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### ReachMD

www.reachmd.com  
info@reachmd.com  
(866) 423-7849

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## Peripheral Artery Disease: How New Stent Options Are Revolutionizing Care

Announcer:

This is ReachMD.

Welcome to this special program, titled “Peripheral Artery Disease: How New Stent Options are Revolutionizing Care,” developed in partnership with Boston Scientific.

Your host is Dr. Matt Birnholz.

Dr. Birnholz:

Peripheral artery disease, or PAD, is very similar to coronary artery disease in its root cause, but when it comes to revascularization options, such as stenting, the choices in treatment have often been different, but that’s starting to change with new drug-eluting stent options entering the clinical arena, and today we’re going to focus on the impacts of these recent advances.

This is ReachMD, and I’m Dr. Matt Birnholz. Joining me to discuss the latest updates in PAD care is Dr. William Gray, President of Lankenau Heart Institute at Main Line Health. Dr. Gray, welcome to the program.

Dr. Gray:

Thanks, Matt. It's good to be here.

Dr. Birnholz:

To start us off, let's get a better sense of the scope and burden of this disease. Just how prevalent is PAD now, and what would you say the impacts on patient health are in relation to where the blockages most commonly develop?

Dr. Gray:

Well, to start with, the prevalence of PAD is actually probably underestimated, but the most recent numbers give us a US prevalence of about 10 million to 12 million people in the United States, and as we see an aging population—and this disease can come along with aging—that's likely to increase. As it relates to the impacts of patient health, where the blockages are likely to develop, it's actually quite varied. For instance, most patients with PAD in the legs will have either an asymptomatic course—and they actually do fairly well if we look at them over a 10-year time span horizon in terms of mortality and cardiovascular events—and if you take the other end of the spectrum, patients with critical limb ischemia, where they actually have tissue loss, those patients do very poorly over a 10-year horizon with less than 40% survival. And so in between, those patients are the patients who have peripheral arterial disease but who don't have a threatening disease—that is they are not having tissue loss—but they have limitations in their lifestyle. They have claudication, pain in their calves typically when they try to walk more than a few dozen yards, and that type of lifestyle limitation, although it sounds relatively benign, if we compare that to other things, like orthopedic hip or knee problems, is just as limiting and problematic for the patients who want to be active, be with their families, walk with their wives or husbands, play with their grandchildren and so on, even push the cart at the grocery store.

Dr. Birnholz:

That's interesting. It seems like that broader point, of course, is for those, such as yourself, who have a lot of expertise in this area in treating this, if you've seen 1 case of PAD, you've seen 1 case of PAD, because, as you were talking about, comorbidities, location of blockages, number of blockages, they all create completely different clinical scenarios and they all are completely unique. Is that correct?

Dr. Gray:

That's fair to say. There are certain patterns of distribution, but by and large, each patient is a snowflake in the best sense of the word, yes.

Dr. Birnholz:

Traditionally speaking, how were patients most commonly treated for PAD, and has this differed from approaches to coronary artery disease management?

Dr. Gray:

The evolution of treatment for PAD has really lagged behind what we've seen in the advances of coronary artery disease management. Just a level set there, as most people know, we went from doing angioplasty to bare-metal stents to drug-eluting stents and a whole host of accessories for coronary artery disease which allow us to revascularize even the most difficult lesions and maintain patency into a year and beyond with restenosis rates in the low-single digits. In peripheral arterial disease, we face different challenges. The vessels are larger, which is to the benefit of the patient and the physician treating them because it typically would lead to longer durable results, but the problem has been that the SFA, superficial femoral artery, and popliteal which connects to it behind the knee, which is the most likely locus of disease in patients with claudication, is the longest vessel in the body without a major branch. It is subject to significant torsion, both axial and longitudinal. It is subject to external compression. And even with a simple bending of the knee, we see that the vessel ripples because of the access vessel being pinched. And as we age, the vessel stiffens and you impose a little bit of calcification or vascular atherosclerosis and the vessel starts to actually fold. So, it's been more of a challenge because it's a hostile environment, more hostile than the coronary, for all the physical reasons I just talked about, but also the burden of atherosclerosis.

Lastly, I would say that while the classic therapy has typically been walking, for patients who exercise, they might not get the bang for the buck that they're putting in in terms of recruitment of collaterals, and that really depends on the health of the collaterals. A diabetic doesn't have as healthy a collateral as the nondiabetic patient. The medications may not be as effective or they may not be tolerated or they may be contraindicated because of other reasons. And surgery is major vascular repair, and it may require a vein or conduit, artificial conduit, and while it works well, it does fail occasionally, and the patient is left, then, back where they started but with a big surgical procedure.

So, the bottom line is that all this allowed for the nonsurgical endovascular approach for peripheral arterial disease to kind of slide in over the last 20 years, and as devices have developed and technology is advanced, we have seen better and better long-term outcomes for our patients.

Dr. Birnholz:

That's a really interesting point, because it seems like, at least to this point, the very idea of having a long-term view on benefits associated with treating PAD as opposed to a relatively immobile heart protected by a ribcage, there has not been an ability to really look long-term due to these challenges, but that does seem to be changing with the entrance of some of these newer approaches, such as drug-eluting stents that you alluded to. Maybe you can take us through how this treatment approach made the jump from coronary to peripheral targets.

Dr. Gray:

Sure, and it wasn't an easy jump, so I am glad we are able to talk about that. I think it's been a frustration for many people who are familiar with the tremendous success that drug-eluting stents have had in the coronary world to see that we have not been able to translate that effectively into the peripheral world in the same time period. You'll recall the coronary DES were introduced in 2003, and the first drug-eluting stent—or drug-coated stent I should say—for peripheral arterial disease wasn't introduced until 10 years later, almost. And there are several reasons for that. There were a couple of false starts. There were the 2 devices which had drug and polymer on them and with the same kind of logic that was used for coronary disease in terms of elution profiles and drugs that we used, specifically sirolimus analogs. But for reasons that are still not very clear, neither one of those devices seemed to be effective in reducing long-term restenosis like they were in the coronaries. And there was a bit of a hiatus for a while until we saw paclitaxel-coated stents without polymer come on the scene and in a trial clearly proved themselves superior to balloon angioplasty, which was the standard care at the time, and even bare-metal stent, which was an advance.

So, what were the differences? How did we finally get some success in the SFA/popliteal territories with drug-eluting stents? And the answer is it probably had to do with the choice of drug. Sirolimus analogs are good drugs, and where the restenosis timeline peaks around 3 months or so for coronary disease, the restenosis timeline for peripheral arterial disease and the SFA and popliteal restenosis peaks in the 10- to 12-month range. So, sirolimus and its analogs don't really have tissue residence long enough to address that much more prolonged restenosis timeline. They would have to be modified somehow to do that, and the original drug-eluting stents didn't modify them or elute them long enough to allow for that timeline to be addressed.

Paclitaxel, on the other hand, is highly lipophilic. It does not need to be modified in order to have long-term residence in the tissue. The first drug-coated stent was with paclitaxel and no polymers, so it really delivered a bolus of paclitaxel. The next iteration of drug-eluting stents in the SFA and popliteal region had paclitaxel but now with a polymer coating which allowed elution profile to be extended even farther into the 10-month window of restenosis, and so now we're talking about the opportunity to really dial in the drug to fit the vascular territory that we're treating, and that has led to improvements in overall performance of the drug-eluting stents, almost on par now with coronary stents.

Dr. Birnholz:

For those just tuning in, you're listening to ReachMD. I'm Dr. Matt Birnholz, and I'm speaking with Dr. William Gray about recent procedural advances in the management of peripheral artery disease.

Dr. Gray, let's come back to that. It's interesting to see that history, the long gap between CAD and

PAD, what was probably initially chalked up to restenosis rates based on torque pressure difference and saying, “Well, I guess that’s just the deal with the area,” versus looking at it and saying, “Maybe our drugs need to change to be able to help this and create a better outcome for patients.” But why don’t we then focus on the sustained-release drug-eluting stents and what kind of opportunity they’ve represented for preventing restenosis. I actually understand that you’ve led some research efforts putting sustained-release treatments more firmly on the map, so can you give us a brief overview of that research and how you got involved in it?

Dr. Gray:

Well, I’ve been in this field for quite a long time, and so I’ve been involved along the way and heavily involved with a lot of the research that has been done, and I was asked to lead a trial called the IMPERIAL trial, which was meant to look at this thesis that prolonged drug elution of paclitaxel in the SFA and popliteal would favorably compare to the prior model of drug-coated stent and have at least the same or greater benefit in terms of preventing restenosis. The 2 devices that were involved was the Eluvia stent, with paclitaxel and a polymer coating which allowed long-term elution of paclitaxel, and that was compared to the Zilver PTX stent, which was at the time the standard of care and had been a significant advance in our ability to treat patients requiring stents in the SFA.

So, that trial was a global trial—Japan, Europe, the US—and recruited 465 patients. The primary endpoints for safety were the typical 30-day and 1-year safety endpoints of freedom from amputation, reintervention and death, and then the efficacy endpoints really centered around 1-year freedom from loss of patency.

From a safety perspective, there were trends towards improvement in thrombosis and stent fracture in the Eluvia group, and at 1 year the efficacy outcomes showed that the Eluvia stent was statistically superior to the Zilver stent with a TLR rate, target lesion revascularization rate, of 4.5% in the Eluvia arm and double that, 9%, in the Zilver PTX arm. Now, just to put that in perspective, having low single-digit target lesion revascularization rates puts us nearly on par with where we are with coronary artery disease. So this, I think, 5 years ago, many of us in this field would have not believed that we would ever get here, and it really makes our ability to treat patients, both with simple and complete lesions, much more robust and durable.

Dr. Birnholz:

And let’s put it in another perspective and talk about impacts on those patients, specifically the quality of life, their responses. What kind of impacts did you see from that angle from the trial itself and perhaps ongoing?

Dr. Gray:

That's a great question, and really the most important one, isn't it? We can talk about the science and the mechanistic measures all we want, but really it depends on how the patient feels. And what we found was that in all patients, the patients improved from preprocedure to post-procedure, and that's 30 days, and then from 30 days to 1 year did not have any real decline in their overall satisfaction or activity levels, which is a huge benefit for the patients that we're treating. Obviously, this is still too early to say, but the trial is a pretty good weathervane, and I suspect we'll start to see this durability of patency long-term translate into greater patient benefits and satisfaction.

Dr. Birnholz:

Dr. Gray, as my last question to you, why don't we stick with that weathervane theme, and let me put out to you: Is there anything promising on the horizon, then, as far as a perspective for the next steps?

Dr. Gray:

A great question, and you might say, "Well, game over, this is all we needed and we got a great result," and so on.

The problems are not entirely solved, however, because we still have issues around heavily calcified vessels, which nobody has really tackled, instant restenosis, long total occlusions, which may be difficult to cross. The challenges today really revolve around our ability to have some enabling technologies which allow us to deliver, then, the final blow, which is the drug-coated balloon or the drug-eluting stent, and those technologies are coming. We have studies ongoing for something called lithoplasty, which allows us to actually break up the calcium in situ without embolizing it, a balloon, which kind of emits shockwaves, other technologies which allow direct injection of drug into peripheral vessels to condition them better and so on, but also enabling the initial success of lesion crossing and the ability to actually open the vessel before we deliver that coup de grace of antiproliferative therapy.

Dr. Birnholz:

Well, Dr. Gray, given the increasing prevalence of this disease and how much it clearly impacts patient health, it's been great catching up with you on the latest therapies and novel new directions that you've just talked about. I'm really looking forward to having you back for more updates as they develop. Thanks again for your time today.

Dr. Gray:

Matt, I appreciate the opportunity. Good talking to you.

Dr. Birnholz:

I'm Dr. Matt Birnholz. For access to this and other related episodes, visit [reachmd.com](https://reachmd.com). Thanks for listening.

Announcer:

The preceding program was developed in partnership with Boston Scientific.

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