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Editorial

Balancing Affordability and Need: Should We Use Renal Denervation in Hypertension Management?

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Globally, high blood pressure (BP) is the most important modifiable risk factor for cardiovascular disease[1] and has become the leading attributable risk factor for death, accounting for 10.8 million deaths in 2019.[2] This risk is higher in women than in men and in Black adults than in non-Black adults.[3] In the United States (US), approximately half of the population is affected by hypertension. Consequently, hypertension represents a significant financial burden not only for the individuals affected, who incur nearly $2000 higher annual health care expenditures than their nonhypertensive peers but also for the US health care system.[4] Health care costs associated with hypertension are estimated to account for $131 billion per year.[4]

The treatment of arterial hypertension is of particular importance. Undoubtedly, lifestyle modifications are the foundation of antihypertensive therapy.[5,6] In addition, most patients will require medication to control their BP.[5] In the 1950s, the introduction of thiazide diuretics was a major advancement in pharmacologic therapy because they were orally available, effectively reduced BP, and were well tolerated.[7] Soon after, the trial of the US Veterans Administration Cooperative Study Group on Antihypertensive Agents published in 1967 demonstrated for the first time that lowering BP with antihypertensive medications reduced cardiovascular morbidity and mortality.[8]

There is now a large body of evidence demonstrating that angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics, which are recommended as first-line medications, reduce cardiovascular events and improve mortality.[5] An individual participant-level data meta-analysis, including data from 613,815 participants, showed that every 10 mm Hg reduction in systolic BP decreases the relative risk of cardiovascular events by 20%, coronary heart disease by 17%, stroke by 23%, heart failure by 28%, and all-cause mortality by 13%.[9] Despite the availability of these first-line medications at low cost, and the majority of which are generic, many patients fail to achieve adequate BP control as recommended by current guidelines.[5] A serial cross-sectional analysis of National Health and Nutrition Examination Survey data, weighted to be representative of US adults, showed that BP control to <140/<90 mm Hg increased and plateaued between 2013 and 2014 at 53.8%, but then declined to 43.7% in 2017-2018 across age- and race-ethnicity groups.[10] Because the target BP has since been lowered to <130/<80 mm Hg,[5] control rates may be even lower.

To address issues related to medication, such as declining adherence over time, several interventional approaches were introduced for the treatment of hypertension, most notably catheter-based renal denervation (RDN). Initially, there was excitement about marked BP drops in early unblinded studies, but doubts arose about BP-lowering efficacy following the publication of the first sham-controlled SYMPLICITY HTN-3 trial.[11] However, consistent office and ambulatory BP reductions have now been demonstrated in several sham-controlled studies using different catheter systems.[11] Importantly, none of the RDN trials have raised any serious procedure-related safety concerns beyond the known risks associated with femoral arterial access procedures.[11] Based on these trials, the 2023 European Society of Hypertension hypertension guidelines consider RDN a treatment option for uncontrolled hypertension,[12] and radiofrequency and ultrasound catheter systems have been approved by the US Food and Drug Administration.

In this issue of *JSCAI*, Kandzari et al[13] report the results of a cost-effectiveness analysis of radiofrequency RDN in the US. The costs and effects of RDN were projected using a decision-analytic Markov model adapted from a prior report assessing the cost-effectiveness in the United Kingdom.[14] The treatment options (RDN vs treatment with 1, 2, or 3 medications), demographic characteristics (mean age 55 years, baseline systolic office BP 166 mm Hg), and reductions in systolic office BP (–9.9 mm Hg in the RDN group vs –4.9 mm Hg in the sham group) were based on the SPYRAL HTN-ON MED full cohort trial investigating the Symplicity Spyral RDN system (Medtronic).[15] The development of cardiovascular events was based on multivariable risk equations from large cohort studies, such as the Framingham Heart Study, Prospective Cardiovascular Münster, and the National Health and Nutrition Examination Survey.[13] The relative risk reductions in clinical events were calculated based on a meta-analysis including data from 47 randomized

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controlled trials investigating antihypertensive medications.[16] The analysis demonstrated a significant reduction in clinical events, with relative risks of 0.88 for myocardial infarction, 0.80 for stroke, and 0.85 for cardiovascular death over 10 years. Over a lifetime, the calculated risk reductions would add 0.34 quality-adjusted life years (QALY) at an additional cost of $11,275, resulting in an incremental cost-effectiveness ratio of $32,732 per QALY. When applying the willingness-to-pay thresholds of $50,000 per QALY for high-value interventions and $150,000 per QALY for intermediate-value interventions, radiofrequency RDN would be considered high-value in the US health care system. Notably, these cost-effectiveness findings were robust across several patient risk profiles.

These findings are reassuring, as the procedure's cost-effectiveness is one of the critical questions regarding the clinical adoption of RDN. Today, concerns about costs limit the widespread use and reimbursement by payers; however, it is important to note that this analysis has some limitations, which the authors have acknowledged, and relies on 2 major assumptions:

1. The reduction in BP following RDN is maintained for life.
2. The BP decrease associated with RDN translates into a similar reduction in cardiovascular outcomes as with antihypertensive medications.

Although nonrandomized studies and registries support both assumptions, they should not be conflated to imply causality. Nonrandomized, follow-up data from the sham-controlled SPYRAL HTN-ON MED pilot[17] and RADIANCE-HTN SOLO trials[18] indicate a sustained BP-lowering effect for up to 3 years. Similarly, single-center studies report sustained BP reductions for up to 10 years.[19] Longer-term follow-up data from randomized controlled trials are desirable but are challenged by several factors as follows: (1) the unblinding of patients and outcome assessors, (2) crossover to RDN of patients initially allocated to the sham group, (3) aging-related longitudinal BP changes, (4) the addition of antihypertensive medications to facilitate BP control, (5) dynamic changes in drug adherence over time, and (6) development of a coexisting illness unrelated to hypertension. Although renal sympathetic reinnervation is a theoretical concern, there is no clear evidence for regain of nerve function following RDN.[20]

Regarding the second assumption, whether BP lowering following RDN reduces cardiovascular outcomes to the same extent as medications is unknown. BP is accepted as a surrogate outcome by both clinicians and regulators, including the Food and Drug Administration, and observational studies, which naturally have limitations, suggest associations between RDN and reduced risk of cardiovascular disease events[21]; however, meta-analyses provide inconsistent evidence on the strength of the association between BP reductions and improvements in cardiovascular outcomes.[22] Importantly, harmful off-target effects associated with RDN, which could counter the beneficial effect of BP reduction and prevent a reduction in cardiovascular events, have not been identified. Conversely, RDN could offer advantages over certain medications by reducing sympathetic nervous system activity, which is also associated with other conditions such as diabetes, atrial fibrillation, metabolic syndrome, and heart failure.[23] Additionally, unlike antihypertensive medications, the BP reductions seen with RDN are not influenced by factors such as adherence, pharmacokinetics, and pharmacodynamics, and they are sustained throughout the day and night.[11]

The authors should be congratulated for conducting this analysis, which adds another critical piece to the puzzle by showing that RDN in the US health care system might be cost effective and a valuable addition to established hypertension management approaches. Although it may be impractical and expensive to carry out outcome studies for RDN in hypertension or patients at risk, we should accept the challenge and work toward overcoming the obstacle of conducting cardiovascular outcome trials with modern trial designs and methods.

Declaration of competing interest

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