# The Use of Renal Artery Denervation in Atrial Fibrillation Patients: A Review of Literature

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## Abstract

Renal denervation (RDN) is a minimally invasive procedure by which ultrasound guided ablation or radiofrequency ablation is used to target sympathetic nerves within the walls of renal arteries causing a decrease in their activity and consequently, a reduction in the patient's blood pressure. Although RDN has emerged as a novel therapy for the treatment of resistant hypertension (HTN), its indication spectrum and new therapeutic options are still broadening. HTN remains the main risk factor for the development and maintenance of many cardiovascular diseases including AF. Therefore, initial findings suggest that renal artery ablation proposes to be an innovative intervention in the treatment of AF through the precise targeting of efferent sympathetic and afferent sensory renal nerve signaling, selectively ablating the renal sympathetic nerves. Nevertheless, the efficacy and long-term results of RDN continues to be the focus of ongoing investigation and exploration.

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## Introduction

Renal denervation (RDN) is a minimally invasive procedure by which ultrasound guided ablation or radiofrequency ablation is used to target sympathetic nerves within the walls of renal arteries causing a decrease in their activity and consequently, a reduction in the patient's blood pressure. This has been found to be helpful in treating many patients with refractory hypertension (HTN) [1]. RDN has shown its safety and effectiveness in multiple randomized controlled trials like (Symplicity HTN-1 and Symplicity HTN-2), which showed significant reductions in blood pressure among those with treatment-resistant HTN [2,3]. However, the first randomized sham-controlled study conducted in 2014, the Simplicity HTN-3, has shown the opposite. Randomly assigned patients underwent RDN and were compared with a control group. Unfortunately, their blood pressure reductions were insignificant after 6 months of the procedure [4]. Since RDN is aimed at the sympathetic nervous system activity (SNS), RDN has the potential to treat not only HTN, but also other conditions involving the SNS like heart failure (HF), cardiac arrhythmias, and chronic renal failure. Moreover, recent studies have shown that RDN demonstrates antiarrhythmic effects, which when combined with pulmonary vein isolation, has proven to be beneficial for patients with atrial fibrillation (AF) [5]. A study conducted in 2017 found that RDN when added to pulmonary vein isolation (PVI) showed promising improvements in blood pressure, as well as decreased AF recurrences compared with PVI alone in patients with both AF and resistant HTN [6]. Additional research and clinical trials are still ongoing to determine the sustained effectiveness and safety of RDN as a viable therapeutic approach for the management of AF. Pathophysiology of atrial fibrillation and the role of sympathetic activation AF is the most common sustained arrhythmia and is linked to significant morbidity and mortality [7]. Age-dependent prevalence of AF is estimated to be 0.5% in the general population under 40, ¿5% in the over 65 age group, and ¿10% in the over 80 age group [8]. A wide range of clinical and experimental findings indicate that the existence of modifiable concomitant cardiovascular risk factors, such as obesity, HTN, and sleep-disordered breathing, may accelerate the course of AF [7]. (Figure 1) Prior research has indicated that autonomic nerve system (ANS) activity is critical to atrial arrhythmogenesis [9-11].

According to studies on the sympathetic limb of the ANS, atrial sensitivity to AF formation and post-ablation AF recurrence is greatly decreased when sympathetic tone is suppressed [12]. Activation of the ANS can lead to notable and diverse alterations in atrial electrophysiology, resulting in the onset of atrial tachyarrhythmias such as atrial tachycardia and AF. The role of the ANS in the development of atrial arrhythmias is further

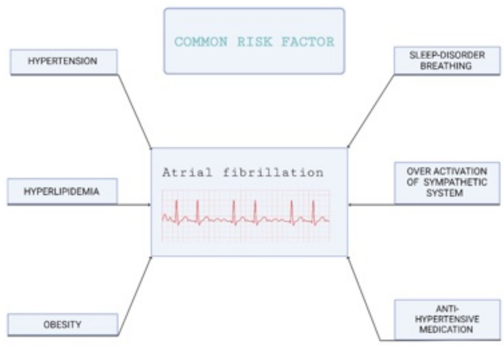


Figure 1: Common risk factors associated with atrial fibrillation.

substantiated by the circadian fluctuations observed in the occurrence of symptomatic AF in humans [13]. Techniques that alter autonomic activity mainly by decreasing sympathetic outflow have been shown to decrease the occurrence of atrial arrhythmias, either spontaneous or induced in both humans and animal models. This suggests that these approaches may find use in the treatment of AF [14].

## Renal denervation as a novel interventional therapy for atrial fibrillation

AF is one of the most common cardiac arrhythmias encountered in clinical practice. Current treatment strategies aimed at the management of AF include antiarrhythmic drug (AAD) therapy and catheter ablation. Yet, several studies have proved that these therapies hold several limitations. AADs are known to be ineffective for maintaining a normal sinus rhythm at the long term [15]. However, while catheter ablation has shown to be more effective in the maintenance of a normal sinus rhythm compared to AADs, it carries a risk for several uncommon complications including bleeding, cardiac perforation, stroke, and myocardial infarction [16]. (Figure 2). Thus, many studies are aiming to explore alternative therapies for treating AF that spare patients the side effects and poor efficacy of antiarrhythmic drugs as well as the risks associated with catheter ablation.

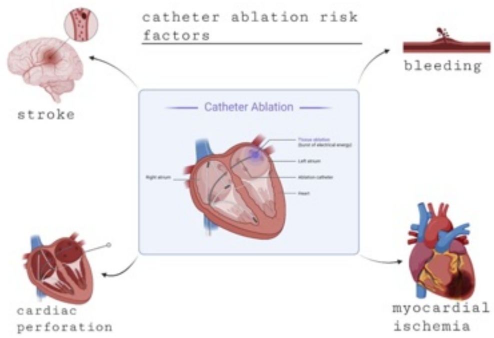


Figure 2: Illustrative overview of key risks associated with catheter ablation therapy.

Although, RDN has emerged as a novel therapy for the treatment of resistant HTN, its indication spectrum and new therapeutic options are still broadening. HTN remains the main risk factor for the development and maintenance of many cardiovascular diseases including AF. Therefore, initial findings suggest that renal artery ablation proposes to be an innovative intervention in the treatment of AF through the precise targeting of efferent sympathetic and afferent sensory renal nerve signalling, selectively ablating the renal sympathetic nerves. This would contribute to enhanced blood pressure by interrupting the communication between the kidneys and the ANS [12]. (Supplementary Material). This conclusion was questioned by the results of sham-controlled Simplicity HTN-3 trial which failed to portray consistent efficacy in the reduction of the blood pressure [17]. Later trials highlighted that adherence, antihypertensive medications, improper procedural methods, and a lack of operator experience contributed to the null effects of the trial.

# Clinical evidence and outcomes of renal denervation in atrial fibrillation

The benefits of RDN were successfully retrieved by SPYRAL HTN-OFF MED trial [18]. The study provided biological proof in the efficacy of catheter based RDN in lowering the blood pressure of patients with HTN not treated with antihypertensive medications. Potential limitations to this trial included its small sample size and inconsistent recording of blood pressure readings. Moreover, some patients met the escape criteria due to antihypertensive medications detected in their urine or serum [18]. With recent trials supporting the resurgence of RDN, further findings have also emphasised the potential of its therapeutic uses in AF, as HTN is an established risk factor for AF. While the pathophysiological link between HTN and AF remains vague, one review proposed that the link mainly stems from the structural changes associated with HTN, including ventricular hypertrophy and ventricular systolic/diastolic dysfunction [19]. Simultaneously, the activation of the renin angiotensin aldosterone system (RAAS) would further exacerbate structural alterations and hence leading to electrical remodelling and AF. This hypothesis was backed up by one review that portrayed that the ablation of the renal nerves significantly reduced the recurrence of AF by more than 20% when compared to pulmonary vein isolation (PVI) and AADs [17]. Based on these observations, Mahfoud et al. evaluated the plasma renin activity and aldosterone before and after RDN [20]. Their study concluded that neuroendocrine markers for patients who underwent RDN were significantly reduced after 3 months, leading to lower office and 24-hour systolic blood pressure readings. Additionally, a report demonstrated that a reduction in systolic blood pressure decreased the odds of AF persistence and recurrence rates [21]. The first trials evaluating RDN for AF treatment were designed to assess the adjunct role of RDN in combination with catheter based PVI. Pokushalov et al. conducted a randomized study on 27 patients with a history of paroxysmal or persistent AF who had resistant HTN (systolic blood pressure of 160 mm Hg despite the intake of triple drug therapy) solitarily with PVI versus PVI combined with RDN [12]. Results portrayed that RDN significantly reduced the burden of recurrent AF episodes when used alongside with PVI. The AFFORD trial, a single-arm pilot study, including 20 patients complaining from symptomatic paroxysmal or persistent AF, further proved that RDN by itself is a safe and effective option in reducing the burden of AF, as measured by an implantable cardiac monitor (ICM) at a 12-month follow-up [22]. A mean blood pressure drop of 5–10 mmHg was shown to be associated with a 7% decrease in AF load reinforcing the antiarrhythmic benefits of RDN along with pulmonary vein isolation (PVI) in hypertensive patients with symptomatic AF [23]. Notably, both systolic and diastolic blood pressure improvements were sustained at 12 months follow-up, with patients reporting a better quality of life. Nonetheless, whether this approach could be more widely applied to all AF patients, even those without resistant HTN, remains uncertain and warrants further investigation [24]. In pair with these promising results, initial studies have investigated the application of RDN as a standalone therapy. Literature documented a case report of a persistent drug-resistant AF patient, successfully treated with RDN instead of PVI [25]. Not only did AF recurrence cease over an 8 month follow up, but left atrial size and pressure were significantly decreased. In addition, the ERADICATE-AF trial was also performed to evaluate RDN's effect on AF without the addition of AADs when added to standard PVI [26]. This trial included 302 hypertensive patients with paroxysmal AF and sub-optimally controlled HTN despite taking at least 1 antihypertensive therapy. After 12 months of follow-up, freedom from AF was achieved in 56.5% of patients receiving PVI alone, compared to 72.1% in those who underwent PVI combined with RDN [24,26]. These findings underscore RDN's growing role in AF management, particularly in combination with PVI. However, further research is needed to assess its broader applicability, long-term effects, and potential as a stand-alone treatment.

## Challenges, limitations, and future directions for renal denervation in atrial fibrillation patients

Studies on RDN encounter several limitations that warrant consideration. Firstly, the diversity in study designs, patient populations, and methodologies across different trials poses a challenge in drawing universally applicable conclusions. The absence of standardized protocols and procedures for RDN may contribute to variations in outcomes and hinder the establishment of consistent findings. Second, blood pressure measurements were not taken using a standardized protocol in many trials. Thus, given the variability in BP response following RDN, a practical measure to identify optimal candidates for RDN therapies remains a major unmet need. Furthermore, all previously published reviews contain evidence cited from Pokushalov et al., the "first-in-man" study of combined RDN and AF ablation [12].This study itself relatively holds a limited sample size and hence affecting the statistical power and generalizability of the results of other clinical trials. Another common limitation is the long-term follow up data in most of the studies are often scarce ranging between 8 to 12 months following the denervation procedure. This in fact poses a challenging task to assess the sustained efficacy and safety of RDN over extended periods [12,24,26]. Confounding factors such as medication changes, adherence issues, and operator experience also introduce variability [18]. Thus, while efforts are underway to address these limitations, acknowledging these constraints is crucial for a comprehensive understanding of the current state of research on RDN. RDN has shown promise in a wide range of clinical trials, particularly in the management of HTN and reducing the risk of AF. However, it is crucial to acknowledge and understand the potential adverse effects associated with this invasive intervention. RDN might not be renal protective in some situations including bile duct ligation-induced renal failure and ischemia/reperfusion-induced acute kidney injury [27]. Other reported adverse effects include renal artery stenosis, which may occur due to injury during the denervation procedure, leading to a narrowing of the renal arteries. Another concern is the risk of renal impairment, as the procedure might affect renal blood flow. Additionally, there have been instances of renal artery dissection, where the arterial wall is damaged during the denervation process, potentially causing complications. While modern RDN techniques aim to minimize these risks, it is essential for clinicians and researchers to remain vigilant in assessing and addressing adverse effects to ensure the safety of patients undergoing RDN. Ongoing research and advancements in technology are expected to refine the procedure and further mitigate these potential complications [28]. The future of RDN as a treatment for AF is promising yet challenging. One potential direction involves refining patient selection criteria to identify the most suitable candidates for RDN, considering factors beyond HTN, such as autonomic dysfunction. Subsequent trials should also investigate the impact of autonomic blood pressure reduction on AF to ascertain whether the influence of RDN on AF is solely dependent on autonomic reduction or if there exists a mechanism unrelated to blood pressure that contributes to the enhancement in AF. Future research could also explore the optimal timing for RDN in AF management and how possible it is to integrate it within a comprehensive treatment approach. Meanwhile the persisting challenges include the need for standardized protocols, longer-term follow-up data, and larger multicentred trials to establish a consistent efficacy. Clarifying the ideal patient profile for RDN in the context of AF remains a priority. Finally, collaborative efforts among researchers and clinicians are essential to navigate these challenges and pave the way for the integration of RDN into routine clinical practice for AF management.

# Recommendations

To initiate the long-term safety and efficacy of renal denervation as a treatment for atrial fibrillation, further research is needed, including larger multicenter randomized controlled trials with longer follow-up periods. Enhancing patient selection criteria is essential to identify the most suitable candidates for renal denervation by considering factors such as autonomic dysfunction and other hypertension related contributors. Moreover, standardizing renal denervation procedures can minimize variability in outcomes, ensuring more consistent and reliable results. Furthermore, evaluating the best timing for renal denervation in atrial fibrillation management is necessary to maximizing its effectiveness. Finally, advancements in technology and process optimization are needed to address potential adverse effects, such as renal impairment and renal artery stenosis; thereby, improving the overall safety of the procedure.

# Conclusion

RDN has shown promising outcomes in the management of refractory HTN and AF. Given that HTN is considered the primary risk factor for cardiovascular diseases including AF, encouraging findings suggest that combining RDN with PVI significantly reduces AF recurrence. Nevertheless, limitations such as varied study designs, lack of standardized protocols and short-term follow-up need to be considered. While the future of RDN appears, promising ongoing research is essential to address potential side effects and optimize its therapeutic potential.

## Conflict of Interest

The authors declare that they have no competing interests.

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