Peripheral Artery Disease: Epidemiology, Diagnosis, and Management

Marc P. Bonaca MD MPH

Professor of Medicine

Director of Vascular Research

University of Colorado School of Medicine

Peripheral Artery Disease: Burden, Clinical, Presentation & Screening

Dr. BONACA: Hi, my name is Marc Bonaca. I am a professor of medicine, a cardiologist, and a vascular medicine specialist at the University of Colorado School of Medicine. And it's really an honor to be here with the Foundations of Cardiometabolic Health certification course. I'm going to be talking about peripheral artery disease. The epidemiology, diagnosis, and management. These are my disclosures. I work with a research group that receives grant funding from a number of funders, including Janssen and Bayer that supported the VOYAGER PAD trial.

Now, I want to begin with covering the burden of peripheral artery disease, both in terms of prevalence and incidence, the clinical presentations, screening, and some of the complications.

Here are some definitions. PAD. I'll be referring to that multiple times in the talk. That's peripheral artery disease. Please note that the term may be interpreted in different ways. It really refers to any of the arteries outside of the coronary circulation, but for the purposes of this talk, I'll really be focusing on lower extremity peripheral artery disease. CAD is coronary artery disease. Polyvascular disease is symptomatic atherosclerosis in multiple territories. Either the cerebrovasculature, coronary circulation, or the lower extremities. MACE, major adverse cardiovascular events. Those are things like heart attack, strokes, and cardiovascular death. MALE is a more recent term. Major adverse limb events are acute limb ischemia which is sort of a heart attack of the leg. Amputation is something we do in terms of care for patients. Unfortunately, it results in limb loss. And then critical limb-threatening ischemia which is a chronic severe form of PAD.

I want to begin with the notion that atherosclerosis is a systemic disease and many of us have been taught this over our careers. If you have atherosclerosis in one territory, you have it in multiple territories. And that is true. It is a systemic disease with shared pathobiology.

But that being said, patients with symptomatic diseases in these territories really differ both in terms of their morbidity and how they respond to specific therapies. I think the clearest demonstration of that is for patients that have lower extremity peripheral artery disease, they share a high risk of heart attack and stroke than patients with coronary disease or stroke have. Because they have atherosclerosis.

But they are different because they have dominant morbidity of limb vascular events. They have functional decline because they don't have enough blood flow. They get wounds on their feet. They can have a heart attack of the leg or acute limb ischemia. They can have amputations. They are different. And we've learned from trials that their benefit-risk profile with certain therapies is different than those of patients that have coronary artery disease or stroke. We're going to get into that today.

There is overlap for sure. You can see from this Venn diagram from a trial called TRA2P that about one in five patients who have symptomatic atherosclerosis will have polyvascular disease. Some overlap between these different bins of CAD, PAD, or stroke. But a lot of them don't. And so, we need to recognize that the patients that have polyvascular disease, the overlap are different than those who have symptomatic disease in one territory and they are at extremely high risk for polyvascular disease.

Now, what are the drivers of risk in PAD? This is a beautiful analysis that was in Nature Medicine that looked at some of the genetic polymorphisms that are associated with PAD and PAD outcomes. And you can see from the Venn diagram at the right that there are overlapping risk factors. But there are some that really stick out for PAD. And you can see that on the left side of the slide. A little risk. LDL and LPa

are really important in terms of the risk of PAD thrombosis. You can see inflammation with IL-6 and diabetes. Those are some of the key drivers of risk in PAD.

Now, where did the term come from? Well, actually, the first manifestation of peripheral artery disease was a term called claudication and this was actually first described in a horse. There was a horse who was lame and limped. The Latin word for limping is "claudicatio". And so, it was described as claudication.

And it's quite important to note when they examined the cause in this animal for lameness and blood flow obstruction, it was a fibrous clot. And I want you to remember that. Clotting is a particularly bad issue in patients with peripheral artery disease, particularly in the lower extremity arteries. And it was first seen here in the horse in 1831 or described in 1831. And it was really Charcot in 1858 who really defined in humans the syndrome of intermittent claudication.

Why intermittent? Well, the calf pain that occurs due to lack of blood flow only occurs when you reach a threshold of function. When you walk a certain distance you get the pain and when you rest it goes away. That's intermittent claudication. And that's actually a very uncommon manifestation of PAD. It may have been the first described. But if you think about the patients that you may interact with, a very small proportion that has PAD will tell you they have calf pain when they walk and it goes away with rest. And then the majority have other symptoms that we'll talk about.

Peripheral artery disease, for the purpose of this talk, is an occlusive disease in the distal aorta. You can see in the figure on the right the iliac arteries and the arteries below that. The femoral arteries, popliteal, and infrapopliteal distributions. Dominantly caused by atherosclerosis, cholesterol, plaque, and calcification. But there are some unusual causes that can happen in younger people, so always be on the lookout for that. And it is associated with all of the bad things that happen with atherosclerosis like heart attack and stroke. And added to that is limb morbidity. Functional impairment, amputation, and acute limb ischemia.

Now, it is important to note that these patients are different than patients that have dominant coronary disease. And there's heterogeneity in the biology. Not everyone who has leg artery disease really has the same disease process. There on the left side of the slide are the patients that have the typical intimal or subintimal disease, where we have plaque and lipid deposition and plaque formation with occlusion of the artery. But there are patients with PAD that have dominantly calcific disease. They have what's called medial artery calcification. We tend to see this in patients with diabetes and renal dysfunction.

And it's important to note that they may not respond the same way to certain therapies. Understanding the biology of your patient is important. And we'll get into this, but this is part of why certain trials of medical therapies look different in PAD populations and CAD populations.

As I mentioned before, the key drivers of risk are smoking and diabetes. But the disease we see differs a little bit. The traditional smoker with atherosclerosis has atherosclerosis in their distal aorta, iliacs, and femorals. Those patients look different in terms of how they do than the patient who presents with diabetes and renal dysfunction that has a lot of disease in the small vessels below the knee and the microvasculature. These are potent risk factors for PAD, but the PAD they develop looks different and behaves differently.

What is the journey of the patient with peripheral artery disease? Well, moving from left to right on the slide. Most patients initially will develop mild functional symptoms and those symptoms may be quite diverse depending on who you are.

Some people say, "I'm just getting tired. I can't walk as far. Maybe my arthritis is getting worse. My statin is making my muscles hurt." We hear all sorts of things. If you wait for a patient to say, "My calf hurts because of lack of blood flow," you will vastly underdiagnose peripheral artery disease. The earliest manifestations are just functional decline. And anyone that you see that says, "I'm just not walking as far as I used to" that has diabetes and has ever smoked or is over 55 or 65 years old. You should think about screening for peripheral artery disease.

They then progress and have more severe manifestations that are usually overt. Oftentimes, they can be managed with supervised exercise and medications. They then, unfortunately, will progress without appropriate treatment to critical limb-threatening ischemia. This is when we get the chronic occlusive disease and people get wounds that won't heal, rest pain, or gangrene. And they often require amputation or revascularization. And then after that, those patients that require amputation revascularization become at extremely high risk for recurrent events and acute limb ischemia.

This is claudication. Claudico, again, is Latin to limp. It's reproducible discomfort and it's the muscles in the legs. Typically, the calf. And it's a supply-demand mismatch. There's just not enough blood flow to support the muscle with exercise.

There are a couple of classification systems that have been around for a long time to grade the severity of peripheral artery disease. On the left is the Fontaine classification and there are essentially four bins, although, there are more on this slide. But there's the asymptomatic patient. That's one. Class two Fontaine is really claudication stratified by mild or more severe A or B. And then when you get to three and four, it's ischemic rest pain and gangrene. Those are critical limb ischemia patients.

Rutherford has six categories. You can see it on the right. And you can see that one, two, and three are different severities of claudication. Zero is the asymptomatic patient and then those who have four, five, or six have critical limb ischemia. And those with five or six have tissue loss.

How do most people present? But those that present with typical claudication are generally about 15% of those who have peripheral artery disease. You should not only think about peripheral artery disease in people in the green slice of the pie here because you're missing all of the others. And these data are somewhat dated.

This comes from the FRIEND registry. But in that yellow 50% of patients, we've learned that they're really not asymptomatic. None of these patients are asymptomatic. They all have functional impairment if you ask the right questions. But very few of them will describe typical claudication. You should be on the lookout for those in the yellow and those in the red because those are the ones where you diagnose PAD early and prevent the worse complications.

How do you diagnose it? Well, obviously, functional limitation, as I noted on the prior slide, is key. Some of the things that might hint at a more severe disease in the clinic are people that say they have pain in their legs at night. Now, some people attribute that to muscle cramps, leg cramps, or whatever. It may be rest pain, meaning that when the legs are elevated, they don't have the benefit of gravity to help profuse those legs and they get worse pain at night.

When you hear rest pain in somebody with risk factors, be concerned about PAD. They get wounds on their feet that won't heal. They develop claudication or other functional limitation. And really, a lot of those patients who have other cardiovascular diseases, other risk factors, diabetes, or coronary artery disease, you should think about PAD.

What do you notice in the clinic? Well, the most important thing you can do is take the socks off. Feel for pulses. If you can't feel a pulse, that's quite specific for PAD. And if you can't find one no matter how good your pulse exam is, you should think about testing for PAD. You may hear bruits if you listen over some of the larger arteries.

One thing that people don't always think about is hair loss. Patients who have chronic ischemia in the limbs tend to lose the hair over the distal half of the leg or below the knee leg and that is a sign of ischemia. If you see hair loss or sometimes, the skin becomes thin and shiny and even if you see nail dystrophy which may look like a fungal infection of the nail, that may be a sign of chronic ischemia.

You can see in those patients if you lie them down on the table that, sometimes, the feet look kind of white. But if you have them sit up and you put their legs in the dependent position, they really become bright red because the distal arterials are maximally dilated, begging for more blood flow. And you may see evidence of tissue loss. I hope that's not where you're seeing PAD because that's a very end-stage, but if you notice it, it's obviously important. Hopefully, you can find people earlier in the disease state.

When we find it, there are imaging studies. Duplex ultrasonography is often used as a way of defining the levels of disease and severity of disease for people for whom the intervention is planned. They generally get more anatomic or axial imaging, MRI, or CTA. Or they may go and just get conventional angiography with an eye towards procedures.

In patients who don't have severe disease, where you're not planning an intervention, you don't necessarily have to do any imaging. The ankle-brachial index is the test of choice. This is the safest, cheapest, and most potent biomarker for risk that I know of. You don't even have to do a venipuncture on their blood tests. All you have to do is check the blood pressure in the arms and the feet and you can see the simple math here to calculate an ankle-brachial index.

You can see on the left side of the slide the gradations. Anything 0.9 or actually below 0.9 is abnormal. And you can see the grades of mild, moderate, and severe. Just note that there are some patients whose vessels are so diseased and calcified that the cuffs can't compress them. And in that case, you get this unusual finding of a high ABI above 1.3 or 1.4. And if you get that, that's not a reason to celebrate. That just means there's so much disease there that they have non-compressibility artifact. In that case, we get the total brachial index.

The total brachial index, in more detail, is something that can be done in a vascular lab with a tiny cuff and that's because the toe vessels don't calcify, so you can order that test. ABIs, as I mentioned, are potent biomarkers. This is a seminal study that was published in JAMA and it shows the very clear relationships between the ankle-brachial index as it goes down and the increased risk of mortality both for men and women. And you can see when you get to the high ABI at the far right, that's bad too because those vessels are clearly diseased.

The prevalence of PAD has increased dramatically. You can see here a rate of change of about 24% over a decade from 2000 to 2010. The bad news is that this trend is continuing and now, it's estimated there

are about 235 million individuals globally who have PAD. Why? Well, despite the use of statins and trends toward less smoking which have reduced the rates of heart attack and stroke, the really close relationship between age, obesity, and diabetes in PAD has driven an increase in prevalence.

And you can see that prevalence is very dependent on who you are. Here you can see several registries, but I'll draw your attention to the partners' registry at the bottom. If you have a patient in your clinic who's over 70 or they're 50 to 69 with diabetes or smoking, one in three will have PAD. One in three. There's a very high prevalence in certain populations and think about that as you hear about the functional decline and testing.

Now, the prevalence is increasing. You might ask well, maybe that's just because people are looking for it more. I wish that was the case. But actually, we're seeing people show up with a more severe disease. On the left side of the slide, you can see admissions in the United States for people with critical limb ischemia. On the right side of the slide, these are admissions for peripheral artery disease and revascularizations.

And you can see a clear upward trend. This trend is different than what we've seen over those decades for MI and stroke. All of those are increasing now again and that's because the type of PAD occurring now is the PAD that occurs in the setting of diabetes more often than smoking. And diabetes tends to result in a small vessel and microvascular disease with a high rate of wounds and amputation.

I talk about polyvascular disease as a unique subset of patients with PAD. And you can see two trials here. One is EUCLID and one is PEGASUS. Both were large atherosclerosis trials. And what they show you is that if you have symptomatic disease in one territory albeit PAD or CAD in the yellow, you have a very high risk of MACE over the next three years.

What's even worse, though, is if you have symptomatic PAD and CAD. In either dataset, you risk just about doubles. And you can see even after adjusting for baseline differences, there's about a 50 to 60% excess of bad atherothrombotic events occurring in those with more symptomatic territories. This is what has been referred to as metastatic atherosclerosis and these patients do have a risk profile that fits that name.

You can see this here again in another trial called the FOURIER trial, where patients who had PAD were at higher risk than those who had MI or stroke. But when you break out the PAD population, you see that those in yellow who had PAD alone were very high risk. But those in red that had polyvascular disease were at exceptional risk. And that was about 1000 patients here in that trial that had an event rate of about 15%. These are the patients that are at the highest risk.

You can see that risk stratification actually matters even in patients who you know to be high risk. If you think about the patient coming into the hospital with a heart attack or an acute coronary syndrome, ACS, we all know those are the highest risk patients. But if you look for polyvascular disease and diabetes, you can see risk stratification. These are seven-year outcomes in patients that were well treated with ACS alone in green with either diabetes or polyvascular disease in the yellow or blue. And if you put the two together and if you have your ACS patient who has diabetes and polyvascular disease, one out of two will have a heart attack, stroke, or die of cardiovascular causes over the following years. And you can see that very steep risk relationship. Identifying PAD, even if patients you know have CAD, is important.

But many PAD patients don't have known coronary disease and they do behave differently. I'm showing you here two trials on the left, EUCLID and CASPER. And in both of those PAD trials, only about a third had symptomatic coronary disease. These really are different disease states.

And why is that important? Well, there are a lot of things that happen to these patients that are different than coronary patients. If you look at the causes of death on the right side of the slide, from the EUCLID trial, less than 10% of the deaths were typical plaque rupture that we see in coronary disease. There are a lot of other non-cardiovascular diseases and maybe infections due to wounds or limb complications. Non-cardiovascular deaths or other things related to heart failure, for example. We need to understand that this population is more distinct than patients with coronary disease.

And patients with PAD and diabetes are also at higher risk for other complications. It matters. If you know you have a patient with diabetes, why does it matter if you know that they have PAD? Well, they're at higher risk of MACE, higher risk of heart failure, and higher risk of kidney complications. Knowing if someone had PAD is important in terms of their overall risk prediction for MACE and other things.

But now, let's transition to the dominant morbidity. Patients with PAD are different than those with coronary disease or stroke because they have disease in their limbs. And when you look at the slide from the REACH registry on the left, which was observational data or a randomized trial on the right, they tell you the same thing. They're just saying MI and stroke are less than half of the risk. Those are the high event rates you see in red. But look at the yellow. If you want to know what's going to happen to these people and these patients that have PAD over the next three or four years, one in four will need a procedure on their limbs in order to improve blood flow either due to debilitating symptoms or to prevent tissue loss. And rates of amputation or the heart attack of the leg, acute limb ischemia, and are as frequent or more frequent than MI and stroke. We have to think about the yellow bars when we think about patients with PAD.

We know that the risk in this population is different depending on who they are. When you're thinking of limb complications, there are three flavors that you might think about. One is the patient who's had a revascularization ever. Even five years ago or they had an amputation. They, for the rest of their lives, remain at extremely high risk of adverse limb events. You should worry about adverse limb events in them.

There are patients who have claudication but have never required intervention. It may be stable and they're an intermediate risk. And there are those that may just have a low ABI, but no true functional decline, and their risk is relatively low. Really the ones in the bright red bar you should worry about.

Now, I've talked about major adverse limb events. What are they? And I've shown you here an analogy for cardiac complications in the top row and the analogous complication in the limbs to try to present a framework for you. And moving from left to right, we get from more subjective symptomatic manifestations of PAD to things that are really hard outcomes on the right side of the slide. If you think about stable angina in coronary patients, that's claudication in the limbs. Obviously, as that progresses, you can get severe angina that requires revisualization. Just like chronic critical limb ischemia. That's a more advanced form of disease.

What we really worry about is when people have an unstable disease or disease that's threatening the viability of the tissue. In coronary patients, this might be unstable angina or urgent revascularization. In

the limbs, it's urgent peripheral revisualization. And then the most feared complication in the coronary patients is occlusion of a conduit artery vessel that threatens death to the downstream myocardium. Myocardial infarction. And the analogy in the limb is acute limb ischemia.

Critical limb ischemia, as I mentioned, is an advanced form of disease. People who have this do really poorly. You can see only about a third at six months after being diagnosed with CLI will be alive without an amputation. Maybe 45%. About a third are alive with an amputation and one in five are dead. This is a very bad form of the disease.

And then acute limb ischemia in the seminal publication by Marc Creager and Mike Conte. It really is a heart attack of the leg. You can see an unfortunate patient here. This is not a subtle event. Many are unfamiliar with acute limb ischemia because only the vascular surgeons tend to be called in the middle of the night when this occurs. But it actually happens quite frequently. And then this is chronic critical limb ischemia which is not the acute heart attack of the leg but slowly progressive disease that leads to tissue loss and wounds.

Recently, there has been a WifI concept for the diabetic wound and critical limb ischemia which really acknowledges the different factors that play into chronic critical limb ischemia. It's not just ischemia or lack of blood flow. You can see that in the upper right here. But it's that coupled with infection. Often in diabetes, there's a disordered immune system and susceptibility to infection. And then wounds. And if you can't heal the wound, ultimately, you end up with more tissue loss.

Looking at patients holistically for critical limb ischemia is really important. And when we talk about critical limb ischemia as an outcome, it's really heterogeneous. All of these factors contribute.

In contrast, acute limb ischemia is a heart attack of the leg and that really is a thrombotic phenomenon. This is the analogy I often use for acute limb ischemia. It is the STEMI of the leg. It's the acute occlusion of a conduit artery. Usually, it's a clot. Time is a muscle just like in the heart. And how patients do is fully determined by how fast you can reperfuse that leg. And in fact, when there's prolonged ischemia in both territories, the heart or the leg, you get reperfusion injury. And you can see that mortality and adverse outcomes are very high. In all, it may be worse than even with STEMI.

Well, thank you for listening to that section. I'm now going to move on to medical therapy for PAD.

Medical Therapy for PAD: The Basics

Hi, my name is Marc Bonaca. I am a cardiologist and vascular medicine doctor and a professor of medicine at the University of Colorado. I'm not going to speak about medical therapy for PAD and cover the basics. Maybe a little bit beyond the basics too.

Medical therapy for peripheral artery disease over several decades was largely determined by consistent findings in subgroups of large cardiovascular trials. Treating PAD as a high-risk subgroup of a large atherosclerotic population. You can see that in the top row of this slide. The anti-thrombotic trials are collaborative. The ATT looked at aspirin in a lot of people and it showed benefits for reducing MACE and an increase in major bleeding by about 60%. There was no benefit for limb outcomes, but that ended up as a class one in the guidelines.

The CAPRIE trial looked at a very large atherosclerotic population and showed that clopidogrel as monotherapy was a little bit better than aspirin. Maybe even more so in PAD. No benefit for limb outcomes. In fact, more amputations with clopidogrel than with aspirin, but not statistically significant. This was approved in PAD as a subgroup of CAPRIE. It was a subgroup analysis and that's class one in the guidelines.

And the HOPE trial showed ACE inhibitors were good for patients with atherosclerosis. No limb outcome benefit. But it was approved for PAD based on a subgroup.

The WAVE trial showed anticoagulation didn't work for reducing MACE in PAD and actually had an increased risk of bleeding that was really intolerable.

And then the HPS study showed that statins reduced the risk of MACE. In a large population, there was this PAD subgroup that was consistent. That was approved. And there was maybe a trend for revascularization, although, not a lot of definition around that.

And CHARISMA showed, broadly, that DAPT in patients, particularly, with those risk factors, was not beneficial, but maybe subgroups who have atherosclerosis like prior MI, especially, increased bleeding. There was a reduction in hospitalizations in the PAD subgroup. But overall, no convincing benefit for routine DAPT in patients with PAD. That was the development of the guidelines. Aspirin, clopidogrel, or monotherapy. Pick one of those. An ACE inhibitor. If they have hypertension, a statin.

Then in the middle of the slide were really therapies that were developed to prevent limb complications in PAD. And you can see there were no positive trials. Dutch BOA looked at warfarin to prevent thrombotic graft occlusion. No benefit. Three-fold risk of hemorrhagic stroke. CASPER looked at DAPT versus aspirin after bypass and showed no benefit. In fact, there was really a trend towards higher mortality and there was almost a threefold excess in bleeding. No DAPT for PAD. And CASPER looked at that after endovascular revascularization but never recruited. No effective therapies for limb outcomes and one therapy for function. That was cilostazol by the way.

They're really dominated by reducing MACE in patients with atherosclerosis and consistent benefit in those with PAD. Nothing in our toolkit to prevent limb outcomes.

A lot of changed since then. There have been a series of trials that have now demonstrated novel therapies that have benefits for limb outcomes in PAD. TRA2P showed that the addition of vorapaxar to aspirin and/or clopidogrel reduced acute limb ischemia and is approved in PAD.

The EUCLID trial looked at ticagrelor versus clopidogrel and it taught us that these populations are very different. And although ticagrelor was superior to clopidogrel in acute coronary syndrome and chronic CAD, it was not superior to clopidogrel in the EUCLID trial and it's not labeled for PAD.

FOURIER showed PCSK-9 inhibitors reduced limb outcomes in patients with PAD and the ODYSSEY trial has validated those findings. And COMPASS showed in chronic PAD that the addition of low dose rivaroxaban to aspirin reduces adverse limb events including amputation in patients with PAD. For chronic PAD, we have vorapaxar, PCSK-9 inhibitors, and rivaroxaban now that we can add to our armamentarium.

You'll notice on the pie charts here, though, that these were all stable PAD patients and there were very few that had critical limb ischemia and almost none that were post-revascularization. There was really a gap there in our knowledge.

In terms of CLI and diabetes, I do think that we have to recognize that it is multifactorial. It's not just blood clotting or cholesterol, but there is microvascular disease, macrovascular disease, and neuropathy and they play a synergistic role in leading to amputation. In fact, when you look at predictors of amputation in patients with diabetes, you can see that there are macrovascular predictors like ABI, but microvascular disease is an independent predictor beyond ABI alone as is renal dysfunction.

We know from trials like the DECLARE trial that patients with diabetes who have PAD dramatically increased the risk of amputation by about fivefold. But even in those with PAD, one of the dominant causes of amputation is infection. Fifty-one percent were driven by infection and if you don't have PAD, it's about 85%. We need to consider all of the drivers of amputation, not just cholesterol and blood clots, but microvascular disease, infection, and wound healing.

We know that amputation is done differentially in other datasets. This was the EUCLID trial. And you can see that in those with diabetes the pie chart has many colors. There are many drivers of amputation. Infection, wounds, and other things. Whereas in patients without diabetes, it's almost always an ischemic complication. Think about the diabetes patient differently.

What are the goals of our medical therapies? Well, one is to reduce the risk of atherothrombosis. I showed you those trials showing that statins reduced heart attack and stroke. That's important when we know that have atherosclerosis. We also want to improve function. We know that people can't walk and do the things they want to do because of their limb disease. And very importantly, we want to reduce the risk of major adverse limb events like acute limb ischemia.

Again, here is our schema. This is what we want to do with our medical therapy. And you may want to risk stratify. You can't use every drug on every patient. Who are the patients with PAD that you want to treat with some drugs versus others? Who do you really need to worry about?

Well, one lesson we talked about in our first session was polyvascular disease. If you have a patient with PAD who has symptomatic coronary disease or has had carotid disease or stroke, they're in the red bar here. And you need to worry about MACE. You need to do more than antiplatelet monotherapy or just having them on a statin. You need to treat them more intensively because their risk is extremely high. You should be worried about those with polyvascular disease.

And then you should be worried about patients who have microvascular disease and diabetes. Those with diabetes or evidence of microvascular disease here in Josh Beckman's paper were renal dysfunction, albuminuria, retinopathy, and neuropathy. They have an extremely high risk of amputation. Polyvascular patients, patients with diabetes, and evidence of microvascular disease are some of the highest risks.

And you can see then that your treatment options really circle around the figure on the right and they mirror what we know of the genetics. Lifestyle is at the top. Everyone should have a healthy diet. They should have smoking cessation and they should have supervised exercise therapy to improve their function. That is the foundation. You should work on lower lipid risk and modifying lipid risk in those with diabetes.

You should use targeted therapies that reduce the risk of microvascular and macrovascular complications. We don't have any available therapies for inflammatory risk, but it's clearly a driver here. And then very importantly, thrombosis risk. We know thrombosis is a key driver of risk in the PAD population.

As I mentioned, the foundation is a lifestyle with a healthy diet, exercise, and smoking cessation. On the left side of this slide, you can see data for home-based exercise versus no exercise at the very left. There's a significant increase in the ability to walk. On the right side, you can see that supervised exercise is much more potent than home-based exercise and even more potent than revascularization. The far blue bar on the right is supervised exercise. It should be your goal for every patient with symptomatic PAD to improve their function.

On the right side of the slide are outcomes in people getting bypass surgery who did or did not stop smoking. Obviously, you can't randomize people. This is observational data. But you can see if you have a patient with PAD who continues to smoke they're on a different curve and they tend to do much worse than those who are able to stop.

The HOPE trial I mentioned. Here you can see the benefit of ramipril versus placebo in patients with atherosclerosis. You'll note that in the fourth grouping towards the bottom there is peripheral vascular disease. You can see that they were a very high-risk group and that the benefits of ramipril were consistent. For patients who have hypertension or need therapy, ACE inhibitors are preferred.

And then here you can see the heart protection study. Again, patients with PAD are in the highest risk group of patients. If you look at the control arm, the event rate of 30.5, they were at higher risk than anyone else in the study and they had a big reduction in cardiovascular events with statin therapy. Here's it's simvastatin. Statins and lipid-lowering are important. And here you can see the subanalysis showing a trend or reduction toward peripheral vascular events with statins. And this is not well characterized in terms of the drivers, but clearly a signal for broader benefits outside the coronary patients.

There are data that show that beyond reducing the risk of heart attack and stroke statins improve function in patients with PAD and claudication. Here's a nice randomized trial from Emile Mohler, Will Hiatt, and Mark Creager which showed that if you had patients with PAD in the blue that their function, even with exercise, although, it went up a little bit, it plateaued. And then if you added a statin, either 10 or 80 milligrams of atorvastatin, you could significantly increase their function at 12 months. Statins in patients with PAD don't just reduce heart attack and stroke but they improve function.

We also know that additional lipid-lowering beyond statins by adding a PCSK-9 inhibitor like in the FOURIER trial and lowering LDL cholesterol from about 90 milligrams per deciliter down to 30 milligrams per deciliter, had a dramatic reduction in MACE and adverse limb events in patients with peripheral artery disease with a number needed to treat, even at 2.5 years, is just 16.

You can see on this slide those data from FOURIER on the left. The bottom left is major adverse limb events whether it was a significant reduction. And you can see the data for ODYSSEY. This is a trial of alirocumab, another PCSK-9 inhibitor, in patients with acute coronary syndrome. And you can see exactly the same benefit.

PCSK-9 inhibitors, when added to statins, reduce major adverse limb events in patients with peripheral artery disease and should be considered in patients at high risk.

Now, that benefit may be modulated through LDL. You can see in the upper left-hand corner of FOURIER we found that there was a linear relationship between reducing LDL and major adverse limb events. That really holds true to an LDL cholesterol of fewer than 10 milligrams per deciliter.

But what we've also learned is that there's a bad actor called Lp(a). It's part of LDL cholesterol which is really prothrombotic. And when you look at major adverse limb events in the bottom right-hand corner of the slide, in the ODYSSEY trial, the biggest benefit for reduction of major adverse limb events were those with high Lp(a). And we know that PCSK-9 inhibitors reduce Lp(a) by about 25%. It's possible that the dramatic benefits seen in these two trials are both LDL reduction as well as Lp(a) reduction.

There are other therapies that have shown benefits. Icosapent ethyl showed very clear benefits for atherosclerotic protection in a broad population in the REDUCE-IT trial. And these are data that Deepak Bhatt presented for the PAD subgroup. You can see that those with PAD were at higher risk and had an even greater benefit. There was no limb vascular benefit described, but clearly a MACE benefit.

When it comes to our treatment algorithm, starting at the top, foundation of lifestyle, exercise, and smoking cessation. And then moving to the left is lipid risk. Everyone would have an LDL that is reduced. I try to get my patients well below the 70 milligrams per deciliter target. Even below 50 milligrams per deciliter if possible. And I try to utilize combination therapies to achieve that.

What about the patient with diabetes? Well, we have novel therapies. Let me back up. Hemoglobin A1c reduction remains a target in diabetes guidelines. We know that reducing hemoglobin A1c reduces microvascular complications like retinopathy, and nephropathy, and may have some benefits in terms of leading to wounds from neuropathy and the combination of microvascular disease.

Beyond that, there are novel therapies that show really dramatic benefits in broad populations even without diabetes. The SGLT-2 inhibitors show benefits for death, heart failure, and kidney complications, and the GLP-1 agonists show benefits for MACE and for cardiovascular death. These operate through mechanisms independent of glucose-lowering. And the benefits are clearly consistent in those with peripheral artery disease and you can see those for the SGLT-2 inhibitors

At the top, this is from - - analysis from the EMPA-REG trial and for liraglutide here for GLP-1 agonists showing a significant reduction in cardiovascular mortality in patients with PAD. These are important drugs for patients that have PAD and diabetes. And I'll add to that. One agent, liraglutide, has been shown to significantly reduce the risk of amputation. And this is a statistically significant benefit. It really appears to be working through not just macrovascular complications but microvascular. And there's a 35% reduction. The GLP-1 agonists have particularly broad benefits in PAD because they reduce cardiovascular mortality, MACE, and amputations.

There's an ongoing trial right now which is investigating these GLP-1 agonists for broader benefits in PAD and its using functional outcomes. And this is an ongoing trial. If you're at site, I encourage you to work on this trial and enroll patients. For full disclosure, I'm on a site for this as well because I think it'll be really important to know whether there's a functional benefit of the GLP-1 agonists added to their amputation benefit.

There was a signal for one of the SGLT-2 inhibitors that caused a lot of concern for amputation. This was in the CANVAS trial. You can see a two-fold risk of amputation with canagliflozin versus placebo. There really was no clear explanation, but the finding was very consistent even after adjudication. And the highest absolute risk was in those who had a history of amputation.

Now, this was relooked at in a series of other trials. This is the CREDENCE trial with the same drug, where there was not a significant excess. Numerically more, but not statistically significant. And it's important

to note this trial was conducted differently. People who were at high risk of amputation were excluded and there was exceptional foot care during the trial. Whether the absence of an effect in CREDENCE was because of who was enrolled and how people took care of their feet or whether it was just a spurious observation in the other trial, is unclear.

That being said, the FDA has removed the black box for this. And myself included, I don't worry about amputation risk with SGLT-2 inhibitors with the exception of somebody's in the hospital with a threatened limb and critical limb ischemia. I may not start at that time, but once the limb is stabilized, then I use them in broad patients with PAD and diabetes. And that's because of this.

These are data from the DECLARE trial. The benefits are clearly there in patients with PAD and diabetes. And then actually, the absolute benefits appear even greater in those with PAD because they are at higher risk. We don't want to deny really important therapies for our PAD patients. I think clear benefits from MACE and heart failure, as well as kidney complications in PAD.

One study with an amputation risk. Unclear whether the absence of validation was because subsequent trials had a lower risk population for amputation or whether it was good foot care or whether it just wasn't a true observation. But I think you should use them. You may want to start them after limb stabilization and somebody with a threatened limb. But obviously, use them in patients who don't have a threatened limb and use them along with good foot hygiene, patient selection, and agent selection.

We talked about the foundation of lifestyle and function. We talked about getting lipids very low. Using combination therapy. For diabetes, obviously, A1c reduction. I would reach for a GLP-1 agonist for reducing MACE, CV death, and amputation. In patients who also have heart failure or chronic kidney disease, you may want to prioritize SGLT-2 inhibitors. I think both are beneficial. And ultimately, I might start with the GLP-1 agonists, but then add an SGLT-2 quickly when I can, unless, of course, with heart failure and kidney complications. I want to then prioritize the SGLT-2.

Well, thank you for your attention. I really appreciate it. That concludes the non-antithrombotic medical therapies. And in our next section, we'll talk about antithrombotic therapies.

Antiplatelet Therapy for PAD

Hi, my name is Marc Bonaca. I'm a vascular medicine specialist at the University of Colorado. It's an honor to be part of this course on the foundations of cardiometabolic health. In this certification course, I'm talking about peripheral artery disease. And in this section, I'm focusing on antithrombic therapies.

We know that thrombosis plays a critical role in the pathogenesis of PAD and worse complications in PAD. We know it from the first observations in the 1830s of PAD in actually a horse that showed a fibrous clot. We know from pathological specimens that in patients that have severe disease we see a lot of clots below the knee even in the absence of atherosclerosis. Treating and preventing the clot is core to caring for PAD.

What are data for therapies? Well, this is the antithrombotic trial collaboration. You can see that aspirin was beneficial. It was beneficial overall. And here in patients with claudication requiring bypass surgery, it's aspirin versus placebo and this is aspirin at multiple doses. Even some non-aspirin agents. But it reduced MACE by about 23% and it increased bleeding by about 60%. Aspirin is class 1 in the PAD

guidelines right now for the prevention of MACE. Please note that aspirin had no benefit for preventing amputation or limb outcomes.

We know that clopidogrel is beneficial and head-to-head ticagrelor was not better than clopidogrel. Ticagrelor is not labeled for symptomatic PAD because of this. And more P2I-12 inhibition was not the answer to improving outcomes in this important EUCLID trial. With the caveat in those who have concomitant coronary disease, there is a benefit. We see that in trials like PEGASUS and THEMIS, but that's really prescribed for a CAD indication. And for those with PAD alone, there's no benefit to more potent P2I-12 inhibition.

Now, we know that thrombosis is complicated and it's not just the platelets. And this nice figure here shows that one of the cornerstones is platelet activation, so using aspirin or clopidogrel as monotherapy for that. But thrombin is a core driver. It not only drives coagulation but is the most potent activator of platelets. We need to interrupt the thrombin-mediated risk in patients with PAD.

Well, how can you do that? This explains in part why more antiplatelet therapy hasn't worked. And here when we look at the CASPER trial, the combination of DAPT which works in coronary patients did not work in peripheral artery disease. DAPT does not address thrombin mediated risk and therefore when you add clopidogrel to aspirin in PAD patients after bypass, there's no benefit for MACE and limb outcomes and there's about a three-fold risk of major or moderate bleeding. DAPT is not the answer to PAD.

Now, some people have looked at interrupting thrombin generation through vitamin K antagonists. And although there are people who do use warfarin for selected patients in broader populations, not only does this not improve limb outcomes but it's really associated with a prohibitive risk of bleeding. A three and a half fold of hemorrhagic stroke. We don't routinely use warfarin in PAD.

There is an agent called vorapaxar which was designed to address thrombin-mediated risk through its action on the platelet. It's a PAR-1 antagonist. It was derived from the bark of the Australian magnolia and it was developed initially as an anti-restenosis drug. And you can see some of the animal models that support that on the right side of the slide. And when you add vorapaxar to aspirin or DAPT by interrupting thrombin mediated risk, you can see that there's a dramatic benefit in reducing acute limb ischemia. You can see that on the right slide of the slide. There's about a 42% reduction in adverse limb events. This really shows you that interrupting thrombin-mediated risk is important in this population beyond aspirin or clopidogrel.

And you can see that the benefits for vorapaxar were the greatest in those who either had polyvascular disease on the left or had a prior revascularization labeled PAD alone. But those were the highest risk patients for thrombin-mediated events.

Now, these findings were later validated in the landmark COMPASS trial. COMPASS looked at interrupting thrombin-mediated risk through a different mechanism. This was with targeted factor 10A inhibition and using a very low dose, established in the coronary patients by Mike Gibson and Jess Mega in the ATLAS trials. Rivaroxaban 2.5 milligrams twice daily. It's about 25% of the dose we use for therapeutic anticoagulation. And when combined with aspirin, it reduced MACE cardiovascular death and increased bleeding. You can see the major bleeding risk was about a 70% excess, but a clear net benefit in this population.

And I think from a PAD perspective, what's so exciting about this is the benefits for major adverse limb events. At the bottom of the slide, you can see the hazard ratio was 0.54. That's about a 46% reduction. That's almost exactly the same as what was observed with vorapaxar. And it's validation if you add a mechanism that interrupts thrombin mediated risk to an antiplatelet, you can really reduce these bad limb outcomes in PAD. And in this trial, there was a 70% reduction in major amputation which is really an important outcome in this population.

You can see that the benefits of rivaroxaban were consistent across all of the different populations with peripheral artery disease. And it was therefore even for carotid disease.

Now, one gap in our understanding is what to do around procedures because we know that those patients who have procedures are at the highest risk. Now, the VOYAGER-PAD trial is built on the TRA2P trial and the COMPASS trials and it said let's look at the combination of aspirin and interrupting thrombin generation with low dose rivaroxaban. And let's even allow clopidogrel in the background and see if there's added benefit for reducing the combination of irreversible harm events to the heart, limbs, and brain.

And low and behold, at the highest risk point, these patients with PAD undergoing revisualization had significant risk. About one in five had an adverse event over three years and there was an absolute risk reduction with rivaroxaban of 2.6% or the number needed to treat of under 40. There was more bleeding. Here it's about a 40% excess, but a clear net benefit with a number needed to harm of 125.

You can see that the benefit in this population was really driven by the limb outcomes and that's what we expect because we know thrombin is such a bad actor. The highest risk event in VOYAGER was acute limb ischemia with an event rate of almost 8%. And there was a significant reduction and that really drove the benefit along with consistent transfer, amputation, stroke, and MI. We didn't see a benefit for CV death because we know CV death, in this population, isn't driven by thrombosis. Whereas acute limb events are.

There were a host of secondary outcomes which were shown to be positive in the trial. I'll draw your attention to two. The second set of bars from the left is unplanned limb revascularization. This is very frequent and this is that patient who has the revascularization procedure and has to come back unexpectedly because there's a problem. And this was significantly reduced with an absolute risk reduction of about 2.5%. And then the fourth set of bars is really the primary outcome with all-cause mortality.

And what you can see here is for this fourth set of bars is that when you add an all-cause mortality rivaroxaban significantly reduced event-free survival with an absolute risk reduction of 2.6% or a number needed to treat of less than 40. It's a really important benefit in this high-risk population.

As I mentioned, there was more bleeding. It was about a 40% excess. You can see that on the left slide of the slide and you can see the difference in absolute events was quite modest. There was no increase in intracranial hemorrhage or fatal bleeding. And when you look at more sensitive bleeding measures on the light, obviously, the bars get higher because they're more sensitive. But the relative difference is about the same. It's about a 30 to 40% excess.

Importantly, we saw no trends for procedural bleeding with the addition of rivaroxaban even when given after revascularization. There were no excess and takeback bleeds. No statistically significant excess and no excess in bleeding when looking at any revascularizations on the right.

The take-home here is that when added to COMPASS-VOYAGER as a second positive trial showing net benefit, in the PAD patients who've had revascularization, there is a six to one benefit-risk ratio. You can see that on the left side of the slide with the numbers of events prevented versus caused.

And you can see the pattern of benefit on the right is that the benefit in blue in events prevented continues to accrue over time for those patients that unfortunately have a bleeding event. Those usually happen early. And when they don't happen, that risk really plateaus.

People have asked about clopidogrel. You'll remember early in the talk I showed you that the EUCLID trial showed that more P2I-12 inhibition was not the answer in PAD. We have to interrupt thrombin. And that's exactly what the clopidogrel subgroup analysis from VOYAGER shows us. Whether you use clopidogrel or not on the left versus the right, it makes no difference because it doesn't modify these events. And rivaroxaban, in terms of both relative benefit and relative risk and absolute terms, was entirely consistent regardless of whether you used clopidogrel. P2I-12 inhibitors don't interrupt thrombin-mediated risk and therefore, there's no effect modification here.

The one thing that DAPT does do when it's part of triple therapy is increase bleeding risk. Patients who were on long courses of clopidogrel or DAPT had more bleeding and we see a significant trend here in terms of an interaction. And that for the patients who were on it for a month or less, there was no clear pattern for bleeding.

What's the take-home? You need to interrupt thrombin-mediated risk in patients with PAD that aren't at high bleeding risk. Rivaroxaban does this. It has the best evidence. As an alternative, you could use vorapaxar. Regardless, you should do more than just an antiplatelet. If you have a patient who's on DAPT and there's no reason than PAD, I'd try to shorten that duration to about a month or less if possible and then continue them on aspirin and likely, rivaroxaban.

These are the data I spoke to you before about thrombosis as a risk driver. It's not just atherosclerosis. These are sections from arteries of patients that unfortunately had critical limb ischemia. And what you can see in the pictures is there's not a lot of atherosclerosis. It's all laminar clot. These recurrent clots in the legs. Many of them are sub symptomatic. Patients don't know they're having them, but they're having artery to artery embolism and laminar clot. It's slowly clogging the vessels and leading to critical limb ischemia and amputation down the road.

We can interrupt this with better therapies. In VOYAGER, we had a very large CLI cohort of around 1500 patients. You can see that although revascularization worked for patients with claudication, that benefit was associated with a high risk of adverse limb outcomes. Don't be fooled that the patient who's going to get a stent or a balloon for claudication is a low-risk patient.

This slide tells you that even though they feel better because they had that balloon or the stent, their risk profiles, what you see here in the red, even if you're giving them aspirin, DAPT, statins, or whatever, you have an extremely high risk of adverse limb events because their vasculature has been disrupted and they have severe enough disease to require revascularization. You now need to worry about adverse events

in these patients. And you can see the benefit of rivaroxaban here in the middle of the slide was statistically significant and important.

For the CLI patients, we often look at net outcomes because they're such a sick population. And here you can see the net outcome. This was a prespecified outcome of irreversible harm events to the heart, limb, and brain, all-cause mortality, and irreversible harm bleeding. Intracranial hemorrhage or fatal bleeding. For this net outcome, you can see whether patients had critical limb ischemia on the left or claudication on the right. There was a significant reduction with rivaroxaban that exceeded 30%. And the absolute benefits were even greater. The number needed to treat was 18 for CLI or 26 for patients with claudication.

These data tell you that thrombin plays such a critical role in these net outcomes for these patients and that interrupting thrombin-mediated risk is an important factor in PAD. And we know that this population is one that is characterized by a lot of recurrent events.

The benefits for VOYAGER and COMPASS were shown for the first events, but when you look at this analysis, you can see that the benefit really was not just for the first events on the left side of the slide, but the second event, third event, and fourth and subsequent events. They were all prevented with the more potent antithrombotic strategy interrupting thrombin-mediated risk. And you can see the absolute benefits. Out of 100 patients, there are 88 events. That's a very high event rate over three years. This is total events including recurrent events and there was a significant reduction and a large absolute benefit when you add an effective strategy.

Thank you very much for your attention. That covered antithrombotic therapy for PAD.

PAD: Other Therapeutic Approaches and Individualization of Treatment

Now, I'm going to focus on other therapeutic approaches and individualization of treatment. How do we risk stratify? How do we figure out what drug for which patient?

My name is Marc Bonaca. I'm a professor of medicine and vascular medicine specialist at the University of Colorado. In our prior sections, we talked about treating patients with PAD. We talked about the top. The foundation lifestyle intervention, functional focus, supervised exercise, diet, maybe cilostazol if not contraindicated, and clearly, smoking cessation.

Moving to the left. We talked about lipid risk. Getting the LDL cholesterol very low. Ideally, before 50 milligrams per deciliter. Using combination therapies may be a benefit for LPa reduction. For some patients, maybe icosapent ethyl. For patients with PAD and diabetes, lowering A1c, foot hygiene, GLP-1 agonists reduce amputation and cardiovascular death, as well as SGLT-2 inhibitors. And then on the right side, we talked about thrombosis risk. Antiplatelet monotherapy, a class 1 indication for reducing MACE. No benefit to modifying limb outcomes. For high-risk patients, for those who have polyvascular disease, or ever had an intervention on their limbs at any time, they need more than antiplatelet monotherapy. If they're not high bleeding risk, the best data are for adding low dose rivaroxaban 2.5 milligrams twice daily as an alternative. On-label, you can prescribe vorapaxar. DAPT has not shown benefits for reducing these outcomes, particularly in the limb outcomes in the PAD-only population.

Now, let's talk about some other therapies. What about functional? Well, there are two drugs that are approved for functional outcomes. One is pentoxifylline. This was approved in 1984. We don't have a

clear sense of how it works. You can see in the bullet there are some hypothetical benefits. In trials, subsequent to its approval, it has not shown many benefits beyond placebo. It's not widely used and it's not strongly endorsed in the guidelines. Cilostazol is a phosphodiesterase inhibitor. It was approved in 1999. The mechanism of benefit is also unclear. It may have some antiplatelet effects, but it's not considered sufficient for atherothrombosis protection. It's only used for functional benefit. And it is contraindicated in patients who have a history of congestive heart failure. Cilostazol works. There's good data for it. Many patients have difficulty tolerating it at higher doses due to GI toxicity, but it is something that should be considered in patients who have a symptomatic issue or a functional issue with PAD.

Now, what about vascular intervention? You can see the different patient types with PAD. There's the chronic PAD patient. For those patients, there's no need to revascularize and it really is determined by a patient and their clinician in terms of when their disease is so severe that they will benefit from revisualization for symptomatic benefit. This is a class two recommendation in the guidelines. And we know that there are risks of intervention. It really is a shared decision-making model.

For patients who have threatened limb, the heart attack of the leg. Acute limb ischemia or chronic critical limb ischemia. It is a class one indication to revascularize to try to prevent tissue loss. At the bottom of the slide, you can see for different patients we select different types of interventions. And endovascular therapy on the left is very attractive because there's no incision. It's less invasive, has a fast recovery, and minimal anesthesia, and it can really often be done on an outpatient basis. And depending on where it is and the type of devices you use, there are high patency rates. On the right side of the slide, you can see surgical interventions which are usually endarterectomy or bypass. This is a bigger procedure. They're at higher risk from a cardiovascular perspective. Anesthesia. Longer recovery. But they do provide options for patients that don't have an endovascular option.

How do you decide? Every institution is different. We strongly advocate for multidisciplinary decision-making, including vascular medicine, vascular surgery, cardiology, and others. And taking into account the patient profile, patient risk, and things like their anatomy, comorbidities, and other options such as what's available at your institution. There will be more data on this from the BEST-CLI trial which is looking at the best initial strategy in patients with critical limb ischemia.

For risk-reduction therapies. Lifestyle, smoking cessation, getting blood pressure under control, and LDL lowering antiplatelet therapy. I think for MACE reduction, obviously, antiplatelet monotherapy. And then for diabetes, you may want to consider GLP-1 agonists or SGLT-2 inhibitors. I think they clearly have potent and important benefits beyond glucose-lowering.

For patients that aren't at high bleeding risk, add aspirin and rivaroxaban. If they have a prior MI, you could add ticagrelor, but if they don't, the on-label uses would be rivaroxaban or vorapaxar. And then for lowering limb outcomes, get LDL very low. Consider PCSK-9 inhibitors. Again, rivaroxaban and/or vorapaxar. And then for symptomatic patients who have claudication, cilostazol.

These are the different therapies that we've talked about. And you can't just pick one to improve outcomes in PAD. You really have to treat all of these axes of risk. But sometimes, you're faced with a patient in front of you and there are a lot of drugs and other considerations that you may want to tailor. Use the most effective therapy for the highest risk patient.

What do I think about it? Well, I think about patients in two dens. All patients with PAD have functional decline and all patients with PAD are at high risk. But those patients with PAD who've never had an intervention to their leg. An endovascular intervention, surgery, amputation, or those who don't have any symptomatic disease in the coronaries.

Meaning no one's ever had to do an angioplasty. They've never had an MI. They've never had a stroke. Those are high-risk patients and I think that they can be treated with smoking cessation, diet and exercise, and absolute antiplatelet monotherapy. Maybe a more potent strategy, but I think you can decide there in terms of shared decision-making. Get the LDL very low. That's safe. Treat their hypertension and optimize their diabetes management. If they are symptomatic, consider cilostazol.

In contrast, if we have a patient who has symptomatic PAD and they've never had something done to their legs. They've had a bypass, endarterectomy, amputation, or a stent. Even if it was five or seven years ago, it doesn't matter. They're at extremely high risk. Or the patient with PAD who has coronary artery disease. They've had a coronary bypass, a coronary stent, a heart attack, or a stroke. These are really extremely high-risk patients and I don't think you want to have that risk unmitigated.

In the clinic, my approach is to try to really intensify their therapies. I think the most obvious would be to add an antithrombotic or a thrombin-directed antithrombotic like rivaroxaban. As an alternative, you could use vorapaxar. But I don't think aspirin monotherapy is enough for these patients.

Obviously, you'd have to stratify bleeding risk. If they're a high bleeding risk, maybe antiplatelet monotherapy is all you can do. If they're not a high bleeding risk, you really should consider a more potent strategy. I really do try to push their LDLs below 50 milligrams per deciliter. I try to reach for a PCSK-9 if needed and I really try to get them on a GLP-1 agonist.

But when I'm in the clinic, I think of those in the yellow versus the red and if they're in the red, although all these patients are high risk, these are really the extremely high risk.

Now, let me just transition for a moment to reality. These are data that a colleague, Reena Pande, published in 2011 and that was a long time ago. And at that time, she showed us that medical therapies are underutilized and they're particularly underutilized in patients with PAD when they don't have any other known vascular disease. PAD alone, meaning they don't have a coronary history. They've not seen a cardiologist. Rates of statins of 20% or less. ACE inhibitors are similar and not very good for antiplatelet therapy either.

I wish I could tell you that's improved. These are data from a decade later. They were published in JACC, showing the same thing. In fact, if you look at the left side of the slide, patients with PAD in the gray are the highest risk patients. When you look at the bottom left, for all-cause mortality, PAD-only is the worst thing you could have. And then look at the right slide of the slide. It's about a million patients. And in those PAD-only patients, only one in three are actually on a statin and around 16% are on a high-intensity statin. And this just isn't good enough. There's a huge gap in treatment for PAD specifically.

These are even more recent data that Connie Hess in our group published, showing that we are not achieving our lipid goals in patients with PAD. And you can see here, over time, there's very little change. And what I think is really interesting here is we all know that there's therapeutic inertia. It's hard to change therapy in the clinic when people are feeling well. But when people have an acute event, there's really an opportunity to intensify therapy.

On the right side of this slide, you can see that for patients who have an MI or stroke more often that's done. The patients are up titrated. About 55% of patients are intensified and the achieved LDL goes from 91 down to 77. Now, that's not good enough, but it's better than if you look at those patients who have a major adverse limb event, where only 40% are up titrated and the achieved LDL was only 80 milligrams per deciliter. And those patients who have no event where there's almost nothing done.

You can see that we need to do better overall and we really need to recognize when patients come in with these issues that's the opportunity to really get their LDLs as low as possible. We should be doing it in the clinic too, but don't let an opportunity pass when somebody is having an intervention to really rethink their medical therapy.

One option for improving the provision of care is implementation science. This is a trial called OPTIMIZE-PAD, led by Connie Hess in our group. And that is using a multidisciplinary team to improve the provision of care with the support of algorithms, pharmacists, and a care team model.

This is the schema for OPTIMIZE and you can see that patients are being followed either through the standard of care or with this care team model and looking at achieved LDL.

I want to summarize here. We covered a lot of ground today. Peripheral artery disease is common. It's out there. You may not think you see it a lot, but it's out there. And about one in three patients that are over 55 with a history of diabetes, smoking, or are over 75 have PAD. Although, most of them will tell you that or they'll report an atypical history that they've got the disease. More than 200 million people across the globe have it. It's about estimated at about 235 million now.

PAD patients are unique. They have high cardiovascular risk. Things like MI and stroke. But they also added to that, have a very high risk of adverse limb outcomes like acute limb ischemia and amputation. Not all PAD patients are the same. Those that have more severe symptoms are at higher risk. Those patients who've ever had revascularization or amputation are at extremely high risk of adverse limb events. Those patients with polyvascular disease are at extremely high risk for MI and stroke.

There are a few therapies that have been demonstrated to be efficacious in dedicated PAD cohorts. They are very few. You can count them on one hand. And very few therapies have shown a benefit for limb outcomes. We need to do more and study therapies in PAD populations and for limb outcomes and we need to utilize those therapies. Drugs like GLP-1 agonists, PCSK-9 inhibitors, and low dose rivaroxaban all have shown clear benefits for this population and should be leveraged.

And that brings me to my last point which is we need to do better as a community in addressing the gaps that underly some of our lack of utilization of effective therapies. And it's specific to PAD. We have underutilization in all high-risk patients, but PAD is the most undertreated and we need to work together to solve that.

And we need to also recognize that those gaps are not uniform and that there are populations where disparities, systems of care, and other factors have really led to higher risk and worse outcomes such as African American communities and other communities with poor access to medical care. We need to pay particular attention to those vulnerable populations and improve the provision of care.

Thank you for your time. I really appreciate the opportunity of being part of this course. Hopefully, this was a helpful overview of peripheral artery disease. Please let me know if you have any questions. And I look forward to working together to improve outcomes in this high-risk population. Thank you.