Effect of Renal Denervation on Recurrence of Atrial Fibrillation: A Meta-Analysis

Running title: Atrial Fibrillation decreased by Renal Denervation

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Abstract

Renal denervation (RDN) is a novel percutaneous procedure that reduces the sympathetic activity to the atria and the systemic blood pressure, both of which can potentially decrease atrial fibrillation (AF) recurrence. Pulmonary vein isolation (PVI) via radiofrequency or cryoablation is performed in treatment-refractory patients with atrial fibrillation. We performed a systematic review and meta-analysis to study the effects of RDN on AF recurrences with PVI vs. isolated PVI. We searched PubMed, Medline, and Google Scholar database from January 01, 2005, to January 01, 2020, for randomized control trials (RCTs) that compared the PVI for atrial fibrillation treatment with or without RDN. The primary endpoint was freedom from AF recurrence with a follow-up period of 12 months. We selected 5 RCTs comprising a total of 496 patients (249 in RDN+PVI arm and 246 in PVI only arm). RevMan Version 5.3 Copenhagen was used to calculate relative risk (RR) of dichotomous data using a random-effects model for our review and analysis. The use of RDN in addition to PVI lead significantly more patients who were free from AF recurrence compared to PVI alone at 12 months (173 vs. 119; RR=2.70; 95% confidence interval (CI) =1.59–4.59, p=0.0002, I^2=36%). The analysis showed a significant benefit of RDN addition to PVI in reducing the AF recurrence. This is an interesting finding which needs further investigation to evaluate the safety of concomitant RDN and PVI and effect on long term survival.

Keywords: Renal Denervation; Pulmonary vein isolation; Atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia. [1] The management of AF can be challenging as some patients remain asymptomatic while others present with decremental quality of life. [1] Atrial fibrillation increases the risk of stroke, hospitalization for heart failure, late cognitive impairment, and mortality. [1, 2] The ideal approach for the treatment of AF is rhythm control, but it is sometimes hard to accomplish with anti-rhythmic drugs only. [3] Since the proposal of Haïssaguerre's theory regarding ectopic beats originating from pulmonary veins in the late 90s [4] the technique of AF ablation by pulmonary vein isolation (PVI) has substantially evolved into one of the mainstays of the rhythm control strategy. [5] Hypertension (HTN) is a significant risk factor for developing AF. The incidence of AF also increases with left ventricular (LV) hypertrophy, coronary heart disease, and heart failure. [6] Atrial fibrillation patients complicated with uncontrolled hypertension are associated with worse clinical prognosis. [7] The increase in sympathetic tone frequently precedes the onset of AF [8], and excessive sympathetic activation can predict recurrences of AF after catheter ablation. [9] The events involved in triggering AF involve stimulation of canine cervical vagal trunk, which shortens the AF effective refractory period (ERP), thereby increasing its frequency and duration. Autonomic denervation has been found beneficial in patients subjected to PVI for AF as it affects both the parasympathetic and sympathetic components of the autonomic innervation to the atria. [10, 11] Renal denervation (RDN) affects the sympathetic nervous system and decreases blood pressure; therefore, it may have an additive or synergistic effect on the reduction of recurrence of AF after PVI. There have been a few randomized controlled trials (RCT) that have attempted to add RDN procedure to PVI and to compare PVI alone for the treatment of AF. [12-15] The meta-analysis by Atti et al. [16] and Ukena et al. [17] analyzed five and six studies in their meta-analysis, respectively. However, these meta-analyses had duplication of data in Pokushalov et al. [6] and Romanov et al. [18] studies that used the same RCTs from clinicaltrials.gov. There was a duplication of data between the two studies of Pokushalov (6,13) as the second study by Pokushalov et al. (13) reported the incorporation of 27 subjects from its earlier published study. (6) Another meta-analysis from Chen et al. used non- RCTs in the analysis as well. [19] We have, therefore, conducted this systematic review and

meta-analysis, including 5 RCTs to evaluate the effectiveness of combined RDN with PVI on reducing AF recurrence compared to isolated PVI.

Materials and Methods:

We completed our systematic review following the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines. [20] We searched for RCTs using MEDLINE, PUBMED, and Google Scholar databases from January 01, 2005, till May 1, 2020, for RCT using RDN and PVI in patients with AF. We used the following keywords and MeSH terms: renal denervation, RDN, pulmonary vein isolation, PVI, ablation, atrial fibrillation, and AFIB. We combined search terms using Boolean operators 'OR' and 'AND'.

Our search strategy identified a total of 23 citations. After reviewing the abstracts of 23 studies, 16 were excluded because either they were duplication of the studies or were non-randomized studies. We completed the second search by reviewing the references of 7 RCTs. Two reviewers (M.S.R. and W.J.S.) reviewed the full text of 7 identified studies. They excluded one study because it was the study design for the RCT [21] and two studies had a reproduction of its results in the subsequent paper. (6, 17) After a careful systematic review, four research articles, including 5 RCTs, were included in the final qualitative and quantitative analysis. One research article had incorporated the results of two RCTs. (13)

Inclusion criteria: The eligibility criteria for our systematic review included (1) human subjects aged greater than or equal to 18 years, (2) randomized to RDN + PVI vs. PVI alone, and (3) reported AF recurrence at 12 months.

M.S.R. extracted data into predefined fields on a Microsoft Excel sheet for baseline characteristics and study outcomes. W.J.S. cross-checked the data and made the necessary corrections. The two reviewers resolved any discrepancies with mutual discussion and understanding. Figure 1 shows the study flow diagram. We assessed the quality of the individual study using the Cochrane collaboration’s tool for determining the risk of bias in randomized trials. [22]

Our primary clinical outcome was of recurrence of AF at 12 months. We used the longest available follow-up data from individual studies for our analysis.

We performed meta-analysis using the random-effects model and the Mantel-Haenszel method in Review Manager (RevMan) Version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen) to calculate the odds ratio (OR). We reported results as a forest plot. A two-sided p-value of <0.05 was considered statistically significant.

We used I^2 statistics to calculate the heterogeneity. We considered I^2>50% as substantial heterogeneity, as explained in the Cochrane Handbook for Systematic Reviews. [23] We performed a sensitivity analysis for substantial heterogeneity

Results:

We included 5 RCTs with a total of 496 patients (RDN with PVI=249 and PVI alone=247) for the analysis. The baseline characteristics of individual trials are listed in Table 1. The characteristics of each study are summarized in Table 2. Assessment of Cochrane risk of bias is summarized in Table 3.
We noticed a significantly higher number of patients who were free from recurrence of AF at the 12-month period in the RDN with PVI arm, compared to PVI alone, (173 vs. 119, OR = 2.70, 95% confidence interval = 1.59 – 4.59, p = 0.0002, I^2 = 36%). Figure 2.

Discussion:

Rhythm control is the treatment of choice for AF; however, in patients with inadequate response to medical therapy alone, the catheter ablation to isolate pulmonary veins is the treatment of choice. [12, 14] While PVI has shown a higher success rate than pharmacological treatment, it still has a significantly high failure rate of 20%-50% requiring repeat ablations for AF recurrence after an initially successful procedure. [12] Increased sympathetic activation is a predictor for AF recurrences after PVI. [13] Recently, in addition

to PVI, RDN (which involves the use of radiofrequency energy via a percutaneous catheter system) is used to disrupt the renal sympathetic activity. [12-15] Our analysis showed that the patients who underwent RDN, in addition to PVI, had significantly reduced AF recurrence compared to patients who underwent PVI alone.

The cardiac sympathetic drive is known to contribute to the onset and progression of AF by shortening the AF effective refractory period (ERP), [12, 13, 16, 24] Persistent or recurrent AF progressively diminishes atrial ERP, increasing ERP dispersion and other atrial remodeling changes, which thereby maintain AF by giving rise to more such events. [24] The administration of ANS blockers helps in reducing atrial heterogeneity, hence reversing atrial electrical remodeling. [24] The events initiating AF maintain a high blood pressure due to sympathetic activity, which forms a vicious pathological cycle between hypertension and AF. [14] Persistent hypertension results in cardiac structural changes leading to impaired LV diastolic function, which is associated with increased risk of AF. [14]

Renal denervation is a novel procedure that ablates the renal sympathetic innervation. By disrupting renal sympathetic nerves connection with the ANS, the systemic sympathetic tone can be reduced. [12] Per the literature, RDN prevents atrial electrophysiological changes, improves fibrosis, and reduces atrial sympathetic nerve sprouting in addition to blood pressure control. Renal denervation has been tested for resistant hypertension with promising outcomes, as demonstrated by SIMPLICITY trials and metanalyses. [12, 25] By decreasing the arterial hypertension, RDN also subsequently helps in reversing LV and LA remodeling. [14] Renal denervation has shown to improve left ventricular longitudinal strain, reduce end-systolic volume, and decrease in cardiac fibrosis. All these effects, in turn, lead to an overall improved cardiac function and inhibits activation of the renin-angiotensin-aldosterone system in the kidney. [26, 27] Two studies included in our analysis, Eradicate HF, and Kiuchi et al. [15] showed improvement in left atrial diameter in the RDN group more than the isolated PVI group. However, no significant change was determined in the left ventricular ejection fraction (LVEF) in the ERADICATE-HF study, but Kiuchi et al.

reported improvement in LVEF in the RDN group. [12, 15] This improvement in the left atrial diameter is likely the result of a reduction in afterload with RDN and left ventricular end-diastolic pressure.

Four studies that included patients with resistant hypertension also reported a decrease in overall blood pressure compared to baseline. (12-14) Kiuchi et al. [15] in their study with controlled hypertension subjects, showed a significant reduction in AF recurrence in the RDN group compared to PVI alone without any significant change in BP at the end of follow up period of 12 months. These findings suggest that irrespective of the BP control, RDN may have a direct effect on preventing the recurrence of atrial fibrillation. PVI eliminates the principal triggering source for AF; however, for patients with substantial pathology in the atrial substrate, additional intervention such as RDN can have a sustained antiarrhythmic effect. The results from Kiuchi et al. [15] suggest that freedom from AF recurrence is not only accomplished by BP control but through other pathways, including reverse cardiac modeling and suppression of sympatholytic activity resulting in anti-arrhythmic activity and a better AF control by prolonging the atrial ERP. [12, 28]

The utilization of RDN, in addition to PVI in the treatment of AF, is appropriate without any significant increase in procedure associated complications. [14, 15] However, ERADICATE – HF reported 4.5% of subjects developing complications in RDN + PVI as compared to 4.7% in isolated PVI group, but it was not statistically significant. [12]

Our results show a significant benefit in reducing AF recurrence when PVI is combined with RDN as compared to PVI alone for the treatment of AF. We believe large randomized trials are needed with extended follow up times to compare the effectiveness and safety of the addition of RDN to PVI in the treatment of AF. One important factor to look at in future studies if there is any improvement in the left atrial volume index since the left atrial volume index of ≥ 34 ml/m^2 is associated with an increased risk of AF recurrence.

The strengths of our analysis are that we only included RCTs as compared to the previous meta-analysis, which also included non-randomized studies and had duplication of data. Secondly, our analysis has more patients than any meta-analysis reported to date on this topic. Thirdly, despite small sample sizes of individual studies, our analysis only has moderate heterogeneity of 36%.

There were several limitations in our meta-analysis which include 1) Our analysis consists of five RCTs with small sample sizes which increases the risk of heterogeneity and bias, therefore to determine the actual clinical benefit of RDN in treating AF, large RCTs are needed with adequate power, 2) the follow-up period after RDN + PVI was one year only and did not have a longer follow-up to determine the recurrence rate of AF after 12 months, 3) over time, the technique of AF ablation has been changing from radiofrequency ablation to cryo-ablation, if there is any difference in the two approaches, it is not addressed, 4) most trials used patients with resistant HTN, but all patients in our daily practice don't have resistant HTN, if this analysis is applicable to the non-resistant HTN patients remains unknown.

In conclusion, our analysis results identify that RDN, in addition to PVI, reduces the risk of AF recurrence at 12 months compared to PVI alone.

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Studies	Eradicate HF 2020		Kiuchi 2018		Kiuchi 2016		Pokushalov 2014			
Interventions	**RDN + PVI**	**PVI**	**RDN + PVI**	**PVI + MRA**	**RDN + PVI**	**PVI**	**RDN + PVI**	**PVI**	**RDN + PVI**	**PVI**
							Moderate HTN		**Resistant HTN**	
N	154	148	33	36	21	24	23	21	18	18
Age (median/mean ± SD)	59	60	56.8 ± 6.5	58.4 ± 5.1	68 ± 9	66 ± 9	56 ± 5	56 ± 6	57 ± 7	56 ±7
Males n.	91	91	25	30	13	16	17	14	14	13
Paroxysmal AFIB – n.	N/A	N/A	33	36	12	15	13	12	4	6
Persistent AFIB – n.	N/A	N/A	0	0	9	9	10	9	14	12
Diabetes – n.	16	18	8	10	16	13	3	2	2	2
Coronary Artery Disease – n.	14	10	5	9	12	14	2	2	3	2
BP mmHg – mean (SD)										
Systolic	150 ± 9	151 ± 9	N/A	N/A	N/A	N/A	150 ± 6	151 ± 5	180 ± 15	179 ± 14
Diastolic	90 ± 7	90 ± 7	N/A	N/A	N/A	N/A	84 ± 7	83 ± 7	95 ± 12	93 ± 11
Estimated GFR (ml/min/1.73 m²)	79 ± 11	76 ± 11	69.2 ± 6.7	66.7± 7.7	59.3 ± 13.3	60.5 ± 15.9	72.8 ± 9.6	76.6 ± 9.1	78.8 ± 7.7	77.5 ±8
Echocardiography – mean (SD)										
LVEF % – mean ± SD	62 ± 5	62 ± 5	62.2 ± 7.2	61.2 ± 5.7	62.7 ± 6.6	63.5 ± 6.8	59 ± 4	60 ± 4	60 ± 5	62 ±5
LA diameter (mm) – mean ± SD	48 ± 3	47 ± 3	N/A	N/A	45.1 ± 3.2	44.9 ± 3.9	47 ± 5	46 ± 4	48 ± 5	49 ±4
Antihypertensive drugs – n.	N/A	N/A	3.5 ± 0.5	3.7 ± 0.4	3.41 ± 0.6	3.3 ± 0.5	3.0 ± 0.2	3.0 ± 0.2	3.8 ± 0.9	3.9 ± 0.9
ACEI or ARB – n. (%)	154 (100)	148 (100)	33 (100)	36 (100)	24 (100)	21 (100)	23 (100)	21 (100)	17 (94)	18 (100)
CCB – n. (%)	104 (67.5)	105 (70.9)	33 (100)	36 (100)	24 (100)	21 (100)	16 (70)	14 (67)	15 (83)	14 (78)
Beta Blocker – n. (%)	36 (23.3)	32 (21.6)	18 (55)	25 (69)	14 (67)	15 (63)	5 (22)	6 (29)	10 (56)	11 (61)
Diuretic – n. (%)	27 (17.5)	27 (18.2)	33 (100)	36 (100)	16 (76)	16 (67)	23 (100)	21 (100)	18 (100)	17 (94)

RDN = Renal Denervation; PVI = Pulmonary Vein Isolation; AFIB = Atrial Fibrillation; BP = Blood Pressure; GFR = Glomerular Filtration Rate; LVEF = Left ventricular ejection fraction; LA = Left Atrial; ACEi = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; CCB = Calcium Chanel Blocker

Table 1 – Baseline Characteristics Table

Name	Eradicate-HF 2020	Kiuchi 2018	Kiuchi 2016	Pokushalov 2014
Design	Multicenter, single-blind, randomized clinical trial	Single-center, prospective, longitudinal, randomized, double-blind study	Single-center, prospective, longitudinal, randomized, double-blind study	Two different prospective randomized double-blinded studies
Country	Russian Federation, Poland, Germany (5 sites)	Brazil	Brazil	Unavailable
Publication date	2020	2018	2016	2014
Journal	JAMA	JICE	Kidney Res Clin Pract	Heart rhythm
Enrollment	April 2013 - March 2018	January 2014 until June 2015	January 2014 to January 2015	Unavailable
Population	HTN despite taking at least 1 antihypertensive medication, paroxysmal AF, and plans for ablation	Uncontrolled HTN despite taking 3 or more medications, paroxysmal AF, age of 18 to 70 years, symptomatic drug-refractory AF in patients referred for catheter ablation of AF	Controlled hypertension, symptomatic paroxysmal AF and/or persistent AF, stage 2 or 3 CKD, and a dual-chamber pacemaker	symptomatic paroxysmal AF and/or persistent AF and resistant hypertension with more than 3 antihypertensive drugs
Intervention vs Comparison	RDN + PVI vs PVI	RDN + PVI vs PVI + spironolactone	RDN + PVI vs PVI	RDN + PVI vs PVI
Primary Outcome	Freedom from AF, atrial flutter, or atrial tachycardia at 12 months	30-s recurrence of the arrhythmia and the AF burden recorded by the pacemaker	30-second recurrence of AF recorded by the pacemaker	recurrence of 30 seconds of atrial tachyarrhythmia, including AF and left atrial flutter/tachycardia
Follow up duration	12 months	12 months	12 months	12 months

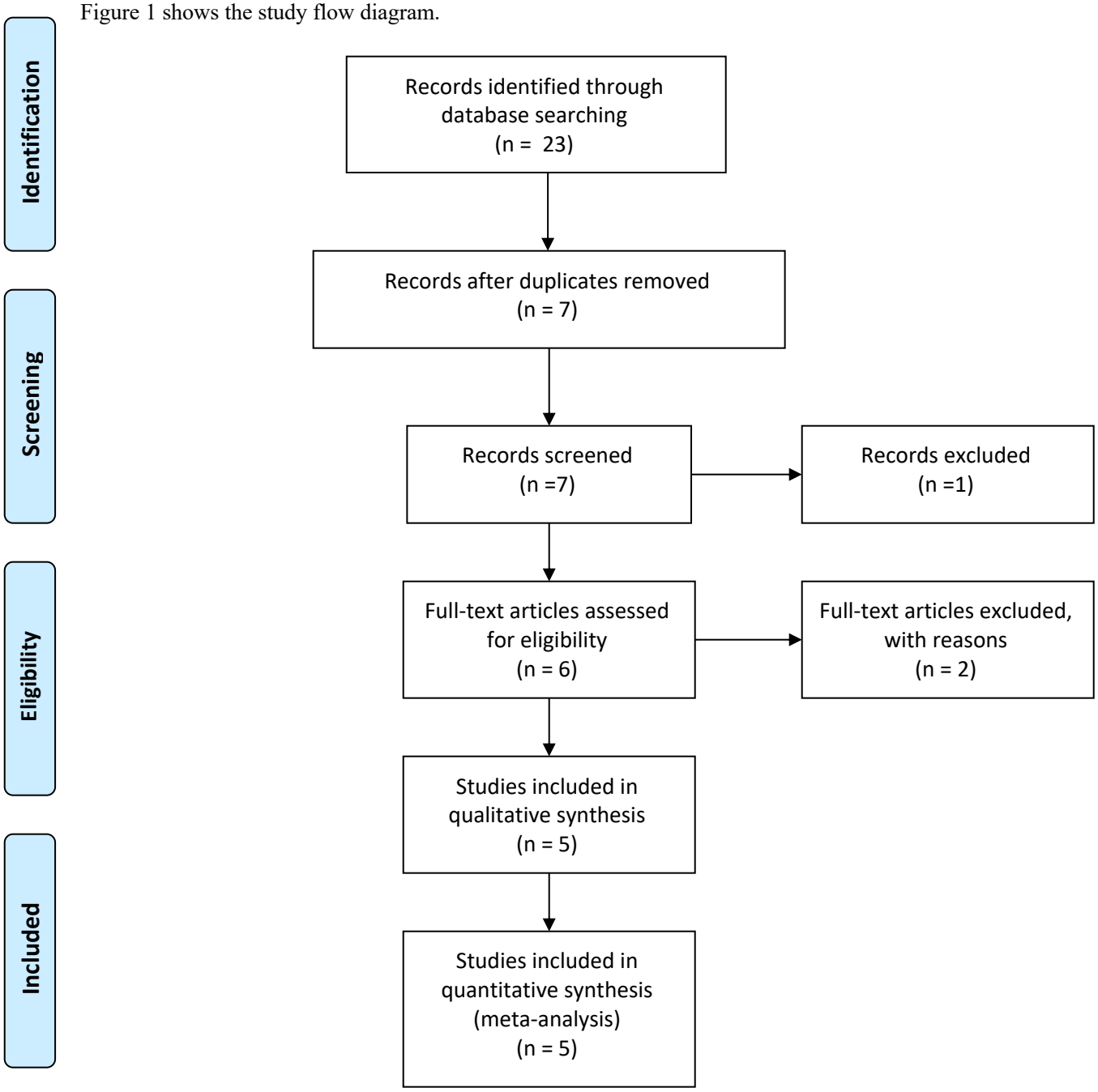
Table 2: Characteristics and Differences of RCTs

Name	Eradicate -HF trial 2020	Kiuchi 2018	Kiuchi 2016	Pokushalov 2014
Selection Bias Random Sequence	**Low Risk** Electronic (Permuted Blocks)	**Unclear Risk** Unclear Method	**Unclear Risk** Unclear Method	**Unclear Risk** Unclear Method
Allocation Concealment	**Low Risk** Sealed Envelope	**Unclear Risk** Unclear Description	**Unclear Risk** Unclear Description	**Unclear Risk** Unclear Description
Performance Bias Blinding of Participant and Personnel	**Low Risk** Blinded by Investigators	**Low Risk** Both were blinded	**Low Risk** Both were blinded	**Low Risk** Both were blinded
Detection Bias Blinding of Outcome Assessment	**Low Risk**	**Low Risk** Data collectors were blinded	**Low Risk** Data collectors were blinded	**Low Risk** Data collectors were blinded
Attrition bias Incomplete Outcome Data	**High Risk** Lost to follow up	**Low Risk**	**Low Risk**	**High Risk** Lost to follow up

Table 3- Cochrane Bias Assessment

PRISMA 2009 Flow Diagram

Figure 1 shows the study flow diagram.



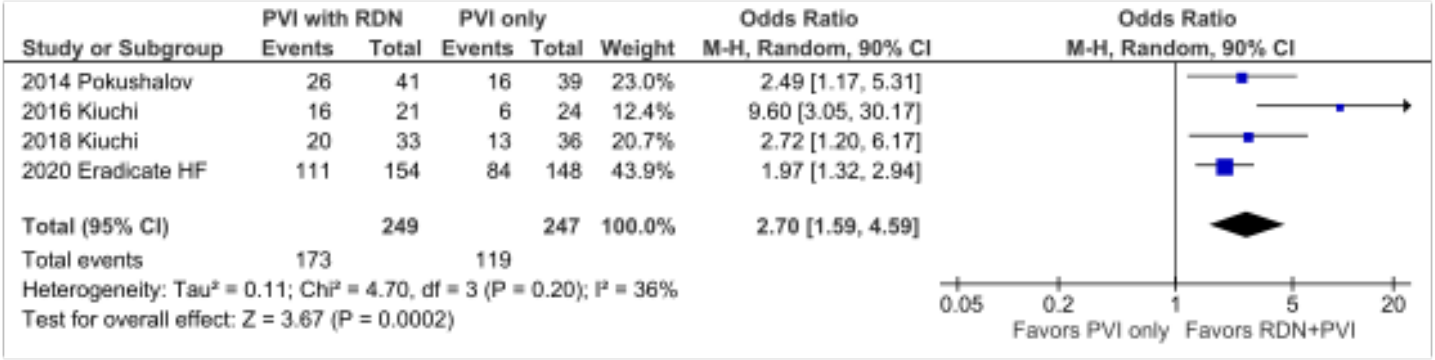


Figure 2 showing the comparison of the number of patients who were free from atrial fibrillation recurrence at the 12-month period in the RDN with PVI arm, compared to PVI alone

RDN = Renal denervation, PVI = Pulmonary vein isolation