

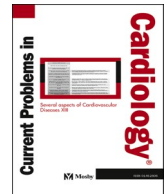
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Invited Review Article



Examining the provision of renal denervation therapy in low- and middle-income nations: Current landscape, challenges, future prospects—A mini perspective review

Hareesha Rishab Bharadwaj^{a,*}, Joecelyn Kirani Tan^b, Syed Hasham Ali^c,
Nicholas Aderinto^d, Muhammad Hamza Shah^e,
Mohammed Dheyaa Marsool Marsool^f, Jyoti Jain^g, Priyal Dalal^h

^a Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom

^b Faculty of Medicine, University of St Andrews, St Andrews, Scotland, United Kingdom

^c Faculty of Medicine, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan

^d Internal Medicine Department, LAUTECH Teaching Hospital, Oyo, Nigeria

^e School of Medicine, Queen's University Belfast, Belfast, United Kingdom

^f Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq

^g Intern, Department of Internal Medicine, All India Institute of Medical Sciences (AIIMS), Jodhpur, Rajasthan, India

^h School of Medicine, University of Central Lancashire, Preston, United Kingdom

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ABSTRACT

This paper delves into Renal Denervation Therapy as a promising intervention for resistant hypertension in low- and middle-income countries. With rates of hypertension increasing in LMICs due to lifestyle factors, RDN presents a potentially transformative approach. The methodology involves a comprehensive literature review, focusing on studies in LMICs that unveil proactive developments in standardized guidelines and precision targeting in clinical trials. LMICs actively contribute to research, emphasizing the safety and efficacy of RDN. However, despite these strides, the current landscape reveals challenges, encompassing initial costs, economic disparities, and limitations in healthcare infrastructure. Despite these hurdles, the paper envisions promising future prospects, emphasizing innovative strategies for cost-effective RDN implementation. It advocates for global collaboration and partnerships with international organizations, proposing the expansion of the Global SYMPPLICITY Registry to include more LMICs; a testament to a commitment to research advancement. The paper concludes by highlighting comprehensive strategies to overcome challenges, making RDN financially viable in resource-limited settings. It underscores the potential for RDN to enhance global healthcare outcomes, particularly in regions grappling with diverse economic and healthcare challenges.

Introduction

Renal denervation (RDN) therapy has emerged as a promising intervention for resistant hypertension, offering a potentially transformative approach to managing a condition that has become a burgeoning public health concern, particularly in low- and

* Corresponding author.

E-mail address: hareesha.bharadwaj@student.manchester.ac.uk (H.R. Bharadwaj).

Abbreviations

ACE-Is	Angiotensin-converting enzyme inhibitors
BP	Blood Pressure
CCBs	Calcium channel blockers
CKD	Chronic Kidney Disease
CVD	Cardiovascular diseases
GSR	Global SYMPLICITY Registry
LMICs	Low- and middle-income countries
RDN	Renal denervation
SBP	Systolic blood pressure

middle-income countries (LMICs). Characterized by the radiofrequency ablation of afferent sympathetic nerves within the renal artery, RDN has demonstrated efficacy in reducing hypertension and mitigating renal end-organ damage,¹ drawing inspiration from the historical roots of splanchnicectomy.²

In LMICs, the escalating prevalence of hypertension, fueled by sedentary lifestyles and dietary habits rich in sodium and fat, has reached alarming proportions.³ Statistics underscore the urgency, with a substantial portion of chronic hypertensive patients concentrated in South and East Asia. The resulting mortality and morbidity burdens are disproportionately high in LMICs, as evidenced by Global Burden of Disease data highlighting elevated death rates and disease-associated disability.⁴

The existing landscape of hypertension management in LMICs reveals significant challenges. While antihypertensive medications, particularly calcium channel blockers (CCBs) and angiotensin-converting enzyme inhibitors (ACE-Is), are readily available, the sub-optimal monitoring of prescriptions, poor compliance rates, and a lack of follow-up pose formidable obstacles to underfunded and mismanaged healthcare systems.⁵ Notably, poor compliance serves as a risk factor for resistant hypertension, necessitating a novel and more sustainable treatment approach.⁶

RDN emerges as a promising candidate for addressing the multifaceted challenges of hypertension management in LMICs. Firstly, it presents an opportunity to reduce or eliminate post-procedural drug intake, alleviating financial burdens on households in regions where healthcare expenditures are predominantly out-of-pocket. Studies demonstrate a marked reduction in prescribed hypertensives post-RDN, underscoring its potential to reshape the economic dynamics of hypertension care.⁷

Secondly, the skepticism surrounding surgical interventions in LMICs, often fueled by high illiteracy rates, can be mitigated by the minimally invasive nature of RDN. The procedure involves a small incision and promises quicker recovery, making it more palatable in regions where surgical apprehension prevails.^{8,9}

This paper critically assesses the role of RDN in the context of resistant hypertension, delving beyond its efficacy to explore its applicability in LMICs. The examination extends to the intricate challenges and opportunities tied to RDN implementation, encompassing considerations of healthcare infrastructure, accessibility, and economic factors, whilst also suggesting future prospects. Through this nuanced exploration, our paper aims to contribute valuable perspectives on RDN's potential in reshaping hypertension management, particularly in regions marked by varying healthcare and economic conditions.

Methodology

This narrative review employed a rigorous methodology involving a comprehensive search of published literature with a focus on studies conducted in LMICs. A detailed search string is provided in Appendix 1. The inclusion criteria accommodated studies of various designs, including observational, case-control, cohort, and randomized controlled trials.

Databases such as PubMed, Google Scholar, the Cochrane Library, EMBASE, CINAHL, SCOPUS and Scielo were enlisted for the literature search. No limitations of time were introduced, with results ranging from inception to 16th December 2023. Precise search terms, including "hypertension", "resistant hypertension", "renal denervation", "renal sympathetic denervation", were combined with geographical identifiers such as individual countries categorized as LMICs by the World Bank, "LMICs", and "low-middle income countries". This approach ensured that the literature search targeted our specific area of interest. Furthermore, a manual search was conducted to find references for recently published, procedure-specific reviews to further the precision of this article. Stand-alone abstracts, unpublished studies, and trial protocols were excluded from the review.

Current landscape of RDN in LMICs

Recent developments in RDN influence the landscape of hypertension management in LMICs. Several notable trends are emerging, demonstrating a proactive approach to guideline adoption, tailoring recommendations for resistant hypertension, implementing precision targeting in clinical trials, and fostering ongoing research.

Development and adoption of standardized guidelines

LMICs are increasingly adopting guidelines to steer the utilization of RDN in hypertension management through a continued

emphasis on research. These guidelines provide clear indications for RDN, emphasizing its application in refractory or resistant hypertension cases.

Recent advancements in RDN therapy, particularly in Thailand and Malaysia, highlight the adoption of standardized guidelines for hypertension management. The Thai Hypertension Society's guidelines for RDN use in refractory or resistant hypertension encompass patients with established atherosclerotic cardiovascular disease (CVD), progressive organ damage, multidrug intolerance, or non-adherence.¹⁰ This approach has demonstrated significant success, as evidenced by a case series from Thailand showing substantial efficacy of RDN in treatment-resistant hypertension. Despite exhaustive pharmacological treatments with 5–8 classes of antihypertensive drugs, RDN led to marked hemodynamic improvements, including an average reduction of 35.2 mm Hg in systolic blood pressure (SBP) at a 3-month follow-up.¹¹ Similarly, in Malaysia, the prevalence of resistant hypertension, found to be 8.8 % in a cross-sectional survey, led to the development of specific guidelines by the Malaysian Working Group Consensus.¹² These guidelines target patients with treatment-resistant hypertension, focusing on those non-adherent to multiple medications and managing polypharmacy for various comorbidities.¹³ This tailored approach recognizes the unique challenges presented by resistant hypertension and positions RDN as an essential tool in addressing these challenges.

Precision targeting in clinical trials: Optimizing treatment response

LMICs are at the forefront of shaping the landscape of RDN through the implementation of precision targeting in clinical trials. This innovative approach involves the deliberate enrollment of individuals based on specific blood pressure (BP) criteria, reflecting a broader paradigm shift towards personalized or precision medicine in RDN research.

China's strategic engagement with RDN is exemplified by an ongoing 245-patient trial that adopts a meticulous patient selection strategy. This trial focuses on individuals with 24-h SBP ≥ 135 mm Hg and office SBP < 170 mm Hg.¹⁴ This precise enrollment criteria targets patients predominantly characterized by mild to moderate hypertension. The intention behind this selective strategy is to potentially enhance the responsiveness of patients to RDN-induced changes in sympathetic tone.

Moreover, a recent observational pilot study conducted in China further illustrates the commitment to precision targeting in RDN research.¹⁵ In this study, eight Chronic Kidney Disease (CKD) patients with office BP $\geq 150/90$ mm Hg and confirmed 24-hour ambulatory SBP ≥ 135 mm Hg underwent RDN. The results demonstrated a substantial reduction in BP post-procedure. Office BP decreased by $22.1 \pm 12.0/11.0 \pm 8.8$ mm Hg, and 24-h ambulatory BP showed a reduction of $18 \pm 13.7/9.3 \pm 7.7$ mm Hg over the six-month follow-up period.

The strategic goal underlying these initiatives is to optimize treatment responsiveness by tailoring interventions to the unique profiles of individual patients. By focusing on specific BP criteria and physiological characteristics, such as investigating the effect of RDN on patients with Diabetes and CKD, LMICs are paving the way for more effective and targeted RDN interventions. These endeavors in precision targeting, supported by observational studies within LMICs, not only contribute valuable insights but also highlight the potential for significant BP reduction without adverse effects on critical physiological parameters. This strategic and personalized approach is anticipated to redefine the landscape of RDN research, especially in regions with diverse patient populations and varying healthcare challenges.^{14,15}

Continued research and development in LMICs

LMICs are at the vanguard of ongoing research initiatives aimed at advancing the comprehension and application of RDN in the sphere of hypertension management. These pioneering research endeavors, characterized by their exploration of avant-garde techniques, diverse patient populations, and investigations into long-term outcomes, significantly contribute to the burgeoning body of evidence substantiating the safety and efficacy of RDN. In recent years, the landscape has witnessed the inception of several pivotal clinical trials, with components conducted within LMICs, notably exemplified by the Global SYMPPLICITY trial. Simultaneously, the assimilation of cutting-edge catheter technologies in LMICs has been a pivotal focus, coupled with an unwavering commitment to the continued scrutiny of the clinical safety and efficacy of RDN therapies in LMIC settings.¹⁴⁻¹⁶

Moreover, the trajectory of research emanating from LMICs is witnessing an escalating trajectory, exemplified by a sustained upsurge in scholarly contributions delving into the intricacies of RDN. LMICs are not merely passive recipients of evolving knowledge but are active contributors to the global scientific discourse. These multifaceted endeavors, spanning precision targeting strategies, observational studies, and real-world registries, underscore the steadfast commitment of LMICs to fostering continuous innovation and refinement in the domain of RDN for the effective management of hypertension.

Challenges

The implementation of RDN therapy encounters various challenges, as highlighted by Hu et al. (2023).¹⁷ A primary obstacle is the significant initial costs associated with the procedure. These expenses encompass acquiring cutting-edge equipment, providing specialized personnel training, and establishing necessary facilities, thus imposing a substantial financial burden.¹⁸ Notably, the costs of advanced catheter-based devices and the essential infrastructure can be considerable, posing a formidable barrier to the widespread adoption of RDN therapy.

This financial challenge is compounded by economic disparities between high and low-income countries, intensifying the complexities surrounding implementation.¹⁹ The existing financial divides not only limit the potential reach and impact of RDN therapy but also hinder its transformative benefits in LMICs. Additionally, reimbursement policies and insurance complications further affect

the accessibility and affordability of this advanced medical intervention. For example, inadequate coverage by reimbursement policies can result in limited patient access, impeding the integration of RDN therapy into healthcare systems.²⁰ Beyond economic considerations, the state of healthcare infrastructure plays a pivotal role in determining the success of RDN therapy implementation.²¹ Insufficient infrastructure is evident in various aspects, including a shortage of medical facilities, limited access to essential medical technologies, and a need for specialized healthcare personnel.

In remote or underserved regions, the absence of catheterisation laboratories dedicated to RDN poses a significant barrier.²¹ Addressing this challenge requires not only meeting immediate physical needs but also investing in skilled healthcare professionals, comprehensive training programs, and an interconnected network of healthcare services to support the demands of sophisticated medical interventions.

Moreover, healthcare professionals encounter challenges in seeking expertise and dedicated training programs for RDN procedures. The specialized nature of this therapeutic approach demands a unique skill set that often surpasses the scope of traditional medical education. The challenge lies in the need for more formalized training programs and standardized protocols to ensure consistency in the skill levels of healthcare professionals. Resistance within existing healthcare systems further complicates the adoption process, arising from factors such as unfamiliarity with the novel procedure, concerns about efficacy or safety, and reluctance to deviate from established medical practices. This resistance, stemming from skepticism among healthcare providers accustomed to traditional treatment methods, is exacerbated by concerns about the therapy's effectiveness, potential side effects, and uncertainties about patient outcomes.^{16-19,21} Addressing these challenges requires a concerted effort to foster understanding, provide formalized training, and establish a supportive environment for the successful implementation of RDN therapy.

Future prospects

In the context of challenges associated with the implementation of RDN therapy in LMICs, there exists an expansive terrain rich in opportunities for innovative strategies and global collaboration. Initiatives aimed at exploring and developing cost-effective RDN implementation models are pivotal, demanding meticulous design to streamline processes, optimize resource utilization, and ultimately reduce overall costs. This approach renders the therapy financially viable for healthcare systems in resource-limited settings. Additionally, the establishment of collaborative efforts with international organizations and strategic partnerships emerges as a key driver for sustainable implementation.

To enhance cost-effectiveness, partnerships with international organizations can facilitate access to shared resources, enabling the pooling of knowledge, expertise, and infrastructure. Notably, as discussed previously, initial trials indicate that the utilization of RDN therapy for hypertension treatment over a decade has proven safe and effective, particularly in cases of resistant hypertension.^{10,14,15,22} Furthermore, evidence demonstrates effective reduction of BP over 24 hours, especially during nighttime, alleviating organ damage and CVD without adverse effects on renal function.^{10,15} However, challenges persist, such as limited skilled interventionists, particularly in Thailand.¹⁰ This involves joint initiatives to develop mentorship programs aimed at upskilling healthcare professionals in LMICs. Additionally, establishing robust funding networks for infrastructures and facilitating knowledge sharing in policymaking are essential components of these collaborative efforts. Such comprehensive initiatives not only address immediate challenges but also contribute to the sustainable development of resources, skills, and expertise in LMICs, fostering an environment conducive to the successful implementation of RDN.

Effective collaboration at the local level is paramount to ensuring widespread enhancement in the implementation of RDN therapy. A notable example is a multicenter trial in China dedicated to investigating the safety and efficacy of RDN treatment for resistant hypertension. The dissemination of findings from this trial extends beyond academic circles, reaching participating hospitals, policymakers, and the broader healthcare community across the nation.¹⁴ This expansive national network not only contributes to the improvement of patient care but also plays a pivotal role in informing healthcare policies and supporting ongoing research efforts.

In Malaysia, a consensus publication underscores the significance of RDN in hypertension management, consolidating clinical data, offering guidance on patient selection, and facilitating the robust dissemination of findings within the Malaysian healthcare landscape. This dissemination is complemented by concerted efforts in continuous professional development and training, thereby elevating the standards of local hypertension management.¹³ Given the constraints of limited resources in LMICs, optimizing resource utilization becomes imperative for the development of effective hypertensive management strategies. Local collaborations, as illustrated by these instances, serve as pivotal drivers in harnessing existing resources efficiently, fostering sustainable improvements in the landscape of hypertension care within LMICs.

Simultaneously, the future of RDN is intrinsically tied to ongoing research and innovation. A robust commitment to studying the therapy's efficacy, safety, and patient outcomes through continuous clinical trials and research initiatives is essential. The relevance of this approach becomes evident when considering the aforementioned clinical trials conducted in Thailand, Iran, South Africa, and China (Global SYMPPLICITY) to assess the safety and efficacy of RDN in LMICs.^{10,14-16,22} Building upon this foundation, an extension of the commitment to global collaboration could involve strategic initiatives, such as the establishment of a subsidiary within the Global SYMPPLICITY Registry (GSR). This subsidiary would be specifically designed to encompass a more extensive representation of LMICs in its registry and actively contribute to the development of RDN clinical trials in these regions.

A compelling illustration supporting this proposal is drawn from the results of a South African trial. In this trial, the safety and efficacy outcomes of RDN in South African patients were found to be in alignment with the results obtained from the worldwide GSR.¹⁶ This consistency underscores the promising potential of implementing RDN in LMICs and emphasizes the generalisability of findings from broader global studies to specific healthcare contexts in these regions. The proposition to expand the GSR in this manner reflects a commitment to advancing research and ensuring that RDN evolves in tandem with emerging technologies and advancements. Such

proactive measures are crucial for maintaining the therapy's relevance and effectiveness across diverse healthcare contexts, contributing to its successful integration in LMICs and addressing the unique challenges associated with these settings.

Conclusion

In conclusion, the examination of RDN introduction in LMICs reveals challenges and promising opportunities. RDN's potential for treating resistant hypertension is rooted in historical practices, yet barriers like initial costs, economic disparities, and healthcare infrastructure limitations exist. Despite challenges, future prospects are promising with innovative strategies and global collaboration. Initiatives for cost-effective RDN implementation, coupled with collaboration with international organizations, emerge as key drivers. Expanding the GSR to include more LMICs reflects a commitment to research advancement. Addressing challenges through comprehensive strategies can make RDN financially viable in resource-limited settings, significantly improving global healthcare outcomes.

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CRediT authorship contribution statement

Hareesha Rishab Bharadwaj: Conceptualization, Formal analysis, Project administration, Methodology, Writing – original draft, Supervision. **Joecelyn Kirani Tan:** Methodology, Writing – original draft. **Syed Hasham Ali:** Methodology, Writing – original draft. **Nicholas Aderinto:** Methodology, Writing – original draft. **Muhammad Hamza Shah:** Methodology, Writing – original draft. **Mohammed Dheyaa Marsool Marsool:** Methodology, Writing – original draft. **Jyoti Jain:** Writing – original draft. **Priyal Dalal:** Methodology, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Hareesha Rishab Bharadwaj takes complete responsibility for the integrity of the study, and affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, and that no important aspects of the study have been omitted, and that any discrepancies have been explained and addressed.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.cpcardiol.2023.102357](https://doi.org/10.1016/j.cpcardiol.2023.102357).

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