

# Renal Sympathetic Denervation: From Bench to Bedside or the Other Way Around?

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Arterial hypertension is ubiquitous, and takes an important toll in terms of resources, morbidity and mortality [1]. Established international estimates reported in 2003 an age and sex-adjusted prevalence of arterial hypertension of 28% in North America and of 44% in Europe, but even higher figures are likely today and in the future [2]. Beside life-style changes, a plethora of different drug classes and individual agents are available to manage hypertension, such as alpha-blockers, angiotensin-2 receptor blockers, angiotensinogen-converting enzyme inhibitors, beta-blockers, calcium-channel antagonists, and diuretics [1]. Several combinations of these agents can be envisioned, but experts still disagree on which is the best first-line agent and which combo regimen is associated with the most favorable risk-benefit and cost-benefit profile [3,4].

Despite such generous options, several patients with hypertension may be considered resistant, refractory or unresponsive to treatment. Several definitions may be applied [5-7], but we may tentatively suggest to consider resistant those requiring at least 4 drugs (including a diuretic) belonging to different classes to reach Systolic Blood Pressure (SBP) or diastolic Blood Pressure (DBP) levels <140/90, or those having SBP/DBP >140/90 despite a regimen including 3 agents (including a diuretic) from different pharmacologic classes. Management of such resistant or refractory subjects remains challenging, especially because several reasons, including poor compliance or major comorbidities (e.g. end-stage renal failure), may explain this occurrence and yet prove themselves difficult to address. Indeed, increasing dosages or adding other agents remain the most common approaches to tackle resistant patients, despite limited efficacy.

A recent breakthrough in this field of clinical practice has been the introduction of transcatheter renal sympathetic denervation [8]. This procedure is based on the historical heritage of surgical denervation [9] and exploits the availability of miniaturized catheters enabling safe intra-luminal radiofrequency ablation of the renal arteries. Several data have been reported on the Ardian device (Medtronic, Minneapolis, MN, USA), which is a device compatible with transfemoral access, and selective ablates nerve fibers running around the renal artery [10]. These procedure appears to have several potential advantages, including of course the reduction in both SBP and DBP, and the requirement for fewer antihypertensive medications [6,8]. Strikingly, several pleiotropic effects have been reported, either preliminarily or based on already established evidence, including effects on glycemic control, cardiac remodeling, and, possibly, ovarian function [11-20]. Benefits of renal sympathetic denervation seem to go even beyond the mere effects on blood pressure or the function of other organs and systems, as quality of life improvements have also been demonstrated [21]. In addition, renal sympathetic denervation may be already, despite being technologically and clinically in its infancy, cost-effective, especially when performed in younger subjects [22].

These procedure is not devoid of cons, of course. These may include its invasiveness and the complications potentially associated with vascular access and renal artery instrumentation [23,24]. In addition, costs could not be justifiable in all socio-economic contexts, especially if drug prices will plummet due to patent expirations. Other areas of uncertainty include the lack of very long-term follow-up data,

Biomarker, process, organ or system where favorable effects have been reported	Evidence
Albuminuria	Preliminary clinical data
Arterial stiffness	Preliminary clinical data
Atrial fibrillation recurrence after pulmonary vein isolation	Strong clinical data
Blood pressure	Strong clinical data
Cardiac remodeling	Preliminary animal data
Glycemic control and insulin resistance	Preliminary clinical data
Heart failure symptoms	Preliminary clinical data
Heart rate and atrioventricular conduction	Preliminary clinical data
Polycystic ovary syndrome	Preliminary clinical data
Sleep duration	Preliminary clinical data
Ventricular tachycardia recurrence in hypertrophic cardiomyopathy	Preliminary clinical data

Table 1: Potential effects of renal sympathetic denervation.

the limited evidence on the effect of renal sympathetic denervation in patients with severe but yet adequately controlled hypertension, and the lack, so far, of means to dose-adjust or titrate the effect of renal sympathetic denervation in the individual patient. However, several devices are currently being developed or tested in alternative to the Ardian device involving more than 20 different competing biomedical companies, and some operators have gone so far as to use standard electrophysiology catheters for renal ablation [25] (Table 1).

Our belief is that such developments, as well as the accruing experience in thousands of patients worldwide, will improve the implementation of this promising and ground-breaking therapy. In the meanwhile, we must also continue to devote substantial resources to basic and translational research projects focusing on the underlying pathophysiology, hopeful to seamlessly yet repeatedly move from bench to bedside and the other way around.

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