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Effect of Renal Denervation and Catheter Ablation vs Catheter Ablation Alone on Atrial Fibrillation Recurrence Among Patients With Paroxysmal Atrial Fibrillation and Hypertension

The ERADICATE-AF Randomized Clinical Trial

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IMPORTANCE Renal denervation can reduce cardiac sympathetic activity that may result in an antiarrhythmic effect on atrial fibrillation.

OBJECTIVE To determine whether renal denervation when added to pulmonary vein isolation enhances long-term antiarrhythmic efficacy.

DESIGN, SETTING, AND PARTICIPANTS The Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation (ERADICATE-AF) trial was an investigator-initiated, multicenter, single-blind, randomized clinical trial conducted at 5 referral centers for catheter ablation of atrial fibrillation in the Russian Federation, Poland, and Germany. A total of 302 patients with hypertension despite taking at least 1 antihypertensive medication, paroxysmal atrial fibrillation, and plans for ablation were enrolled from April 2013 to March 2018. Follow-up concluded in March 2019.

INTERVENTIONS Patients were randomized to either pulmonary vein isolation alone (n = 148) or pulmonary vein isolation plus renal denervation (n = 154). Complete pulmonary vein isolation to v an end point of elimination of all pulmonary vein potentials; renal denervation using an irrigated-tip ablation catheter delivering radiofrequency energy to discrete sites in a spiral pattern from distal to proximal in both renal arteries.

MAIN OUTCOMES AND MEASURES The primary end point was freedom from atrial fibrillation, atrial flutter, or atrial tachycardia at 12 months. Secondary end points included procedural complications within 30 days and blood pressure control at 6 and 12 months.

RESULTS Of the 302 randomized patients (median age, 60 years [interquartile range, 55-65 years]; 182 men [60.3%]), 283 (93.7%) completed the trial. All successfully underwent their assigned procedures. Freedom from atrial fibrillation, flutter, or tachycardia at 12 months was observed in 84 of 148 (56.5%) of those undergoing pulmonary vein isolation alone and in 111 of 154 (72.1%) of those undergoing pulmonary vein isolation plus renal denervation (hazard ratio, 0.57; 95% CI, 0.38 to 0.85; $P = .006$). Of 5 prespecified secondary end points, 4 are reported and 3 differed between groups. Mean systolic blood pressure from baseline to 12 months decreased from 151 mm Hg to 147 mm Hg in the isolation-only group and from 150 mm Hg to 135 mm Hg in the renal denervation group (between-group difference, −13 mm Hg; 95% CI, −15 to −11 mm Hg; $P < .001$). Procedural complications occurred in 7 patients (4.7%) in the isolation-only group and 7 (4.5%) of the renal denervation group.

CONCLUSIONS AND RELEVANCE Among patients with paroxysmal atrial fibrillation and hypertension, renal denervation added to catheter ablation, compared with catheter ablation alone, significantly increased the likelihood of freedom from atrial fibrillation at 12 months. The lack of a formal sham-control renal denervation procedure should be considered in interpreting the results of this trial.

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Visual Abstract

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Supplemental content

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The autonomic nervous system plays an important part in the initiation and perpetuation of atrial fibrillation.[1,2] Increased central sympathetic outflow and efferent cardiac sympathetic nerve stimulation can enhance the development of atrial fibrillation.

Renal denervation has emerged as a novel therapy for resistant hypertension, accomplished by ablating the renal sympathetic efferent and afferent nerves that interact with the central autonomic nervous system.[3] Following renal denervation, systemic sympathetic tone is reduced.[4] However, the SYMPLICITY HTN-3 trial[5] failed to demonstrate lower blood pressure in the renal denervation group compared with the sham control group. Following this trial, the therapeutic value of renal denervation in hypertension has been under debate, although recent smaller and carefully designed trials of a more limited scope have shown statistically significant antihypertensive effects.[6-8]

Catheter ablation via pulmonary vein isolation is an option for the many patients who have unsatisfactory responses to pharmacological therapy for atrial fibrillation. Although more effective than drug therapy for reducing atrial fibrillation recurrence,[9] ablation has a failure rate of 20% to 50%, a common need for repeat procedures,[10,11] and a significant long-term atrial fibrillation recurrence rate even after initial success.[12]

A pilot study assessed the effect of catheter ablation with or without renal denervation for patients with refractory atrial fibrillation and drug-resistant hypertension.[13] There were significant reductions with combined catheter ablation and renal denervation in atrial fibrillation recurrence, as well as systolic and diastolic blood pressures. The addition of renal denervation to pulmonary vein isolation was technically feasible and not accompanied by an increase in procedural complications.

The Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation (ERADICATE-AF), a large multicenter, single-blind, randomized clinical trial, was designed to test the hypothesis that renal denervation in addition to pulmonary vein isolation would enhance long-term antiarrhythmic efficacy compared with pulmonary vein isolation alone among patients with atrial fibrillation and hypertension.

Key Points

Question Does performing renal denervation with catheter ablation reduce the recurrence of atrial fibrillation among patients with hypertension and paroxysmal atrial fibrillation referred for catheter ablation?

Findings In this randomized clinical trial involving 302 patients, renal denervation added to catheter ablation, compared with catheter ablation alone, resulted in a statistically significantly greater proportion of patients who were free from atrial fibrillation over 12 months (72.1% vs 56.5%).

Meaning Renal denervation added to catheter ablation, compared with catheter ablation alone, significantly increased the likelihood of freedom from atrial fibrillation at 12 months.

Methods

Each site's institutional review board or ethics committee approved the study. Written informed consent was obtained from all patients.

This trial was supported by local research funds at participating institutions and no funds were provided by industry.

The protocol and statistical analysis plan are available in Supplement 1.

Study Population

Eligible patients were at least 18 years of age with a history of symptomatic paroxysmal atrial fibrillation and who had plans for a guideline-supported[10] catheter ablation procedure. *Paroxysmal atrial fibrillation* was defined as atrial fibrillation of a duration up to 7 days before spontaneous termination. Patients were also eligible if they had a history of clinically significant hypertension, defined as systolic blood pressure of 130 mm Hg or higher, diastolic blood pressure of 80 mm Hg or higher, or both and were taking at least 1 antihypertensive medication. Patients were excluded if they were unable to undergo an atrial fibrillation catheter ablation, had a previous left atrial ablation for any atrial arrhythmia, New York Heart Association (NYHA) class IV congestive heart failure or left ventricular ejection fraction less than 25%, persistent atrial fibrillation (duration >7 days), renal artery anatomy considered ineligible for treatment based on preablation magnetic resonance angiography, a history of renal artery intervention, impaired renal function with an estimated glomerular filtration rate of less than 45 mL/min/1.73 m^2 using the Modification Diet in Renal Disease calculation, or a life expectancy of less than 1 year for any medical condition.

Patients at 5 participating centers in the Russian Federation, Poland, and Germany who met enrollment criteria and consented to the study were randomized 1:1 to receive catheter ablation using pulmonary vein isolation alone or to catheter ablation using pulmonary vein isolation with the addition of renal denervation. Secure electronic randomization of eligible patients was provided by Sealed Envelope (London, United Kingdom; http://www.sealedenvelope.com). Randomization was stratified by center and used the random permuted-block technique with varying block size (4 or 8, chosen at random), which was concealed from investigators.

Trial Procedures

The atrial fibrillation ablation procedure included only pulmonary vein isolation without adjunctive left atrial lesion sets. A cavotricuspid isthmus line was placed in patients with either a history of electrocardiogram (ECG)–determined typical atrial flutter or if induced during the procedure. Additional details are provided in the eMethods section in Supplement 2.

Renal denervation was performed via femoral artery access after real-time 3-dimentional aorta-renal artery maps were constructed with the use of an ablation catheter (3.5-mm tip Thermocool family, Biosense Webster Inc) and an electroanatomic navigation system (CARTO, Biosense Webster Inc). The latter facilitated placing lesions in 3-dimensional space for

the goal of creating a spiral lesion set along the length of each renal artery. Additional details as well as examples were provided in the pilot study.[13] Mapping and ablation were performed after pulmonary vein isolation and under an identical sedation protocol used for atrial fibrillation ablation. Radiofrequency energy of 8 to 12 W (via a Stockert generator, Biosense Webster Inc) was applied discretely from the first distal main renal artery bifurcation back to the junction of the renal artery and the aorta. The duration of each radiofrequency delivery was 2 minutes, and lesions (separated by ≥5 mm) were created both longitudinally and rotationally within each renal artery in a spiral fashion.[13] To confirm renal denervation, high-frequency stimulation, if available at the local center, was performed before the initial and after each radiofrequency delivery within the renal artery. The criterion for success was met when the sudden increase of blood pressure of 15 mm Hg was eliminated. If high-frequency stimulation was not used or did not generate a hypertensive response, the renal denervation was performed on an anatomic basis only. The vast majority of patients underwent renal denervation using a standard irrigated-tip ablation catheter, identical to catheters used for ablation of cardiac arrhythmias. In select patients, operators elected to use a specifically designed and approved single or multielectrode radiofrequency delivery system for renal denervation based on local availability.

Systemic anticoagulation was administered to the patients for a minimum of 1 month before and after the procedure, including warfarin or a direct oral anticoagulant. The ablation procedure was performed on an uninterrupted anticoagulant regimen. Long-term management of anticoagulation was conducted according to the baseline risk status for embolic stroke and ablation guidelines.[10]

The operating physician was inevitably aware of the randomization assignment, but the patient was not informed. The blinding of the patient was maintained by the performance of renal denervation with uninterrupted sedation during the ablation procedure.

Trial End Points

The primary end point of this study was freedom from atrial fibrillation recurrence at 12 months and not taking antiarrhythmic drugs (not including the predefined 3-month blanking period following the ablation procedure). This end point was defined by atrial fibrillation duration of 30 seconds or more captured by ECG monitoring or any clinical presentation with atrial fibrillation. The definition of *atrial fibrillation* also included any observed atrial flutter or atrial tachycardia of 30 seconds or longer. The protocol specified 7-day Holter recordings at 3, 6, 9, and 12 months. Follow-up visits were scheduled at 1, 3, 6, 9, and 12 months. Patients were not permitted to be treated with antiarrhythmic drugs in follow-up, and if started, treatment was considered failed. Repeat ablation procedures were not permitted or if performed, considered a treatment failure. All procedure and outpatient adverse events were recorded.

Several prespecified secondary end points were prospectively collected. Blood pressure control was compared with baseline at 6 and 12 months (see eMethods for measurement methods in Supplement 2). Investigators were instructed to maintain the patients' antihypertensive medical regimens unless there was an adverse effect. Transthoracic echocardiograms were acquired at baseline and at 12 months. The study did not use an echo core lab. Measurements included left atrial diameter, interventricular septal thickness, and left ventricular ejection fraction. The occurrence of major adverse cardiac events was collected and included death, stroke, heart failure, major hemorrhage, nonstroke thromboembolic events, and cardiovascular hospitalization, to be reported individually and as a composite. Procedural adverse events included cardiac, vascular, renal, and other complications, and the duration of fluoroscopy and the procedure. Atrial fibrillation outcomes for patients while taking antiarrhythmic drugs were collected but have not been analyzed for this report. Plasma biomarkers and quality-of-life instruments were prespecified as secondary outcomes in the protocol but were eliminated once the study started. The performance of blood pressure measurement, the interpretation of the Holter recordings and the echocardiogram, and the collection of clinical events including cardiovascular hospitalization were completed by physicians and staff who were unaware of the patient treatment assignment.

Statistical Analysis

The trial plan intended to randomize a total of 300 patients in equal proportions to undergo atrial fibrillation ablation with pulmonary vein isolation alone or atrial fibrillation ablation with pulmonary vein isolation plus renal denervation. This sample size provided 80% power to detect a 40% difference in the 1-year incidence of recurrent atrial fibrillation, flutter, or tachycardia (from 40% to 24%) with probability of type I error fixed at 5%. Ablation success rates using pulmonary vein isolation alone have been reported in the range of 50% to 60%, and it was reasoned that an increase in the success rate to approximately 75% would be clinically meaningful and consistent with testing of other adjunctive interventional approaches.[10]

The primary end point analysis was performed according to the randomization group and was based on time-to-event analysis. Additionally, in a post hoc analysis, we assessed robustness of treatment effect by restricting the primary end point analysis to atrial fibrillation only. Between- and within-group comparisons of continuous data were performed with unpaired and paired *t* tests, respectively. Repeated blood pressure measurements were compared using linear mixed-effects models with treatment and time as fixed effects and participant as random effect. Post hoc analyses included primary end point and blood pressure analyses based on whether high-frequency stimulation was applied during renal denervation. Additionally, we performed mediation analysis to estimate the effect of renal denervation on time to atrial fibrillation, using blood pressure reduction as a mediating variable. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Missing data were not imputed. A 2-sided *P* value of less than .05 was considered statistically significant. All the analyses were executed using R Core Team version 3.5.0 statistical software

(http://www.R-project.org). Additional description of the statistical analysis is available in the eMethods in Supplement 2.

Results

Patients

A total of 392 patients were screened based on the presence of paroxysmal atrial fibrillation and hypertension when they were referred for catheter ablation at the enrolling sites from April 2013 to March 2018, and 90 patients were ineligible (**Figure 1**). The remaining 302 patients were randomized to receive either pulmonary vein isolation only (148 patients) or pulmonary vein isolation plus renal denervation (154 patients), and all patients underwent the assigned ablation procedure. During subsequent follow-up, 2 patients in each group died; 8 patients in the isolation-only group and 7 patients in the renal denervation group were lost to follow-up. There were no crossovers. Follow-up was completed in March 2019. For the 283 participants who completed the follow-up, all data were available for the primary end point, and less than 5% of data were missing for secondary end points.

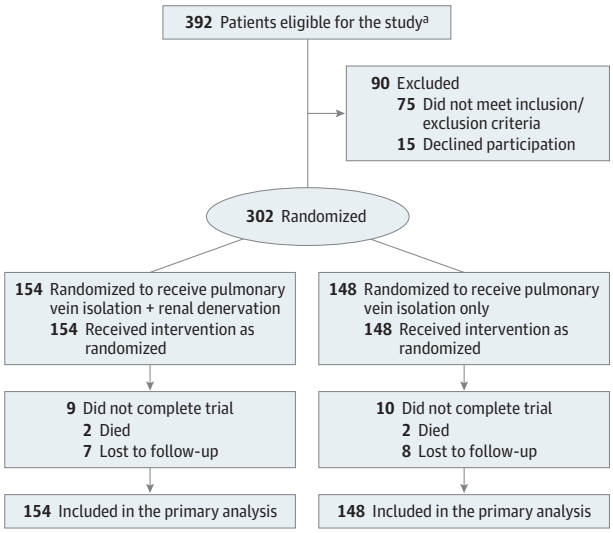
The demographics and clinical characteristics of the randomized patients were similar and are shown in **Table 1**. Among patients taking a median of 2 antihypertensive medications, the mean blood pressure was elevated in both groups: among those in the isolation-only group the mean systolic blood pressure was 151 mm Hg (95% CI, 148-151 mm Hg) and the diastolic blood pressure, 90 mm Hg (95% CI, 88-91 mm Hg) and among those in the renal denervation group, the mean systolic blood pressure was 150 mm Hg (95% CI, 149-152 mm Hg) and the diastolic blood pressure, 90 mm Hg (95% CI, 89-91 mm Hg).

Procedures

All patients in both groups had successful pulmonary vein isolation. In the isolation-only group, the mean cryoenergy delivery time was 16.9 minutes (95% CI, 15.8-18.0 minutes) and in the renal denervation group, 16.2 minutes (95% CI, 15.1-17.2 minutes; $P = .37$). Twenty-three patients (15.5%) in the isolation-only group and 26 patients (16.9%) in the renal denervation group underwent isthmus ablation for atrial fibrillation ($P = .75$).

The mean procedure time was significantly longer for the renal denervation group (190.2 minutes; 95% CI, 186.3-194.1 minutes) than it was for the isolation-alone group (167.3 minutes; 95% CI, 164.1-170.4 minutes; $P < .001$). Fluoroscopy was significantly longer for the renal denervation group (mean, 31.2 minutes; 95% CI, 29.1-33.3 minutes) than for the isolation-only group (mean, 25.6 minutes; 95% CI, 24.1-27.2; $P < .001$). High-frequency stimulation was used for 88 patients (57%) to help define the end point of renal denervation, and the remaining 66 patients (43%) underwent an anatomically guided procedure. Of these 88 patients, 13 patients did not exhibit a hypertensive response and therefore underwent an anatomically guided procedure. Radiofrequency energy was delivered to a median of 6 sites (95% CI, 6-7) in each renal artery using a standard irrigated-tip ablation catheter among 148 patients (96%) or a catheter designed and approved for renal denervation for 6 patients (4%).

Figure 1. Patient Flow in the Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation (ERADICATE-AF) Trial



[a] Sites were not required to provide screening logs during the recruitment phase. Thus, the number of patients assessed for eligibility is not available.

End Points

Primary End Point

The primary end point of freedom from atrial fibrillation, flutter, or tachycardia recurrence at 12 months was observed in 84 of 148 patients (56.5%) in the isolation-only group and in 111 of 154 patients (72.1%) in the renal denervation group. The hazard ratio (HR) for atrial fibrillation, flutter, or tachycardia recurrence favored the renal denervation group: 0.57 (95% CI, 0.38 to 0.85) with a *P* value of .006 by log-rank test (**Figure 2**). Of the 64 primary events in the isolation-only group and the 43 events in the renal denervation group, only 4 and 3 events were atrial flutter or tachycardia, and the remainder of each total was atrial fibrillation. Using an atrial fibrillation–only primary end point resulted in an HR of 0.55 (95% CI, 0.37-0.83; $P = .004$).

Prespecified Secondary End Points

Blood pressure control over the length of follow-up was examined compared with baseline measures (eFigure in Supplement 2). At 12 months, the mean baseline systolic blood pressure for the isolation-only group decreased from 151 mm Hg (95% CI, 148 to 151 mm Hg) to 147 (95% CI, 146 to 149) mm Hg, for a mean reduction of 3 mm Hg (95% CI, 0 to 5 mm Hg; $P = .07$). The mean baseline systolic blood pressure for the renal denervation group decreased from 150 mm Hg (95% CI, 149 to 152 mm Hg) to 135 mm Hg (95% CI, 133 to 136 mm Hg), for a mean reduction of 16 mm Hg (95% CI, 14 to 18 mm Hg; $P < .001$). The between-group difference was -13 mm Hg (95% CI, −15 to −11 mm Hg; $P < .001$).

At 12 months the mean diastolic blood pressure for the isolation-only group decreased from 90 mm Hg (95% CI, 88 to 91 mm Hg) to 88 mm Hg (95% CI, 86 to 89 mm Hg), for a mean reduction of 2 mm Hg (95% CI, 0 to 5 mm Hg; $P = .06$). For the

Table 1. Baseline Demographics and Clinical Characteristics

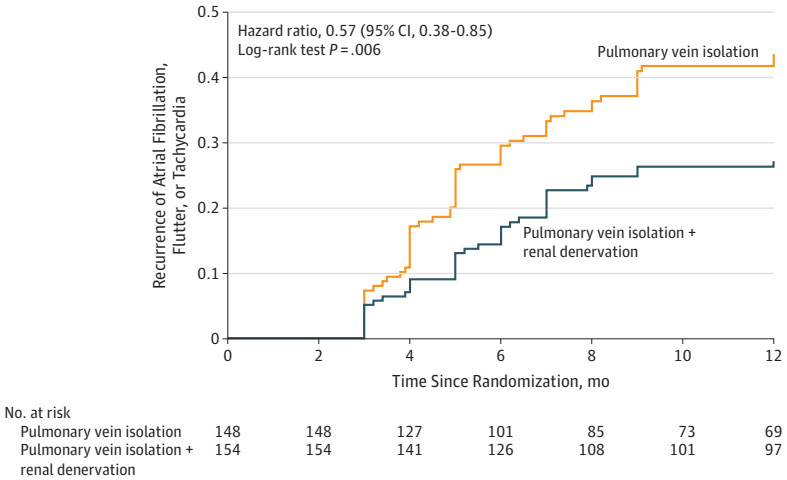
Baseline Characteristic	Pulmonary Vein Isolation	
	With Renal Denervation (n = 154)	Alone (n = 148)
Age, median (IQR), y	59 (54-65)	60 (58-65)
Sex, No. (%)		
Men	91 (59.1)	91 (61.5)
Women	63 (40.9)	57 (38.5)
Atrial fibrillation history, median (IQR), y	3.6 (2.9-4.1)	3.6 (3.1-4.2)
Sinus rhythm at ablation, No. (%)	130 (86.4)	128 (86.4)
Medical history, No. (%)		
NYHA class II heart failure[a]	119 (77.3)	117 (79.1)
Obesity	22 (16.8)	25 (16.8)
Diabetes	16 (10.3)	18 (12.1)
Coronary artery disease	14 (9.1)	10 (6.7)
Blood pressure, mean (SD), mm Hg		
Systolic	150 (9)	151 (9)
Diastolic	90 (7)	90 (7)
Serum creatinine, mean (SD), mg/dL	0.83 (0.11)	0.83 (0.11)
Estimated GFR, mL/min/1.73 m^2	79 (11)	76 (11)
Echocardiography, mean (SD)		
Left ventricular ejection fraction, %	62 (5)	62 (5)
Left atrial diameter, mm	48 (3)	47 (3)
Interventricular septum width, mean (SD), mm	12 (2)	12 (1)
Antihypertensive drugs, No. (%)		
ACEI or ARB	154 (100)	148 (100)
Calcium channel blocker	104 (67.5)	105 (70.9)
β-Blocker	36 (23.3)	32 (21.6)
Diuretic	27 (17.5)	27 (18.2)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; NYHA, New York Heart Association.

SI conversion factor: To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

[a] NYHA classification scale I-IV; class II connotes slight limitation with physical activity.

Figure 2. Atrial Fibrillation, Flutter, or Tachycardia Occurrence



Atrial fibrillation, flutter, or tachycardia among patients randomized to pulmonary vein isolation were followed up for a median of 9 months (interquartile range [IQR], 5-12] months) or pulmonary vein isolation plus renal denervation for a median of 12 moths [IQR, 7-12] months). A 3-month blanking period precedes primary end point capture.

renal denervation group, the mean baseline diastolic blood pressure decreased from 90 mm Hg (95% CI, 89 to 91 mm Hg) to 79 (95% CI, 77 to 80) mm Hg, for a mean reduction of 11 mm Hg (95% CI, 10 to 13 mm Hg; $P < .001$). The between-group difference was -10 mm Hg (95% CI, -11 to -8 mm Hg; $P < .001$). Additional data are available in eResults in Supplement 2.

Echocardiographic results are detailed in eResults in Supplement 2.

Seven patients in each group had a complication: 4.7% in the isolation-only group and 4.5% in the renal denervation group for an absolute risk difference of 0.1% (95% CI, -4.0% to 4.4%; $P > .99$). Additional details are provided in the eResults

Table 2. Primary and Secondary End Points (per Randomization Group)

	Events, No. (%) of Patients Pulmonary Vein Isolation		Kaplan-Meier 12-Month Event Rate, % Pulmonary Vein Isolation				
	With Renal Denervation (n = 154)	Alone (n = 148)	With Renal Denervation (n = 154)	Alone (n = 148)	Absolute Difference	Hazard Ratio (95% CI)[a]	*P* Value[b]
Primary end point of atrial fibrillation, flutter, or tachycardia	43 (27.9)	64 (43.2)	27.9	43.5	−15.6 (−23.2 to −7.9)	0.57 (0.38 to 0.85)	.006
Secondary end points: systolic blood pressure reduction at 12 mo[c]							
≥10 mm Hg	121 (78.5)	32 (21.6)	79.6	23.0	56.6 (52.1 to 61.7)	3.59 (2.43 to 5.31)	.001
≥20 mm Hg	59 (38.3)	5 (3.3)	39.6	3.6	36.0 (32.1 to 39.9)	11.23 (14.50 to 27.98)	.001
Echo variables at 12 mo							
Left ventricular ejection fraction increase ≥5%[d]	13 (8.4)	3 (2.0)	12.4	2.3	10.1 (6.6 to 13.5)	3.34 (0.95 to 11.75)	.056
Left atrial size reduction ≥2 mm	73 (47.4)	9 (6.0)	60.0	9.0	51.0 (45.7 to 56.2)	6.13 (3.06 to 12.26)	.001
Interventricular septal thickness reduction ≥2 mm	79 (51.2)	16 (10.8)	64.5	16.2	48.3 (42.6 to 54.0)	3.76 (2.19 to 6.44)	.001
Procedural complications	7 (4.5)	7 (4.7)	4.5	4.7	−0.2 (−1.8 to 1.5)	0.96 (0.33 to 2.74)	.96
Hospitalization[d]	8 (5.2)	18 (12.1)	6.3	17.1	−10.8 (−14.9 to −6.6)	0.36 (0.15 to 0.84)	.01
Death	2 (1.3)	2 (1.3)	1.6	1.7	−0.1 (−1.5 to 1.3)	0.84 (0.11 to 6.03)	.90

[a] Hazard ratio for comparing pulmonary vein isolation plus renal denervation vs pulmonary vein isolation alone.

[b] *P* value from Wald test in a univariable mixed-effects Cox regression model with a time-to-event object (ie, an end point in first column) as dependent variable, group as fixed effect and center as random effect.

[c] Blood pressure outcomes were prespecified secondary end points but the cut points presented in this table were post hoc designations.

[d] Post hoc outcome.

of Supplement 2. There were no renal artery or femoral artery complications. All complications in both groups were attributed to the pulmonary vein isolation procedure.

The composite fatal and nonfatal major adverse cardiac events totaled 20, with 10 in each group. Two patients died in each group during follow-up, none related to the ablation procedure. In the renal denervation group, 1 patient had fatal myocardial infarction 9 months after randomization and 1 patient died of a noncardiovascular cause 7 months after randomization. In the pulmonary vein isolation only group, 1 patient, despite anticoagulation, had a fatal stroke 8 months after randomization and 1 patient died of a noncardiovascular cause 7 months after randomization.

A comparison of the primary, secondary, and adverse event end points in both study groups and the associated HRs are shown in **Table 2.**

Additional and Post Hoc Analyses

In the pulmonary vein isolation only group, 18 patients (12.2%) were hospitalized for cardiovascular causes (16 for atrial fibrillation–related symptoms and 2 for hypertensive crisis) vs 8 patients (5.2%) (5 for atrial fibrillation–related symptoms, 2 for cardiac or vascular surgery, 1 for myocardial infarction) in the renal denervation group (absolute risk reduction, 7.0%; 95% CI, 1.6%-12.5%; *P* = .03).

Of the 88 patients who had high-frequency stimulation during the renal denervation procedure, the primary end point occurred in 23 patients (14.9%) vs 19 patients (12.3%) in those without high-frequency stimulation (HR, 0.85; 95% CI, 0.46-1.57). At 12 months, systolic blood pressure among patients who had high-frequency stimulation (median, 120 mm Hg; interquartile range [IQR], 120-130 mm Hg) did not differ significantly from those who had not (median, 125 mm Hg; IQR, 125-135 mm Hg; *P* = .16).

Mediation analysis indicated that patients who had undergone renal denervation developed atrial fibrillation 3.2 months (95% CI, 0.6 to 5.9 months) later than patients in the isolation-only group (total effect). The degree of systolic blood pressure reduction had no statistically significant contribution to this effect: -0.1 months for 1-mm Hg reduction (95% CI, −1.6 to 1.3 month) (indirect effect).

Discussion

Among patients with symptomatic paroxysmal atrial fibrillation with a history of suboptimally controlled hypertension who were referred for catheter ablation, this trial demonstrated that the addition of renal denervation to pulmonary vein isolation resulted in significantly increased likelihood of freedom from atrial fibrillation over 12 months compared with ablation alone.

The renal denervation component of the procedure was accomplished without any additional risk of complications and added a small amount of procedural and fluoroscopy times. Specifically, there were no renal or renal artery complications during the inpatient phase and throughout follow-up. The addition of renal denervation was also associated with significantly better blood pressure control and significantly lesser need for cardiovascular hospitalization.

Renal denervation was developed for the treatment of resistant hypertension and is accomplished by ablating the renal sympathetic efferent and afferent nerves that interact with the central autonomic nervous system.[3] The potential for an antiarrhythmic effect of renal denervation is based on the observation of reduced systemic sympathetic tone as demonstrated by a decrease in norepinephrine spillover and muscle sympathetic nerve activity.[4] The heart is richly innervated by autonomic nerve fibers, and adrenergic activation may act as a trigger on a vulnerable substrate, maintain a source for the clinical development of atrial fibrillation, or both.[1] Preclinical research indicated several potential atrial antiarrhythmic effects of renal denervation including less slowed or heterogeneous conduction, shorter and less dispersed refractoriness, less fibrosis, reduced neurohumoral activation, less sympathetic nerve sprouting, and diminished stellate ganglion activity.[14-19]

Given this foundation of cardiac effects of renal denervation, a small, pilot, randomized trial was conducted involving a diverse sample of 27 patients with paroxysmal or persistent atrial fibrillation and with hypertension (systolic blood pressure >160 mm Hg) resistant to at least 3 medications. The patients who underwent renal denervation had a lower rate of atrial fibrillation recurrences, with 69% free of atrial fibrillation at 1 year.[13]

Although many ablation systems have been developed for the specific purpose of achieving renal denervation, this study primarily used standard irrigated-tip ablation catheters (with a modified protocol) that are commonly used for the treatment of a variety of arrhythmias due to deeper and larger lesion size and avoidance of char formation.[20] For 57% of patients who underwent renal denervation in the present study, the technical end point was elimination of the hypertensive response to high-frequency stimulation in the renal artery, but in the 43% of patients who did not have this guidance, the arrhythmia outcomes were similar.

The use of renal denervation for the therapeutic goal of blood pressure control in resistant hypertension was questioned by the results of the sham-controlled SYMPLICITY HTN-3 trial.[5] In this 6-month multicenter study involving more than 500 patients, both office and 24-hour ambulatory blood pressure were similar between the renal denervation and the control groups. The design and technical application of renal denervation in SYMPLICITY HTN-3 have been critiqued,[21,22] and more recent randomized trials have shown significant antihypertensive effects resulting in decreased systolic blood pressure of 7 and 9 mm Hg at 2 and 6 months, respectively, on ambulatory blood pressure monitor.[6,8] In the current study, there was a significant improvement in blood pressure control over time in the renal denervation–group only, confirming an antihypertensive effect. The patients enrolled in this study did not formally have resistant hypertension but rather had suboptimal blood pressure control despite taking at least 1 antihypertensive drug. The results of this study were based on repeated office blood pressure measurements and may overestimate the antihypertensive effect of renal denervation; ambulatory blood pressure monitoring was not part of the protocol because blood pressure control was not the primary focus of this trial.

The mechanism by which renal denervation improved atrial fibrillation outcome may have involved better blood pressure control, a direct antiarrhythmic effect mediated by sympatholysis, or both. However, intensified medical anti-hypertensive therapy periablation has not been associated with improved postprocedural outcomes,[23] and the anti-arrhythmic effects of renal denervation seen across the spectrum of resistant to milder hypertension, in the setting of ventricular arrhythmias[24] and other conditions such as sleep apnea and heart failure,[25] suggest that a unifying mechanism of therapeutic action could be the reduction of central sympathetic output. Consistent with this proposed mechanism, the outcome in this study was not correlated with blood pressure control.

This study followed a noninvasive ECG monitoring schedule that was rigorous and exceeded standards for clinical trials of atrial fibrillation ablation.[10] An implantable loop recorder was not used because it was not part of the standards for clinical trial follow-up.[10] Given the intensity of ECG recording implemented, the absence of antiarrhythmic drug use, and a 30-second definition of atrial fibrillation, flutter, or tachycardia, the results of pulmonary vein isolation alone in this trial were in the range observed in large randomized trial data sets.[25]

Limitations

This study has several limitations. First, this study involved patients with hypertension and cannot be extrapolated to patients who are not hypertensive. Second, blood pressure control before enrollment was suboptimal, a common finding among patients with hypertension.[26] Third, it cannot be certain if other techniques of renal denervation would have the same effects. Fourth, the renal denervation procedure was not formally sham controlled, but because of atrial fibrillation ablation, all patients were sedated, blinded, and not informed about which type of procedure they received, and underwent an invasive procedure that would be difficult to distinguish between pulmonary vein isolation only or if renal denervation was added. Fifth, a single operator performed one or both procedures, depending on study group, and it was not feasible to add a second operator for the renal denervation portion alone to facilitate double blinding. Sixth, the study was not powered to perform subgroup analyses. Seventh, an approach that used the same irrigated-tip catheter for both pulmonary vein isolation and renal denervation would be efficient and potentially more cost-effective. However, cryoballoons were used routinely for pulmonary vein isolation in the participating centers prior to the launch of this trial, and a radiofrequency technique was not implemented to avoid biasing the results in the control group.

Conclusions

Among patients with paroxysmal atrial fibrillation and hypertension, renal denervation added to catheter ablation, compared with catheter ablation alone, significantly increased the likelihood of freedom from atrial fibrillation at 12 months. The lack of a formal sham-control renal denervation procedure should be considered in interpreting the results of this trial.

ARTICLE INFORMATION

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Correction: This article was corrected online March 3, 2020, for a mislabled row stub in Table 2.

Author Contributions: Drs Steinberg and Romanov had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Steinberg, Shabanov, Losik, Ivanickiy, Pokushalov, Romanov.
Acquisition, analysis, or interpretation of data: Steinberg, Ponomarev, Kropotkin, Polyakov, Ptaszynski, Keweloh, Yao, Pokushalov, Romanov.
Drafting of the manuscript: Steinberg, Ponomarev, Losik, Ivanickiy, Polyakov, Yao, Pokushalov, Romanov.
Critical revision of the manuscript for important intellectual content: Shabanov, Ponomarev, Kropotkin, Ptaszynski, Keweloh, Romanov.
Statistical analysis: Ponomarev, Romanov.
Obtained funding: Pokushalov.
Administrative, technical, or material support: Shabanov, Kropotkin, Polyakov, Ptaszynski, Keweloh, Yao, Pokushalov, Romanov.
Supervision: Steinberg, Pokushalov.

Conflict of Interest Disclosures: Dr Steinberg reported serving as a consultant for Medtronic, Biosense Webster, National Cardiac, Allergan, Atricure, Corfigo, Omron; having equity in National Cardiac Inc and AliveCor; and receiving research support from the National Institutes of Health and Medtronic. Dr Ptaszynski reported receiving personal fees from Medtronic and Johnson & Johnson. No other disclosures were reported.

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Additional Information: *Clinical Sites and Enrollment:* E. Meshalkin National Medical Research Center, Novosibirsk (129 patients), Federal Center of Cardiovascular Surgery, Krasnoyarsk (118 patients), Federal Center of Cardiovascular Surgery, Khabarovosk (43 patients), Medical University, Lodz (8 patients), and Unfallkrankenhaus, Berlin (4 patients).

Data Sharing Statement: See Supplement 3.

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