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MULTIMEDIA REPORT

Renal sympathetic denervation in addition to pulmonary vein isolation reduces the recurrence rate of atrial fibrillation: an updated meta-analysis of randomized control trials

Jakrin Kewcharoen [1] · Wasawat Vutthikraivit [2] · Pattara Rattanawong [3] · Narut Prasitlumkum [1] · Nazem W. Akoum [4] · T. Jared Bunch [5] · Leenhapong Navaravong [5]

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Abstract

Background/purpose Atrial fibrillation (AF) is the most common arrhythmia worldwide. The sympathetic nervous system plays an important role in initiation and maintenance of AF. Recent studies have shown that renal sympathetic denervation (RSD) reduced AF recurrences after conventional pulmonary vein isolation (PVI). Studies that have evaluated the role of RSD as an adjuvant to PVI have included different patient populations, ablation strategies, and follow-up approaches. We performed a meta-analysis to assess the potential incremental impact of RSD to PVI.

Methods We searched the databases of MEDLINE and EMBASE from inception to January 2020. Included studies were randomized controlled trials (RCTs) that compared the recurrence rates of AF in patients who underwent PVI and RSD versus PVI alone. Data from each study were combined using the random effects model to calculate odds ratios (OR) and 95% confidence intervals (CIs).

Results Three RCTs consisted of four different studies during 2014–2020 involving 451 AF patients (223 patients underwent PVI alone and 228 patients underwent PVI with RSD) were included in the meta-analysis. Compared with PVI alone, the PVI with RSD group had a significantly lower risk of AF recurrence (pooled OR = 0.63, 95%CI 0.50–0.80, $p < 0.001$, $I^2 = 0.0\%$). There was no publication bias observed in funnel plot as well as no small-study effect observed in Egger's test.

Conclusions Our systematic review and meta-analysis demonstrated a significant reduction of AF recurrence in select hypertensive patients who underwent RSD in addition to PVI compared with PVI alone. Larger studies are needed to validate the benefits of this approach in other AF populations and across different ablation strategies.

Keywords Atrial fibrillation · Renal sympathetic denervation · Pulmonary vein isolation · Hypertension

Jakrin Kewcharoen and Wasawat Vutthikraivit contributed equally to this work.

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✉ Jakrin Kewcharoen
jakrin@hawaii.edu

1 University of Hawaii Internal Medicine Residency Program, 1356 Lusitana St, 7th floor, Honolulu, HI 96813, USA

2 Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX, USA

3 Department of Cardiology, Mayo Clinic, Scottsdale, AZ, USA

4 Division of Cardiovascular Medicine, University of Washington School of Medicine, Seattle, WA, USA

5 Division of Cardiovascular Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA

1 Introduction

Atrial fibrillation (AF) affects over 33.5 million people worldwide and is considered to be the most sustained common arrhythmia with significant effects on cardiovascular-related morbidity and mortality [1–3]. This arrhythmia is commonly known to contribute and interact with other coexisting medical conditions, including heart failure, which leads to worse prognosis that with either disease entity alone [2, 4, 5].

Hypertension is a well-known risk factor for incident AF and its progression [1, 6] and is associated with an increased sympathetic tone. Studies have reported that increases in sympathetic tone are observed in humans prior to the onset of AF [7]. Excessive sympathetic activation has also been found to be associated with recurrences of AF after catheter ablation [8]. Moreover, autonomic modulation by targeted ablation of atrial ganglionic plexi has been found to be beneficial in patients undergoing ablation for AF to reduce risk of arrhythmia recurrences [9–11]. These studies and others have led physicians and scientists to believe that the autonomic nervous system plays an important role in precipitation and maintenance of AF [12, 13].

Renal sympathetic denervation (RSD) is a technique that has been recently tested to control blood pressure by reducing renal sympathetic afferent and efferent activities in resistant hypertension [14–18]. As RSD can effectively decrease sympathetic tone [16], it may also have an anti-arrhythmic effect with respect to both AF and ventricular arrhythmias [19]. Pokushalov et al. and Kiuchi et al. reported that RSD, when combined with PVI, reduces recurrence of AF in patients with severe resistant hypertension and chronic kidney disease, respectively [20–22]. Recently, a larger RCT, the Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation (ERADICATE-AF) trial, also reported that added RSD to conventional PVI significantly decreased the recurrence rate of AF in patients with hypertension [23].

In this study, our objective was to perform a meta-analysis of RCT to explore the impact of RSD in addition to PVI, across multiple trial populations, on recurrence of AF after catheter ablation compared with conventional PVI.

2 Methods

2.1 Search strategy

Two investigators (WV and PR) independently searched for published studies indexed in PubMed and EMBASE databases from inception to January 2020 using the search terms including "renal sympathetic denervation," "pulmonary vein isolation," and "atrial fibrillation" (described in online supplementary data). No language limitation filter was applied. An additional manual search for additional pertinent studies using the references from retrieved articles was also completed.

2.2 Inclusion criteria

The inclusion criteria were as follows:

1. Original RCT studies that reported AF outcomes after RSD in patients who underwent PVI.
2. Studies must have included recurrence rates of AF following RSD and PVI as the primary or secondary outcomes.
3. Studies must have included participants who underwent PVI alone without RSD that were used as a control population with similar follow-up assessment.

Exclusion criteria included non-peer-reviewed studies, observational studies, cohort studies, case reports, case series, animal studies, abstract-only manuscripts, editorial comments, and anecdotal articles.

Study eligibility was independently determined by the two investigators noted above. Differences in the determination of study eligibility were resolved by mutual consensus. The quality of each study and risk of bias was independently evaluated by the Cochrane risk-of-bias tool for randomized trials [24].

2.3 Data extraction

A standardized data collection form was used to obtain the following data from each study including name of the first author, year of publication, country of origin, study population, inclusion and exclusion criteria, number of participants, age, PVI and RSD procedure details, baseline blood pressure, primary outcome, and follow-up duration.

To ensure accuracy, this data extraction process was independently performed by all investigators. Any data discrepancy was also resolved by referring back to the original articles.

2.4 Statistical analysis

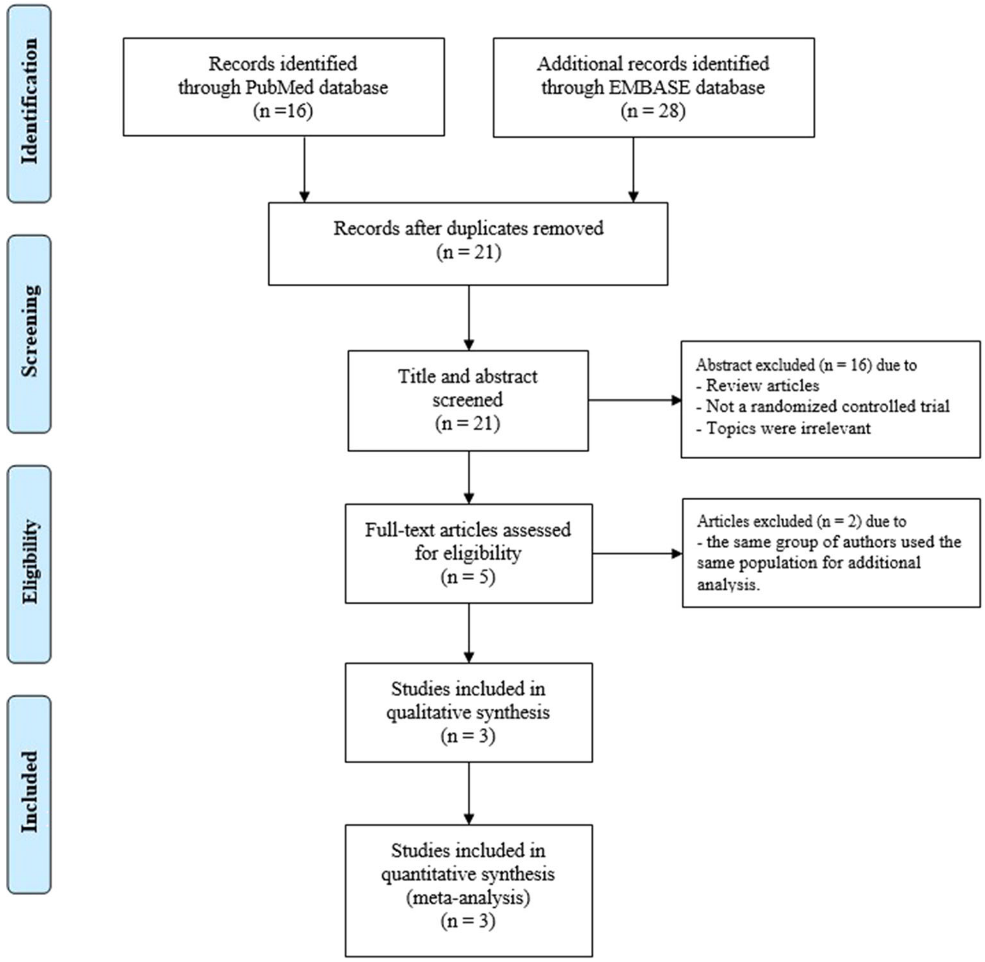
We performed a meta-analysis of included studies using a random effects model and the generic inverse-variance method of DerSimonian and Laird [25]. We extracted from these studies the rate of recurrent AF of the PVI with RSD and PVI alone groups. The extracted studies were excluded from the analysis if they did not contain enough information required for continuous data comparison. The heterogeneity of effect size estimates was firstly assessed using forest plots to detect non-overlapping confidence interval (CI), and then was calculated using the Q statistic and I^2 statistic. For the Q statistic, substantial heterogeneity was defined as $p < 0.10$. The I^2 statistic ranges in value from 0 to 100% ($I^2 < 25\%$, low heterogeneity; $I^2 = 25–50\%$, moderate heterogeneity; and $I^2 > 50\%$, substantial heterogeneity). A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting one study at a time. Publication bias was assessed using funnel plot and Egger's regression tests [26] ($p < 0.05$ was considered significant). All statistical tests were performed using the STATA 14.1 software (College Station, TX).

3 Results

3.1 Description of included studies

Our search strategy yielded 40 potentially relevant articles (15 articles from MEDLINE and 25 articles from EMBASE) as shown in Fig. 1. After the exclusion of 15 duplicated articles, 25 articles underwent title and abstract review. Twenty studies

Fig. 1 PRISMA flow diagram



were excluded as there were review articles, not RCTs or topics were irrelevant, leaving 5 articles for a full-length article review. Two articles were excluded as the same group of authors used the same population for additional analysis. No additional articles were added through manual search. Thus, three articles met the all eligibility criteria and were included in the data analysis.

The study by Pokushalov et al. reported the results from 2 different prospective randomized studies [20]. Therefore, those 2 different randomized control trials were considered 2 different study populations (moderate resistant hypertension and resistant hypertension) in our meta-analysis as shown in Table 1. The 2 other studies included were done by Kiuchi et al. and Steinberg et al. [23, 27] A summary of the included studies is provided in Table 1.

The Cochrane risk-of-bias tool for randomized trials is demonstrated in Table 2.

3.2 Meta-analysis results

We found that PVI with RSD was associated with a significantly lower risk of AF recurrence at 12 months compared with PVI alone (pooled odds ratio = 0.63, 95%CI 0.50–0.80, $p < 0.001$, $I^2 = 0.0\%$). The forest plot of the analysis and study weights is shown in Fig. 2.

We aimed to evaluate mean systolic and diastolic blood pressure at follow-up, and complications of PVI with RSD. However, outcome of mean blood pressure differences was not available, and thus, we do not have sufficient raw data to analyze for a weighted mean difference. Only the study by Steinberg et al. reported procedural complication incidence of the two groups, which was not statistically different; thus, we did not perform a meta-analysis.

3.3 Procedural complications

Steinberg et al. reported no significant difference in procedural complications at 30 days following the procedure [23]. In the PVI group, there were 4 femoral venous vascular events not requiring intervention, 1 transient phrenic nerve palsy, 1 cardiac tamponade successfully resolved with pericardiocentesis, and 1 pneumothorax. In the PVI with RSD group, 6 patients had femoral venous vascular events not requiring intervention and 1 transient phrenic nerve palsy. All complications were

Table 1 Study characteristics of included studies in the meta-analysis

First author, country, year	Study population/inclusion criteria	Exclusion criteria	Total participants (n)/age	PVI procedure	RSD procedure	Mean baseline SBP/DBP	Freedom from AF at 12 months (PVI + RSD vs PVI alone)	Conclusion
Pokushalov, Russia, 2014 [20]	Patients with a history of symptomatic paroxysmal AF and/or persistent AF and moderate resistant hypertension (≥ 140/90 and < 160/100 mmHg)	Secondary hypertension besides RAS, severe RAS or bilateral RAS, CHF NYHA classification II-IV, LVEF < 35%, transverse left atrial diameter > 60 mm, previous AF ablation, previous renal artery intervention,	44 (PVI 21, PVS + RSD 23)/mean age; PVI 56 ± 6, PVS + RSD 56 ± 5	Mapping: CARTO[¥] Ablation: encircling ipsilateral PVs, 43 °C, 35 W, 0.5 cm from PV ostia at anterior wall, and was reduced to 43 °C, 30 W, 1 cm from PV ostia at posterior wall	Mapping: CARTO[¥] and NaviStar ThermoCool[¥] Ablation: simplicity renal denervation system[π], RF of 8–12 W, from the first distal main renal artery bifurcation to the ostium, 60–120 s, up to 6 lesions (separated by > 5 mm)	PVI 151 ± 5/83 ± 7, PVS + RSD 150 ± 6/84 ± 7	65% versus 52%	The rate of AF recurrence was lower in the PVI + RSD group for the severe resistant hypertension subgroup but not in the moderate hypertension subgroup. SBP and DBP in both subgroups were significantly decreased
Pokushalov, Russia, 2014 [20]	Patients with a history of symptomatic paroxysmal AF and/or persistent AF and severe resistant hypertension (≥ 160/100 mmHg)	amiodarone use, DM type 1	36 (PVI 18, PVS + RSD 18)/mean age; PVI 56 ± 6, PVI + RSD 57 ± 7	Endpoint: demonstration of bidirectional PV block	for each renal artery Endpoint: sudden increase of blood pressure (> 15 mmHg) was eliminated in the presence of HFS	PVI 179 ± 14/93 ± 11, PVS + RSD 180 ± 15/95 ± 12	61% versus 28%	from baseline.
Kiuchi, Brazil, 2018 [27]	Patients with a history of uncontrolled hypertension (≥ 130/80 mmHg) with maximum anti-hypertensive medication with symptomatic and drug-refractory paroxysmal AF with CKD, and a dual-chamber pacemaker	Significant valvular disease, ACS, CVA, renovascular abnormalities, CHF NYHA classification II–IV, previous AF ablation procedure, amiodarone use	69 (PVI 36, PVS + RSD 33)/mean age; PVI 59 ± 15, PVS + RSD 60 ± 14	Mapping: EnSite Velocity[£] Ablation: encircling ipsilateral PVs, 43 °C, 35 W, 0.5 cm from PV ostia at anterior wall, and was reduced to 43 °C, 30 W, 1 cm from PV ostia at posterior wall Endpoint: disappearance or the dissociation of PV potentials	Mapping: EnligHTN™ guide catheter[£] Ablation: EnligHTN™ multielectrode renal denervation ablation catheter[£], RF of 8-W power at the main trunk of the bilateral renal arteries, 60 s, at least 8 lesions per renal artery Endpoint: N/A	PVI 119 ± 8/79 ± 8, PVS + RSD 121 ± 9/79 ± 6	61% versus 36%	The PVI + RSD group had a higher AF event-free rate, more BP reduction, and improvement of renal function.
Steinberg; Russia, Poland, and Germany; 2019 [23]	Patients with a history of symptomatic paroxysmal AF planning for catheter ablation with a history of hypertension (≥ 130/80 mmHg) and on at least 1 anti-hypertensive medication	Previous left atrial ablation, CHF NYHA IV, LVEF < 25%, persistent AF, ineligible renal artery anatomy, previous renal artery intervention, GFR < 45 mL/min/1.73 m^2, life expectancy < 1 year	302 (PVI 148, PVS + RSD 154)-/median age (IQR); PVI 59 (54–65), PVS + RSD 60 (58–65)	Mapping: N/A Ablation: cryoballoon catheter[π], 1–2 freezes/-vein, 180–240 s Endpoint: disappearance or the dissociation of PV potentials and exit block	Mapping: CARTO[¥] and NaviStar ThermoCool[¥] Ablation: Stockert generator[¥], RF of 8–12 W from the first distal main renal artery bifurcation back to the junction of the renal artery and the aorta, 2 min (separated by > 5 mm) Endpoint: sudden increase of blood pressure (> 15 mmHg) was	PVI 150 ± 9/90 ± 7, PVS + RSD 151 ± 9/90 ± 7	*72.1% versus 56.5%	Freedom from AF, flutter, or tachycardia recurrence at 12 months was higher in the PVI + RSD group. Mean SBP and DBP were significantly lower in the PVI + RSD group at 6 months and 12 months.

Table 1 (continued)

First author, country, year	Study population/inclusion criteria	Exclusion criteria	Total participants (*n*)/age	PVI procedure	RSD procedure	Mean baseline SBP/DBP	Freedom from AF at 12 months (PVI + RSD vs PVI alone)	Conclusion
					eliminated in the presence of HFS			

ACS acute coronary syndrome, *AF* atrial fibrillation, *CHF* congestive heart failure, *CKD* chronic kidney disease, *CVA* cerebrovascular accident, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *GFR* glomerular filtration rate, *HFS* high-frequency stimulation, *PVI* pulmonary vein isolation, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *RF* radiofrequency, *RCTs* randomized controlled trials, *RSD* renal sympathetic denervation, *SBP* systolic blood pressure

*Combined atrial fibrillation, atrial flutter, and other atrial tachycardia

¥ Biosense Webster Inc., Diamond Bar, CA, USA

£ St Jude Medical Inc., St Paul, MN, USA

π Medtronic Inc., Minneapolis, MN, USA

attributed to the PVI procedure and there were no reported renal or renal artery complications. Both Kiuchi et al. and Pokoshalov et al. also did not find complications from RSD and did not describe complications from PVI in detail [20, 27].

3.4 Blood pressure

Every study reported mean systolic and diastolic blood pressure before and after RSD. The findings from all 4 studies were similar and consistently showed that PVI with RSD significantly lowered the mean systolic and diastolic blood pressure at 12 months as compared with the PVI alone. Kiuchi et al. and Steinberg et al. perform additional analysis to evaluate the association between AF recurrence and blood pressure reduction. Kiuchi et al. reported that there was a negative association between the degree of mean systolic BP reduction and mean AF burden at the 12th month in the PVI with RSD group ($r = -0.74$, 95%CI -0.92 to -0.32, $p = 0.003$), but not in the PVI group [27]. Steinberg et al. found that the degree of systolic blood pressure reduction was not related to time-to-AF (1 mmHg reduction was associated with -0.1-month reduction, 95%CI -1.6 to 1.3 month) [23]. Pokushalov et al. did not perform any statistical analysis to evaluate this association.

3.5 Evaluation for publication bias

As shown in Fig. 3, the funnel plot was evaluated, and visual inspection showed a fairly symmetrical distribution of study estimates. Egger's test for small-study effect had a p value of 0.593, and we concluded that there was no statistically significant evidence of small-study effects.

4 Discussion

Our meta-analysis study showed a collective significant reduction of AF recurrence in patients who underwent RSD in addition to PVI compared with conventional PVI. The benefit was seen in both trials that used radiofrequency ablation and cryothermal balloon ablation.

Based on a multicenter RCT comparing PVI with pharmacological rhythm control, PVI is recommended in patients with symptomatic paroxysmal or persistent AF refractory to anti-arrhythmic medications [28]. In current clinical practice, PVI is considered a first-line therapy in symptomatic AF patients with a low risk of stroke, no structural heart disease, and a state preference for interventional treatment [29]. Pulmonary vein isolation also can be considered a first-line therapy in select patients with congestive heart failure [30–32]. However, long-term recurrence rates even in healthier patients with PVI alone remain suboptimal. As coexistent risk factors and AF severity increase, long-term recurrence rates after PVI

Table 2 The Cochrane risk-of-bias tool for randomized trials

First author, year	Selection bias		Performance bias	Detection bias	Distribution bias	Reporting bias	Other bias	Overall bias risk
	Random sequence generation	Allocation concealment						
Kiuchi 2018	Low	Unclear	Low	Low	Low	Low	Low	Low
Pokushalov 2014	Low	Low	Low	Low	Low	Low	Low	Low
Steinberg 2020	Low	Low	Low	Low	Low	Low	Low	Low

alone are even lower [33]. However, it is still unclear whether any additional intervention beyond PVI is beneficial in terms of reducing the recurrence of AF. The Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part II (STAR AF II) reported that PVI with complex fractionated atrial electrogram or linear ablation did not reduce the rate of recurrent AF among patients with persistent AF [34].

The benefit of RSD is likely multifactorial from the reduced vascular tone leading to reduced preload and afterload and improved atrial unloading, decreased sympathetic activity, or additional autonomic modulation. However, there were conflicting results among different populations. Pokushalov et al. reported a significant reduction of AF recurrences in patients with severe resistant hypertension but not in moderately resistant hypertension [20]. Similarly, Kiuchi et al. previously revealed that the addition of RSD to PVI significantly reduced AF recurrences in patients with chronic kidney disease, stage 4, but not stage 2 or 3 [22]. Therefore, the impact of RSD on the recurrence of AF after catheter ablation was heterogenous in different populations in this analysis. A previous meta-analysis reported RSD in addition to PVI improves clinical outcomes in patients with a history of hypertension and either paroxysmal or persistent AF [35]. However, some of the included studies in the meta-analysis were not RCT [22], some studies used the data from the same patient database [21, 36], and a recent RCT was published that augmented the collective experience and used cryothermal balloon ablation for PVI [23]. We thus performed an updated systematic review and meta-analysis of only RCTs to explore the effect of RSD combined with PVI on AF recurrence.

In contrast to previous RCTs by Pokushalov et al. and Kiuchi et al. that focused on a specific population groups of moderate-to-severe resistant hypertension and CKD [20, 27], respectively, the most recent RCT by Steinberg et al. focused on an AF population without such comorbidities [23]. Every study demonstrated a reduction in AF recurrence favoring the PVI with RSD group, but statistically significance was only achieved in the studies by Kiuchi et al. and Steinberg et al. In the analysis by Pokushalov et al., the authors suggested that the non-statistical significance was due to the limited number of participants. This study also had higher mean baseline BP than the study populations from the other two RCTs, which

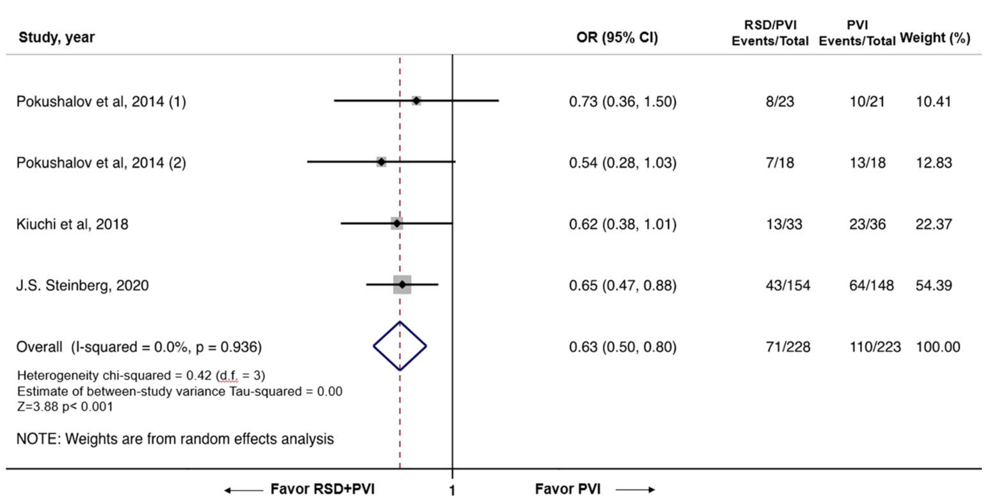


Fig. 2 Forest plot of the included studies demonstrating the association between recurrence of atrial fibrillation between renal sympathetic denervation in addition to pulmonary vein isolation compared with pulmonary vein isolation alone: (1) symptomatic paroxysmal AF and/or persistent AF and moderate resistant hypertension (≥ 140/90 and < 160/100 mmHg); (2) symptomatic AF and/or persistent AF and severe resistant hypertension (≥ 160/100 mmHg). RSD, renal sympathetic denervation; PVI, pulmonary vein isolation; AF, atrial fibrillation

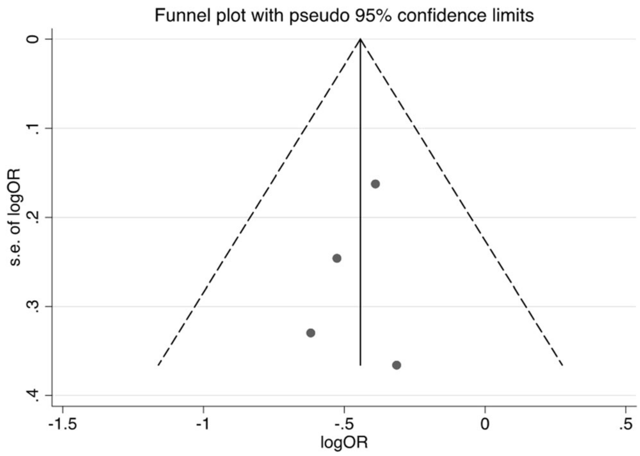


Fig. 3 Funnel plot of the included studies. Circles represented the included studies

may have contributed to lower long-term success rates of freedom from AF post ablation independent of the additional adjuvant RSD treatment.

Regarding the method of RSD, every study used RF ablation technique for RSD. The detail of RSD procedure is shown in Table 1. Steinberg et al. and Pokushalov et al. used the same mapping techniques and procedure endpoint as the elimination of a sudden increase of blood pressure (> 15 mmHg from invasive arterial monitoring) in the presence of high-frequency stimulation. Kiuchi et al. did not report procedural endpoint [27]. Pokushalov et al. reported a 100% success rate [20], whereas Steinberg et al. did not specifically describe this [23].

Pokushalov et al. were the only authors to include persistent AF in their study [20]. The subgroup analysis by AF type (paroxysmal vs persistent) demonstrated that PVI with RSD significantly reduced AF recurrent rates in the persistent AF group, but not in the paroxysmal AF group. Interestingly, Kiuchi et al. and Steinberg et al. included only paroxysmal AF patients, and both found a significant reduction of arrhythmia recurrence risk [23, 27]. The non-significant findings in the paroxysmal AF group within the Pokushalov et al. study could be due to the small number of participants as mentioned above. Nevertheless, despite a relatively small enrolled population, the findings by Pokushalov et al. suggested that RSD in addition to PVI may be beneficial in persistent AF. Additional work is required to understand the role of RSD in persistent AF patients including an adequately powered RCT to further explore this finding.

Regarding complications from RSD, only the study by Steinberg et al. compared complications between the 2 groups, which did not significantly differ between the 2 groups [23]. Kiuchi et al. and Pokoshalov et al. did not find complications from RSD [20, 27]. Thus, from our systematic review, it appears that the benefit was seen without a generalized increase in complications when RSD is added to PVI.

Previous RCT revealed that aggressive blood pressure control did not reduce atrial arrhythmia recurrence following PVI [37]. In our systematic review, every study showed that PVI with RSD was able to significantly decrease the mean systolic and diastolic blood pressure as compared with the PVI alone, but it was unclear whether this led to AF reduction or not. Interestingly, Kiuchi et al. found that a higher degree of systolic blood pressure reduction was associated with decreased AF burden [27], whereas Steinberg et al. reported that degree of systolic blood pressure was not related to time-to-AF during the 12-month follow-up [23]. The anti-arrhythmic effects of RSD, both atria and ventricle, have been observed in several trials and were seen across multiple populations not only in hypertension population but also in myocardial infarction, sleep apnea, CKD, and heart failure [38–45]. This suggested that the mechanism may also be secondary to a direct anti-arrhythmic effect from reducing central sympathetic output rather than blood pressure reduction alone. Nevertheless, more data is needed to evaluate whether the reduction in blood pressure is related to the reduction in AF recurrence or not.

5 Limitations

Our systematic review and meta-analysis have several limitations. As RSD in this population is considered a novel intervention, we only found 3 eligible articles consisting of only 4 populations to include in our study, 3 of which were conducted by the same author group and have a similar trial protocol. Thus, the number of participants is relatively small. However, we evaluated for small-study effect via Egger's test and found a non-significant effect as mentioned in our results. Secondly, the included studies used different approaches to PVI (radiofrequency ablation vs cryothermal balloon ablation), discrete patient populations, and different definitions for HTN inclusion criteria, and used a couple of specific disease-related comorbidity groups of AF patients. For example, Pokushalov et al. conducted the trial in patients with severe and moderate resistant hypertension [20], whereas the participants in Kiuchi et al.'s trial were with CKD [27]. The inclusion of specific disease characteristics limits the generalizability of these results in isolation and in aggregate. As RSD is considered an adjuvant approach with PVI, evaluating the relative benefit across different populations is needed. Lastly, although every study each reported a mean systolic and diastolic blood pressure at baseline and follow-up, we did not have mean blood pressure differences or sufficient raw data to analyze for a weighted mean difference.

6 Conclusion

This study is an updated meta-analysis of RCTs evaluating the impact of RSD in addition to PVI on recurrence of AF after catheter ablation compared with conventional PVI, which broadens the AF populations studied as well as the approach used to PVI. Our meta-analysis study showed a significant reduction of AF recurrence at 12 months in patients who underwent RSD in addition to PVI compared with PVI alone. More prospective randomized controlled studies should be done in other specific population groups, in particular those with elevated sympathetic tone such as congestive heart failure, to evaluate for a potential benefit of RSD in addition to PVI in reducing AF recurrence.

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Authors' contribution Jakrin Kewcharoen: Conception design, data interpretation, statistical analysis, revision of the manuscript, final approval

Wasawat Vutthikraivit: Conception design, data acquisition, data interpretation, drafting of the manuscript, revision of the manuscript, final approval

Pattara Rattanawong: Corresponding, data interpretation, final approval

Narut Prasitlumkum: Data acquisition, data interpretation, drafting of the manuscript, revision of the manuscript, final approval

Chanavuth Kanitsoraphan: Statistical analysis, drafting of the manuscript, final approval

Nazem W Akoum: Drafting and revision of the manuscript, proofreading, final approval

T Jared Bunch: Drafting and revision of the manuscript, proofreading, final approval

Leenhapong Navaravong: Drafting and revision of the manuscript, proofreading, final approval

Availability of data and material Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Code availability Not applicable.

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