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A leading interventional cardiologist and clinical trialist discusses new advancements in vascular therapy and his thoughts on the emerging trial data.

How might catheter-based therapies be successful in treating renal hypertension? What clinical progress has been made in this area?

The exceptional results of the Symplicity I and Symplicity II trials exploring percutaneous renal sympathetic nerve ablation (published in 2009 and late last year) have engaged and excited several medical communities, not just endovascular interventionists but nephrologists, heart failure, and hypertension specialists. In doing so, this innovative technology has focal attention on the importance of hypersympathetic activity and its important role in resistant hypertension, heart failure, and several other pathologies. These two studies, using the Symplicity catheter (Ardian, Inc., Mountain View, CA), applied a low dose of radiofrequency energy percutaneously to the renal intima, resulting in ablation of renal sympathetic afferent and efferent nerves.

The Symplicity I trial, a proof-of-concept feasibility trial, established that the technology is both safe and effective and resulted in the substantial reduction in blood pressure in patients with resistant hypertension at 12-month follow-up. Symplicity II, a randomized controlled crossover trial against medical therapy, expanded on the results of the Symplicity I trial, with 98% of the patients in the medically treated arm crossing over to the treatment arm after 6 months. Importantly, a fascinating by-product of renal denervation in treating patients with resistant hypertension and concomitant diabetes has emerged, namely improved glucose control. This may relate to the reduction in peripheral sympathetic tone, resulting in improved skeletal muscle perfusion and improved glucose metabolism. Therefore, amazingly, this novel procedure may provide protection in patients with resistant hypertension and metabolic disorders at high risk for cardiovascular events. We anxiously await the initiation of the Symplicity III US pivotal trial, which is set to start enrollment later this year. This large, multicenter trial will incorporate a sham control arm along with several other unique trial design features, including a 2-week run-in period to document medical compliance of all patients and resistant hypertension before randomization. Studies applying this technology in other disease states in which hypersympathetic activity is present, including heart failure, cardiorenal syndromes, and obstructive sleep apnea, are being contemplated. I have been privileged to be involved with the US pilot trial and appreciate firsthand what a substantial impact this relatively simple and straightforward procedure can have on patients' lives.

How did interventional vascular therapy first come to be considered an option in treating erectile dysfunction (ED)?

This interventional vascular therapy was the brainchild of engineers at Medtronic (Minneapolis, MN). They correctly noted that a significant percentage of men have vascular disease as the etiology of their ED. Indeed, ED may predate the clinical onset of coronary disease or symptomatic peripheral arterial disease (PAD) by 3 years. Importantly, these engineers confirmed that an endovascular solution, namely drug-eluting steel stents, could be a possible solution in vasculogenic ED because they established that metal stents placed in cadaver internal pudendal arteries (IPAs) were protected from potential external crush injury by strong pelvic ligaments.

What can you tell us about the goals, design, and the progress of the ZEN trial?

The ZEN trial (Zotarolimus-Eluting Peripheral Stent System for the Treatment of Erectile Dysfunction in Males With Suboptimal Response to PDE5 Inhibitors) is a first-in-man, feasibility, safety trial initiated in 2009, which has taught us a lot about the many challenges associated with endovascular therapies in this vascular bed. We are "writing the book" as we go because this is a new anatomical bed for the study investigators requiring us to develop new methods for patient recruitment, best practices for obtaining IPA angiograms, the application of catheters used in other vascular beds and concerns about radiation exposure. In the end, I believe that as a result of our ZEN experience, we now have a general appreciation that the deployment of a drug-eluting stent in an IPA can be done safely. The question as to

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whether it is effective in improving erectile function will have to await the analyses of the entire cohort.

The ZEN trial is anticipated to conclude enrollment in late April, and its companion study, the IMPASSE trial (Incidence of Male Pudendal Artery Stenosis in Suboptimal Erections Study), will initiate enrollment. This important angiographic prevalence study will evaluate the angiographic patterns of atherosclerosis in erectile-related arteries in men with suspected or known coronary artery disease or PAD undergoing diagnostic angiography. At the time of the diagnostic procedure, they will undergo pelvic angiography with specific assessment of atherosclerotic disease involving their IPAs. Postprocedure, patients will be questioned regarding possible ED symptoms, and a correlation between their angiographic patterns of potential disease will be correlated against clinical symptoms. Importantly, all patients will be followed for 3 years to assess symptoms. IMPASSE will allow investigators to correlate potential angiographic disease patterns and ED symptoms and the potential development of future ED symptoms in this male population with known or suspected coronary artery disease and PAD.

What are any other new horizons you foresee in applying vascular interventional techniques or technologies toward conditions not previously treated via endovascular means?

I believe the work being done by Italian surgeon Paolo Zamboni, Drs. Michael Dake, Nick Hopkins, and others regarding the endovascular therapies for central thoracic vein angioplasty and possible stenting as a potential treatment of multiple sclerosis (MS) is fascinating. Chronic cerebrospinal venous insufficiency hypothesizes that chronic toxic iron overload in the brain is at the root of MS. Initial observations by Dr. Zamboni suggested that patients with various stages of MS had abnormal duplex Doppler central venous flow patterns, whereas control subjects did not. His initial reports that central thoracic vein balloon angioplasty in these patients resulted in an improvement of MS set off a firestorm of controversy among interventionists, neurologists, and MS advocacy groups. Of course, his initial findings were uncontrolled, nonrandomized, and included relatively few patients. Nonetheless, this field is moving very quickly and recently generated a position paper from the Society of Interventional Radiology; these authors noted that although the available data were inconclusive, they pushed for a well-controlled, randomized clinical trial.

I understand that the MS societies in the US and Canada have pledged millions of dollars to underwrite several international studies with substantially more rigor. If this technique is able to identify the appropriate MS population

that could potentially benefit, it would be a substantial step forward for these patients. It proves to me that we should keep an open mind and pursue well-designed, appropriately powered, and adjudicated trials before rushing to conclusions, one way or the other.

What did the 12-month results of the XCELL show regarding patency and durability?

The 12-month results of the XCELL study demonstrated to us that the association between a functional endpoint such as angiographically defined tibial stent patency and important patient-centric endpoints such as limb salvage, wound healing, and pain relief is very complex and requires larger cohort sizes with longer follow-up to discern any direct correlation among vessel patency, overall limb salvage—which was a respectable 90% at 12 months—and wound healing. In this regard, 47% of Rutherford class 5 and 6 patients experienced complete wound healing by 6 months, a number comparable to surgical results. Importantly, the parameter of time-to-complete wound healing was actually shorter with recent surgical data by nearly 2.5 months.

Although no one would disagree with the general statement that an "open artery is better than a closed artery," when it comes to critical limb ischemia patients and healing wounds, the issue is much more complex. It is important that we consider the patency of the wound-related artery and balance our endovascular attempts to maintain stent/vessel patency (primary assisted patency) and wound healing as well as patient function. Although the 6-month angiographic Xpert stent (Abbott Vascular, Santa Clara, CA) restenosis rate was nearly 60%, the 90% 12-month limb salvage rate noted in XCELL was similar to those noted in many surgical trials of critical limb ischemia at the same time point. Importantly, the 30-day safety parameters of amputation-free survival, all-cause death, and target lesion revascularization–associated stenting were exceptionally low, especially when compared to recently published surgical performance goals.

What do you consider to be the most important data publication or presentations in the past 2 years?

The CREST trial, the National Institutes of Health–sponsored randomized trial of carotid endarterectomy versus carotid stenting has to be number one. The results of this 10-year trial were a tremendous undertaking, randomizing over 2,500 patients, and provided substantial insights into which patient cohorts are best served by carotid stenting and which patients are best served by surgery. The results established the substantial equivalence between carotid stenting and surgery in stroke prevention between the two groups and in both symptomatic and asymptomatic cohorts. Importantly, subgroup analyses provided direction to neurologists, vascular surgeons, and cardiologists who perform these procedures and refer these patients. On the heels of CREST, the CARE carotid stent registry, sponsored by seven medical societies and including nearly 140 medical centers, following more than 12,500 patients undergoing either stenting or surgery, has added a real-world look on the different referral patterns for these patients.

Another important publication was the results of the THUNDER trial in 2008; this relatively small proof-of-concept trial has sparked a completely new field combining angioplasty balloons as drug delivery with the application of paclitaxel. This trial, along with the FemPac trial, has spawned multiple subsequent trials presently enrolling in the European Union. Importantly, we have learned very quickly that drug-eluting balloons alone may not be sufficient in promoting or maintaining vessel patency, whether in the superficial femoral artery or tibial arteries. Trials combining atherectomy and drug-coated balloons are presently contemplated. These data will also focus on the importance of combining vessel patency with patient-centric endpoints, whether it be wound healing, limb salvage, or the validated improvement of claudication and walking distance.

Which current study do you most anticipate the findings from and why?

There is great anticipation in the endovascular community surrounding the pending results of the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial, the randomized assessment of optimal medical therapy versus primary renal stenting in hypertensive patients with atherosclerotic renal artery lesions. Although these results are anticipated, there is also general concern in the community that this trial, which was very slow to enroll, was compromised by potential operator bias. I suspect the primary reason for the slow enrollment was that clinical equipoise was not at play—that is to say, investigators or referring physicians felt there were specific patients who they knew would be best served by stenting and hence did not subject them to randomization. However, while the incidence of the hard endpoints of death, myocardial infarction, cerebrovascular accident, and/or progression to renal failure will generate great interest, any difference in blood pressure improvement between the two treatment arms will be closely analyzed. ■

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