Renal Denervation for the Treatment of Ventricular Arrhythmias: A Systematic Review and Meta-Analysis

SHORT TITLE: Ventricular Arrhythmias and Renal Denervation

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ABSTRACT

Introduction

Ventricular arrhythmias (VAs) are a major cause of morbidity and mortality in patients with heart disease. Recent studies evaluated the effect of renal denervation (RDN) on the occurrence of VAs. We conducted a systematic review and meta-analysis to determine the efficacy and safety of this procedure.

Methods and results

A systematic search of the literature was performed to identify studies that evaluated the use of RDN for the management of VAs. Primary outcomes were reduction in the number of VAs and implantable cardioverter-defibrillator (ICD) therapies. Secondary outcomes were changes in blood pressure and renal function.

Ten studies (152 patients) were included in the meta-analysis. RDN was associated with a reduction in the number of VAs, ATP (antitachycardia pacing), ICD shocks and overall ICD therapies of 3,53events/patient/month (95%CI=-5,48 to -1,57), 2,86events/patient/month (95%CI=-4,09 to -1,63), 2,04events/patient/month (95%CI=-2,12 to -1,97), and 2,68events/patient/month (95%CI=-3,58 to -1,78), respectively. Periprocedural adverse events occurred in 1,23% of patients and no significant changes were seen in blood pressure or renal function.

Conclusions

In patients with refractory VAs, RDN was associated with a reduction in the number of VAs and ICD therapies, and was shown to be a safe procedure.

KEYWORDS:

Renal denervation, ventricular arrhythmias, implantable cardioverter-defibrillator, antitachycardia pacing, ICD shocks.

INTRODUCTION

Ventricular arrhythmias (VAs) are associated with increased morbidity and mortality[1]. Despite recent progress in the development of therapeutic resources, the treatment of VAs remains challenging in clinical practice. The development and maintenance of VAs suffer high influence from the autonomic nervous system (ANS), especially sympathetic activity[2,3]. Since traditional therapies appear to insufficiently suppress VAs in certain patients, several new modalities such as renal denervation (RDN) have been studied to modulate the ANS by decreasing the sympathetic tone and intensifying the vagal tone.

The impact of RDN on the treatment of VAs was initially studied in animals in the setting of myocardial ischemia[4]. In humans, RDN has been firstly tested in patients with heart failure and VAs refractory to conventional treatment, with positive results[5]. Few other studies have followed[6,7], all of them showing a reduction in the number of VAs and implantable cardioverter-defibrillator (ICD) therapies. All these studies are limited by relatively small sample sizes. Hence, we conducted a systematic review of the literature and meta-analysis to evaluate the efficacy of RDN in reducing the number of VAs as well as the safety of the procedure.

METHODS

Search strategy and selection criteria

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for meta-analysis (supplementary appendix – table 1).

A systematic search of the literature was performed from inception up until February 2020. Studies were assessed by online search in the PubMed search engine with the following Medical Subject Heading (MESH): renal denervation, arrhythmia, ventricular, tachycardia. All selected articles references were manually searched for relevant studies.

We included case reports, case series, prospective and retrospective cohorts and randomized clinical trials (RCTs) that evaluated patients with refractory VAs undergoing RDN. Review articles, animal studies, and publications that did not report enough data were excluded (figure 1).

Data extraction

One author reviewed the titles and abstracts of all retrieved articles to identify potentially relevant ones. These articles were fully read afterwards. Two independent authors have separately searched the selected publications and extracted data using a pre-specified extraction form. Any discrepancies were resolved after discussion in conjunction with a third investigator. The data included author name, publication year, study design, patient demographics and outcomes.

Type of exposition

All studies included patients undergoing RDN and a few studies had a control group in which the procedure was not performed. Most of them were on

at least 2 antiarrhythmic drugs and several were previously submitted to cardiac catheter ablation.

Outcome measures

Primary outcomes were differences in the number of VT/VF (ventricular tachycardia and/or ventricular fibrillation) and ICD therapies (ATP and/or shock) between pre and post RDN procedure.

Secondary outcomes were changes in blood pressure (BP) (office and ambulatory monitoring) and renal function (measured either by serum creatinine or estimated glomerular filtration rate [eGFR]) pre and post RDN.

Statistical analysis

Statistics of VAs and ICD therapies were described in different manners among the evaluated studies. Data reported as means and standard deviations or medians and interquartile ranges were equally selected approaches. In addition, some studies presented total events in different time intervals, and some reported monthly rates. We chose to transform all the reports in monthly rates to perform meta-analysis for primary outcomes, to minimize bias caused by different follow up periods.

All meta-analyses were performed for mean pre-post difference. We used exactly the difference standard deviation when it was possible to estimate. For articles presenting statistics for pre and post treatment separately, we estimate difference standard deviation assuming that between group correlation was 0.5, based on the mean value achieved from the papers where it was possible to measure pre-post dependence. Nevertheless, we performed sensitivity analyses

assuming that pre and post measures were independent groups, presenting a conservative estimative.

Meta-analysis weights were estimated by the inverse of variance method, the DerSimonian-Laird estimator. The analysis were performed with the software R 3.6.3[8] with meta package[9].

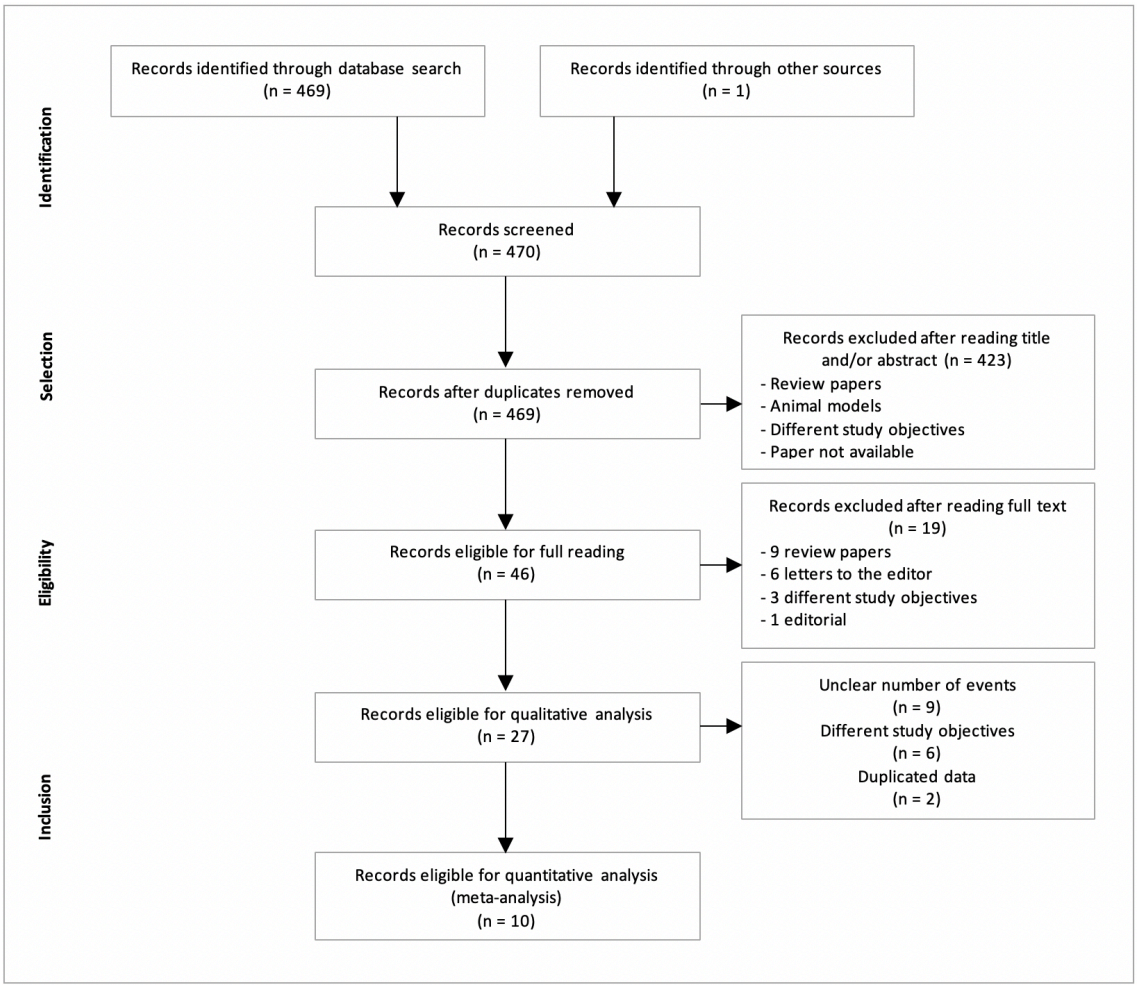
Assessment of risk of bias was made by visual inspection of symmetry of funnel plot. Sensitivity analysis were performed in order to evaluate the effects of RDN considering the groups independent and to find potential origins of heterogeneity between the selected studies.

RESULTS

Literature Search and study characteristics

We identified 469 studies in the online database and one study in a paper references; 424 studies were excluded after review of the title and/or abstract, mostly for being review articles, animal studies or not related to the topic of interest. A total of 27 studies were included in the systematic review; 17 of them were excluded from the meta-analysis due to insufficient data or inclusion of patients already cited in other publications. One study analyzed the effect of RDN in combination of cardiac sympathetic denervation and it was excluded from the analysis[10]. The PRISMA flow diagram for the selection of studies is presented in Figure 1.

Figure 1 – PRISMA flow diagram



The 10 studies included in the meta-analysis were published between 2012 and 2018 and incorporated a total of 152 patients (76 underwent RDN). The mean age was 58±13 years and 74.4% of the overall population was male. All included patients had cardiomyopathies (main etiologies: ischemic, dilated, hypertrophic, and Chagas disease). Eight studies reported the number of VT/VF as primary outcome, and nine studies reported the number of ICD therapies (ATP and/or ICD shock) as their main outcome. Mean follow-up period was 9.7±4 months (table 1).

Table 1 - Details of studies included in the meta-analysis

AUTHOR	JOURNAL	YEAR	TYPE OF STUDY	N	TYPE OF CARDIOMYOPATHY	AGE	FEMALE%	OUTCOME	FOLLOW UP
Jiang et al (39)	International Heart Journal	2018	Case series	8	Dilated, ischemic, hypertrophic, idiopathic	51.4±14.3	12,5	VA, ATP, ICD shock	Median 15 months (6-30)
Vander et al (11)	Journal of Geriatric Cardiology	2017	Case series	1	Dilated	36	0	ATP, ICD shock	5 months
Kiuchi et al (15)	Oncotarget	2017	Clinical trial	20	Ischemic and non-ischemic; CKD stage 4	70±13	35	ATP, ICD shock	18 months
Evranos et al (23)	The American Journal of Cardiology	2016	Retrospective cohort	16	Dilated, ischemic, arrhythmogenic right ventricle dysplasia	66±15	25	VA, ATP, ICD shock	Median 15 months (6-20)
Ukena et al (12)	Clinical Research in Cardiology	2016	Case series	13	Ischemic and non-ischemic	59.2±14.4	0	VA, ICD shock	12 months
Armaganijan et al (16)	JACC: Cardiovascular Interventions	2015	Prospective cohort	10	Chagas, dilated and ischemic	64.5±6.3	50	VA, ATP, ICD shock	Median 180 days (18 days-6 months)
Remo et al (7)	Heart Rhythm	2014	Case series	4	Ischemic and non-ischemic	68,83,63, 60	25	VA, ICD shock	8.8 ± 2.6 months (5-11 months)
Chen et al (40)	Chinese Medical Journal	2013	Case report	1	Tachycardia induced	42	0	VA	6 months
Staico et al (6)	EuroIntervention	2014	Case report	1	Dilated	62	0	VA, ATP, ICD shock	5 months
Ukena et al (5)	Clinical Research in Cardiology	2012	Case series	2	Hypertrophic and dilated	67,57	0	VA, ATP	5-6 months

ATP = antitachycardia pacing; ICD = implantable cardioverter defibrillator; N = number of patients; VAs = ventricular arrhythmias

Since most of the studies were case series with a relatively small number of patients, we assessed the majority of the patients separately for individual characteristics, outcomes, and time of follow-up (supplementary appendix – table 2). One study[11] included two case reports: one patient had no ICD (the outcome was measured by the number of external defibrillator shocks) and was, therefore, excluded from the analysis.

Ukena et al[12] published a series of 13 cases. Three of them were reported as individual case reports[5,13,14] and for this reason two publications were excluded from the analysis[13,14].

Kiuchi et al[15] evaluated patients with stages 1 to 4 chronic kidney disease (CKD). Stage 4 comprised of 40 patients, 20 of which were submitted to RDN. This specific group was selected to evaluate the efficacy of RDN. Due to the lack of information regarding the number of ICD therapies in patients with CKD stage 4 prior to RDN, we extrapolated the data from those with CKD stage 4 who did not undergo RDN as if the number of ICD therapies in this group were similar to the intervention group before the procedure.

Most of the lost to follow-up were related to death. Most deaths were related to heart failure (HF) and/or sepsis[12,16]. None of the reported deaths was caused by VAs.

Five studies analyzed the impact of RDN on the number of premature ventricular complexes (PVCs). Given the high coefficient of variation and/or not enough information, these were not included in the meta-analysis.

Qualitative analysis

Ventricular arrhythmias

Out of the 27 studies selected for the qualitative analysis, 17 evaluated the impact of RDN on the management of VT/VF. Eight studies were eligible for the meta-analysis and nine for literature review only. Studies details are represented in table 1 and in the supplementary appendix – table 3.

ICD therapies (ATP and/or ICD shock)

A total of 13 studies analyzed the reduction in the number of ICD therapies, 9 of which were included in the meta-analysis. Studies details are described in table 1 and in the supplementary appendix – table 3.

Premature ventricular complexes

Six studies reported the effects of RDN on PVCs. Three of them evaluated patients with resistant hypertension[17,18,19], two assessed patients with no significant comorbidities, except for the high incidence of PVCs[20,21], and one was a report case of a patient with congenital long QT syndrome[22]. The studies details are summarized in the supplementary appendix – table 3.

Periprocedural complications

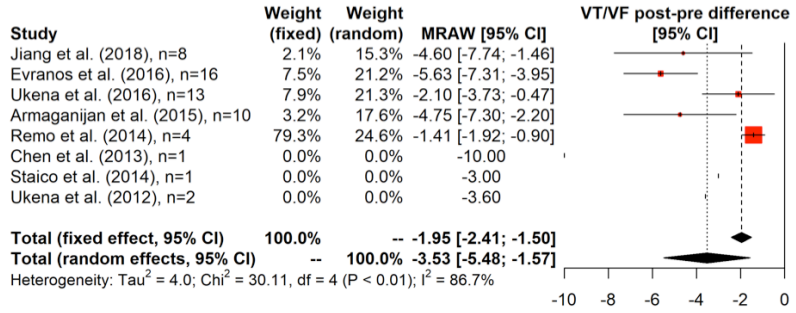
There were few reports (4/325 patients) of periprocedural adverse events (supplementary appendix – table 4): severe bradycardia requiring adrenaline infusion[16], small non-flow-limiting dissection in the right mid-renal artery, transient slow-flow in angiography resolved with nitroglycerine and a IIB/IIIA inhibitor[7]; and transient slow flow in the left renal artery, which did not require intervention[10].

Quantitative synthesis

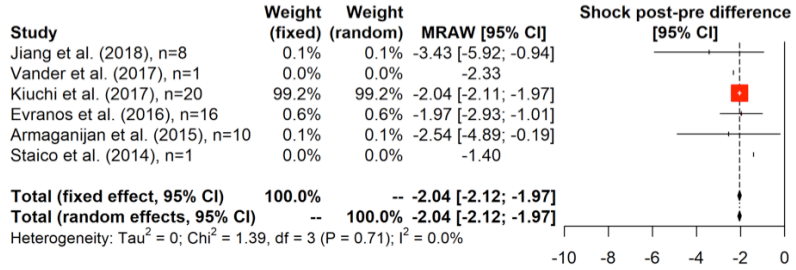
Overall the number of VT/VF, ICD shocks, ATP and ICD therapies were significantly reduced after RDN. A reduction of 3.53 VAs/patient/month (95%CI = -5.48 to -1.57) was observed during 6 months of follow-up compared to 6 months prior to the procedure. Likewise, there was a reduction in the number of ICD shocks of 2.04 shocks/patient/month (95%CI = -2.12 to -1.97), number of ATP of 2.86 events/patient/month (95%CI = -4.09 to -1.63) and overall ICD therapies of 2.68 therapies/patient/month (95%CI = -3.58 to -1.78) (figure 2).

FIGURE 2 – Forest Plots showing the difference between the number of VT/VF(A), ICD shocks(B), ATP(C) and ICD therapies(D) in patients pre and post RDN

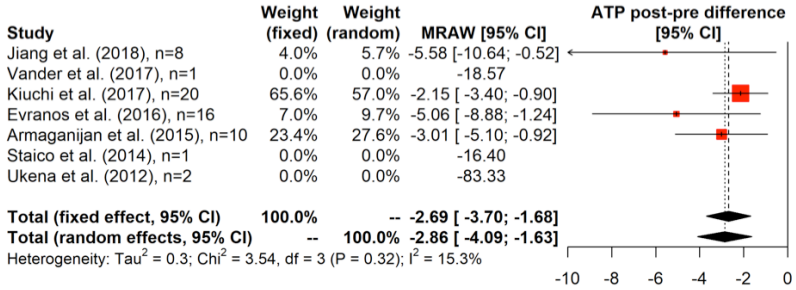
A)



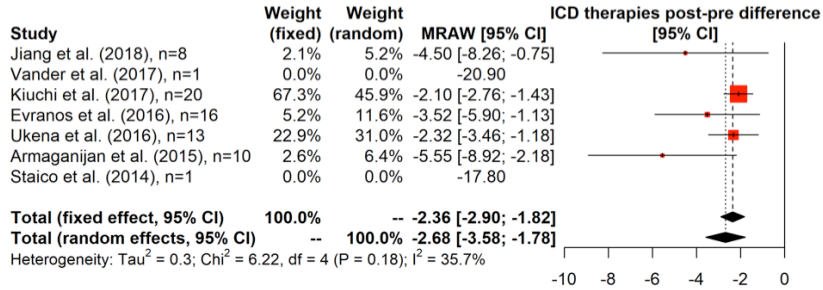
B)



C)



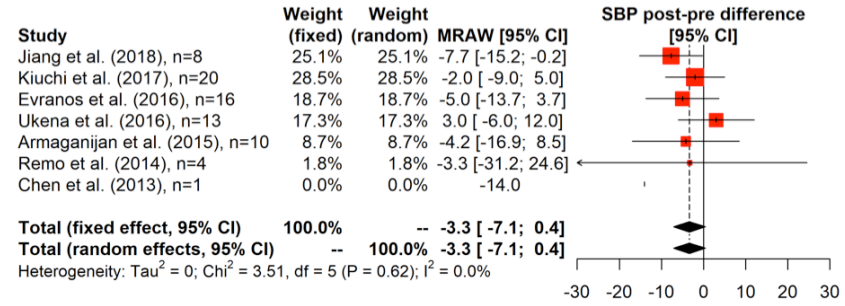
D)



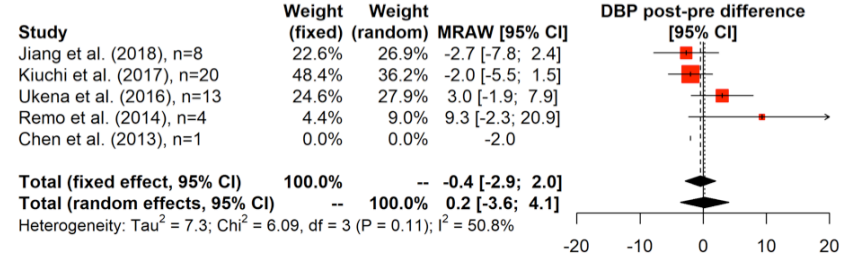
No significant changes in systolic or diastolic blood pressure (SBP and DBP, respectively) were observed in the pooled analysis (reduction of 3.3 mmHg [95%CI = -7.1 to 0.,4] and 0.2 mmHg [95%CI = -3.6 to 4.1] post RDN, respectively). No renal impairment was observed either (0.22 mg/dL reduction in serum creatinine [95%CI = -0.48 to 0.05] and 2.37 mL/min/1.73m^2 increase in eGFR [95%CI = -9.98 to 14.71] post RDN compared to baseline) (figure 3).

FIGURE 3 – Forest Plots showing the difference between SBP(A), DBP(B), creatinine values(C) and eGFR(D) pre and post RDN

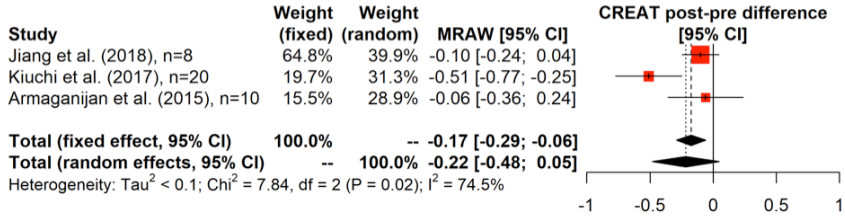
A)



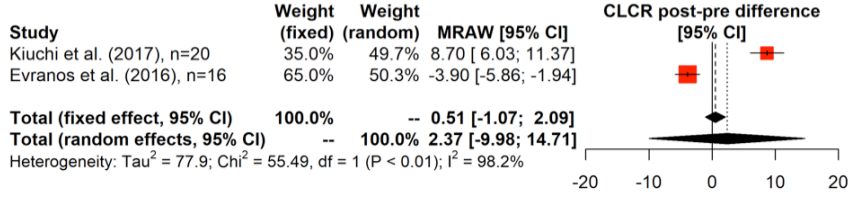
B)



C)



D)



Evaluation of heterogeneity

When analyzing the reduction in the number of VAs after RDN, we found a high heterogeneity between studies (I^2=86.7%, $P_{heterogeneity}$<0.01). There was no evidence of significant heterogeneity between studies selected for ATP, ICD shocks and ICD therapies evaluation (I^2=15.3%, $P_{heterogeneity}$=0.32; I^2=0.0%, $P_{heterogeneity}$=0.71, and I^2=35.7%, $P_{heterogeneity}$=0.18, respectively) (figure 2).

Publication bias

Publication bias was evaluated by visual inspection of symmetry of funnel plots (supplementary appendix – figures 1-8). The funnel plot for VAs showed asymmetry (supplementary appendix – figure 1), suggesting a possible publication bias determined by one study[23]. The funnel plot for eGFR also showed asymmetry (supplementary appendix – figure 8), however, there were only 2 studies included for this outcome. No evidence of publication bias was identified for the other outcomes.

Sensitivity analysis

Sensitivity analysis considering the groups independent (supplementary appendix – figures 9-17) showed similar results. Differences in outcomes comparing pre and post RDN were -3.4 for VT/VF (95%CI = -5.4 to -1.4), -2.3 for ICD therapies (95%CI = -3.0 to -1.7), -2.5 for ATP (95%CI = -3.5 to -1.5) and -2.0 for ICD shock (95%CI = -2.1 to -2.0).

High heterogeneity was found among the studies that analyzed the number of VT/VF, which was mainly driven by Evranos et al[23]. Further analysis (supplementary appendix – figures 9 and 18) excluding this study showed no

significant changes in the result (reduction of 2.74 events/patient/month [95%CI = -4.32 to -1.16], and of 2.4 events/patient/month when using the independent model [95%CI = -4.0 to -0.9]). Funnel plot for eGFR also suggested publication bias, but this outcome only included 2 studies, therefore performing a sensitivity analysis was not possible.

DISCUSSION

Our findings showed that in patients with VAs refractory to standard treatment with antiarrhythmics and catheter ablation, RDN was associated with a significant reduction in the number of VAs and ICD therapies as compared to pre-procedure. The number of both VAs or ICD therapies was reduced already in the first days after the procedure and became close to zero after 6 months. Benefits of RDN were also seen in the setting of frequent PVCs. Renal denervation was shown to be safe, with very few periprocedural adverse events. In most of the studies, SBP and DBP as well as renal function remained unchanged after the procedure.

The ANS plays a significant role in the development and maintenance of VAs[24,25]. VAs are usually precipitated by sympathetic activity and suppressed by vagal tone. There is an intimate relationship between the hyperinnervation that occurs following myocardial injury and VAs, including nerve sprouting, upregulation of nerve growth factor and electrical heterogeneity with areas of denervation[26]. Ultimately, all these factors lead to heterogeneity of excitability, shortening of effective ventricular refractory period and increased ventricular automaticity, predisposing to VAs[26,27,28].

Despite the advances in pharmacological and interventional therapies, VAs remain an important cause of mortality among patients with structural heart disease[1]. The kidneys are also closely connected to the sympathetic nervous system and an important regulator of its activity[29].

Neuromodulation has emerged as an alternative approach for treatment of various pathologies associated with elevated sympathetic tone, such as cardiac arrhythmias, hypertension and heart failure. Neuromodulations aims at restoring autonomic imbalance by decreasing sympathetic or increasing parasympathetic activity[30].

Renal denervation represents a device-based procedure that employs radiofrequency, ultra-sound or alcohol-injection to target sympathetic nerve fibers along renal arteries[31,32]. Recently published randomized, controlled trials, using revised RDN techniques and technologies, have proven the effectiveness and safety of the procedure in patients with and without concomitant antihypertensive medication[33,34,35]. One may speculate that the results achieved with RDN to control VAs may be even better with the performance of the procedure with the novel catheter technologies.

The impact of renal sympathetic denervation in VAs was initially studied in animals in a myocardial-ischemia model[4,36]. The first-in-man experience tested the procedure in patients with heart failure and VAs refractory to conventional treatment[5]. In both patients, the number of VAs was significantly reduced in the first days, and finally disappeared after 6 months. The main mechanism by which RDN reduces sympathetic activity on the heart may be related to the interruption of afferent sympathetic signaling to central nervous system which, in turn, reduces autonomic efferences on the heart and vessels. Reduction in

sympathetic stimulation decreases ventricular vulnerability to malignant arrhythmias and increases the threshold for ventricular fibrillation[37]. Of note, in the SPYRAL-OFF MED study average and minimum morning heart rate were significantly reduced at 3 months for RDN compared with sham patients indicating alterations in sympathetic activity of the heart[38].

The finding that RDN has no significant effects on BP and renal function favors the use of this procedure in patients in whom the frequency of potentially severe malignant arrhythmias is higher, that is, in patients with heart failure and hemodynamic compromise. Reduction in BP could further aggravate the clinical condition of treated patients.

The present meta-analysis suggests that RDN is a safe and effective procedure in the context of VAs refractory to conventional treatment. In clinical practice, this procedure could be considered in patients with cardiomyopathy, persistent VAs and/or ICD therapies that do not respond to antiarrhythmic drugs and catheter ablation. However, larger randomized clinical trials are required to finally assess the value of RDN in the treatment of VAs. A few RCTs evaluating the effect of RDN in the treatment of VAs are ongoing.

However, some limitations of this study should be acknowledged. This is a meta-analysis of observational studies, and therefore the quality of studies is lower than randomized clinical trials. We found high heterogeneity between some of the selected studies. The studied population also showed relevant heterogeneity, once it included patients with different causes of heart disease as well as patients on different types and dosage of antiarrhythmic drugs. A few patients underwent previous cardiac catheter ablation. Additionally, RDN procedure variations included the system employed, type of catheter, number

and sites of ablation, power delivered, and personal experience of the operator. Finally, since the way the data was reported by each study was different, we had to assume that the number of events at 6 months was equally distributed in each month. This assumption, despite being reasonable, might have influenced the direction of our results.

CONCLUSION

In patients with VAs refractory to optimal medical treatment with antiarrhythmic drugs and catheter ablation, RDN was associated with a significant reduction in the number of VAs and ICD therapies as compared to the pre-procedural status. Our findings also showed that RDN is safe, with very few periprocedural adverse events and no significant changes in BP and renal function. Randomized clinical trials are needed to validate our findings.

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SUPPLEMENTARY APPENDIX

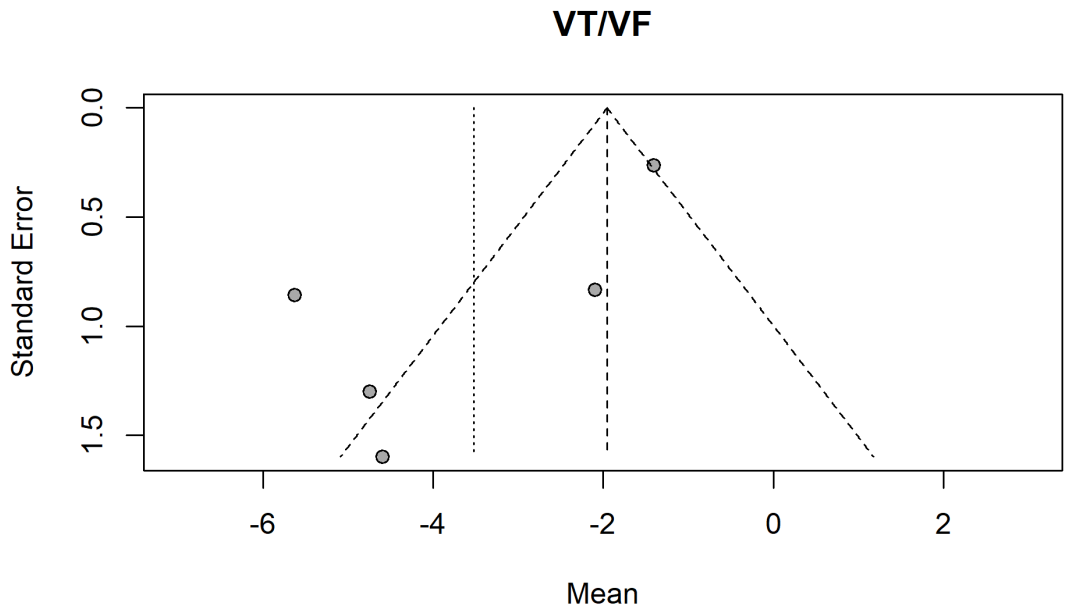
Supplementary Appendix – Table 1 – PRISMA Checklist

Supplementary Appendix – Table 2 – Details of patients of each case report/case series included in the meta-analysis

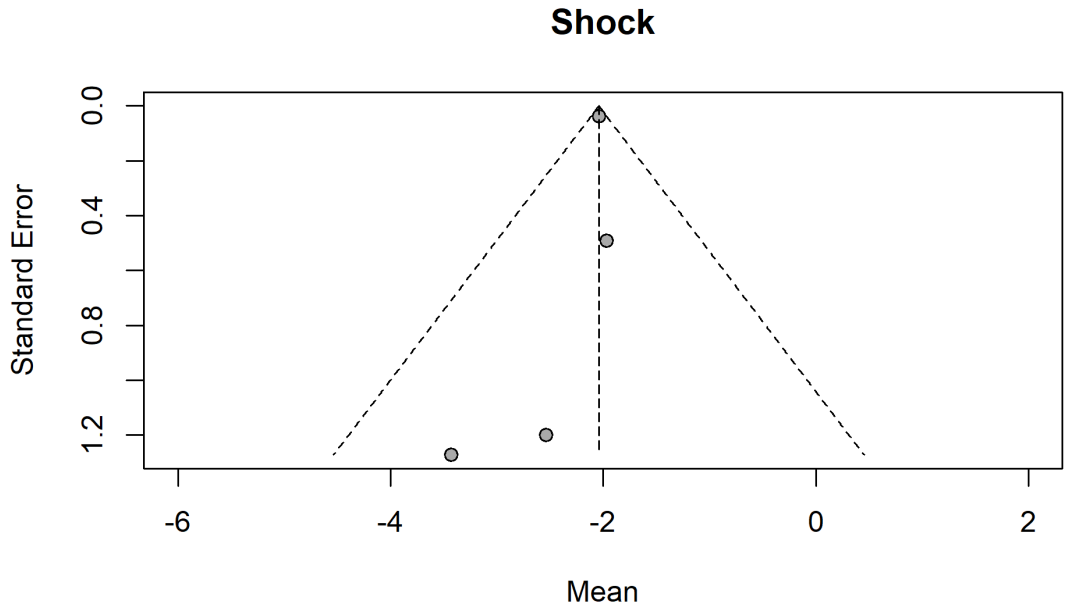
Supplementary Appendix – Table 3 – Details of studies included in the systematic review only

Supplementary Appendix – Table 4 – Renal Denervation associated complications

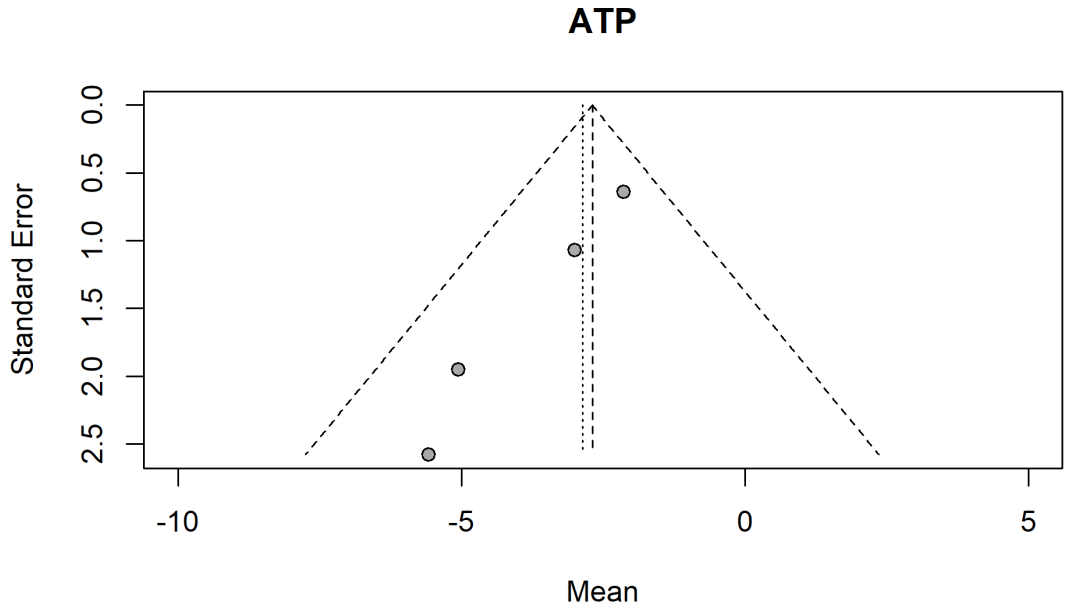
Supplementary Appendix – Figure 1: Funnel Plot for publication bias in the studies - VT/VF



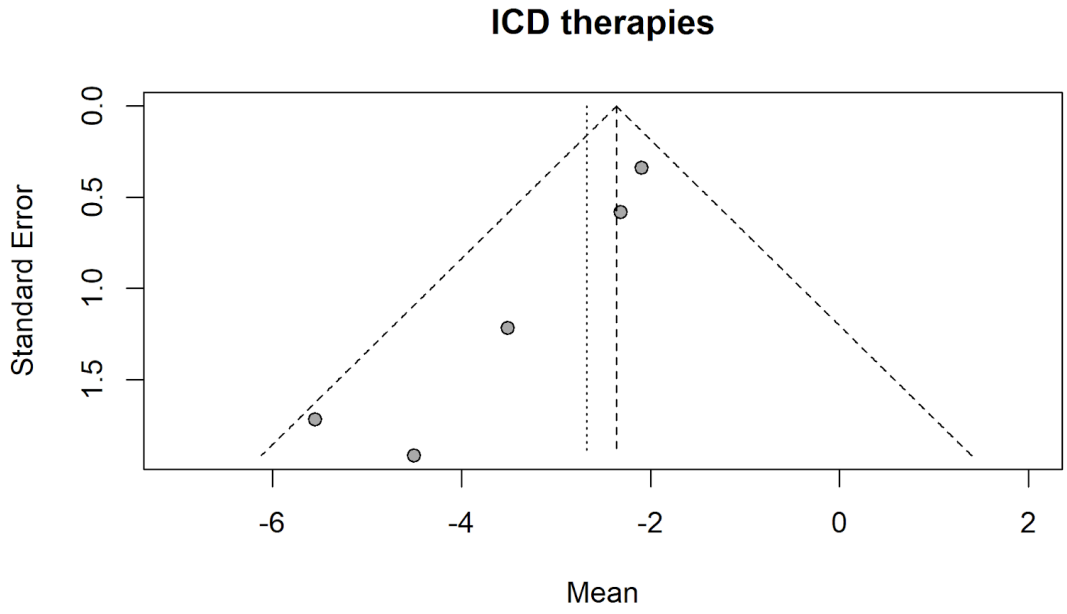
Supplementary Appendix – Figure 2: Funnel Plot for publication bias in the studies - ICD shocks



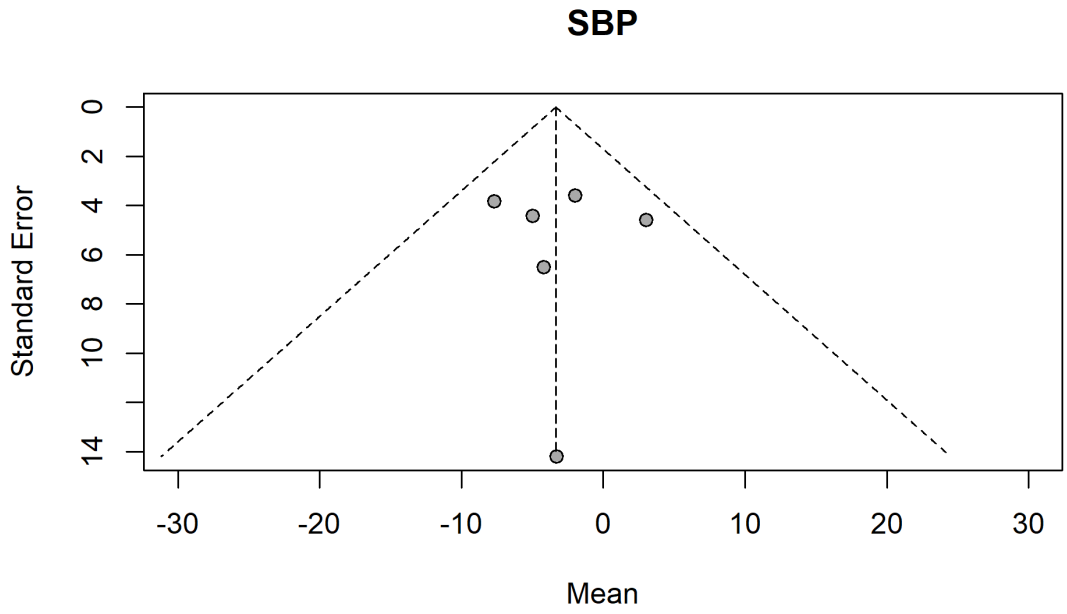
Supplementary Appendix – Figure 3: Funnel Plot for publication bias in the studies - ATP



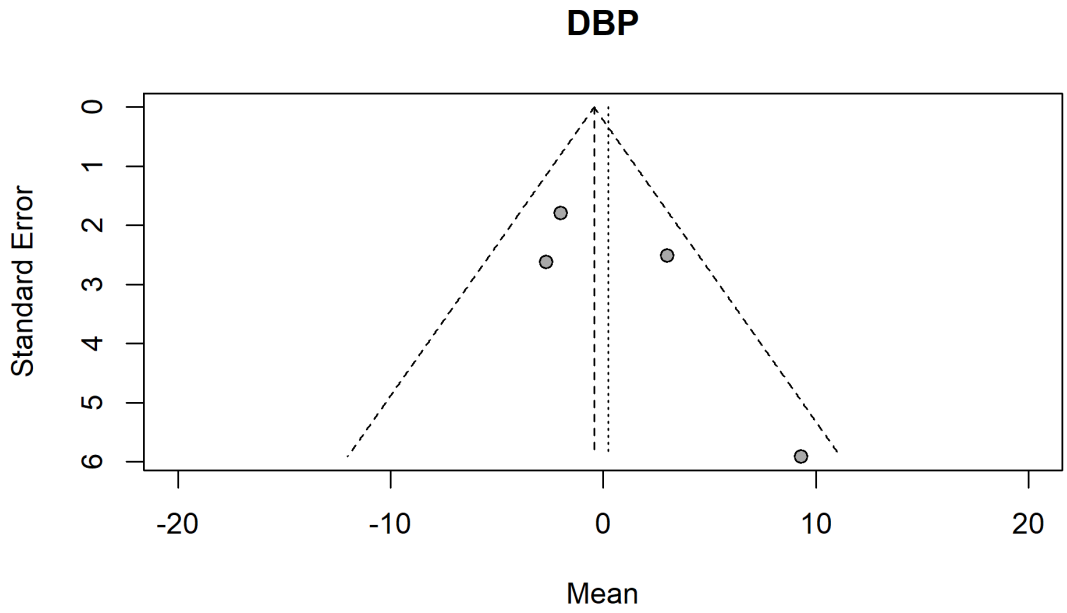
Supplementary Appendix – Figure 4: Funnel Plot for publication bias in the studies - ICD therapies



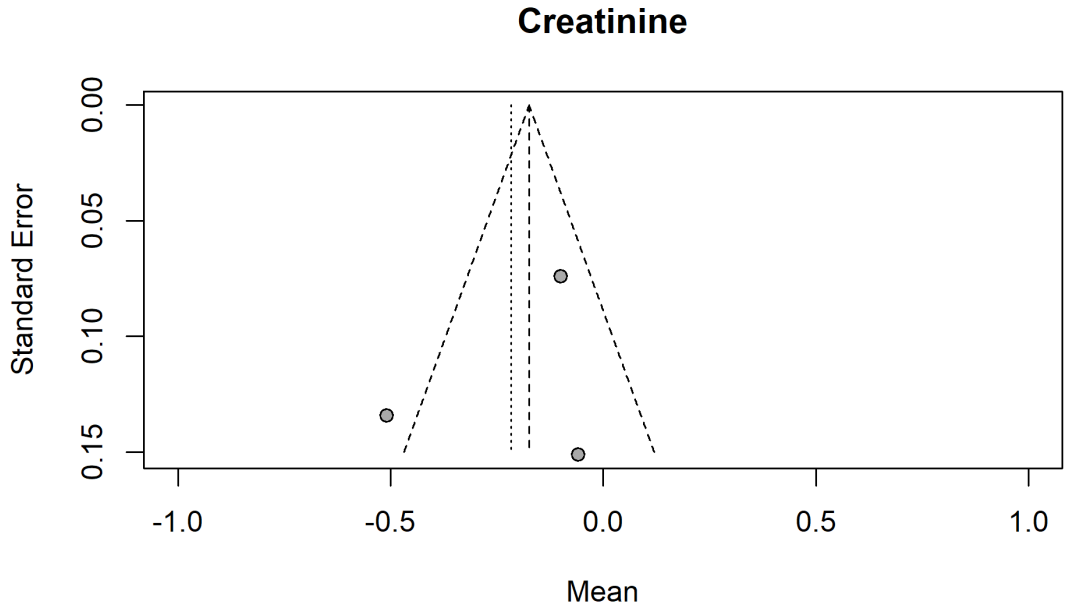
Supplementary Appendix – Figure 5: Funnel Plot for publication bias in the studies - SBP



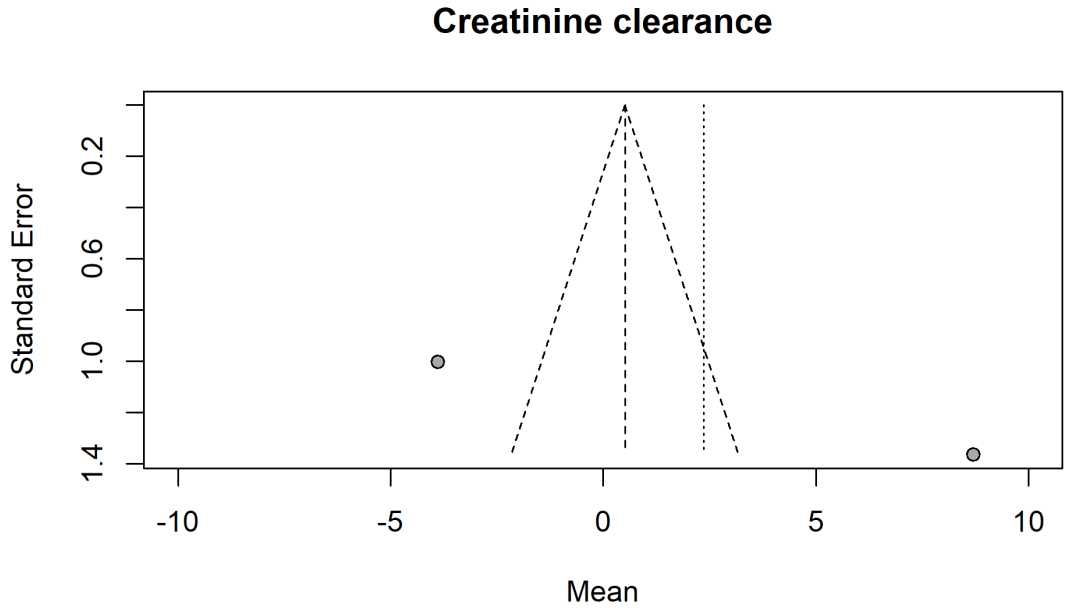
Supplementary Appendix – Figure 6: Funnel Plot for publication bias in the studies - DBP



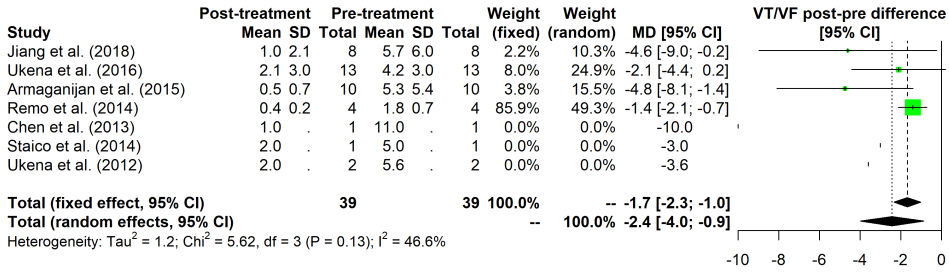
Supplementary Appendix – Figure 7: Funnel Plot for publication bias in the studies - creatinine



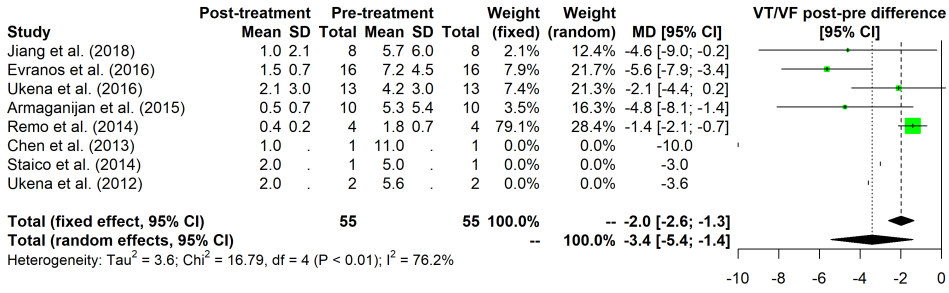
Supplementary Appendix – Figure 8: Funnel Plot for publication bias in the studies - eGFR



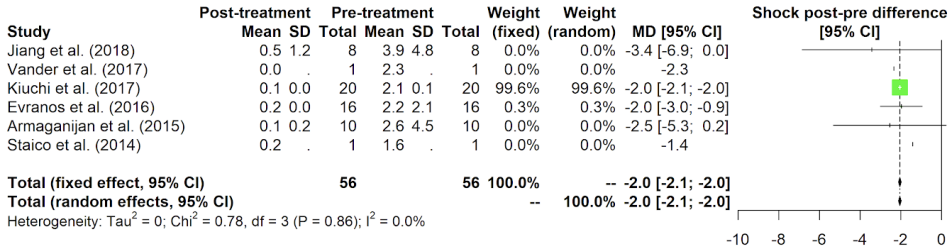
Supplementary Appendix – Figure 9: Forest Plot showing the reduction in the number of VAs in patients pre and post RDN - independent groups, without Evranos



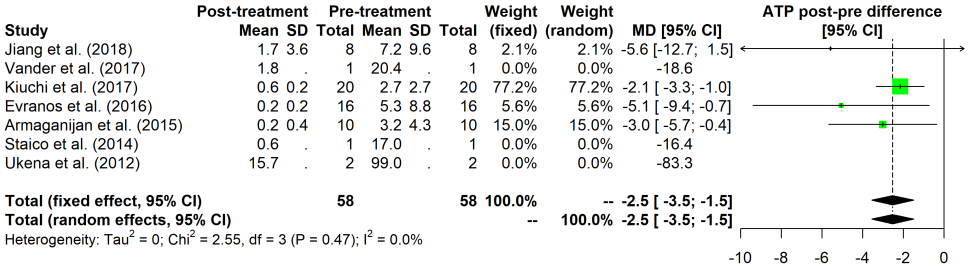
Supplementary Appendix – Figure 10: Forest Plot showing the reduction in the number of VAs in patients pre and post RDN - independent groups



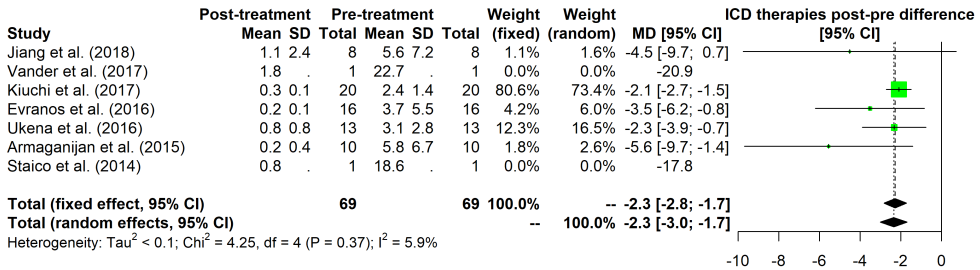
Supplementary Appendix – Figure 11: Forest Plot showing the reduction in the number of ICD shocks in patients pre and post RDN - independent groups



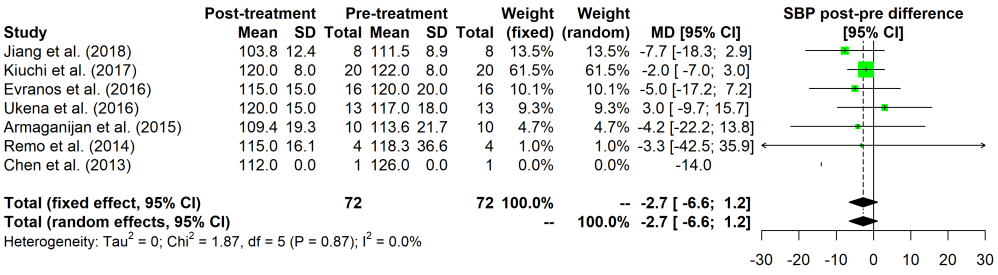
Supplementary Appendix – Figure 12: Forest Plot showing the reduction in the number of ATP in patients pre and post RDN - independent groups



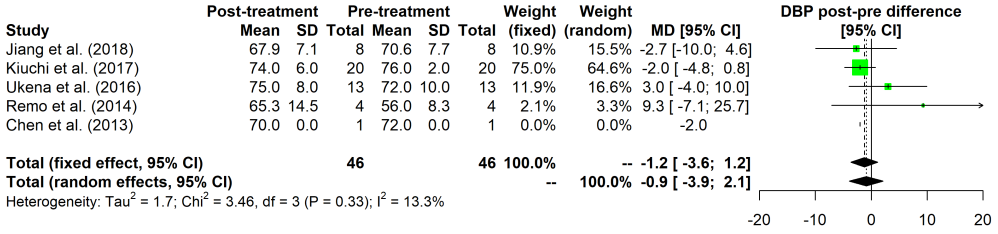
Supplementary Appendix – Figure 13: Forest Plot showing the reduction in the number of ICD therapies in patients pre and post RDN - independent groups



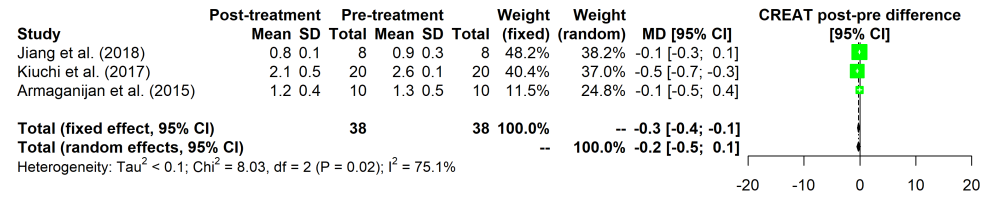
Supplementary Appendix – Figure 14: Forest Plot sowing the change in SBP pre and post RDN - independent groups



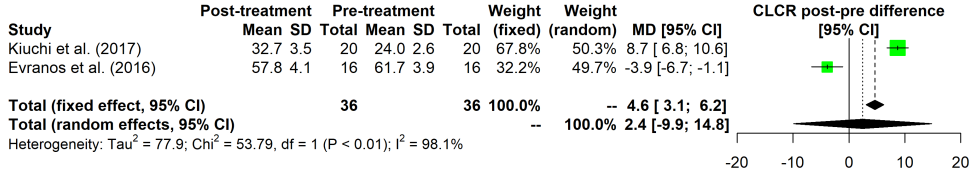
Supplementary Appendix – Figure 15: Forest Plot showing the change in DBP pre and post RDN - independent groups



Supplementary Appendix – Figure 16: Forest Plot showing the change in creatinine value pre and post RDN - independent groups



Supplementary Appendix – Figure 17: Forest Plot showing the change in eGFR pre and post RDN - independent groups



Supplementary Appendix – Figure 18: Forest Plot showing the difference between the number of VT/VF in patients pre and post RDN - without Evranos et al