Assessing Renal Denervation Studies

Editor-in-Chief of the *European Heart Journal* and EnligHTNment Principal Investigator, Thomas F. Lüscher, MD, FRCP, FESC, discusses study challenges and current literature.

With the increasing amount of papers being published on renal denervation, have the standards for what merits publication evolved? If so, in what ways?

Yes, certainly. Initially, we were very interested to see proof-of-concept papers on new devices and their effects in the renal artery. Now, we need more efficacy data in larger populations and, eventually, larger trials.

Each large-scale trial has its challenges, but are there any design difficulties that are specific to the resistant hypertension population? How are these being addressed in today's trials?

Yes, this is a real issue. We cannot do a placebo-controlled trial. Resistant hypertension, however, has been well defined in the guidelines (eg, three drugs, including a diuretic, and blood pressure [BP] > 140 mm Hg). This is the standard we use for the EnligHTNment trial, which is currently enrolling 5,000 patients. Eventually, major cardiovascular events (MACE) must be the endpoint.

There are two issues with BP: if it is achievable to match BP precisely, then a reduction in MACE would indicate that the sympathetic nervous system is a major driver of these events, and interfering with the sympathetic nervous system specifically reduces MACE. If renal nerve ablation is more consistent and/or effective as a BP-lowering measure and therefore reduces MACE, this could be another important message that comes out of current trials.

From the perspective of both an editor and a leading investigator, what are the challenges posed by this patient population in your ability to determine whether a therapy is as useful as a study indicates, as opposed to a result of a trial design shifting results in one direction or another?

Any device trial has the problem of crossovers (ie, patients in the control group receiving the device or the device-related treatment for clinical reasons). This usu-

Dr. Lüscher's Must-Read Scientific Papers on Renal Denervation

Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial.
Symplicity HTN-2 Investigators, Esler MD, Krum H, et al.
Lancet. 2010;376:1903–1909.

Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial.
Worthley SG, Tsioufis CP, Worthley MI, et al.
Eur Heart J. 2013;34:2132–2140.

Effects of renal denervation with a standard irrigated cardiac ablation catheter on blood pressure and renal function in patients with chronic kidney disease and resistant hypertension.
Kiuchi MG, Maia GL, de Queiroz Carreira MA, et al.
Eur Heart J. 2013;34:2114–2121.

The human sympathetic nervous system: its relevance in hypertension and heart failure.
Parati G, Esler M.
Eur Heart J. 2012;33:1058–1066.

Vascular lesions induced by renal nerve ablation as assessed by optical coherence tomography: pre- and post-procedural comparison with the Simplicity catheter system and the EnligHTN multi-electrode renal denervation catheter.
Templin C, Jaguszewski M, Ghadri JR, et al.
Eur Heart J. 2013;34:2141–2148.

Expert consensus document from the European Society of Cardiology on catheter-based renal denervation.
Mahfoud F, Lüscher TF, Andersson B, et al.
Eur Heart J. 2013;34:2149–2157.

ally dilutes the power of the study by 10% to 18%. Furthermore, with devices, there is usually a smaller number of patients enrolled, particularly at the introduction of a new device for financial reasons; this, again dilutes the study's power. The basic medical treatment in the control and intervention groups has to match somehow, which is also quite a challenge. Finally, because such trials take 4 to 5 years, the technology might evolve substantially by the time the results become available and may no longer reflect current practice.

As principal investigator of the EnligHTNment trial, what can you tell us about its design and goals?

It is our ambition to show that renal nerve ablation with the EnligHTN renal denervation system (St. Jude Medical, St. Paul, MN) is superior to current medical therapy over a follow-up period of 5 years in 5,000 patients. We will randomize patients to standard medical care and renal nerve ablation on top of medical therapy. The primary endpoint will be MACE.

What are the design elements that allow for one trial to evaluate both hypertension reduction and other possible utilities of denervation technology?

EnligHTNment will have substudies looking at several aspects of denervation utility. Although they have not yet been finalized, silent atrial fibrillation, left ventricular hypertrophy, metabolic syndrome, and 24-hour BP are being considered.

What early indicators are there to guide the premise that denervation may reduce stroke and heart attack?

The impressive BP lowering in this patient group is very promising. Furthermore, the sympathetic nervous system has effects on glucose metabolism, renal function, left ventricular hypertrophy, and vascular function—all aspects that may be important for reducing stroke and heart attack. ■

Thomas F. Lüscher, MD, FRCP, FESC, is Editor-in-Chief of the European Heart Journal *and is Professor and Chairman of Cardiology at the University Hospital Zurich and Director of CardioVascular Research at the Institute of Physiology of the University Zurich, in Zurich, Switzerland. He has disclosed that he is a consulant to and receives research grants from Medtronic and St. Jude. Dr. Lüscher may be reached at +41 44 255 21 21; cardiotfl@gmx.ch.*