Activation of the sympathetic nervous system plays an important role in the development and disease progression of hypertension and its comorbidities. Antihypertensive treatment approaches have focused on abrogation of activated neurohormonal systems associated with these conditions, including the renin–angiotensin–aldosterone system and the sympathetic nervous system. Despite the availability of effective antihypertensive drugs, certain patients remain uncontrolled to target blood pressure (BP) values. For these patients with uncontrolled hypertension, new device-based treatments have been developed, such as surgically implanted baroreceptor stimulators and catheter-based renal denervation. The available evidence suggests that renal denervation reduces renal sympathetic activity and office BP, as well as ambulatory BP in open-label registries and randomized, controlled trials in certain patients, but not in all patients. The BP-lowering effect of intensified drug treatment, with special focus on aldosterone antagonist treatment, compared with catheter-based renal denervation has not been investigated in detail.

In this issue, the prospective, randomized, open-label multicenter PRAGUE-15 trial by Rosa et al investigated the efficacy and safety of catheter-based renal denervation (using Medtronic’s Symplicity device) versus intensified pharmacological treatment, including spironolactone in patients with mild to moderate resistant hypertension (office systolic BP [SBP] at the baseline, >140 mm Hg; 24-hour BP at the baseline, >130 mm Hg). The adherence of patients was confirmed by plasma toxicological analyses at the beginning (but unfortunately not after 6 months), and secondary causes of hypertension were excluded systematically. The study provides interesting insights about the efficacy and safety of intensified drug treatment and catheter-based renal denervation in patients with resistant hypertension.

Aldosterone Antagonists and Renal Denervation
Friends or Foes?
Felix Mahfoud, Luis M. Ruilope, Michael Böhm, Roland E. Schmieder

See related article, pp 407–413

Aldosterone Antagonists in Resistant Hypertension: Effective and Safe?
The significant BP change (24-hour SBP, −8.1 mm Hg; P=0.001 and office SBP, −14.3 mm Hg; P<0.001) in the intensified drug treatment group of PRAGUE-15 was mostly driven by patients in whom spironolactone was added and continued. Spironolactone has been shown to lower BP and affects hypertensive organ damage positively, the latter, in part, occurring independent of spironolactone being available for ≥50 years, the evidence of its use in prospective, randomized, placebo-controlled trials in patients with resistant hypertension is still limited. The addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT) trial demonstrated that the addition of 25 mg of spironolactone (n=59) compared with placebo (n=58) in patients with resistant hypertension (on average treated with 4.5 antihypertensive drugs) is able to reduce daytime SBP by 5.4 mm Hg (P=0.024) and nighttime SBP by 8.6 mm Hg (P=0.011), whereas the fall of the respective diastolic values was not significant. In another multicenter, double-blind, placebo-controlled study in patients with 24-hour BP >130/80 mm Hg, despite triple antihypertensive therapy and type 2 diabetes mellitus, the effect of adding 25 mg of spironolactone (n=57) or placebo (n=55) has been evaluated. Placebo-corrected BP changes were −8.9 mm Hg and −3.7 mm Hg for 24-hour SBP and diastolic BP (P=0.001), respectively. The reductions of BP in the above-mentioned trials, including PRAGUE-15, were significantly lower compared with BP reductions documented in previous trials. The clinical use of aldosterone antagonists is often limited by adverse effects (overall 39% patients in the pharmacological group of PRAGUE-15 experienced adverse events), such as worsening of renal function, hyperkalemia, antiandrogen effects, and others, which obviously impact long-term treatment compliance. The risk of hyperkalemia, for instance, associated with the use of spironolactone can increase from 11% in treatment of resistant hypertension as in PRAGUE-15 to 39% in patients with chronic heart failure with impaired renal function (estimated glomerular filtration rate, <60 mL/min per 1.73 m²). In particular, unexpected decrease in renal function because of developing comorbidities comprises the safety of aldosterone antagonists, especially in patients with concomitant diuretic therapy and already existing blockade of the renin–angiotensin system. In the pharmacological group of PRAGUE-15, serum creatinine increased and in parallel, creatinine clearance decreased significantly, between-group differences were borderline significant. Furthermore, 1 patient with diabetic nephropathy developed significant worsening of renal function, which persisted after its discontinuation, indicating that patients receiving intensified drug treatment require regular follow-up examination. The full
side effect profile of adding the aldosterone antagonist spironolactone to resistant hypertensive patients can only be judged after longer term follow-up (>6 months) because hyperkalemia incidence will increase over time.

**Renal Denervation and Spironolactone: Addition to or Instead of?**

In PRAGUE-15, renal denervation and intensified drug treatment reduced office and ambulatory BP in patients with mild to moderate resistant hypertension to a similar extent. However, several aspects should be taken into consideration, while discussing the BP-lowering effect after renal denervation in PRAGUE-15, which was less pronounced compared with other studies. Baseline SBP has been identified as a predictor of response to treatment. The fact that baseline BP (office, 159 mm Hg; 24-hour, 149 mm Hg) was lower compared with previous published trials might, in part, account for the smaller BP-lowering effect after the procedure. Preliminary data indicate that the effect in those patients is less pronounced compared with patients with severe resistant hypertension. The knowledge about the importance of the complex underlying human renal anatomy and physiology, and biophysics of radiofrequency lesion formation is evolving, and it has become clear that the impact of procedural performance was underestimated. This is especially important because there are no means of assessing effective destruction of renal sympathetic nerves intraprocedurally. Interestingly, post hoc analyses from the randomized, sham-controlled Symplicity HTN-3 study, which did not meet its primary efficacy endpoint, showed that renal denervation can effectively lower office and 24-hour BP in patients not responding to spironolactone therapy.

**What Next?**

In this issue, the findings presented by Rosa et al prompt several questions that need to be answered in the near future.

1. If renal denervation is as effective as intensified drug treatment in lowering blood pressure, should we give patients the choice?
2. Should renal denervation be offered to patients who refuse initiation of spironolactone, who are at risk to develop, or who have experienced serious side effects?
3. Is renal denervation a valid therapy option for patients not responding to spironolactone treatment?

It will require additional rigorously performed, randomized, controlled clinical studies to determine the role of renal denervation in hypertension treatment finally, with or without spironolactone.

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**References**


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