Renal denervation: Clinical lessons from around the world

David Kandzari, MD: Hello. I'm David Kandzari from the Piedmont Heart Institute in Atlanta, GA. It's my pleasure to welcome you to this editorial discussion entitled Renal denervation: Clinical lessons from around the world. Today I'm joined by two of my friends and colleagues, Dr Christian Ukena from the Saarland University Hospital in Homburg, Germany, as well as Dr Stephen Worthley from the University of Adelaide in Australia. Welcome, Stephen, Christian, to this program.

Stephen Worthley, MD: Hello, Dave.

Christian Ukena, MD: Hello.

Dr Kandzari: As you both know—you've been very involved in renal-denervation therapy for hypertension for some time now—we've recognized that for decades therapies have been directed toward the underlying mechanisms of hypertension, whether they are vasodilator therapies or therapies designed to interrupt the neurohormonal system. We now might add to the pharmacologic armamentarium new therapies with devices to affect renal denervation. Christian, let's begin with you. Can you give us a background of the renal efferent and afferent nerve physiology and its relationship to hypertension and other disease states?

Dr Ukena: Sure. The sympathetic nervous system is involved in the genesis of hypertension. Sympathetic nerve fibers lie around the renal arteries in the adventitia. There is a feedback mechanism, triggered by—for instance, renal ischemia. Renal affluent nerve activity is elevated, mediated by the hypothalamus, to an elevated efferent nerve activity, for instance a kidney with all mechanisms increasing blood pressure.

Dr Kandzari: Stephen, early studies with surgical sympathectomy of interrupting the nervous system—the communication between the renal nerves and the central nervous system—were very effective in mediating hypertension, reducing blood pressure in patients with very severe hypertension. But of course it was a very invasive procedure fraught with a number of complications. What have been the more recent clinical-trial data with catheter-based—more precise, more selective—renal-denervation therapy?
**Dr Worthley:** Dave, as you know, in Australia, we’ve been fortunate to be involved with some of those early first-in-human studies. Obviously **SYMPLICITY HTN-1** was the leader and really set the scene for the use of an endovascular device for the purpose of causing renal denervation for the treatment of high blood pressure. SYMPLICITY HTN-1, the single-electrode catheter from Ardian, subsequently taken under the umbrella of Medtronic, showed us that it was safe and feasible to undertake an endovascular treatment to cause renal denervation and that in fact it actually led to a significant reduction in blood pressure that was seen early. In that study in just over 40 patients we saw 14/10-mm-Hg reduction in that 30 days that seemed to continue to increase with time. And even as we’ve seeing more recent data after three years, we’re seeing [a] 25- to 30-mm-Hg reduction with that technique.

What's interesting is that by today's standards it was a fairly modest renal denervation [that was] performed. What I mean by that is there were 3.7 mean lesions performed in one renal artery and four in the other. Certainly the adequacy of the renal denervation was probably modest, and yet we saw these quite significant striking reductions in blood pressure.

**Dr Kandzari:** That's an interesting point that you raise regarding the technique and the procedure itself. Before we talk a little bit about the safety of the procedure too, are there any predictors that we can identify right now that would identify those individuals who would benefit most from the procedure itself?

**Dr Worthley:** Sure, David. We’ve certainly seen quite a bit of data that have been pooled from the SYMPLICITY HTN-1 and the subsequent randomized control trial with just over 100 patients in **SYMPLICITY HTN-2**. When we’ve looked at predictors of the delta in blood-pressure reduction, we’ve certainly seen that the absolute baseline blood pressure is probably one of the most robust predictors. That means that the higher your baseline office blood pressure that you start with, the great the absolute reduction in blood pressure that you would expect to see.

It's contingent perhaps a little around some other predictors. Some data sets have suggested that higher heart rate at baseline predicts better response, and that's perhaps a surrogate of baseline resting sympathetic activity. It might intuitively suggest to you that, yes, that would help predict a better response if you're going to induce a reduction in sympathetic activity. The relationship of some other
predictors, I think is a little tenuous. Things like reduction in heart rate, is that related to high blood pressure? Certainly Christian and his group have suggested that perhaps that is a little tenuous, but some data sets from the ENLIGHTN-1 trial (that we've been involved with) have actually shown that it is related.

One of the issues, though, that you are well aware of, is we've seen that there is probably this 20% give-or-take nonresponder rate. Although we have just mentioned some predictors, they are clearly imperfect because our ability to a priori work out who is going to be that nonresponder I think is fairly limited at the moment.

**Dr Kandzari:** Christian, what do we know about the safety of the procedure, particularly with preservation of electrolyte and the homeostatic mechanisms with regard to renal stenosis, for instance, or complications related to the procedure?

**Dr Ukena:** From our work—from clinical trials as well as from real-world experience—we see that renal denervation is a safe procedure. Unlike the initial surgical approach, it does not have any complications such as orthostatic hypertension, syncope, and gastrointestinal side effects. So far published we've seen side effects concerning the femoral-access complications in a minor number of cases. But we do not see any worsening of the renal function after the procedure. Additionally we do not very [frequently] observe any dissections or other problems caused to the renal artery.

**Dr Worthley:** It's an interesting point, though. There certainly seems to be a low-frequency event, though, of renal-artery stenosis in the case where there is some preexisting atherosclerosis. Certainly it doesn't seem to be a factor when there is normal renal artery anatomy to start, but certainly out of the HTN-1 data set there was one patient. We've seen that same frequency of events in the ENLIGHTN-1 trial. Perhaps causing endothelial injury may—over larger data sets—emerge as a low-frequency inducer of renal atherosclerotic progression. But it seems perhaps only in the presence of underlying atherosclerotic disease.

**Dr Kandzari:** With regard to safety and effectiveness of this procedure, let's expand this beyond the clinical trials to real-world clinical practice. To be sure and select the geographies, Christian, Germany being one of the leading examples, this therapy is now routinely available as part of routine clinical practice, whereas at Stephen's and my institution it's still limited to clinical trials. What has
been the clinical real-world experience, Christian, with this therapy? In particular, I'll ask you: Is there what we might call an indication creep, where there is an expansion of treatment for patients with blood pressure that's elevated but may not have necessarily met the clinical-trial criteria?

**Dr Ukena:** Concerning the safety of the procedure: We have to say that [it's] similar to those [data] that have been published in the trials—it's a safe procedure. Concerning the indication: Actually, we've seen a broadening of the indications, which in particularly is due to the cost of many hospitals in Germany of performing this and trying to recruit patients, and maybe there is a lesson here for patient selection. What we've seen so far from the registry and the first results available is that when you go to the milder forms of hypertension you do not see the same effectiveness as we saw in the clinical trials. Just remember in the SYMPLICITY trails patients included had a blood pressure of 180/100. Those in the real-world often have a much milder form of hypertension.

**Dr Kandzari:** In fact, we're currently in the design of new trials that are evaluating renal denervation in more moderate—but resistant—hypertension as well. Let's talk a little bit about setting level expectations for this procedure. In real-world clinical practice a patient clearly knows what treatment he or she received. There's a big desire among patients to reduce their pharmacologic burden. Many of these very potent antihypertensive agents have very adverse side effects to them. The patients themselves I think after treatment might want to discontinue therapy. We know patients are generally not always compliant with their antihypertensive agents to begin with. How do you manage this in practice and how do you try to ensure that you are still going to achieve the same results that we've seen in the trials?

**Dr Ukena:** As an interventionalist you need close cooperation. You need a team, similar to a "heart team." You need to cooperate with hypertension experts, with nephrologists, for instance, somebody who takes care of the patient selection before the procedure and takes care of the follow-up procedures, and someone who talks to the patient and ensures that he stays on his medication just for a while—maybe six months after the procedure—[until we] see the results of the procedure. We, as interventionalists, have a new situation where we do not see immediate results in the cath lab. We have to wait a certain amount of time, and therefore it is important that the patient stays on medication.
In the real world it's often not achievable. Many patients change their medications—increase and decrease it—and therefore many of the results we see in the real world do not affect the patients [in the same way] as what we saw in the trials.

Dr Kandzari: Let's turn this now to the patient's perspective, Stephen, and specifically address what do we know about quality of life after renal denervation or cost-effectiveness.

Dr Worthley: One of the things, David, is it's going to be a real hard ask for renal denervation to be cost-effective vs medications if we're thinking about that erosion, if you like, as a replacement therapy because off-patent antihypertensives are so cheap. However, if we look at the data that are being studied to date—which has been as an adjunct to antihypertensive therapy in resistant patients—that's a different kettle of fish. Although we haven't had studies that have embedded pharmacoeconomic processes in the trial design, we certainly know that, in terms of the reductions in blood pressure, we would expect that the implied reductions in mortality and heart events would actually be very cost-effective.

For example, we know that every 10-mm-Hg reduction in blood pressure affords us about a 20% to 25% reduction in death, MI, and stroke. Therefore, when we look at the magnitude of reduction in blood pressure that we're seeing at the moment—which is almost 30 mm Hg at six and 12 months—well, that's a three-time reduction in heart end points. We would expect them to be very cost-effective. However, I think that studies that are going to look prospectively at heart end points, death, MI, and stroke, and embedding those pharmacoeconomic data are going to be important for us to get some clarity around what the benefits are going to be.

Dr Kandzari: Just as you have implied, too, there are some data from the NICE registry and the Framingham database that would at least in modeling suggest that the cost-effectiveness ratio exists throughout all levels of blood-pressure treatment until the reduction in systolic blood pressure becomes less than about 10 or 11 mm Hg, which is only maybe about a third of what we've seen from the clinical trials. It's interesting, though, that this is a field where the practice of the therapy has far exceeded the science behind it. We're just now coming back and learning about the anatomical distribution of the renal nerves. We're learning more about cost-effectiveness and quality of life. We will learn in these very large and ambitious trials that are forthcoming about the impact on stroke and cardiovascular death and
heart failure. Let's just talk briefly about the expansion of this therapy—of renal denervation, Christian, in reducing the hypersympathetic signature and having other effects in other disease conditions that we might not have intuitively related to hypertension.

**Dr Ukena:** Renal denervation is fascinating. We have the possibility actually for modeling empathetic activity. As I mentioned earlier, we reduce maybe the sympathetic efferent activity by renal denervation. Therefore, we reduce blood pressure, but maybe also other diseases . . . affected by the sympathetic activity. For instance, glucose metabolism is positively influenced. We see a reduction of heart rate and maybe also improvements of other arrhythmia burdens. Of course, for cardiologists, one of the most important diseases, heart failure, may also be positively influenced by this new method.

**Dr Kandzari:** More to come with those other expanding indications that truly could expand this novel therapy to a breadth of other disease conditions we might never have thought previously related to at least renal-denervation therapy.

Stephen, in the pursuit of doing this procedure, in just a short time, it's hard to believe that the first catheter that has been studied in the SYMPLICITY trials now is sort of termed the "first-generation" catheter, as there are so many other technologies out there beyond radiofrequency energy, with ultrasound, external ultrasound, and direct drug delivery. I know that both of you are in involved with some of these technologies. Can you just give us a little bit of perspective of these technologies and their purpose?

**Dr Worthley:** Yes, sure, David. There is no doubt that a single electrode-based system with radiofrequency is definitely considered "first generation." We've seen the shift from catheters that are made by companies like Ardian, Vessix, and the EnligHTN-1 Institute, where they are all multielectrode (or a variant thereof) in terms of their delivery. What they've done is take away the risk that you're not going to get an idealized set of lesions that is in theory going to allow you to give a great renal-denervation process. It makes the procedure faster and in theory easier. Whether that translates to safer . . . . The problem is that it is such a low-frequency safety issue anyway that it is hard to think that it would.

There are a plethora of companies, though, which are in this space at the moment. We've certainly seen other technologies that you've mentioned. I've seen microwave, ultrasound, various pharmacological
injections potentially, and beyond, but it's hard to believe that all of those are going to come to clinical fruition. Really, it's "low-hanging fruit" to get something that's a multielectrode system, and I think that we're going to see that take the space in the next six months. The iterations beyond and how much they are going to improve, it is hard to know. Certainly a paradigm shift would be the ability to do renal denervation noninvasively, but I think that's a long way away from reality.

**Dr Kandzari:** A final comment from you, Stephen, and then you Christian. Specific to hypertension, what's the next big direction that this therapy is going to go? What is the next big issue for us to study?

**Dr Worthley:** I really think it is the erosion that you mentioned, David. Resistant hypertension—three or more agents, on a diuretic, systolic blood pressure over 160—I think all of us feel really comfortable. Getting some greater clarity on that group that has got lower blood pressure, we've seen some early pilot data, but more robust, long-term data [are needed]. Patients that are intolerant of medications—it's a big group that we all see in clinical practice but it has not been studied to date—do they have the same benefit? Seeing the hard outcomes and pharmacoeconomics—that's going to come clearly with time and will emerge in the next year or two.

**Dr Kandzari:** Christian, your thoughts?

**Dr Ukena:** Essentially, it's the same. I think first of all we have to agree that when going to lower hypertension we will also probably see lower effects of renal denervation. From an interventionalist's perspective, one of the most important topics currently is actually to shorten the procedure time, make it easier, and to decrease the rates of nonresponders—a completely open field, is it maybe a problem of the procedure? Is it a problem of wrong patient selection? That is another interesting topic: How to reduce nonresponders and how to proceed with those who do not respond after renal denervation.

**Dr Kandzari:** There is still a great deal to learn with regard to renal denervation for hypertension, new indications expanding beyond hypertension to the hypersympathetic signature, and new technologies. Stephen, Christian, I want to thank you both for a great discussion.