



Renal Denervation Returns: Reading a Second Generation of Sham-Controlled Trials in Resistant Hypertension

Emeric Bonnetain^{1*}, Sigrun Hallgrimsdottir², Mirko Zanolli³

¹*Department of Hypertension, Breton Cardiovascular Centre, Rennes, France*

²*Department of Nephrology, Hekla Institute of Cardiovascular Medicine, Selfoss, Iceland*

³*Department of Interventional Cardiology, Friulian Institute of Cardiovascular Medicine, Trieste, Italy*

*Correspondence to: Emeric Bonnetain, Department of Hypertension, Breton Cardiovascular Centre, Rennes, France
E-mail: e.bonnetain@bcc-rennes.fr

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Introduction

Catheter-based renal denervation ablates sympathetic nerve fibres running along the renal artery wall, and had been expected to become a routine third option for resistant hypertension until the sham-controlled Symplicity HTN-3 trial found no significant benefit over sham in 2014. Rather than ending the field, that failure forced a redesign: newer catheters with confirmed circumferential ablation, pre-specified drug-adherence testing, and rigorous sham-procedure control. A second generation of trials built on this redesign has now reported, and its results are more interesting, and more genuinely uncertain, than either a simple vindication or a simple repeat failure.

This review reads three of these trials -- SPYRAL HTN-ON MED, SPYRAL HTN-OFF MED Pivotal, and RADIANCE-HTN TRIO -- alongside their long-term follow-up data, a meta-analysis restricted to second-generation devices, the responder-prediction literature, and the guideline and cost-effectiveness verdicts that have followed, to ask what a cardiologist managing resistant hypertension should actually take from this body of evidence.

Resistant hypertension -- blood pressure that remains above goal despite three or more antihypertensive drugs, including a diuretic -- affects a meaningful minority of treated hypertensive patients and carries excess cardiovascular risk beyond what BP level alone predicts, in part because of poor adherence, in part because of genuinely difficult-to-treat physiology. A device-based option that does not depend on

daily adherence is attractive for exactly this population, which is also why the honest size of its effect, and the open question of who benefits most, both matter more here than in a condition with abundant effective oral options.

Material and Methods

This is a narrative review drawing on the primary publications of SPYRAL HTN-ON MED, SPYRAL HTN-OFF MED Pivotal, and RADIANCE-HTN TRIO, their subsequent long-term follow-up reports, a meta-analysis of sham-controlled renal denervation trials with a second-generation subgroup, the 2024 ESC hypertension guideline, a systematic review of patient-level predictors of response, and a contemporary US cost-effectiveness analysis, identified through the sources cited here and citation tracking between them, without a pre-registered protocol or systematic search string. All percentages, mmHg values, hazard/odds estimates, and p-values reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated.

Results

SPYRAL HTN-ON MED: a real effect that behaves differently in office versus ambulatory BP

SPYRAL HTN-ON MED randomized 337 patients with uncontrolled hypertension on one to three antihypertensive drugs to renal denervation or a sham procedure, with drugs held constant and adherence confirmed by drug-level testing through the primary 6-month endpoint [1]. Office systolic BP fell by 9.9 mmHg with denervation versus 5.1 mmHg with sham (difference 4.8 mmHg, $p=0.001$), but the 24-hour ambulatory systolic difference was smaller and not statistically significant at 6 months (2.0 mmHg, $p=0.12$) [1]. Figure 1 sets both office and ambulatory results out together, alongside the other two trials reviewed here.

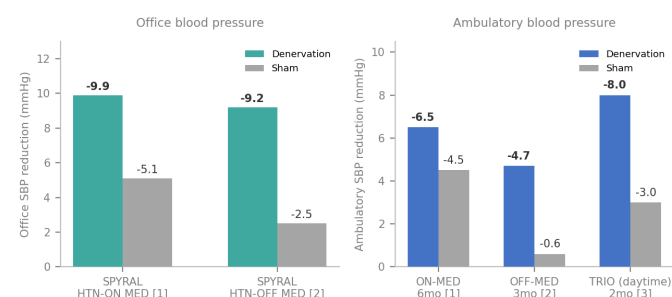


Figure 1: Office and ambulatory systolic BP reduction, denervation versus sham, across the three trials reviewed [1,2,3].

After 6 months, patients and investigators were unblinded and medications could be adjusted in both arms; by 24 months, average antihypertensive drug count had risen from about 2 to about 3 in both groups with no significant between-arm difference ($p=0.26$) [4]. Under these less-controlled conditions the office-BP difference actually shrank to 8.2 mmHg and lost formal statistical significance ($p=0.07$), while the 24-hour ambulatory difference grew to 10.0 mmHg and became significant ($p=0.004$) [4]. Figure 2 places these treatment effects, and the pooled second-generation estimate discussed below, on a single comparative scale, and Figure 3 tracks how the same trial's office and ambulatory effects moved in opposite directions between 6 and 24 months. At 24 months, 83.3% of the denervation group had 24-hour systolic BP below 140 mmHg versus 43.8% of the sham group ($p=0.002$) [4].

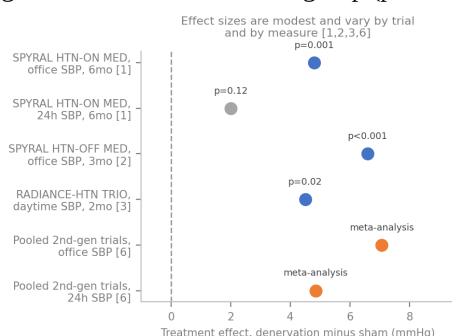


Figure 2: Between-group treatment effects (denervation minus sham) across the three trials and the pooled second-generation meta-analysis estimate [1,2,3,6].

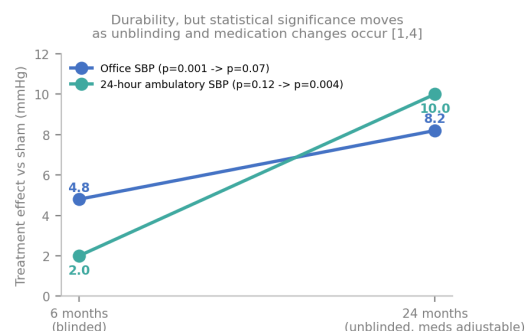


Figure 3: SPYRAL HTN-ON MED treatment effect from 6 to 24 months: office SBP loses formal significance as ambulatory SBP gains it [1,4].

SPYRAL HTN-OFF MED Pivotal: a cleaner signal without background drugs

Because concurrent antihypertensive drugs and their adjustment can obscure a device effect, SPYRAL HTN-OFF MED Pivotal tested denervation in 331 patients who were off all antihypertensive medication, with an office SBP of 150 to under 180 mmHg and a 24-hour ambulatory SBP of 140 to under 170 mmHg required at baseline [2]. At 3 months, office systolic BP fell by 9.2 mmHg with denervation versus 2.5 mmHg with sham (difference 6.6 mmHg, $p<0.001$), and 24-hour ambulatory systolic BP fell by 4.7 mmHg versus 0.6 mmHg (difference 4.0 mmHg, $p<0.001$) [2]. Safety through 3 months was reassuring: one hypertensive crisis requiring hospitalization occurred in the denervation arm and one new stroke occurred in the sham arm [2].

RADIANCE-HTN TRIO: a rigorously confirmed resistant-hypertension population

RADIANCE-HTN TRIO used ultrasound (rather than radiofrequency) energy and, unlike the two SPYRAL trials, enrolled a population whose resistant hypertension was confirmed by a run-in period rather than assumed at screening: of 989 patients initially assessed, 853 were excluded after being switched to a fixed-dose triple combination pill for 4 weeks, either because BP normalized on the pill or because daytime ambulatory BP fell below the 135/85 mmHg threshold required for randomization [3]. Figure 4 sets this selection funnel out in full. Only the remaining 136 patients (69 denervation, 67 sham) were randomized, and daytime ambulatory systolic BP fell by 8.0 mmHg with denervation versus 3.0 mmHg with sham at 2 months (difference 4.5 mmHg, $p=0.02$) [3]. Safety events through 2 months included one femoral access-site pseudoaneurysm requiring intervention, one sudden cardiac death judged unrelated to the procedure, and one transient acute kidney injury attributed to a co-administered diuretic rather than to denervation itself [3].

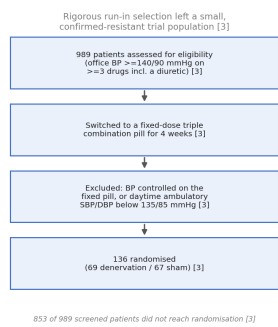


Figure 4: Patient selection funnel in RADIANCE-HTN TRIO: a confirmatory run-in excluded most screened patients before randomisation [3].

Durability, mechanism, and the honest size of the pooled effect

Figure 5 sets out the mechanism these three trials are testing: catheter-delivered radiofrequency or ultrasound energy ablates perivascular sympathetic afferent and efferent nerve fibres running along the renal artery wall, reducing renal and central sympathetic drive that contributes to resistant hypertension. At 36 months of single-arm follow-up after sham-arm crossover, RADIANCE-HTN TRIO patients maintained an office SBP reduction of 8.0 mmHg from baseline, alongside a modest rise in medication count (+0.6 drugs from baseline, p=0.004) and no new safety signal, including no clinically significant (greater than 50%) renal artery stenosis on site-reported imaging [5]. A meta-analysis restricted to second-generation trials (RADIANCE-HTN SOLO, SPYRAL HTN-OFF MED, and SPYRAL HTN-ON MED) estimates a pooled office systolic effect of 7.07 mmHg and a pooled 24-hour ambulatory effect of 4.85 mmHg, both larger than the pooled effect across all sham-controlled trials to date (office 5.53 mmHg, ambulatory 3.65 mmHg), consistent with genuine improvement in device and trial design since Symplicity HTN-3 [6].

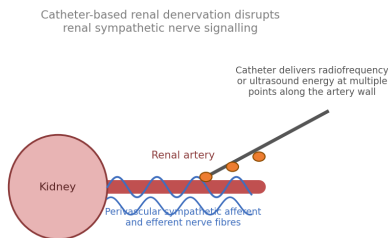


Figure 5: Mechanism of catheter-based renal denervation: ablation of perivascular renal sympathetic nerve fibres.

Both SPYRAL trials used radiofrequency ablation from a multi-electrode catheter, while RADIANCE-HTN TRIO used circumferential ultrasound energy from a balloon-based catheter -- a different mechanism reaching the same nerve target, and each produced a significant sham-adjusted effect in its own trial [1,2,3].

Who responds more, and who decides

A systematic review of patient-level predictors, drawn from 17 observational studies rather than the randomized trials themselves, found that a higher resting heart rate and a lower pulse wave velocity were each associated with a larger ambulatory BP response, on the order of an additional 4 to 9 mmHg of reduction depending on the measure [8]. Figure 6 sets these effect sizes out directly. Higher baseline BP, orthostatic hypertension, greater nocturnal BP variability, and heightened renin-angiotensin activity were also associated with better response, while younger age, preserved kidney function, and non-Black ethnicity showed weaker, lower-certainty associations [8]. None of this amounts to a validated way to select patients prospectively before the procedure -- it describes who happened to respond in observational cohorts, not a prospectively tested selection rule.

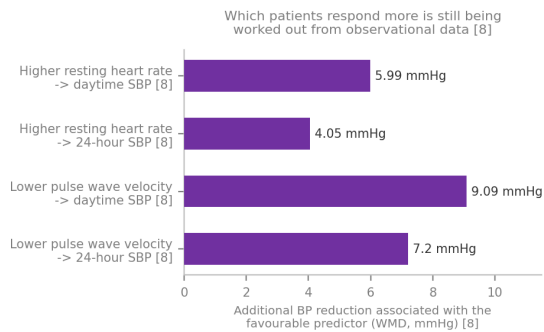


Figure 6: Observational predictors of a larger ambulatory BP response to renal denervation, with associated effect sizes [8].

The 2024 ESC hypertension guideline reflects this same modesty in its formal recommendation: renal denervation received only a Class IIb recommendation (may be considered) for patients with uncontrolled BP despite three or more drugs, extended cautiously to higher-risk patients on fewer than three drugs, conditional on shared decision-making, multidisciplinary assessment, and delivery at medium-to-high-volume centres, and explicitly not recommended for eGFR below 40 mL/min/1.73m2 or secondary causes of hypertension [7]. The guideline stopped short of a Class I recommendation because evidence of improved hard cardiovascular outcomes, rather than blood pressure reduction alone, remains limited [7].

Trial	N	Device/energy	Comparator	Primary result
SPYRAL HTN-ON MED [1]	337	Radiofrequency	Sham, on drugs	Office SBP -9.9 vs -5.1 (p=0.001)
SPYRAL HTN-OFF MED [2]	331	Radiofrequency	Sham, off drugs	Office SBP -9.2 vs -2.5 (p<0.001)
RADIANCE-HT N TRIO [3]	136	Ultrasound	Sham, triple pill	Daytime SBP -8.0 vs -3.0 (p=0.02)

Table 1: Design and headline result of the three second-generation sham-controlled trials reviewed here [1,2,3].

Discussion

Taken together, these three trials support a real, sham-adjusted blood-pressure-lowering effect of catheter-based renal denervation in resistant and uncontrolled hypertension, a conclusion that would have seemed premature after Symplicity HTN-3. The effect is genuine but modest: a pooled second-generation estimate of roughly 5 to 7 mmHg in office SBP and under 5 mmHg in 24-hour ambulatory SBP is clinically useful on top of maximal medical therapy, but it is not a cure for resistant hypertension, and it is smaller than what full adherence to existing drugs would achieve in many of these same patients [6]. SPYRAL HTN-ON MED's own 24-month data illustrate a genuine complication in interpreting durability data of this kind: once unblinding and medication adjustment are permitted, office BP -- the measure most familiar to clinicians and patients -- becomes the less reliable signal, while ambulatory BP becomes the more reliable one, the opposite of how these measures are usually prioritized in practice [1,4].

For the practicing cardiologist or hypertension specialist, the clearest current use case mirrors RADIANCE-HTN TRIO's own selection process: confirming genuine treatment resistance with a structured medication run-in and ambulatory monitoring before referring for the procedure, rather than offering it to anyone with an elevated office reading on three drugs [3]. The responder-prediction literature offers hypotheses -- higher heart rate, lower arterial stiffness, higher baseline BP -- worth discussing with patients, but not yet a validated selection tool [8]. Cost is also a genuine, not theoretical, constraint: a US cost-effectiveness analysis put the procedure's incremental cost at \$32,732 per quality-adjusted life-year over a lifetime horizon, below the conventional \$50,000 threshold in 91.3% of simulations, but ranging up to \$70,846 in older patients and requiring the procedure, imaging follow-up, and specialist referral infrastructure that not every health system or patient can access equally [9]. Table 2 sets the durability and safety findings from the two trials with the longest follow-up out together, and Table 3 sets the cost-effectiveness findings out by patient subgroup.

Trial (follow-up)	Population	Medication change	Safety at longest follow-up
SPYRAL HTN-ON MED (24 months) [4]	206 RDN, 131 sham	~2 to ~3 drugs, both arms (not different, p=0.26)	1 hypertensive crisis/stroke (RDN, day 427); 1 CV death (sham)
RADIANCE-HTN TRIO (36 months) [5]	All treated after sham crossover	+0.6 drugs from baseline (p=0.004)	No new signal; no >50% renal artery stenosis on imaging

Table 2: Medication burden and safety at the longest reported follow-up for the two trials with extended data [4,5].

Patient subgroup	ICER (\$/QALY)	Below \$50,000 threshold
Base case, lifetime horizon	32,732	Yes
Age 45-80 years (range)	33,040-70,846	Mostly (older ages less favourable)
Baseline office SBP 140-175 mmHg	31,884-41,524	Yes across range

Table 3: Incremental cost-effectiveness of radiofrequency renal denervation by patient subgroup, US analysis [9].

None of this changes the underlying arithmetic for an individual patient: a 5 to 9 mmHg office reduction and a smaller ambulatory reduction, achieved once, against a procedure with a small but real complication rate and a cost that only clears standard value thresholds in the majority, not the entirety, of modeled scenarios [1,2,3,9]. That arithmetic supports renal denervation as a genuine option for carefully selected, confirmed-resistant patients rather than as a routine third-line intervention for anyone with an elevated office reading.

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and its conclusions rest on three trials plus their follow-up reports rather than an exhaustive search of the renal denervation literature. RADIANCE-HTN TRIO's 36-month data come from a single-arm cohort after the sham arm crossed over to active treatment, so they describe durability of treated patients, not a continuing sham-controlled comparison, and the paper itself flags that only office BP, not ambulatory BP, was available at that visit [5]. The responder-prediction findings summarized here come from observational cohorts of variable quality, not from prospective randomized selection, so they should be read as hypotheses for future trials rather than as a ready-made patient-selection algorithm [8]. Finally, none of the three headline trials was powered or designed to detect a difference in hard cardiovascular outcomes such as stroke or myocardial infarction, so this review's conclusions are limited to blood pressure endpoints, exactly the gap the ESC guideline cited in withholding a Class I recommendation [7].

A further point worth stating plainly for practice: the three trials reviewed here used two different energy sources (radiofrequency in both SPYRAL trials, ultrasound in RADIANCE-HTN TRIO) and two different baseline medication conditions (on background drugs in SPYRAL HTN-ON MED, off all drugs in SPYRAL HTN-OFF MED Pivotal, on a fixed triple pill in RADIANCE-HTN TRIO), so the review's pooled second-generation estimate of roughly 5 to 7 mmHg in office SBP is an average across meaningfully different clinical scenarios, not a single reproducible number a clinician can quote for every patient in front of them [1,2,3,6]

The 24-month SPYRAL HTN-ON MED data add a second practical caution: because the ambulatory signal only became significant once patients were unblinded and medications could change, a clinician reading only the 6-month primary result, where the ambulatory difference was not significant, would have reached a different conclusion than one reading the 24-month update, underscoring why durability data deserve as much attention as the headline primary endpoint before this procedure is recommended to an individual patient [1,4].

The safety profile across all three trials is also worth restating in one place, because it is easy for a genuinely modest procedural risk to be either overstated or understated in isolation. Across roughly 800 randomized patients between the three trials, the adjudicated device- or procedure-related serious events reported were: one hypertensive crisis requiring hospitalization and one stroke in SPYRAL HTN-OFF MED Pivotal (one in each arm) [2]; one hypertensive crisis or stroke in the denervation arm and one unrelated cardiovascular death in the sham arm of SPYRAL HTN-ON MED by 24 months [4]; and one femoral pseudoaneurysm requiring intervention, one sudden cardiac death judged unrelated to the procedure, and one transient acute kidney injury attributed to a diuretic rather than to denervation in RADIANCE-HTN TRIO [3]. No trial reported a clinically significant renal artery stenosis attributable to the ablation itself, and RADIANCE-HTN TRIO's 36-month imaging follow-up specifically confirmed no new such finding [5]. This is a reassuring safety record for an invasive procedure, but it is a record built on a few hundred patients per trial followed for at most three years, which is a genuinely smaller and shorter evidence base than exists for the antihypertensive drug classes renal denervation is meant to supplement rather than replace. None of the three trials was powered to detect a difference in stroke, myocardial infarction, or cardiovascular death, so any expectation of a proportional reduction in hard outcomes rests on extrapolation from blood-pressure epidemiology, not a direct finding [1,2,3]. The ESC guideline's Class IIb wording -- "may be considered" rather than "is recommended" -- is a deliberate reflection of exactly this gap, and it is the single most important caveat for a cardiologist to carry into a conversation with a patient who has already read enthusiastic press coverage of these same trials [7]. A patient who asks whether this procedure will prevent a future heart attack or stroke, rather than simply lower a number on a cuff, deserves an honest answer: that question has not yet been directly tested.

Conclusion

A second generation of sham-controlled trials has established that catheter-based renal denervation lowers blood pressure beyond sham in resistant and uncontrolled hypertension, reversing the pessimism that followed Symplicity HTN-3. The effect is real but modest, differently sized and differently significant depending on whether office or ambulatory BP is measured and how long medication changes have been allowed to accumulate, and it is not yet clear which individual patients benefit most. For now, renal denervation belongs in the hands of specialists who confirm genuine resistance before referral, discuss a realistic effect size rather than a cure, and weigh a real but bounded procedural risk and cost against a benefit measured in single-digit millimetres of mercury.

1. Mahfoud F, Kandzari DE, Kario K, et al. "Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial". *Lancet* 399(2022):1401-1410.
2. Bohm M, Kario K, Kandzari DE, et al. "Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial". *Lancet* 395(2020):1444-1451.
3. Azizi M, Sanghvi K, Saxena M, et al. "Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial". *Lancet* 397(2021):2476-2486.
4. Kandzari DE, et al. "Long-Term Safety and Efficacy of Renal Denervation: 24-Month Results From the SPYRAL HTN-ON MED Trial". *Circ Cardiovasc Interv* (2025), Epub ahead of print.
5. Azizi M, et al. "36-month durability of ultrasound renal denervation for hypertension resistant to combination therapy in RADIANCE-HTN TRIO". *Hypertens Res* (2024), Epub ahead of print.
6. Sardar P, Bhatt DL, Kirtane AJ, et al. "Sham-Controlled Randomized Trials of Catheter-Based Renal Denervation in Patients With Hypertension". *J Am Coll Cardiol* 73(2019):1633-1642.
7. McEvoy JW, McCarthy CP, Bruno RM, et al. "2024 ESC Guidelines for the management of elevated blood pressure and hypertension". *Eur Heart J* 45(2024):3912-4018.
8. Hu XR, Liao GZ, Wang JW, et al. "Patient-Specific Factors Predicting Renal Denervation Response in Patients With Hypertension: A Systematic Review and Meta-Analysis". *J Am Heart Assoc* 13(2024):e034915.
9. Kandzari DE, Cao KN, Ryschon AM, et al. "Catheter-Based Radiofrequency Renal Denervation in the United States: A Cost-Effectiveness Analysis Based on Contemporary Evidence". *J Soc Cardiovasc Angiogr Interv* (2024), Epub ahead of print.

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