The overall prevalence of hypertension in adults globally is estimated to be 30–45% with even higher rates of >60% in people aged above 60 years (1). It is expected that the number of people with hypertension will further grow by 15% to 20% and reach ~1.5 billion in 2025 (2). A systolic blood pressure (BP) ≥140 mmHg contributes substantially to the mortality and disability burden (70%), mostly related to ischemic and hemorrhagic stroke (1.5 and 2 million, respectively), and ischemic heart disease (4.9 million) (3). While lifestyle modification and antihypertensive (AH) pharmacotherapy are highly effective in reducing elevated BP, many patients remain uncontrolled due to a variety of reasons including non-adherence and non-compliance, intolerance to prescribed drugs, or true treatment resistance. Some of these patients may benefit from novel interventional procedures such as catheter-based renal denervation (RDN) as a suitable alternative.

Indeed, initial proof-of-concept studies and randomized controlled clinical trials (Symplicity HTN-1 and HTN-2) demonstrated significant BP-lowering efficacy as add on therapy to concomitant drug therapy (4,5). However, the randomized, blinded, sham-controlled Symplicity HTN-3 trial (6) failed to demonstrate the superiority of RDN in BP-lowering compared to a sham control group at 6 months post procedure. The unexpected results of the Symplicity HTN-3 trial have been extensively discussed and attributed to some possible confounding factors (7) which were taken into account in the design of studies in the post-Symplicity HTN-3 era.

A decade after the publication of the original proof-of-concept RDN study (4) recent evidence from appropriately designed trials have resulted in a renewed interest in RDN. These include the DENERHTN trial (8), the SPYRAL HTN-OFF MED (9) and RADIANCE-HTN SOLO (10) trials, both in drug-naïve hypertensive patients, as well as the SPYRAL HTN-ON MED trial (11) in hypertensive patients on concomitant AH therapy. All of these studies demonstrated a significant and clinically relevant reduction in ambulatory BP compared to respective control groups. Evidence is, therefore, now available from a number of properly designed, randomized, sham-controlled trials confirming the BP-lowering efficacy of a catheter-based RDN approach (12). Based on findings from recent large scale outcome studies a decrease in office BP of around 10 mmHg, as achieved in these RDN trials, if maintained in the long-term, would likely be associated with a reduction in cardiovascular (CV) events by ~25%.

Very recently, an updated study-level meta-analysis of all published sham-controlled randomized trials evaluated the effect of RDN on BP in uncontrolled hypertensive subjects (13). Six trials (Table 1) that met the inclusion and exclusion criteria were identified by the authors. These trials involved a total of 977 participants (582 randomized to RDN and 395 to sham). Four out of 6 trials allowed...
<table>
<thead>
<tr>
<th>1st author or trial name (Ref.)</th>
<th>Total patients (RDN/Sham)</th>
<th>Follow-up duration (Months)</th>
<th>Denervation method</th>
<th>Enrollment period</th>
<th>Participating centers</th>
<th>Trial design</th>
<th>Endpoints</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desch et al. (14)</td>
<td>32/35</td>
<td>6</td>
<td>RF ablation¹</td>
<td>06/2012 to 01/2014</td>
<td>Single-centre, Leipzig, Germany</td>
<td>Sham-controlled, randomized, single-center trial</td>
<td>The primary efficacy endpoint was the change in 24-hour systolic ABPM at 6 months between groups in the intention to treat population</td>
<td>There were no deaths, other serious adverse events, or vascular complications</td>
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<tr>
<td>RADIANCE-HTN SOLO (10)</td>
<td>74/72</td>
<td>2</td>
<td>Endovascular Ultrasound²</td>
<td>03/28/2016 to 12/28/2017</td>
<td>21 US hospitals and 18 European centres</td>
<td>Sham-controlled, randomized, single-blind trial</td>
<td>The primary effectiveness endpoint was the change in daytime ABPM at 2 months in the intention-to-treat population</td>
<td>No major adverse events occurred and reported adverse events were infrequent</td>
</tr>
<tr>
<td>ReSET (15)</td>
<td>36/33</td>
<td>6</td>
<td>RF ablation³</td>
<td>NA</td>
<td>Single-centre, Skejby, Denmark</td>
<td>Sham-controlled, randomized, double-blind, single-center trial</td>
<td>The primary efficacy endpoint was defined as the mean change in daytime systolic ABPM from baseline to 3 months in the RDN group as compared with the sham group</td>
<td>No procedural complications were reported apart from two cases of self-limiting femoral hematoma. A few patients reported adverse reactions during follow-up. One RDN patient and two SHAM patients were shortly hospitalized during follow-up due to increasing BPs. One sham patient suffered a stroke and one sham patient had a percutaneous coronary intervention due to unstable angina. Both incidents occurred several weeks after the sham procedure and were not considered procedure related</td>
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<tr>
<td>SPYRAL HTN-OFF MED (9)</td>
<td>38/42</td>
<td>3</td>
<td>RF ablation³</td>
<td>06/25/2015 to 01/30/2017</td>
<td>21 US centres, Europe, Japan, and Australia</td>
<td>Proof-of-concept, sham-controlled, randomized, single-blind, trial</td>
<td>The primary efficacy endpoint was the BP reduction based on ABPM measurements assessed at 3 months</td>
<td>No major procedural or clinical safety events were observed in either RDN or sham control groups throughout the 3 months</td>
</tr>
<tr>
<td>SPYRAL HTN-ON MED (11)</td>
<td>38/42</td>
<td>6</td>
<td>RF ablation³</td>
<td>07/22/2015 to 06/14/2017</td>
<td>25 centres in the US, the UK, Germany, Greece, Austria, Japan, and Australia</td>
<td>Proof-of-concept, sham-controlled, randomized, single-blind, trial</td>
<td>The primary efficacy endpoint was BP change from baseline, based on ABPM assessed at 6 months, as compared between treatment groups</td>
<td>No procedural and safety events through 6 months follow up were reported</td>
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Table 1 (continued)
the maintenance of stable optimal medical therapy in both groups, while two trials enrolled individuals who were off AH drugs for at least 3–4 weeks prior to randomization. The three trials applying second-generation RDN devices—SPYRAL HTN-ON MED, SPYRAL HTN-OFF MED, and RADIANCE-HTN SOLO, were designed and performed RDN with more attention to procedural techniques, the number of ablations, monitoring of adherence in some, and appropriate patient selection. The Symplicity HTN-3 trial provided ~55% of all patients included in this meta-analysis. Mean patients age ranged from ~53 to 65 years, 54–87% were male, and median follow-up ranged from 2 to 6 months. Five trials used radiofrequency (RF) energy and 1 used ultrasound for RDN (Table 1).

Importantly, all studies used ambulatory BP measurements as the primary endpoint, which has been shown to be superior to office measurements at predicting CV events (16,17). The meta-analysis revealed that reductions in 24-h ambulatory systolic blood pressure (ASBP) were significantly greater with RDN than sham procedures (weighted mean differences: \(WMD = -3.65 \text{ mmHg}, 95\% \text{ CI: } -5.33 \text{ to } -1.98 \text{ mmHg}; P<0.0001; I^2 = 0\%\)) (Figure 1A). RDN was also associated with a significant decrease in 24-h ambulatory diastolic blood pressure (ADBP) compared with the sham group (\(WMD = -1.71 \text{ mmHg}, 95\% \text{ CI: } -3.06 \text{ to } -0.35 \text{ mmHg}; P=0.01; I^2 = 38\%\)) (Figure 1B) (13). In addition, both daytime ASBP (\(WMD = -4.07 \text{ mmHg}, 95\% \text{ CI: } -6.46 \text{ to } -1.68 \text{ mmHg}; P<0.001; I^2 = 31\%\)) and daytime ADBP (\(WMD = -1.57 \text{ mmHg}, 95\% \text{ CI: } -2.73 \text{ to } -0.42 \text{ mmHg}; P=0.008; I^2 = 0\%\)) were substantially decreased by RDN in comparison to sham procedures. Changes in night-time ASBP and ADBP were similar between RDN and sham procedures.

The RDN office systolic (\(WMD = -5.53 \text{ mmHg}, 95\% \text{ CI: } -8.18 \text{ to } -2.87 \text{ mmHg}; P<0.001; I^2 = 0\%\)) and diastolic (\(WMD = -3.37 \text{ mmHg}, 95\% \text{ CI: } -4.86 \text{ to } -1.88 \text{ mmHg}; P<0.001; I^2 = 0\%\)) BP-lowering effect was also superior in comparison to sham procedures.

The ASBP fall caused by RDN was consistent regardless of whether AH drugs were present. Compared with first-generation trials, a significantly more significant reduction of daytime ASBP was observed with RDN in second-generation trials (\(6.12 \text{ vs. } 2.14 \text{ mmHg}; P \text{ interaction } = 0.04\)), but no interaction was described for 24-h ASBP, night-time ASBP or office BP. The ADBP reduction achieved by RDN was statistically significant only in second-generation trials (\(WMD = -2.98 \text{ mmHg}, 95\% \text{ CI: } -5.10 \text{ to } -0.86 \text{ mmHg}; P=0.006\)).

No significant difference in the changes from baseline

### Table 1 (continued)

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<tr>
<td>1</td>
<td>Symplicity HTN-3 (6)</td>
<td>364/171</td>
<td>6</td>
<td>10/2011 to 05/2013 US</td>
<td>RF ablation</td>
<td>Prospective, single-blind, randomized, sham-controlled trial</td>
<td>The primary efficacy endpoint was the mean change in office systolic BP from baseline to 6 months in the denervation group (0.14%), and 6 months in the sham group (0.6%), for a difference of 0.8 percentage points (95% CI: 0.9 to 2.5; P=0.67).</td>
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<td>Symplicity HTN-3 (6)</td>
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<td>4</td>
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Figure 1 24-h ambulatory systolic and diastolic blood pressure changes with RSD versus sham-controlled group. (A) Ambulatory systolic blood pressure (mmHg); (B) ambulatory diastolic blood pressure (mmHg). The size of central markers reflects the weight of each study. CI, confidence interval; IV, inverse variance; RADIANCE-HTN SOLO, a study of the ReCor medical paradise system in clinical hypertension; ReSET, renal sympathetomy in treatment resistant essential hypertension, a sham controlled randomized trial; RSD, renal sympathetic denervation; SPYRAL HTN-OFF MED, global clinical study of renal denervation with the Symplicity Spyral™ multi-electrode renal denervation system in patients with uncontrolled hypertension in the absence of antihypertensive medications; SPYRAL HTN-ON MED, global clinical study of renal denervation with the Symplicity Spyral™ multi-electrode renal denervation system in patients with uncontrolled hypertension on standard medical therapy. With permission from (13).

in estimated glomerular filtration rate between the RDN and sham procedure groups in first- or second-generation trials was demonstrated. No major periprocedural adverse events were reported in either group in 5 trials. Symplicity HTN-3 reported significant adverse events in 1.4% of the RDN group and 0.6% of the sham-controlled group. Meta-regression with multiple covariates did not detect any confounding factors/effect modifiers for changes in ASBP.

To put these findings into context, it is worthwhile to compare the BP-lowering effect of RDN with those of commonly used AH drugs in placebo-controlled trials. Indeed, a recent meta-analysis of 52 placebo-controlled studies, including 9,500 patients found that a variety of AH drug regimens reduced ASBP and office SBP by 1.4 and 4.6 mmHg, respectively (18). While perhaps not directly comparable, findings from these two meta-analyses comparing RDN vs. AH drug treatment with their relevant controls (sham and placebo, respectively) do indicate that the ASBP-lowering effect of RDN may be superior to that of a single AH drug (~2.5 times the effect size). Assuming that the BP-lowering effect of RDN is consistently observed and durable, this approach may offer several benefits over time and overcome the inherent limitations of AH drug therapy including drug intolerance, non-adherence, and variability in BP control due to trough levels (11). AH medications have produced less pronounced effects on BP in placebo-controlled when compared with non-placebo controlled single-arm studies. Likewise, RDN demonstrated a more
pronounced reduction in BP in single-arm studies, which evaluated pre- and post-RDN treatment effects (19,20).

An obvious question in this context is whether RDN is ready for more widespread clinical use. The latest RDN trials have been designed in collaboration with the US Food and Drug Administration and are still considered proof-of-concept studies to be extended into pivotal trials as currently ongoing. The results presented in the aforementioned meta-analysis, however, reinforce the safety and efficacy of RDN for BP reduction and emphasize the importance of incorporating relevant modifications into trials design (e.g., randomized sham-controlled trials, selection of patients with combined systolic and diastolic hypertension rather than isolated systolic hypertension (21), procedural techniques employed, AH drugs regimen prescribed, highly experienced operators, endpoint ascertainment, and others). Longer-term follow up will be required to ultimately determine the vascular safety of RDN. The ongoing pivotal studies have incorporated these features and will provide more robust and much-needed evidence to inform several remaining questions and will allow appropriate positioning of RDN as an alternative approach to lower BP in clinical medicine.

Acknowledgments

None.

Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References
