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.5 Spironolactone has been shown to lower BP and affects hypertensive organ damage positively, the latter, in part, occurring BP independently.6 Despite 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) trial7 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.8 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, and 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).9 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-15,3 serum creatinine increased and in parallel, creatinine clearance decreased significantly, between-group differences were borderline significant. Furthermore, 1 patient with diabetic nephropathy developed 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,\(^1\) 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.\(^1\) Baseline SBP has been identified as a predictor of response to treatment. The fact that baseline BP (office, 159 mmHg; 24-hour, 149 mmHg) was lower compared with previous published trials might, in part, account for the smaller BP-lowering effect after the procedure.\(^1\)

In PRAGUE-15 included patients with mild to moderate resistant hypertension (office BP at baseline, >140 mmHg; 24-hour BP at baseline, >130 mmHg). Preliminary data indicate that the effect in those patients is less pronounced compared with patients with severe resistant hypertension.\(^2\) 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.\(^3\) 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,\(^4\) which did not meet its primary efficacy endpoint, showed that the number of radiofrequency ablations and circumferential treatment correlated positively to BP response.\(^5\) In the present study, experienced and well-trained interventionists performed all renal denervation procedures using a monopolar radiofrequency device. However, in 7 patients (14%) undergoing renal denervation, the recommended number of complete radiofrequency ablations (≥4 per side) was not reached, of which 2 had only unilateral ablations. Interestingly, when comparing the small group of patients with <4 ablations per side to the group with ≥4 ablations per side, the BP and heart rate changes were numerically higher in the latter (office SBP, −4.7 versus −14.0 mmHg; office diastolic BP, +0.9 mmHg versus −9.2 mmHg; 24-hour SBP, −5.0 versus −9.2 mmHg; heart rate, +1.2 versus −4.4 beats per minute). The between-group differences were not statistically significant. The authors of PRAGUE-15\(^6\) analyzed their data according to the intention-to-treat principle, an approach that is objectionable in face of a relatively small number of patients and the obvious pilot character of the study because of its premature stop. Per-protocol analyses with exclusion of patients receiving suboptimal treatment could have provided interesting insights. New renal denervation catheter developments and scientifically sound treatment recommendations might help to increase treatment success further. Although, the 6-month results of PRAGUE-15\(^6\) confirmed the safety of renal denervation, currently available and next generation renal denervation devices have to show favorable safety profiles, especially long-term vascular safety because concerns have been raised that the procedure might induce renal artery stenosis.

The role of aldosterone antagonist treatment in patients undergoing renal denervation is of special interest. A European multicenter study documented a significant reduction in the mean 24-hour BP by 11.9/7.1 mmHg (both \(P<0.001\)) in the subgroup of patients (n=78), who were treated with spironolactone, which was comparable with the BP reduction in the entire cohort (n=346). Interestingly, post hoc analyses from the Symplicity HTN-3 trial\(^5\) identified prescription of an aldosterone antagonist at baseline as a positive predictor for increasing change in office SBP over time. One could argue that renal denervation contributes an additive BP-lowering effect to the pre-existing neurohormonal blockade in patients treated with aldosterone antagonists. In light of concerns about the long-term safety of spironolactone, and the fact that not all patients respond to such treatment, controversy exists whether the use of aldosterone antagonists is a prerequisite eligibility criterion to undergo renal denervation. Indeed, both the European Society of Cardiology\(^6\) and the European Hypertension Society consensus documents\(^7\) do not generally recommend that only patients in whom treatment with mineralocorticoid receptor antagonists has failed should be considered for renal denervation. Preliminary data from a Spanish group, although, suggests that renal denervation can effectively lower office and 24-hour BP in patients not responding to spironolactone therapy.\(^8\)

**What Next?**

In this issue, the findings presented by Rosa et al\(^5\) 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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