Kidneys have an extensive network of afferent unmyelinated fibers that transmit important sensory information to the central nervous system. There are important interactions between the kidney and the heart in various cardiac conditions, which are mediated by autonomic nervous system output. These include up-regulation of the sympathetic nerve system, activation of the renin-angiotensin-aldosterone system and vasopressin secretion.

Given resistance to drug therapy, activation of the sympathetic nervous system, the role of renal nerves in the development of hypertension (HTN), and the ease of approach of the sympathetic fibers by catheter based techniques, resistant HTN was the ideal candidate for interventional approaches which have collectively become known as renal artery denervation (RDN).

Sympathetic fibers course in the adventitia of the renal arteries, are mostly situated within 2 mm to 3 mm of the inner layer of the renal artery, and can be easily reached and interrupted transarterially using thermal (e.g. radiofrequency, RF) energy. The objective of RF ablation is to place discrete lesions in a circumferential pattern, but not at the same cross-section of the vessel so as to minimize the risk of renal artery stenosis.

A series of trials were conducted to test RDN for the treatment of resistant HTN, and in general were positive with a fall of approximately 30/10 mm Hg in office BP readings and lesser falls with ambulatory BP monitoring. A number of criticisms were raised about the study designs and these provocative findings, and the penultimate trial, SYMPLICITY-HTN-3, was conducted to address these concerns and to provide definitive evidence of the efficacy of RDN as an antihypertensive intervention prior to FDA approval. The momentum of RDN use for the therapeutic goal of BP control in resistant hypertensive patients came to an abrupt halt with the release of the sham-controlled SYMPLICITY HTN-3 trial. In this six month multicenter study of more than 500 patients, both office and 24-hour ambulatory BP were similar in the RDN and control groups. The design and technical application of RDN in SYMPLICITY HTN-3, however, were extensively criticized, and more recent non-pivotal randomized trials have shown promising antihypertensive effects. Nonetheless, these recent trial results were a major setback to the field of RDN, at least for treatment of HTN.

Of note, none of the anti-HTN studies suggested an important incidence of renal vascular complications resulting from RDN, and renal artery stenosis was very rare.

The first-in-man pilot blinded randomized clinical trial of RDN for atrial fibrillation (AF) was conducted by Dr. Steinberg and included 27 patients with a mixture of paroxysmal and persistent AF, and a history of resistant HTN, who were referred for catheter ablation. At the 12-month follow-up examination, 9 of the 13 (69%) standard ablation plus RDN group were AF-free. In contrast, in the standard ablation arm, only 4 of the 14 (29%) patients were AF-free on no antiarrhythmic drugs (P = 0.033).

Based on the favorable pilot data, The Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation Trial (ERADICATE-AF) was designed to test the hypothesis that RDN in addition to pulmonary vein isolation (PVI) enhances long-term antiarrhythmic efficacy in comparison to PVI alone for patients with AF and HTN and suboptimal BP control in a large multicenter, single-blind, randomized clinical trial. The study was designed by Dr. Jonathan Steinberg who served as principal investigator of this international effort conducted across Europe.

Of the 302 randomized patients, all successfully underwent their assigned procedure(s). Freedom from AF at twelve months was observed in 84 of 148 (56.5%) of the PVI only group and in 111 of 154 (72.1%) of the PVI + RDN group (hazard ratio, 0.57; P = 0.004) (Figure 1). Mean systolic blood pressure from baseline to twelve months decreased from 151 mm to 147 mm Hg in the PVI only group and from 150 mm to 135 mm Hg in the PVI + RDN group (between-group difference, -13 mm Hg; P < .001). Procedural complications occurred in 4.6% of the PVI only group and 4.7% of the PVI + RDN group.

The authors concluded that among patients with paroxysmal AF and HTN, RDN added to catheter ablation, compared with catheter ablation alone, significantly increased the likelihood of freedom from AF at twelve months without an increase in complications.
The trial results represent an important advance in interventional therapy for AF, and are notable for using a noncardiac complementary ablation target to optimize the therapeutic outcome. Further, it promotes the value of neuromodulation as a therapeutic tool for cardiac arrhythmias. Catheter ablation via PVI is certainly an acceptable option in the many patients who have unsatisfactory responses to pharmacologic therapy for AF. Although superior to drug therapy for reducing AF recurrence, ablation has a failure rate of 20-30%, a need for repeat procedures, and a not insignificant long-term AF recurrence rate even after initial success.

We believe that RDN is now reasonable to employ to increase the success rate of catheter ablation for AF in patients with HTN. RDN will shortly be introduced as part of our comprehensive management and ablation program for patients with AF.