ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Renal Denervation for Uncontrolled Hypertension

A Health Technology Assessment

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Ontario Health

Key Messages

What Is This Health Technology Assessment About?

Blood pressure is used as an indication of how well the heart and blood vessels are working. When a person's average blood pressure is higher than the accepted target value, they are diagnosed with hypertension (high blood pressure). Over time, if not treated effectively, hypertension increases a person's risk of heart disease, stroke, kidney disease, and death. For most people, hypertension can be managed by making lifestyle changes and taking medication. But when blood pressure remains high despite treatment, a person is considered to have uncontrolled hypertension, which is associated with a higher risk of more serious health outcomes.

Renal denervation is a minimally invasive procedure that may provide an additional treatment option for people with uncontrolled hypertension. In this procedure, a catheter (a long, thin, flexible tube) is used to deliver energy to the walls of the arteries leading to the kidneys, which disrupts nerve signals that regulate blood pressure.

This health technology assessment looked at how safe, effective, and cost-effective renal denervation is as an adjunctive (additional) treatment to standard care (e.g., lifestyle changes and medication) for adults with uncontrolled hypertension. It also looked at the budget impact of publicly funding renal denervation and at the experiences, preferences, and values of people with hypertension.

What Did This Health Technology Assessment Find?

Adults with uncontrolled hypertension who received renal denervation consistently demonstrated a greater reduction in blood pressure compared with those who did not, and no significant differences in safety outcomes or adverse events were found between the 2 groups.

Compared with standard care alone, the addition of renal denervation to standard care is more costly but also more effective. We estimate that publicly funding renal denervation for adults with uncontrolled hypertension in Ontario over the next 5 years would cost an additional $0.42 million to $3.78 million annually.

Our review of the quantitative evidence of patient and provider preferences and values found that about 30% of people with uncontrolled hypertension preferred renal denervation over treatment with medication, with younger individuals and those with poor medication adherence more likely to favour it. People we spoke with who had undergone renal denervation reported lower blood pressure, fewer doctor's visits, and greater peace of mind than those who had not. Some also reported a reduction in medication; however, it is important to note that renal denervation does not guarantee a reduction in the need for medication. Those with hypertension who had not undergone the procedure reported being open to it if it were recommended by a physician after other treatment options had failed. Barriers to accessing renal denervation included limited awareness of the procedure and limited geographic access.

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Citation

TBD

Abstract

Background

When blood pressure remains elevated despite treatment, a person is considered to have uncontrolled hypertension, which increases the risk of serious health outcomes (e.g., cardiovascular disease, stroke, kidney failure, and death) over time. Renal denervation, a minimally invasive procedure targeting sympathetic nerves in the wall of renal arteries, has emerged as a promising adjunctive treatment to standard care (e.g., health behaviour modifications and antihypertensive medications). We conducted a health technology assessment of renal denervation for adults with uncontrolled hypertension, which included an evaluation of effectiveness, safety, cost-effectiveness, the budget impact of publicly funding renal denervation, and patient and provider preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included systematic review using the Risk of Bias in Systematic Reviews (ROBIS) tool. We performed a systematic economic literature search and conducted a cost–utility analysis with a lifetime horizon from a public payer perspective. We also analyzed the budget impact of publicly funding renal denervation in adults with uncontrolled hypertension in Ontario. To contextualize the potential value of renal denervation, we conducted a review of the quantitative evidence of patient and provider preferences and values, and we spoke with people with hypertension.

Results

We included 10 systematic reviews of randomized controlled trials in our clinical evidence review, all of which showed that renal denervation statistically significantly lowered systolic blood pressure more than standard care (by a mean of 2.1–6.3 mmHg), regardless of the type of renal denervation system used, the blood pressure end points assessed, and whether people were taking antihypertensive medications at the time of the procedure. Renal denervation in addition to standard care is more effective and more expensive than standard care alone. The incremental cost-effectiveness ratio of renal denervation in addition to standard care compared with standard care alone is $121,237 per quality-adjusted life-year (QALY) gained over a lifetime horizon. The probability of renal denervation in addition to standard care being cost-effective versus standard care alone is 0% at a willingness-to-pay (WTP) of $50,000 per QALY gained, 18.02% at a WTP of $100,000 per QALY gained, and 80.50% at a WTP of $150,000 per QALY gained. The cost-effectiveness results were sensitive to changes in time horizon, assumptions about the duration of treatment effect, and the cost of the renal denervation procedure (including the cost of the renal denervation system). The annual budget impact of publicly funding renal denervation for adults with uncontrolled hypertension in Ontario over the next 5 years ranges from an additional $0.42 million in year 1 to an additional $3.78 million in year 5. Our review of the quantitative evidence of patient and provider preferences and values found that about 30% of patients preferred renal denervation over drug therapy, with younger individuals and those with poor medication adherence more likely to favour it. All interview participants expressed a positive view of renal denervation. Those we spoke with who had undergone the procedure reported lower blood pressure, fewer doctor's visits, and greater peace of mind compared with those who had not, and some reported a reduction in medication. Others reported being open to renal denervation if it were recommended by

their physician after other treatments had failed. Barriers to accessing renal denervation included limited awareness of the procedure and limited geographic access.

Conclusions

In our overview of reviews, we found that renal denervation consistently lowers blood pressure more than standard care in adults with uncontrolled hypertension, including treatment-resistant hypertension. No statistically significant differences in safety outcomes or adverse events between groups were reported in the included reviews. Renal denervation in addition to standard care is more effective and more expensive than standard care alone. We estimate that publicly funding renal denervation for adults with uncontrolled hypertension in Ontario would result in additional annual costs of between $0.42 million and $3.78 million over the next 5 years. Our review of the quantitative evidence of patient and provider preferences and values and our direct patient engagement findings highlight renal denervation as a potential treatment option for adults with uncontrolled hypertension. Renal denervation was viewed favourably by all those we interviewed, particularly when other treatments have failed.

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Objective

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of renal denervation as an adjunctive treatment to standard care in adults with uncontrolled hypertension. It also evaluates the budget impact of publicly funding renal denervation for uncontrolled hypertension and the experiences, preferences, and values of adults with uncontrolled hypertension.

Background

Health Condition

A blood pressure reading measures the force (pressure) of blood against the walls of the arteries as the heart pumps and is used as an indication of how well the heart and blood vessels are functioning. Blood pressure consists of 2 types of pressure: systolic (pressure during a heartbeat) and diastolic (pressure between heartbeats). It is expressed as systolic pressure over diastolic pressure in millimeters of mercury (e.g., 120/80 mmHg).[1]

Routine measurement of blood pressure (whether in a doctor's office or at home) can be a useful tool to assess one's cardiovascular health. In general, a blood pressure equal to or less than 120/80 mmHg is considered normal, but target values can vary slightly depending on the measuring device, the individual conducting the measurement, and the medical history and health conditions of the person whose blood pressure is being measured.[2]

When average blood pressure is higher than the accepted target value, a person is diagnosed with hypertension (high blood pressure), which means the heart needs to work harder to circulate blood throughout the body.[1] While the condition may not always present with immediate, discernable symptoms, the diagnosis carries a substantial risk of adverse health outcomes over time, such as cardiovascular disease, stroke, kidney disease, and death.[3]

Hypertension is a chronic condition that can be broadly grouped into 2 categories: primary and secondary. Primary, or essential, hypertension is the most common type and develops over years with no identifiable cause. Age, genetics, and lifestyle choices are common risk factors for this type of hypertension.[4] Secondary hypertension is caused by an underlying condition (e.g., primary aldosteronism, renovascular disease, certain medications), may appear suddenly, often results in higher blood pressure than primary hypertension, and is best controlled by treating the underlying condition.

Uncontrolled Hypertension

Hypertension can be effectively managed in about 60% of people through health behaviour modifications and the appropriate use of antihypertensive medications. When office blood pressure readings consistently remain below 130/80 mmHg, a person's hypertension is considered under control.[5] However, if blood pressure remains elevated despite treatment, a person is considered to have uncontrolled hypertension and is at a higher risk of more serious health outcomes.[6] Treatment-resistant hypertension (also called resistant hypertension) is a subtype of uncontrolled hypertension that persists even after a person is treated with at least 3 classes of antihypertensive medications at optimal doses, including a diuretic.[6-8]

Clinical Need and Population of Interest

Nearly 1 in 4 adults (about 8 million people) in Canada have chronic hypertension, and an average of 1,150 Canadians are newly diagnosed with hypertension every day.[9,10]

In Ontario, 18.8% of people aged 12 years and older (more than 2 million people) were reported as having a diagnosis of hypertension in 2022. The prevalence of hypertension increases with age and is estimated to affect 47% of people aged 65 years and older.[9,11,12] In addition to older populations, hypertension also disproportionately affects those living in rural and remote settings. In Ontario, Black and South Asian people are 3 times more likely to have hypertension than white people.[2,4]

Uncontrolled Hypertension

Although the management of hypertension in Ontario has evolved over the years, poor blood pressure control remains a concern.[3,13] In Canada, it is estimated that 17% of people with hypertension do not know they have it[3,14] and that approximately 30% of adults receiving treatment for hypertension have uncontrolled hypertension.[6,15] Among adults with uncontrolled hypertension in Canada in 2022, 245,700, or about 5%, were found to have treatment-resistant hypertension.[6]

Current Treatment Options

In 2024, Ontario Health published a quality standard outlining high-quality care in the community for adults with hypertension.[1] The quality standard describes the diagnosis and treatment of primary hypertension using a stepwise approach beginning with health behaviour modifications, followed by the prescription of antihypertensive medications. Figure 1 provides a simplified clinical pathway for hypertension management in Ontario, adapted from the Hypertension Canada guidelines[16] and input from clinical experts.

People with elevated office blood pressure readings typically undergo ambulatory blood pressure monitoring (i.e., measuring blood pressure during routine daily activities, usually during a 24-hour period) to rule out “white-coat” hypertension (i.e., high blood pressure readings only when in a clinical setting) and to confirm a diagnosis.[1] If ambulatory monitoring is not feasible (e.g., for cost reasons, because it is currently not publicly funded in Ontario) or is declined, home blood pressure monitoring (i.e., measuring blood pressure at rest at specific times of day) is an alternative.

It is recommended that people with hypertension be monitored regularly by their clinicians.[1] Follow-up assessments should take place at least every 3 to 6 months. People with higher blood pressure may need more frequent assessments (i.e., every 1–2 months) until their target blood pressure is achieved.

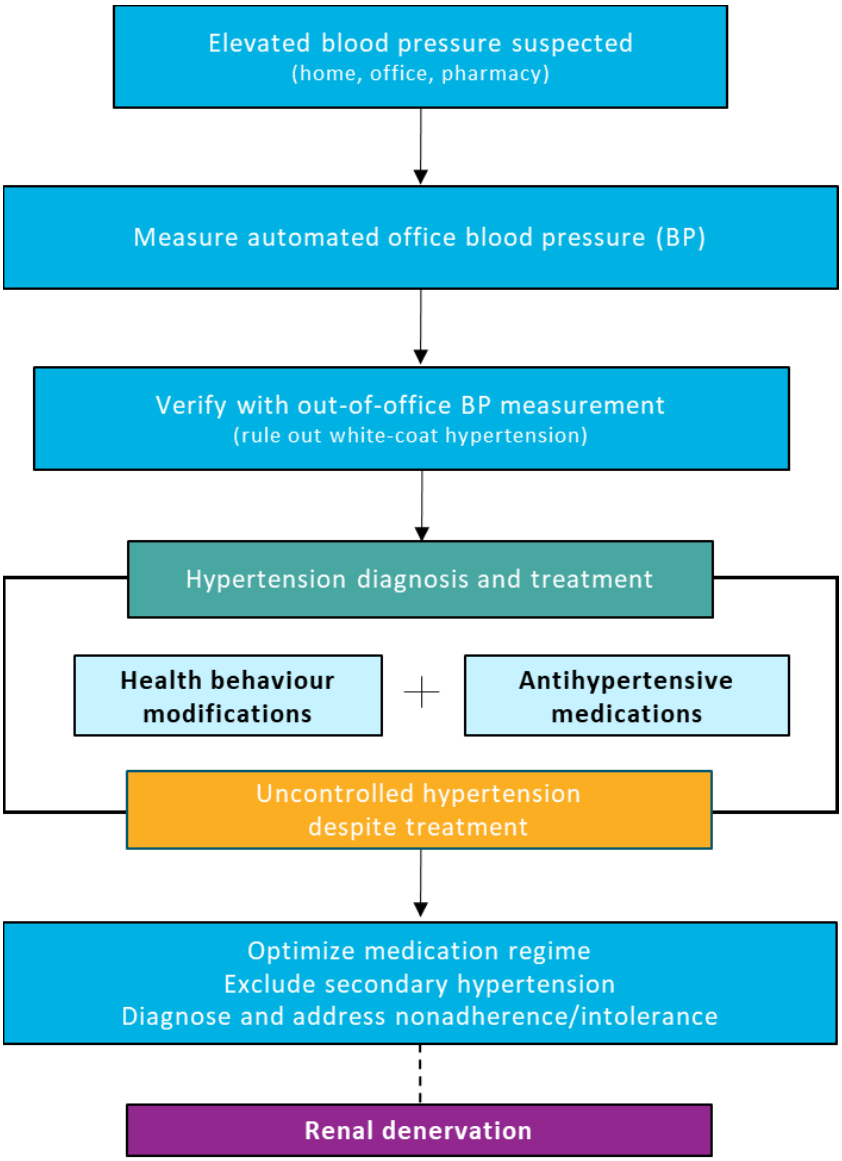

Figure 1: Simplified Clinical Pathway for Hypertension Management in Ontario

Health Behaviour Modifications

After a diagnosis of hypertension, the first line of management is health behaviour modifications (Table 1).[2,17] The target for each health behaviour modification will vary according to each person's age and overall health. Sustained health behaviour modifications are effective in lowering blood pressure and in some cases are enough to prevent hypertension.[18]

Table 1: Health Behaviour Modifications for Hypertension

Health behaviour modification	Description
Healthy diet	Consumption of fruits, vegetables, low-fat dairy, whole grains, fibre-rich foods, and plant-based proteins, as well as foods low in saturated fats and cholesterol as per the Dietary Approaches to Stop Hypertension (DASH) diet, with or without the help of a dietitian Reduce sodium intake to 2,000 mg/day Ensure sufficient dietary potassium intake
Physical exercise	Regular moderate exercise like walking, jogging, cycling, or swimming in addition to routine activities, as health permits
Weight management	Maintaining a healthy weight in relation to age and height with the help of dietary education, increased physical activity and exercise, and behavioural interventions
Limiting alcohol	Abstinence from alcohol or limiting to 2 drinks per day or less; however, for people with hypertension, no amount of alcohol is considered safe
Quitting smoking	Smoking cessation with the help of behavioural support, intensive counselling, motivational interviewing, nicotine replacement products, medications, and referrals to programs like the Smoking Treatment for Ontario Patients (STOP) Program
Stress management	Limiting stress levels through relaxation techniques, individualized cognitive-behavioural interventions, and referral to a psychologist or counselling, as needed

Antihypertensive Medications

If health behaviour modifications alone are insufficient to maintain blood pressure within a controlled range, clinicians may move on to pharmacological intervention using antihypertensive medications. For people with uncontrolled hypertension, multiple classes of medications may be considered (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], thiazide or thiazide-like diuretics, calcium channel blockers), each of which has a unique mechanism to lower blood pressure.[2,5,17] For people with treatment-resistant hypertension, further options are available (e.g., spironolactone, bisoprolol, doxazosin, amiloride, eplerenone, or clonidine as an adjunctive treatment).[16] It is common for a person to need more than 1 type of antihypertensive medication to achieve control. In some cases, people may need 3 to 4 medications (sometimes 5 or more), and it can take time to establish which medication or combination of medications works best with minimal side effects.

Limitations of Current Treatments

Despite the implementation of health behaviour modifications and the use of multiple antihypertensive medications, some people continue to experience elevated blood pressure levels.

The inability to implement or follow current treatment protocols for hypertension may contribute to the prevalence of uncontrolled hypertension. For example, socioeconomic barriers can prevent people from making effective health behaviour modifications. Implementing health behaviour modifications can be challenging when social (e.g., cultural beliefs, education), economic (e.g., income, employment), and physical environmental factors (e.g., access to healthy food, ability to exercise) are not ideal.[2,19] Nonadherence (i.e., not adhering to one's prescribed regimen) and intolerance or resistance to medications (i.e., owing to negative side effects) may also contribute to the persistence of uncontrolled hypertension.

In people with treatment-resistant hypertension, once the possibility of nonadherence to medication is addressed, potential secondary causes of hypertension should be evaluated. People with primary aldosteronism, for example, can be effectively treated with the addition of spironolactone to their medication regimen.[5,20-22] However, once these options have been exhausted, apart from adding a fifth or sixth medication, few other therapeutic options remain.

Health Technology Under Review

In recent years, device-based procedures, often targeting the autonomic nervous system, have been introduced as an additional treatment option for the management of hypertension. One such procedure is renal denervation.[23]

The sympathetic nervous system, which regulates the body's fight-or-flight response, innervates multiple organ systems, including key structural components of the kidneys.[24] Over time, in people with hypertension, overactivity of this system triggers a chain reaction that leads to increased renin excretion, elevated blood volume, increased arterial tone and blood vessel resistance, and ultimately a rise in blood pressure.[24-26]

Renal denervation is a minimally invasive procedure that targets the afferent and efferent nerves to the kidneys, which run in the walls of the renal arteries (the arteries to the kidneys). Typically performed by an interventional cardiologist, radiologist, or vascular surgeon, the procedure employs radiofrequency-, ultrasound-, or alcohol-based nerve ablation delivered through a catheter to disrupt nerve signals without harming the arteries.[24-26] This disruption interrupts the communication network among the heart, kidneys, and brain that regulates blood pressure.

The radiofrequency-based procedure involves a needle puncture in the groin to insert a catheter into the femoral artery. The catheter is moved into the renal artery using fluoroscopy (i.e., x-ray) as a visual guide. Once in place, a generator supplies energy pulses that are delivered through the electrode (or electrodes) of the catheter to ablate the nerves in 1 or more locations. The procedure is performed in 1 kidney and then the other during a single session.[24,27]

Regulatory Information

The Symplicity Spyral renal denervation system is currently the only such device licensed by Health Canada (licence no. 110911, device class IV) (Medtronic, email communication, September 11, 2024). The US Food and Drug Administration (FDA) has approved the system for similar indications (PMA P220026).[28]

The Health Canada licensing statement for the Symplicity Spyral system is as follows: "The Symplicity Spyral multi-electrode renal denervation catheter and Symplicity G3 RF generator are indicated to reduce blood pressure as an adjunctive treatment in essential hypertension patients. The Symplicity Spyral system is intended for patients in whom blood pressure remains uncontrolled despite lifestyle modifications and guideline-driven medical therapy with antihypertensive medications or when guideline-driven medical therapy is poorly tolerated" (Medtronic, email communication, September 11, 2024).

The Symplicity Spyral system used to be available only through Health Canada's Special Access Program, but as of June 2024, it is available directly from the manufacturer, Medtronic, without need for special access authorization, for suitable people with uncontrolled hypertension. Other renal denervation

systems with varying mechanisms of action exist, some with FDA approval, but are not yet approved by Health Canada.

Ontario, Canadian, and International Context

Ontario and Canada

Renal denervation is not widely accessible across Canada and is not publicly funded in Ontario. To date, to the best of our knowledge, clinicians at Toronto's Sunnybrook Health Sciences Centre, St. Michael's Hospital, and the University Health Network, as well as at the Ottawa Hospital and London Health Sciences Centre, have been involved in research on renal denervation. However, only 2 hospitals in the province currently offer the procedure, both in Toronto. Of 33 people referred for renal denervation, the team at Sunnybrook Health Sciences Centre has thus far completed the procedure for 11. (Mina Madan, MD, email communication, July 23, 2025). Costs for the system and procedure at Sunnybrook are currently being covered by hospital foundation and philanthropic funds. St. Michael's Hospital has access to a system through its participation in the Symplicity Spyral international clinical trial and has conducted 2 procedures to date (Medtronic, email communication, August 2024).

Hypertension Canada's 2020 comprehensive guidelines[16] do not mention the use of renal denervation, but it is discussed in guidelines specific to treatment-resistant hypertension published the same year.[8] At the time of the publication of these guidelines, evidence for device-based therapies like renal denervation was considered promising but insufficient to make a recommendation. Likewise, Hypertension Canada's 2025 guideline for the diagnosis and treatment of hypertension in adults in primary care[5] did not address renal denervation in its 9 recommendations, but it may be included as a topic of interest in the group's upcoming comprehensive guidelines.

International

Several international cardiovascular guidelines and consensus statements address the use of renal denervation in people with hypertension. The 2024 European Society of Cardiology (ESC) guidelines recommend the use of renal denervation in people with an unmet clinical need and where cost savings can play a role in the form of reduced cardiovascular events.[23] This includes people with treatment-resistant hypertension who have elevated blood pressure despite the use of 3 medications, including a diuretic, as well as those with uncontrolled hypertension taking fewer than 3 medications but who have an increased cardiovascular risk. The guidelines recommend against using renal denervation in people with impaired renal function, as first-line treatment for hypertension, and for the treatment of secondary hypertension.

In 2024, the American Heart Association (AHA) published a scientific statement on renal denervation for the treatment of hypertension that reported on the safety and efficacy of the procedure.[22] The statement highlights important clinical considerations for patient selection and recommends testing for secondary causes of hypertension for all renal denervation candidates. Both the ESC and AHA guidelines discuss the use of multidisciplinary hypertension teams and involving patients in making decisions regarding their treatment.[22,23] Table 2 summarizes select international guidelines and consensus statements.

Medtronic reports that the Symplicity Spyral renal denervation system is currently being used commercially in over 90 countries, with some form of public funding available in several jurisdictions

(Medtronic, email communication, September 11, 2024). Medtronic estimates that around 25,000 people have been treated with its system worldwide, and the company has created a data registry to follow these people's long-term outcomes.

Table 2: Select Guidelines and Consensus Statements Addressing Renal Denervation

Guideline or consensus statement	Guidance
Proceedings from Expert Consensus Roundtable on Renal Denervation Treatment for Use in Hypertension Patients (2021)[7]	"Renal denervation may be appropriate for: patients with persistent uncontrolled hypertension despite the prescription of guideline-based therapy and patients who are intolerant of or unable to remain adherent to their medication regimes; patients in whom hypertension is confirmed by alternative means of blood pressure monitoring other than office blood pressure measurement alone; and patients in whom secondary causes of hypertension have been excluded."
2022 Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension[29]	"Renal denervation should be considered as a BP-lowering strategy in hypertensive patients with high cardiovascular risk, such as resistant or masked uncontrolled hypertension, established [atherosclerotic cardiovascular disease], intolerant or nonadherent to antihypertensive drugs, or features indicative of neurogenic hypertension after careful clinical and imaging evaluation."
2022 Malaysian Working Group Consensus Statement on Renal Denervation for Management of Arterial Hypertension[30]	"Renal denervation will be most beneficial to patients: for whom blood pressure remains high or above target despite full adherence with the maximum appropriate combination of pharmacological agents that can be tolerated; with resistant hypertension; with a history of repeated non-adherence despite numerous counselling sessions; on polypharmacy for multiple comorbidities; with multiple end-organ damage, with high cardiovascular risk; unwilling to take long-term pharmacotherapy; with an intolerance to antihypertensive medications."
2023 European Society of Hypertension Guidelines for the Management of Arterial Hypertension[31]	"Renal denervation can be considered a treatment option in patients with an eGFR > 40 ml/min/1.73m^2 who have uncontrolled blood pressure despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life; and as an additional treatment option in patients with true resistant hypertension if eGFR is > 40 ml/min/1.73m^2." "Selection of patients to whom renal denervation is offered should be done in a shared decision-making process after objective and complete patient's information and should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure."
2024 European Society of Cardiology Guidelines for the Management of Elevated Blood Pressure and Hypertension[23]	"Renal denervation, performed in a medium-to-high volume centre, may be considered for resistant hypertension patients who have BP that is uncontrolled despite a three BP-lowering drug combination (including a thiazide or thiazide-like diuretic), or for patients with both increased CVD risk and uncontrolled hypertension on fewer than three drugs, if they express a preference to undergo renal denervation after a shared risk-benefit discussion and multidisciplinary assessment." "Renal denervation is not recommended as a first-line BP-lowering intervention for hypertension, or for treating hypertension in patients with moderate-to-severely impaired renal function (eGFR < 40 ml/min/1.73m^2) or secondary causes of hypertension, until further evidence is available."

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

Equity Context

We use the PROGRESS-Plus framework[32] to help explicitly consider health equity in our health technology assessments. PROGRESS-Plus is a health equity framework used to identify population and individual characteristics across which health inequities may exist. These characteristics include place of residence; race or ethnicity, culture, or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics that stratify health opportunities and outcomes.

Expert Consultation

We engaged with clinical and methodological experts at Ontario Health (CorHealth) and with interventional cardiologists, nephrologists, and other clinicians with expertise in hypertension, experience using renal denervation systems, or knowledge of the research literature to help inform the development and refinement of the research questions, review methods, and review results, as well as to contextualize the evidence on renal denervation for uncontrolled hypertension to Ontario.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD #42025641644), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the clinical effectiveness and safety of renal denervation as an adjunctive treatment to standard care in adults with uncontrolled hypertension?

Methods

Overview of Reviews Approach

When scoping the literature, we identified a rapid health technology narrative review conducted by Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies in Health) published in March 2024.[33] We also identified 6 other relevant systematic reviews published since then.[34-39] Of these, Sharp et al,[39] published in 2024, was a comprehensive review that appeared to be of good quality and captured the full scope of our research question. For this reason, we planned to leverage and update this review by searching for additional randomized controlled trials (RCTs) and systematic reviews published since its final search date.

During the screening process, we identified many systematic reviews published since the final search date of the Sharp et al review[39] that outnumbered the total number of RCTs published in the same period. We therefore decided to apply an overview-of-reviews approach, in alignment with the *Cochrane Handbook for Systematic Reviews of Interventions* (*Cochrane Handbook*).[40] We prioritized systematic reviews that met our inclusion criteria based on various clinical and methodological factors, including the following:

- Recency and comprehensiveness
- Quality assessment conducted on primary studies
- Primary studies were RCTs (not observational studies)
- Sufficiently broad patient population (i.e., did not focus on a specific population) to align with our research question
- Considered to be at sufficiently low risk of bias and of high methodological quality (according to the Risk of Bias in Systematic Reviews [ROBIS] tool[41])

Clinical Literature Search

We performed a clinical literature search on December 13, 2024, to retrieve studies published from January 1, 2023, until the search date. Since we were updating the search by Sharp et al,[39] who searched until May 10, 2023, we used January 1, 2023, as our start date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. Methodological filters were used to limit retrieval to systematic

reviews, meta-analyses, health technology assessments, and RCTs. The final search strategy was peer-reviewed using the PRESS Checklist.[42]

We created database auto-alerts in MEDLINE and Embase and monitored them until March 1, 2025. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published since May 2023
- RCTs, health technology assessments, systematic reviews

Exclusion Criteria

- Editorials, commentaries, case reports, conference abstracts, letters, nonrandomized studies, narrative or nonsystematic reviews
- Animal and in vitro studies

Participants

Inclusion Criteria

- Adults (aged ≥ 18 years) with uncontrolled hypertension (e.g., blood pressure ≥ 140/90 mmHg) despite standard care, including health behaviour modifications and the use of antihypertensive medications, including:
  - Adults with treatment-resistant hypertension (e.g., those whose hypertension is not controlled despite taking ≥ 3 classes of antihypertensive medications)
  - Adults with nonresistant hypertension (e.g., those whose hypertension is not controlled despite taking < 3 classes of antihypertensive medications)
  - Adults intolerant to antihypertensive medications

Exclusion Criteria

- Adults with uncontrolled hypertension who have not received standard care (e.g., medical therapy)
- Adults with secondary hypertension
- Children (as defined by the studies)

Interventions

Inclusion Criteria

- First- or second-generation catheter-based renal denervation systems using radiofrequency-, ultrasound-, or alcohol-mediated ablation
    - Patients can be receiving medical therapy (e.g., antihypertensive medications) at the time of renal denervation

Exclusion Criteria

- Methods of renal denervation not involving catheterization
- Renal denervation for conditions other than hypertension

Comparators

Inclusion Criteria

- Standard care (e.g., medical therapy)
- Sham procedure (e.g., renal angiography alone, use of renal denervation generator sounds)

Exclusion Criteria

- Other types of catheter-based renal denervation systems
- Methods of renal denervation not involving catheterization

Outcome Measures

- Systolic and diastolic blood pressure (e.g., via 24-hour ambulatory, office, home, daytime, or nighttime readings)
- Hypertensive crisis
- Myocardial infarction
- Heart failure
- Ischemic stroke
- Renal function (i.e., estimated glomerular filtration rate [eGFR])
- Renal failure
- Health care system or hospital use
- Change in medication use
- Quality of life
- Mortality
- Safety of procedure, adverse events related to procedure, complications (e.g., vascular)

Timing

- As an adjunctive therapy to standard care (i.e., health behaviour modifications and antihypertensive medication[s])

Literature Screening

Two reviewers screened titles and abstracts to assess the eligibility of a sample of 100 citations to validate the inclusion and exclusion criteria. A single reviewer then screened all remaining citations using Covidence[43] and obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search; clinical experts were also consulted for feedback on omissions regarding pivotal studies. We report citation flow and reasons for excluding full-text articles according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement.[44]

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., objective, study design, population, intervention, comparators, ROBIS quality assessment items)
- Outcomes (e.g., outcome definition, number of studies/participants, mean difference with confidence intervals, time points, measurement of heterogeneity)

Equity Considerations

Potential equity issues related to the research question were identified during scoping. These included the increased rates of hypertension in Black and South Asian populations compared with white populations and socioeconomic and geographic factors related to access to specialized clinicians and centres able to conduct renal denervation. We were unable to undertake any equity-related subgroup analyses as information about these populations was not reported in the included systematic reviews.

Statistical Analysis

We identified recent systematic reviews that addressed our research question, and we reported their meta-analysis findings narratively, considering the presence and extent of clinical, methodological, and statistical heterogeneity when interpreting the results.

Subgroup Analyses

Subgroup and sensitivity analyses were performed by the systematic review authors to explore differences in the data and to highlight gaps in the current literature.

We reported the results of subgroup and sensitivity analyses of the following groups as reported in the included systematic reviews:

- Type of uncontrolled hypertension: treatment-resistant or nonresistant
- Type of renal denervation system: radiofrequency, ultrasound, or alcohol
- Whether patients were on or off medication at the time of renal denervation

Critical Appraisal of Evidence

We assessed the risk of bias of the included systematic reviews using the ROBIS tool (Appendix 2).[41]

We limited our overview to systematic reviews that conducted and reported a critical appraisal of their included primary studies. When included systematic reviews rated the certainty of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*,[45] we reported those ratings. The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall ratings reflect the systematic review authors' certainty in the evidence.

Results

Clinical Literature Search

The clinical literature search yielded 396 citations, including grey literature results and after removing duplicates, published between January 1, 2023, and December 13, 2024. We did not identify additional eligible studies from other sources, including database alerts. We identified 27 published systematic reviews that initially met our inclusion criteria, of which we selected 10. See Appendix 3 for a list of the 17 systematic reviews excluded after full-text review. Figure 2 presents the PRISMA flow diagram for the clinical literature search.

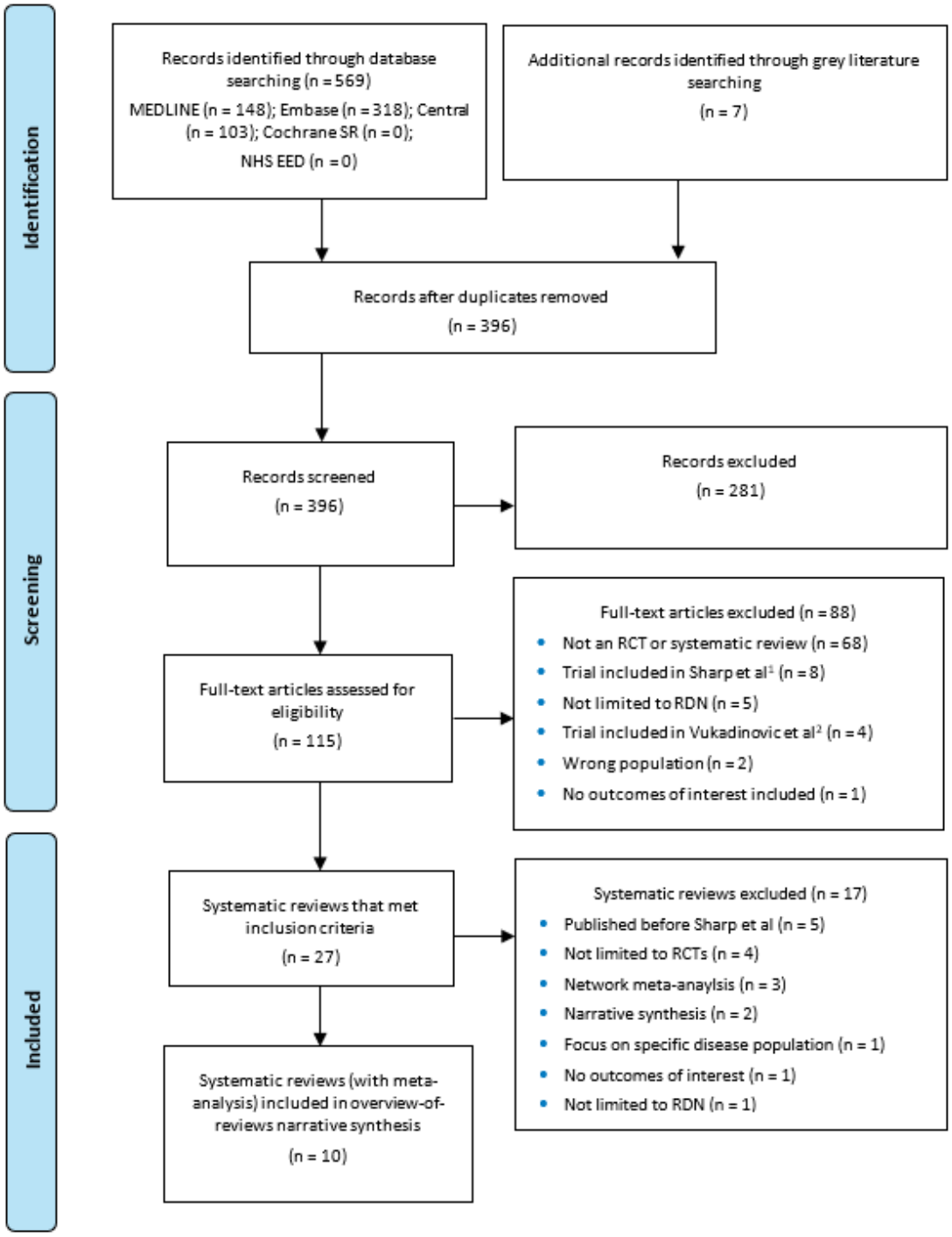

Figure 2: PRISMA Flow Diagram – Clinical Systematic Review

PRISMA flow diagram showing the clinical systematic review. The clinical literature search yielded 396 citations, including grey literature results and after removing duplicates, published between January 1, 2023, and December 13, 2024. We screened the abstracts of the 396 identified studies and excluded 281. We assessed the full text of 115 articles and excluded a further 88. In the end, we included 10 systematic reviews in the overview of reviews.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial; RDN, renal denervation.

Source: Adapted from Page et al.[44]

Characteristics of Included Systematic Reviews

Our full-text screening identified 27 systematic reviews that met our inclusion criteria. After consideration of clinical and methodological factors, we included the 10 systematic reviews that were the most recent, relevant, and methodologically sound. We reported the results of these systematic reviews by outcome and subgroup.

There was substantial overlap in the trials evaluated in the 10 included systematic reviews. Given that Sharp et al[39] was the most comprehensive in terms of population, intervention, and outcomes, it had the greatest overlap with the other reviews. (Appendix 4, Table A2, provides further details on the overlap across primary studies.) Although all 10 included systematic reviews included only RCTs and were published in 2024, because of slight variations in inclusion criteria, search dates, and methodological approaches, each review includes a different number of RCTs and reports on different populations and outcomes. Table 3 summarizes the scope of each included systematic review.

Six reviews reported on the broader population of people with uncontrolled hypertension,[34-36,39,46,47] whereas 4 limited their population to people with treatment-resistant hypertension,[37,48-50] and 1 conducted subgroup analyses for those with treatment-resistant hypertension.[39] Of note, the 4 reviews that included only participants with treatment-resistant hypertension were conducted in Brazil, and there was some overlap in authors in these studies.[37,48-50] However, we included all 4 because each addressed a different subgroup of interest. Two reviews conducted analyses for people on and off medication,[39,46] and 1 included only people off medication.[47]

Six reviews assessed any type of renal denervation system (i.e., radiofrequency-, ultrasound-, or alcohol-based),[35,36,39,46,47,49] whereas 3 assessed only radiofrequency-based renal denervation,[34,37,48] and 1 assessed only ultrasound-based renal denervation.[50]

In terms of comparators, 5 reviews were inclusive of any control arm, including medical therapy, standard care, placebo, and sham,[37,39,46,49,50] and 5 were limited to sham-controlled trials only.[34-36,47,48]

Change in blood pressure was the main outcome reported in all included systematic reviews. It was reported as follows:

- Office blood pressure: 10 reviews[34-37,39,46-50]
- 24-hour ambulatory blood pressure: 9 reviews[34-37,39,46-48,50]
- Daytime blood pressure: 6 reviews[35,36,39,46,48,50]
- Nighttime blood pressure: 6 reviews[35,36,39,46,48,50]
- Home blood pressure: 3 reviews[35,46,50]

Table 3: Scope of Included Systematic Reviews

Author, year	No. of included RCTs, countries	Search date range	Quality assessment tool used	Participants				Intervention				Comparator		Blood pressure outcomes				
				UN HTN	RS HTN	ON-MED	OFF-MED	RF RDN	US RDN	ALC RDN	2nd-gen RDN	Sham	SC	Office	24-h	Day	Night	Home
Sharp et al, 2024[39]	25 (16 in MAs) Germany, United Kingdom	Inception–June 2023	RoB	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mufarrih et al, 2024[46]	15 United States	NR	GRADE QUADAS-2	X		X	X	X	X	X		X	X	X	X	X	X	X
Ogoyama et al, 2024[35]	14 Japan	Inception November 2023	RoB 2	X				X	X	X		X		X	X	X	X	X
Vukadinović et al, 2024[36]	13 France, Germany, Switzer-land, United States	January 2000–January 2024	RoB 2	X				X	X	X		X		X	X	X	X	
Wang et al, 2024[47]	4 China	Inception–May 2024	RoB	X			X	X	X	X		X		X	X			
Silvinato et al, 2024[34]	3 Brazil	Inception–January 2024	GRADE RoB 2	X				X			X	X		X	X			
Sobreira et al, 2024[37]	10 Brazil	Inception–February 2024	RoB 2		X			X				X	X	X	X			
Dantas et al, 2024[48]	9 Argentina, Brazil	NR	RoB 2		X			X			X	X		X	X	X	X	
Maia et al, 2024[50]	5 Brazil	Inception–February 2024	RoB 2		X				X			X	X	X	X	X	X	X
Gonçalves et al, 2024[49]	21 Brazil, Pakistan	Inception–February 2024	RoB 2		X			X	X	X		X	X	X[a]				

Table 3 notes

Abbreviations: 2nd-gen RDN, second-generation renal denervation system; ALC RDN, alcohol-based renal denervation; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MA, meta-analysis; OFF-MED, patients off medication; ON-MED, patients on medication; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies, version 2; RF RDN, radiofrequency-based renal denervation; RoB, Cochrane Risk-of-Bias Tool for Randomized Trials; RoB 2, Cochrane Risk-of-Bias Tool for Randomized Trials, version 2; RS HTN, treatment-resistant hypertension only; SC, standard care (including antihypertensive medications); Sham, sham-controlled studies; UN HTN, uncontrolled hypertension; US RDN, ultrasound-based renal denervation.

[a]Assumed office blood pressure reported.

Risk of Bias in the Included Systematic Reviews

We assessed the risk of bias of the 10 included systematic reviews using the ROBIS tool (Appendix 2, Table A1).[41] We assessed all as having a low risk of bias.

In each systematic review, the study authors conducted risk-of-bias assessments for the included primary studies using the Cochrane Risk-of-Bias Tool for Randomized Trials (RoB); the Cochrane Risk-of-Bias Tool for Randomized Trials, version 2 (RoB 2); or the Quality Assessment of Diagnostic Accuracy Studies, version 2 (QUADAS-2). Included primary studies were generally reported as having low to moderate risk of bias owing to concerns about confounding factors after the primary follow-up end point.

The authors of 2 systematic reviews also conducted GRADE assessments.[34,46] The GRADE quality of evidence for the blood pressure outcomes reported in these reviews was rated as Low to Moderate.

Findings of the Included Systematic Reviews

Since this is an overview of reviews that includes multiple systematic reviews with substantial overlap in primary studies, in accordance with *Cochrane Handbook* recommendations,[40] we selected the most recent, comprehensive, and relevant review that had low risk of bias (according to our ROBIS assessment)—Sharp et al[39]—as our primary systematic review for reporting clinical outcomes and for use in our economic model. In the tables and narrative syntheses that follow, we first report the findings from Sharp et al[39] for each outcome and subgroup, followed by a summary of findings from all other relevant reviews.

Sharp et al[39] included trials of any type of renal denervation system in people with uncontrolled hypertension, and they addressed potential heterogeneity with subgroup and sensitivity analyses based on type of uncontrolled hypertension (treatment-resistant or nonresistant), population (on or off medication), comparator (sham-controlled trials only), and type of renal denervation system (radiofrequency-based, ultrasound-based, or second-generation). Findings were also reported grouped by time of follow-up: primary (2–6 months following renal denervation) and last available follow-up (up to 36 months after renal denervation).

Table 4 presents select mean differences from Sharp et al[39] for various subgroups. If substantial statistical heterogeneity was identified and removed in a sensitivity analysis by the authors, the mean difference associated with the lower I^2 value was selected (I^2 being a measure of heterogeneity that indicates the percentage of variance that is likely attributable to study heterogeneity). In addition to the primary and last available follow-up mean differences from Sharp et al,[39] we also included the range of mean differences reported by all reviews that conducted a meta-analysis applicable to that category. Appendix 5 (Tables A3 to A7) provides a full list of mean differences with confidence intervals and I^2 values for all reviews.

Table 4: Mean Differences in Systolic and Diastolic Blood Pressure at Primary and Last Follow-Up Reported in Relevant Systematic Reviews – Office And 24-Hour Ambulatory

Outcome	Systolic blood pressure, mmHg			Diastolic blood pressure, mmHg		
	Sharp et al, 2024[39]			Sharp et al, 2024[39]		
	MD, primary follow-up (I^2)	MD, last follow-up (I^2)	Range of MDs reported across systematic reviews (I^2)	MD, primary follow-up (I^2)	MD, last follow-up (I^2)	Range of MDs reported across systematic reviews (I^2)
OFFICE BLOOD PRESSURE						
Any type of uncontrolled hypertension						
Any RDN, any comparator	**−5.6 (0%)**[a]	**−5.0 (24%)**[a]	NA	**−3.1 (0%)**[a]	**−2.5 (6%)**[a]	NA
Any RDN, sham-controlled only	**−5.2 (0%)**	**−4.5 (14%)**	−6.6 (82%) to −4.5 (14%)	**−2.8 (7%)**	**−2.1 (12%)**	−3.1 (0%) to −2.1 (12%)
On-med only, any RDN, any comparator	**−5.0 (17%)**[a]	**−4.4 (33%)**[a]	−6.4 (83%) to −4.4 (33%)	**−2.5 (0%)**[a]	**−2.1 (8%)**[a]	−3.2 (73%) to −2.1 (8%)
Off-med only, any RDN, any comparator	**−6.3 (0%)**	**−5.7 (6%)**	−6.3 (0%) to −4.76 (49%)	**−3.8 (0%)**	**−3.0 (0%)**	−3.8 (0%) to −2.14 (79%)
RF only, any comparator or sham	**−5.8 (22%)**[a]	**−5.6 (31%)**[a]	−5.8 (2%) to −4.5 (58%)	**−3.2 (0%)**[a]	**−3.1 (0%)**[a]	−3.2 (0%) to −2.03 (0%)
Second-generation RDN system only, any comparator	**−5.5 (0%)**	**−4.9 (0%)**	NA	**−3.0 (15%)**	**−2.1 (33%)**	NA
US only, any comparator	**−5.2 (0%)**	−3.8 (0%)	−5.37 (0%) to −3.8 (0%)	**−3.0 (6%)**	−1.3 (0%)	−3.0 (6%) to −1.3 (0%)
Treatment-resistant hypertension						
Any RDN, any comparator	**−4.8 (19%)**[a]	**−4.1 (33%)**[a]	NA	**−2.9 (0%)**[a]	**−2.3 (19%)**[a]	NA
RF only, any comparator	**−6.3 (32%)**[a]	**− 6.3 32%)**[a]	−9.6 (83% to −6.3 (32%)	**−3.6 (0%)**[a]	**−3.6 (0%)**[a]	−5.6 (63%) to −3.6 (0%)
24-HOUR AMBULATORY BLOOD PRESSURE						
Any type of uncontrolled hypertension						
Any RDN, any comparator	**−3.6 (41%)**	**−3.3 (40%)**	NA	**−1.9 (38%)**	**−1.7 (43%)**	NA
Any RDN, sham-controlled only	**−3.0 (34%)**	**−2.6 (27%)**	−3.3 (5%) to −2.6 (27%)	**−1.7 (51%)**	**−1.3 (54%)**	−2.0 (42%) to −1.3 (54%)
On-med only, any RDN, any comparator	**−3.2 (33%)**	**−2.8 (37%)**	−3.2 (33%) to −2.23 (16%)	**−1.2 (5%)**	**−1.1 (4%)**	−1.2 (5%) to −1.1 (4%)
Off-med only, any RDN, any comparator	−3.6 (61%)	−3.8 (48%)	−4.62 (0%) to −3.6 (61%)	−2.9 (55%)	−2.4 (62%)	−2.9 (55%) to −1.4 (91%)
RF only, any comparator or sham	**−3.2 (45%)**	**−3.6 (25%)**	−3.6 (25%) to −2.2 (19%)	**−1.8 (30%)**	**−1.8 (18%)**	−2.2 (57%) to −0.98 (46%)
Second-generation RDN system only, any comparator	**−3.7 (25%)**	−2.5 (57%)	NA	**−2.1 (52%)**	−1.6 (68%)	NA
US only, any comparator	**−4.3 (24%)**	−1.7 (70%)	−4.31 (29%) to −1.7 (70%)	−2.1 (60%)	−1.2 (77%)	−2.3 (55%) to −1.2 (77%)
Treatment-resistant hypertension						
Any RDN, any comparator	**−3.6 (29%)**	**−3.2 (35%)**	NA	**1.3 (13%)**	**1.1 (13%)**	NA
RF only, any comparator	**−4.0 (34%)**	**−4.0 (29%)**	−4.8 (34%) to −4.0 (29%)	−1.4 (26%)	−1.5 (20%)	−2.4 (59%) to −1.4 (26%)

Abbreviations: MD, mean difference; NA, not applicable (no mean differences for that category were reported in any other review); off-med, patients not taking medication; on-med, patients taking medication; RDN, renal denervation; RF, radiofrequency; US, ultrasound.

Note: Bold text indicates a statistically significant mean difference.

[a]Mean difference after outlier study (Symplicity HTN-2) removed.

Office Blood Pressure

All 10 included systematic reviews reported pooled analyses of systolic and/or diastolic office blood pressure. (Appendix 5, Table A3, provides further details on office blood pressure reported across relevant included systematic reviews.)

Uncontrolled Hypertension

In a broad meta-analysis of 13 trials, Sharp et al[39] reported that at primary follow-up (2–6 months), office systolic and diastolic blood pressure measurements were statistically significantly reduced in people with uncontrolled hypertension who received renal denervation (any type) compared with those who did not. The authors reported a mean difference in systolic blood pressure (SBP) of −8.5 mmHg (95% confidence interval [CI], −13.5 to −6.12; I^2 = 75%) and in diastolic blood pressure (DBP) of −4.0 mmHg (95% CI, −5.8 to −2.2; I^2 = 56%) compared with any control. However, considerable heterogeneity was seen in both office blood pressure outcomes, and 1 trial was identified as the primary source (Symplicity HTN-2). When this trial was omitted, the previously observed heterogeneity was no longer present (i.e., I^2 = 0). And although the change in mean blood pressure was smaller, it remained statistically significant and in favour of renal denervation (SBP mean difference [MD], −5.6 mmHg [95% CI, −7.2 to −4.0; I^2 = 0%]; DBP MD, −3.1 mmHg [95% CI, −4.1 to −2.1; I^2 = 0%]). At last available follow-up, Sharp et al[39] reported findings that continued to be in favour of renal denervation for both SBP (MD, −5.0 mmHg [95% CI, −6.9 to −3.1; I^2 = 24%]) and DBP (MD, −2.5 mmHg [95% CI, −3.6 to −1.5; I^2 = 6%]).

Renal Denervation Versus Sham

Sharp et al[39] reported that at primary follow-up, participants who received renal denervation experienced a statistically significantly larger reduction in blood pressure than those who received a sham procedure (SBP MD, −5.2 mmHg [95% CI, −6.7 to −3.6; I^2 = 0%]; DBP MD, −2.8 mmHg [95% CI, −4.1 to −1.6; I^2 = 7%]). These results were sustained at last follow-up (SBP MD, −4.5 mmHg [95% CI, −6.5 to −2.5; I^2 = 14%]; DBP MD, −2.1 mmHg [95% CI, −3.4 to −0.9; I^2 = 12%]).

Two other reviews reported similar differences in blood pressure favouring renal denervation over sham control. Vukadinović et al[36] reported a −6.62 mmHg (95% CI, −9.66 to −3.57) mean difference in SBP and a −3.49 mmHg (95% CI, −5.40 to −1.59) mean difference in DBP, though with considerable heterogeneity (I^2 = 82%). When 2 outlier trials (Netrod RDN and TARGET BP I) were removed, potential heterogeneity was substantially reduced (I^2 = 0), and the reported mean differences in SBP (−5.2 mmHg [95% CI, −6.5 to −3.8]) and DBP (−3.1 mmHg [95% CI, –4.0 to –2.2]) were similar to those reported by Sharp et al.[39] Ogoyama et al[35] included 10 sham-controlled trials in their analyses and also reported comparable mean differences in SBP (−4.95 mmHg [95% CI, −6.37 to −3.54; I^2 = 0%]) and DBP (−2.79 mmHg [95% CI, −3.67 to −1.90; I^2 = 0%]), favouring RDN.

On and Off Medication

Sharp et al[39] included 9 trials (excluding the Symplicity HTN-2 outlier) with patients who were taking medication at the time of renal denervation and 3 trials with patients who were not taking medication at the time of renal denervation. For those on medication, at primary follow-up, mean differences in SBP and DBP were statistically significant and similar to the overall mean differences in office SBP (−5.0 mmHg [95% CI, −7.5 to −2.4; I^2 = 17%]) and DBP (−2.5 mmHg [95% CI, −3.9 to −1.2; I^2 = 0%]). For

patients off medication, Sharp et al[39] reported a slightly larger reduction in SBP (MD, −6.3 mmHg [95% CI, −8.1 to −4.5; I^2 = 0%]) and DBP (MD, −3.8 mmHg [95% CI, −5.8 to −1.7; I^2 = 0%]).

Mufarrih et al[46] reported blood pressure changes for those taking and not taking medication at the time of renal denervation, and they evaluated the certainty of the evidence using the GRADE framework. For those on medication at primary follow-up, the reported mean differences in office SBP and DBP were slightly higher than those reported by Sharp et al.[39] Mean differences were in favour of renal denervation over sham but with substantial heterogeneity (SBP MD, −6.39 mmHg [95% CI, −11.49 to −1.30; I^2 = 83%; GRADE: Low]; DBP MD, −3.17 mmHg [95% CI, −5.54 to −0.80; I^2 = 73%; GRADE: Moderate]). For participants not taking medication, the reported mean differences in office SBP and DBP were smaller than those reported by Sharp et al.[39] Mean differences were in favour of renal denervation, again with considerable heterogeneity (SBP MD, −4.76 mmHg [95% CI, −7.57 to −1.94; I^2 = 49%; GRADE: Low]; DBP MD, −2.14 mmHg [95% CI, −4.59 to 0.30; I^2 = 79%; GRADE: Low]).

Wang et al[47] included only trials of patients off medication. The review included 4 RCTs and reported a mean difference in office SBP of −5.83 mmHg (95% CI, −7.93 to −3.72; I^2 = 19%) and in office DBP of −3.57 mmHg (95% CI, −4.89 to −2.25; I^2 = 11%), both in favour of renal denervation over sham and falling between the values reported in the reviews by Sharp et al[39] and Mufarrih et al.[46]

Type of Renal Denervation System: Radiofrequency, Ultrasound, or Second-Generation

Several reviews reported change in office SBP by type of renal denervation system. Sharp et al[39] included 9 RCTs comparing radiofrequency-based renal denervation with any type of control or standard care. A statistically significant reduction in mean SBP was reported at primary follow-up (MD, −5.8 mmHg [95% CI, −8.3 to −3.3; I^2 = 22%]) and last follow-up (MD, −5.6 mmHg [95% CI, −8.2 to −3.1; I^2 = 31%]), after removing the Symplicity HTN-2 outlier study. DBP changes at primary follow-up (MD, −3.2 mmHg [95% CI, −4.6 to −1.8; I^2 = 0%]) and last follow-up (MD, −3.1 mmHg [95% CI, −4.4 to −1.8; I^2 = 0%]) were smaller but remained in favour of renal denervation.

Two reviews included studies using radiofrequency-based renal denervation, but these reviews limited eligibility to sham-controlled studies.[34,35] In the 5 RCTs included by Ogoyama et al,[35] a statistically significant reduction of −4.66 mmHg in mean SBP (95% CI, −6.66 to −2.65; I^2 = 8.3%) was reported in favour of renal denervation, as was a smaller but still statistically significant reduction of −2.74 mmHg in mean DBP (95% CI, −4.12 to −1.35; I^2 = 23.6%), also in favour of renal denervation. Silvinato et al[34] also reported mean differences in favour of renal denervation at both primary follow-up (SBP MD, −4.48 mmHg [95% CI, −6.48 to −2.49; I^2 = 58%; GRADE: Low]; DBP MD, −2.63 mmHg [95% CI, −3.86 to −1.4; I^2 = 66%; GRADE: Low]) and last follow-up (SBP MD, −5.7 mmHg [95% CI, −8.45 to −2.96; I^2 = 62%; GRADE: Low]; DBP MD, −2.03 mmHg [95% CI, −3.84 to −0.22; I^2 = 0%; GRADE: Moderate]). Both reviews reported values slightly lower than those reported by Sharp et al.[39]

When limiting their analysis to trials using only ultrasound-based systems, Sharp et al[39] included 4 RCTs and reported statistically significant reductions in mean SBP of −5.2 mmHg (95% CI, −8.2 to −2.2; I^2 = 0%) and in mean DBP of −3.0 mmHg (95% CI, −5.7 to −0.2; I^2 = 6%), in favour of renal denervation. Ogoyama et al[35] supported these findings, reporting a similar SBP change of −5.37 mmHg (95% CI, −7.80 to −2.95; I^2 = 0%) and a similar DBP change of −2.77 mmHg (95% CI, −4.43 to −1.11; I^2 = 2.2%) at primary follow-up.

Sharp et al[39] also pooled data from trials comparing newer second-generation renal denervation systems with any control. Six RCTs reported similar office blood pressure changes between primary and last follow-up for both SBP and DBP.

Treatment-Resistant Hypertension

Four reviews reported mean blood pressure differences in people with treatment-resistant hypertension.[37,39,48,50] In a meta-analysis of 9 RCTs (excluding the Symplicity HTN-2 outlier study), Sharp et al[39] reported statistically significant reductions in mean SBP of −4.8 mmHg (95% CI, −7.8 to −1.8; I^2 = 19%) and in mean DBP of −2.9 mmHg (95% CI, −4.7 to −1.2; I^2 = 0%), in favour of renal denervation over any control. Renal denervation continued to demonstrate reductions in SBP and DBP at last follow-up (SBP MD, −4.1 mmHg [95% CI, −7.5 to −0.7; I^2 = 33%]; DBP MD, −2.3 mmHg [95% CI, −4.4 to −0.2; I^2 = 19%]). These differences are slightly lower than those reported in the overall uncontrolled hypertension analyses.

However, when Sharp et al[39] pooled 6 RCTs that included only participants with treatment-resistant hypertension and assessed only radiofrequency-based renal denervation, larger reductions in mean SBP and DBP were reported: office SBP, −6.3 mmHg (95% CI, −10.9 to −1.6; I^2 = 32%); office DBP, −3.6 mmHg (95% CI, −5.9 to −1.3; I^2 = 0%). Sobreira et al[37] identified 8 RCTs (including the Symplicity HTN-2 trial identified earlier as causing substantial heterogeneity in the analyses of Sharp et al[39]) and reported blood pressure differences and I^2 estimates that were much larger than those reported by Sharp et al[39] (SBP MD, −9.6 mmHg [95% CI, −16.8 to −2.3; I^2 = 83%]; DBP MD, −5.6 [95% CI, −8.4 to −2.8; I^2 = 63%]). However, the authors noted that removing the Symplicity HTN-2 trial decreased heterogeneity to 59% for SBP and 38% for DBP.

Sharp et al[39] did not conduct subgroup analyses for ultrasound-based renal denervation or second-generation renal denervation systems in people with treatment-resistant hypertension. However, Maia et al[50] reported statistically significant reductions in 24-hour SBP and 24-hour DBP across 5 RCTs comparing ultrasound-based renal denervation with control (SBP MD, −4.5 mmHg [95% CI, −7.7 to −1.2; I^2 = 47%]; DBP MD, −2.0 [95% CI, −4.0 to −0.1; I^2 = 27%]). Further, Dantas et al[48] reported a statistically significant reduction in SBP of −6.05 (95% CI, −11.3 to −0.8; I^2 = 90%) across 7 sham-controlled RCTs of second-generation renal denervation systems, though with considerable heterogeneity.

24-Hour Ambulatory Blood Pressure

Nine reviews reported pooled analyses of systolic and/or diastolic 24-hour ambulatory blood pressure. (Appendix 5, Table A4, provides further details on 24-hour ambulatory blood pressure reported across relevant included systematic reviews.)

Uncontrolled Hypertension

In a broad meta-analysis of 16 trials, Sharp et al[39] reported that 24-hour ambulatory blood pressure was statistically significantly reduced at primary follow-up in people with uncontrolled hypertension who received renal denervation (any type) compared with those who did not, with a mean difference in SBP of −3.6 mmHg (95% CI, −5.2 to −2.0; I^2 = 41%) and in DBP of −1.9 mmHg (95% CI, −2.9 to −0.9; I^2 = 38%). This change in blood pressure favouring renal denervation continued through last available follow-up, with a mean difference in SBP of −3.3 mmHg (95% CI, −5.0 to −1.6; I^2 = 40%) and in DBP of −1.7 mmHg (95% CI, −2.7 to −0.7; I^2 = 43%).

Renal Denervation Versus Sham

Across 10 RCTs, Sharp et al[39] reported that participants receiving renal denervation experienced a statistically significantly larger reduction in blood pressure than those receiving sham procedures at primary follow-up (SBP MD, −3.0 mmHg [95% CI, −4.7 to −1.4; I^2 = 34%]; DBP MD, −1.7 mmHg [95% CI, −2.8 to −0.5; I^2 = 51%]). These results were sustained at last follow-up (SBP MD, −2.6 mmHg [95% CI, −4.2 to −1.0; I^2 = 27%]; DBP MD, −1.3 mmHg [95% CI, −2.5 to −0.2; I^2 = 54%]).

Two other systematic reviews reported similar mean differences in blood pressure favouring renal denervation over sham control.[35,36] Across 12 RCTs (excluding the Netrod RDN and TARGET BP I trials, identified as outliers), at primary follow-up, Vukadinović et al[36] reported statistically significant mean differences in SBP (−3.3 mmHg [95% CI, −4.3 to −2.2; I^2 = 5%]) and DBP (−2.0 mmHg [95% CI, −2.9 to −1.0; I^2 = 42%]) that were slightly larger than those reported by Sharp et al.[39] Ogoyama et al[35] included 12 sham-controlled trials in their analyses and reported statistically significant mean differences in SBP (−2.81 mmHg [95% CI, −4.09 to −1.53; I^2 = 31.4%] and DBP (−1.47 mmHg [95% CI, −2.39 to −0.56; I^2 = 47.8%]) that were comparable to the findings reported by Sharp et al.[39]

On and Off Medication

Across 12 RCTs of people on medication, Sharp et al[39] reported statistically significant reductions in mean SBP and DBP in favour of renal denervation over any control at primary follow-up that were slightly lower than those in the overall analyses (SBP MD, −3.2 mmHg [95% CI, −5.2 to −1.2; I^2 = 33%]; DBP MD, −1.2 mmHg [95% CI, −2.3 to −0.2; I^2 = 5%]). At last follow-up, these differences were smaller but remained statistically significant. Meanwhile, across 4 RCTs that included people off medication, Sharp et al[39] reported reductions in blood pressure that supported renal denervation but did not reach statistical significance (SBP MD, −3.6 mmHg [95% CI, −8.8 to 1.6; I^2 = 61%]; DBP MD, −2.9 mmHg [95% CI, −6.1 to 0.4; I^2 = 55%]).

In Mufarrih et al,[46] the mean difference in 24-hour ambulatory SBP for people on medication was −2.23 mmHg (95% CI, −3.56 to −0.90; I^2 = 16%; GRADE: Moderate) in favour of renal denervation over sham, but this was a slightly smaller reduction than that reported by Sharp et al.[39] Mufarrih et al[46] reported a mean difference in 24-hour ambulatory DBP of −1.16 mmHg (95% CI, −1.96 to −0.35; I^2 = 0%; GRADE: Moderate), also in favour of renal denervation. For people off medication, similar to the findings of Sharp et al,[39] the mean difference in DBP was not statistically significant (MD, −1.36 mmHg [95% CI, −4.11 to 1.40; I^2 = 91%; GRADE: Moderate]). However, unlike in Sharp et al,[39] the reduction in SBP was statistically significant, in favour of renal denervation (MD, −3.70 mmHg [95% CI, −5.41 to −2.00; I^2 = 31%; GRADE: Moderate]).

Across 4 RCTs of people off medication, Wang et al[47] reported a statistically significant reduction in 24-hour ambulatory SBP of −4.62 mmHg (95% CI, −6.14 to −3.10; I^2 = 0%), in favour of renal denervation over control. But unlike the reviews by Sharp et al[39] and Mufarrih et al,[46] the reported mean difference in DBP of −2.56 mmHg (95% CI, −4.13 to −0.98; I^2 = 57%) was also statistically significant.

Type of Renal Denervation System: Radiofrequency, Second-Generation, and Ultrasound

Sharp et al[39] included 12 RCTs comparing radiofrequency-based renal denervation with any control. A statistically significant reduction in mean SBP was reported in favour of radiofrequency-based renal denervation at primary follow-up (MD, −3.2 mmHg [95% CI, −5.4 to −1.1; I^2 = 45%]) and last follow-up

(MD, −3.6 mmHg [95% CI, −5.2 to −1.9; I^2 = 25%]). Diastolic blood pressure changes at primary follow-up (MD, −1.8 mmHg [95% CI, −3.0 to −0.5; I^2 = 30%]) and last follow-up (MD, −1.8 mmHg [95% CI, −2.9 to −0.7; I^2 = 18%]) were smaller but remained consistent with the overall analyses.

Sharp et al[39] also pooled data from trials comparing second-generation renal denervation systems with any control. Six RCTs were included, and statistically significant reductions in 24-hour ambulatory blood pressure were reported at primary and last follow-up for both SBP and DBP, in favour of renal denervation.

Two reviews included studies comparing radiofrequency-based renal denervation with sham control. Meta-analyses of 7 RCTs by Ogoyama et al[35] reported a statistically significant reduction in mean SBP of −2.20 mmHg (95% CI, −3.77 to −0.63; I^2 = 18.8%), in favour of renal denervation, and a very small, nonsignificant reduction of −0.98 in mean DBP (95% CI, −2.24 to 0.28; I^2 = 45.8%). Silvinato et al[34] included 3 RCTs and also reported a mean difference in SBP in favour of renal denervation at both primary follow-up (MD, −2.5 mmHg [95% CI, −4 to −1; I^2 = 72%; GRADE: Low) and last follow-up (MD, −2.33 mmHg [95% CI, −4.54 to −0.12; I^2 = 10%; GRADE: Moderate). Additionally, the reduction in DBP was statistically significant at primary follow-up (MD, −2.18 mmHg [95% CI, −3.17 to −1.2; I^2 = 57%; GRADE: Low]) but not at last follow-up (MD, −1.07 mmHg [95% CI, −2.66 to 0.53; I^2 = 0%; GRADE: Moderate]).

When limiting their analysis to trials using only ultrasound-based systems, Sharp et al[39] included 4 RCTs and reported a statistically significant reduction in mean SBP of −4.3 mmHg (95% CI, −7.8 to −0.8; I^2 = 24%), in favour of renal denervation. Ogoyama et al[35] reported nearly the same reduction in mean SBP (−4.31 mmHg [95% CI, −6.43 to −2.18; I^2 = 29%]) for renal denervation at primary follow-up. In both reviews, similar mean differences in DBP favouring renal denervation were reported; however, Ogoyama et al[35] reported the difference as statistically significant (MD, −2.28 mmHg [95% CI, −3.84 to −0.72; I^2 = 54.7%]), whereas Sharp et al[39] did not (MD, −2.1 mmHg [95% CI, −4.8 to 0.5; I^2 = 60%]).

Treatment-Resistant Hypertension

Four reviews reported mean blood pressure differences for people with treatment-resistant hypertension. In meta-analyses of 12 RCTs comparing renal denervation with any control, Sharp et al[39] reported statistically significant reductions in mean 24-hour ambulatory blood pressure, favouring renal denervation: −3.6 mmHg (95% CI, −5.8 to −1.4; I^2 = 29%) for SBP and −1.3 mmHg (95% CI, −2.6 to −0.1; I^2 = 13%) for DBP. Renal denervation continued to demonstrate a reduction in SBP and DBP at last follow-up (SBP MD, −3.2 mmHg [95% CI, −5.6 to −0.9; I^2 = 35%]; DBP MD, −1.1 mmHg [95% CI, −2.4 to −0.1; I^2 = 13%]). These differences are similar to those reported by Sharp et al[39] in their overall analyses of uncontrolled hypertension.

Sharp et al[39] conducted a sensitivity analysis of 10 RCTs that assessed only radiofrequency-based renal denervation. At primary follow-up, the authors reported a statistically significant reduction in mean SBP of −4.0 mmHg (95% CI, −6.6 to −1.3; I^2 = 34%) and a nonsignificant reduction in mean DBP of −1.4 mmHg (95% CI, −3.0 to 0.2; I^2 = 26%), favouring renal denervation. Sobreira et al[37] also identified 10 RCTs using only radiofrequency-based renal denervation. Their resulting SBP and DBP mean differences were both statistically significant and larger than those reported by Sharp et al[39] (SBP MD, −4.9 mmHg [95% CI, −7.3 to −2.4; I^2 = 34%]; DBP MD, −2.4 mmHg [95% CI, −4.2 to −0.5; I^2 = 59%]); however, potential heterogeneity was noted.

Sharp et al[39] did not conduct subgroup analyses for ultrasound-based renal denervation or second-generation renal denervation systems in people with treatment-resistant hypertension. However, Maia et al[50] reported statistically significant reductions in 24-hour SBP and DBP across 5 RCTs assessing ultrasound-based renal denervation versus sham (SBP MD, −3.5 mmHg [95% CI, −5.6 to −1.3; I^2 = 29%]; DBP MD, −2.2 [95% CI, −3.7 to −0.7; I^2 = 43%]).

Further, Dantas et al[48] reported a statistically significant mean difference in SBP of −3.7 (95% CI, −5.5 to −2.0; I^2 = 34%) across 9 sham-controlled RCTs of second-generation renal denervation systems.

Daytime Blood Pressure

Six reviews reported pooled analyses of systolic and/or diastolic daytime blood pressure. (Appendix 5, Table A5, provides further details on daytime blood pressure reported across relevant included systematic reviews.)

Uncontrolled Hypertension

In a broad meta-analysis of 13 trials, Sharp et al[39] reported that daytime blood pressure at primary follow-up was statistically significantly reduced in people with uncontrolled hypertension who received renal denervation (any type) compared with those who did not. The authors reported a mean difference in SBP of −3.9 mmHg (95% CI, −5.6 to −2.2; I^2 = 37%) and in DBP of −2.1 mmHg (95% CI, −3.2 to −1.0; I^2 = 45%). At last follow-up, mean differences in daytime SBP and DBP were smaller but remained statistically significant.

Renal Denervation Versus Sham

In a meta-analysis of 9 RCTs comparing renal denervation (any type) with sham control, Sharp et al[39] reported statistically significant reductions in mean daytime SBP (MD, −3.6 mmHg [95% CI, −5.4 to −1.9; I^2 = 36%]) and DBP (MD, −1.9 mmHg [95% CI, −3.1 to −0.8; I^2 = 45%]) at primary follow-up, in favour of renal denervation. The differences at last follow-up were smaller but remained statistically significant.

In a meta-analysis of 6 RCTs by Vukadinović et al[36] (excluding the Netrod RDN and TARGET BP I trials, identified as outliers), the authors reported a statistically significant mean difference in SBP of −3.6 mmHg (95% CI, −5.5 to −1.7; I^2 = 51%) at primary follow-up, favouring renal denervation; this reduction was similar to that reported by Sharp et al.[39] They also reported a statistically significant mean difference in DBP of −2.9 mmHg (95% CI, −4.48 to −1.31; I^2 = 73%) at primary follow-up, which was a slightly larger difference and I^2 than reported by Sharp et al.[39] Ogoyama et al[35] included 11 sham-controlled trials in their review and reported statistically significant mean differences in daytime SBP and DBP, favouring renal denervation, that were comparable to those reported by Sharp et al[39] (SBP MD, −3.17 mmHg [95% CI, −4.75 to −1.58; I^2 = 41%]; DBP MD, −1.88 mmHg [95% CI, −3.08 to −0.68; I^2 = 51%]).

On and Off Medication

In Sharp et al,[39] 10 trials comparing renal denervation with any control in people taking medication at the time of renal denervation and 3 trials with people off medication at the time of renal denervation reported changes in daytime blood pressure. For those on medication, at primary follow-up, mean differences in SBP and DBP were statistically significant yet smaller than those reported in the overall analyses (SBP MD, −2.5 mmHg [95% CI, −4.5 to −0.5; I^2 = 20%]; DBP MD, −1.2 mmHg [95% CI, −2.5 to 0.0;

I^2 = 21%]). For patients off medication, at primary follow-up, Sharp et al[39] reported statistically significant reductions in SBP and DBP that were larger than in those on medication (SBP MD, −5.4 mmHg [95% CI, −8.2 to −2.5; I^2 = 0%]; DBP MD, −3.3 mmHg [95% CI, −5.2 to −1.5; I^2 = 0%]).

Across 8 sham-controlled RCTs, Murfarrih et al[46] reported statistically significant reductions in daytime SBP and DBP in people on medication: SBP MD, −2.62 mmHg (95% CI, −4.14 to −1.11; I^2 = 3%; GRADE: Moderate); DBP MD, −1.47 mmHg (95% CI, −2.50 to −0.45; I^2 = 0%; GRADE: Moderate). People off medication also experienced reductions in daytime SBP and DBT, but these were not statistically significant (GRADE: Moderate–High).

Type of Renal Denervation System: Radiofrequency, Ultrasound, or Second-Generation

Sharp et al[39] included 9 RCTs comparing radiofrequency-based renal denervation with any type of control or standard care. A statistically significant reduction in mean SBP was reported for renal denervation at primary follow-up (MD, −3.1 mmHg [95% CI, −5.4 to −0.8; I^2 = 34%]), a reduction that persisted through last follow-up. For DBP, a smaller but still statistically significant reduction was reported for renal denervation at primary follow-up (MD, −1.8 mmHg [95% CI, −3.5 to −0.1; I^2 = 48%]); this reduction also persisted through last follow-up.

When limiting their analysis to trials using only ultrasound-based systems, Sharp et al[39] included 4 RCTs and reported large statistically significant reductions in mean SBP and mean DBP at primary follow-up, in favour of renal denervation (SBP MD, −5.4 mmHg [95% CI, −8.4 to −2.3; I^2 = 3%]; DBP MD, −2.7 mmHg [95% CI, −4.9 to −0.5; I^2 = 31%]). However, these differences did not remain statistically significant at last follow-up.

Sharp et al[39] also pooled data from trials using second-generation renal denervation systems only. Six RCTs reported large and statistically significant reductions in mean daytime SBP (MD, −4.1 mmHg [95% CI, −6.4 to −1.9; I^2 = 42%]) and DBP (MD, −2.5 mmHg [95% CI, −3.9 to −1.1; I^2 = 41%]), in favour of renal denervation.

Treatment-Resistant Hypertension

In a meta-analysis of 9 RCTs comparing renal denervation with control in people with treatment-resistant hypertension, Sharp et al[39] reported a statistically significant reduction in daytime SBP at primary follow-up (MD, −3.1 mmHg [95% CI, −5.8 to −0.5; I^2 = 23%]), in favour of renal denervation. However, the difference in daytime DBP between groups was not statistically significant. In a sensitivity analysis of 7 RCTs that compared radiofrequency-based renal denervation with control, no statistically significant differences were found between groups at primary or last follow-up.

Sharp et al[39] did not conduct subgroup analyses for ultrasound-based renal denervation or second-generation renal denervation systems. However, Maia et al[50] reported a statistically significant reduction in daytime SBP and DBP, favouring ultrasound-based renal denervation over control, across 4 RCTs (SBP MD, −4.0 mmHg [95% CI, −6.19 to −1.82; I^2 = 26%]; DBP MD, −2.5 mmHg [95% CI, −3.86 to −1.20; I^2 = 26%]). Across 7 RCTs comparing second-generation renal denervation systems with sham procedures, Dantas et al[48] reported a statistically significant mean difference in SBP of −4.1 (95% CI, −5.84 to −2.37; I^2 = 0%), in favour of renal denervation.

Nighttime Blood Pressure

Six reviews reported pooled analyses of systolic and/or diastolic nighttime blood pressure. (Appendix 5, Table A6, provides further details on nighttime blood pressure reported across relevant included systematic reviews.)

Uncontrolled Hypertension

In a broad meta-analysis of 13 RCTs, Sharp et al[39] reported that at primary follow-up, nighttime blood pressure was statistically significantly reduced in people with uncontrolled hypertension who received renal denervation (any type) compared with those who did not. The authors reported a mean difference in SBP of −3.5 mmHg (95% CI, −5.2 to −1.7; I^2 = 37%) and in DBP of −1.6 mmHg (95% CI, −3.2 to −0.1; I^2 = 53%). At last follow-up, the mean differences in daytime SBP and DBP were smaller but remained statistically significant.

Renal Denervation Versus Sham

For nighttime blood pressure, Sharp et al[39] did not conduct an analysis of sham-controlled studies, but 2 other reviews reported findings in this subgroup of studies. Across 8 RCTs, at primary follow-up, Vukadinović et al[36] reported statistically significant reductions in mean SBP (MD, −4.46 mmHg [95% CI, −6.07 to −2.84; I^2 = 32%]) and DBP (MD, −2.6 mmHg [95% CI, −3.73 to −1.46; I^2 = 30%]), in favour of renal denervation. Across 11 sham-controlled trials, Ogoyama et al[35] also reported statistically significant mean differences in SBP (MD, −3.41 mmHg [95% CI, −4.69 to −2.13; I^2 = 0%]) and DBP (MD, −1.61 mmHg [95% CI, −3.06 to −0.17; I^2 = 48%]), in favour of renal denervation.

On and Off Medication

Across 10 RCTs that included only people on medication, at primary follow-up, Sharp et al[39] reported a statistically significant reduction in mean SBP (MD, −2.8 mmHg [95% CI, −5.4 to −0.2; I^2 = 42%]) and a nonsignificant reduction in mean DBP (MD, −1.1 mmHg [95% CI, −2.7 to 0.5; I^2 = 45%]), both in favour of renal denervation but smaller than those reported in the overall analyses. At last follow-up, these differences were not statistically significant.

Across 3 RCTs that included only people off medication, Sharp et al[39] reported blood pressure reductions that supported renal denervation over control but did not reach statistical significance (SBP MD, −4.2 mmHg [95% CI, −8.5 to 0.1; I^2 = 13%]; DBP MD, −2.8 mmHg [95% CI, −7.3 to 1.6; I^2 = 58%]).

For people on medication, Mufarrih et al[46] reported a statistically significant reduction in nighttime SBP (MD, −2.7 mmHg [95% CI, −5.13 to −0.27; I^2 = 31%; GRADE: Low]) and a nonsignificant reduction in nighttime DBP (MD, −1.06 mmHg [95% CI, −2.46 to 0.34; I^2 = 49%; GRADE: High]), both in favour of renal denervation over sham. For people off medication, no significant between-groups differences were found (SBP MD, −2.16 mmHg [95% CI, −5.64 to 1.32; I^2 = 78%; GRADE: Moderate]; DBP MD, −0.56 mmHg [95% CI, −2.24 to 1.12; I^2 = 49%; GRADE: Low]).

Radiofrequency-Based Renal Denervation Versus Control

Sharp et al[39] included 9 RCTs comparing radiofrequency-based renal denervation with any type of control. The reduction in mean SBP at primary follow-up was statistically significant (MD, −3.5 mmHg [95% CI, −6.0 to −1.0; I^2 = 49%]), and the change was similar at last follow-up. However, the reductions in

DBP reported at primary follow-up (MD, −1.5 mmHg [95% CI, −3.6 to 0.6; I^2 = 57%]) and last follow-up (MD, −1.7 mmHg [95% CI, −3.5 to 0.1; I^2 = 49%]) were not statistically significant.

Treatment-Resistant Hypertension

In a meta-analysis of 10 RCTs comparing renal denervation with standard care in people with treatment-resistant hypertension, Sharp et al[39] found no statistically significant difference in nighttime blood pressure (SBP MD, −2.7 mmHg [95% CI, −6.4 to 1.0; I^2 = 48%]; DBP MD, −0.9 mmHg [95% CI, −3.1 to 1.4; I^2 = 50%]). A further sensitivity analysis of 8 RCTs assessing only radiofrequency-based renal denervation also found no statistically significant difference between renal denervation and control at primary or last follow-up.

Sharp et al[39] did not conduct subgroup analyses for ultrasound-based renal denervation or second-generation renal denervation systems. However, Maia et al[50] reported statistically significant reductions in daytime SBP and DBP across 4 RCTs, favouring ultrasound-based renal denervation over control (SBP MD, −3.69 mmHg [95% CI, −6.03 to −1.35; I^2 = 15%]; DBP MD, −2.46 mmHg [95% CI, −4.56 to – 0.37; I^2 = 52%]). Across 7 RCTs comparing second-generation renal denervation systems with sham procedures, Dantas et al[48] reported a statistically significant mean difference in SBP of −1.8 (95% CI, −3.9 to −0.28; I^2 = 0%), in favour of renal denervation.

Home Blood Pressure

Sharp et al[39] did not report on home blood pressure. However, 3 reviews reported this outcome by various subgroups (Appendix 5, Table A7).[35,46,50]

Other Clinical Outcomes

In addition to change in blood pressure, we were also interested in reviews that looked at the effectiveness of renal denervation on long-term clinical outcomes such as hypertensive crisis, myocardial infarction, heart failure, ischemic stroke, renal function deterioration or failure, health resource use, and quality of life. The reviews we included did not explicitly list these as clinical outcomes of interest; however, some reported these outcomes as harms in their assessment of safety and adverse events, as reported below.

Change in the Use of Antihypertensive Medications

One review reported on change in medication use. Mufarrih et al[46] conducted pooled analyses of the change in mean number of antihypertensive medications as reported in 7 trials of people on medication and 4 trials of people off medication. Compared with control, no statistically significant difference was reported for either subgroup using renal denervation (on medication: MD, −0.02 [95% CI, −0.17 to 0.13; I^2 = 83%); off medication: MD, −0.13 [95% CI, −0.46 to 0.21; I^2 = 69%]).

Safety: Adverse Events and Complications

Seven reviews reported safety outcomes including adverse events and complications after undergoing renal denervation. Some reviews pooled data from multiple studies, whereas others reported individual safety outcomes narratively or as counts. Overall, across reviews, no statistically significant differences were reported. However, it is important to note that renal denervation is a minimally invasive endovascular procedure with a unique risk profile (e.g., femoral artery access site bleeding, artery dissection) compared with medication.

In Sharp et al,[39] 4 RCTs reported data on serious adverse events at primary follow-up and found no statistically significant difference between renal denervation and control (relative risk [RR] = 1.1 [95% CI, 0.6–2.0; I^2 = 0%]). Similar findings were reported at last follow-up, as well as in subgroups of people with treatment-resistant hypertension (RR = 1.2 [95% CI, 0.5–2.9; I^2 = 0%]) and those receiving radiofrequency-based renal denervation (RR = 1.1 [95% CI, 0.6–2.0; I^2 = 0%]).

Mufarrih et al[46] reported adverse events in similar frequencies for the renal denervation and sham control groups. For example, hypertensive crisis was reported in 24 of 1,368 participants in the renal denervation group versus 21 of 973 participants in the control group; stroke was reported in 9 of 1,334 in the renal denervation group versus 7 of 917 in the control group; renal artery stenosis was reported in 3 of 1,199 in the renal denervation group versus 0 of 839 in the control group; hospitalization for heart failure was reported in 9 of 657 in the renal denervation group versus 3 of 384 in the control group; and death was reported in 3 of 1,300 in the renal denervation group versus 2 of 930 in the control group.

Ogoyama et al[35] reported few adverse events associated with renal denervation within the primary follow-up period.

Vukadinovic et al[36] reported no statistically significant difference in safety outcomes (including vascular complications, renal artery stenosis, hypertensive crisis, stroke, hospitalization, and all-cause deaths) between renal denervation and sham control. They also reported no statistically significant change in renal function (based on estimated glomerular filtration rate [eGFR]) between renal denervation (–0.75 mL/min per 1.73 m^2 [95% CI, –2.0 to 0.5; P = 0.24]) and sham control (–0.62 mL/min per 1.73 m^2 [95% CI, –2.2 to 1.0; P = 0.43]).

Wang et al[47] included 4 RCTs reporting safety outcomes, 2 of which reported no adverse events. Of those that did, 1 reported no statistically significant safety events for the first 3 months following renal denervation. However, within 6 months, 1 person who received renal denervation experienced an acute hypertensive crisis that was reversed with medication, and, within 6 to 12 months, another patient developed renal artery stenosis (> 70%), renal failure, and congestive heart failure. No statistically significant changes in eGFR or mean blood levels were observed. The fourth RCT reported no major safety events caused by the renal denervation system or procedure and reported no significant difference in safety end points between groups.

Across 3 RCTs, Silvinato et al[34] assessed a composite outcome of severe adverse events (including hypertensive crisis requiring medical attention, new stroke, and vascular complications) comparing radiofrequency-based renal denervation with a sham procedure followed to 6 months. No statistically significant difference was found between the 2 procedures (risk difference = 0.00 [95% CI, −0.02 to 0.01]; P = 0.93; I^2 = 0%; GRADE: Moderate]).

Sobreira et al[37] found that, compared with control, participants in the renal denervation group experienced a nonsignificant increase in nonserious adverse events (odds ratio [OR] = 2.24 [95% CI, 0.37–13.37; P = 0.18; I^2= 42%]). According to the review authors, compared with control, participants who received renal denervation also experienced clinically relevant (but not statistically significant) increases in adverse events such as hypertensive crisis (OR = 1.39 [95% CI, 0.26–7.39; P = 0.69; I^2 = 0%]) and stroke (OR = 1.15 [95% CI, 0.56–2.35; P = 0.70; I^2 = 0%]). Sufficient data on death, procedure complications, acute coronary events, and atrial fibrillation were not available to make comparisons.

Relevant Network Meta-analyses

Our literature search identified 3 network meta-analyses published in 2024 and 2025 that were related to our research question; however, because of differences in statistical methodology, we did not include these in our overview of reviews. These studies are as follows:

- Abouelmagd AA, Hassanien ME, Shehata RIA, Kaoud OA, Hamouda H, Abbas OF, Gaballah M. Comparing the efficacy of renal artery denervation in uncontrolled hypertension: a systematic review and network meta-analysis. Cureus. 2024;16(10): e70805.
- Bangalore S, Haisum Maqsood M, Bakris GL, Rao SV, Messerli FH. Renal denervation – radiofrequency vs. ultrasound: insights from a mixed treatment comparison meta-analysis of randomized sham-controlled trials. J Hypertens. 2025;143(2):325-35.
- Tian Z, Barbosa CV, Lang H, Bauersachs J, Melk A, Schmidt BMW. Efficacy of pharmacological and interventional treatment for resistant hypertension: a network meta-analysis. Cardiovasc Res. 2024;120(1):108-19.

Discussion

Renal denervation is proposed as an adjunctive treatment option for adults with uncontrolled hypertension. In our comprehensive review of the literature, we included 10 recent systematic reviews of RCTs that consistently demonstrated that renal denervation lowers blood pressure more than standard care or sham procedures – regardless of the type of renal denervation system used, the outcomes assessed, and whether participants were taking antihypertensive medications at the time of the procedure. These findings align with international guidance[22,23] and support current clinical practice in Ontario.

In the absence of more direct long-term clinical outcomes being reported in the included reviews, we used change in blood pressure as a surrogate outcome. The blood pressure reductions reported in our overview may be considered clinically meaningful according to studies reporting that similar reductions in SBP are associated with reductions in stroke, heart disease and heart failure, and incidence of cardiovascular events and death.[6,51,52]

In Ontario, office blood pressure is used as an early indicator of hypertension, and 24-hour ambulatory blood pressure monitoring is recommended to confirm a hypertension diagnosis.[2] Accordingly, we focused on these 2 outcomes in our reporting. Statistically significant blood pressure reductions were reported in favour of renal denervation over control at primary follow-up (2–6 months) and, in some cases, at last available follow-up (up to 36 months) across the various subgroup and sensitivity analyses reported in the primary systematic review (Sharp et al[39]) of this overview of reviews. In 2 of the other included reviews, sensitivity analyses of 2 trials followed to 36 months also reported a statistically significant difference in favour of renal denervation over sham procedures. The longer follow-up values were less certain owing to the presence of confounding factors noted in some trials after 6 months; however, these findings align with registry and long-term observational cohort data suggesting that the benefits and safety of renal denervation are sustained over time.[38]

A recent rapid health technology review of renal denervation from Canada's Drug Agency suggested that, compared with a sham procedure, renal denervation could lead to a reduction in blood pressure in

adults with uncontrolled nonresistant hypertension.[33] Our overview of reviews provides further support for this finding and adds that a statistically significant reduction in blood pressure is also seen in adults with treatment-resistant hypertension. People with treatment-resistant hypertension typically take multiple medications; however, it is estimated that about 35% of this population are nonadherent to their medication regimen.[53] Though renal denervation has not been specifically evaluated in people who may be nonadherent to medical therapy, it may offer another option to support hypertension management in this group.

As depicted in Figure 1, when considering candidates for renal denervation, it will be important not only to assess for nonadherence but also to screen for and treat secondary causes of hypertension; doing so will allow clinicians to determine which candidates are truly treatment resistant. For example, primary aldosteronism is one of the largest causes of secondary hypertension but has very low screening rates and is both underdiagnosed and undertreated in Ontario.[54] Involving patients in decision-making regarding whether to undergo renal denervation will be central to managing their expectations given that blood pressure reductions following the procedure vary across patients, patients will likely have to continue taking some or all of their current medications, and the procedure is more invasive than medical therapy alone.

After attempting to manage hypertension via health behaviour modifications, optimizing antihypertensive medications, ruling out secondary hypertension, and diagnosing and treating nonadherence (as needed), renal denervation may benefit people with uncontrolled hypertension, including those with treatment-resistant hypertension.

Strengths and Limitations

We conducted an overview of reviews on a topic that has been widely studied and whose findings are consistent across reviews. Two strengths of the overview are that we conducted a critical appraisal of the identified systematic reviews and that we assessed the overlap across reviews. We ultimately selected Sharp et al[39] as our main review based on recency, comprehensiveness, and low risk of bias. Sharp et al[39] conducted several relevant subgroup and sensitivity analyses that we were able to leverage. In addition, when statistical heterogeneity was present, it was often investigated, and some of the included reviews presented appropriate sensitivity (e.g., adjusted meta-analysis) results.

As with any overview of reviews, however, reporting existing pooled analyses of results has some limitations. First, there was a high degree of overlap in the trials assessed in the 10 included reviews, and in order not to double-count results, we selected 1 review as the main review and supplemented its results with the findings of the others. Second, the observed effect of renal denervation in the included reviews was based on blood pressure, which acted as a proxy for long-term clinical outcomes of interest not reported in the primary studies and therefore not included in the reviews. Third, many of the included trials had short follow-up periods (2–6 months), and findings for last available follow-up ranged from 6 months to 3 years. Fourth, meta-analysis was conducted in all reviews despite potential clinical, methodological, or statistical heterogeneity between the primary studies (although most reviews investigated potential reasons for heterogeneity through sensitivity analyses). Fifth, only 2 reviews evaluated the certainty of the evidence according to the GRADE framework; thus, we were unable to comment on this for most outcomes. Finally, all reviews were conducted, quality was assessed, and findings were interpreted by different authors, which could explain differences in reported effect sizes despite the inclusion of the same RCTs.

Conclusions

Systolic Blood Pressure

- At primary follow-up, compared with control:
  - Renal denervation demonstrates a statistically significantly greater reduction in all SBP outcomes (i.e., office, 24-hour ambulatory, daytime, nighttime, home) in people with *uncontrolled hypertension* (MD range across subgroups and sensitivity analyses: 2.8–6.3 mmHg)
  - Renal denervation demonstrates a statistically significantly greater reduction in office, 24-hour ambulatory, daytime, and home SBP in people with *treatment-resistant hypertension* (MD range across subgroups and sensitivity analyses: 3.1–6.3 mmHg)
- At last available follow-up, compared with control:
  - Renal denervation demonstrates a statistically significantly greater reduction in all SBP outcomes (office, 24-hour ambulatory, daytime, nighttime, home) in people with *uncontrolled hypertension* (MD range across subgroups and sensitivity analyses: 2.1–6.3 mmHg)
  - Renal denervation demonstrates a statistically significantly greater reduction in office and 24-hour ambulatory SBP in people with *treatment-resistant hypertension* (MD range across subgroups and sensitivity analyses: 3.2–6.3 mmHg)

Change in Number of Medications

Regardless of whether people were taking antihypertensive medications at the time of the procedure, the change in mean number of medications taken by people in the renal denervation group was not statistically significant compared with those in the control group.

Other Clinical Outcomes

The outcomes of hypertensive crisis, myocardial infarction, heart failure, ischemic stroke, renal function or failure, health care use, and quality of life were not explicitly reported in the included systematic reviews, but some were reported as safety outcomes (adverse events or complications).

Safety Outcomes

Although renal denervation is a more invasive treatment than medical therapy alone and therefore has a unique risk profile, the included systematic reviews found no statistically significant differences in safety outcomes or adverse events between renal denervation and control.

Economic Evidence

Research Question

What is the cost-effectiveness of renal denervation as an adjunctive treatment to standard care compared with standard care alone in adults with uncontrolled hypertension?

Methods

Economic Literature Search

We performed an economic literature search on December 5, 2024, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase, and monitored them until May 29, 2025. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text studies published since database inception
- Cost–utility, cost-effectiveness, cost–benefit, cost–consequence, or cost-minimization analyses

Exclusion Criteria

- Narrative or systematic reviews, noncomparative costing (feasibility) studies, cost-of-illness studies, letters or editorials, case reports, commentaries, abstracts, posters, or unpublished studies

Population

Inclusion Criteria

- Adults (aged ≥ 18 years) with uncontrolled hypertension (e.g., blood pressure ≥ 140/90 mmHg) despite standard care, including health behaviour modifications and the use of antihypertensive medications, including:
  - Adults with treatment-resistant hypertension (e.g., those whose hypertension is not controlled despite taking ≥ 3 classes of antihypertensive medications)

- Adults with nonresistant hypertension (e.g., those whose hypertension is not controlled despite taking < 3 classes of antihypertensive medications)
- Adults intolerant to antihypertensive medications

Exclusion Criteria

- Adults with uncontrolled hypertension who have not received standard care (e.g., medical therapy)
- Adults with secondary hypertension
- Children (as defined by the studies)

Interventions

Inclusion Criteria

- First- or second-generation catheter-based renal denervation systems using radiofrequency-, ultrasound-, or alcohol-mediated ablation
  - Patients can be receiving medical therapy (e.g., antihypertensive medications) at the time of renal denervation

Exclusion Criteria

- Methods of renal denervation not involving catheterization
- Renal denervation for conditions other than hypertension

Comparators

Inclusion Criteria

- Standard care (e.g., medical therapy)
- Sham procedure (e.g., renal angiography alone, use of renal denervation generator sounds)

Exclusion Criteria

- Other types of catheter-based renal denervation systems
- Methods of renal denervation not involving catheterization

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years [QALYs])
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios (ICERs)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[43] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

We contacted study authors to provide clarification as needed.

Study Applicability

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[55] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Using this checklist, we assessed the applicability of each study to the research question (directly, partially, or not applicable).

Results

Economic Literature Search

The economic literature search yielded 386 citations, including grey literature results and after removing duplicates, published from database inception until December 5, 2024. We identified 1 additional eligible study from other sources, including database alerts (monitored until May 29, 2025). In total, we identified 5 cost-effectiveness studies that met our inclusion criteria. See Appendix 6 for a list of selected studies excluded after full-text review. Figure 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

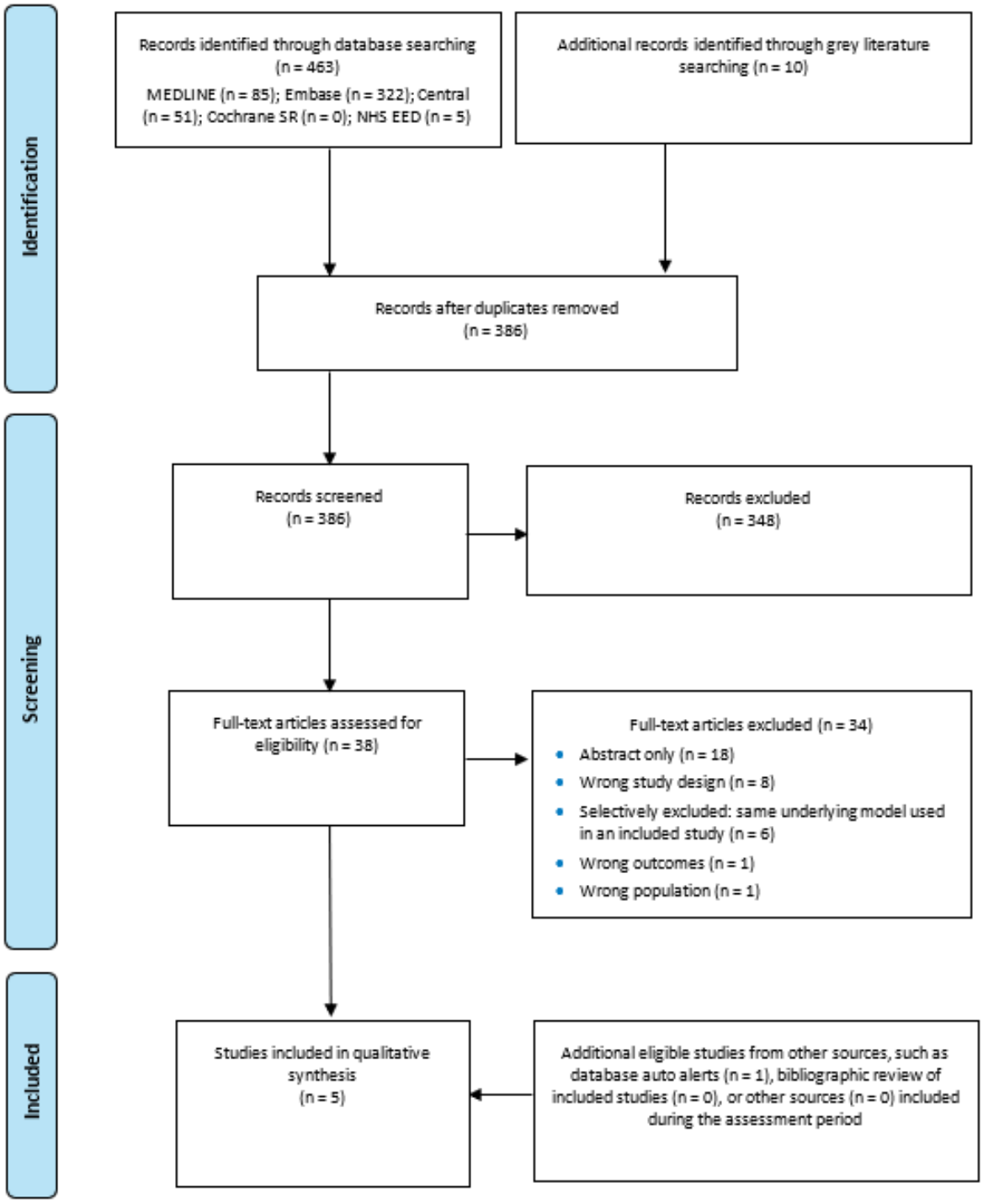

Figure 3: PRISMA Flow Diagram – Economic Systematic Review

PRISMA flow diagram showing the economic systematic review. The economic literature search yielded 386 citations, including grey literature results and after removing duplicates, published between database inception and December 5, 2024. We screened the abstracts of the 386 identified studies and excluded 348. We assessed the full text of 38 articles and excluded a further 34. We identified 1 additional study via database auto-alerts. In the end, we included 5 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[44]

Overview of Included Economic Studies

We identified 5 studies that met our inclusion criteria (Table 5). All studies conducted cost–utility analyses using QALYs as the primary effectiveness measure. One study also presented results in life-years,[56] and another reported relative risk reductions in cardiovascular event outcomes.[57]

One study, McFarlane et al,[57] was based in Canada. The remaining studies were based in Australia,[58] the United Kingdom,[56,59] and Germany.[60] All studies used a Markov model structure to estimate the health outcomes and associated costs of renal denervation in comparison with standard care over a lifetime horizon. All studies took a public payer perspective.

The populations in the included economic studies varied with respect to level of hypertension control. None of the included studies considered all people with uncontrolled hypertension or the subpopulation of people with treatment-resistant hypertension. Most defined treatment-resistant hypertension as a blood pressure equal to or greater than 140/90 mmHg despite treatment with at least 3 classes of antihypertensive medications, including a diuretic. McFarlane et al[57] considered an uncontrolled, but not treatment-resistant, population.

The interventions considered also varied in the included studies. Two studies focused on radiofrequency-based renal denervation,[57,58] 1 focused on ultrasound-based renal denervation,[56] and 1 analyzed both radiofrequency- and ultrasound-based renal denervation.[59] The comparator in all studies was standard care, which included the use of antihypertensive medications.

All studies adopted a risk model–based approach to estimate longer-term health outcomes following reductions in blood pressure. Owing to the lack of published clinical trials comparing cardiovascular event end points in people treated with renal denervation and standard care, the models used reductions in systolic blood pressure (SBP) as a surrogate end point. These data were combined with other published data and risk equations to drive differences in event rates. For the reference case, all analyses assumed that the reduction in SBP associated with renal denervation would translate into reductions in events such as stroke and heart failure and that the reduction would be sustained over a person's lifetime.

McFarlane et al[57] and Taylor et al[56] adapted a previously developed model to the context of their countries.[61] Dorenkamp et al[60] used a previously validated hypertension model relevant to the German context, whereas Health Technology Wales[59] and Chowdhury et al[58] developed their own Markov models.

The analyses varied in how blood pressure reductions affected cardiovascular event outcomes. Health Technology Wales[59] used a cardiovascular event risk calculator with reduced SBP levels to derive transition probabilities for those who underwent renal denervation. Chowdhury et al,[58] Dorenkamp et al,[60] McFarlane et al,[57] and Taylor et al[56] estimated changes to cardiovascular risk based on the relative risks reported in a published meta-analysis of antihypertensive medication trials. McFarlane et al[57] and Taylor et al[56] referenced relative risk values of 0.78, 0.63, and 0.54 per 10 mmHg reduction in SBP for angina or coronary heart disease, stroke, and heart failure, respectively, as reported by Thomopoulos et al.[62] Chowdhury et al[58] and Dorenkamp et al[60] used similar relative risk values.

All studies found renal denervation to be more costly but also more effective than standard care. For people with treatment-resistant hypertension in the United Kingdom, using an effect size of a 1.8 mmHg reduction in SBP derived from their own meta-analyses, Health Technology Wales[59] found ultrasound-

and radiofrequency-based renal denervation to increase costs by £5,173 and to increase QALYs by 0.02, resulting in an ICER of £233,841 per QALY over a lifetime horizon. Chowdhury et al[58] conducted their analyses in the same population but using a different modeling approach, and they derived their reference case effect estimate of a 5.7 mmHg reduction in SBP from the Symplicity HTN-3 trial.[63] Using this effect size and costs relevant to the Australian public payer, they estimated that renal denervation would increase costs by $8,696.56 AUD and quality of life by 0.18 QALYs, resulting in an ICER of $47,130 AUD over a lifetime horizon for people with treatment-resistant hypertension.

However, for a similar treatment-resistant population in Germany, Dorenkamp et al[60] assumed a 20 mmHg reduction in SBP with renal denervation based on the earlier Symplicity HTN trials. Dorenkamp et al[60] conducted separate analyses for men and women and for age groups between 30 and 90 years. Considering men and women 60 years of age, the study found that renal denervation resulted in a gain of 0.98 QALYs in men and 0.88 QALYs in women and led to additional costs of €2,589 for men and €2,044 for women. The resulting ICERs were similar for men (€2,642/QALY) and women (€2,323/QALY). Incremental cost-effectiveness ratios increased with age.

Taylor et al[56] found that ultrasound-based renal denervation resulted in a gain of 0.63 QALYs at an increased cost of £3,523, resulting in an ICER of £5,600 per QALY gained (95% confident interval [CI], £5,463 to £5,739) over a lifetime horizon when compared with standard care alone. This analysis was based on a mean reduction in SBP of 8.5 ± 19.1 mmHg with renal denervation in a treatment-resistant population, as reported in the RADIANCE-HTN TRIO trial.[64]

McFarlane et al[57] was the only included study to consider people with uncontrolled hypertension, but it excluded people on more than 3 antihypertensive medications. Using SPYRAL HTN-ON MED trial data in their reference case, the authors assumed an effect size of a 4.9 mmHg reduction in office SBP, resulting in a gain of 0.51 QALYs and an increase in costs of $6,031, resulting in an ICER of $11,809 per QALY gained (95% CI, $4,489 to $22,587/QALY).

Table 5: Characteristics of Studies Included in the Economic Literature Review

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Chowdhury, 2018,[58] Australia	Cost–utility analysis Markov model Public health care payer Lifetime	Adults with treatment-resistant hypertension aged less than 65 y without initial cardiovascular disease Mean age: 60 y Baseline office SBP: 163 mmHg	Catheter-based renal denervation + standard care Standard care alone (i.e., full doses of 3 antihypertensive medications, including a diuretic)	Total mean QALYS (calculated): RDN: 11.4 QALYs SC: 11.2 QALYs Mean difference: 0.18 QALYs	Total mean cost (calculated), 2017 AUD RDN: $34,970.55 SC: $26,273.97 Mean difference: $8,696.56	ICER: $47,130/QALY (considered cost-effective by the authors based on a $50,000/QALY WTP threshold). RDN was cost-effective when the 10-year cardiovascular risk reduction was at least 13.2
Dorenkamp et al, 2013,[60] Germany	Cost–utility analysis Markov model Public health care payer Lifetime	Adults with treatment-resistant hypertension Mean age, base-case analysis: 60 y Baseline office SBP, men: 180 mmHg Baseline office SBP, women: 183 mmHg	Catheter-based renal denervation + standard care Standard care alone (i.e., full doses of 3 antihypertensive medications, including a diuretic)	*Base case results* Total mean QALYS, effectiveness Men: RDN: 11.91 SC: 10.93 Mean difference: 0.98 QALYs Women: RDN: 14.12 SC: 13.24 Mean difference: 0.88 QALYs	*Base case results* Total mean cost, 2012 EUR Men: RDN: €29,738 SC: €27,149 Mean difference: €2,589 Women: RDN: €29,005 SC: €26,961 Mean difference: €2,044	The resulting ICERs were similar for men (€2,642/QALY) and women (€2,323/QALY) DSA: Relative cost-effectiveness was most sensitive to the SBP-lowering effect of RDN, the rate of RDN nonresponders, and the costs associated with the RDN procedure PSA: In comparison with SC, RDN resulted in an increase in QALYs in 99.3% of simulations in men and in 98.9% of simulations in women
Health Technology Wales,[59] 2023, United Kingdom	Cost–utility analysis Markov model Public health care payer Lifetime	Adults with treatment-resistant hypertension Mean age: 57.4 y 39% female Baseline office SBP: 163 mmHg	Radiofrequency- and ultrasound-based renal denervation + standard care Standard care alone (i.e., antihypertensive medications)	Total mean QALYs: RDN: 16.33 SC: 16.31 Mean difference: 0.02	Total mean cost, 2021 GBP: RDN: £11,697 SC: £6,524 Mean difference: £5,173	ICER: £233,841/QALY DSA: Cost-effectiveness most sensitive to the SBP reduction associated with RDN

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
McFarlane et al, 2024,[57] Canada	Cost–utility analysis Markov model Public health care payer Lifetime	Adults with uncontrolled hypertension taking 1–3 antihypertensive medications Mean age: 55 y Baseline office SBP: 163 mmHg	Radiofrequency-based renal denervation + standard care Standard care alone (i.e., antihypertensive medications)	Total mean QALYs: RDN: 15.81 SC: 15.30 Mean difference: 0.51	Total mean cost, 2023 CAD: RDN: $73,971 SC: $67,040 Mean difference: $6,031	ICER: $11,809/QALY (95% CI, $4,489 to $22,587/QALY) DSA: Findings were robust across sensitivity analyses, including various ages, baseline SBP measurements, treatment effects, relative risks, discount rates, and time horizons
Taylor et al, 2024,[56] United Kingdom	Cost–utility analysis Markov model Public health care payer Lifetime	Adults with treatment-resistant hypertension (BP ≥ 140/90 mmHg despite treatment with at least 3 antihypertensive medications, including a diuretic) Mean age: 52.6 y Baseline office SBP: 176 mmHg	Endovascular ultrasound–based renal denervation + standard care Standard care alone	Total mean QALYs and LYs: RDN: 12.12 QALYs, 15.14 LYs SC: 11.49 QALYs, 14.37 LYs Mean difference: 0.63 QALYs, 0.77 LYs	Total mean cost, 2021/22 GBP: RDN: £34,784 SC: £31,261 Mean difference: £3,523	Overall base-case ICER, RDN: £5,600/QALY (95% CI, £5,463 to £5,739 Modelling demonstrated > 99% probability that the ICER is below the £20,000–£30,000/QALY WTP threshold in the United Kingdom Results were consistent across sensitivity analyses and validation checks

Abbreviations: CI, confidence interval; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; LY, life-year; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; RDN, renal denervation; SBP, systolic blood pressure; SC, standard care; WTP, willingness-to-pay.

Applicability and Limitations of the Included Studies

Appendix 7 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. All 5 studies were deemed partially applicable to the research question.

The studies by Health Technology Wales,[59] Dorenkamp et al,[60] Taylor et al,[56] and Chowdhury et al[58] were conducted outside Canada, and it is unclear whether the estimated costs, resource use, and clinical management of hypertension reported in these studies would be comparable with practice in Ontario. The cost–utility analysis conducted by McFarlane et al[57] was relevant to the Ontario setting, but it did not consider our exact population of interest (i.e., they excluded people with treatment-resistant hypertension).

Excluded studies

We selective excluded 6 studies. Although they used the same underlying model as in the Canadian study conducted by McFarlane et al,[57] they were less applicable to our research question because they considered health care payer perspectives of countries other than Canada. Appendix 6 provides a list of the studies we excluded and the reasons for exclusion.

Discussion

We identified 5 relevant studies that compared the addition of renal denervation (radiofrequency-based, ultrasound-based, or both) to standard care with standard care alone. All studies found the addition of renal denervation to standard care was associated with increased costs, but effectiveness results varied, ranging from QALYs comparable to those associated with standard care alone to substantial QALY gains for renal denervation.[59] This variation in results was driven primarily by the uncertainty surrounding the effect of renal denervation on SBP, the impact of SBP reductions on cardiovascular event rates, and the baseline risk of cardiovascular events.

The Canadian cost–utility analysis conducted by McFarlane et al[57] estimated increased costs and increased QALYs for renal denervation versus standard care, resulting in an estimated ICER of $11,809 per QALY gained. The authors found radiofrequency-based renal denervation to be cost-effective. Based on modelling assumptions about the effect of SBP reduction, the authors suggested that renal denervation could reduce cardiovascular events, partially offsetting the additional cost of renal denervation. Renal denervation remained cost-effective across the sensitivity analyses conducted; however, the authors did not consider the use of renal denervation in the treatment-resistant population.

In contrast, the 4 other included studies focused on people with treatment-resistant hypertension. However, because these analyses were conducted in jurisdictions other than Canada, it is unclear whether their results would be applicable to the Ontario context. It is also unclear how uncertainty surrounding renal denervation procedure costs and the assumption of treatment effect duration would affect cost-effectiveness.

The baseline risk of predicted cardiovascular is an are important determinant of cost-effectiveness results. The included studies estimated transition probabilities using a variety of methods, including distributions observed in registry data and risk calculators based on observational data. Dorenkamp et al[60] conducted separate analyses for men and women based on age, and their results indicated that the

cost-effectiveness of renal denervation in addition to standard care increased with age when compared with standard care alone. Chowdhury et al[58] presented their analyses stratified by baseline risk of cardiovascular events. McFarlane et al[57] highlighted the cost-effectiveness of renal denervation under certain conditions, such as by targeting people with a high predicted cardiovascular risk.

All included studies modelled the long-term risk of cardiovascular events in relation to short-term changes in blood pressure captured in the clinical evidence. There is also uncertainty surrounding the effect size of renal denervation on SBP and the subsequent impact of SBP change on cardiovascular events. Changes in SBP ranging from a reduction of 1.8 mmHg in 24-hour ambulatory SBP[59] to a reduction of 20 mmHg in office SBP[60] were used in the included analyses. The analyses also varied in how changes in SBP were considered to affect long-term cardiovascular event risk. In some analyses, the decreased cardiovascular risk experienced by people treated with renal denervation was recalculated using the same methods used to estimate baseline risk but with a lower SBP value. Taylor et al[56] argued that this approach does not accurately reflect the change in the risk of clinical events as a result of a change in SBP owing to an intervention to reduce blood pressure. To address this limitation, they translated the SBP reduction associated with renal denervation into a reduction in cardiovascular events based on the relative risks reported by previously published meta-analyses of the effect of antihypertensive medications.[62]

Given these limitations, the cost-effectiveness of renal denervation is unclear. The uncertainty related to the impact of renal denervation on SBP, the impact of SBP reduction on long-term cardiovascular event risk, and baseline cardiovascular event risk is substantial.

Conclusions

The cost-effectiveness of renal denervation in Ontario is unclear. We identified 5 studies deemed partially applicable to our research question. All studies found that renal denervation increased costs and QALYs. There is uncertainty related to the duration and size of the treatment effect and the impact of SBP reductions on long-term cardiovascular event risks. Because of these limitations, we conducted a primary economic evaluation.

Primary Economic Evaluation

The published economic evaluations identified in the economic literature review addressed the intervention of interest; however, there is uncertainty related to the duration and size of the treatment effect and the impact of reductions in systolic blood pressure (SBP) on long-term cardiovascular event risks. Owing to these limitations, we conducted a primary economic evaluation.

Research Question

What is the cost-effectiveness of renal denervation as an adjunctive treatment to standard care compared with standard care alone in adults with uncontrolled hypertension from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[65] The content of this report is based on a previously developed economic project plan. We adapted a hypertension model developed by Health Technology Wales (HTW) to the Ontario context.[59]

Type of Analysis

We conducted a cost–utility analysis. The effectiveness outcome was quality-adjusted life-years (QALYs), which consider both a person's survival and health-related quality of life. A cost–utility analysis allowed us to estimate changes in costs and health-related quality-of-life owing to the addition of renal denervation to standard care compared with standard care alone.

Population of Interest

Our population of interest was adults (≥ 18 years of age) with uncontrolled hypertension, defined as an office blood pressure greater than 140/90 mmHg despite standard care, including health behaviour modifications and the use of antihypertensive medications. This population includes adults with treatment-resistant hypertension (e.g., those whose hypertension is not controlled despite taking ≥ 3 classes of antihypertensive medications, adults with nonresistant hypertension (e.g., those whose hypertension is not controlled despite taking < 3 classes of antihypertensive medications), and adults intolerant to antihypertensive medications.

Subgroup Analysis

We performed subgroup analyses based on number of antihypertensive medications taken (i.e., for people with treatment-resistant hypertension and for those not taking any antihypertensive medications).

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

We conducted scenario analyses to help address equity considerations for people living in rural and remote communities.

Intervention and Comparators

Intervention: Renal Denervation as an Adjunctive Treatment to Standard Care

Renal denervation is a minimally invasive procedure that targets the afferent and efferent nerves in the kidneys to reverse their overactivity. Typically performed by an interventional cardiologist, vascular surgeon, or radiologist, the procedure employs radiofrequency, ultrasound, or alcohol-based energy delivered through a catheter to disrupt nerve signals without harming the arteries.[24-26]

Renal denervation could be offered to adults for the management of uncontrolled hypertension. The procedure can be performed at various points within the overall strategy of hypertension management (e.g., after 1–3 antihypertensive medications have been tried but before the addition of a fourth). People who receive renal denervation may still need to implement health behaviour modifications (e.g., diet, exercise) and take antihypertensive medications.

In our reference case, we considered all catheter-based renal denervation systems as the intervention of interest. However, only 1 renal denervation system currently has Health Canada approval: the radiofrequency-based Symplicity Spyral renal denervation system. We used the cost of this system in the reference case analysis, assuming other systems would have a similar cost. We conducted scenario analyses considering the effect of only radiofrequency-based systems and only ultrasound-based systems.

Table 6 describes the intervention, comparator, population, and outcomes evaluated in our primary economic model.

Table 6: Intervention and Comparator Evaluated in the Primary Economic Model

Intervention	Comparator	Population	Outcomes
Catheter-based renal denervation using radiofrequency-, ultrasound-, or alcohol-mediated ablation as an adjunctive treatment to standard care	Standard care alone (i.e., antihypertensive medications)	Adults with uncontrolled hypertension defined as an office blood pressure of > 140/90 mmHg despite health behaviour modifications and the use of antihypertensive medications	Costs, quality of life, adverse events, stroke, heart failure, mortality

Comparator: Standard Care Alone

Standard care for adults with uncontrolled hypertension includes health behaviour modifications and medical therapy in the form of antihypertensive medications. An individual may require more than 1 type of medication, and some may need 5 or more to achieve optimal control. Despite the implementation of health behaviour modifications and the use of multiple antihypertensive medications, some people continue to experience hypertension.

Time Horizon and Discounting

As in the HTW analysis,[59] we used a lifelong time horizon in our reference case analysis because renal denervation is likely to affect health and cost outcomes for the lifetime of an individual diagnosed with hypertension (since renal denervation permanently ablates the sympathetic nerves in the renal arteries). A lifetime horizon was used to ensure that all relevant costs and outcomes were considered. We also considered a 10-year time horizon to match the follow-up duration observed in the clinical evidence. An annual cycle length was chosen as it was thought to reflect the level of granularity required.

In accordance with Canada's Drug Agency guidelines,[66] we applied an annual discount rate of 1.5% to both costs and QALYs incurred after the first year.

Main Assumptions

We adopted the following assumptions from the HTW model[59]:

- We assumed that changes in systolic blood pressure (SBP) in combination with risk equations would accurately model changes in cardiovascular events for adults receiving renal denervation and standard care. (We were unable to identify studies comparing clinical end points such as stroke or death for the intervention and comparator.)
- As a simplifying modelling assumption, we assumed that people could experience only 1 cardiovascular event per 1-year cycle (though they could experience multiple instances of the same event) and that people could progress to a different event state only if the outcomes associated with that event state were more severe than the previous event experienced. This approach has been used in most published cost-effectiveness analyses of renal denervation.
- We assumed that the blood pressure of people in the standard care cohort would remain constant from baseline over the model time horizon. In the reference case, for the standard care cohort, we assumed that medical therapies such as antihypertensive medication would not affect blood pressure. The assumption of no change represents an average outcome, reflecting that both increases and decreases may occur over time but without evidence of a consistent trend in the absence of further intervention.[67]
- We assumed that the treatment effect sourced from the clinical evidence review would be applicable to the Ontario context.
- People were assumed to have had no prior cardiovascular events, manifest coronary heart disease, or end-stage renal disease. This assumption was made based on the available clinical evidence, to simplify modeling, and to ensure predictive validity of the multivariate risk equations used in the model.

In addition to the HTW assumptions,[59] we also made the following assumptions:

- Based on long-term follow-up studies, we assumed that the effect of renal denervation on blood pressure would be maintained throughout the lifetime horizon. Renal denervation is intended as a

one-time procedure that provides the recipient with an "always on" blood pressure–lowering effect with no physiological need for reintervention.

- We assumed that people in either cohort could be taking antihypertensive medications since renal denervation is meant to be used in adjunct with standard care. Changes in medication for people who receive renal denervation were informed by our clinical evidence review.

Model Structure

We made some modifications to the Markov model developed by HTW.[59] Our Markov model (Figure 4) consisted of 8 health states that captured the natural history of hypertension. The 8 health states were as follows: hypertension alone, stable angina, unstable angina, transient ischemic attack, myocardial infarction, heart failure, stroke, and death. People started and remained in the hypertension-alone health state unless they experienced a cardiovascular event, in which case they transitioned to the corresponding health state. Cardiovascular events were associated with a reduction in quality of life, a higher risk of mortality, and increased treatment costs.

Similar to other economic evaluations on renal denervation,[57] the model assumed that people could progress to a different health state only if the outcomes associated with that state were more severe than those of the previous health state experienced. Therefore, people with stable angina could transition to any of the other cardiovascular health states in a subsequent cycle. However, people who experienced a stroke could not transition to a different health state because stroke was deemed the most severe. At any point in the model, people could die from any-cause mortality or event-related mortality.

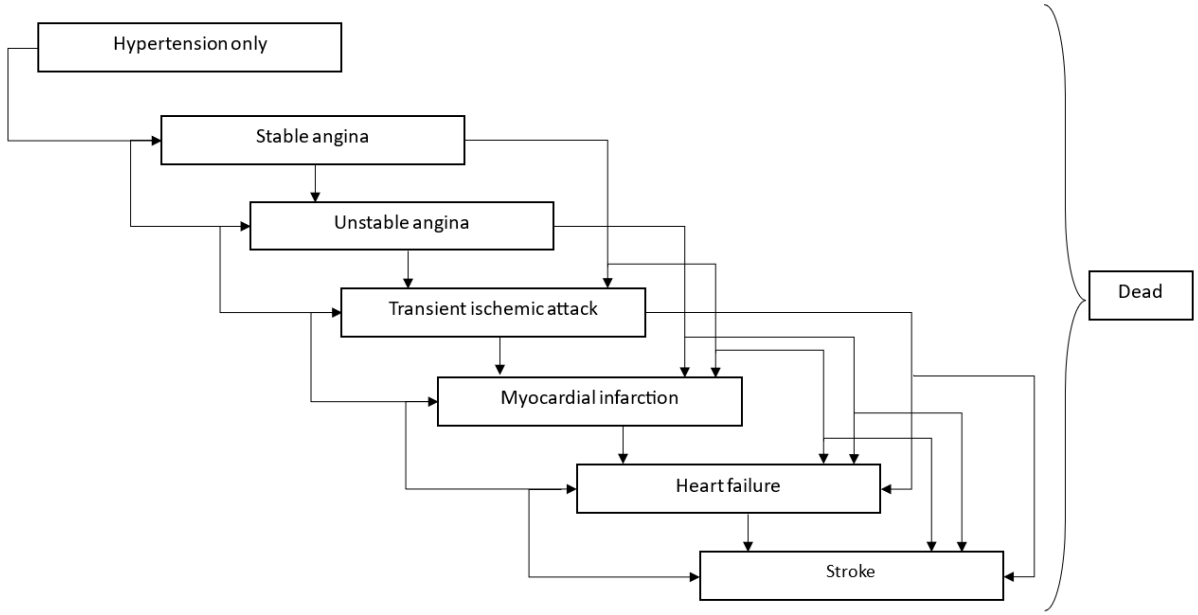

Figure 4: Markov Model Structure

Clinical Outcomes and Utility Parameters

Natural History

The main clinical outcomes we considered were informed by our clinical evidence review and included blood pressure control, change in mean number of antihypertensive medications, and serious procedure-related adverse events.

We estimated the probability of transitioning between health states using previously published multivariable risk calculators. In the reference case, 10-year risk was calculated from the Framingham Risk Score according to the framework developed by d'Agostino et al.[68] The Framingham Risk Score estimates the risk of developing cardiovascular disease over the next 10 years based on risk factors such as age, sex, SBP, diabetes status, and body mass index (BMI). The outcome of the risk calculator is a composite 10-year risk prediction of cardiovascular disease including coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure. Table 7 lists the overall 10-year cardiovascular risk for standard care.

The characteristics and risk factors used to inform the risk calculator were based on the baseline demographics of participants in the SPYRAL HTN-ON MED trial as reported by Kandzari et al.[69] The average age of the cohort was estimated to be 54.97 years, and 80% of participants were estimated to be male. Baseline SBP was estimated to be 163 mmHg based on a baseline weighted average from both arms of the SPYRAL HTN-ON MED trial.[69] It was estimated that 13% of participants had type 2 diabetes and that average BMI was 31.67 kg/m^2. All participants were assumed to be taking antihypertensive medications.

Following the HTW approach,[59] we estimated cardiovascular risk for women with diabetes, women without diabetes, men with diabetes, and men without diabetes. The proportions listed in the previous paragraph were then used to estimate a weighted average risk that applied to the whole population.

We separated the overall 10-year risk into individual estimates for each of the following events: stable angina, unstable angina, transient ischemic attack, myocardial infarction, heart failure, and stroke. We used inputs from a previously published health technology assessment from Ontario Health,[70] d'Agostino et al,[68] and the HTW analysis[59] to estimate what proportion of the overall 10-year risk was attributable to each modelled event (e.g., stroke, myocardial infraction). We assumed that the proportions remained constant over the model time horizon.

We explored the possibility of incorporating renal failure using a separate risk calculator. However, meta-analyses found no significant interaction for change in renal function between renal denervation and sham control.[36] Further, a published cost-effectiveness analysis of radiofrequency-based renal denervation in Canada found no difference in the probability of end-stage renal disease between renal denervation and standard care at 10 years.[57] Therefore, we omitted renal failure from this analysis.

Table 7: Natural History Inputs Used in the Economic Model

Model Parameter	Value[a]	Reference
Overall cardiovascular risk at 10 years – standard care	**30.3%**	D'Agostino et al, 2008 (Framingham Risk Calculator)[68]
Estimated event proportions		
Stable angina	34.0%	Calculated based on d'Agostino et al, 2008,[68] and HTW 2023[59]
Unstable angina	7.3%	Calculated based on d'Agostino et al, 2008,[68] and HTW, 2023[59]
Transient ischemic attack	5.1%	Calculated based on d'Agostino et al, 2008,[68] and HTW, 2023[59]
Myocardial infarction	16.0%	Calculated based on d'Agostino et al, 2008,[68] and HTW, 2023[59]
Heart failure	16.0%	Calculated based on d'Agostino et al, 2008,[68] and HTW, 2023[59]
Stroke	12.6%	Calculated based on d'Agostino et al, 2008,[68] and HTW, 2023[59]
Death from cardiovascular disease	13.2%	Calculated based on d'Agostino et al, 2008,[68] and HTW, 2023[59]
Annual probability of cardiovascular event		
Stable angina	1.08%	Calculated
Unstable angina	0.22%	Calculated
Transient ischemic attack	0.16%	Calculated
Myocardial infarction	0.50%	Calculated
Heart failure	0.36%	Calculated
Stroke	0.39%	Calculated
Death from cardiovascular disease	0.41%	Calculated

[a]Numbers may appear inexact due to rounding.

Impact of Renal Denervation on Natural History

At the time of writing, there have been no clinical trials comparing cardiovascular events in adults treated with renal denervation and those treated with standard care. The primary efficacy end point reported in most randomized controlled trials and meta-analyses of renal denervation is change in SBP. Therefore, we calculated expected changes to cardiovascular risk based on changes in SBP.

Our clinical evidence review found that renal denervation may improve blood pressure control among adults with uncontrolled hypertension, including treatment-resistant hypertension.

In our reference case analysis, we estimated that renal denervation would reduce office SBP by 5.0 mmHg (95% confidence interval [CI], −6.9 to −3.1). We derived this estimate from the meta-analysis by Sharp et al[39] identified in our clinical evidence review. The meta-analysis included a wide range of trials on radiofrequency-, ultrasound-, and alcohol-based renal denervation, and it included adults with uncontrolled and treatment-resistant hypertension. The authors also conducted meta-analyses for population subgroups and evaluated the three types of renal denervation separately; the results of these subgroup meta-analyses were used to inform the clinical inputs of our various scenario analyses.

The average baseline office SBP across both arms of the SPYRAL HTN-ON MED trial was 163.0 mmHg. Using the same approach to estimate standard care risk described in the section above, we re-estimated cardiovascular risk for the population receiving renal denervation in addition to standard care by using a lower SBP of 158.0 mmHg. We conducted scenario analyses using changes in ambulatory SBP. Sharp et al[39] found that renal denervation reduced ambulatory SBP by 3.3 mmHg (95% CI, −5.0 to −1.6).

There is limited long-term follow-up data from high-quality randomized controlled trials of renal denervation. Beyond what follow-up data are available from clinical trials, we assumed that SBP would remain stable based on longer-term observational studies and registry data.[71] We examined this assumption in scenario analyses.

As mentioned in the economic evidence review, some cost-effectiveness studies[56,57] have translated the blood pressure reduction associated with renal denervation into a change in the risk of cardiovascular events based on the relative risks reported in the literature.[62] We also explored this approach in a scenario analysis.

Impact of Renal Denervation on the Use of Antihypertensive Medications

We considered the impact of renal denervation on the use of antihypertensive medications. Renal denervation is meant to be used in adjunct to medical therapy, so we assumed that people in both cohorts would be taking antihypertensive medications.

The clinical evidence review found that in adults with hypertension, renal denervation leads to no statistically significant difference in mean number of medications used compared with controls. Therefore, we assumed that there would be no difference in use of antihypertensive medications for people who have undergone renal denervation.

We assumed that the mean numbers of antihypertensive medications taken by people with uncontrolled and treatment-resistant hypertension were 1.8 ± 1.0 and 4.9 ± 1.4, respectively, based on the baseline demographic characteristics of participants in studies of radiofrequency-based renal denervation.[69,72] These numbers are similar to those among people with uncontrolled hypertension in Canada.[6]

Adverse Events

The clinical evidence review found no statistically significant differences in safety outcomes across the included systematic reviews that evaluated that outcome. Sharp et al[39] conducted a random effects meta-analysis of 4 trials reporting data for serious adverse events at primary follow-up and found no statistically significant difference between people who received renal denervation and those in the control groups (relative risk [RR]: 1.1 [95% CI, 0.6–2.0; I^2 0%]).

In the SPYRAL HTN-ON MED trial, 1 of 253 participants experienced an adverse event requiring intervention (femoral pseudoaneurysm repair at the access site without sequelae).[57,69] Using this information, we calculated a probability of procedure-related complications over the follow-up period of 0.4%. We applied this probability to all people who underwent renal denervation. We assumed that no adverse events would be associated with standard care alone.

Table 8 lists the summary estimates used in the economic model.

Table 8: Summary Estimates Used in the Economic Model

Variable	Mean difference (95% CI)	Reference
Office SBP	−5.0 (−6.9 to −3.1)	Clinical evidence review
Procedure-related complications	0.4%	Kandzari et al, 2023[69]

Abbreviations: CI, confidence interval; SBP, systolic blood pressure.

Mortality

We included mortality in the model through general mortality and event-related mortality. We used Statistics Canada life tables to estimate the baseline mortality rates assumed to apply to the population with uncontrolled hypertension.[73] We then applied event-specific mortality to the baseline risk using standardized mortality ratios for each event. We sourced standardized mortality ratios from the HTW analysis,[59] which scored them from an economic analysis conducted by the United Kingdom's National Institute for Health and Care Excellence (NICE) on the diagnosis and management of hypertension in adults.[74] Since heart failure was not included in the HTW model, we sourced this risk directly from the NICE analysis.

Table 9 presents the standardized mortality ratios used in the economic model.

Table 9: Mortality Multipliers

Event	Standardized mortality ratio, mean (95% CI)	Reference
Stable angina	1.95 (1.65–2.31)	HTW, 2023[59](from Rosengren et al, 1998[75])
Unstable angina	2.19 (2.05–2.33)	HTW, 2023[59](from NICE, 2013[76])
Transient ischemic attack	1.40 (1.10–1.80)	HTW, 2023[59] (from Dennis et al, 1989[77])
Myocardial infarction	2.68 (2.48–2.91)	HTW, 2023[59] (from Brønnum-Hansen et al, 2001[78])
Heart failure	2.20[a]	NICE, 2018[79]; NICE, 2019[74]
Stroke	2.72 (2.59–2.85)	HTW, 2023[59] (from Brønnum-Hansen et al, 2001[78])

Abbreviations: CI, confidence interval; HTW, Health Technology Wales; NICE, National Institute for Health and Care Excellence.
[a]CI not reported, so we assumed a standard error of 10% of the mean for the probabilistic analysis.

Health State Utilities

A health state utility represents a person's preference for a certain health state or outcome. Utilities are often measured on a scale ranging from 0 (death) to 1 (full health).

Table 10 lists the health-related quality-of-life utility values applied in our analysis. We based health-state-specific utilities on estimates from the cost-effectiveness analyses performed by McFarlane et al[57] and Marra et al,[67] with references to Sullivan et al.[80,81] Utility values were derived from a published catalogue of EQ-5D utility values representing patient population preferences in the United States, which we assumed to be similar to the preferences of the same populations in Ontario. Based on the assumption in a previous cost-effectiveness analysis by Health Quality Ontario (now Ontario Health), we used the utility associated with the hypertension-alone general-population norm for the transient ischemic attack health state.[70]

A major limitation of this analysis is that utility estimates are applied consistently to all people in a health state. However, the utility of a person in the stroke health state who had previously experienced a myocardial infarction would likely be worse than that of a person in the stroke state who had not previously experienced a myocardial infarction. Thus, the model likely underestimates the benefits of reducing hypertension-related cardiovascular events.

Table 10: Utilities Used in the Economic Model

Health state	Utility (SE)	Distribution	Reference
Hypertension alone	0.867	–	Marra et al, 2017[67]; Sullivan et al, 2005[81]
Stable angina	0.709 (0.071)	Beta	McFarlane et al, 2024[57] (from Marra et al, 2017,[67] and Sullivan et al, 2005[81])
Unstable angina	0.709 (0.071)	Beta	McFarlane et al, 2024[57] (from Marra et al, 2017,[67] and Sullivan et al, 2005[81])
Transient ischemic attack	0.867 (0.087)	Beta	Health Quality Ontario, 2012[70]
Myocardial infarction	0.725 (0.073)	Beta	McFarlane et al, 2024[57] (from Marra et al, 2017,[67] and Sullivan et al, 2005[81])
Heart failure	0.636 (0.064)	Beta	McFarlane et al, 2024[57] (from Marra et al, 2017,[67] and Sullivan et al, 2005[81])
Stroke	0.694 (0.069)	Beta	McFarlane et al, 2024[57] (from Marra et al, 2017,[67] and Sullivan et al, 2005[81])

Abbreviation: SE, standard error.

Cost Parameters

We obtained cost inputs from Ontario sources, the published literature, and clinical experts. We estimated the fees for the renal denervation procedure and professional visits from the Ontario *Schedule of Benefits: Physician Services Under the Health Insurance Act* (Schedule of Benefits).[82] All costs were reported in 2024 Canadian dollars. When costs in 2024 Canadian dollars were not available, we used the Statistics Canada Consumer Price Index[83] to adjust costs to 2024 Canadian dollars.

Table 11 summarizes the cost parameters used in the economic model. The total cost of renal denervation as an adjunctive treatment to standard care included mean health care costs, including the costs of the procedure itself (i.e., procedure, physician visits, procedure-related complications) and the costs related to hypertension and associated events.

It is important to note that publicly funding renal denervation in Ontario may require a new physician fee code or codes. Changes to the Schedule of Benefits are jointly negotiated between the Ministry of Health and the Ontario Medical Association.

Table 11: Costs Used in the Economic Model

Variable	Unit cost, $	Duration or quantity	Total cost, $	Reference
Standard care alone				
Annual cost of antihypertensive medications	518.88	12 months[a]	125.05	Ontario Drug Benefit Formulary, 2023[84]
Annual cost of physician visits for hypertension management	38.55	3	115.65	Schedule of Benefits, 2023[82] (code A168)
Cardiovascular events				
Stable angina	4,740	Each year in health state	4,740	McFarlane et al, 2024[57]
Unstable angina (first year)	4,897	First year in health state	4,897	McFarlane et al, 2024[57]
Unstable angina (subsequent years)	4,740	Subsequent years in health state	4,740	McFarlane et al, 2024[57]
Transient ischemic attack (first and subsequent years)	5,506	Each year in health state	5,506	HTW, 2023[59]
HF (first year)	16,674	First year in health state	16,674	McFarlane et al, 2024[57]
HF (Subsequent years)	3,003	Subsequent years in health state	3,003	McFarlane et al, 2024[57]
Stroke (acute)	33,406	–	33,406	McFarlane et al, 2024[57]
Stroke (first year)	57,299	First year in health state	57,299	McFarlane et al, 2024[57]
Stroke (subsequent years)	16,248	Subsequent years in health state	16,248	McFarlane et al, 2024[57]
MI (first year)	8,192	First year in health state	8,192	McFarlane et al, 2024[57]
MI (subsequent years)	4, 240	Subsequent years in health state	4, 240	McFarlane et al, 2024[57]
Renal denervation and standard care				
Procedure-related costs				
Pre-procedure costs	651.75	1	657.75	Calculation based on Schedule of Benefits,[82] A603, A605, J128, J021, J022, X409 and X451/X455
Catheter	12,000	1	12,000	Medtronic[b]
Radiofrequency generator	56,000	0.0067 per procedure	373	Medtronic[b], calculation
Catheterization lab facility cost	1,425	1	1,425	Ontario Health (CorHealth)[c]
Overnight hospital stay	1,794	1	1,794	IHIACC, 2024 (per diem rate for ward)[85]
Lead physician fee	362	1	362	Schedule of Benefits, 2023[82] (codes J021, J022)
Physician assistant fee	12.51	14 units[d]	175.14	Schedule of Benefits, 2023[82]; assumption
Anesthesiologist fee	15.49	14 units[d]	216.86	Schedule of Benefits, 2023[82] (code J021)
Physician fees for proceduralist visits during initial hospitalization	61.25	2	122.50	Schedule of Benefits, 2023[82] (coded A604)
Post-procedure physician fee for follow-up	38.05	4	152.20	Schedule of Benefits, 2023[82] (code A608)
Procedure-related complication costs	13,959	0.04	55.17	Jacobson et al, 2007[86]; Kandzari et al, 2023[69]

Variable	Unit cost, $	Duration or quantity	Total cost, $	Reference
Long-term follow-up and maintenance costs				
Annual cost of antihypertensive medications	519	12 months[a]	125	Ontario Drug Benefit Formulary, 2023[84]
Annual physician visits for hypertension management	38.55	3	115.65	Schedule of Benefits, 2023[82] (code A168)

Abbreviations: CIHI, Canadian Institute for Health Information; HTW, Health Technology Wales; IHIACC, Interprovincial Health Insurance Agreements Coordinating Committee.

[a]Assumes that the medications costs of 24.1% of people with uncontrolled hypertension are covered by a public drug plan.[87]

[b]Medtronic, email communication, September 11, 2024.

[c]Ontario Health (CorHealth), email communication, February 20, 2025.

[d]14 units = 6 basic units + 8 time units (assuming a 90-minute procedure time).

Renal Denervation System

We obtained the cost of a radiofrequency-based renal denervation system from the manufacturer (Medtronic, email communication, September 11, 2024). The Symplicity Spyral renal denervation system is a radiofrequency-based device consisting of 2 main components: a radiofrequency generator and a multi-electrode renal denervation catheter. The generator is reusable and has been validated for up to 5 years of use, and its list price is $56,000. We assumed a 5-year lifespan and divided the list price by the estimated number of people treated in 5 years. Based on input from clinical experts and the manufacturer, we assumed that approximately 24 to 36 procedures would be performed per center per year. Thus, we calculated the per-procedure cost of the generator as $373 ($56,000 ÷ 5 years ÷ 30 people) (Medtronic, email communication, September 11, 2004; Sheldon Tobe, MD, email communication, March 6, 2025).The renal denervation catheter is single-use and has an estimated unit cost of $12,000 (Medtronic, email communication, September 11, 2024). (However, the same catheter can be used for both kidneys in a single procedure).

Pre-procedure

We estimated the cost of a preoperative assessment to be $651.75 (considering 2 specialist visits and the average cost of tests). We assumed that a preoperative assessment for renal denervation includes a consultation with an interventionalist (to assess whether renal denervation is indicated) and 1 follow-up visit. Schedule of Benefits code A603 (medical-specific assessment by cardiologist) or A605 (consultation by cardiologist) may be claimed for the initial visit.[82] We thus used $121.60 as the cost of an initial visit for preoperative assessment (i.e., the average of the costs for A603 [$81.55] and A605 [$161.65]), and we used $81.55 as the cost of a follow-up visit (A603).

Various tests can be used to assess people for eligibility for renal denervation. Pre-imaging work up can include Doppler ultrasound, computerized tomography (CT) angiography, or magnetic resonance (MR) angiography. Local practice involves CT angiography of the abdomen and pelvis for all renal denervation candidates. As there is no specific Schedule of Benefits code for renal CT angiography, we assumed the procedure would be claimed using a combination of the codes for catheterization and abdominal CT scan (e.g., J021, J022 [× 4], and X409), for a total cost of $448.60. Most renal denervation candidates will also have other tests as part of their hypertension workup regardless of consideration for renal denervation; thus, we excluded the costs of these tests. We also did not include the cost of a visit to a hypertension specialist for referral to a renal denervation center because we assumed that members of

this population are already being regularly followed by a hypertension specialist (Sheldon Tobe, MD, email communication, March 6, 2025).

Procedure

Based on information provided by our clinical experts and Medtronic, renal denervation is done in a specialized cardiac center by interventional cardiologists, vascular surgeons, or interventional radiologists with expertise in catheter-based procedures, usually under conscious sedation delivered intravenously. An anaesthesiologist may be required if the person is experiencing pain. Clinical experts required an anaesthesiologist in a local pilot study; however, international experience shows that an anesthesiologist may not always be needed. For our reference case analysis, we assumed that an anesthesiologist and a physician assistant would be required in addition to the lead physician.

The renal denervation procedure takes approximately 1 hour to complete (considering catheter time as the time from insertion to removal[69]), although an additional 30 minutes might be spent in the catheterization laboratory. Based on a procedure time of 1.5 hours, we estimated that total physician fees for the procedure would be $754 (calculated based on assumptions and a combination of Schedule of Benefits codes J021 and J022[82]).

Although renal denervation can be performed on an outpatient basis, a 1-night stay is typically required. Thus, we assumed that patients would spend 1 night in the hospital following the procedure. We included the cost of 2 visits from an interventionalist during hospital admission (Schedule of Benefits code A604 [medical-specific reassessment by cardiologist][82]).

We estimated the cost of the catheterization lab to be $1,425 (based on the provincial average cost of a diagnostic catheterization, calculated using total direct cost plus 30% indirect cost [Ontario Health (CorHealth), email communication, February 20, 2025]). We estimated the unit cost for a ward stay to be $1,794 (the mean of the combines or split rate for wards of the 20 designated regional cardiac hospitals in Ontario).[85]

We assumed that physicians with experience of catheter-based procedures would be qualified to perform renal denervation. The manufacturer noted that they provide training on their renal denervation system and proctor the first 5 procedures done by a physician using the system; therefore, we did not include training costs in our analysis (Medtronic, email communication, September 11, 2024). All aspects of the intervention are within the expertise of Canadian interventionalists with training in catheter-based procedures, and if any additional training is required, it would likely be funded by the manufacturer rather than a public payer. As such, we did not include training costs in the base case.

Post-procedure Follow-Up

Follow-up care for renal denervation includes 3 to 4 clinical visits, typically at 6 weeks, 2 to 3 months, 6 to 8 months, and 1 year following the procedure. People referred by nephrologists return to their nephrologist for follow-up (Sheldon Tobe, MD, email communication, March 6, 2025). We estimated the cost of follow-up in the immediate postoperative period to be $186.50 (including 4 follow-up visits to an interventionalist; Schedule of Benefits code A608 [partial assessment by cardiologist] or a combination of code A161 [complex medical-specific reassessment by nephrologist] and A168 [partial assessment by nephrologist][82]).

Long-Term Follow-Up and Maintenance

In the reference case, we assumed that people would be discharged back to their usual care providers and that no additional follow-up cost specific to renal denervation would be needed. We conducted a scenario analysis that assumed that renal denervation would be required every 10 years to maintain the treatment effect, and we assumed that the cost of the repeat procedure would be the same as the initial procedure.

Adverse Events

We derived the cost associated with procedure-related complications from a costing study on burden of complications during percutaneous coronary intervention.[86] We estimated this cost to be $13,959 when inflated to 2024 CAD. Considering a probability of 0.04 for procedure-related complications requiring intervention,[69] we calculated an average per-person cost of $55.17 for adverse events.

Standard Care

Health resource use related to hypertension management can include physician visits, visits with other types of health care providers, prescription medications, outpatient tests and procedures, emergency department visits, hospital outpatient visits, and hospitalizations. It is recommended that people with hypertension be monitored regularly by their clinicians.[2] Follow-up assessments are recommended at least every 3 to 6 months, but those with more severe hypertension may require more frequent assessments (i.e., every 1–2 months) until their target blood pressure is achieved.

We assumed that all people would be followed by a hypertension specialist regardless of intervention. We estimated an annual per-person cost of $240.70 for standard care, based on the annual per-person cost of antihypertensive medications covered by a public drug plan in this cohort ($125.05)[84] and the cost of 3 follow-up visits with a hypertension specialist ($115.65) (Schedule of Benefits code A168).[82]

Antihypertensive Medications

Table 11 presents the average annual per-person cost of antihypertensive medications. For the standard care cohort, we assumed an average use of antihypertensive medications by people with uncontrolled hypertension.

As mentioned earlier, we assumed that the mean numbers of antihypertensive medications taken by people with uncontrolled and treatment-resistant hypertension were 1.8 ± 1.0 and 4.9 ± 1.4.[69,72] These numbers are similar to those among people with uncontrolled hypertension in Canada.[6]

To calculate the average annual cost of antihypertensive medications, we searched the unit prices of the most commonly prescribed antihypertensive medications for uncontrolled hypertension in the Ontario Drug Benefit formulary.[84] We multiplied the average dose by the unit price of each drug to obtain the daily cost and then multiplied the daily cost by 365 to approximate the yearly cost. For each drug, we also incorporated pharmacy mark-up and dispensing fees. For our reference case analysis, we included both populations, assuming an equal proportion for both groups.

We evaluated costs from both Ministry of Health and societal perspectives. From a societal perspective, the total annual cost of antihypertensive medications for uncontrolled hypertension was $518.88. For

the Ministry of Health perspective, we assumed that 24.1% of people would be covered under a public drug plan.[87] Thus, from a Ministry of Health perspective, the average annual cost of antihypertensive medications for standard care was $125.05.

Cardiovascular Events

We included the initial costs associated with treating and managing cardiovascular events (i.e., angina, transient ischemic attack, myocardial infarction, heart failure, stroke), as well as the costs associated with ongoing treatment and maintenance following the index events. We sourced most event costs from the economic analysis by McFarlane et al[57] (which included references to other published studies, including a 2012 health technology assessment by Health Quality Ontario[70]) and the HTW analysis.[59] As McFarlane et al[57] presented event costs using a price year of 2023, we inflated the costs they reported to 2024 CAD using the Statistics Canada Consumer Price Index.[83]

Internal Validation

The secondary health economist conducted formal internal validation. This process included testing the mathematical logic of the model, checking for errors, and ensuring the accuracy of parameter inputs and equations.

Equity Considerations

Economic evaluations inherently focus on horizontal equity (i.e., people with similar characteristics are treated in a similar way). Where possible, we conducted subgroup or scenario analyses to best address vertical equity, which allows for people with different characteristics to be treated differently according to their needs.

In our economic evaluation, the use of QALYs reflects horizontal equity because equal social value is assigned to each unit of health effect, regardless of the characteristics of the people who receive those effects or the condition being treated.

We considered equity in term of access to renal denervation. In particular, we investigated the potential additional costs borne by people living in remote Northern Ontario communities by conducting a scenario analysis in which Northern Health Travel Grant Program funding is used to help people living in Northern Ontario who must travel long distances to access medical specialist services.[88]

Analysis

We calculated the reference case of this analysis by running 5,000 simulations (probabilistic analysis) that simultaneously captured the uncertainty in all parameters expected to vary. We set distributions for variables within the model. Tables 8, 9, 10, and 11 list the model variables and corresponding distributions. We calculated mean costs with credible intervals and mean QALYs with credible intervals for each intervention assessed. We also calculated mean incremental costs with credible intervals, incremental QALYs with credible intervals, and ICERs for renal denervation versus standard care.

We present the results of the probabilistic analysis in a cost-effectiveness acceptability curve and in a scatter plot on a cost-effectiveness plane. Although $50,000 per QALY and $100,000 per QALY are not used as definitive willingness-to-pay (WTP) thresholds, including graphical indications of the location of the results relative to these guideposts facilitates interpretation of the findings and comparison with

historical decisions. We also present uncertainty quantitatively as the probability that an intervention is cost-effective at the previously mentioned WTP guideposts. And we present this uncertainty qualitatively in 1 of 5 categories defined by the Ontario Decision Framework[89]: highly likely to be cost-effective (80–100% probability of being cost-effective), moderately likely to be cost-effective (60–79% probability), uncertain if cost-effective (40–59% probability), moderately likely not to be cost-effective (20–39% probability), or highly likely not to be cost-effective (0–19% probability).

Scenario Analyses

We conducted the following scenario analyses by modifying various parameter inputs and applying alternative assumptions:

- Scenario 1: Treatment-resistant population; in this scenario, we considered renal denervation for a population with uncontrolled hypertension taking more than 3 antihypertensive medications. For this analysis, we used a mean difference in SBP of −4.1 mmHg (95% CI, −7.5 to −0.7) to inform the change in the probability of cardiovascular events, based on Sharp et al.[39]
- Scenarios 2, 3, and 4: Change in time horizon; 1-year, 5-year, and 10-year time horizons explored.
- Scenarios 5 and 6: Cost of renal denervation procedure increased or decreased by 50% (± $8,681).
- Scenarios 7 and 8: Higher or lower treatment effect of renal denervation; treatment effect is doubled (10 mmHg) or halved (2.5 mmHg).
- Scenario 9: Assumption about the long-term stability of blood pressure reduction with renal denervation; we assumed that after 10 years, renal denervation would be required again to maintain the treatment effect.
- Scenarios 10 and 11: Change in baseline cardiovascular risk; baseline cardiovascular risk is doubled (60.4%) or halved (15.1%).
- Scenario 12: Relative risk reductions from Thomopoulos et al[62]; we calculated the probability of cardiovascular events with renal denervation by applying relative risks from Thomopoulos et al,[62] adjusting based on renal denervation treatment effect size (−5 mmHg) to the baseline probabilities of cardiovascular events.
- Scenario 13: Change in 24-hour ambulatory SBP; we assumed a mean difference in SBP of −3.3 mmHg (95% CI, −5.0 to −1.6), informed by Sharp et al.[39]
- Scenarios 14: Off-medication cohort; we assumed a mean difference in SBP of −5.7 mmHg (95% CI, −9.3 to −2.0), informed by Sharp et al.[39]
- Scenario 15: Radiofrequency-based renal denervation only; we assumed a mean difference in SBP of −5.6 mmHg (95% CI, −8.2 to −3.1), informed by Sharp et al.[39]
- Scenario 16: Ultrasound-based renal denervation only; we assumed a mean difference in SBP of −3.8 mmHg (95% CI, −7.8 to −0.3), informed by Sharp et al.[39]
- Scenario 17: Northern Health Travel Grant; in this scenario, we included the cost of a grant to help cover travel costs for people living in Northern Ontario (approximately 6% of Ontario's population[90]) who must travel long distances to access medical specialist services. We assumed a total per-person payment of $455 to cover a trip to an urban centre to undergo renal denervation ($205 for travel +

$250 for 3 nights of lodging). A physician fee of $10.25 (Schedule of Benefits code K036) is also required for completion of the grant application form.

Table 12 summarizes the scenario analyses we explored.

Table 12: Variables Varied in Scenario Analyses

Scenario and parameter	Reference case	Scenario analysis
1: Treartment-resistant population	Population includes all those with uncontrolled hypertension, including treatment-resistant hypertension	Population includes only those with treatment-resistant hypertension using an SBP change of −4.1 mm Hg (95% CI, −7.5 to −0.7), informed by Sharp et al[39]
2–4: Change in time horizon	Lifetime horizon	1-year, 5-year, and 10-year time horizons explored
5–6: Cost of RDN procedure increased or decreased by 50%	Using the list price of the RDN system; assuming a 1-night hospital stay and associated procedure costs	Increasing or decreasing the total cost of RDN procedure by 50% (± $8,681.40)
7–8: Higher or lower treatment effect of RDN	Assuming an SBP MD of −5.0 mmHg	Assuming RDN treatment effect is doubled (10 mmHg) or halved (2.5 mmHg)
9: Long-term stability of blood pressure reduction	Assuming RDN has a lifetime treatment effect	Assuming a second RDN procedure is needed after 10 years to maintain treatment effect
10–11: Change in baseline cardiovascular risk	Using the baseline cardiovascular risk reported in d'Agostino et al,[68] considering the characteristics of the uncontrolled hypertension population (30.2%)	Baseline cardiovascular risk is doubled (60.4%) or halved (15.1%)
12: Relative risk reductions from Thomopoulos et al[62]	Probability of events with RDN calculated based on d'Agostino et al,[68] using a lower SBP value (28.8%)	Probability of events with RDN calculated using relative risk reductions reported by Thomopoulos et al[62]
13: Change in 24-hour ambulatory SBP	Assuming an office SBP MD of −5.0 (95% CI, −6.9 to −3.1)	Assuming an office SBP MD of −3.3 mmHg (95% CI, −5.0 to −1.6), informed by Sharp et al[39]
14: Off-medication cohort	Assuming an SBP MD of −5.0 (95% CI, −6.9 to −3.1), considering all people with uncontrolled hypertension (incluing those on and off medications)	Assuming an SBP MD of −5.7 mmHg (95% CI, −9.3 to −2.0), informed by Sharp et al[39]
15: Radiofrequency-based RDN only	Assuming an SBP MD of −5.0 (95% CI, −6.9 to −3.1), considering all types of RDN	Assuming an SBP MD of −5.6 mmHg (95% CI, −8.2 to −3.1), informed by Sharp et al[39]
16: Ultrasound-based RDN only	Assuming an SBP MD of −5.0 (95% CI, −6.9 to −3.1), considering all types of RDN	Assuming an SBP MD of −3.8 mmHg (95% CI, −7.8 to −0.3), informed by Sharp et al[39]
17: Northern Health Travel Grant	Not including the Northern Health Travel Grant	Assuming some travel grant payment for people from Northern Ontario communities

Abbreviations: CI, confidence interval; MD, mean difference; RDN; renal denervation; SBP, systolic blood pressure; WTP, willingness to pay.

Results

Reference Case Analysis

Table 13 provides the results of the reference case analysis from the perspective of the Ministry of Health. The mean total costs for renal denervation in addition to standard care and standard care alone were $63,391.25 and $47,875.28, respectively. Renal denervation in addition to standard care had a higher overall incremental cost of $15,515.97 owing to procedure and additional follow-up costs, although there were some reduced costs associated with fewer cardiovascular events. Renal

denervation in addition to standard care resulted in an increase of 0.13 QALYs. For renal denervation in addition to standard care, the mean total effect was 17.26 QALYs; for standard care alone, the mean total effect was 17.13 QALYs. Compared with standard care alone, renal denervation in addition to standard care resulted in an ICER of $121,237 per QALY over a lifetime horizon.

Table 13: Reference Case Analysis Results

Strategy	Average total cost, $ (95% CI)	Incremental cost, $ (95% CI)[a,b]	Average total QALYs, (95% CI)	Incremental effect, (95% CI)[b,c]	ICER
Standard care alone	47,875.28 (39,384.67 to 60,183.19)	–	17.13 (16.68 to 17.56)	–	–
Renal denervation in addition to standard care	63,391.25 (55,112.61 to 75,444.94)	15,515.97 (14,684.30 to 16,227.77)	17.26 (16.82 to 17.69)	0.13 (0.08 to 0.18)	121,237

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

[a]Incremental cost = average cost (strategy B) – average cost (strategy A).

[b]Results may appear inexact due to rounding.

[c]Incremental effect = average effect (strategy B) – average effect (strategy A).

Figure 5 presents the results of our probabilistic analysis in a cost-effectiveness acceptability curve, and Figure 6 presents them as a scatter plot on a cost-effectiveness plane. The probability that renal denervation in addition to standard care is more cost-effective than standard care alone at several WTP values is as follows:

- $50,000 per QALY: 0%
- $100,000 per QALY: 18.02%
- $150,000 per QALY: 80.50%
- $200,000 per QALY: 96.78%

These findings indicate that renal denervation in addition to standard care versus standard care alone is highly unlikely to be cost-effective at WTP values of $50,000 and $100,000 per QALY gained, moderately likely to be cost-effective at a WTP value of $150,000 per QALY gained, and highly likely to be cost-effective at a WTP value of $200,000 per QALY gained.

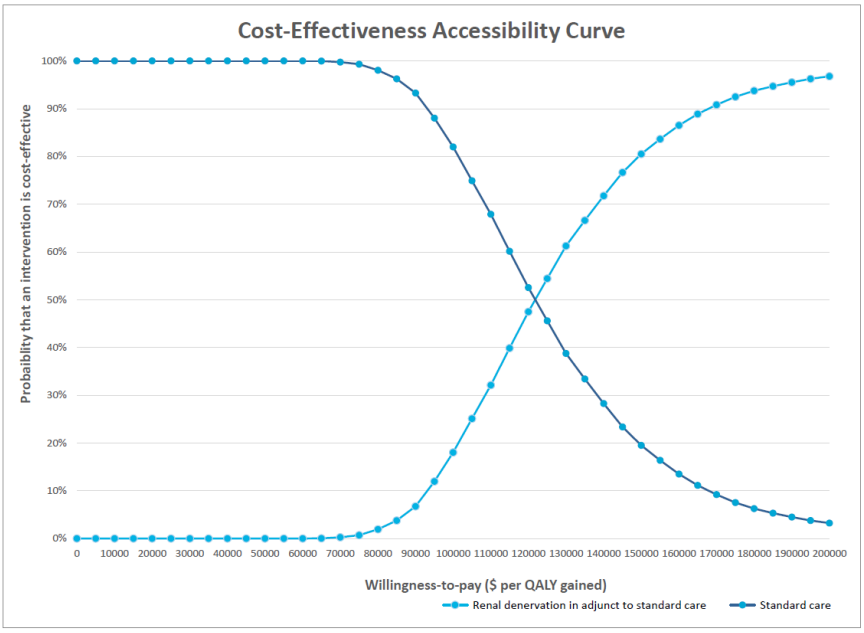

Figure 5: Cost-Effectiveness Acceptability Curve

A cost-effectiveness acceptability curve showing the results of the probabilistic analysis. Renal denervation in addition to standard care was highly unlikely to be cost-effective at WTP values of $50,000 and $100,000 per QALY gained, moderately likely to be cost-effective at a WTP value of $150,000 per QALY gained, and highly likely to be cost-effective at a WTP value of $200,000 per QALY gained.
Abbreviations: QALY, quality-adjusted life-year; WTP, willingness to pay (expressed in additional $ per 1 QALY gained).

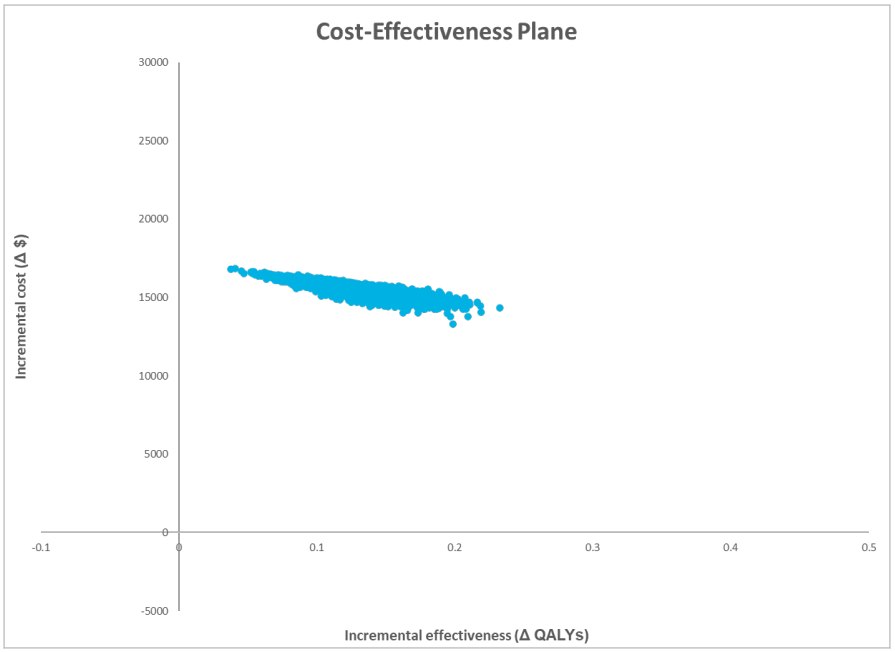

Figure 6: Scatter Plot of Probabilistic Results

A scatter plot of probabilistic results showing the findings from the 5,000 model iterations.
Abbreviation: QALY, quality-adjusted life-year.

Scenario Analysis

Table 14 and Figure 7 provide a summary of the results of the scenario analyses.

Table 14: Scenario Analysis Results

Scenario	Average total cost, $	Incremental cost, $[a,b]	Average total effect, QALYs	Incremental effect, QALYs[b,c]	ICER, $/QALY
Reference case	SC: 47,875.28 RDN: 63,391.25	15,515.97	SC: 17.13 RDN: 17.26	0.13	121,237
1: Treartment-resistant population	SC: 47,934.56 RDN: 63,827.08	15,892.53	SC: 17.12 RDN: 17.23	0.11	151,264
2: 1-year time horizon	SC: 791.31 RDN: 18,126.10	17,333.79	SC: 0.86 RDN: 0.86	0.00	42,109,501
3: 5-year time horizon	SC: 5,235.34 RDN: 22,388.45	17,153.11	SC: 4.05 RDN: 4.06	0.01	3,108,261
4: 10-year time horizon	SC: 12,910.41 RDN: 29,740.65	16,830.24	SC: 7.56 RDN: 7.58	0.02	949,454
5: Higher cost of RDN procedure	SC: 47,934.56 RDN: 72,184.66	24,250.10	SC: 17.12 RDN: 17.25	0.13	188,955
6: Lower cost of RDN procedure	SC: 47,934.56 RDN: 54,821.85	6,887.29	SC: 17.12 RDN: 17.25	0.13	53,665
7: Higher treatment effect (−10 mmHg)	SC: 47,934.56 RDN: 61,698.23	13,763.68	SC: 17.12 RDN: 17.38	0.26	53,156
8: Lower treatment effect (−2.5 mmHg)	SC: 47,934.56 RDN: 64,401.85	16,467.30	SC: 17.12 RDN: 17.19	0.06	257,807
9: Long-term stability of blood pressure reduction	SC: 47,934.56 RDN: 92,146.62	44,212.06	SC: 17.12 RDN: 17.25	0.13	344,498
10: Baseline cardiovascular risk doubled (60.4%)	SC: 77,514.11 RDN: 92,203.62	14,689.51	SC: 15.24 RDN: 15.39	0.15	97,365
11: Baseline cardiovascular risk halved (15.1%)	SC: 28,970.94 RDN: 45,252.60	16,281.66	SC: 18.55 RDN: 18.64	0.09	190,040
12: Relative risk reductions from Thomopoulos et al[62]	SC: 47,934.56 RDN: $59,099.45	11,164.90	SC: 17.12 RDN: 17.49	0.36	30,873
13: Change in 24-hour ambulatory SBP (−3.3 mmHg)	SC: 47,934.56 RDN: 64,114.62	16,180.06	SC: 17.12 RDN: 17.21	0.09	191,617
14: Off-medication cohort	SC: 47,934.56 RDN: 63,251.14	15,316.59	SC: 17.12 RDN: 17.27	0.15	104,558
15: Radiofrequency-based RDN only	SC: 47,934.56 RDN: 63,287.62	15,352.61	SC: 17.12 RDN: 17.27	0.14	106,694
16: Ultrasound-based RDN only	SC: 47,934.56 RDN: 63,934.94	16,000.39	SC: 17.12 RDN: 17.22	0.10	164,404
17: Northern Health Travel Grant	SC: 47,934.56 RDN: 63,531.17	15,596.61	SC: 17.12 RDN: 17.25	0.13	121,528

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RDN, renal denervation in addition to standard care; SC, standard care alone.

[a]Incremental cost = average cost (strategy B) − average cost (strategy A).

Table 14 notes continued

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

[d]Incremental effect = average effect (strategy B) − average effect (strategy A).

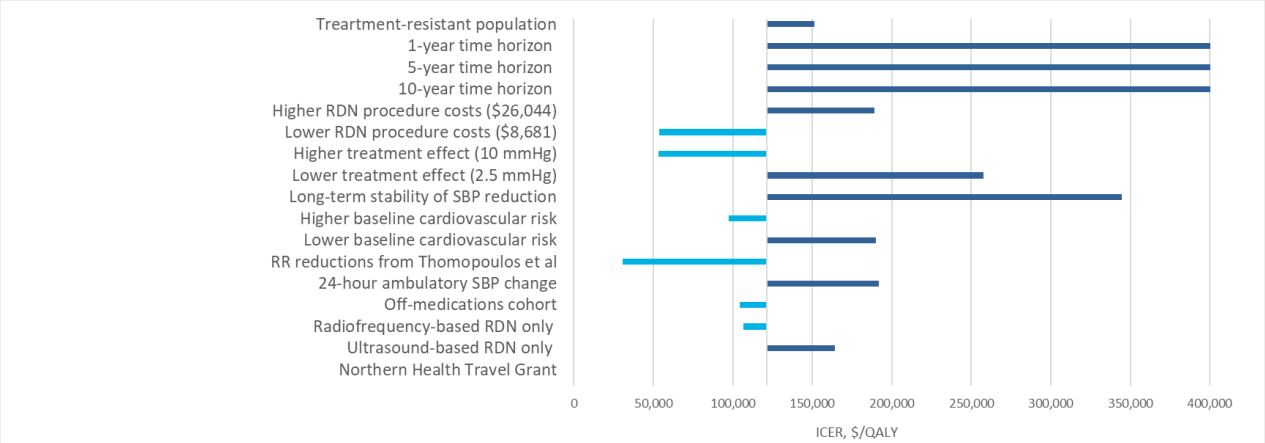

Figure 7: Bar Graph of Scenario Analysis Results

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; RDN, renal denervation; RR, relative risk; SBP, systolic blood pressure.

Our scenario analyses showed that some parameters affected the results more substantially than others. Overall, the cost-effectiveness results comparing renal denervation (all types) in addition to standard care with standard care alone were most sensitive to the following:

- When calculating the probability of cardiovascular events with renal denervation by applying the relative risk values reported by Thomopoulos et al[62]; using this method projected a greater reduction in cardiovascular events
- When a shorter time horizon was used; this finding indicates that renal denervation has a high upfront cost but a long-term benefit in SBP control
- When the treatment effect of renal denervation was increased or decreased
- When the cost of renal denervation was increased or decreased

The cost-effectiveness of radiofrequency-based renal denervation only – but not of ultrasound-based renal denervation only – was found to be more favourable compared with the reference case (ICERs: $106,694/QALY, $164,404/QALY and $121,237/QALY, respectively, for radiofrequency-based renal denervation, ultrasound-based renal denervation, and all types of renal denervation in the reference case).

Discussion

Our reference case results showed that renal denervation in addition to standard care for adults with uncontrolled hypertension would result in improved health outcomes as well as increased costs. The

cost of the renal denervation procedure ($17,362 per person) was partially offset by savings associated with a reduction in cardiovascular event costs (−$1,784). This finding was consistent with the findings of other published economic studies, which also suggested that renal denervation may lead to increased costs and QALYs. However, our reference case ICER is much higher than that of the Canadian cost-effectiveness analysis by McFarlane et al,[57] which found renal denervation to be cost-effective with an ICER of $11,809 per QALY.

The treatment effect estimate of a −5 mmHg reduction in SBP used in our analysis was similar, although our model considered all adults with uncontrolled hypertension and all types of renal denervation. The difference in results was driven primarily by the methods applied to translate the treatment effect of SBP reduction into a reduction in cardiovascular events. We adapted the model and followed the methods used in the HTW cost-effectiveness analysis,[59] and we recalculated cardiovascular risk with the Framingham Risk Calculator, using the lower blood pressure value following renal denervation. In contrast, McFarlane et al[57] calculated the probability of cardiovascular events with renal denervation by applying relative risks from a meta-analysis of RCTs on antihypertensive medications,[62] adjusted based on the renal denervation treatment effect size (−4.9 mmHg), to the baseline probabilities of cardiovascular events. This method resulted in a much more substantial reduction in predicted cardiovascular events than in our reference case analysis. When we conducted a scenario analysis applying this approach, the ICER was reduced to $30,873 per QALY.

The impact of SBP change on cardiovascular events remains the key uncertainty in economic analyses considering renal denervation. Because clinical studies of renal denervation have focused on the surrogate end point of SBP reduction, we had to make assumptions to translate changes in SBP into changes in cardiovascular event rate. Our analysis has the same limitations as in the existing literature in that it had to rely on the accuracy of the risk calculations and major modeling assumptions. Thus, our results should be interpreted with caution.

When we compared our reference case, conducted over a lifetime horizon, to scenarios conducted over 1-year or 5-year time horizons, renal denervation in addition to standard care had less favourable cost-effectiveness results. These scenario analyses showed that the benefit of renal denervation is accrued over time to offset the high initial cost of the renal denervation procedure. We assumed that the initial treatment effect of renal denervation would be sustained throughout a person's lifetime, based on long-term registry data.[71]

Our sensitivity analysis found that the cost-effectiveness results were highly sensitive to the cost of the renal denervation procedure (including the cost of the renal denervation system) and the type of renal denervation used, with radiofrequency-based renal denervation being associated with a more favourable ICER than ultrasound-based renal denervation.

It is also important to consider barriers to accessing specialized care for uncontrolled hypertension in Ontario. As described in the clinical evidence review, it is likely that renal denervation would be performed at level 7 Regional Cardiac Program hospitals, all of which are in large urban centres. Thus, access for some people may be limited. However, if follow-up care could be provided at satellite centres by appropriately trained health care professionals, then some travel-related and out-of-pocket costs could be mitigated. In a scenario analysis, we captured the cost of a grant for travel and accommodation expenses for people living in Northern Ontario who must travel a substantial distance to receive renal denervation.

Equity Considerations

Public funding for renal denervation may improve access to effective treatment for those who cannot afford the treatment out of pocket or who do not have private insurance coverage. Further, funding this technology could reduce inequity by improving access for people in remote areas who require regular drug monitoring or treatments that are delivered at a physician's office. We captured some of the additional costs borne by patients living in remote Northern Ontario communities by conducting a scenario analysis that considered the cost of the Northern Health Travel Grant.

Strengths and Limitations

Our study has several strengths. We used pooled clinical effect estimates for renal denervation resulting from a comprehensive literature search (for further details, see the clinical evidence review). We sourced costs and resource use inputs reflective of those incurred in Ontario. We used a lifetime horizon in our model to capture improved health outcomes during the lifetime of people with uncontrolled hypertension. Our model assessed renal denervation in a range of populations and considered all types of renal denervation, and we conducted extensive scenario analyses on key model parameters.

Our analysis also has some limitations. Our analysis was limited by a lack of evidence on cardiovascular event end points and a lack of high-quality long-term evidence. We therefore extrapolated change in cardiovascular event end points from change in SBP, and we assumed that the treatment effect would be maintained throughout a person's lifetime. Doing so may have overestimated the impact of renal denervation in addition to standard care versus standard care alone.

Further, limitations in our modelling approach may have underestimated the costs and quality-of-life losses associated with recurrent or additional cardiovascular events. In our analysis, utility estimates were applied consistently to all people in a health state. However, the utility of a person in the stroke state who has previously experienced a myocardial infarction would likely be worse than that of a person in the stroke state who has not had a myocardial infarction. Additionally, because only 1 renal denervation system currently has Health Canada approval, we assumed that the cost of this system would apply to all systems should others become available.

Conclusions

In adults with uncontrolled hypertension, compared with standard care alone, renal denervation in addition to standard care was associated with 0.13 QALYs gained and an additional cost of $15,515.97 per person, resulting in an ICER of $121,237 per QALY over a lifetime horizon. These results were most sensitive to changes in time horizon, renal denervation procedure cost, and assumptions about the duration of treatment effect. Our findings should be interpreted with caution because of the uncertainty in how SBP reduction relates to cardiovascular risk reduction.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding renal denervation as an adjunctive treatment to standard care for adults with uncontrolled hypertension?

Methods

Analytic Framework

We estimated the budget impact of publicly funding renal denervation using the cost difference between two scenarios: (1) current clinical practice without public funding for renal denervation (the current scenario), and (2) anticipated clinical practice with public funding for renal denervation (the new scenario). Figure 8 presents the model schematic.

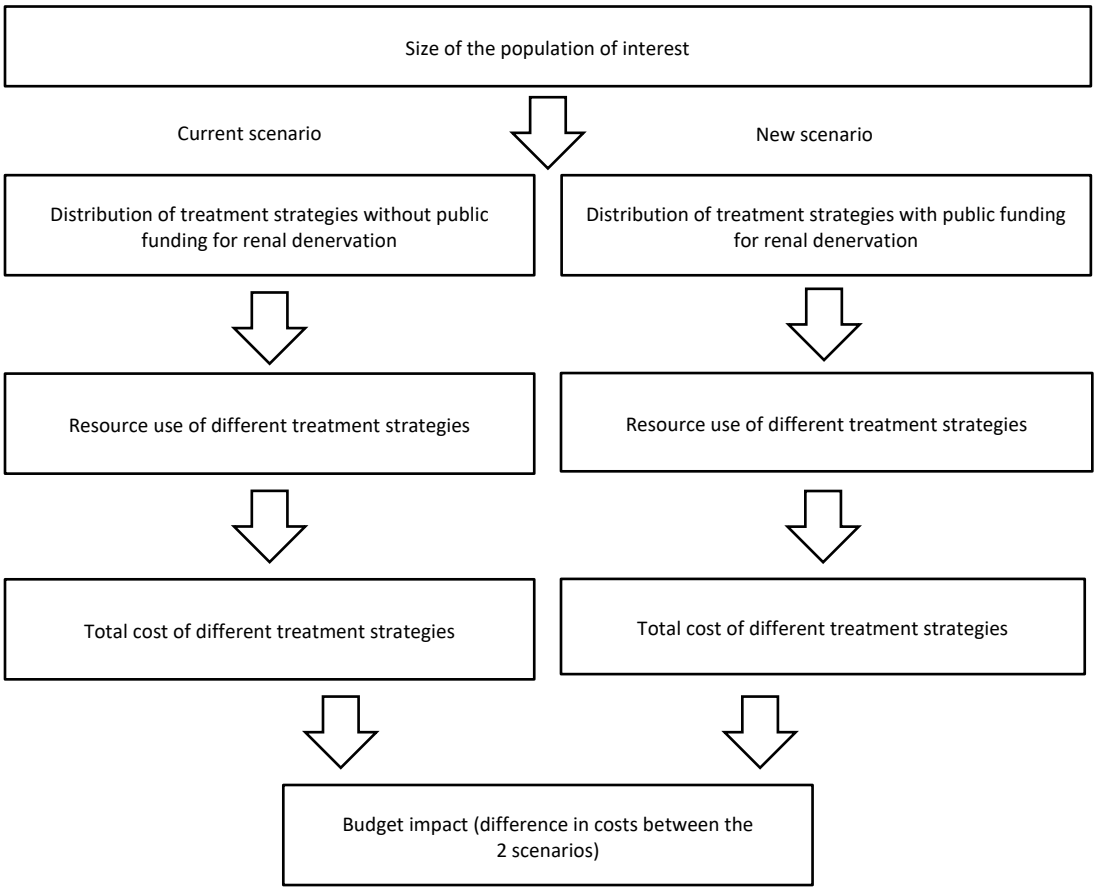

Figure 8: Schematic Model of Budget Impact

Flow chart describing the model for the budget impact analysis. Based on the size of the population of interest, we created 2 scenarios: the current scenario, which would explore the distribution of treatment strategies, resource use, and total costs without public funding for renal denervation, and the new scenario, which would explore the distribution of treatment strategies, resource use, and total costs with public funding for renal denervation. The budget impact would represent the difference in costs between the 2 scenarios.

Key Assumptions

We made the following assumptions:

- 48 people would receive renal denervation in the first year of public funding for renal denervation
- The number of people undergoing renal denervation would increase annually by 50% over the next 5 years
- The cost of renal denervation would stay constant over the next 5 years. (The cost of renal denervation includes start-up and implementation costs; we did not consider training costs, as described in the primary economic evaluation)
- The treatment strategies for adults with uncontrolled hypertension would remain constant over the next 5 years

Population of Interest

Our population of interest was adults (≥ 18 years of age) with uncontrolled hypertension, defined as an office blood pressure greater than 140/90 mmHg despite standard care, including health behaviour modifications and the use of antihypertensive medications. This population includes 3 subpopulations: adults with treatment-resistant hypertension (i.e., those whose hypertension is not controlled despite taking 3 or more classes of antihypertensive medications, including a diuretic), adults with nonresistant hypertension (i.e., those whose hypertension is not controlled despite taking fewer than 3 classes of antihypertensive medications), and adults intolerant to antihypertensive medications.

Given the size of this population, the number of renal denervation procedures conducted is likely to be influenced by the surgical capacity of hospitals. Because of the complex interplay among the variables involved in identifying potential candidates for renal denervation, we were unable to derive the estimated number of adults eligible for renal denervation in Ontario from administrative databases or the published literature. As such, we based our estimate of the size of the population of interest on clinical expert opinion and manufacturer experience.

Table 15 describes our estimated volume of intervention over the next 5 years.

Table 15: Volume of Intervention

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Standard care alone, n	24	48	84	138	219	513
Renal denervation in addition to standard care, n	24	24	24	24	24	120
New scenario						
Standard care alone, n	0	0	0	0	0	0
Renal denervation in addition to standard care, n	48	72	108	162	243	633

Current Intervention Mix

In the current scenario, standard care for adults with uncontrolled hypertension includes health behaviour modifications and the use of antihypertensive medications.

Only 1 renal denervation system is currently licensed for use in Canada: the Symplicity Spyral renal denervation system. However, it is not publicly funded in Ontario. Prior to Health Canada approval in June 2024, the Symplicity Spyral system was available through Health Canada's Special Access Program.

Only 2 hospitals in Ontario currently offer renal denervation, both in Toronto. Of 33 people referred for renal denervation, the team at Toronto's Sunnybrook Health Sciences Centre has thus far conducted the procedure for 11. According to a clinical expert, 2 additional people have been referred and are waiting for the procedure (Mina Madan, MD, email communication, July 23, 2025). Costs for the system and procedure at Sunnybrook are currently being covered by hospital foundation and philanthropic funds. St. Michael's Hospital had access to a system through its participation in the Symplicity Spyral international clinical trial and has conducted 2 procedures to date (Medtronic, email communication, August 2024). Based on clinical expert opinion, we assumed that 2 renal denervation procedures are completed each month at each site with access to renal denervation in the current scenario. We assumed that without public funding, this number would remain the same; thus, a total of 24 people per year would receive renal denervation in years 1 through 5 (Sheldon Tobe, MD, email communication, March 6, 2025).

Uptake of the New Intervention and New Intervention Mix

In the new scenario, adults with uncontrolled hypertension may be eligible for renal denervation in addition to standard care. If renal denervation were publicly funded, it is estimated that 1 centre could initially perform 24 to 36 procedures a year (Sheldon Tobe, MD, email communication, March 6, 2025).

Renal denervation is typically performed by an interventional cardiologist, radiologist, or vascular surgeon. The procedure is performed in an interventional suite, such as a catheterization laboratory, in a hospital with a level 7 Regional Cardiac Program (RCP), of which there are currently 11 in Ontario. To date, clinicians at Sunnybrook Health Sciences Centre, St. Michael's Hospital, the University Health Network (in Toronto), the Ottawa Hospital, and London Health Sciences Centre have been involved in research on renal denervation.

If renal denervation is publicly funded, it is likely that all procedures would initially be performed at Sunnybrook and St. Michael's, given their established expertise and processes. Over time, it may become available at other sites with established hypertension centers with experience in catheter-based procedures. Given that the infrastructure and expertise needed to perform this interventional procedure is not currently in place across the province, we expect that the uptake of this intervention will start low. In the new scenario, we thus assumed that 48 people would receive renal denervation in year 1 and that uptake would increase by 50% each year, for a total of 243 people receiving renal denervation in year 5. We considered a larger volume of people eligible for renal denervation in a scenario analysis.

Resources and Costs

We included both health technology–associated resource use and costs (i.e., the direct costs of renal denervation) and disease-associated resource use and costs (i.e., all health care costs). For health

technology–associated resource use and costs, we included the mean costs associated with renal denervation. For disease-associated costs, we ran companion cost-effectiveness analyses (previously described) over the time horizon of the budget impact analysis (without discounting) to obtain the relevant costs.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. We present both total costs and disaggregated costs by categories. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

In our sensitivity analyses, we explored the following 7 scenarios:

- Scenario 1: Assuming a 50% increase in uptake for renal denervation
- Scenario 2: Assuming a 50% reduction in uptake for renal denervation
- Scenario 3: Assuming a 300% increase in uptake for renal denervation
- Scenario 4: Assuming a 50% increase in the cost of renal denervation equipment
- Scenario 5: Assuming a 50% decrease in the cost of renal denervation equipment
- Scenario 6: Assuming renal denervation is used only in adults with treatment-resistant hypertension
- Scenario 7: Assuming some people in Northern Ontario may receive funding from the Northern Health Travel Grant to access the procedure

Results

Reference Case

Table 16 summarizes the potential budget impact of publicly funding renal denervation for the treatment of uncontrolled hypertension in adults over the next 5 years from the perspective of the Ontario Ministry of Health. We estimate that public funding for renal denervation would lead to additional costs of $0.42 million in year 1, increasing to $3.78 million in year 5, for a total of $8.87 million over 5 years (assuming renal denervation is performed in a total of 633 people).

Table 16: Budget Impact Analysis Results

Scenario	Budget impact, $ million[a,b,c]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario	**0.45**	**0.51**	**0.62**	**0.78**	**1.02**	**3.38**
Medication and monitoring costs	0.01	0.03	0.05	0.09	0.15	0.34
Cardiovascular event costs	0.03	0.07	0.15	0.27	0.46	0.98
Renal denervation costs	0.42	0.42	0.42	0.42	0.42	2.08
New scenario	**0.86**	**1.34**	**2.06**	**3.14**	**4.77**	**12.16**
Medication and monitoring costs	0.01	0.03	0.05	0.09	0.15	0.34
Cardiovascular event costs	0.03	0.07	0.14	0.26	0.44	0.94
Renal denervation costs	0.83	1.25	1.88	2.81	4.22	10.99
Budget impact[b,c]	**0.42**	**0.83**	**1.45**	**2.39**	**3.78**	**8.87**

[a]In 2024 Canadian dollars.

[b]All costs were calculated using the mean cost from the results of the probabilistic analysis described in the primary economic evaluation.

[c]Results may appear inexact due to rounding.

Opportunities for Cost Savings or a Reduction in Health Resource Use

Savings associated with renal denervation were mainly attributed to reduced health care costs associated with fewer cardiovascular events. Additional savings, not captured in this analysis, may also be associated with reduced blood pressure and fewer cardiovascular events (e.g., nursing time in hospitals); however, these are unlikely to be translated into monetary terms in a publicly funded health care system. Savings are likely to lead to improved efficiency in hospitals (e.g., reduced wait times), rather than to direct budget savings. Further, patients may experience reduced costs by avoiding other interventions requiring out-of-pocket costs and by needing fewer doctor's visits (given improved blood pressure control).

Sensitivity Analysis

Table 17 summarizes the results of our scenario analyses. Compared with the reference case, scenarios that considered an increase or decrease in renal denervation costs or volume resulted in a higher or lower budget impact, respectively. The reference case analysis and the 7 scenario analyses yielded total 5-year budget impacts ranging from $3.40 million to $33.41 million. Scenario 3 considered funding renal denervation for approximately 1,900 people over 5 years and led to the greatest change in total budget impact.

Table 17: Budget Impact Analysis Results – Sensitivity Analyses

Scenario	Budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Reference case	0.42	0.83	1.45	2.39	3.78	8.87
1: Volume of RDN procedures increased by 50%	0.85	1.51	2.49	3.97	6.19	15.01
2: Volume of RDN procedures decreased by 50%	0.0	0.21	0.52	0.99	1.69	3.40
3: Volume of RDN procedures increased by 300%	2.16	3.53	5.60	8.72	13.41	33.41
4: Cost of RDN equipment increased by 50%	0.62	1.25	2.18	3.58	5.69	13.32
5: Cost of RDN equipment decreased by 50%	0.21	0.41	0.72	1.19	1.88	4.42
6: RDN only for treatment-resistant population	0.42	0.83	1.45	2.39	3.79	8.88
7: Northern Health Travel Grant	0.42	0.83	1.46	2.39	3.79	8.89

[a] In 2024 Canadian dollars.

[b]Results may appear inexact due to rounding.

Discussion

We estimate that the budget impact of publicly funding renal denervation in addition to standard care will be an additional $8.87 million over 5 years. This cost derives primarily from the cost of the renal denervation procedure; however, costs are slightly offset by reductions in cardiovascular event–related costs.

The reference case budget impact reflects a smaller volume of patients compared to the number who might be eligible for renal denervation in the first 5 years of public funding because of resource constraints and slow uptake. If renal denervation were publicly funded, uptake would depend on factors such as clinical capacity, patient preference, and awareness of the procedure on the part of primary care clinicians. In the current scenario, we acknowledged that although there is some diffusion of renal denervation in the Ontario health care system, the number of procedures performed is likely to remain limited given the lack of widespread diffusion.

Based on expert opinion, we estimated that, if renal denervation were publicly funded, about 48 procedures would be performed in the first year and that the uptake rate would increase by 50% per year, for a total of 633 procedures funded over 5 years. It is important to note that at present, many potentially eligible patients are not referred for renal denervation because of a lack of awareness of this technology among clinicians. An increase in awareness may lead to an increase in the number of eligible patients referred and thus a subsequent increase in budget impact. In scenario 1, we considered a 50% increase in the volume assumed for the reference case (e.g., 72 procedures in the first year, increasing by 150% a year, for a total of 950 procedures funded over 5 years) and found that the total budget impact would be $15.01 million over 5 years.

Equity Considerations

We conducted a scenario analysis that reflected a scenario in which people living in Northern Ontario access the Northern Health Travel Grant to help with travel-related costs to access renal denervation. In this scenario, the change to the budget impact was minimal.

Strengths and Limitations

In terms of the strengths of our budget impact analysis, our estimates were derived from our primary economic evaluation, for which we obtained clinical parameters from the clinical evidence review and derived cost parameters primarily from Canadian sources. Further, we sourced the cost of a renal denervation system directly from a manufacturer. We also validated our assumptions and estimates with clinical experts with expertise in the use of renal denervation for uncontrolled hypertension.

Our budget impact analysis also had several limitations. First, it was based on the economic model developed in our primary economic evaluation, so the limitations of the economic model also apply to our budget impact analysis. Second, we estimated the potential uptake of renal denervation over the next 5 years based on a combination of factors including expert opinion, so our estimates are highly uncertain. Last, our budget impact estimates of renal denervation were based on costs for a single renal denervation system. Should other systems (with varying costs) become available in Ontario, the applicability of our analysis may be limited.

Conclusions

We estimate that publicly funding renal denervation in Ontario for the treatment of uncontrolled hypertension in adults would cost an additional $0.42 million in year 1, increasing to $3.78 million in year 5, for a total of $8.87 million over 5 years.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of adults with lived experience of hypertension, as well as the preferences and perceptions of both people with hypertension and providers of renal denervation.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other care partners, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[91-93] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of a technology or intervention on people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of adults with hypertension in 2 ways:

- A review by Ontario Health of the quantitative evidence of patient and provider preferences and values
- Direct engagement by Ontario Health with adults with hypertension through interviews

Quantitative Evidence

Research Questions

- What is the relative preference of patients and providers for renal denervation compared with antihypertensive medications or no treatment?
- What is the relative importance of key attributes of renal denervation, and what trade-offs between attributes are patients and providers willing to make?

Methods

Literature Search

We performed a literature search for quantitative evidence of preferences and values on January 13, 2025, to retrieve studies published from database inception until the search date. We used the Ovid interface to search MEDLINE and the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL). The search was based on the population and intervention of the clinical search strategy with a methodological filter applied to limit retrieval to quantitative evidence of preferences and values (modified from Selva et al[94]).

We created database auto-alerts in MEDLINE and CINAHL and monitored them until March 2025. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Key study designs (e.g., observational, surveys, questionnaires, rating scales, discrete-choice experiments):
  - Patients' or providers' preferences for renal denervation decision-making for uncontrolled hypertension, and
  - Utility measures: direct techniques (e.g., standard gamble, time trade-off, rating scales) or conjoint analysis (e.g., discrete choice experiment, contingent valuation and willingness-to-pay, probability trade-off), or
  - Nonutility quantitative measures: direct-choice techniques, decision aids, surveys, questionnaires

Exclusion Criteria

- Editorials, commentaries, case reports, conferences abstracts, letters, narrative or nonsystematic reviews, qualitative studies
- Animal and in vitro studies

Participants

Inclusion Criteria

- Adults (≥ 18 years of age) with hypertension; includes controlled, uncontrolled, treatment-resistant, and unspecified hypertension
- Health care providers managing adults with hypertension

Exclusion Criteria

- Children (as defined by the studies)

Interventions

Inclusion Criteria

- First- or second-generation catheter-based renal denervation systems using radiofrequency-, ultrasound-, or alcohol-mediated ablation

Exclusion Criteria

- Methods of renal denervation not involving catheterization
- Renal denervation for conditions other than hypertension

Comparators

Inclusion Criteria

- Standard care (e.g., medical therapy) or no comparator

Exclusion Criteria

- Methods of renal denervation not involving catheterization

Outcome Measures

- Any outcomes related to patient or health care provider satisfaction, preferences, or values
  - Including utility and nonutility measures

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[43] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. Another single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics using a data form to collect information about the following:

- Source (e.g., citation information, contact details, study type)
- Methods (e.g., study design, study duration, participant recruitment)
- Outcomes (e.g., outcomes measured, unit of measurement, time points at which the outcomes were assessed)

Statistical Analysis

Results are summarized narratively. No additional statistical analyses were conducted beyond those reported in the primary studies.

Critical Appraisal of Evidence

We did not undertake a formal critical appraisal of the included studies.

Results

Literature Search

The literature search of the quantitative evidence of preferences and values yielded 275 citations, including grey literature results and after removing duplicates, published between database inception and January 13, 2025. We identified no additional studies from other sources, including database alerts (monitored until March 2025). In total, we identified 6 observational studies that met our inclusion criteria. Figure 9 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the literature search for quantitative evidence of preferences and values.

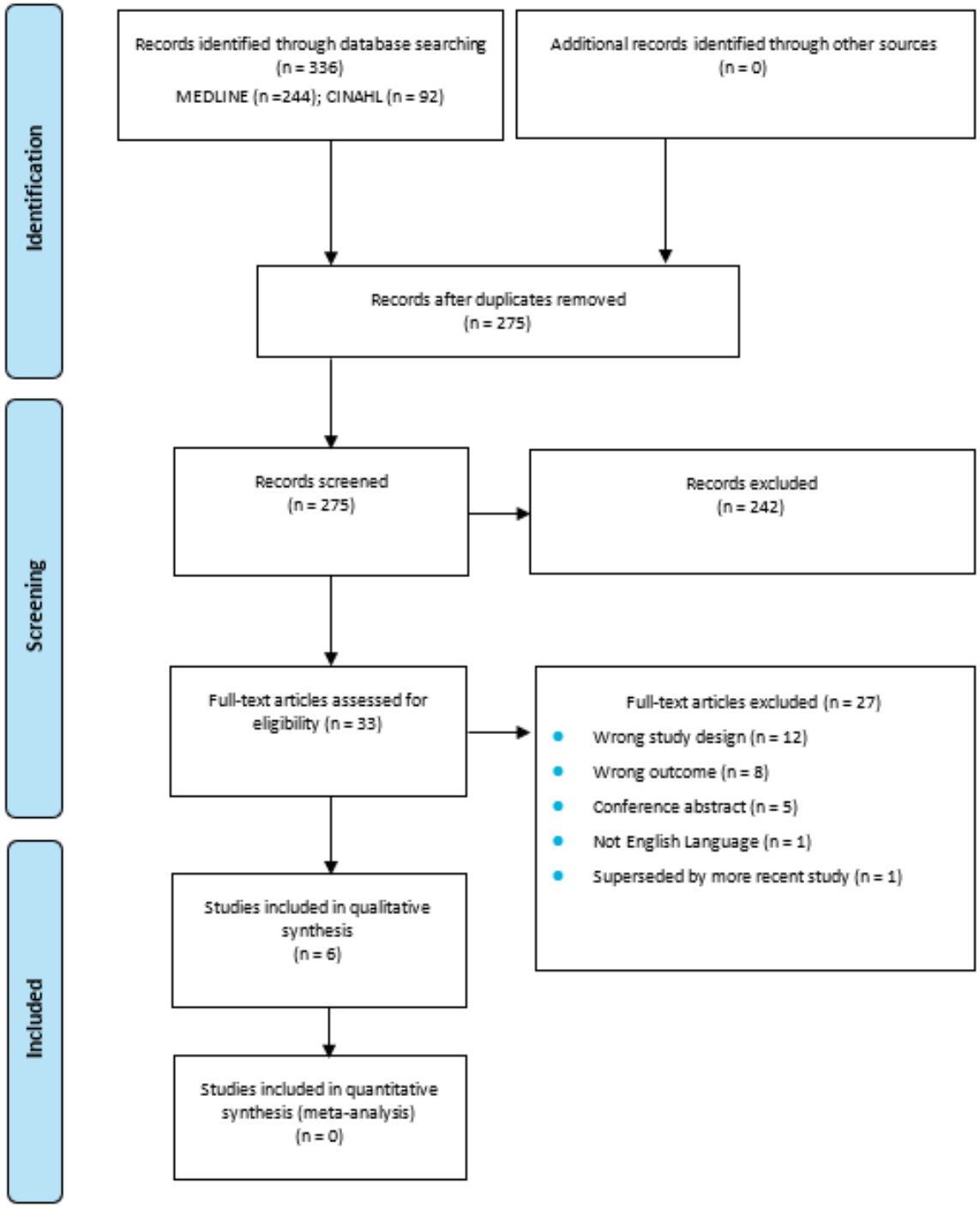

Figure 9: PRISMA Flow Diagram – Quantitative Evidence of Preferences and Values Review

PRISMA flow diagram showing the quantitative evidence of preferences and values review. The literature search for quantitative evidence of preferences and values yielded 275 citations, including grey literature results and after removing duplicates, published between database inception and January 13, 2025. We screened the abstracts of the 275 identified studies and excluded 242. We assessed the full text of 33 articles and excluded a further 27. In the end, we included 6 articles in the qualitative synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[44]

Characteristics of Included Studies

Table 18 lists the characteristics of the 6 included studies. One study used a discrete-choice experiment design,[95] 4 studies[96-99] used surveys, and 1 study[100] used market research assessments.

Table 18: Characteristics of Studies Included in the Quantitative Evidence of Preferences and Values Review

Author, year, country	Study design and methods	Participants	Outcomes
Kandzari et al,[95] 2023, United States	Prospective Discrete-choice experiment Participants selected between treatments using a structured survey Treatment features included interventional, noninterventional, or no hypertension treatment; number of daily BP pills; expected reduction in office SBP; duration of effect; risks of drug side effects, access site pain, and vascular injury	N = 400 survey respondents with **physician-confirmed uncontrolled hypertension** 52% female Mean (SD) age: 59.2 (± 13.0) y Mean (SD)SBP: 155.1 (± 12.3) mmHg Mean (SD) number of antihypertensive medications prescribed at baseline: 1.8 ± 0.9	Preference weights Maximum acceptable risk and minimum acceptable benefit
Kario et al,[96] 2022, Japan	Retrospective Participants had regularly visited medical institutions for the treatment of hypertension with antihypertensive medications Patients were a subset of those who had participated in a March 2020 online electronic survey of patients with hypertension	N = 2,392 patients Patients treated with antihypertensive medications and had home BP recordings available 66% male Mean (SD) age: 59.8 (± 11.6) y Mean (SD) duration of hypertension: 11.4 (±9.5) y **Uncontrolled office SBP (≥130 mmHg) or DBP (≥ 80 mmHg), n (%) = 1,964 (82%)**	Patient preference for treatment with renal denervation
Lin et al[97], 2024, Taiwan	Retrospective Survey circulated to patients taking and not taking antihypertensive medications, either in a clinic or during a hospital admission	N = 46 patients Mean (SD) duration of hypertension: 6.3 (± 1.5) y Mean SBP/DBP: 136.6/80.5 mmHg Nearly 50% of patients had organ damage, and 65% had experienced antihypertensive medication intolerance. **Patients with treatment-resistant hypertension were included; however, the number of patients was not reported**	Patient preference for treatment with renal denervation
Renna et al[98], 2025, Argentina	Prospective Online survey	206 out of 500 invited physicians responded Physicians were primarily cardiologists and internists, with an average of 10 y of professional experience	Physicians' attitudes and knowledge of renal denervation

Author, year, country	Study design and methods	Participants	Outcomes
Schmieder et al,[100] 2021, Europe and the United States	Retrospective Compilation of 19 market research studies (2 published, 17 unpublished internal market assessments) to study patient and physician attitudes to drug therapy and renal denervation for the management of hypertension	*Patients* 2,768 patients diagnosed with **hypertension, either treated or untreated with antihypertensive medications** 42.7% had had hypertension for > 10 y; 15% for more than 20 y 57.9% reported cardiovascular comorbidities Self-reported adherence rates were high: 81% considered themselves always to be adherent with their drug regimens, regardless of side effects or challenging treatment schedules. **The number of patients with treatment-resistant hypertension was not reported** *Physicians* 1,902 physicians who could be actively performing or were interested in performing device-based procedures for hypertension or hypertension specialists who might consider referring patients for a device-based intervention	Patient and physician preferences and attitudes
Zhang et al,[99] 2022, China	Prospective Survey of patients with hypertension who visited a hospital's cardiology department	N = 402 patients Mean (SD) age: 61 (± 12) y 53.9% male[a] Office SBP (SD)/DBP (SD): 138 (± 18)/81 (± 13) mmHg[a] Mean (SD) duration of hypertension: 6.0 (2.0–12.0) y 81.8% on antihypertensive medications[a] **The number of patients with treatment-resistant hypertension was not reported**	Patients' willingness to chose renal denervation Determinants of choosing renal denervation Patient expectations

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.
[a]Details about the descriptive statistics used were not provided by the authors (e.g., mean vs. median, standard deviation vs. standard error, range).

Patient Preferences, Satisfaction, and Values

Five studies reported on patient preferences, satisfaction, or values for renal denervation to treat hypertension (Table 19).[95-100] Three studies reported that approximately 31% to 35% of patients preferred to undergo renal denervation compared to drug therapy.[96,97,99] Two studies reported that patients who had experienced side effects from their antihypertensive medications had a higher preference for renal denervation compared to those who had not experienced side effects.[97,100] Two studies reported that younger patients and those who were less adherent to their medications preferred renal denervation over drug therapy.[96,99]

Kandazari et al[95] assessed patient preference using a discrete-choice experiment design and concluded that patients preferred noninterventional treatments (e.g., medication) over interventional treatments (e.g., renal denervation); however, a reduction of only 2.3 mm Hg in office systolic blood pressure was required to offset this preference. Further, the authors noted that risks of treatment-related adverse events were less influential on choice than was treatment efficacy.[95]

Table 19: Results and Limitations of Renal Denervation Studies Reporting Patient Preferences, Satisfaction, or Values

Author, year, country	Results	Limitations
Kandzari et al,[95] 2022	Reduction in office SBP was the attribute with the strongest influence on treatment choice. The other attributes had lower relative importance; in decreasing order, these were duration of effect, whether treatment was interventional, number of daily pills, risk of vascular injury,[a] and risk of drug side effects *Maximum acceptable risk* Maximum acceptable risk of *drug-related side effects or vascular injury* exceeded 20% for: • Every possible improvement in BP reduction • Every possible improvement in duration of effect • Noninterventional rather than an interventional treatment Maximum acceptable risk of *drug-related side effects* exceeded 20% for every possible reduction in number of BP pills per day Maximum acceptable risk of *vascular injury*[a] exceeded 20% only for reducing the number of BP pills per day from 3 to none *Minimum acceptable benefit* Respondents would require that treatment reduce office SBP by: • Anything > 0 mmHg in exchange for bearing an increase in the risks of *drug-related side effects* by 20% • 1.1 mmHg (95% CI, 0.6–1.6 mmHg) in exchange for bearing an increase in the risks of *vascular injury*[a] by 20% All other attributes being equal, respondents would prefer to avoid interventional treatments, yet only a mean reduction in office SBP of 2.3 mmHg (95% CI, 1.7–2.9 mmHg) was required to offset this preference Overall, the risks of treatment-related adverse events were less influential than treatment efficacy	People surveyed may not represent the broader population of people with uncontrolled hypertension Survey was conducted during the COVID-19 pandemic, and the influence of the pandemic on perceptions related to seeking health care is uncertain The study limited the total number of attributes assessed for a given treatment. Selected attributes were those considered most important to people with uncontrolled hypertension
Kario et al,[96] 2022, Japan	755/2,392 patients (31.6%) expressed a preference for RDN Patient preference for RDN did not vary significantly by number of antihypertensive medications taken, but a higher proportion of younger (< 60 y) versus older (> 60 y) patients preferred RDN (data reported in figure form only) Patient preference: 71% medication nonadherent (1,126/1,582) vs. 28.8% medication adherent (456/1,582), $P < 0.001$	Self-reported internet survey; source verification was not performed, and the sample may not be representative of all people with uncontrolled hypertension
Lin et al,[97] 2024, Taiwan	16/46 (34.8%) patients expressed a preference for RDN 16/16 (100%) patients relied on their physician as their primary source of information and had previously encountered side effects from antihypertensive medications	Unclear data reporting No data for patients who did not express preference for RDN Unclear how many surveys in total were distributed to patients in hospital

Author, year, country	Results	Limitations
Schmieder et al,[100] 2021, Europe and the United States	There was no statistically significant difference in the number of patients willing to undergo RDN between patients with SBP ≤ 130 mmHg and those with SBP ≥ 130 mmHg or ≥ 150 mmHg (P > 0.7 for both) (N = 1666 patients) There was a statistically significant difference in the number of patients willing to undergo RDN between patients not taking antihypertensive medications (57%) and those taking antihypertensive medications (43%) (P < 0.001, raw data not reported) (N = 1,717 patients) Patients who perceived high BP as a major problem had a statistically significantly higher preference for RDN than those who did not (P = 0.029, raw data not reported) Patients who experienced side effects attributed to their antihypertensive medications had a statistically significantly higher preference for RDN than those who had not (P = 0.006, raw data not reported) A statistically significantly greater proportion of patients with comorbidities were willing to consider RDN compared with antihypertensive medications (P = 0.049, raw data not reported) The promise of reduced BP with RDN was a driver of acceptance; approximately 1/3 of patients stated they would be influenced by experiences of other patients (raw data not reported).	Extremely unclear and sparse data reporting No standardized instrument to survey patients' preferences for hypertension management No standardized assessment of patients' educational level or socioeconomic status
Zhang et al,[99] 2022, China	131/402 (32.6%) patients were willing to choose RDN as a BP control strategy *Patient characteristics, those who chose RDN (n = 131) vs. those who did not (n = 271), mean (SD):* • Mean (SD) age: 54 (± 12) y vs. 65 (± 11) y, P < 0.001 • Mean office SBP (SD): 148 (± 20) mmHg vs. 134 (± 16) mmHg, P < 0.001 • Mean office DBP (SD): 86 (± 15) mmHg vs. 78 (± 11) mmHg, P < 0.001 Overall, patients who chose RDN were younger and had a higher SBP and DBP than those who did not *Determinants of choosing RDN* • Physician's recommendation: 125/131 (95.4%) • If RDN would reduce number of pills per day: 86/131 (65.6%) • If RDN would allow for ideal blood pressure control to be achieved: 59/131 (45.0%) • If RDN would eliminate need for antihypertensive medications: 34/131 (26.0%) • Regularly forgetting to take antihypertensive medications: 27/131 (20.6%)	Information about demographics and cardiovascular comorbidities primarily collected via self-report Patients with hypertension visiting other hospital departments not included; thus, possibility of selection bias since patients with hypertension may visit cardiology department more frequently than other departments Most patients (81.8%) were already on antihypertensive medications Some patients may have had secondary hypertension

Abbreviations: BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; RDN, renal denervation; SBP, systolic blood pressure; SD, standard deviation.

[a]Due to an interventional treatment (i.e., renal denervation).

Physician Preferences, Satisfaction, and Values

Two studies reported on physician preferences, satisfaction, or values for renal denervation for patients with hypertension (Table 20).[98,100] Overall, physicians were likely to recommend renal denervation for patients who had high systolic blood pressure (≥ 140 mmHg) or treatment-resistant hypertension. One study reported that physicians were more likely to recommend renal denervation for patients who had high systolic blood pressure (≥ 140 mmHg) and were taking 3 or more antihypertensive medications.[100]

Table 20: Results and Limitations of Renal Denervation Studies Reporting Physician Preferences, Satisfaction, or Values

Author, year, country	Results	Limitations
Renna et al,[98] 2025, Argentina	120/206 (58.1%) physicians considered RDN a viable therapeutic option for treatment-resistant hypertension 124/206 (60%) physicians believed that RDN is safe 68/206 (33.2%) physicians were uncertain about the safety of RDN 14/206 (6.8%) physicians did not consider RDN safe	The low survey response rate (40%) may indicate that physicians who are more engaged or have stronger opinions about RDN may have been more likely to respond. Thus, the generalizability of results to the broader population of physicians may be limited Most responses came from physicians in major urban areas; thus, the findings may not fully represent the geographical diversity of physicians across the entire country
Schmieder et al,[100] 2021, Europe and the United States	Overall, physicians were more likely to recommend RDN for patients with higher SBP (≥ 140 mmHg) and taking 3 or more antihypertensive medications (statistical testing not reported) Physicians reported hurdles to increasing the uptake of RDN in Europe. Reasons for lack of uptake as reported by the surveyed physicians (347 interventional cardiologists and 257 referral cardiologists) include the following: • Patient refuses procedure (interventional cardiologists: 38%; referral cardiologists: 42%) • Inadequate guideline support (interventional cardiologists: 30%; referral cardiologists: 30%) • Stronger supporting data needed (interventional cardiologists: 28%; referral cardiologists: 29%) • More support from peer community needed (interventional cardiologists: 26%; referral cardiologists: 32%) • Cost concerns (interventional cardiologists: 33%; referral cardiologists: 25%)	Unclear and sparse data reporting

Abbreviations: RDN, renal denervation; SBP, systolic blood pressure.

Discussion

Of the 6 studies identified in our literature search, 1 used a discrete-choice experiment design,[95] 4 studies used surveys,[96-99] and 1 study[100] used published and unpublished market reports.

There was variability across studies in the number of participants with treatment-resistant hypertension. For example, in the study by Kandzari et al,[95] all participants had physician-confirmed uncontrolled hypertension.[95] In the study by Kario et al,[96] 82% of participants had uncontrolled office systolic blood pressure. In the other studies, the proportion of patients with treatment-resistant hypertension was not reported.[97,99,100]

From previously published clinical trial end points, Kandzari et al[95] identified hypertension-related outcomes that they considered salient for clinicians and patients. (However, it is unclear whether the authors performed a systematic literature search to obtain their included trials.) From those outcomes, they identified 7 attributes that they considered most important to patients, but it is unclear whether such attributes (e.g., office systolic blood pressure) are considered most important by patients themselves.

Approximately 30% of respondents included in the studies expressed a preference for renal denervation, and younger patients were more likely to prefer renal denervation than older patients.[96,97,99] It is possible that younger patients may be more motivated than older ones to avoid the need for long-term antihypertensive medications and regular physician visits.[96]

Two studies reported that patients with poor adherence to antihypertensive medications preferred renal denervation.[96,99] One possible reason for this is that patients who struggle to adhere to their drug regimen may prefer a treatment that would mean a reduction in medications or eliminate the need for medications altogether.[96] However, patients may still need to take antihypertensive medications after undergoing renal denervation. Indeed, inconsistent adherence to prescribed drugs after the procedure has been reported,[101] as has frequent nonadherence to antihypertensive medications.[96] Two studies reported that patients who had experienced side effects from antihypertensive medications had a higher preference for renal denervation compared with those who had not.[97,100] However, as mentioned, patients may still require antihypertensive medications following renal denervation.

Two studies reported physician preferences for renal denervation.[98,100] One study[98] stated that most physicians considered renal denervation a viable option for treatment-resistant hypertension. The other study[100] reported that physicians were more likely to recommend renal denervation for patients with high systolic blood pressure (≥ 140 mmHg) and for those taking 3 or more antihypertensive medications.

Conclusions

Approximately 30% of patients in the included studies preferred renal denervation over drug therapy. Patients who preferred renal denervation were typically younger and had poor adherence to their antihypertensive medications. Physicians were likely to recommend renal denervation for patients with high systolic blood pressure (≥ 140 mmHg) and for those taking 3 or more antihypertensive medications.

Direct Patient Engagement

Methods

Partnership Plan

The partnership plan for this health technology assessment focused on consultation to examine the experiences of adults with uncontrolled hypertension and those of their families and care partners. We engaged people via telephone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with uncontrolled hypertension, as well as those of their families and care partners.[102] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

Participant Outreach

We used an approach called purposive sampling,[103-106] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of clinical experts to spread the word about this engagement activity and to contact people with uncontrolled hypertension, along with family members and care partners, including those with experience of renal denervation.

Inclusion Criteria

We sought to speak with adults with lived experience of hypertension and with care partners. We included those with and without direct experience of renal denervation.

Exclusion Criteria

We did not set exclusion criteria.

Participants

For this project, we spoke with 10 adults with hypertension, 5 of whom had undergone renal denervation. We also spoke with 1 care partner of a person who had undergone renal denervation.

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 8). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 30 to 60 minutes. The interview was semi-structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[107] Questions focused on the impact of hypertension on the quality of life of people with hypertension, their experiences with treatments to manage hypertension, their experiences with renal denervation, their perceptions of the benefits or limitations of renal denervation, and the impact of the person's health condition and treatments on family members and caregivers. See Appendix 9 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[108,109] We used the qualitative data analysis software program NVivo[110] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impacts of hypertension on the people we interviewed.

Results

Hypertension Diagnosis

Most participants noted that they had no symptoms of hypertension prior to their diagnosis other than occasional high blood pressure readings. Because of this, many had not sought further care. Participants shared various experiences of diagnosis. For some, the diagnosis came during a routine check-up. However, most reported a history of high blood pressure readings attributed to "white-coat syndrome"

(i.e., high blood pressure readings only when in a clinical setting). Others discovered their hypertension after a more serious medical event (e.g., a cardiac arrest) in which hypertension may have played a role. In cases where there were barriers in accessing a primary care physician, obtaining a diagnosis posed a challenge.

> *I didn't have any symptoms. I never had anything. I just checked my blood pressure, and it was really high.*
>
> *Because of the stroke, which was directly related to high blood pressure…that changed everything. I lost my job; I lost my ability to drive.*
>
> *I probably had many years of [blood pressure] readings being high, and it was just chalked up to white-coat syndrome.*
>
> *I often will go to another town for a walk-in clinic if I need something that's pretty minor.…I would say probably [for] 14 to 15 years, any time that I've been having blood pressure taken, it's always been high, and it's never been really recommended to follow up on.*

A few participants reported having symptoms such as fatigue, swelling, headaches, and dizziness that prompted them to investigate further and led to their hypertension diagnosis.

> *I was getting a lot of headaches and just generally not feeling all that great.*
>
> *I was a little bit tired and not full of energy.*

Care Journey

After being diagnosed with hypertension, participants shared the health behaviour modifications they made to manage or lower their blood pressure as guided by their health care providers. Their blood pressure was regularly monitored to assess the effectiveness of these changes. Health behaviour modifications typically included actively monitoring their blood pressure, adjusting their diet, and increasing their exercise levels. All participants noted that they were unable to manage their blood pressure with health behaviour modifications alone and had to supplement those changes with antihypertensive medications.

> *I had to cut out salt. I had to reduce alcohol intake, and I [now] exercise on a regular basis.*
>
> *I started to try exercise and lose some weight and diet. Almost everything I could possibly think of, I did.…[I] cut out alcohol, cut out stimulants. I haven't had a drink in years. I stopped drinking any kind of stimulant, like coffee.*

People we spoke with who had experienced barriers to accessing a primary care physician reported a lack of guidance about how to manage their hypertension with health behaviour modifications.

> *I have so little education about blood pressure.…Actually, I don't even know how dangerous it is or what the effects are for me in my day-to-day life.*

Participants shared that managing their hypertension required frequent visits to multiple health care providers, including their primary care physician and hypertension specialists. These appointments, while necessary for monitoring and adjusting treatment, were time-consuming and often overwhelming. In many cases, more frequent appointments were required because of uncontrolled hypertension and the need for medication adjustments. Many participants expressed frustration with the constant need to coordinate multiple visits. Some participants had to take time off work, particularly when visiting specialists, as appointments outside regular business hours were often unavailable.

> *[Appointments] would be every 2 weeks when it [blood pressure] was not well controlled and when I got complications. Sometimes it would be every couple of months.*
>
> *It's time-consuming. I had to take time off work to bring him to the appointments.*
>
> *When it [blood pressure] was really, really high, they had me coming in once a week to check if it was coming down.*

Participants shared their experiences of trialing various medications and dosages to manage their blood pressure. This trial-and-error process often meant frequent doctor's visits as they worked closely with their health care providers to evaluate each medication's effectiveness and manage side effects. Some commented on the amount of medication they take for other chronic conditions in addition to their antihypertensive medications.

> *The medication started with 1 tablet. Then they strengthened it, and it worked its way over time to 4 tablets a day until this year. I have been up to 5 blood pressure tablets a day.*
>
> *I'm constantly having my blood pressure checked. And as it got more controlled, medications were dropped and some were added on.*
>
> *I'm taking 8 pills, and 3 of them are for blood pressure.*

Most participants said that the cost of medication was not a substantial barrier, primarily because most expenses were covered through private health insurance or the Ontario Drug Benefit program. Participants with private health insurance expressed gratitude for it and noted that it would have been a financial burden without it, especially when trialing various medications.

> *[My medications are] covered through my benefits plan through my employer.*
>
> *[My medications have been] covered by the province since I was 65.*
>
> *I don't think we would have been able to afford it without the private insurance because for a long time we were experimenting with different medications to try to bring it under control. Some were working; some weren't.*

However, those without such coverage reported that paying for their medications out of pocket was a financial burden. Concerns were expressed regarding changes in employment status affecting access to private health insurance coverage.

> *I have no coverage whatsoever.…I'm a single parent, [so] every expense that you can think of is on me to take care of. So it's not easy.*
>
> *In the future, we're going to be self-employed, so it's not going to be covered, and I'll be paying out of pocket.*

A few participants reported experiencing side effects with their antihypertensive medications, and these varied from person to person. While some noted mild symptoms such as dizziness, fatigue, or frequent urination at night, others reported more pronounced effects, such as swelling and mood changes.

> *The main side effects for 1 of the medications were nausea, fatigue, body aches, and swelling of the leg. He was experiencing all of those.*
>
> *I got bad tempered with 1 of [the medications]; it seemed to be consistent with that pill.*
>
> *When I'm doing physically demanding activities, especially if it's warmer weather, the medication can make you feel dizzy to the point where you really [need to] be careful you don't pass out. And you're up a couple or 3 times during the night to use the bathroom.*

Most participants commented on their medication adherence, with many saying that they take their medication as directed by their health care providers. They generally expressed confidence in their regimens. However, a few participants reported encountering challenges in maintaining strict adherence.

> *I'm really good at listening to what my doctor tells me to do, so I didn't have a problem taking the medication.*
>
> *I'm a pretty regimented person, so I'm pretty good at taking my pills.*
>
> *There are lots of days I don't take my medication.…Getting into the routine of anything has always been hard for me.*

Most participants reported that hypertension took a toll on their mental health. The idea of hypertension being a "silent killer" was frequently mentioned, and this concept was a constant source of worry and anxiety for many. The fear of the potential long-term effects of hypertension, such as a heart attack, stroke, and death, weighed on their minds and contributed to their stress and feelings of unease.

> *I have concerns with high blood pressure being known as "the silent killer" through heart attacks or stroke; that was always in the back of my mind.*
>
> *It often shortens people's lives, right? It can take somebody very young, and there are obviously big implications if you die.…I guess your likelihood of heart attack and stroke is exponentially higher when you have high blood pressure.*

Renal Denervation Decision-Making

Most participants were unaware of renal denervation for the treatment of uncontrolled hypertension before being informed about it when we contacted them for our analysis. Most individuals who had experience with the procedure learned about it only when their health care provider presented it as an option. Those with prior knowledge of renal denervation had discovered it through online research.

> *No, I've never heard of that before. It was completely new to me, and it was very interesting. I did not know that it existed.*

> *I learned about it online, and the procedure had fabulous results in [the United Kingdom].*

Participants reflected on the factors they would need to evaluate when considering whether to undergo renal denervation, and they reported seeking guidance from their health care provider before deciding whether renal denervation was a good option for them. Decision-making factors included risks versus benefits, recovery time, and patient testimonials.

> *I would need to be able to have a conversation with the specialist to discuss the risks versus the rewards with the procedure.*

> *I've heard mainly positive stuff, so I probably want to hear about the side effects and recovery.*

> *The lived experience is always powerful – so [learning about] a patient's experience, [from someone] who underwent this procedure, hearing their story or their journey and how it's affected their life. That would definitely be something that would be helpful for me.*

When discussing renal denervation with their health care providers, participants considered factors such as their ongoing struggle with uncontrolled hypertension, which they had been trying to manage for years, and the amount of medication they were taking, as well as side effects they had experienced. They reported that their physicians managed their expectations, explaining that renal denervation would not guarantee a reduction in medication. But it was ultimately seen as a potential option to help manage blood pressure.

> *They were able to get my blood pressure down to a little bit more normal, but I've never hit normal for years and years, and I was on 4 or 5 different medications to try to control it. It was still higher than they wanted…so at a point they talked to me about this other surgery.*

> *One of the reasons they wanted him to do this surgery is they needed to get his blood pressure under control and get him off the medications causing the negative side effects, so he can have some quality of life.*

> *If you can't control it with medication, and you don't have anything else you can control it with, at least this is another viable option that can give people their life back and take away that stress and anxiety of having a stroke one day or [having] your kidneys…fail.*

Participants' views regarding the invasiveness of the procedure varied. Those who had undergone renal denervation reported having concerns about the invasiveness but said they had been reassured about of the safety of the procedure by their health care providers. Some with direct experience of renal denervation said that they had had no concerns.

> *I've had 2 stents installed. Not quite the same procedure [as renal denervation], but a similar procedure, so I wasn't concerned, and the doctor did explain all the risks and so forth to me.*
>
> *I was concerned about where they had to go in, what they were going to be doing. But the doctor explained everything very well to both of us; [they] explained it's relatively low risk considering what's being done.*
>
> *It is a scary procedure when you think about it. Any kind of surgery, you're going to be nervous about it. I was nervous about this. They do go into one of your major veins.*

Participants who had not undergone renal denervation were generally positive toward the procedure and its potential impact. However, they said it would be their last option, after alternative, less invasive interventions such as health behaviour modifications and antihypertensive medications proved unable to control their hypertension. They also mentioned that they would look to their doctor for guidance on whether they would be an ideal candidate for renal denervation. A few were interested in the procedure to reduce their pill burden.

> *[With] any medical procedure, there is a risk. And only if absolutely necessary would I do it.*
>
> *[You would consider renal denervation] if your doctor said that you needed it, and there was no other way to control your blood pressure.*
>
> *I didn't see a problem with it because it is minimally invasive.*
>
> *I would also be interested in it so that I wouldn't have to take as many pills or pills in general. That's another one of the things that adds to my stress.*

For participants who had undergone renal denervation, the time since their procedure ranged between 2 weeks to over 2 years. They all reported feeling that they had been well informed about the procedure and that it had met their expectations. They described it as a relatively straightforward procedure that required imaging prior to the procedure and an overnight hospital stay for recovery and monitoring.

> *It was not a big deal at all. They gave me instructions on where to go, and I went, and they put me under. [I] had the procedure done, and they kept me overnight.*
>
> *It was really quite simple. I was a little bit bruised afterwards, but that's no big deal.*

All participants with direct experience of renal denervation reported a noticeable reduction in their blood pressure following the procedure. Many reported seeing substantial improvements in their blood pressure, which had previously been difficult to control despite health behaviour modifications and

antihypertensive medications. For some, this reduction was immediate, whereas others noticed gradual improvements over time. Most expressed relief and satisfaction with the outcome, as they had struggled with uncontrolled hypertension for years.

> *The amount of medication didn't change, but my blood pressure has come down. I was around 160/70 [mmHg], and now I'm averaging about 145/60 [mmHg].*

> *It usually ran from 179 to 184 [mmHg]…when it was spiking, it was sometimes up to 212/111 [mmHg]. The first 3 to 6 months [after the procedure], my blood pressure was spiking a little bit; then it would come down a little bit more; then it would spike up and come down. Apparently, that's pretty normal. If we were to look at the average now since the surgery, it would be around 135/80 [mmHg], which is kind of a little bit higher than the target they're aiming for but way better than it used to be.*

> *I have a blood pressure monitor at home….When I [use it], the 2 lights come up with the numbers; they come up green where it used to come up orange and red before the procedure[i.e., blood pressure is now under control].*

For some participants, despite the noticeable improvement in their blood pressure, the amount of medication they were taking had remained the same. However, because some had undergone the procedure only within the last 6 months, there may be some changes in medication in the future.

> *The amount of medication didn't change, but my blood pressure has come down.*

> *I'm still taking relatively the same amount of medication with some adjustments. But that's why I'm going back to the doctor; he's adjusting the pills. I'd like to get off a few more, but I think that might take a bit of time.*

For others, however, the reduction in blood pressure following renal denervation allowed them to lower the number of medications they were taking. These participants reported being able to reduce the dosage or frequency of certain medications or, in some cases, eliminate a few medications entirely. This had a positive impact for those who had experienced medication side effects.

> *I'm very, very happy with the procedure, going from 5 tablets down to 1 tablet.*

> *I was on 4 different blood pressure medications; I'm now on 3 of them. The 1 that I lost had the most side effects, and I think that's a pretty expensive drug.*

Participants who had undergone renal denervation commonly reported a substantial reduction in the frequency of their medical appointments. Before the procedure, many had experienced unstable or poorly controlled hypertension, which required frequent appointments for monitoring, sometimes as often as biweekly or weekly. They noted that after undergoing renal denervation, their blood pressure became more stable and manageable. As a result, the need for check-ins was reduced, with most reporting needing only biannual or annual doctor's visits.

> *I got released back [from a hypertension specialist] to my family doctor because at that point, my blood pressure [was] under control, and I figure I'll probably have to see them [the hypertension specialist] once a year.*

> *I see my doctor, I think, every year now. The appointments have gone down significantly.*

People we spoke with reported experiencing peace of mind after getting their blood pressure under control following renal denervation**,** noting the relief they felt from the reduced risk of serious cardiovascular events like heart attack and stroke. Many referred to hypertension as a "silent killer" and expressed how the constant worry about its long-term effects had been emotionally taxing.

> *The quality of life. Psychologically, I feel much better because the risk of me having a stroke is significantly down. I don't like the concept of a stroke and then lying around where you can't speak and you can't talk and you can't walk. I don't want to live like that.*

> *It certainly puts [my] mind at ease knowing that I'm in a better place. My blood pressures in a better place. It puts the thoughts of [having] a stroke or heart attack a little more at ease.*

A few participants who had experienced hypertension symptoms like headaches, fatigue, and swelling reported that these improved or disappeared after effectively managing their blood pressure.

> *The swelling in my legs has gone down, so it's not painful [to] walk anymore. The daily headaches have gone away.*

> *He's been more active than he's ever been…he's feeling better mentally, emotionally, and physically through all of this.*

Barriers to Accessing Renal Denervation

One barrier to accessing renal denervation noted by participants was lack of awareness of the procedure. They stated that they did not become aware of this procedure until it was brought to their attention by their health care provider. Most of those who had not undergone the procedure were unaware of it as a treatment option.

Geography was also mentioned as a barrier to accessing to renal denervation since it is currently available only in Toronto. Participants residing in the Greater Toronto Area expressed gratitude for being able to access renal denervation. Those who lived farther away said they would be willing to travel to Toronto to access it. One participant mentioned travelling a substantial distance to access the procedure.

> *I had no worries at all [about] going to Toronto. But if the system is rolled out, and it can help people in my city with the condition that I had, that would be absolutely awesome.*

> *It's 100 kilometres between [my city] and Toronto.*

Discussion

Direct engagement with people with lived experience of hypertension allowed us to gather diverse perspectives and thoroughly examine their preferences and values, the factors that influenced their

decision-making regarding treatment, and the impact of renal denervation on their health and quality of life. All participants shared their experiences with diagnosis and their treatment journeys.

Participants mentioned concerns over the long-term risks of hypertension and often referred to hypertension as a "silent killer." Thus, they spoke positively about renal denervation as a treatment option when health behaviour modifications and antihypertensive medications fail to effectively lower blood pressure. Another perceived benefit of renal denervation was that it might provide an alternative to antihypertensive medications for those who experience medication side effects or who take many medications. However, as mentioned, renal denervation does not guarantee a reduction in the need for antihypertensive medications.

One limitation of our review was the limited representation of people who had undergone renal denervation, which was likely due to the procedure currently being available only at 2 centres in Toronto, as well as lack of awareness of the procedure among both health care professionals and people with uncontrolled hypertension. Additionally, we had limited perspectives from rural communities and no representation from Northern Ontario. Another limitation is that most participants who had undergone renal denervation had done so only within the past year, so the long-term impact of the treatment remains unclear.

Conclusions

Renal denervation was viewed favourably by all those we interviewed. Those with experience of renal denervation reported a reduction in their blood pressure and fewer doctor's visits. Some also saw a reduction in their antihypertensive medications. The procedure offered peace of mind to those who now have their blood pressure under control. Those who had not undergone renal denervation mentioned being open to the procedure if it were recommended by their health care provider after they had been unable to control their blood pressure with health behaviour modifications and antihypertensive medications. A few expressed interest in the procedure to reduce their medication burden (though renal denervation does not guarantee a reduction in medications). Barriers to accessing renal denervation included lack of awareness and geography. Participants emphasized that implementation should require equitable access.

Preferences and Values Evidence Discussion

Findings from our review of the quantitative evidence of patient and provider preferences and values and from our direct engagement with adults with hypertension highlight renal denervation as a potential treatment option for adults with uncontrolled hypertension. Both sources also reported that physician recommendation strongly influenced patients' openness to the procedure.

The literature review found that about 30% of patients preferred renal denervation over drug therapy, with younger individuals and those with poor medication adherence more likely to favour it. In contrast, direct patient engagement revealed strong support for renal denervation among all participants, particularly as a last resort when other treatments have failed; however, a few participants also reported being open to renal denervation if it could reduce their medication burden.

Two limitations of the direct patient engagement were the low representation of individuals who had undergone renal denervation and the limited number of participants. The quantitative studies included

larger numbers of participants with hypertension (though not all had uncontrolled hypertension) but did not capture the perspectives of those who had undergone renal denervation.

Equity Considerations

Access to renal denervation in Ontario is currently limited, with the procedure available at only 2 centres in Toronto. This presents equity concerns for those living in rural, remote, or Northern regions of the province who may face travel, cost, and logistical barriers to accessing renal denervation.

Preferences and Values Evidence Conclusions

Our review of the quantitative evidence of patient and provider preferences and values revealed that approximately 30% of patients in the included studies preferred renal denervation over drug therapy. Patients who preferred renal denervation were typically younger and had poor adherence to their antihypertensive medications. Physicians were likely to recommend renal denervation for patients with high systolic blood pressure (≥ 140 mmHg) and for those taking 3 or more antihypertensive medications.

All participants interviewed through direct engagement expressed a positive view of renal denervation. Those who had undergone the procedure reported experiencing lower blood pressure, fewer doctor's visits, and increased peace of mind compared with those who had not, with some also noting a reduction in their medication use. Others expressed willingness to consider the procedure if it were recommended by a physician following unsuccessful attempts to manage their hypertension through lifestyle changes and medication. Identified barriers included limited awareness of the procedure and limited geographic access.

Conclusions of the Health Technology Assessment

Our overview of reviews of the clinical evidence found that adults with uncontrolled hypertension, including those with treatment-resistant hypertension, who had undergone renal denervation experienced a greater reduction in systolic blood pressure compared with those who had not. Direct clinical outcomes like hypertensive crisis, myocardial infarction, heart failure, ischemic stroke, renal function or failure, health care use, and quality of life were not explicitly reported in the included reviews. No statistically significant differences in safety outcomes were reported between groups.

Our economic analysis showed that in adults with uncontrolled hypertension, renal denervation in addition to standard care is more effective and more expensive than standard care alone, with an incremental cost-effectiveness ratio of $121,237 per QALY gained over a lifetime horizon. The probability of renal denervation in addition to standard care being cost-effective compared with standard care alone was 18.02% at a WTP of $100,000 per QALY gained and 80.50% at a WTP of $150,000 per QALY gained. We estimate that publicly funding renal denervation for adults with uncontrolled hypertension in Ontario over 5 years would result in additional annual costs ranging from $0.42 million in year 1 to $3.78 million in year 5, for a total of $8.87 million.

Our review of the quantitative evidence of patient and provider preferences and values revealed that approximately 30% of patients in the included studies preferred renal denervation over drug therapy. Patients who preferred renal denervation were typically younger and had poor adherence to their medication regimens. Physicians were likely to recommend renal denervation for patients with high systolic blood pressure (≥ 140 mmHg) and for those taking 3 or more antihypertensive medications.

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Abbreviations

AHA: American Heart Association

BMI: body mass index

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

CI: confidence interval

CT: computerized tomography

DBP: diastolic blood pressure

eGFR: estimated glomerular filtration rate

ESC: European Society of Cardiology

FDA: US Food and Drug Administration

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

HTW: Health Technology Wales

ICER: incremental cost-effectiveness ratio

MD: mean difference

NICE: National Institute for Health and Care Excellence

OR: odds ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: quality-adjusted life-year

QUADAS: Quality Assessment of Diagnostic Accuracy Studies

RCP: Regional Cardiac Program

RCT: randomized controlled trial

RoB: Cochrane Risk-of-Bias Tool for Randomized Trials

ROBIS: Risk of Bias in Systematic Reviews

RR: relative risk

SBP: systolic blood pressure

SD: standard deviation

WTP: willingness-to-pay

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Base case: In economic evaluations, the base case is the "best guess" scenario, including any assumptions, considered most likely to be accurate. In health technology assessments conducted by Ontario Health, the reference case is used as the base case.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness acceptability curve: In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost-effectiveness plane: In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Deterministic sensitivity analysis: Deterministic sensitivity analysis is an approach used to explore uncertainty in the results of an economic evaluation by varying parameter values to observe the potential impact on the cost-effectiveness of the health care intervention of interest. One-way sensitivity analysis accounts for uncertainty in parameter values one at a time, whereas multiway sensitivity analysis accounts for uncertainty in a combination of parameter values simultaneously.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[111] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Health inequity: Health inequities are avoidable inequalities in health between groups of people within countries and between countries.[112] These inequities arise from inequalities within and between societies. Social and economic conditions and their effects on people's lives determine their risk of illness and the actions taken to prevent them becoming ill or treat illness when it occurs.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Markov model: A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Risk difference: Risk difference is the difference in the risk of an outcome occurring between one health care intervention and an alternative intervention.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses involve varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Societal perspective: The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the

aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).

Standard gamble: In economic evaluations, standard gamble is a direct method of measuring people's preferences for various health states. In a standard gamble, respondents are asked about their preference for either (a) remaining in a certain health state for the rest of their life, or (b) a gamble scenario in which there is a chance of having optimal health for the rest of one's life but also a chance of dying immediately. Respondents are surveyed repeatedly, with the risk of immediate death varying each time (e.g., 75% chance of optimal health, 25% chance of immediate death) until they are indifferent about their choice. The standard gamble is considered the gold standard for eliciting preferences as it incorporates individual risk attitudes, unlike other methods of eliciting preferences.

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: December 13, 2024

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2024>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 4, 2024>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2024 Week 49>, Ovid MEDLINE(R) ALL <1946 to December 12, 2024>

Search strategy:

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1 exp Hypertension/ (1398054)
2 (hypertens* or antihypertens* or HTN).ti,ab,kf,jn. (1527264)
3 (((high* or elevat* or increas* or rais* or resistant* or uncontrol* or reduc* or lower* or decreas* or refractor* or white coat* or adheren* or toleran* or intoleran* or MDI or MDIS or ambulatory or office) adj3 (blood pressure* or BP or arterial* or diastolic* or DBP or systolic* or SBP)) or TRH or RHTN).ti,ab,kf. (632866)
4 or/1-3 (2368130)
5 Denervation/ (31139)
6 Sympathectomy/ (16196)
7 (denervat* or sympathectom*).ti,ab,kf. (84897)
8 ((kidney* or renal or nephro* or transcatheter* or catheter* or radiofrequen* or radio frequen* or sympathetic* or ultrasound* or alcohol* or ethanol*) adj6 denerv*).ti,ab,kf. (17367)
9 catheter ablation/ (88689)
10 radiofrequency ablation/ (50381)
11 (((radiofrequenc* or radio frequenc*) adj3 (ablat* or catheter* or transcatheter* or probe* or kidney* or renal or nephro*)) or RDN or RSD).ti,ab,kf. (130145)
12 ((ultrasound* or ultra sound* or alcohol* or ethanol* or kidney* or renal or nephro*) adj3 (ablat* or catheter* or transcatheter*)).ti,ab,kf. (28193)
13 or/5-12 (318116)
14 4 and 13 (23843)
15 (Symplicity* or Spyral* or Vessix* or Enlightn* or HTN ON-MED* or HTN OFF-MED* or (Recor* adj4 Paradise*) or Iberis* or Tivus* or Symapcath* or Confidenht* or Renlane*).ti,ab,kf. (1867)
16 or/14-15 (24165)
17 16 use coch,cctr,cleed (945)
18 Clinical Trials as Topic/ (350410)
19 controlled clinical trials as topic/ (18626)
20 exp Randomized Controlled Trials as Topic/ (518936)
21 controlled clinical trial.pt. (95662)

22 randomized controlled trial.pt. (628276)
23 Pragmatic Clinical Trial.pt. (2493)
24 Random Allocation/ (228951)
25 Single-Blind Method/ (117589)
26 Double-Blind Method/ (554257)
27 Placebos/ (413076)
28 trial.ti. (1233381)
29 (random* or sham or placebo* or RCT*1).ti,ab,kf. (5575225)
30 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,kf. (845483)
31 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,kf. (7854)
32 or/18-31 (6669751)
33 16 and 32 (5554)
34 33 use medall (1579)
35 (Systematic Reviews or Meta Analysis).pt. (212215)
36 Systematic Review/ or Systematic Reviews as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (1133566)
37 ((systematic* or methodologic*) adj3 (review* or overview*)).ti,ab,kf. (871459)
38 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf. (796714)
39 (evidence adj2 (review* or overview* or synthes#s)).ti,ab,kf. (113053)
40 (review of reviews or overview of reviews).ti,ab,kf. (3089)
41 umbrella review*.ti,ab,kf. (4917)
42 GRADE Approach/ (5221)
43 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).ti,ab,kf. (746664)
44 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (903899)
45 cochrane.ti,ab,kf. (380146)
46 (meta regress* or metaregress*).ti,ab,kf. (39342)
47 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).ti,ab,kf. (46404)
48 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (81297)
49 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).ti,ab,kf. (75907)
50 or/35-49 (2157750)
51 16 and 50 (1077)
52 51 use medall (262)
53 17 or 34 or 52 (2633)
54 exp Animals/ not Humans/ (16666475)
55 53 not 54 (1941)
56 Case Reports/ or Comment.pt. or Congress.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. (6834596)
57 55 not 56 (1840)
58 limit 57 to english language [Limit not valid in CDSR; records were retained] (1741)
59 limit 58 to yr="2023 -Current" (251)

60 exp hypertension/ (1398054)
61 (hypertens* or antihypertens* or HTN).tw,kw,kf. (1516692)
62 (((high* or elevat* or increas* or rais* or resistant* or uncontrol* or reduc* or lower* or decreas* or refractor* or white coat* or adheren* or toleran* or intoleran* or MDI or MDIS or ambulatory or office) adj3 (blood pressure* or BP or arterial* or diastolic* or DBP or systolic* or SBP)) or TRH or RHTN).tw,kw,kf. (635901)
63 or/60-62 (2366703)
64 kidney denervation/ (5450)
65 denervation/ (31139)
66 sympathectomy/ (16196)
67 (denervat* or sympathectom*).tw,kw,kf,dv,dm,mv. (85022)
68 ((kidney* or renal or nephro* or transcatheter* or catheter* or radiofrequen* or radio frequen* or sympathetic* or ultrasound* or alcohol* or ethanol*) adj6 denerv*).ti,ab,kf. (17367)
69 radiofrequency catheter ablation/ (46570)
70 catheter ablation/ (88689)
71 radiofrequency ablation/ (50381)
72 (((radiofrequenc* or radio frequenc*) adj3 (ablat* or catheter* or transcatheter* or probe* or kidney* or renal or nephro*)) or RDN or RSD).tw,kw,kf,dv,dm,mv. (131559)
73 ((ultrasound* or ultra sound* or alcohol* or ethanol* or kidney* or renal or nephro*) adj3 (ablat* or catheter* or transcatheter*)).tw,kw,kf,dv,dm,mv. (30281)
74 or/64-73 (321803)
75 63 and 74 (24462)
76 (Symplicity* or Spyral* or Vessix* or Enlightn* or HTN ON-MED* or HTN OFF-MED* or (Recor* adj4 Paradise*) or Iberis* or Tivus* or Symapcath* or Confidenht* or Renlane*).tw,kw,kf,dv,dm,mv. (2109)
77 or/75-76 (24801)
78 "clinical trial (topic)"/ (135268)
79 "controlled clinical trial (topic)"/ (13655)
80 "randomized controlled trial (topic)"/ (286282)
81 randomization/ (234187)
82 Single Blind Procedure/ (57109)
83 Double Blind Procedure/ (223196)
84 placebo/ (406708)
85 trial.ti. (1233381)
86 (random* or sham or placebo* or RCT*1).tw,kw,kf. (5642916)
87 ((singl* or doubl*) adj (blind* or dumm* or mask*)).tw,kw,kf. (885871)
88 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).tw,kw,kf. (8510)
89 or/78-88 (6378648)
90 77 and 89 (5733)
91 Systematic review/ or "systematic review (topic)"/ or exp Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (1100363)
Annotation: Added Systematic review/ or "systematic review (topic)"/ for thoroughness, but these may add many results. Will monitor
92 (meta analy* or metaanaly* or health technolog* assess* or systematic review*).hw. (1121980)
93 ((systematic* or methodologic*) adj3 (review* or overview*)).tw,kw,kf. (886065)
94 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw,kw,kf. (810871)
95 (evidence adj2 (review* or overview* or synthes#s)).tw,kw,kf. (115556)

96 (review of reviews or overview of reviews).tw,kw,kf. (3317)
97 umbrella review*.tw,kw,kf. (4951)
98 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).tw,kw,kf. (756356)
99 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (903899)
100 cochrane.tw,kw,kf. (383809)
101 (meta regress* or metaregress*).tw,kw,kf. (40361)
102 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).tw,kw,kf. (47548)
103 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (81297)
104 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).tw,kw,kf. (115433)
105 or/91-104 (2203600)
106 77 and 105 (1226)
107 90 or 106 (6174)
108 107 use emez (3785)
109 (exp animal/ or nonhuman/) not exp human/ (12352692)
110 108 not 109 (2842)
111 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (12068602)
112 110 not 111 (1868)
113 limit 112 to english language [Limit not valid in CDSR; records were retained] (1766)
114 limit 113 to yr="2023 -Current" (318)
115 59 or 114 (569)
116 115 use medall (148)
117 115 use emez (318)
118 115 use cctr (103)
119 115 use coch (0)
120 115 use cleed (0)
121 remove duplicates from 115 (400)

Economic Evidence Search

Search date: December 5, 2024

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2024>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 4, 2024>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2024 Week 48>, Ovid MEDLINE(R) ALL <1946 to December 04, 2024>

Search strategy:

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1 exp Hypertension/ (1395378)
2 (hypertens* or antihypertens* or HTN).ti,ab,kf,jn. (1524886)
3 (((high* or elevat* or increas* or rais* or resistant* or uncontrol* or reduc* or lower* or decreas* or refractor* or white coat* or adheren* or toleran* or intoleran* or MDI or MDIS or ambulatory or office) adj3 (blood pressure* or BP or arterial* or diastolic* or DBP or systolic* or SBP)) or TRH).ti,ab,kf. (632016)
4 or/1-3 (2364304)
5 Denervation/ (31120)
6 Sympathectomy/ (16187)
7 (denervat* or sympathectom*).ti,ab,kf. (84834)
8 ((kidney* or renal or nephro* or transcatheter* or catheter* or radiofrequen* or radio frequen* or sympathetic* or ultrasound* or alcohol* or ethanol*) adj6 denerv*).ti,ab,kf. (17345)
9 catheter ablation/ (88593)
10 radiofrequency ablation/ (50243)
11 (((radiofrequenc* or radio frequenc*) adj3 (ablat* or catheter* or transcatheter* or probe* or kidney* or renal or nephro*)) or RDN or RSD).ti,ab,kf. (129910)
12 ((ultrasound* or ultra sound* or alcohol* or ethanol* or kidney* or renal or nephro*) adj3 (ablat* or catheter* or transcatheter*)).ti,ab,kf. (28141)
13 or/5-12 (317698)
14 4 and 13 (23804)
15 (Symplicity* or Spyral* or Vessix* or Enlightn* or HTN ON-MED* or HTN OFF-MED* or (Recor* adj4 Paradise*) or Iberis* or Tivus* or Symapcath* or Confidenht* or Renlane*).ti,ab,kf. (1864)
16 or/14-15 (24126)
17 economics/ (267032)
18 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1129997)
19 economics.fs. (479353)
20 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1415795)
21 exp "costs and cost analysis"/ (725960)
22 (cost or costs or costing or costly).ti. (356695)
23 cost effective*.ti,ab,kf. (506729)
24 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kf. (338651)
25 models, economic/ (16953)
26 markov chains/ or monte carlo method/ (116276)
27 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (77157)
28 (markov or markow or monte carlo).ti,ab,kf. (195255)
29 quality-adjusted life years/ (61586)
30 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (125560)
31 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (228530)
32 or/17-31 (3687241)
33 16 and 32 (709)
34 exp Animals/ not Humans/ (16657825)
35 33 not 34 (524)

36 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6829122)
37 35 not 36 (497)
38 limit 37 to english language [Limit not valid in CDSR; records were retained] (473)
39 38 use medall,coch,cctr,cleed (141)
40 exp hypertension/ (1395378)
41 (hypertens* or antihypertens* or HTN).tw,kw,kf. (1514323)
42 (((high* or elevat* or increas* or rais* or resistant* or uncontrol* or reduc* or lower* or decreas* or refractor* or white coat* or adheren* or toleran* or intoleran* or MDI or MDIS or ambulatory or office) adj3 (blood pressure* or BP or arterial* or diastolic* or DBP or systolic* or SBP)) or TRH or RHTN).tw,kw,kf. (635204)
43 or/40-42 (2362887)
44 kidney denervation/ (5443)
45 denervation/ (31120)
46 sympathectomy/ (16187)
47 (denervat* or sympathectom*).tw,kw,kf,dv,dm,mv. (84959)
48 ((kidney* or renal or nephro* or transcatheter* or catheter* or radiofrequen* or radio frequen* or sympathetic* or ultrasound* or alcohol* or ethanol*) adj6 denerv*).ti,ab,kf. (17345)
49 radiofrequency catheter ablation/ (46526)
50 catheter ablation/ (88593)
51 radiofrequency ablation/ (50243)
52 (((radiofrequenc* or radio frequenc*) adj3 (ablat* or catheter* or transcatheter* or probe* or kidney* or renal or nephro*)) or RDN or RSD).tw,kw,kf,dv,dm,mv. (131321)
53 ((ultrasound* or ultra sound* or alcohol* or ethanol* or kidney* or renal or nephro*) adj3 (ablat* or catheter* or transcatheter*)).tw,kw,kf,dv,dm,mv. (30221)
54 or/44-53 (321377)
55 43 and 54 (24422)
56 (Symplicity* or Spyral* or Vessix* or Enlightn* or HTN ON-MED* or HTN OFF-MED* or (Recor* adj4 Paradise*) or Iberis* or Tivus* or Symapcath* or Confidenht* or Renlane*).tw,kw,kf,dv,dm,mv. (2106)
57 or/55-56 (24761)
58 Economics/ (267032)
59 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (158247)
60 Economic Aspect/ or exp Economic Evaluation/ (587403)
61 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1436525)
62 exp "Cost"/ (725960)
63 (cost or costs or costing or costly).ti. (356695)
64 cost effective*.tw,kw,kf. (515754)
65 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kw,kf. (349261)
66 Monte Carlo Method/ (89778)
67 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (80611)
68 (markov or markow or monte carlo).tw,kw,kf. (198751)
69 Quality-Adjusted Life Years/ (61586)
70 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (128935)
71 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (249685)
72 or/58-71 (3178594)
73 57 and 72 (715)

74 (exp animal/ or nonhuman/) not exp human/ (12339673)
75 73 not 74 (702)
76 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (12035610)
77 75 not 76 (550)
78 limit 77 to english language [Limit not valid in CDSR; records were retained] (524)
79 78 use emez (322)
80 39 or 79 (463)
81 80 use medall (85)
82 80 use coch (0)
83 80 use cctr (51)
84 80 use cleed (5)
85 80 use emez (322)
86 remove duplicates from 80 (387)

Quantitative Evidence of Preferences and Values Search

Search date: January 13, 2025

Databases searched: Ovid MEDLINE and EBSCO CINAHL

Database segment: Ovid MEDLINE(R) ALL <1946 to January 10, 2025>

Search strategy:
---
1 exp Hypertension/ (329555)
2 (hypertens* or antihypertens* or HTN).ti,ab,kf,jn. (580017)
3 (((high* or elevat* or increas* or rais* or resistant* or uncontrol* or reduc* or lower* or decreas* or refractor* or white coat* or adheren* or toleran* or intoleran* or MDI or MDIS or ambulatory or office) adj3 (blood pressure* or BP or arterial* or diastolic* or DBP or systolic* or SBP)) or TRH or RHTN).ti,ab,kf. (244788)
4 or/1-3 (774109)
5 Denervation/ (15327)
6 Sympathectomy/ (10096)
7 (denervat* or sympathectom*).ti,ab,kf. (40354)
8 ((kidney* or renal or nephro* or transcatheter* or catheter* or radiofrequen* or radio frequen* or sympathetic* or ultrasound* or alcohol* or ethanol*) adj6 denerv*).ti,ab,kf. (6754)
9 catheter ablation/ (41555)
10 radiofrequency ablation/ (3392)
11 (((radiofrequenc* or radio frequenc*) adj3 (ablat* or catheter* or transcatheter* or probe* or kidney* or renal or nephro*)) or RDN or RSD).ti,ab,kf. (50562)
12 ((ultrasound* or ultra sound* or alcohol* or ethanol* or kidney* or renal or nephro*) adj3 (ablat* or catheter* or transcatheter*)).ti,ab,kf. (10371)
13 or/5-12 (131363)
14 4 and 13 (7949)
15 (Symplicity* or Spyral* or Vessix* or Enlightn* or HTN ON-MED* or HTN OFF-MED* or (Recor* adj4 Paradise*) or Iberis* or Tivus* or Symapcath* or Confidenht* or Renlane*).ti,ab,kf. (467)

16 or/14-15 (8037)
17 Attitude to Health/ (85553)
18 Health Knowledge, Attitudes, Practice/ (134050)
19 Patient Participation/ (30705)
20 Patient Preference/ (11642)
21 Patient Satisfaction/ (93352)
22 Attitude of Health Personnel/ (136872)
23 *Professional-Patient Relations/ (12586)
24 *Physician-Patient Relations/ (37880)
25 Choice Behavior/ (36078)
26 (choice or choices or value* or valuation* or knowledg*).ti. (350538)
27 (preference* or expectation* or attitude* or acceptab* or point of view).ti,ab,kf. (820199)
28 ((clinician* or doctor* or cardiologist* or internist* or interventional cardiologist* or radiologist* or nephrologist* or endocrinologist* or hypertension expert* or hypertension specialist* or (health* adj2 worker*) or patient*1 or personal or physician* or practitioner* or professional*1 or provider* or user*1 or women or men) adj2 (participation or perspective* or perception* or misperception* or perceiv* or satisf* or view* or understand* or misunderstand* or value*1 or knowledg*)).ti,ab,kf. (292923)
29 health perception*.ti,ab,kf. (3674)
30 *Decision Making/ (48119)
31 (clinician* or doctor* or cardiologist* or internist* or interventional cardiologist* or radiologist* or nephrologist* or endocrinologist* or hypertension expert* or hypertension specialist* or (health* adj2 worker*) or patient*1 or personal or physician* or practitioner* or professional*1 or provider* or user*1 or women or men).ti. (3231664)
32 30 and 31 (8809)
33 (decision* and mak*).ti. (42319)
34 (decision mak* or decisions mak*).ti,ab,kf. (249533)
35 33 or 34 (251269)
36 (clinician* or doctor* or cardiologist* or internist* or interventional cardiologist* or radiologist* or nephrologist* or endocrinologist* or hypertension expert* or hypertension specialist* or (health* adj2 worker*) or patient*1 or personal or physician* or practitioner* or professional*1 or provider* or user*1 or women or men).ti,ab,kf. (10792421)
37 35 and 36 (159004)
38 (discrete choice* or decision board* or decision analy* or decision-support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*).ti,ab,kf. (59951)
39 Decision Support Techniques/ (23250)
40 (health and utilit*).ti. (2173)
41 (gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best-worst scaling or time trade-off or TTO or probability trade-off).ti,ab,kf. (18842)
42 (preference based or preference score* or preference elicitation or multiattribute or multi attribute).ti,ab,kf. (4375)
43 ((quality adj2 life) or QOL or QOLs).ti,ab,kf. (447856)
44 or/17-29,32,37-43 (2206513)
45 16 and 44 (297)
46 Case Reports/ or Congress.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. (3570399)
47 45 not 46 (281)

48 exp Animals/ not Humans/ (5297866)
49 47 not 48 (271)
50 limit 49 to english language (244)

CINAHL

#	Query	Results
S1	(MH "Hypertension+")	94,944
S2	TI (hypertens* or antihypertens* HTN) or AB (hypertens* or antihypertens* or HTN)	121,972
S3	TI (((high* or elevat* or increas* or rais* or resistant* or uncontrol* or reduc* or lower* or decreas* or refractor* or white coat* or adheren* or toleran* or intoleran* or MDI or MDIS or ambulatory or office) N3 (blood pressure* or BP or arterial* or diastolic* or DBP or systolic* or SBP)) or TRH or RHTN) or AB (((high* or elevat* or increas* or rais* or resistant* or uncontrol* or reduc* or lower* or decreas* or refractor* or white coat* or adheren* or toleran* or intoleran* or MDI or MDIS or ambulatory or office) N3 (blood pressure* or BP or arterial* or diastolic* or DBP or systolic* or SBP)) or TRH or RHTN)	53,032
S4	S1 OR S2 OR S3	184,810
S5	(MH "Denervation")	1,407
S6	(MH "Sympathectomy")	930
S7	TI (denervat* or sympathectom*) or AB (denervat* or sympathectom*)	3,922
S8	TI ((kidney* or renal or nephro* or transcatheter* or catheter* or radiofrequen* or radio frequen* or sympathetic* or ultrasound* or alcohol* or ethanol*) N6 denerv*) or AB ((kidney* or renal or nephro* or transcatheter* or catheter* or radiofrequen* or radio frequen* or sympathetic* or ultrasound* or alcohol* or ethanol*) N6 denerv*)	1,667
S9	(MH "Catheter Ablation")	18,227
S10	(MH "Radiofrequency Ablation")	1,296
S11	TI (((radiofrequenc* or radio frequenc*) N3 (ablat* or catheter* or transcatheter* or probe* or kidney* or renal or nephro*)) or RDN or RSD) or AB (((radiofrequenc* or radio frequenc*) N3 (ablat* or catheter* or transcatheter* or probe* or kidney* or renal or nephro*)) or RDN or RSD)	9,882
S12	TI ((ultrasound* or ultra sound* or alcohol* or ethanol* or kidney* or renal or nephro*) N3 (ablat* or catheter* or transcatheter*)) or AB ((ultrasound* or ultra sound* or alcohol* or ethanol* or kidney* or renal or nephro*) N3 (ablat* or catheter* or transcatheter*))	3,250
S13	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	29,546
S14	S4 AND S13	1,721
S15	TI (Symplicity* or Spyral* or Vessix* or Enlightn* or HTN ON-MED* or HTN OFF-MED* or (Recor* N4 Paradise*) or Iberis* or Tivus* or Symapcath* or Confidenht* or Renlane*) or AB (Symplicity* or Spyral* or Vessix* or Enlightn* or HTN ON-MED* or HTN OFF-MED* or (Recor* N4 Paradise*) or Iberis* or Tivus* or Symapcath* or Confidenht* or Renlane*)	216
S16	S14 OR S15	1,807
S17	(MH "Attitude to Health")	50,334
S18	(MH "Health Knowledge")	42,418
S19	(MH "Consumer Participation")	25,054
S20	(MH "Patient Preference") or (MH "Patient Satisfaction")	66,923
S21	(MH "Attitude of Health Personnel")	59,164
S22	(MM "Professional-Patient Relations")	15,075
S23	(MM "Physician-Patient Relations")	17,518
S24	(MM "Nurse-Patient Relations")	15,111
S25	TI (choice or choices or value* or valuation* or knowledg*)	126,854

S26 TI (preference* or expectation* or attitude* or acceptab* or point of view) or AB (preference* or expectation* or attitude* or acceptab* or point of view) 264,498
S27 TI ((clinician* or doctor* or cardiologist* or internist* or interventional cardiologist* or radiologist* or nephrologist* or endocrinologist* or hypertension expert* or hypertension specialist* or (health* N2 worker*) or patient or patients or personal or physician* or practitioner* or professional or professionals or provider* or user or users or women or men) N2 (participation or perspective* or perception* or misperception* or perceiv* or satisf* or view* or understand* or misunderstand* or value or values or knowledg*)) or AB ((clinician* or doctor* or cardiologist* or internist* or interventional cardiologist* or radiologist* or nephrologist* or endocrinologist* or hypertension expert* or hypertension specialist* or (health* N2 worker*) or patient or patients or personal or physician* or practitioner* or professional or professionals or provider* or user or users or women or men) N2 (participation or perspective* or perception* or misperception* or perceiv* or satisf* or view* or understand* or misunderstand* or value or values or knowledg*)) 186,063
S28 TI health perception* or AB health perception* 5,666
S29 (MH "Decision Making, Shared") 4,744
S30 (MH "Decision Making, Patient") 16,012
S31 (MH "Decision Making, Family") 4,386
S32 (MM "Decision Making") 27,060
S33 TI (clinician* or doctor* or (health* N2 worker*) or nurse or nurses or patient or patients or personal or physician* or practitioner* or professional or professionals or provider* or user or users or women or men) 1,502,408
S34 S32 AND S33 5,763
S35 TI (decision* and mak*) 23,510
S36 TI (decision mak* or decisions mak*) or AB (decision mak* or decisions mak*) 100,334
S37 S35 OR S36 100,901
S38 TI (clinician* or doctor* or (health* N2 worker*) or nurse or nurses or patient or patients or personal or physician* or practitioner* or professional or professionals or provider* or user or users or women or men) or AB (clinician* or doctor* or (health* N2 worker*) or nurse or nurses or patient or patients or personal or physician* or practitioner* or professional or professionals or provider* or user or users or women or men) 3,290,759
S39 S37 AND S38 72,387
S40 TI (discrete choice* or decision board* or decision analy* or decision support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*) or AB (discrete choice* or decision board* or decision analy* or decision support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*) 31,409
S41 (MH "Decision Support Techniques") 7,911
S42 TI (health and utilit*) 1,291
S43 TI (gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best worst scaling or time trade off or TTO or probability trade off) or AB (gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best worst scaling or time trade off or TTO or probability trade off) 14,948
S44 TI (preference based or preference score* or preference elicitation or multiattribute or multi attribute) or AB (preference based or preference score* or preference elicitation or multiattribute or multi attribute) 1,937
S45 ((quality N2 life) or QOL or QOLs) 256,395
S46 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S34 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 982,137

S47	S16 AND S46	101
S48	PT (Case Study or Letter or Proceedings)	812,490
S49	S47 NOT S48	93
S50	S47 NOT S48	
Limiters - English Language		92

Grey Literature Search

Performed: December 18–20, 2024; January 6–7, 2025

Websites searched: Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), University Of Calgary Health Technology Assessment Unit, Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International HTA Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), National Health Service England (NHS), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Adelaide Health Technology Assessment, Australian Government Medical Services Advisory Committee, Monash Health Centre for Clinical Effectiveness, The Sax Institute, Australian Government Department of Health and Aged Care, Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S), Pharmac, Italian National Agency for Regional Health Services (Aegnas), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment (Austria), The Regional Health Technology Assessment Centre (HTA-centrum), Swedish Agency for Health Technology Assessment and Assessment of Social Services, Norwegian Institute of Public Health - Health Technology Assessments, The Danish Health Technology Council, Ministry of Health Malaysia - Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, PROSPERO, clinicaltrials.gov

Keywords used: renal denervation, sympathectomy, radiofrequency, ablation, catheter, transcatheter, symplicity, spyral, vessix, hypertension, blood pressure, kidney, renale, radiofréquence

Clinical results (included in PRISMA): 7

Economic results (included in PRISMA): 10

Ongoing HTAs (PROSPERO/NICE/MSAC): 27

Ongoing clinical trials: 95

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Systematic Reviews (ROBIS Tool)

	Phase 2				Phase 3
Author, year	**Study eligibility criteria**	**Identification and selection of studies**	**Data collection and study appraisal**	**Synthesis and findings**	**Risk of bias in the review**
Sharp et al, 2024[39]	Low	Low	Low	Low	Low
Mufarrih et al, 2024[46]	Low	Unclear	Low	Low	Low
Ogoyama et al, 2024[35]	Low	Low	Low	Low	Low
Vukadinović et al, 2024[36]	Low	Low	Low	Low	Low
Wang et al, 2024[47]	Low	Low	Low	Low	Low
Silvinato et al, 2024[34]	Low	Low	Low	Low	Low
Sobreira et al, 2024[37]	Low	Low	Low	Low	Low
Dantas et al, 2024[48]	Low	Low	Low	Low	Low
Maia et al, 2024[50]	Low	Low	Low	Low	Low
Gonçalves et al, 2024[49]	Low	Low	Low	Low	Low

Abbreviation: ROBIS, Risk of Bias in Systematic Reviews.

[a]Possible risk-of-bias levels: low, high, unclear.

Appendix 3: Selected Excluded Systematic Reviews – Clinical Evidence

For transparency, we provide a list of reviews that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Abouelmagd AA, Hassanein ME, Shehata RIA, Kaoud OA, Hamouda H, Abbas OF, Gaballah M. Comparing the efficacy of renal artery denervation in uncontrolled hypertension: a systematic review and network meta-analysis. Cureus. 2024 Oct 4;16(10).	Network meta-analysis
Ahmed M, Nudy M, Bussa R, Hajduczok A, Naccarelli GV, Filippone EJ, Foy AJ. A systematic review, meta-analysis, and meta regression of the sham controlled renal denervation randomized controlled trials. Trends Cardiovasc Med. 2023 Nov;33(8):490-98.	Published before Sharp et al, 2024[39]
Ahmed M, Nudy M, Bussa R, Naccarelli GV, Filippone EJ, Foy AJ. A subgroup meta-analysis comparing the renal denervation sham-controlled randomized trials among those with resistant and nonresistant hypertension. Am J Cardiol. 2023;191:119-24	Published before Sharp et al, 2024[39]
Azeez GA, Thirunagari M, Fatima N, Anand A, Palvia AR, Kaur A, Nassar ST. The efficacy of renal denervation in treating resistant hypertension: a systematic review. Cureus. 2024 Aug 16;16(8):e67007.	Narrative synthesis, not limitied to RCTs
Bangalore S, Maqsood MH, Bakris GL, Rao SV, Messerli FH. Renal denervation - radiofrequency vs. ultrasound: insights from a mixed treatment comparison meta-analysis of randomized sham controlled trials. J Hypertens. 2025 Feb 1;43(2):325-335.	Network meta-analysis
Canadian Agency for Drugs and Technologies in Health. CADTH health technology review: renal denervation for uncontrolled hypertension. Can J Health Tech. 2024;4(4):1-44	Narrative synthesis
Fernandes A, David C, Pinto FJ, Costa J, Ferreira JJ, Caldeira D. The effect of catheter-based sham renal denervation in hypertension: systematic review and meta-analysis. BMC Cardiovasc Disord. 2023 May 12;23(1):249.	Published before Sharp et al, 2024,[39] focus on blood-pressure-lowering effect of sham arm
Health Technology Wales. Evidence appraisal report: renal denervation to treat people with resistant hypertension. December 2023.	Narrative synthesis, published before Sharp et al, 2024[39]
Hu XR, Liao GZ, Wang JW, Ye YY, Chen XF, Bai L, Shi FF, Liu K, Peng Y. Patient-specific factors predicting renal denervation response in patients with hypertension: a systematic review and meta-analysis. J Am Heart Assoc. 2024 Jul 16;13(14):e034915.	Not limited to RCTs, focus on patient-specific predictors of change in blood pressure
Mohammad AA, Nawar K, Binks O, Abdulla MH. Effects of renal denervation on kidney function in patients with chronic kidney disease: a systematic review and meta-analysis. J Hum Hypertens. 2024 Jan;38(1):29-44.	Not liimted to RCTS (single-arm studies), specific population (chronic kidney disease)
Pisano A, Iannone LF, Leo A, et al. (2021). Renal denervation for resistant hypertension. Cochrane Database of Systematic Reviews. 11: CD011499.	Published before Sharp et al, 2024[39]
Sesa-Ashton G, Nolde JM, Muente I, Carnagarin R, Macefield VG, Dawood T, Lambert EA, Lambert GW, Walton A, Esler MD, Schlaich MP. Long-term blood pressure reductions following catheter-based renal denervation: a systematic review and meta-analysis. Hypertension. 2024 Jun;81(6).	Not limited to RCTs, no quality appraisal of included studies
Singh S, Rout A, Garg A. Renal denervation in hypertension: an updated meta-analysis of the randomized controlled trials. Catheter Cardiovasc Interv. 2023;102(4): 663-71.	Published before Sharp et al, 2024[39]
Su Q, Li J, Shi F, Yu J. A meta-analysis and review on the effectiveness and safety of renal denervation in managing heart failure with reduced ejection fraction. Ren Fail. 2024 Dec;46(2):2359032.	Specific population (heart failure)
Thrash GW, Wang E, Sun Y, Walker HC, Shirvalkar P, Becker BK, Holland MT. Clinical trials in neuromodulatory treatment of drug-resistant hypertension and the need for spinal cord stimulation trials: a PRISMA systematic review. Bioelectron Med. 2024 Dec 2;10(1):28.	Intervention not limited to renal denervation, no quality appraisal of included studies
Tian Z, Vollmer Barbosa C, Lang H, Bauersachs J, Melk A, Schmidt BMW. Efficacy of pharmacological and interventional treatment for resistant hypertension: a network meta-analysis. Cardiovasc Res. 2024 Feb 27;120(1):108-119.	Network meta-analysis
Xie L, Li Y, Luo S, Huang B. Impact of renal denervation on cardiac remodeling in resistant hypertension: a meta-analysis. Clin Cardiol. 2024 Feb;47(2).	No outcomes of interest

Appendix 4: Overlap of Primary Studies in Included Systematic Reviews – Clinical Evidence

Table A2: Overlap of Primary Studies in Included Systematic Reviews – Clinical Evidence

Trial name/author, year	Systematic review author, year (no. RCTs)										Total
	Sharp et al, 2024[39] (16)	Mufarrih et al, 2024[46] (15)	Ogoyama et al, 2024[35] (14)	Vukadinovic et al, 2024[36] (13)	Sobreira et al, 2024[37] (10)	Dantas et al, 2024[48] (9)	Maia et al, 2024[50] (5)	Wang et al, 2024[47] (4)	Silvinato et al, 2024[34] (3)	Gonçalves et al, 2024[49] (21)	
SPYRAL HTN-OFF MED	X	X	X	X		X		X	X	X	8
RADIANCE-HTN TRIO	X	X	X	X		X	X	X		X	8
SYMPLICITY HTN-3	X	X	XX	X	X	X				X	7
SYMPLICITY FLEX	X	X	X	X	X	X				X	7
SPYRAL HTN-ON MED	X	X	XXX	X	X				X	X	7
RESET	X	X	X	X	X	X				X	7
REDUCE HTN: REINFORCE	X	X	X			X		X	X	X	7
RADIANCE II	X	X		X			X	X		X	7
REQUIRE	X	X	X	X		X	X			X	7
RADIANCE-HTN SOLO	X	X	X	X			X			X	6
Symplicity HTN-2	X	X			X					X	4
DENER-HTN	X	X			X					X	4
WAVE IV		X				X	X			X	4
SYMPATHY	X	X								X	3
Warchol-Celinska et al, 2018	X				X					X	3
Pathak et al, 2023[a]		X	X	X							3
PRAGUE-15					X					X	2
SYMPLICITY HTN-Japan	X				X						2
INSPIRED	X										1
Heradien 2022			X								1
Netrod RDN[a]				X							1
Iberis-HTN*				X							1
TARGET BP I[a]				X							1

Trial name/author, year	Systematic review author, year (no. RCTs)										Total
	Sharp et al, 2024[39] (16)	Mufarrih et al, 2024[46] (15)	Ogoyama et al, 2024[35] (14)	Vukadinovic et al, 2024[36] (13)	Sobreira et al, 2024[37] (10)	Dantas et al, 2024[48] (9)	Maia et al, 2024[50] (5)	Wang et al, 2024[47] (4)	Silvinato et al, 2024[34] (3)	Gonçalves et al, 2024[49] (21)	
OSLO RDN					X						1
Gao 2023						X					1
RADIOSOUND-HTN										X	1
DENERVHTA (DENERV HTN)										X	1
Gosse et al, 2017										X	1
Bergo et al, 2021										X	1
Engholm et al, 2018										X	1

*New RCTs identified in literature search that were not included in Sharp et al[39] but were included in Vukadinovic et al.[36]

Appendix 5: Findings from Included Systematic Reviews – Clinical Evidence

Table A3: Office Blood Pressure Reported in Relevant Systematic Reviews

Review	Follow-up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
SYSTOLIC						
Uncontrolled hypertension						
Sharp et al, 2024[39]	Primary	13 (2,229)	**−8.5**	−13.5 to −3.6	75%	
Sharp et al, 2024[39]	Last	14 (2,253)	**−7.2**	−12.5 to −2.0	76%	
Sharp et al, 2024[39]	Primary (2−6 mo)[a]	12 (2,129)	**−5.6**	−7.2 to −4.0	0%	
Sharp et al, 2024[39]	Last[a]	13 (2,153)	**−5.0**	−6.9 to −3.1	24%	
Sham-controlled						
Sharp et al, 2024[39]	Primary	7 (1,774)	**−5.2**	−6.7 to −3.6	0%	
Sharp et al, 2024[39]	Last	8 (1,798)	**−4.5**	−6.5 to −2.5	14%	
Vukadinović et al, 2024[36]	Primary (2−6 mo)	10 (2,478)	**−6.62**	−9.66 to −3.57	82%	
Vukadinović et al, 2024[36]	1 study removed	9	**−5.2**	−6.5 to −3.8	0%	
Ogoyama et al, 2024[35]	Primary (2−6 mo)	10	**−4.95**	−6.37 to −3.54	0%	
On medication						
Sharp et al, 2024[39]	Primary	10 (1,569)	−9.7	−16.6 to −2.7	81%	
Sharp et al, 2024[39]	Last	10 (1,566)	−9.0	−16.4 to −1.7	83%	
Sharp et al, 2024[39]	Primary (2−6 mo)[a]	9 (1,469)	**−5.0**	−7.5 to −2.4	17%	
Sharp et al, 2024[39]	Last[a]	9 (1,466)	**−4.4**	−7.3 to −1.6	33%	
Mufarrih et al, 2024[46]	Primary (2–6 mo)	8	**−6.39**	−11.49 to −1.30	83%	Low
Off medication						
Sharp et al, 2024[39]	Primary	3 (660)	**−6.3**	−8.1 to −4.5	0%	
Sharp et al, 2024[39]	Last	4 (687)	**−5.7**	−9.3 to −2.0	6%	
Mufarrih et al, 2024[46]	Primary (2−6 mo)	5	**−4.76**	−7.57 to −1.94	49%	Low
Wang et al, 2024[47]		4 (710)	**−5.83**	−7.93 to −3.72	19%	
Radiofrequency						
Sharp et al, 2024[39]	Primary	9 (1,610)	−10.7	−18.3 to −3.2	82%	
Sharp et al, 2024[39]	Last	10 (1,651)	−9.5	−17.0 to −2.0	81%	
Sharp et al, 2024[39]	Primary (2−6 mo)[a]	8 (1,510)	**−5.8**	−8.3 to −3.3	22%	
Sharp et al, 2024[39]	Last[a]	9 (1,551)	**−5.6**	−8.2 to −3.1	31%	
Radiofrequency + sham						
Ogoyama et al, 2024[35]	Primary (2−6 mo)	5 (1,281)	**−4.66**	−6.66 to −2.65	8.3%	
Silvinato et al, 2024[34]	Primary (2−3 mo)	3 (719)	**−4.48**	−6.48 to −2.49	58%	Low
Silvinato et al, 2024[34]	Last (6 mo)	2 (388)	**−5.7**	−8.45 to −2.96	62%	Low
Ultrasound						
Sharp et al, 2024[39]	Primary	4 (619)	**−5.2**	−8.2 to −2.2	0%	
Sharp et al, 2024[39]	Last	4 (602)	**−3.8**	−7.8 to 0.3	0%	

Review	Follow-up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
Ogoyama et al, 2024[35]	Primary (2–6 mo)	4 (635)	**–5.37**	–7.80 to –2.95	0%	
Alcohol						
Ogoyama et al, 2024[35]	Primary (2–6 mo)	1 (104)	**–4.60**	–9.65 to 0.45	NA	
Second-generation system						
Sharp et al, 2024[39]	Primary	6 (1,250)	**–5.5**	–7.0 to –4.0	0%	
Sharp et al, 2024[39]	Last	6 (1,233)	**–4.9**	–7.1 to –2.8	0%	
Treatment-resistant hypertension						
Sharp et al, 2024[39]	Primary	10 (1,338)	–9.6	–16.6 to –2.6	81%	
Sharp et al, 2024[39]	Last	10 (1,335)	–8.9	–16.3 to –1.5	83%	
Sharp et al, 2024[39]	Primary (2–6 mo)[a]	9 (1,238)	**–4.8**	–7.8 to –1.8	19%	
Sharp et al, 2024[39]	Last[a]	9 (1,235)	**–4.1**	–7.5 to –0.7	33%	
Radiofrequency						
Sharp et al, 2024[39]	Primary	8 (1,073)	–11.4	–20.2 to –2.6	84%	
Sharp et al, 2024[39]	Last	8 (1,073)	–11.4	–20.6 to –2.6	84%	
Sharp et al, 2024[39]	Primary (2–6 mo)[a]	7 (973)	**–6.3**	–10.9 to –1.6	32%	
Sharp et al, 2024[39]	Last[a]	7 (973)	**–6.3**	–10.9 to –1.6	32%	
Sobreira et al, 2024[37]		8 (988)	**–9.556**	–16.819 to –2.293	83%	
Ultrasound						
Maia et al, 2024[50]		5 (662)	**–4.459**	–7.710 to –1.208	47%	
Second-generation system or sham-controlled						
Dantas et al, 2024[48]		7	**–6.047**	–11.313 to –0.781	90%	
DIASTOLIC						
Uncontrolled hypertension						
Sharp et al, 2024[39]	Primary	13 (2,229)	–4.0	–5.8 to –2.2	56%	
Sharp et al, 2024[39]	Last	14 (2,253)	–3.3	–5.3 to –1.3	59%	
Sharp et al, 2024[39]	Primary (2–6 mo)[a]	12 (2,129)	**–3.1**	–4.1 to –2.1	0%	
Sharp et al, 2024[39]	Last[a]	13 (2,153)	**–2.5**	–3.6 to –1.5	6%	
Sham-controlled						
Sharp et al, 2024[39]	Primary	7 (1,774)	**–2.8**	–4.1 to –1.6	7%	
Sharp et al, 2024[39]	Last	8 (1,798)	**–2.1**	–3.4 to –0.9	12%	
Vukadinović et al, 2024[36]	Primary (2–6 mo)	10 (2,478)	**–3.49**	–5.40 to –1.59	82%	
Vukadinović et al, 2024[36]	2 studies removed	8	**–3.1**	–4.0 to –2.2	0%	
Ogoyama et al, 2024[35]	Primary (2–6 mo)	10	**–2.79**	–3.67 to –1.90	0%	
On medication						
Sharp et al, 2024[39]	Primary	10(1,569)	–4.3	–7.0 to –1.7	66%	
Sharp et al, 2024[39]	Last	10 (1,566)	–3.9	–6.8 to –0.9	69%	
Sharp et al, 2024[39]	Primary (2–6 mo)[a]	9 (1,469)	**–2.5**	–3.9 to –1.2	0%	
Sharp et al, 2024[39]	Last[a]	9 (1,466)	**–2.1**	–3.6 to –0.7	8%	
Mufarrih et al, 2024[46]	Primary (2–6 mo)	8	**–3.17**	–5.54 to –0.80	73%	Moderate

Review	Follow-up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
Off medication						
Sharp et al, 2024[39]	Primary	3 (660)	**−3.8**	−5.8 to −1.7	0%	
Sharp et al, 2024[39]	Last	4 (687)	**−3.0**	−5.3 to −0.8	0%	
Mufarrih et al, 2024[46]	Primary (2−6 mo)	5	**−2.14**	−4.59 to 0.30	79%	Low
Wang et al, 2024[47]		4 (710)	**−3.57**	−4.89 to −2.25	11%	
Radiofrequency						
Sharp et al, 2024[39]	Primary	9 (1,610)	−4.8	−7.5 to −2.2	66%	
Sharp et al, 2024[39]	Last	10 (1,651)	−4.5	−7.1 to −2.0	63%	
Sharp et al, 2024[39]	Primary (2−6 mo)[a]	8 (1,510)	**−3.2**	−4.6 to −1.8	0%	
Sharp et al, 2024[39]	Last[a]	9 (1,551)	**−3.1**	−4.4 to −1.8	0%	
Radiofrequency + sham						
Ogoyama et al, 2024[35]	Primary (2−6 mo)	5 (1,281)	**−2.74**	−4.12 to −1.35	23.6%	
Silvinato et al, 2024[34]	Primary (2−3 mo)	3 (719)	**−2.63**	−3.86 to −1.4	66%	Low
Silvinato et al, 2024[34]	Last (6 mo)	2 (388)	**−2.03**	−3.84 to −0.22	0%	Moderate
Ultrasound						
Sharp et al, 2024[39]	Primary	4 (619)	**−3.0**	−5.7 to −0.2	6%	
Sharp et al, 2024[39]	Last	4 (602)	**−1.3**	−3.8 to 1.2	0%	
Ogoyama et al, 2024[35]	Primary (2−6 mo)	4 (635)	**−2.77**	−4.43 to −1.11	2.2%	
Alcohol						
Ogoyama et al, 2024[35]	Primary (2−6 mo)	1 (104)	**−2.30**	−5.55 to 0.95	NR	
Second-generation system						
Sharp et al, 2024[39]	Primary	6 (1,250)	**−3.0**	−4.5 to −1.5	15%	
Sharp et al, 2024[39]	Last	6 (1,233)	**−2.1**	−3.9 to −0.3	33%	
Treatment-resistant hypertension						
Sharp et al, 2024[39]	Primary	9 (1,244)	−4.8	(95% CI: −7.8 to −1.8)	65%	
Sharp et al, 2024[39]	Last	9 (1,241)	−4.3	(95% CI: −7.6 to −0.9)	71%	
Sharp et al, 2024[39]	Primary (2−6 mo)[a]	8 (1,144)	**−2.9**	−4.7 to −1.2	0%	
Sharp et al, 2024[39]	Last[a]	8 (1,141)	**−2.3**	−4.4 to −0.2	19%	
Radiofrequency						
Sharp et al, 2024[39]	Primary	7 (979)	−5.9	(95% CI: −9.4 to −2.3)	68%	
Sharp et al, 2024[39]	Last	7 (979)	−5.9	(95% CI: −9.4 to −2.3)	68%	
Sharp et al, 2024[39]	Primary (2−6 mo)[a]	6 (879)	**−3.6**	−5.9 to −1.3	0%	
Sharp et al, 2024[39]	Last[a]	6 (879)	**−3.6**	−5.9 to −1.3	0%	
Sobreira et al, 2024[37]		8 (1,001)	**−5.614**	−8.426 to −2.801	63%	
Ultrasound						
Maia et al, 2024[50]		5 (662)	**−2.039**	−3.975 to −0.102	27%	

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
[a]Removing 1 extreme outlier to substantially reduce heterogeneity (I^2).

Table A4: 24–Hour Ambulatory Blood Pressure Reported in Relevant Systematic Reviews

Review	Follow–up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
SYSTOLIC						
Uncontrolled hypertension						
Sharp et al, 2024[39]	Primary (2–6 mo)	16 (2,268)	**–3.6**	–5.2 to –2.0	41%	
Sharp et al, 2024[39]	Last	16 (2,248)	**–3.3**	–5.0 to –1.6	40%	
Sham-controlled						
Sharp et al, 2024[39]	Primary (2–6 mo)	10 (1,882)	**–3.0**	–4.7 to –1.4	34%	
Sharp et al, 2024[39]	Last	10 (1,862)	**–2.6**	–4.2 to –1.0	27%	
Vukadinović et al, 2024[36]	Primary (2–6 mo)	10 (2,416)	**–4.41**	–6.12 to –2.70	68%	
Vukadinović et al, 2024[36]	Removing outlier	8	**–3.3**	–4.3 to –2.2	5%	
Ogoyama et al, 2024[35]	Primary (2–6 mo)	12	**–2.81**	–4.09 to –1.53	31.4%	
On medication						
Sharp et al, 2024[39]	Primary	12 (1,585)	**–3.2**	–5.2 to –1.2	33%	
Sharp et al, 2024[39]	Last	12 (1,585)	**–2.8**	–4.8 to –0.8	37%	
Mufarrih et al, 2024[46]	Primary (2–6 mo)	10	**–2.23**	–3.56 to –0.90	16%	Moderate
Off medication						
Sharp et al, 2024[39]	Primary	4 (683)	**–3.6**	–8.8 to 1.6	61%	
Sharp et al, 2024[39]	Last	4 (663)	**–3.8**	–7.9 to 0.3	48%	
Mufarrih et al, 2024[46]	Primary (2–6 mo)	5 (439 + 343)	**–3.70**	–5.41 to –2.00	31%	Moderate
Wang et al, 2024[47]		4 (358 + 278)	**–4.62**	–6.14 to –3.10	0%	
Radiofrequency						
Sharp et al, 2024[39]	Primary (2–6 mo)	12 (1,640)	**–3.2**	–5.4 to –1.1	45%	
Sharp et al, 2024[39]	Last	12 (1,635)	**–3.6**	–5.2 to –1.9	25%	
Radiofrequency + sham						
Ogoyama et al, 2024[35]	Primary (2–6 mo)	7 (1323)	**–2.20**	–3.77 to –0.63	18.8%	
Silvinato et al, 2024[34]	Primary (2–3 mo)	3 (719)	**–2.5**	–4 to –1	72%	Low
Silvinato et al, 2024[34]	Last (6 mo)	2 (388)	**–2.33**	–4.54 to –0.12	10%	Moderate
Ultrasound						
Sharp et al, 2024[39]	Primary	4 (628)	**–4.3**	–7.8 to –0.8	24%	
Sharp et al, 2024[39]	Last	4 (613)	**–1.7**	–7.1 to 3.7	70%	
Ogoyama et al, 2024[35]	Primary (2–6 mo)	4 (642)	**–4.31**	–6.43 to –2.18	29%	
Alcohol						
Ogoyama et al, 2024[35]	Primary (2–6 mo)	1 (100)	**–1.50**	–4.75 to 1.75	NR	
Second-generation system						
Sharp et al, 2024[39]	Primary	6 (1,210)	**–3.7**	–5.6 to –1.8	25%	
Sharp et al, 2024[39]	Last	6 (1,195)	**–2.5**	–5.2 to 0.3	57%	
Treatment-resistant hypertension						
Sharp et al, 2024[39]	Primary (2–6 mo)	12 (1,368)	**–3.6**	–5.8 to –1.4	29%	
Sharp et al, 2024[39]	Last	12 (1,368)	**–3.2**	–5.6 to –0.9	35%	

Review	Follow–up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
Radiofrequency						
Sharp et al, 2024[39]	Primary (2–6 mo)	10 (1,102)	**–4.0**	–6.6 to –1.3	34%	
Sharp et al, 2024[39]	Last	10 (1,103)	**–4.0**	–6.6 to –1.5	29%	
Sobreira et al, 2024[37]		10 (1,066)	**–4.848**	–7.268 to –2.428	34%	
Ultrasound						
Maia et al, 2024[50]		5 (669)	**–3.449**	–5.625 to –1.273	29%	
Second-generation system or sham-controlled						
Dantas et al, 2024[48]		9	**–3.729**	–5.449 to –2.009	34%	
DIASTOLIC						
Uncontrolled hypertension						
Sharp et al, 2024[39]	Primary (2–6 mo)	15 (2,221)	**–1.9**	–2.9 to –0.9	38%	
Sharp et al, 2024[39]	Last	16 (2,248)	**–1.7**	–2.7 to –0.7	43%	
Sham-controlled						
Sharp et al, 2024[39]	Primary (2–6 mo)	9 (1,835)	**–1.7**	–2.8 to –0.5	51%	
Sharp et al, 2024[39]	Last	10 (1,862)	**–1.3**	–2.5 to –0.2	54%	
Vukadinović et al, 2024[36]	Primary (2–6 mo)	10 (2,416)	**–2.55**	–3.58 to –1.52	60%	
Vukadinović et al, 2024[36]	Removing outlier	8	**–2.0**	–2.9 to –1.0	42%	
Ogoyama et al, 2024[35]	Primary (2–6 mo)	12	**–1.47**	–2.39 to –0.56	47.8%	
On medication						
Sharp et al, 2024[39]	Primary (2–6 mo)	12 (1,585)	**–1.2**	–2.3 to –0.2	5%	
Sharp et al, 2024[39]	Last	12 (1,585)	**–1.1**	–2.1 to –0.1	4%	
Mufarrih et al, 2024	Primary (2–6 mo)	10	**–1.16**	–1.96 to –0.35	0%	Moderate
Off medication						
Sharp et al, 2024[39]	Primary (2–6 mo)	3 (636)	**–2.9**	–6.1 to 0.4	55%	
Sharp et al, 2024[39]	Last	4 (663)	**–2.4**	–5.5 to 0.6	62%	
Mufarrih et al, 2024[46]	Primary (2–6 mo)	5	**–1.36**	–4.11 to 1.40	91%	Moderate
Wang et al, 2024[47]		4 (683)	**–2.56**	–4.13 to –0.98	57%	
Radiofrequency						
Sharp et al, 2024[39]	Primary (2–6 mo)	11 (1,593)	**–1.8**	–3.0 to –0.5	30%	
Sharp et al, 2024[39]	Last	12 (1,635)	**–1.8**	–2.9 to –0.7	18%	
Radiofrequency + sham						
Ogoyama et al, 2024[35]	Primary (2–6 mo)	7 (1,323)	**–0.98**	–2.24 to 0.28	45.8%	
Silvinato et al, 2024[34]	Primary (2–3 mo)	3 (719)	**–2.18**	–3.17 to –1.2	57%	Low
Silvinato et al, 2024[34]	Last (6 mo)	2 (388)	**–1.07**	–2.66 to 0.53	0%	Moderate
Ultrasound						
Sharp et al, 2024[39]	Primary (2–6 mo)	4 (628)	**–2.1**	–4.8 to 0.5	60%	
Sharp et al, 2024[39]	Last	4 (613)	**–1.2**	–4.7 to 2.4	77%	
Ogoyama et al, 2024[35]	Primary (2–6 mo)	4 (642)	**–2.28**	–3.84 to –0.72	54.7%	
Alcohol						
Ogoyama et al, 2024[35]	Alcohol-mediated	1 (100)	**–0.90**	–3.25 to 1.45	NR	

Review	Follow–up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
Second-generation system						
Sharp et al, 2024[39]	Primary	6 (1,210)	−2.1	−3.6 to −0.7	52%	
Sharp et al, 2024[39]	Last	6 (1,195)	−1.6	−3.5 to 0.4	68%	
Treatment-resistant hypertension						
Sharp et al, 2024[39]	Primary (2−6 mo)	11 (1,277)	**−1.3**	−2.6 to −0.1	13%	
Sharp et al, 2024[39]	Last	11 (1,277)	**−1.1**	−2.4 to −0.1	13%	
Radiofrequency						
Sharp et al, 2024[39]	Primary (2−6 mo)	9 (1,011)	**−1.4**	−3.0 to 0.2	26%	
Sharp et al, 2024[39]	Last	9 (1,012)	**−1.5**	−3.0 to 0.0	20%	
Sobreira et al, 2024[37]		10 (1,066)	**−2.359**	−4.19 to −0.529	59%	
Ultrasound						
Maia et al, 2024[50]		5 (669)	**−2.210**	−3.709 to −0.712	43%	

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Table A5: Daytime Blood Pressure Reported in Relevant Systematic Reviews

Review	Follow-up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
SYSTOLIC						
Uncontrolled hypertension						
Sharp et al, 2024[39]	Primary (2−6 mo)	13 (2,145)	−3.9	−5.6 to −2.2	37%	
Sharp et al, 2024[39]	Last	13 (2,125)	−3.0	−4.8 to −1.2	38%	
Sham-controlled						
Sharp et al, 2024[39]	Primary (2−6 mo)	9 (1,845)	−3.6	−5.4 to −1.9	36%	
Sharp et al, 2024[39]	Last	9 (1,825)	−2.7	−4.4 to −0.9	33%	
Vukadinović et al, 2024[36]	Primary (2−6 mo)	8 (2,023)	−5.17	−7.57 to −2.77	76%	
Vukadinović et al, 2024[36]	Removing outliers	6	−3.6	−5.5 to −1.7	51%	
Ogoyama et al, 2024[35]	Primary (2−6 mo)	11	−3.17	−4.75 to −1.58	41.2%	
On medication						
Sharp et al, 2024[39]	Primary (2−6 mo)	10 (1,503)	−2.5	−4.5 to −0.5	20%	
Sharp et al, 2024[39]	Last	10 (1,497)	−2.1	−4.1 to −0.1	23%	
Mufarrih et al, 2024[46]	Primary (2−6 mo)	8	−2.62	−4.14 to −1.11	3%	Moderate
Off medication						
Sharp et al, 2024[39]	Primary (2−6 mo)	3 (642)	−5.4	−8.2 to −2.5	0%	
Sharp et al, 2024[39]	Last	3 (628)	−4.2	−10.3 to 2.0	50%	
Mufarrih et al, 2024[46]	Primary (2−6 mo)	4	−2.95	−8.79 to 2.89	95%	High
Radiofrequency						
Sharp et al, 2024[39]	Primary (2−6 mo)	9 (1,518)	−3.1	−5.4 to −0.8	34%	
Sharp et al, 2024[39]	Last	9 (1,519)	−3.2	−5.4 to −1.0	31%	
Ultrasound						
Sharp et al, 2024[39]	Primary (2−6 mo)	4 (627)	−5.4	−8.4 to −2.3	3%	

Review	Follow-up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
Sharp et al, 2024[39]	Last	4 (606)	−2.3	−7.3 to 2.7	62%	
Second-generation system						
Sharp et al, 2024[39]	Primary	6 (1,214)	−4.1	−6.4 to −1.9	42%	
Sharp et al, 2024[39]	Last	6 (1,193)	−2.7	−5.3 to −0.1	51%	
Treatment-resistant hypertension						
Sharp et al, 2024[39]	Primary (2–6 mo)	9 (1,194)	−3.1	−5.8 to −0.5	23%	
Sharp et al, 2024[39]	Last	9 (1,188)	−2.6	−5.5 to 0.2	30%	
Radiofrequency						
Sharp et al, 2024[39]	Primary (2–6 mo)	7 (931)	−3.5	−7.5 to 0.4	39%	
Sharp et al, 2024[39]	Last	7 (932)	−3.7	−7.6 to 0.1	36%	
Ultrasound						
Maia et al, 2024[50]		4 (622)	−4.004	−6.190 to −1.817	26%	
Second-generation system or sham-controlled						
Dantas et al, 2024[48]		7	−4.108	−5.842 to −2.374	0%	
DIASTOLIC						
Uncontrolled hypertension						
Sharp et al, 2024[39]	Primary (2–6 mo)	13 (2,139)	−2.1	−3.2 to −1.0	45%	
Sharp et al, 2024[39]	Last	13 (2,125)	−1.7	−3.0 to −0.5	53%	
Sham-controlled						
Sharp et al, 2024[39]	Primary (2–6 mo)	9 (1,839)	−1.9	−3.1 to −0.8	45%	
Sharp et al, 2024[39]	Last	9 (1,825)	−1.5	−2.8 to −0.2	54%	
Vukadinović et al, 2024[36]	Primary (2–6 mo)	7 (1,722)	−2.90	−4.48 to −1.31	73%	
Ogoyama et al, 2024[35]	Primary (2–6 mo)	9	−1.88	−3.08 to −0.68	51.2%	
On medication						
Sharp et al, 2024[39]	Primary (2–6 mo)	10 (1,497)	−1.2	−2.5 to −0.0	21%	
Sharp et al, 2024[39]	Last	10 (1,497)	−1.1	−2.3 to 0.2	23%	
Mufarrih et al, 2024[46]		7	−1.47	−2.50 to −0.45	0%	Moderate
Off medication						
Sharp et al, 2024[39]	Primary (2–6 mo)	3 (642)	−3.3	−5.2 to −1.5	0%	
Sharp et al, 2024[39]	Last	3 (628)	−2.8	−7.5 to 1.9	64%	
Mufarrih et al, 2024[46]		4	−1.51	−5.74 to 2.72	94%	High
Radiofrequency						
Sharp et al, 2024[39]	Primary (2–6 mo)	9 (1,518)	−1.8	−3.5 to −0.1	48%	
Sharp et al, 2024[39]	Last	9 (1,519)	−1.9	−3.5 to −0.2	46%	
Ultrasound						
Sharp et al, 2024[39]	Primary (2–6 mo)	4 (621)	−2.7	−4.9 to −0.5	31%	
Sharp et al, 2024[39]	Last	4 (606)	−1.4	−4.8 to 2.0	71%	
Second-generation system						
Sharp et al, 2024[39]	Primary	6 (1,208)	−2.5	−3.9 to −1.1	41%	
Sharp et al, 2024[39]	Last	6 (1,193)	−1.8	−3.7 to 0.2	64%	

Review	Follow-up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
Treatment-resistant hypertension						
Sharp et al, 2024[39]	Primary (2–6 mo)	9 (1,188)	−1.4	−3.1 to 0.2	29%	
Sharp et al, 2024[39]	Last	9 (n=1,188)	−1.2	−2.9 to 0.5	31%	
Radiofrequency						
Sharp et al, 2024[39]	Primary (2–6 mo)	7 (931)	−1.7	−4.2 to 0.9	45%	
Sharp et al, 2024[39]	Last	7 (932)	−1.7	−4.2 to 0.7	42%	
Ultrasound						
Maia et al, 2024[50]		4 (613)	−2.530	−3.857 to −1.202	26%	

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Table A6: Nighttime Blood Pressure Reported in Relevant Systematic Reviews

Review	Follow-up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
SYSTOLIC						
Uncontrolled hypertension						
Sharp et al, 2024[39]	Primary (2–6 mo)	13 (2,161)	−3.5	−5.2 to −1.7	37%	
Sharp et al, 2024[39]	Overall (last)	13 (2,147)	−2.9	−5.0 to −0.8	42%	
Sham-controlled						
Vukadinović et al, 2024[36]		8 (2,030)	−4.46	−6.07 to −2.84	32%	
Ogoyama et al, 2024[35]	Primary (2–6 mo)	11	−3.41	−4.69 to −2.13	0%	
On medication						
Sharp et al, 2024[39]	Primary (2–6 mo)	10 (1,514)	−2.8	−5.4 to −0.2	42%	
Sharp et al, 2024[39]	Last	10 (1,514)	−2.4	−5.1 to 0.2	40%	
Mufarrih et al, 2024[46]		8	−2.70	−5.13 to −0.27	31%	Low
Off medication						
Sharp et al, 2024[39]	Primary (2–6 mo)	3 (647)	−4.2	−8.5 to 0.1	13%	
Sharp et al, 2024[39]	Last	3 (633)	−3.7	−11.1 to 3.6)	53%	
Mufarrih et al, 2024[46]		4	−2.16	−5.64 to 1.32	78%	Moderate
Radiofrequency						
Sharp et al, 2024[39]	Primary (2–6 mo)	9 (1,535)	−3.5	−6.0 to −1.0	49%	
Sharp et al, 2024[39]	Last	9 (1,536)	−3.6	−5.9 to −1.3	40%	
Treatment-resistant hypertension						
Sharp et al, 2024[39]	Primary (2–6 mo)	10 (1,296)	−2.7	−6.4 to 1.0	48%	
Sharp et al, 2024[39]	Last	10 (1,296)	−2.3	−5.8 to 1.2	46%	
Radiofrequency						
Sharp et al, 2024[39]	Primary (2–6 mo)	8 (1,031)	−2.8	−8.0 to 2.4	56%	
Sharp et al, 2024[39]	Last	8 (1,032)	−3.2	−7.6 to 1.2	50%	
Ultrasound						
Maia et al, 2024[50]		4 (621)	−3.692	−6.033 to −1.352	15%	

Review	Follow-up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
Second-generation system or sham-controlled						
Dantas et al, 2024[48]		7	−1.813	−3.901 to 0.276	0%	
DIASTOLIC						
Uncontrolled hypertension						
Sharp et al, 2024[39]	Primary (2−6 mo)	13 (2,161)	−1.6	−3.2 to −0.1	55%	
Sharp et al, 2024[39]	Last	13 (2,147)	−1.5	−3.0 to −0.0	53%	
Sham-controlled						
Vukadinović et al, 2024[36]		7 (1,729)	−2.60	−3.73 to −1.46	30%	
Ogoyama et al, 2024[35]	Primary (2−6 mo)	9	−1.61	−3.06 to −0.17	48%	
On medication						
Sharp et al, 2024[39]	Primary (2−6 mo)	10 (1,514)	−1.1	−2.7 to 0.5	45%	
Sharp et al, 2024[39]	Last	10 (1,514)	−1.1	−2.5 to 0.4	33%	
Mufarrih et al, 2024[46]		7	−1.06	−2.46 to 0.34	49%	High
Off medication						
Sharp et al, 2024[39]	Primary (2−6 mo)	3 (647)	−2.8	−7.3 to 1.6	58%	
Sharp et al, 2024[39]	Last	3 (633)	−2.5	−8.9 to 3.9	70%	
Mufarrih et al, 2024[46]		4	−0.56	−2.24 to 1.12	49%	Low
Radiofrequency						
Sharp et al, 2024[39]	Primary (2−6mos)	9 (1,535)	−1.5	−3.6 to 0.6	57%	
Sharp et al, 2024[39]	Last	9 (1,536)	−1.7	−3.5 to 0.1	49%	
Treatment-resistant hypertension						
Sharp et al, 2024[39]	Primary (2−6 mo)	9 (1,202)	−0.9	−3.1 to 1.4	50%	
Sharp et al, 2024[39]	Last	9 (1,202)	−0.9	−2.7 to 0.9	39%	
Radiofrequency						
Sharp et al, 2024[39]	Primary (2−6 mo)	7 (937)	−0.8	−4.1 to 2.4	59%	
Sharp et al, 2024[39]	Last	7 (938)	−1.1	−3.7 to 1.5	51%	
Ultrasound						
Maia et al, 2024[50]		4 (621)	−2.462	−4.557 to −0.368	52%	

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Table A7: Home Blood Pressure Reported in Relevant Systematic Reviews

Review	Follow-up	No. of studies (no. patients)	Mean difference	95% CI	I^2	GRADE (if reported)
SYSTOLIC						
Uncontrolled hypertension						
Sham-controlled						
Ogoyama et al, 2024[35]	Primary (2–6 mo)	5	−4.64	−7.44 to −1.84	68.6%	
On medication						
Mufarrih et al, 2024[46]		5	−6.08	−11.54 to −0.61	86%	High
Off medication						
Mufarrih et al, 2024[46]		2	−3.28	−5.96 to −0.61	0%	Low
Treatment-resistant hypertension						
Ultrasound						
Maia et al, 2024[50]		4 (596)	−4.415	−7.172 to −1.658	58%	
DIASTOLIC						
Uncontrolled hypertension						
Sham-controlled						
Ogoyama et al, 2024[35]	Primary (2–6 mo)	5	−2.28	−4.30 to −0.26	78.4%	
On Medication						
Mufarrih et al, 2024[46]		5	−3.16	−6.51 to 0.19	85%	Moderate
Off Medication						
Mufarrih et al, 2024[46]		2	−2.09	−4.73 to 0.56	59%	Low
Treatment-resistant hypertension						
Ultrasound						
Maia et al, 2024[50]		4 (596)	−2.439	−4.330 to −0.547	63%	

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

Appendix 6: Selected Excluded Studies – Economic Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Geisler BP, Egan BM, Cohen JT, Garner AM, Akehurst RL, Esler MD, et al. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. J Am Coll Cardiol. 2012;60(14):1271-7.	Same underlying model used in an included Canadian study
Gladwell D, Henry T, Cook M, Akehurst R. Cost effectiveness of renal denervation therapy for the treatment of resistant hypertension in the UK. Appl Health Econ Health Policy. 2014;12(6):611-22.	Same underlying model used in an included Canadian study
Henry TL, De Brouwer BF, Van Keep MM, Blankestijn PJ, Bots ML, Koffijberg H. Cost-effectiveness of renal denervation therapy for the treatment of resistant hypertension in the Netherlands. J Med Econ. 2015;18(1):76-87.	Same underlying model used in an included Canadian study
Kandzari DE, Cao KN, Ryschon AM, Sharp ASP, Pietzsch JB. Catheter-based radiofrequency renal denervation in the United States: a cost-effectiveness analysis based on contemporary evidence. J Soc Cardiovasc Angiogr Interv. 2024;3(10):102234.	Same underlying model used in an included Canadian study
Kario K, Cao KN, Tanaka Y, Ryschon AM, Pietzsch JB. Cost-effectiveness of radiofrequency renal denervation for uncontrolled hypertension in Japan. J Clin Hypertens. 2024;26(12):1502-12.	Same underlying model used in an included Canadian study
Pietzsch JB, Geisler BP, Esler MD. Gender differences in added benefit of catheter-based renal denervation for resistant hypertension: model-based estimation of unadjusted and quality-adjusted life year gains in males and females. Eur Heart J. 2013;34(suppl 1).	Abstract only
Sharp ASP, Cao KN, Esler MD, Kandzari DE, Lobo MD, Schmieder RE, et al. Cost-effectiveness of catheter-based radiofrequency renal denervation for the treatment of uncontrolled hypertension: an analysis for the UK based on recent clinical evidence. Eur Heart J Qual Care Clin Outcomes. 2024;10(8):698-708.	Same underlying model used in an included Canadian study

Appendix 7: Results of Applicability Checklists for Studies Included in the Economic Literature Review

Table A8: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Renal Denervation

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment[a]
Chowdhury et al, 2018,[58] Australia	Partially	Partially	Partially	Yes	No	Yes, 5%	Yes	No	Partially applicable
Dorenkamp et al, 2013,[60] Germany	Partially	Partially	No	Yes	Partially	Yes, 3%	Yes	No	Not applicable
Health Technology Wales, 2023,[59] United Kingdom	Partially	Partially	Partially	Yes	No	Yes, 3%	Yes	No	Partially applicable
McFarlane et al, 2024,[57] Canada	Partially	Partially	Yes	Yes,	No	Yes, 1.5%	Yes	No	Partially applicable
Taylor et al, 2024,[56] United Kingdom	Partially	Partially	Partially	Yes	No	Yes	Yes	No	Partially applicable

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Appendix 8: Letter of Information

LETTER OF INFORMATION

Ontario Health

Ontario Health is conducting a review of **Renal Denervation.** The purpose is to better understand whether this intervention should be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and caregivers of those who have been diagnosed with uncontrolled high blood pressure and who may or may not have experience with renal denervation.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30-40 minutes of your time for a phone interview
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION IN VOLVES

If you agree to share your experiences, you will be asked to have an interview with Ontario Health (OH) staff. OH staff will contact interested participants by collecting contact information (i.e., email address and/or phone number) to set up an interview. The interview will last about 30-40 minutes. It will be held over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about you or your loved one's condition and your perspectives about your diagnosis and treatment options in Ontario. Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until a year after the project completion. After a year post completion, the records will be destroyed. If you are sending us personal information by email, please be aware that electronic communication is not always secure and can be vulnerable to interception.

Ontario Health is designated an "institution" by the *Freedom of Information and Protection of Privacy Act* (FIPPA) and is collecting your personal information pursuant to FIPPA and the *Connecting Care Act, 2019* to support the Health Technology Assessment Program. If you have any questions regarding Ontario Health's collection and use of personal information for the purposes of this program, please contact Team Lead, Jigna Mistry noted below.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

IF YOU ARE INTERESTED, PLEASE CONTACT US:

DOCUMENTATION OF INFORMED CONSENT

We will give you a copy of this informed consent form after you and the OH staff have signed and dated it.

By signing this form, you confirm that:

- You agree to participate in this interview.
- You understand that your participation is voluntary.
- You understand the purpose, activities, risks and benefits of participating in this interview.
- You authorize the OH staff to use your data as explained in this form.
- OH staff have answered your questions to your satisfaction.

Please check the appropriate boxes:

- You give permission to the OH staff to audio record your interview: YES ☐ NO ☐

Name of Participant (please print):

_____

Signature of Participant (please sign):

_____

Name of OH Staff:

_____

Signature of OH Staff:

_____

Place: _____

Date: _____

Note: For participants who are unable to electronically sign the consent form with their permission to participate in this interview, OH staff will audio-record participants' consent prior to their interview and retain a record of participants' verbal consent through OH's dedicated secure network drive.

Appendix 9: Interview Guide

Renal Denervation Interview Guide

If possible, please click here or the link below to watch a video on renal denervation (Symplicity procedure): https://europe.medtronic.com/xd-en/healthcare-professionals/therapies-procedures/cardiovascular/renal-denervation/referrals-patient-selection/patient-education-materials.html

Diagnosis and Burden of Disease

- Do you have any symptoms related to hypertension? If so, what are they?
- How long ago were you diagnosed with hypertension?
- Journey to control hypertension
  - Treatment options explored
    - Medication: amount of medication, taking medication as directed, side effects, costs
    - Lifestyle changes: diet, exercise, stress, alcohol intake
    - Doctor's appointments
- Impact of hypertension on day-to-day, work, social life, mental health, quality of life

No Experience with Renal Denervation

- Awareness
- Decision-making factors
  - What information would you need to guide your decision-making:
    - Openness to renal denervation
    - Concern over invasiveness
    - Expectation of blood pressure control, pill burden, other factors
- What would it mean to you to have your blood pressure under control?

Experience with Renal Denervation

- Awareness of renal denervation
- Decision-making factors
  - Concern over invasiveness
  - Physician guidance
  - Other
- Experience with renal denervation: pre-procedure, post-procedure, follow-up care
- Equity: access, cost, geography (remote)
- Impact: medication, blood pressure, quality of life, doctor's appointments

References

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We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

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