

Is There a Role for Device Therapies in Resistant Hypertension?

The CON Side

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In this piece, I will argue that device-based therapies for resistant hypertension (RH), although interesting and meritorious of further study, do not yet deserve a prominent role in the management of patients with RH. This argument is on the basis of the limited availability of controlled studies using devices, the cost and uncertain long-term effectiveness of device modalities, and the successful track record of medical therapy.

First, let me define the demand for advanced therapies in RH. RH is defined as the BP of a hypertensive patient that remains above goal despite the concurrent use of three antihypertensive agents of different classes, preferably including a blocker of the renin-angiotensin system, a calcium channel blocker, and a thiazide-type diuretic (1). The prevalence of RH in the general hypertensive population is 12%–18%, on the basis of office BP measurements >140/90 mm Hg (1), an estimate that is expected to increase by approximately 2% when the 130/80 mm Hg threshold is applied to high-risk patients (2). Approximately one third of these patients have normal 24-hour BP (1), and a sizable portion is nonadherent to prescribed medications; therefore, approximately 5%–10% of hypertensive patients would ultimately qualify as having true RH. The current approach to the treatment of RH calls for adequate dosing of complementary medications, preferential use of long-acting thiazide diuretics (e.g., chlorthalidone), and the addition of a mineralocorticoid antagonist (e.g., spironolactone) (1). When such a strategy is used, BP goal is achieved in up to 90% of patients (3). Hence, about 0.5%–1% of hypertensive patients (approximately 750,000–1.5 million adults in the United States) would benefit from alternative approaches to treatment, such as referral to hypertension specialists for more advanced drug combinations or the use of device therapies.

I acknowledge the importance of treatment nonadherence and medication intolerance in RH. Nonadherence is present in 7%–60% of patients with RH (1). Intolerance to antihypertensive medications leading to treatment discontinuation is present in 7%–17% of unselected patients participating in clinical trials (4), and intolerance to three or more drug classes has been

documented in approximately 3% of patients attending a hypertension clinic (5). Unfortunately, limited data are available on device therapy in this subgroup of patients. An uncontrolled, multinational study of renal denervation (RDN) in 53 patients not receiving antihypertensive drugs, of which 30 were due to intolerance to medications, observed a 5.7/4.0 mm Hg reduction in 24-hour BP 6 months after RDN, with high variability in responses (6). Therefore, although this is an area of opportunity, available data do not yet allow recommendations for use.

As noted in the Table 1, several device therapies have been studied in RH. All have been consistently effective in uncontrolled studies, but controlled trials have been negative or not yet completed. Some of the technologies, such as externally delivered ultrasound for RDN or central arteriovenous fistula creation, have been recently removed from further development because of lack of efficacy or complications. Baroreflex activation therapy is a technology that involves use of a device designed to produce chronic stimulation of the carotid sinus, resulting in prolonged decrease in sympathetic tone (7). Baroreflex activation therapy holds some promise on the basis of long-term results (up to 6 years of follow-up) of a previously used device (CVRx Rheos; CVRx, Minneapolis, MN), which was associated with excessive local complications at the time of implantation and is no longer available (8,9). The device currently undergoing testing (Barostim Neo, also produced by CVRx) provides advancements that minimize procedural complications (smaller lead, unilateral implantation) and battery longevity (3 years), and the US Food and Drug Administration recently approved it for use in advanced heart failure. Uncontrolled results in RH are encouraging (10) (Table 1); however, given the substantial changes in hardware design, it cannot be accepted as equivalent to the older device until controlled studies are available. Differently from other technologies, percutaneous (endovascular) RDN has been adequately studied, both in clinical trials and large registries. Therefore, the current state of affairs in device therapy impedes extension of clinical use beyond RDN, so I will restrict further discussion solely to RDN.

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Table 1. Summary of device therapies used in resistant hypertension

| Therapy | Technique/Device | Comments |
|--|--|---|
| Catheter-based renal denervation | Radiofrequency ablation, RFA (Symplicity ^a , Spyral ^b) Intravascular high-frequency ultrasound ablation, US (Paradise ^b) Transarterial alcohol ablation (Peregrine ^c) | Approved for use in hypertension in several continents. Modest BP reduction (24-h BP decrease by 4.1–4.6/1.8–4.3 mm Hg at 3 mo) in patients not on medications (RFA [12], US [11]). Extensive uncontrolled registry data show sustained efficacy in hypertension (25). Only a sham-controlled, randomized trial in resistant hypertension did not show difference (24-h BP difference 2.0/1.0 mm Hg at 6 mo) (24,34). |
| Renal denervation with external ultrasound | Externally delivered ultrasound waves directed at the renal sympathetic nerves ^d | After initial favorable results in an uncontrolled study (35), a sham-controlled trial was prematurely terminated for lack of efficacy on BP (24-h BP reduction at 24 wk 1.2/0.5 mm Hg versus sham) (36). |
| Baroreflex amplification device | MobiusHD device ^e | Significant 24-h BP reduction after 6 mo (21/12 mm Hg) in proof-of-concept, uncontrolled trial (37). No controlled studies available yet (ongoing). |
| Baroreflex activation therapy | CVRx Barostim Neo device ^f | Approved for hypertension treatment in Europe. Approved by FDA for use in advanced heart failure in August 2019. Significant office BP reduction at 6 mo (26.0/12.4 mm Hg) in an uncontrolled study (10). An older device version has sustained efficacy in RH (8,9) but high implantation complication rates (8). Ongoing randomized trials with Barostim Neo device. |
| Central arteriovenous fistula creation | ROX coupler device ^g | Significant 24-h BP reduction after 6 mo (13.5/14.6 mm Hg) (38) and 1 yr (12.6/15.3 mm Hg) (39) in a controlled RH study (control group was usual care, not a sham procedure). Company terminated device trial in May 2019 owing to increased risk of heart failure. No longer in development. |

RFA, radiofrequency ablation; US, ultrasound; RH, resistant hypertension.

^aMedtronic, Dublin, Ireland.

^bReCor Medical, Palo Alto, CA.

^cAblative Solutions, San Jose, CA.

^dKona Medical, Issaquah, WA.

^eVascular Dynamics, Mountain View, CA.

^fCVRx, Minneapolis, MN.

^gROX Medical, San Clemente, CA.

Efficacy of RDN in Untreated and Nonresistant Hypertension

RDN resulted in a 24-hour BP reduction of 5.5–7.0/4.4–4.8 mm Hg (4.1–4.6/1.8–4.3 mm Hg when sham-adjusted) in two sham-controlled trials of untreated hypertensive patients, serving as biologic proof-of-concept that the intervention lowers BP (11,12). Likewise, RDN produced a 9.0/6.0 mm Hg reduction in 24-hour BP (7.4/4.1 mm Hg when sham-adjusted) in a sham-controlled study of patients

receiving one to three antihypertensive medications (13). However, the observed effect size observed in these trials is relatively small when compared with the effects of antihypertensive agents in similar populations, as shown by a meta-analysis of 15,289 patients receiving monotherapy with angiotensin receptor blockers documenting an average 24-hour BP reduction of 13.0/8.3 mm Hg (14). Therefore, it appears that the overall effect of RDN in uncomplicated hypertension is less than that of standard antihypertensive medications.

Efficacy of RDN in RH

Several recent meta-analyses evaluated the effect of RDN on uncontrolled or resistant hypertension, with variable results because of different methodology of study selection (15–18). Three of the meta-analyses did not find a significant effect of RDN on BP (15,17,18). However, I believe that it is the recently published meta-analysis by Cheng *et al.* that is most relevant to catheter-based RDN (16). The authors included 12 randomized, controlled trials with more than 40 hypertensive patients (six trials with sham procedure control) that reported ambulatory BP results during follow-up (2–6 months, mean 5.4 months) (16). Their meta-analysis was not restricted to RH; three of the 12 studies were not in RH patients, and one was of RH in patients with sleep apnea. They found a significant decrease in average 24-hour BP of 4.0/2.1 mm Hg (95% confidence interval, –2.6 to –5.5/–1.1 to –3.1 mm Hg) after RDN, with most studies finding numeric reductions in BP, but they were statistically significant in only six out of 12 studies (16). Therefore, the overall effect of RDN in RH is modest in the best-case scenario, and insignificant in other analyses.

Comparative Effects of RDN against Guideline-Directed Management of RH

On the basis of current consensus by leading hypertension specialists (1), aldosterone antagonists are the cornerstone of the treatment of RH, thus it follows that any proposed comparison of treatment efficacy in RH must be against aldosterone antagonists. A meta-analysis of the add-on effect of spironolactone in RH showed a BP reduction of 8.7/4.1 mm Hg (95% confidence interval, –8.6 to –8.8/–3.8 to –4.5 mm Hg) (19). In addition, the tolerability of spironolactone in RH clinical trials is quite good. In the PATHWAY-2 trial, overall adverse events (19%) and discontinuation due to side effects (1%) were similar to placebo (15% and 1%, respectively) (20). In the Anglo-Scandinavian Cardiac Outcomes Trial–BP Lowering Arm (ASCOT-BPLA), spironolactone was added as fourth drug in 1411 patients who remained uncontrolled on standard therapy (21). After a median exposure of 1.3 years, spironolactone was discontinued due to side effects in only 6% of patients. In contrast, data from a randomized trial of RDN versus optimized medical therapy including preferential use of spironolactone showed a high intolerance rate to spironolactone (39%) (22).

It is estimated that only about 30% of patients with RH would not qualify for aldosterone antagonist therapy on the basis of baseline low renal function (eGFR < 50 ml/min) or serum potassium > 4.5 mmol/L (23). Despite these estimates, guideline-concordant therapy using aldosterone antagonists is low in clinical trials and registries of RDN in RH (23%–26%) (22,24–26). Understanding the impact of use of aldosterone antagonists on the effect of RDN in RH is essential to define the value of RDN. Data from three clinical trials help fill this gap. The Czech study PRAGUE-15 randomized 106 patients with RH to either RDN or medical therapy that included spironolactone if tolerated (22). At baseline, 25% of patients in the RDN group were taking an aldosterone antagonist and remained on it. In the medical therapy group, 24% were on one at baseline, and 61% were receiving spironolactone at 6 months (39% did not tolerate it due to hyperkalemia [11%] or other side effects). Both

interventions resulted in similar reductions in average 24-hour BP at 6 months (8.6/5.7 mm Hg for RDN, 8.1/4.5 mm Hg for medical therapy; $P=0.87/0.48$) (22). The PRAGUE-15 investigators have published updated results after 12 and 24 months of follow-up showing persistence of effects and numerically better BP control in patients who continue to tolerate spironolactone (although not statistically significant) (27,28); findings also extended to patients who crossed over to the opposite group after 1 year (28).

The much smaller Spanish trial Denervacion en Hipertension Arterial randomized 24 patients with RH to RDN or spironolactone (25 mg daily, force-titrated to 50 mg daily after 1 month) (29). After 6 months, spironolactone resulted in a much larger 24-hour BP reduction than RDN (17.9/6.6 mm Hg in favor of spironolactone, $P=0.01/0.04$).

The third study was the French trial Renal Denervation in Hypertension (DENER-HTN), which randomized 106 patients with RH to either stepped medical therapy starting with spironolactone, followed by the addition of bisoprolol, prazosin, and rilmenidine, or to the same stepped therapy plus RDN (30). At 6 months, the 24-hour BP was 5.9/3.1 mm Hg lower in the RDN group ($P=0.02/0.05$), and BP control rates were higher in the RDN group (40% versus 19% on the basis of 24-hour BP; $P=0.03$). Most patients had similar progressive escalation of medications, and at the end of the study 79% of patients in both groups were receiving spironolactone (30).

My interpretation of these three relevant studies is that RDN is equivalent at best, and inferior at worst, than spironolactone-based treatment of RH. However, DENER-HTN suggests that RDN may provide additional BP control when added to a stepped medical therapy that includes spironolactone (30). A corollary to this would be that there might be value of RDN in patients who remain uncontrolled despite adequate doses of an aldosterone antagonist.

Safety and Cost Considerations

Bilateral RDN is performed under 60 minutes with the administration of approximately 129 ± 78 ml of contrast (25). Among 998 procedures in the Global SYMPPLICITY Registry, there were six peri-procedural complications (two renal artery dissections, three femoral artery pseudoaneurysms, and one groin hematoma) (31). The long-term safety of RDN has also been evaluated through clinical registries. One-year follow-up of 2112 patients identified three cases of *de novo* renal artery stenosis (0.1%), 19 cases of 50% increase in serum creatinine (0.9%), and nine cases of progression to ESKD (0.4%) (25). Extended follow-up to 3 years ($N=1345$) revealed a total of four cases of renal artery stenosis (0.3%), 24 cases of increased serum creatinine (2%), and 23 cases of ESKD (2%) (25). Fifty nine (4%) patients died after 3 years, 29 of which were due to cardiovascular causes. Unfortunately, these are not controlled data, so we cannot contextually interpret the magnitude of these findings. However, given the high complexity of this population, I suspect these numbers to do not reflect any increase in complication rates. Overall, my sense is that, in experienced hands, RDN is a safe procedure. However, one key area that requires further study is the adequacy of BP response to acute hypotensive illnesses (hemorrhage, sepsis) in patients who have undergone RDN. Hypertensive sheep treated with RDN

exhibit larger BP reduction and blunted heart rate and plasma renin activity responses during hemorrhage (32). Clarification of this important question in patients who have undergone RDN is an essential element of the safety evaluation of the procedure.

A recent Australian study addressed the issue of cost-effectiveness of RDN (33). Using a model assumption of 24-hour systolic BP reduction of 5.7 mm Hg and procedural costs of AU\$9531 (approximately US\$6484), RDN would result in acceptable costs per quality-adjusted life years when the baseline 10-year cardiovascular risk was >13% (33). The major problem with the applicability of this analysis to the United States is the cost estimate, which is likely to be much higher than the authors' imputed value on the basis of costs in Australia. In addition, they did not include the likelihood of reintervention. Despite the known regrowth of renal nerves within months of surgical denervation in humans and experimental animals (7), 3-year registry data show that only 10 patients (0.6%) were subjected to reintervention (25). Whether this will change over longer-term follow-up remains unknown. Because patients who undergo RDN require similar clinical follow-up as patients on medical therapy (office visits, laboratory testing for renal function and electrolytes) and may also require periodic imaging of the renal arteries, clinical costs at follow-up are likely to be higher than for medically treated patients.

Conclusions

RDN is the only device modality with enough data for detailed discussion at this time. Available data indicate a modest BP reduction that is sustained over at least 3 years with a good safety profile and infrequent need for reintervention. However, the observed efficacy and safety of aldosterone antagonists make them the first choice in RH. RDN may be considered in patients who remain resistant despite aldosterone antagonists. Perhaps the greatest value of device therapies will be in patients who are intolerant to medications, although this use has not yet been adequately studied. Therefore, I must conclude that device therapies do not yet deserve a prominent role in the management of hypertension, whether resistant or not.

Author Contributions

A. Peixoto conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

Disclosures

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References

- Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, Egan BM, Flack JM, Gidding SS, Judd E, Lackland DT, Laffer CL, Newton-Cheh C, Smith SM, Taler SJ, Textor SC, Turan TN, White WB; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease;

Council on Quality of Care and Outcomes Research; and Stroke Council: Resistant hypertension: Detection, evaluation, and management: A scientific statement from the American Heart Association. *Hypertension* 72: e53–e90, 2018

- Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P: Prevalence of apparent treatment-resistant hypertension in the United States. *Hypertension* 73: 424–431, 2019
- Acelajado MC, Pisoni R, Dudenbostel T, Dell'Italia LJ, Cartmill F, Zhang B, Cofield SS, Oparil S, Calhoun DA: Refractory hypertension: Definition, prevalence, and patient characteristics. *J Clin Hypertens (Greenwich)* 14: 7–12, 2012
- Ross SD, Akhras KS, Zhang S, Rozinsky M, Nalysnyk L: Discontinuation of antihypertensive drugs due to adverse events: A systematic review and meta-analysis. *Pharmacotherapy* 21: 940–953, 2001
- Okeahialam BN: Multidrug intolerance in the treatment of hypertension: Result from an audit of a specialized hypertension service. *Ther Adv Drug Saf* 8: 253–258, 2017
- De Jager RL, Sanders MF, Bots ML, Lobo MD, Ewen S, Beefink MM, Böhm M, Daemen J, Dörr O, Hering D, Mahfoud F, Nef H, Ott C, Saxena M, Schmieder RE, Schlaich MP, Spiering W, Tonino PA, Verloop WL, Vink EE, Voncken EJ, Voskuil M, Worthley SG, Blankestijn PJ: Renal denervation in hypertensive patients not on blood pressure lowering drugs. *Clin Res Cardiol* 105: 755–762, 2016
- Lohmeier TE, Hall JE: Device-based neuromodulation for resistant hypertension therapy. *Circ Res* 124: 1071–1093, 2019
- Bisognano JD, Bakris G, Nadim MK, Sanchez L, Kroon AA, Schafer J, de Leeuw PW, Sica DA: Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: Results from the double-blind, randomized, placebo-controlled rheos pivotal trial. *J Am Coll Cardiol* 58: 765–773, 2011
- de Leeuw PW, Bisognano JD, Bakris GL, Nadim MK, Haller H, Kroon AA; DEBuT-HT and Rheos Trial Investigators: Sustained reduction of blood pressure with baroreceptor activation therapy: Results of the 6-year open follow-up. *Hypertension* 69: 836–843, 2017
- Hoppe UC, Brandt MC, Wachter R, Beige J, Rump LC, Kroon AA, Cates AW, Lovett EG, Haller H: Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: Results from the Barostim Neo trial. *J Am Soc Hypertens* 6: 270–276, 2012
- Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, Basile J, Kirtane AJ, Wang Y, Lobo MD, Saxena M, Feyz L, Rader F, Lurz P, Sayer J, Sapoval M, Levy T, Sanghvi K, Abraham J, Sharp ASP, Fisher NDL, Bloch MJ, Reeve-Stoffer H, Coleman L, Mullin C, Mauri L; RADIANCE-HTN Investigators: Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): A multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 391: 2335–2345, 2018
- Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, Ewen S, Tsioufis K, Tousoulis D, Sharp ASP, Watkinson AF, Schmieder RE, Schmid A, Choi JW, East C, Walton A, Hopper I, Cohen DL, Wilensky R, Lee DP, Ma A, Devireddy CM, Lea JP, Lurz PC, Fengler K, Davies J, Chapman N, Cohen SA, DeBruin V, Fahy M, Jones DE, Rothman M, Böhm M; SPYRAL HTN-OFF MED trial investigators*: Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): A randomised, sham-controlled, proof-of-concept trial. *Lancet* 390: 2160–2170, 2017
- Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, Tsioufis K, Tousoulis D, Choi JW, East C, Brar S, Cohen SA, Fahy M, Pilcher G, Kario K; SPYRAL HTN-ON MED Trial Investigators: Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 391: 2346–2355, 2018
- Makani H, Bangalore S, Supariwala A, Romero J, Argulian E, Messerli FH: Antihypertensive efficacy of angiotensin receptor blockers as monotherapy as evaluated by ambulatory blood pressure monitoring: A meta-analysis. *Eur Heart J* 35: 1732–1742, 2014

15. Agasthi P, Shipman J, Arsanjani R, Ashukem M, Girardo ME, Yerasi C, Venepally NR, Fortuin FD, Mookadam F: Renal denervation for resistant hypertension in the contemporary era: A systematic review and meta-analysis. *Sci Rep* 9: 6200, 2019
 16. Cheng X, Zhang D, Luo S, Qin S: Effect of catheter-based renal denervation on uncontrolled hypertension: A systematic review and meta-analysis. *Mayo Clin Proc* 94: 1695–1706, 2019
 17. Fadl Elmula FEM, Feng YM, Jacobs L, Larstorp AC, Kjeldsen SE, Persu A, Staessen JA; European Network COordinating research on Renal Denervation (ENCOReD): Sham or no sham control: That is the question in trials of renal denervation for resistant hypertension. A systematic meta-analysis. *Blood Press* 26: 195–203, 2017
 18. Pappaccogli M, Covella M, Berra E, Fulcheri C, Di Monaco S, Perlo E, Burrello J, Monticone S, Rossato D, Rabbia F, Veglio F: Effectiveness of renal denervation in resistant hypertension: A meta-analysis of 11 controlled studies. *High Blood Press Cardiovasc Prev* 25: 167–176, 2018
 19. Liu L, Xu B, Ju Y: Addition of spironolactone in patients with resistant hypertension: A meta-analysis of randomized controlled trials. *Clin Exp Hypertens* 39: 257–263, 2017
 20. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, Mackenzie I, Padmanabhan S, Brown MJ; British Hypertension Society's PATHWAY Studies Group: Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomised, double-blind, crossover trial. *Lancet* 386: 2059–2068, 2015
 21. Chapman N, Dobson J, Wilson S, Dahlöf B, Sever PS, Wedel H, Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial Investigators: Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 49: 839–845, 2007
 22. Rosa J, Widimský P, Toušek P, Petrák O, Čurila K, Waldauf P, Bednář F, Zelinka T, Holaj R, Strauch B, Somlóová Z, Táborský M, Václavík J, Kociánová E, Branny M, Nykl I, Jiravský O, Widimský J Jr: Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: Six-month results from the PRAGUE-15 study. *Hypertension* 65: 407–413, 2015
 23. Egan BM, Li J: Role of aldosterone blockade in resistant hypertension. *Semin Nephrol* 34: 273–284, 2014
 24. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators: A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 370: 1393–1401, 2014
 25. Mahfoud F, Böhm M, Schmieder R, Narkiewicz K, Ewen S, Ruilope L, Schlaich M, Williams B, Fahy M, Mancia G: Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. *Eur Heart J* 40: 3474–3482, 2019
 26. Fengler K, Rommel KP, Blazek S, Besler C, Hartung P, von Roeder M, Petzold M, Winkler S, Höllriegel R, Desch S, Thiele H, Lurz P: A three-arm randomized trial of different renal denervation devices and techniques in patients with resistant hypertension (RADIOSOUND-HTN). *Circulation* 139: 590–600, 2019
 27. Rosa J, Widimský P, Waldauf P, Lambert L, Zelinka T, Táborský M, Branny M, Toušek P, Petrák O, Čurila K, Bednář F, Holaj R, Strauch B, Václavík J, Nykl I, Krátká Z, Kociánová E, Jiravský O, Rappová G, Indra T, Widimský J Jr: Role of adding spironolactone and renal denervation in true resistant hypertension: One-year outcomes of randomized PRAGUE-15 study. *Hypertension* 67: 397–403, 2016
 28. Rosa J, Widimský P, Waldauf P, Zelinka T, Petrák O, Táborský M, Branny M, Toušek P, Čurila K, Lambert L, Bednář F, Holaj R, Strauch B, Václavík J, Kociánová E, Nykl I, Jiravský O, Rappová G, Indra T, Krátká Z, Widimský J Jr: Renal denervation in comparison with intensified pharmacotherapy in true resistant hypertension: 2-year outcomes of randomized PRAGUE-15 study. *J Hypertens* 35: 1093–1099, 2017
 29. Oliveras A, Armario P, Clarà A, Sans-Atxer L, Vázquez S, Pascual J, De la Sierra A: Spironolactone versus sympathetic renal denervation to treat true resistant hypertension: Results from the DENERVHTA study - a randomized controlled trial. *J Hypertens* 34: 1863–1871, 2016
 30. Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, Midulla M, Mounier-Véhier C, Courand PY, Lantelme P, Denolle T, Doumap-Collas C, Trillaud H, Pereira H, Plouin PF, Chatellier G; Renal Denervation for Hypertension (DENERHTN) investigators: Optimum and stepped care standardised anti-hypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): A multicentre, open-label, randomised controlled trial. *Lancet* 385: 1957–1965, 2015
 31. Böhm M, Mahfoud F, Ukena C, Hoppe UC, Narkiewicz K, Negoita M, Ruilope L, Schlaich MP, Schmieder RE, Whitbourn R, Williams B, Zeymer U, Zirlik A, Mancia G; GSR Investigators: First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. *Hypertension* 65: 766–774, 2015
 32. Singh RR, Sajeesh V, Booth LC, McArdle Z, May CN, Head GA, Moritz KM, Schlaich MP, Denton KM: Catheter-based renal denervation exacerbates blood pressure fall during hemorrhage. *J Am Coll Cardiol* 69: 951–964, 2017
 33. Chowdhury EK, Reid CM, Zomer E, Kelly DJ, Liew D: Cost-effectiveness of renal denervation therapy for treatment-resistant hypertension: A best case scenario. *Am J Hypertens* 31: 1156–1163, 2018
 34. Bakris GL, Townsend RR, Liu M, Cohen SA, D'Agostino R, Flack JM, Kandzari DE, Katzen BT, Leon MB, Mauri L, Negoita M, O'Neill WW, Oparil S, Rocha-Singh K, Bhatt DL; SYMPLICITY HTN-3 Investigators: Impact of renal denervation on 24-hour ambulatory blood pressure: Results from SYMPLICITY HTN-3. *J Am Coll Cardiol* 64: 1071–1078, 2014
 35. Neuzil P, Ormiston J, Brinton TJ, Starek Z, Esler M, Dawood O, Anderson TL, Gertner M, Whitbourne R, Schmieder RE: Externally delivered focused ultrasound for renal denervation. *JACC Cardiovasc Interv* 9: 1292–1299, 2016
 36. Schmieder RE, Ott C, Toennes SW, Bramlage P, Gertner M, Dawood O, Baumgart P, O'Brien B, Dasgupta I, Nickenig G, Ormiston J, Saxena M, Sharp ASP, Sievert H, Spinar J, Starek Z, Weil J, Wenzel U, Witkowski A, Lobo MD: Phase II randomized sham-controlled study of renal denervation for individuals with uncontrolled hypertension - WAVE IV. *J Hypertens* 36: 680–689, 2018
 37. Spiering W, Williams B, Van der Heyden J, van Kleef M, Lo R, Versmissen J, Moelker A, Kroon A, Reuter H, Ansel G, Stone GW, Bates M; CALM-FIM_EUR investigators: Endovascular baroreflex amplification for resistant hypertension: A safety and proof-of-principle clinical study. *Lancet* 390: 2655–2661, 2017
 38. Lobo MD, Sobotka PA, Stanton A, Cockcroft JR, Sulke N, Dolan E, van der Giet M, Hoyer J, Furniss SS, Foran JP, Witkowski A, Januszewicz A, Schoors D, Tsioufis K, Rensing BJ, Scott B, Ng GA, Ott C, Schmieder RE; ROX CONTROL HTN Investigators: Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): A randomised controlled trial. *Lancet* 385: 1634–1641, 2015
 39. Lobo MD, Ott C, Sobotka PA, Saxena M, Stanton A, Cockcroft JR, Sulke N, Dolan E, van der Giet M, Hoyer J, Furniss SS, Foran JP, Witkowski A, Januszewicz A, Schoors D, Tsioufis K, Rensing BJ, Scott B, Ng GA, Schmieder RE: Central iliac arteriovenous anastomosis for uncontrolled hypertension: One-year results from the ROX CONTROL HTN trial. *Hypertension* 70: 1099–1105, 2017
- See related commentary, "Is There Any Role for Device Therapies in Resistant Hypertension? Commentary" and debate, "Is There Any Role for Device Therapies in Resistant Hypertension? PRO," on pages 14–15 and 6–8, respectively.