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Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial



Michel Azizi*, Roland E Schmieder, Felix Mahfoud, Michael A Weber, Joost Daemen, Justin Davies, Jan Basile, Ajay J Kirtane, Yale Wang, Melvin D Lobo, Manish Saxena, Lida Feyz, Florian Rader, Philipp Lurz, Jeremy Sayer, Marc Sapoval, Terry Levy, Kintur Sanghvi, Josephine Abraham, Andrew S P Sharp, Naomi D L Fisher, Michael J Bloch, Helen Reeve-Stoffer, Leslie Coleman, Christopher Mullin, Laura Mauri*, on behalf of the RADIANCE-HTN Investigators†

Summary

Background Early studies suggest that radiofrequency-based renal denervation reduces blood pressure in patients with moderate hypertension. We investigated whether an alternative technology using endovascular ultrasound renal denervation reduces ambulatory blood pressure in patients with hypertension in the absence of antihypertensive medications.

Methods RADIANCE-HTN SOLO was a multicentre, international, single-blind, randomised, sham-controlled trial done at 21 centres in the USA and 18 in Europe. Patients with combined systolic–diastolic hypertension aged 18–75 years were eligible if they had ambulatory blood pressure greater than or equal to 135/85 mm Hg and less than 170/105 mm Hg after a 4-week discontinuation of up to two antihypertensive medications and had suitable renal artery anatomy. Patients were randomised (1:1) to undergo renal denervation with the Paradise system (ReCor Medical, Palo Alto, CA, USA) or a sham procedure consisting of renal angiography only. The randomisation sequence was computer generated and stratified by centres with randomised blocks of four or six and permutation of treatments within each block. Patients and outcome assessors were blinded to randomisation. The primary effectiveness endpoint was the change in daytime ambulatory systolic blood pressure at 2 months in the intention-to-treat population. Patients were to remain off antihypertensive medications throughout the 2 months of follow-up unless specified blood pressure criteria were exceeded. Major adverse events included all-cause mortality, renal failure, an embolic event with end-organ damage, renal artery or other major vascular complications requiring intervention, or admission to hospital for hypertensive crisis within 30 days and new renal artery stenosis within 6 months. This study is registered with ClinicalTrials.gov, number NCT02649426.

Findings Between March 28, 2016, and Dec 28, 2017, 803 patients were screened for eligibility and 146 were randomised to undergo renal denervation (n=74) or a sham procedure (n=72). The reduction in daytime ambulatory systolic blood pressure was greater with renal denervation (−8.5 mm Hg, SD 9.3) than with the sham procedure (−2.2 mm Hg, SD 10.0; baseline-adjusted difference between groups: −6.3 mm Hg, 95% CI −9.4 to −3.1, p=0.0001). No major adverse events were reported in either group.

Interpretation Compared with a sham procedure, endovascular ultrasound renal denervation reduced ambulatory blood pressure at 2 months in patients with combined systolic–diastolic hypertension in the absence of medications.

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Introduction

Targeted endovascular catheter-based denervation of the renal efferent and afferent nerves with minimally invasive approaches has been investigated as a novel blood pressure lowering treatment for resistant hypertension.¹ Although in initial randomised trials, catheter-directed radiofrequency ablation was associated with blood pressure reduction,^{2,3} a subsequent sham-controlled study did not show improvement in blood pressure control.⁴

Several features of this sham-controlled trial might have limited its ability to show blood pressure reduction following renal denervation.⁵ These include uncertainty regarding the completeness of denervation, variable

adherence to antihypertensive medications among patients during follow-up, and a population including patients with isolated systolic hypertension or substantial vascular stiffness that might be difficult to reverse.^{6,7} Subsequently, trials have been designed with more attention to procedural technique and the inclusion of patients with less severe hypertension in order to examine the blood pressure lowering efficacy of catheter-based renal denervation in the absence of antihypertensive medications.^{6,8} The results of one such study support the ability of renal denervation with a multielectrode radiofrequency ablation device to reduce blood pressure.⁹

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed up to April 15, 2018, without time or language restriction with the terms "renal denervation", "hypertension", "randomised", "hypertension", and various combinations of those words to identify systematic reviews, meta-analyses, and randomised controlled trials of blood pressure lowering efficacy of renal denervation. We identified 11 meta-analyses that included randomised and non-randomised controlled trials of patients with uncontrolled hypertension despite being treated with antihypertensive medications. The 2017 Cochrane Collaboration meta-analysis that included 12 eligible sham and non-sham controlled studies (1149 participants) showed moderate quality evidence that renal denervation did not change office or ambulatory blood pressure compared with standard or intensified antihypertensive therapy. This meta-analysis did not include trials assessing the effect of renal denervation in patients with hypertension in the absence of antihypertensive medications. Since the publication of these meta-analyses, interim analysis of the SPYRAL HTN-OFF MED randomised, sham-controlled trial reported reduction in 24-h ambulatory systolic blood pressure with radiofrequency-based renal denervation compared with a sham procedure at 3 months in the absence of antihypertensive medications.

An alternative technology has been developed that delivers ultrasound energy to thermally ablate the renal sympathetic nerves (Paradise renal denervation system, ReCor Medical, Palo Alto, CA, USA). Placed percutaneously within the main renal arteries and centred by a low pressure, water-filled cooling balloon (appendix), this endovascular catheter achieves a circumferential ring of ablation^{10,11} at a depth of 1–6 mm from the vessel lumen in animal models (data on file, ReCor Medical), which is the expected location of the efferent and afferent renal nerves in the adventitia.¹² In patients with resistant hypertension, feasibility studies have shown reductions in blood pressure and a low incidence of adverse events, albeit without comparison with a sham procedure.^{13,14}

We designed the RADIANCE-HTN trial to compare the blood pressure lowering efficacy of this endovascular ultrasound renal denervation system with a sham procedure in two separate cohorts: patients with mild-to-moderate hypertension, who underwent randomisation while off antihypertensive medications (SOLO cohort), and patients with uncontrolled hypertension despite receiving three antihypertensive medications (TRIO cohort).¹⁵ Each cohort was independently powered to detect a difference between renal denervation and the sham procedure in terms of the primary endpoint, of change in daytime ambulatory systolic blood pressure at 2 months. In this Article, we report the primary results of the RADIANCE-HTN randomised trial in the SOLO cohort.

Added value of this study

The RADIANCE-HTN SOLO trial was designed to show the effect of endovascular ultrasound renal denervation on ambulatory blood pressure compared with a sham procedure in patients with combined systolic-diastolic hypertension who were off antihypertensive medications. This study was powered for efficacy and our results showed a greater reduction in daytime and 24-h systolic ambulatory blood pressure at 2 months in patients who underwent renal denervation than in patients who underwent a sham procedure.

Implications of all the available evidence

The RADIANCE-HTN SOLO and SPYRAL HTN-OFF MED trials enrolled largely similar patient populations, and yielded consistent results, showing that catheter-based renal denervation, using ultrasound or radiofrequency, lowers blood pressure among patients with hypertension who are off antihypertensive medications. The results of both trials will inform the design of future studies in this population to provide additional safety and long-term efficacy data, which will be important to establish the role of renal denervation in the treatment of hypertension.

Methods

Study design and participants

RADIANCE-HTN SOLO is a multicentre, international, single-blind, randomised, sham-controlled trial. The design of the RADIANCE-HTN trials has been described previously.¹⁵ Participants were recruited into the SOLO cohort of the RADIANCE-HTN trial from 21 hospitals in the USA and 18 in Europe (France, Germany, the Netherlands, Belgium, and the UK; appendix). The study was approved by local ethics committees or institutional review boards and was done in accordance with the declaration of Helsinki. All participants provided written informed consent.

Patients were recruited from existing practices at study centres, were referred to study centres, or were invited via local web-based or traditional advertising campaigns. Briefly, eligible patients were men or women aged 18–75 years with combined systolic-diastolic hypertension that was either uncontrolled on zero to two antihypertensive medications (average seated office systolic and diastolic blood pressure of $\geq 140/90$ mm Hg, but $< 180/110$ mm Hg) or controlled on one to two antihypertensive medications (average seated office blood pressure $< 140/90$ mm Hg). Patients also needed to have an estimated glomerular filtration rate (eGFR) of greater than or equal to 40 mL/min per 1.73 m² (based on the Modification of Diet in Renal Disease formula) and no history of cardiovascular or cerebrovascular events. All antihypertensive medications were discontinued for 4 weeks before the ambulatory

blood pressure assessment to determine eligibility. Patients with subsequent daytime ambulatory systolic blood pressure of at least 135 mm Hg and diastolic blood pressure at least 85 mm Hg and less than 170/105 mm Hg, and suitable renal artery anatomy on pre-randomisation renal CT angiography or magnetic resonance (MR) angiography, underwent subsequent selective renal angiography via femoral arterial access to confirm anatomical eligibility.

Randomisation and masking

Patients were randomised in a 1:1 ratio to receive renal denervation or a sham procedure. The randomisation sequence was computer generated and stratified by centres with randomised blocks of four or six and permutation of treatments within each block. The randomised treatment assignment was accessible only to the staff responsible for performing the procedures through dedicated web-based software. The randomisation assignment was masked for 6 months after randomisation for patients, outcome assessors, and clinicians involved in follow-up care.

Procedures

After the post-randomisation qualifying renal angiogram, patients assigned to the renal denervation group underwent immediate endovascular ultrasound nerve ablation, whereas those randomised to the sham group had no further endovascular procedure.

Renal nerve ablation was done with the Paradise endovascular ultrasound renal denervation system. A minimum of two sonications of 7 s each were delivered in the main branch of the right and left renal artery, separated longitudinally by 5 mm, according to individual treatment plans developed on the basis of the pre-randomisation CT or MR angiography. To prevent unmasking, all patients who underwent the catheter-directed renal angiography were sedated and wore headphones and eye covers. Patients completed a questionnaire to assess the effectiveness of masking at discharge and 2-month follow-up. Pain was assessed with a visual analogue scale before the procedure and before discharge.¹⁶

Patients were evaluated at clinical visits at baseline and at 1 month and 2 months after randomisation. Seated office blood pressure and heart rate, adverse events, and concomitant medications were recorded and laboratory assessments were done at each visit.

After a 5-min rest in the seated position, three office blood pressure measurements were taken 1 min apart, with the last two readings averaged and used as the office blood pressure reading. Patients were requested to measure their blood pressure at home after a 5-min rest in the sitting position in the morning and evening for 7 consecutive days before every outpatient visit. The same validated electronic device (Omron M10-IT, Omron Healthcare, Kyoto, Japan) was used for both office and

home blood pressure measurements. All patients remained off antihypertensive medications until 2 months after randomisation unless office blood pressure reached 180/110 mm Hg or home blood pressure reached 170/105 mm Hg before the 2-month evaluation, in which case patients received escape antihypertensive treatment. At 2 months, a specific drug titration protocol¹⁵ was initiated if the average blood pressure at home was greater than or equal to 135 mm Hg systolic or 85 mm Hg diastolic.

24-h ambulatory blood pressure measurements were performed at baseline and at 2 months post randomisation by use of an upper arm portable blood pressure monitor (Microlife WatchBP, Taipei, Taiwan). Blood pressure was recorded every 20 min during daytime (0700–2200 h) and every 30 min during the night (2200–0700 h). The ambulatory blood pressure measurement was repeated if fewer than 21 daytime blood pressure measurements were recorded. All ambulatory blood pressure recordings were sent to a core laboratory (dabl, Dublin, Ireland), with treatment assignments masked. Renal duplex ultrasound was planned at 2 months in patients who underwent randomisation (except at one centre where MR angiography was done). Patients with elevated peak systolic velocities or increased aortic to renal artery velocity ratios on duplex ultrasound underwent renal CT or MR angiography to assess for renal artery stenosis. All patients who underwent randomisation consented to complete 3 years of follow-up.

Outcomes

The primary efficacy endpoint was the mean change in daytime ambulatory systolic blood pressure from baseline to 2 months. Secondary efficacy endpoints specified for hierarchical testing were change in average 24-h ambulatory systolic blood pressure, average 24-h ambulatory diastolic blood pressure, average night-time ambulatory systolic blood pressure, and average night-time ambulatory diastolic blood pressure at 2 months, in this order. Additional specified secondary efficacy endpoints included change in daytime ambulatory diastolic blood pressure, office and home systolic and diastolic blood pressures, ambulatory and office heart rates, and the proportion of patients with controlled blood pressure (<135/85 mm Hg for daytime ambulatory, <130/80 mm Hg for 24-h ambulatory, or <140/90 mm Hg for office blood pressure). We also assessed change in eGFR at 2 months, as well as the percentage of patients who had a greater than 5 mm Hg decrease in daytime ambulatory systolic blood pressure, and the percentage of patients who started oral antihypertensive monotherapy according to protocol-defined criteria after the 2-month ambulatory blood pressure measurement. Changes in plasma biomarkers and antihypertensive medication burden will be evaluated after 6-month follow-up and reported subsequently.

Prespecified major adverse events included all-cause mortality, renal failure (eGFR <15 mL/min per 1.73 m²,

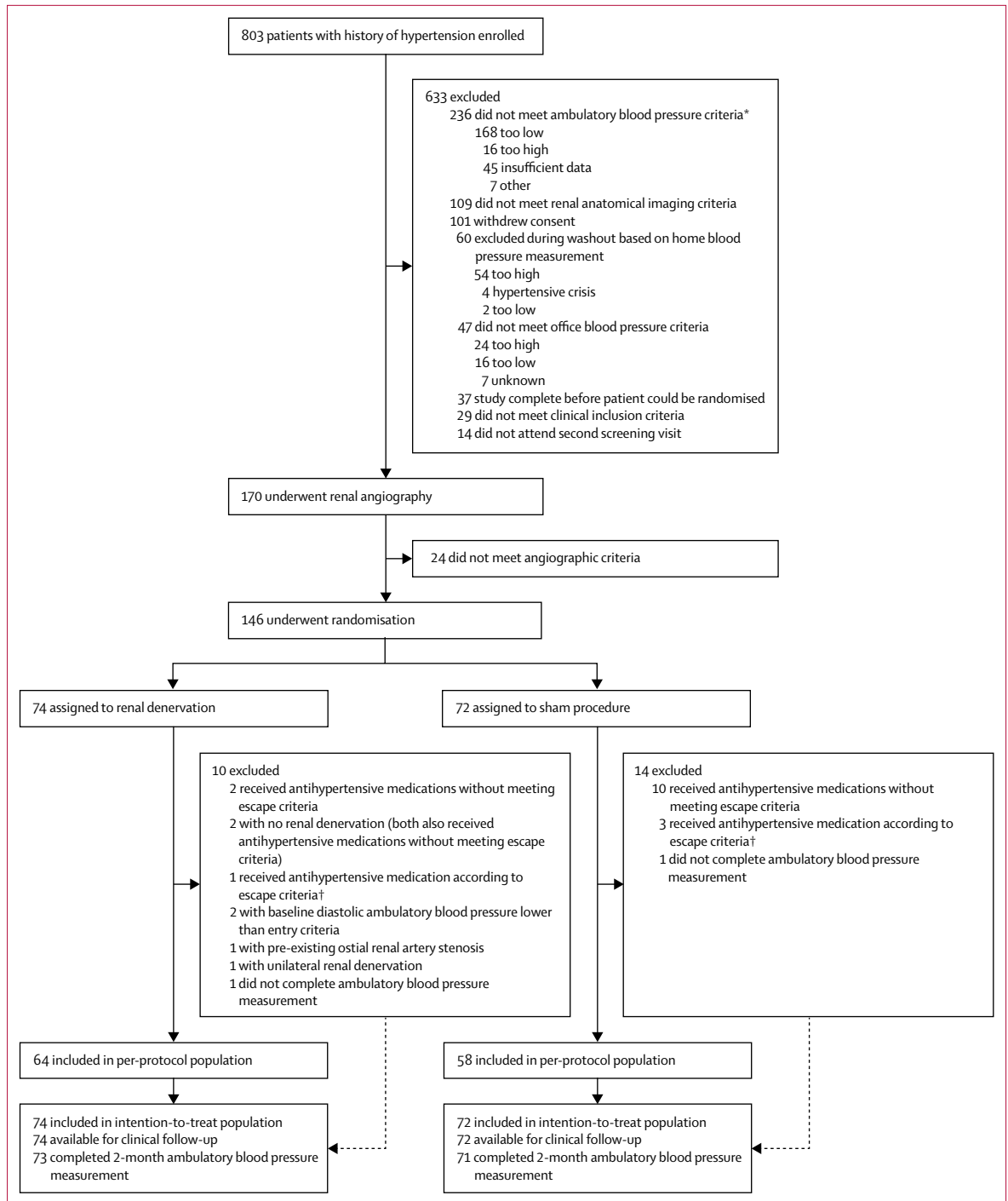


Figure 1: Trial profile

*Daytime ambulatory blood pressure $\geq 135/85$ mm Hg and $< 170/105$ mm Hg. †Office blood pressure $\geq 180/110$ mm Hg or home blood pressure $\geq 170/105$ mm Hg.

need for renal replacement therapy, or doubling of serum creatinine), an embolic event with end-organ damage, renal artery or other major vascular complications requiring intervention, hospital admission for hypertensive crisis within 30 days, and new renal artery stenosis ($>70\%$) within 6 months. Additional prespecified

safety endpoints included hypotensive emergency; hospital admission for heart failure; stroke, transient ischaemic attack, or cerebrovascular accident; acute myocardial infarction (ST-elevation myocardial infarction or non-ST elevation myocardial infarction); any coronary revascularisation; procedure-related pain lasting longer

than 2 days; new renal artery stenosis greater than 50% by duplex ultrasound and confirmed by renal CT or MR angiography; and need for renal artery angioplasty and, stenting, or both.

Sites were required to report all adverse events. All potential device, procedural, or serious adverse events were sent for independent adjudication. An independent data safety and monitoring board reviewed the study data quarterly for all enrolled patients.

Statistical analysis

The study was designed to compare the blood pressure lowering effect of renal denervation versus a sham procedure as assessed by daytime systolic ambulatory blood pressure monitoring at 2 months. Assuming a 6 mm Hg difference in change in daytime ambulatory systolic blood pressure at 2 months between the renal denervation and the sham groups,¹⁷ a common SD of 12 mm Hg, 1:1 randomisation, and a two-sided type 1 error rate of 5%, a sample size of 128 evaluable patients would yield 80% power. To account for up to 10% missing data on the primary endpoint, we planned to randomise a total 146 patients in the study.

The primary statistical analysis was performed on the intention-to-treat (ITT) population, and secondary confirmation was performed on the per-protocol population. The per-protocol population excluded patients who did not meet baseline daytime ambulatory systolic or diastolic blood pressure or renal artery anatomical inclusion criteria, patients in the renal denervation group who did not receive bilateral renal denervation, patients who were treated with antihypertensive medications before the 2-month ambulatory blood pressure measurement (according to protocol criteria or according to physician's or patient's decision), and patients who did not complete the 2-month ambulatory blood pressure assessment.

For the analysis of the primary endpoint in the ITT population, patients who met the protocol criteria for antihypertensive drug treatment before 2 months and patients with missing 2-month ambulatory blood pressure data were assigned their baseline value of daytime ambulatory systolic blood pressure at 2 months. Evaluable data were used for all other analyses. As a sensitivity analysis to evaluate the potential effect of missing observations, tipping point analysis was performed on the primary endpoint. We assessed treatment effect (change in blood pressure parameters, heart rate, or eGFR from baseline) using analysis of covariance, including the baseline value as a covariate. For the secondary endpoints specified for hierarchical analysis, tests were performed in order, until the first non-significant test, such that subsequent secondary endpoints would not be used to make labelling claims; however, these results are provided for descriptive purposes.

When the change in blood pressure parameters, heart rate, or eGFR from baseline was not normally distributed, a baseline-adjusted analysis of covariance

	Renal denervation (n=74)	Sham procedure (n=72)
Age (years)	54.4 (10.2)	53.8 (10.0)
Female sex	28 (38%)	33 (46%)
Race		
White	60 (81%)	52 (72%)
Black	12 (16%)	13 (18%)
Other	2 (3%)	7 (10%)
Body-mass index (kg/m ²)	29.9 (5.9)	29.0 (5.0)
Abdominal obesity*	41 (56%)	44 (61%)
eGFR (mL/min per 1.73 m ²)	84.7 (16.2)	83.2 (16.1)
eGFR <60 mL/min per 1.73 m ² *	1 (1%)	3 (4%)
Diabetes		
Type 1	0	0
Type 2	2 (3%)	5 (7%)
Obstructive sleep apnoea*	6 (8%)	8 (11%)
Office systolic blood pressure before antihypertensive medication washout (mm Hg)	142.6 (14.7)	144.6 (15.9)
Office diastolic blood pressure before antihypertensive medication washout (mm Hg)	92.3 (10.1)	93.6 (8.3)
Office heart rate before antihypertensive medication washout (bpm)	72.0 (12.1)	72.6 (12.3)
Number of antihypertensive medications at screening		
0†	12 (16%)	16 (22%)
1	33 (45%)	28 (39%)
2	28 (38%)	27 (38%)
3‡	1 (1%)	1 (1%)
Types of medication at screening in patients on medications		
Renin angiotensin system blockers		
Angiotensin converting enzyme inhibitor	29 (47%)	28 (50%)
Angiotensin receptor blocker	13 (21%)	13 (23%)
Direct renin inhibitor	2 (3%)	0
Calcium channel blocker	20 (32%)	21 (38%)
Diuretic	9 (15%)	5 (9%)
Beta blocker	5 (8%)	7 (13%)
Alpha-1 receptor blocker	3 (5%)	1 (2%)
Spironolactone	0	1 (2%)

Data are n (%) or mean (SD). eGFR=estimated glomerular filtration rate. bpm=beats per minute. *Abdominal obesity status not available in one patient in renal denervation group, eGFR data were unavailable in one patient in the renal denervation group and three patients in the sham group, and sleep apnoea status was unavailable in one patient in the sham group. †Nine patients were drug naive in the renal denervation (three patients) and sham (six patients) groups and 19 were drug intolerant or had chosen not to take antihypertensive medications (nine in the renal denervation group and ten in the sham group). ‡Two patients were discovered to have been on three antihypertensive medications at screening.

Table 1: Baseline demographic and clinical characteristics of the intention-to-treat population

based on ranked data was also done. Treatment interactions were assessed with linear regression models adjusting for baseline daytime ambulatory systolic blood pressure for subgroups prespecified in the statistical analysis plan (ethnicity, age, sex, geography, baseline daytime ambulatory systolic blood pressure, baseline office blood pressure, and abdominal obesity). Abdominal obesity was defined as a waist circumference greater than 102 cm for men and greater than 88 cm for women. Bang and James blinding indices were calculated.^{18,19}

	Renal denervation			Sham procedure			Mean between-group difference adjusted for baseline blood pressure (95% CI)	p value
	Randomisation	2 months	Difference	Randomisation	2 months	Difference		
Daytime ambulatory blood pressure (mm Hg)								
Patients with data	74	74	74	72	72	72
Systolic blood pressure	150.3 (7.8)	141.9 (11.9)	-8.5 (9.3)	150.0 (9.8)	147.9 (13.3)	-2.2 (10.0)	-6.3 (-9.4 to -3.1)	0.0001
Diastolic blood pressure	93.1 (4.8)	87.9 (7.1)	-5.1 (5.9)	93.5 (5.5)	90.9 (7.9)	-2.6 (6.5)	-2.6 (-4.6 to -0.6)	0.01 (0.006*)
24-h ambulatory blood pressure (mm Hg)								
Patients with data	74	74	74	72	72	72
Systolic blood pressure	142.6 (8.1)	135.6 (11.4)	-7.0 (8.6)	143.8 (10.4)	140.7 (11.8)	-3.1 (9.7)	-4.1 (-7.1 to -1.2)	0.006
Diastolic blood pressure	87.3 (5.0)	83.0 (6.8)	-4.4 (5.8)	88.6 (5.7)	85.7 (7.1)	-3.0 (6.1)	-1.8 (-3.7 to 0.2)	0.07
Night-time ambulatory blood pressure (mm Hg)								
Patients with data	74	74	74	71	71	71
Systolic blood pressure	130.3 (11.9)	125.6 (12.8)	-4.8 (11.7)	132.5 (13.7)	129.4 (13.1)	-3.1 (11.5)	-2.5 (-6.0 to 0.9)	0.15
Diastolic blood pressure	78.2 (8.0)	74.8 (8.5)	-3.3 (8.5)	80.0 (8.1)	77.3 (8.5)	-2.7 (7.3)	-1.4 (-3.8 to 1.0)	0.25
Office blood pressure (mm Hg)								
Patients with data	74	74	74	72	72	72
Systolic blood pressure	154.5 (12.4)	143.7 (16.1)	-10.8 (13.6)	153.6 (15.7)	149.7 (17.4)	-3.9 (17.4)	-6.5 (-11.3 to -1.8)	0.007 (0.0007*)
Diastolic blood pressure	99.7 (7.7)	94.2 (10.1)	-5.5 (8.4)	99.1 (9.4)	98.0 (10.0)	-1.2 (10.0)	-4.1 (-7.0 to -1.3)	0.005
Home blood pressure (mm Hg)								
Patients with data	71	71	71	72	72	72
Systolic blood pressure	147.5 (8.8)	139.4 (11.7)	-8.1 (9.7)	147.7 (12.3)	146.6 (15.4)	-1.1 (10.6)	-7.1 (-10.4 to -3.8)	<0.0001 (<0.0001*)
Diastolic blood pressure	94.8 (6.9)	89.9 (7.8)	-4.9 (6.7)	94.6 (7.0)	93.3 (8.5)	-1.3 (6.2)	-3.6 (-5.6 to -1.5)	0.0009

Data are mean (SD) unless otherwise noted. p values are from analysis of covariance, adjusting for baseline value. *p value by baseline adjusted analysis of covariance on ranked data.

Table 2: Primary and secondary efficacy endpoints

Continuous variables are expressed as mean (SD), unless otherwise specified, and between-group differences are expressed with their two-sided 95% CIs. We used the SAS software version 9.4. We deemed a p value lower than 0.05 to be significant. Confidence intervals of differences between treatment groups and p values for secondary endpoints not included in the hierarchical testing procedure are provided for descriptive purposes only. This study is registered with ClinicalTrials.gov, number NCT02649426.

Role of the funding source

The study was funded by ReCor Medical. The trial executive committee designed the protocol in conjunction with the sponsor. The sponsor was responsible for the selection of clinical sites in collaboration with the executive committee, as well as the collection and monitoring of the data. Statistical analyses were performed by NAMSA (Minneapolis, MN, USA) and independently validated by the Baim Institute for Clinical Research (Boston, MA, USA). The manuscript was written by MA and LM with significant contributions from the co-authors. The sponsor assisted in figure and table generation, copy editing, and formatting. All authors had access to all the data, and MA and LM were responsible for the decision to submit the manuscript.

Results

Between March 28, 2016, and Dec 28, 2017, 803 patients with a history of hypertension were enrolled into the SOLO cohort of the RADIANCE-HTN trial. After a 4-week period during which all antihypertensive medications were discontinued, 170 patients met both daytime ambulatory blood pressure and non-invasive imaging criteria and thus underwent subsequent renal angiography. Anatomical reasons for exclusion during non-invasive imaging or renal catheter angiography are shown in the appendix. 146 patients met the angiographic criteria for randomisation (74 allocated to renal denervation and 72 allocated to sham procedure; figure 1). No patients were lost to follow-up at 2 months.

Baseline characteristics are shown in table 1 and were similar across the study groups. The mean age was 54.1 years (SD 10.1). Of the 146 patients who underwent randomisation, 61 (42%) were female and 25 (17%) were black. 85 (58%) patients had abdominal obesity. At the time of enrolment, 28 (19%) patients were not receiving any antihypertensive medications (nine were drug naive and 19 were drug intolerant or had chosen not to take antihypertensive medications), 61 (42%) were receiving one medication, and 55 (38%) were receiving two medications (table 1).

Patients in the renal denervation group received a total average of 5.4 (SD 1.0) ultrasound emissions with an average total ablation time of 37.9 s (SD 6.7). Including angiography, the average total procedure time was 72 min for the renal denervation group versus 38 min for the sham group ($p < 0.0001$; appendix). 33 study sites assigned patients to the renal denervation group. These 33 sites performed an average of 2.2 renal denervation procedures per site (range 1–7). Two or more bilateral ablative ultrasound emissions were administered to 71 (96%) patients. One patient in the renal denervation group received only unilateral treatment because of ostial renal artery tortuosity. Two patients received no renal denervation: one due to ostial renal artery tortuosity and the other due to a non-functioning generator, which was ascertained after randomisation but before renal denervation catheter insertion. There was no difference between groups in post-procedure pain (appendix). The Bang and James blinding indices are shown in the appendix.

In the ITT population, there was a greater reduction in the primary endpoint, daytime ambulatory systolic blood pressure at 2 months, in the renal denervation group (-8.5 mm Hg, SD 9.3) compared with the sham group (-2.2 mm Hg, SD 10.0; between-group difference of -6.3 mm Hg, 95% CI -9.4 to -3.1 mm Hg, $p = 0.0001$; table 2 and figure 2). Changes in daytime ambulatory diastolic blood pressure, 24-h ambulatory, night-time ambulatory, home, and office systolic and diastolic blood pressures are shown in table 2 and figure 2. The tipping point sensitivity analysis on the primary endpoint showed the primary results to be robust (appendix).

Five patients in the renal denervation group and 13 in the sham group were treated with antihypertensive medications before the 2-month ambulatory blood pressure measurement by physicians masked to treatment assignment: one patient in the renal denervation group and three patients in the sham group were treated after meeting protocol-defined escape criteria, whereas four and ten patients, respectively, were treated on the basis of the physician's decision or patient preference, despite not meeting protocol-defined criteria (appendix). After completion of the 2-month ambulatory blood pressure measurement, 41 (55%) of 74 patients in the renal denervation group and 57 (79%) of 72 patients in the sham group received antihypertensive treatment ($p = 0.002$; appendix). Individual patient changes in daytime ambulatory systolic blood pressure by treatment group are shown in figure 3. 49 (66%) of 74 patients had a decrease of at least 5 mm Hg in daytime ambulatory systolic blood pressure in the renal denervation group compared with 24 (33%) of 72 in the sham procedure group ($p = 0.0001$). In the renal denervation group, 15 (20%) patients attained controlled daytime ambulatory blood pressure ($< 135/85$ mm Hg) in the absence of antihypertensive medications compared with two (3%) patients in the sham group ($p = 0.001$; table 3). There were no within-group or

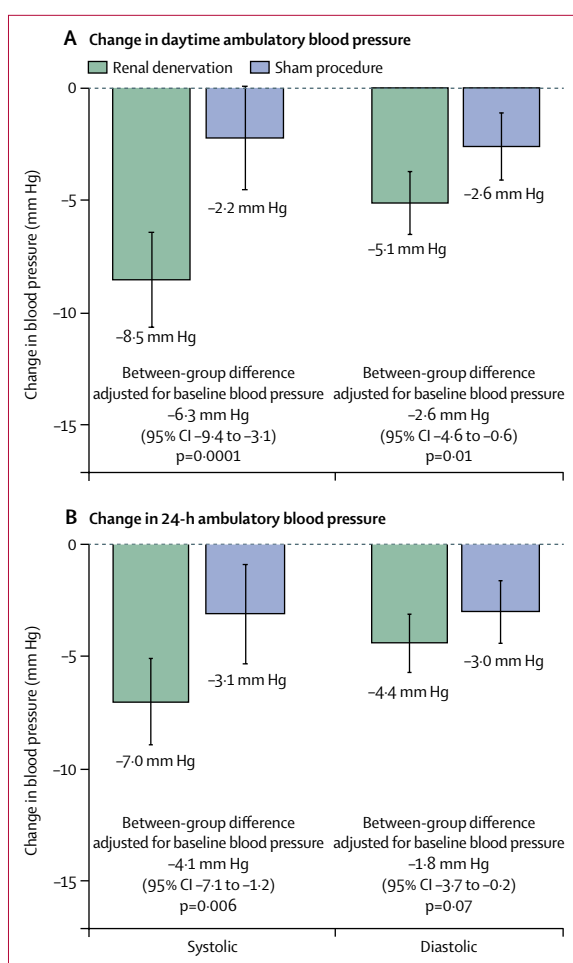


Figure 2: Change in ambulatory blood pressure from baseline to 2 months in the intention-to-treat population

74 patients in the renal denervation group and 72 patients in the sham procedure group were included in the analysis of (A) daytime ambulatory systolic and diastolic blood pressure and (B) 24-h ambulatory systolic and diastolic blood pressure. Data are presented as mean and 95% CIs.

between-group differences in office or ambulatory heart rate at 2 months (appendix).

Baseline characteristics were similar across both study groups in the per-protocol population (appendix). In the per-protocol analysis, the change in daytime ambulatory systolic blood pressure was -8.5 mm Hg (SD 9.6) in the renal denervation group ($n = 64$) and -0.1 mm Hg (SD 8.5) in the sham group ($n = 58$; between-group difference of -8.2 mm Hg, 95% CI -11.5 to -5.0 mm Hg, $p < 0.0001$) and effects of renal denervation on other blood pressure measures were consistent (appendix). 14 (22%) of 64 patients in the per-protocol renal denervation group attained controlled daytime ambulatory blood pressure without added antihypertensive medication at 2 months compared with two (3%) of 58 in the sham group ($p = 0.003$; table 3).

There were no major adverse events in either group at 30 days (appendix). Procedure-related pain lasting

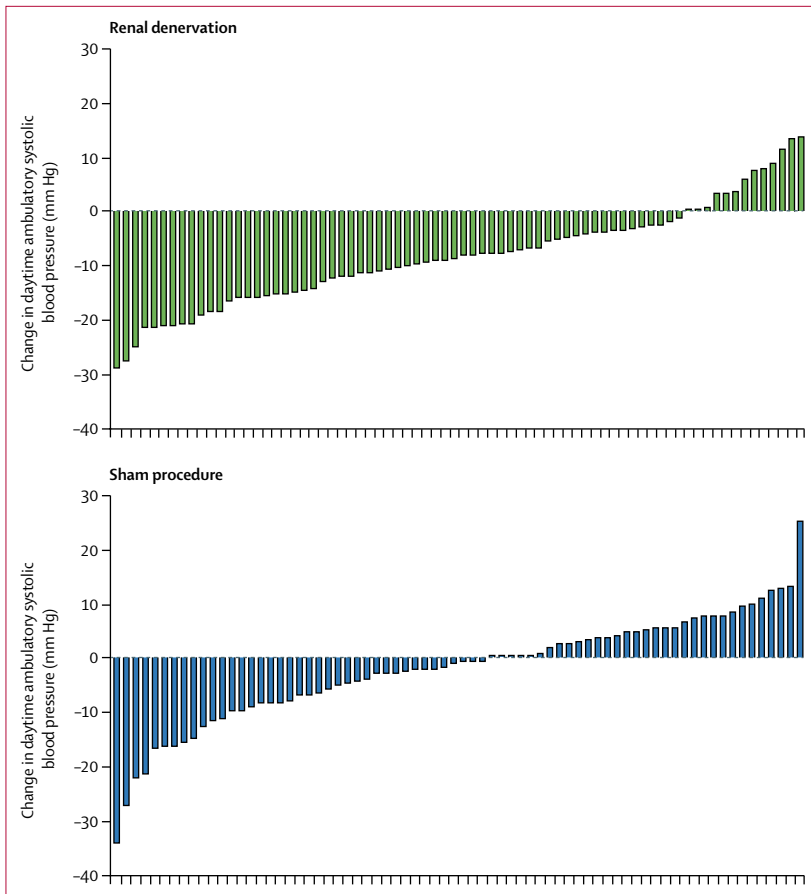


Figure 3: Individual patient changes in daytime ambulatory systolic blood pressure from baseline to 2 months

Patients shown are those included in the intention-to-treat population.

	Renal denervation	Sham procedure	p value
Intention-to-treat population			
Patients included in analysis	74	72	..
Daytime ambulatory blood pressure <135/85 mm Hg	17 (23%)	8 (11%)	0.06
24-h ambulatory blood pressure <130/80 mm Hg	20 (27%)	6 (8%)	0.003
Office blood pressure <140/90 mm Hg	19 (26%)	10 (14%)	0.07
Patients achieving controlled blood pressure in the absence of antihypertensive medication (intention-to-treat population*)			
Patients included in analysis	74	72	..
Daytime ambulatory blood pressure <135/85 mm Hg	15 (20%)	2 (3%)	0.001
24-h ambulatory blood pressure <130/80 mm Hg	18 (24%)	2 (3%)	0.0002
Office blood pressure <140/90 mm Hg	17 (23%)	5 (7%)	0.01
Per-protocol population			
Patients included in analysis	64	58	..
Daytime ambulatory blood pressure <135/85 mm Hg	14 (22%)	2 (3%)	0.003
24-h ambulatory blood pressure <130/80 mm Hg	16 (25%)	2 (3%)	0.0008
Office blood pressure <140/90 mm Hg	15 (23%)	5 (9%)	0.03

Data are n (%) unless otherwise noted. *Intention-to-treat population includes five patients in the renal denervation group and 13 patients in the sham group who restarted medications before the 2-month ambulatory blood pressure measurement evaluation.

Table 3: Patients achieving controlled blood pressure by population and treatment group

longer than 2 days occurred at a similar frequency eight [11%] patients) in both groups. 2-month non-invasive renal artery imaging was available in 71 of 74 patients in the renal denervation group and 68 of 72 patients in the sham group. No new renal artery stenosis greater than 50% was detected in either group at 2 months. At 2 months there was no significant difference in changes in eGFR between the treatment groups (adjusted mean difference -0.6 , 95 % CI -4.4 to 3.2 , $p=0.75$; appendix). As of writing, 94 patients (47 in each group) have reached the 6-month follow-up visit. 6-month imaging was available in 43 patients in the renal denervation group and 41 patients in the sham group. At 6 months, one patient in the renal denervation group underwent renal artery stent placement. For this patient, independent review of their preprocedural and 6-month postprocedure renal artery imaging showed that there was a pre-existing ostial renal artery stenosis (40–50% on MR angiography, 44% on renal angiography), which would have met the criteria for exclusion but was not recognised at the time of randomisation, and a 57% ostial renal artery stenosis on renal angiography before renal artery stenting at 6 months.

The effect of renal denervation on the primary efficacy endpoint was consistent across several prespecified subgroups, except in the abdominal obesity subgroup, in which a greater treatment effect was observed (appendix). Although patients with and without abdominal obesity in the renal denervation group each had reductions in daytime ambulatory blood pressure, this interaction seemed to be related to a larger than expected daytime ambulatory blood pressure reduction in patients without abdominal obesity in the sham group (appendix). The number of ultrasound emissions was not a predictor of reduction in daytime ambulatory systolic blood pressure in the renal denervation group ($p_{\text{interaction}}=0.33$; appendix).

Discussion

Among patients with combined systolic–diastolic hypertension who were not taking or had been withdrawn from antihypertensive medications, endovascular ultrasound renal denervation achieved a greater reduction in daytime ambulatory systolic blood pressure at 2 months than did a sham procedure. This blood pressure lowering effect was consistent for daytime ambulatory diastolic and 24-h ambulatory systolic blood pressure, as well as office and home systolic and diastolic blood pressures. The blood pressure lowering effect of renal denervation was consistent across age, sex, ethnicity, geography, and varying baseline blood pressures.

The renal denervation group had an average reduction in daytime ambulatory systolic blood pressure of 8.5 mm Hg, which was 6.3 mm Hg greater than the reduction in the sham group in the ITT analysis. However, antihypertensive medications were used more commonly during follow-up in the sham group ($n=13$) than in the renal denervation group ($n=5$) either according to protocol defined safety

criteria or physician or patient decision. The per-protocol analysis excluding such patients who received medications after randomisation from both groups reflects the true off-medication blood pressure lowering treatment effect. Indeed, in the per-protocol analysis, the change in daytime ambulatory systolic blood pressure was similar in the renal denervation group compared with the ITT analysis (-8.5 mm Hg) but was much smaller in the sham group (-0.1 mm Hg), increasing the adjusted between-group difference to 8.2 mm Hg in favour of the renal denervation group. In the per-protocol analysis, patients who underwent renal denervation were more likely to achieve daytime ambulatory blood pressure control than patients in the sham group (22% vs 3%, respectively, $p=0.003$).

We observed lower baseline ambulatory blood pressures during the night-time than in the daytime, and consequently, the reduction in night-time ambulatory blood pressure with renal denervation was smaller in magnitude than the daytime reduction at 2 months. Even so, in the per-protocol analysis excluding patients receiving antihypertensive medications, renal denervation was associated with a greater night-time ambulatory blood pressure reduction than the sham procedure.

We observed consistent findings across home and office blood pressures. While only a quarter of patients treated with renal denervation achieved normalised blood pressure at 2 months, if maintained in the long term, the average 10.8 mm Hg reduction in office systolic blood pressure we observed after renal denervation is of a magnitude previously associated with a reduction in cardiovascular events for antihypertensive drug therapy.²⁰

The reduction in 24-h ambulatory systolic blood pressure with renal denervation and the difference compared with the sham procedure at 2 months (-7.0 mm Hg and -4.1 mm Hg in the ITT analysis, respectively) were consistent with those observed at 3 months in the SPYRAL HTN-OFF MED study (-5.5 mm Hg and -4.6 mm Hg, respectively).⁹ Although both studies enrolled patients with hypertension who were off antihypertensive medications and used a sham procedure for the control group, there were some differences in the study populations and conduct. Our study enrolled a greater proportion of women and black patients, and the average ambulatory systolic blood pressure before randomisation was lower. The method used for renal nerve ablation also differed, as we used endovascular ultrasound, not radiofrequency. The ultrasound catheter is designed to be placed in the main renal arteries, before the first bifurcation, and ablative energy can be targeted to 1 mm below the luminal surface. By contrast, the Spyral multielectrode catheter (Medtronic, Galway, Ireland) is designed to target the main distal and branch renal arteries and delivers radiofrequency energy through the endothelium.²¹ The endovascular ultrasound catheter delivers energy circumferentially, rather than from individual radiofrequency electrodes. Nevertheless, the blood pressure lowering effects were similar between

the techniques, despite fewer ablations being used with the endovascular ultrasound catheter than the multielectrode radiofrequency catheter.⁹ The effects of ultrasound sonication are not generalisable across modes of delivery (ie, endovascular vs extracorporeal); indeed, extracorporeal ultrasound renal denervation did not reduce blood pressure when compared with a sham procedure.²²

This blinded, sham-controlled randomised trial to evaluate the blood pressure lowering effect of endovascular ultrasound renal denervation has several strengths. First, the study was prospectively powered to show the superiority of renal denervation compared with a sham procedure in terms of decreasing daytime ambulatory systolic blood pressure and is, to our knowledge, the largest randomised trial to date of renal denervation in patients not on antihypertensive medications. Second, we carefully selected patients for randomisation, by ensuring that they were younger than 75 years to avoid isolated systolic hypertension and increased arterial stiffness,^{23,24} and they remained hypertensive by both systolic and diastolic ambulatory blood pressure criteria after a 4-week off-medication period to avoid the confounding effect of antihypertensive medications and variable patient adherence to treatment.²⁵ Third, we made efforts to reduce variability due to the conduct of the renal denervation procedure as well as office, home, and ambulatory blood pressure measurement technique, and treatment of hypertension during the follow-up period. We chose to measure daytime ambulatory blood pressure because a lower interpatient variability in this metric has been reported in previous studies.¹⁷ Daytime ambulatory blood pressure has been shown to be a predictor of total and cardiovascular mortality, similar to night-time ambulatory blood pressure.²⁶

Our study has limitations. First, additional follow-up beyond 2 months will be required to establish whether the magnitude of the blood pressure lowering effect remains over time. For patient safety, we chose to minimise the duration that patients were off antihypertensive medications,²⁷ yet we observed a significant treatment effect over this period. Although some studies show increasing antihypertensive effects of renal denervation over time,²⁸ functional renal nerve regeneration is possible with time,²⁹ therefore, longer-term follow-up of the treatment effect is planned up to 3 years. Second, for this procedure and other methods of renal denervation, there is no immediate operator feedback about whether denervation is achieved. Third, although in this study no major adverse events occurred and reported adverse events were infrequent, longer follow-up of this trial and greater numbers of patients undergoing renal denervation will be necessary to provide greater assurance of safety and to exclude rare adverse events. Analysis of larger numbers of treated patients will also allow for more power to understand which groups of patients might derive greater or lesser benefit. Fourth, 55% of patients treated with renal denervation had insufficient control of blood

pressure to remain off medications after 2 months. Fifth, we assessed antihypertensive medication use after randomisation on the basis of reporting by patients or their physicians, and we did not test serum or urine for medication adherence, because we did not expect surreptitious use of medications. We did observe that reported medication use—for both protocol and non-protocol qualifying reasons—were more common in the sham group. This greater usage of medications in the sham group would bias our results towards the null. We plan to assess differences in the burden of medications between treatment groups in follow-up. Finally, while this study was conducted in a well defined population, whether the results will extend to the ongoing study of patients with resistant hypertension is not yet known.¹⁵

In conclusion, in patients with combined systolic–diastolic primary hypertension who were not receiving antihypertensive medications, renal denervation with endovascular ultrasound safely reduced ambulatory, home, and office blood pressure by more than a sham procedure at 2 months. Continued follow-up of the present population and additional studies will be important to evaluate the durability and long-term clinical impact of renal denervation in patients with various forms of hypertension.

Contributors

MA, LM, RES, FM, MAW, JDae, JDav, JB, AJK, CM, HR-S, and LC participated in the design of the study. MA, LM, RES, FM, MAW, JDae, JDav, JB, AJK, YW, LF, MDL, MSax, FR, PL, JS, MSap, TL, KS, JA, ASPs, NDLF, MJB, CM, HR-S, and LC participated in patient data collection. All authors analysed and interpreted the data. CM was the study biostatistician responsible for the statistical analyses. Statistical analyses were validated independently by the Baim Institute (Boston, MA, USA). MA and LM wrote the first draft of the report. All authors participated in the writing of the report, agreed on the content of the manuscript, reviewed drafts, and approved the final version.

Declaration of interests

MA has received research grants from The French Ministry of Health, Servier, Novartis, and Quantum genomics; has received honoraria for advisory board meetings from Actelion; and has received speakers' honoraria from CVRx, Servier, and Astra. RES has received grant support and personal fees from ReCor Medical, Medtronic, Ablative Solutions, and ROX Medical. FM is supported by Deutsche Gesellschaft für Kardiologie, Deutsche Hochdruckliga, and Deutsche Forschungsgemeinschaft (SFB TRR 219), and has received grant support and personal fees from ReCor Medical and Medtronic. MAW has received personal fees from ReCor Medical, Medtronic, Boston Scientific, Ablative Solutions, Omron, Astellas, and Menarini. JDae has received grant support from Medtronic, Boston Scientific, Abbott, and Acist Medical and has received personal fees from ReCor Medical, Medtronic, Pythagoras, and Acist Medical. JDav has received grant support and personal fees from ReCor Medical, Medtronic, and Philips. JB has received grant support and personal fees from ReCor Medical. AJK has received grant support to Columbia University and Cardiovascular Research Foundation from ReCor Medical, Medtronic, Abbott Vascular, Boston Scientific, Abiomed, CathWorks, Siemens, and Philips. MDL has received personal fees from ReCor Medical, Medtronic, St Jude Medical, KONA Medical, CVRx, and Cardiosonic. MSax has received personal fees from The Medicines Company and Esperion Therapeutics. FR has received personal fees from MyoKardia. PL has received personal fees from ReCor Medical. MSap has received personal fees from ReCor Medical. KS has received grant support from Medtronic and Volcano Corp and personal fees from Medtronic, Cordis, and Volcano Corp. ASPs has received personal fees from

ReCor Medical and Medtronic. NDLF has received grant support from ReCor Medical. HR-S and LC are employees of ReCor Medical. CM is an employee of NAMSA, a contractor for ReCor Medical. LM has received a research grant to the institution and personal fees as principal investigator from ReCor related to the current work and has received grants to the institution unrelated outside the current work from Abbott, Boston Scientific, and St Jude Medical, and personal fees from Medtronic. LM anticipates employment by Medtronic as of June, 2018. All other authors declare no competing interests.

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