
**eMethods.** Trial Procedures, End Points, and Statistical Analysis

**eResults.** Search strategy for EMBASE (using Embase.com)

**eFigure.** Office Blood Pressure at Baseline, 6 Months, and 12 Months After Randomization

**eReference**

This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods

**Trial Procedures**

Patient anesthesia was administered as moderate sedation for pulmonary vein isolation and renal denervation with fentanyl, and sibazon or midazolam. Sedation was titrated so patients would not experience any pain during the procedure, especially during the renal denervation component, if performed. Arterial and venous access was usually achieved through cannulation of the right and/or left femoral arteries and veins. Full systemic anticoagulation was instituted to a target activated clotting time of approximately 350 seconds or greater.

Pulmonary vein isolation was accomplished by a 28 mm cryoballoon catheter (Medtronic, Inc., Minneapolis, MN), with 1-2 freezes/vein of duration 180-240 seconds. Complete pulmonary vein isolation was the goal of the ablation procedure and confirmed by a multielectrode mapping catheter within each PV that demonstrated disappearance or dissociation of all PV potentials, and exit block.

Systemic anticoagulation was administered to the patient 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.

**Trial End Points**

BP was determined manually at the study visits as the mean of 3 consecutive readings. Patients were asked to sit quietly for 5 minutes before initial BP measurement. Cuff size was selected based on patient arm circumference. Each BP measurement was separated by 1-2 minutes. Ambulatory BP monitoring was not performed.

**Statistical Analysis**

The primary outcome analysis was done according to the randomization group and was based on time to event analysis of the primary end point. Periods at risk of arrhythmia were defined in months for each person, such that each period between the end of the blanking period and the first arrhythmia event or between the end of the blanking period and censoring date, constituted a separate observation. An observation that did not result in an event could end in death, loss to follow-up or end of the study period (i.e. 12 months). The cumulative probability for AF/AFL/AT was calculated using a Kaplan-Meier estimator. The log-rank test was used to explore differences of freedom from the primary end point between the two groups. Additionally, a mixed-effects univariable Cox regression model with group as fixed effect and center as random effect was used to estimate the hazards ratio (HR) of AF/AFL/AT as primary end point associated with the addition of renal denervation to pulmonary vein isolation. The constant relative hazard assumption was investigated by correlating scaled Schoenfeld residuals with a suitable transformation of time, along with a global test for the model as a whole. The assumption of linearity between log-hazard ratio and the covariate was assessed graphically by plotting Martingale residuals against the covariate. Based on the above methods, relevant assumptions of Cox proportional hazards model were considered as valid. Between-group comparisons of continuous data were done with an unpaired t-test. Data on adverse events were collected for the period between the date of randomization and the end of the 12 months follow-up period. Additionally in a post-hoc analysis, we assessed robustness of treatment effect by restricting the primary end point analysis to AF only. Ordinal data were compared with Mann-Whitney test. Repeated BP measurements were compared using linear mixed-effects models with treatment and time as fixed effects and participant as random effect to account for within-participant correlation. The P values reported by mixed-effects models were corrected for multiplicity using the Tukey’s single-step method. The cut points for the secondary echocardiographic endpoints were selected based on commonly employed clinical values. Post-hoc analyses included primary end point and BP analyses based on whether high frequency stimulation was applied during renal denervation. Additionally, we performed mediation analysis to estimate total, direct and indirect effects of renal denervation on time to AF, using systolic BR reduction as a mediating variable as described by Fulcher et al.1 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 two-sided P value of less than 0.05 was considered statistically significant. All the analyses were executed using R Core Team version 3.5.0 statistical software (Vienna, Austria; www.R-project.org).

A post-hoc analysis tested if the use of high frequency stimulation was associated with AF outcomes and BP control. The echocardiographic end points were prespecified as continuous variables, but also tested post hoc with a cutpoint of 2 mm for left atrial size reduction and interventricular septal thickness reduction, and 5% for left ventricular ejection fraction improvement.
eResults

Prespecified Secondary End Points. Mean baseline SBP was 151 mm Hg (95% CI, 148 to 151 mm Hg) in the renal denervation group and 150 mm Hg (95% CI, 149 to 152 mm Hg) in the pulmonary vein isolation only group. While there was no statistically significant change in the pulmonary vein isolation only group at 6 and 12 months relative to baseline, -2 (95% CI, -3 to 0) (P=0.07) and -3 (95% CI, -3 to 0) mm Hg (P=0.06), respectively, the pulmonary vein isolation plus renal denervation group had a statistically significant reduction in SBP at 6 and 12 months of 15 (95% CI, 13 to 16) (P<0.001) and 16 (95% CI, 14 to 17) mm Hg (P<0.001), respectively. This was reflected in between-group differences of -13 (95% CI, -15 to -11) (P<0.001) and -13 (95% CI, -15 to -11) mm Hg (P<0.001) at 6 and 12 months, respectively.

Mean baseline DBP was 90 mm Hg (95% CI, 88 to 91 mm Hg) in the renal denervation group and 89 mm Hg (95% CI, 88 to 91 mm Hg) in the pulmonary vein isolation only group. While there was no significant change in the pulmonary vein isolation only group at 6 and 12 months relative to baseline, -1 (95% CI, -2 to 0) (P=0.08) and -3 (95% CI, -4 to 1) mm Hg (P=0.10), respectively, the pulmonary vein isolation plus renal denervation group had a significant reduction in DBP at 6 and 12 months of 11 (95% CI, 10 to 12) (P<0.001) and 11 (95% CI, 10 to 12) (P<0.001) mm Hg, respectively. The between-group differences were -10 (95% CI, -11 to -9) (P<0.001) and -10 (95% CI, -13 to -10) mm Hg (P<0.001) at 6 and 12 months, respectively.

The echocardiogram revealed that the baseline left atrial diameter was 48 (95% CI, 47 to 49) mm in the renal denervation group and 48 (95% CI, 46 to 49) mm in the pulmonary vein isolation only group (P=0.10). At 12 months, left atrial diameter was 47 (95 CI, 46 to 47) mm (mean reduction of 1 [95% CI, 0.1 to 1.2] mm; P<0.001) in the former group and 47 (95% CI, 47 to 48) mm (mean reduction of 0.7 [95% CI, 0.5 to 0.9] mm; P=0.01) in the latter. The between-group difference at 12 months was -0.5 (95% CI, -1.1 to -0.1) (P=0.01) mm. The addition of renal denervation resulted in a significant decrease of interventricular septal thickness from 12 (95% CI, 11 to 12) mm to 10.2 (95% CI, 10 to 11) mm (mean reduction of 1.8 [95% CI, 1.5 to 2.1] mm; P<0.001). In the pulmonary vein isolation only group, interventricular septal thickness decreased from 12 (95% CI, 11 to 12) mm to 11.9 (95% CI, 11.7 to 12.1) mm (mean reduction of 0.1 [95% CI, -0.2 to 0.5] mm, P=0.27); between group difference was -1.7 (95% CI, -2.1 to -1.3) (P<0.001) mm. There was no significant change in LV ejection fraction in either group.

Procedural Adverse Events. In the pulmonary vein isolation group, complications were comprised of 4 femoral venous vascular events not requiring intervention, 1 transient phrenic nerve palsy, 1 cardiac tamponade successfully resolved with pericardiocentesis and 1 pneumothorax (after subclavian vein puncture for placement of a coronary sinus catheter). In the pulmonary vein isolation plus renal denervation, complications were comprised of 6 femoral venous vascular events not requiring intervention and 1 transient phrenic nerve palsy.

eFigure Legend

eFigure 1. Office Blood Pressure at Baseline, 6 Months, and 12 Months After Randomization

Data are means (SDs). Repeated measures are corrected for multiplicity using Tukey’s single step technique.

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