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Examining the Biodegradable Stent

You are listening to ReachMD, the Channel for Medical Professionals. Welcome to Heart Matters where leading Cardiology experts explore the latest trend, technologies, and clinical development in Cardiology practice. Your host for Heart Matters is Dr. Doug Weaver, President of the American College of Cardiology.

Will drug-eluting stents prove safer and more effective without a metal structure? For all their merits, current stent technology still presents a series of drawback including the severe complication of late thrombosis. Biodegradable stents may hold the key to minimizing this and other concerns. What are the most promising areas of research in this area? Our guest today is Dr. Martin Leon, an interventional cardiologist and Associate Director of the Center for Interventional Vascular Therapy at Columbia University Medical Center in New York City.

DR. DOUG WEAVER:

Welcome Dr. Leon.

DR. MARTIN LEON:

Thank you Dr. Weaver.

DR. DOUG WEAVER:

Marty, can you tell us a little bit first about what are the currently available stents that are out there right now including both bare metal and drug eluting and their differences?

DR. MARTIN LEON:

Well, bare-metal stents were first introduced in the United States in 1994. They have evolved dramatically over the subsequent almost 15 years. They are now thinner, they are now much more flexible, there are more flexible delivery systems and they have some improved properties. In fashion now are different alloys generally made of cobalt derivatives and these devices now can navigate almost anywhere in the coronary tree. They have a great benefit of being easy to use, very predictable in their outcomes, but they still do cause a relatively high frequency of in-stent restenosis, particularly in high-risk subsets such as diabetics or patients with diffuse

disease, long lesions, or in smaller vessels. As a result for a period of many years, we worked on the solution to restenosis, which is to put a drug that would be locally delivered on that very same stent platform to prevent neointimal hyperplasia or restenosis, so drug-eluting stents became available in 2003 with the first the sirolimus-eluting stent and in 2004 which was the second the paclitaxel-eluting stent. So, these were bare-metal stents, it was the earlier stainless steel platform not the newer or more flexible cobalt alloys, so they were not quite as deliverable, but they had the virtue of being able to elude drug into the vessel wall and were profoundly effective in reducing restenosis. What we didn't realize in those early years was that there was a price to pay. Either the drug in terms of its significant effect on vessel wall healing or the polymer itself, which was carrying the drug and regulating its release kinetics induced some pathobiologic changes in the vessel wall and those changes have resulted in a low frequency, but finite number of cases of late and very late stent thrombosis necessitating much longer obligatory dual antiplatelet therapy. So, that had been the dark side of drug-eluting stents. Restenosis profoundly reduced to may be 5% or even less, but this issue of a new complication. So, just this year, we have had 2 newly approved drug-eluting stents in the United States. The first is a zotarolimus-eluting stent, which is a sirolimus analog on a very different release kinetic platform. The second is an everolimus-eluting stent, also on a biostable polymer platform. Now, both of these new stents have the fenestrate, very flexible cobalt alloy backbone, so they are very easy to deliver. So, this is a major improvement over the first generation, very much like the current best bare-metal stents, but they also had the virtue we think that at least the data we currently have with the zotarolimus-eluting stent indicates that it appears to be safer than the first generation drug-eluting stents because the polymer is much more biocompatible, healing responses are much more predictable and the drug itself is released more quickly, so we are confident at least that safety seems to be improved with one of these new drug-eluting stents. The second, the everolimus-eluting stent, in direct randomized trial comparisons suggest a significant improvement in efficacy and even lower restenosis rate than first degeneration devices, so I think we have improved the technology now that we have very modern deliverable drug-eluting stents that may have both safety and efficacy benefits more than the earlier generations.

DR. DOUG WEAVER:

Does the drug matter? As far as we know, it sounds like even the polymer matters and that this is evolving our understanding of the biology of these things?

DR. MARTIN LEON:

It's a great question Doug, we think that frankly the drug probably doesn't matter as much, as long as you are within a drug class at a reasonable dose and release kinetics within a window, so sirolimus-appearing compound of what we call the limuses is probably no better or worse than everolimus or zotarolimus or several other analogs that are being used outside the United States. Paclitaxel, the other drug is also effective, but doesn't have as liberal a dose window. So, at higher doses greater toxicity, at lower doses less efficacy. So, a little bit less predictable. The polymer definitely matters and many of these polymers can be reactive. They can be inflammatory, they can be thrombogenic and we didn't realize how much in the early days.

DR. DOUG WEAVER:

Very, very interesting. I note that you say that most of these things are now made of cobalt alloys and is that primarily to make them more flexible and deliverable or is there something else above the metal scaffolding that's important?

DR. MARTIN LEON:

Again, a good question. Cobalt is an interesting alloy because it maintains the radiopacity, it's more radiodense even though you can thin the material. By thinning the material, it improves flexibility. It reduces profile, so it does significantly improve the deliverability, but you can still see it, which is why cobalt has been chosen. There are some other alloys that are being looked at that have platinum elements or other radiodense elements, but this has very much become the invoke material for current metal stents.

DR. DOUG WEAVER:

So, drug-eluting stents be used in all patients. Are there certain conditions that they seem to work better than bare-metal stents?

DR. MARTIN LEON:

From the standpoint of restenosis, uniformly drug-eluting stents outperform bare-metal stents, but the relative magnitude of the difference is exaggerated in the high restenosis risk patients. So, if you have a patient that has a large vessel, a very focal lesion in the right coronary artery, bare-metal stents do pretty well. Even though drug-eluting stents might do better, the absolute difference is not enough perhaps to justify that they be used in all situations. So, we have now rather than had more of a default approach to drug-eluting stents, which is to say we would use them almost uniformly in 90% of patients. We have a much more selective attitude about how to use them. So, clearly the patient's ability to comply with dual antiplatelet therapy for a variety of reasons, I think, determines in part whether we use bare-metal or drug-eluting stents. There are certain conditions like acute myocardial infarction. We just had the horizons drop, presented at TCT and yes drug-eluting stents did outperform bare-metal stents, but the relative difference wasn't that great in an AMI patients who might present in the middle of the night where you don't know the ability of the patient to be compliant for the long term on dual antiplatelet therapy, you might prefer to use bare-metal stents. So, we think that there are several specific scenarios where there are preferences of bare metal versus drug-eluting stents and in most centers now the overall use of DES has dropped from that high of 90% to 70% and some centers to as low as 50%.

DR. DOUG WEAVER:

If you are joining us now, you are listening to Heart Matters on ReachMD, the Channel for Medical Professionals. I am your host, Dr. Doug Weaver. Our guest is Dr. Martin Leon, Associate Director of the Center for Interventional Vascular Therapy at Columbia University Medical Center in New York City. We are discussing the potential from proving stent technology with biodegradable stents as well as other aspects about stents.

Can you use too many of these stents? It would appear that the technology has improved that we can deliver them in most places and can deliver them to multiple arteries. Is there any downside regarding the numbers of stents that you put in a patient?

DR. MARTIN LEON:

Many patients ask me that, is there any upper limit? There is no fixed upper limit in terms of the number of stents that we can use, but I think that good judgment dictates when enough is enough. In a patient that has complex multivessel disease, where you are going to be using 5, 6, 8 stents to treat multiple lesions, you have to begin questioning, if that's the best therapy in that patient and if bypass surgery would be a preferred alternative for revascularization. So, we think that although there is no fixed number that there was another interesting study presented at ESC and TCT called the SYNTAX trial that really looked at this and in those patients that really do have critical anatomy with multivessel disease requiring many, many drug-eluting stents, I think that bypass surgery is preferred from the standpoint of repeat revascularization and possibly also late safety.

DR. DOUG WEAVER:

Now, biodegradable stents have been talked about for at least a decade. Why haven't they made it yet?

DR. MARTIN LEON:

I mean that's the holy ground now. That is what people are hoping in 2015, we can get rid of this bare-metal backbone so we don't have a skeleton outlining our coronary arteries and we can have materials like suture that degrade over time. It's been difficult. These biopolymers that we are using, the degradation process itself often induces inflammatory reactions, it can be possibly thrombogenic. The biologic behavior in patients is different in animals and different on the bench, so it is a tricky biotechnology program, although I will say that there has been enormous progress over the last 3 years with fully bioabsorbable stents. So, there now are several first in man studies that had been completed, one that is achieved at 2-year followup with a bioabsorbable polymer that is impregnated with a sirolimus analog, everolimus. Thirty patients were treated and followed for 2 years. Device appeared at least in that small number of patients to be safe. There were no complications. The stent clearly did absorb and degrade over a period of many months and by 2 years it was completely gone and the effect of the drug was very profound in eliminating restenosis and unexpectedly at 2 years, we actually saw positive remodeling or dilatation of the artery with preserved vasoreactivity, suggesting that we had now restored endothelial function of the vessel at the stent site. So, this is quietly very exciting. Some of the continued problems, we have only studied a small number of patients. It took thousands of patients to uncover some of the complications that we found with drug-eluting stents. We need many more patients to look for untoward effects. The mechanical integrity of these devices, we were talking about this new slick cobalt alloy stents. These devices are thicker, they are clunkier if you will, they are harder to deliver, they have more recoil, so the mechanical properties have not been optimized, but you can imagine as technology progresses that there is a likelihood that we will develop bioabsorbable drug-eluting stents in the future that may improve safety, remove that metal scaffold which has major advantages without incurring any new complications, but it will take years of additional study.

DR. DOUG WEAVER:

What do you think is next? So, will it be another disruptive technology for patients?

DR. MARTIN LEON:

There are a lot of interesting new things people are looking at. So, for instance, we have used drug-eluting stents because we felt that when you injure the vessel wall that you need a drug to really abort an aberrant healing response with neointimal hyperplasia and scar tissue, but there may be other ways of delivering effective drugs without incurring some of the negative consequences of putting in stents, so there is a whole new technology of delivering drugs via balloon catheters, via absorbable nanoparticles, that's an interesting project that several people are working on and that may be one of the future therapies to try to prevent restenosis. I also think on the coronary side where we failed is that we've still not been able to identify those patients that have rupture-prone plaque that causes heart attacks and to try to effectively treat those patients and I am hoping that over the next generation, we will have better invasive and non-invasive techniques to identify those patients and those lesions and come up with interventional solution so that we can not just abort a heart attack in progress, but abort a heart attack before it might have happened. So, those are 2 areas that I am particularly interested in.

DR. DOUG WEAVER:

Very exciting.

We have been talking with Dr. Marty Leon about the perspective role of biodegradable structures for coronary stent as well as polymer technology in upgrading the safety and efficacy of stent devices.

Dr. Leon, thank you very much for being our guest.

DR. MARTIN LEON:

Thank you, Doug.

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