed, my forefoot throbs, it aches. I dangle it off the bed and it feels better." Or they may say, "I have this wound on my foot that hasn't healed in a couple of weeks despite taking care of it." The rest pain and the tissue loss is a little bit more of that end-stage of peripheral vascular disease, and that's the patient population that's really at risk of limb loss once they hit that diagnosis.

Host: Exercise remains a challenging course for patients with PAD as it is such a limiting factor. And we'll get into that a little bit more. But before we discuss the Penn Advanced Limb Preservation Program or the PALP Program at Penn Medicine, can you discuss a few terms? Critical limb ischemia was replaced by chronic limb-threatening ischemia. Can you speak just a little bit about why this happened?

Elizabeth Anne Genovese, MD: Absolutely. So, approximately two years ago, there was a multisocietal guideline that came out called the Global Vascular Guidelines that really look at PAD and our end-stage patient population, the critical limb ischemia patients, as it is traditionally known as. And this has, again, always been the patients with rest pain and tissue loss. And the initial thought behind the terminology *critical limb ischemia* came from years ago, over 20 years ago, where a lot of the disease that came with peripheral arterial disease was secondary to smoking. And there was this idea that there was a certain kind of threshold that patients had with regards to their arterial perfusion. And once they pass that threshold, then they were at risk of losing their limb.

What we see now in our more modern patient population is, while smoking still plays a very strong and important risk factor for developing PAD, there's this high prevalence of concomitant, poorly controlled diabetes. So now, people are at risk of losing their limb, not only because of arterial insufficiency, but the other

factors that come along with having diabetes, such as neuropathy, conformational changes in the foot, poor wound healing due to the diabetes and the local microbiome that we see in the foot. And so, we've changed our thinking to get rid of the idea of a certain threshold, a certain cutoff of arterial perfusion, now to more the global picture of looking at patients and changing the terminology to chronic limb-threatening ischemia, meaning we know there's underlying arterial insufficiency, we have perfusion defects to the foot, but that there are a variety of things that not only contribute to the risk of limb loss, but that we also need to very actively address in order to be a comprehensive program and providers to allow for limb salvage.

Host: So, tell us a little bit about the PALP Program at the Hospital of the University of Pennsylvania. Give us a little bit of your team overview, the multidisciplinary goals of the program. Tell us a little bit about it.

Elizabeth Anne Genovese, MD: This is a really exciting program that we've created here that's very unique to HUP. We have developed over the past year a really nice foundation of a multidisciplinary program. And so, what this is allowing us to do is approach patients from every facet of their medical care in order to optimize their ability to wound heal. So, we have worked with particularly Podiatry here at HUP. We have developed antibiotic pathways and guidelines, specifically with the Antibiotic Stewardship Program here at HUP, to not only develop empiric antibiotic pathways when patients come in with foot infections or wounds, but also empiric pathways to kind of guide our antibiotics once a patient is leaving the hospital to not only optimize specific coverage, but also to minimize the overuse of antibiotics at an outpatient level.

When we're this, we're involving not only Vascular Surgery, Podiatry, Infectious Disease, but we're also working with other ancillary service lines that we traditionally think of. So, Cardiovascular Medicine or Cardiology to make sure we're optimizing their hypertension and their lipid management while there's an inpatient in the hospital. We're working very closely with Diabetes and Endocrine to make sure their glucoses are well controlled. So, we're trying to take a very holistic and multidisciplinary approach while we have these patients as a captive audience, and the inpatient to really set them up for success once they are discharged.

Host: What a comprehensive program. And PAD has several stages, Dr. Genovese, with chronic limb-threatening ischemia or CLTI is the final step. Often, before amputation, what marks the demarcation between those stages? Why is the disease so often progressive despite the management that you were just discussing? Can reocclusion or the other sequelae be prevented?

Elizabeth Anne Genovese, MD: This is a tough disease process. And so, there's a lot of things that contribute to the development of PAD. And once we've gotten there, once patients are symptomatic in one form or another, there's been years and years of disease pathology and atherosclerosis that has led to this point.

The demarcation from claudication to chronic limb-threatening ischemia really is the difference between "It hurts when I walk" versus "I have rest pain or I have wounds or tissue loss." Once you transition from rest pain in the foot or tissue loss, whether it's gangrene, an ulcer, a wound that doesn't heal, patients are at a 20-25% risk of limb loss in the first year and mortality in the first year. So, it's a very morbid disease process. When we start talking about optimizing patients and reducing re-occlusion, reintervention, it's really about risk factor modification.

So, smoking cessation is always number one on our list of what we're approaching with patients. But again, also making sure those other risk factors that led to this disease process modified and optimized as much as possible, not only in the hospital, but once patients leave the hospital and they're in the outpatient setting.

Host: How do you define success in amputation-free survival? Speak about that a little bit.

Elizabeth Anne Genovese, MD: I think what we all look at with success in this field is avoiding major limb loss. And so, in that effect, it usually often includes some sort of revascularization procedure, whether it's an open surgical bypass or advanced endovascular techniques in conjunction with either wound debridements or potentially some minor amputations, forefoot amputations. Those are all considered success, because what we're just trying to avoid is a below-the-knee or an above-the-knee amputation.

Host: There are some patients, for whom no option is available. Who are these patients, and why are they considered to have no options for treatment? When does it get to that point?

Elizabeth Anne Genovese, MD: There's two kinds of patients who are "no option", meaning we don't have anything to offer them with regards to limb salvage.

So, the first is really severe comorbidities, extreme frailty, or extensive tissue loss. These are patients who ultimately we can't offer them things, because we'll either hurt them as a whole in trying to offer them something, or there's just no salvageable limb left due to the tissue loss.

There's another bucket, though, of no-option CLTI patients that traditionally we haven't had surgical or endovascular options for. So, this is a patient population where we've really had arterial blockages in the smallest vessels in the foot.

With diabetes, renal insufficiency, and end-stage renal disease being so rampant, it's really attacking and occluding these smaller blood vessels. So, we will see patients have flow in their aortoiliac system, they have it in their fem-pop system. And then, we start to see some disease in their tibials, but then we have nothing that comes back in the foot. And traditionally, if you don't have a blood vessel that reconstitutes in the foot, we don't have any target for a bypass or for an endovascular procedure. So, this is that no-option patient population that we've developed some new techniques to bring blood flow to the foot in the absence of arterial targets in the foot.

Host: This is a fascinating conversation, Dr. Genovese. And you're currently participating in a clinical trial of a device designed for the no-option population known as LimFlow system. Explain a little bit about the system's novel approach in no-options critical limb ischemia.

Elizabeth Anne Genovese, MD: Yes, absolutely. So, the wonderful thing about the PALP Program here at HUP is that we have access to a number of clinical trials, where we get access to the latest and the greatest upcoming technology, particularly with regards to infrainguinal occlusive disease. The LimFlow system is designed specifically for this no-option CLTI patient population that lacks an arterial target in the foot. So, these are patients we can't perform an endovascular revascularization, because there's just, again, no target in the foot.

So, the LimFlow system, which we're a part of with PROMISE III, is a system where we perform a deep venous arterialization. So, the general concept is instead of bringing blood flow into the foot through the arteries, we're utilizing the venous system in the foot to perfuse the tissue. So, what does that mean? We're actually perfusing the venous network through the arterial system. So, the LimFlow system is a novel group of technologies where we perform this deep venous arterialization. So, we create a crossover point from the arteries below the knee directly into the veins below the knee. We modify the valves in the vein and we place a covered stent in order to directly perfuse the foot through the venous system. And so, over time, over a one month to six-week period, we really create this very robust network of flow in the foot through the veins, through neovascularization in order to perfuse the tissues in the foot through the venous system itself and not through the arterial system.

Host: Dr. Genovese, as we wrap up, how can people with questions about everything we've discussed here today, PAD, CLTI, or the LimFlow study, contact the PALP program at the Hospital of the University of Pennsylvania? And summarize everything, what you would like other providers to take away from this fascinating conversation today.

Elizabeth Anne Genovese, MD: We can always be contacted. We have a PALP hotline number, which is 215-662-4748 or I can always be directly contacted through email. And I can always help guide people in either through the inpatient system or through our outpatient system, whatever kind of works best for patients to get in, whatever touch point is easier for those patients. But it's a really

wonderful program with a lot of people very dedicated to treating and optimizing this patient population. I have great partners here in the Podiatric realm, in the Infectious Disease realm, in the Cardiology realm, who are all very, very dedicated to treating this patient population, and it is a fantastic team.

Host: Thank you so much, Dr. Genovese, for such an engaging conversation. To refer your patient to Dr. Genovese at Penn Medicine, please call our 24/7 provider-only line at 877-937-PENN, or you can submit your referral via our secure online referral form by visiting our website at pennmedicine.org/referyourpatient. That concludes this episode from the specialists at Penn Medicine. I'm Melanie Cole.