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Cost-Effectiveness and Clinical Effectiveness of Catheter-Based Renal Denervation for Resistant Hypertension

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Objectives The purpose of this study was to assess cost-effectiveness and long-term clinical benefits of renal denervation in resistant hypertensive patients.

Background Resistant hypertension affects 12% of hypertensive persons. In the Symplicity HTN-2 randomized controlled trial, catheter-based renal denervation (RDN) lowered systolic blood pressure by 32 ± 23 mm Hg from 178 ± 18 mm Hg at baseline.

Methods A state-transition model was used to predict the effect of RDN and standard of care on 10-year and lifetime probabilities of stroke, myocardial infarction, all coronary heart disease, heart failure, end-stage renal disease, and median survival. We adopted a societal perspective and estimated an incremental cost-effectiveness ratio in U.S. dollars per quality-adjusted life-year, both discounted at 3% per year. Robustness and uncertainty were evaluated using deterministic and probabilistic sensitivity analyses.

Results Renal denervation substantially reduced event probabilities (10-year/lifetime relative risks: stroke 0.70/0.83; myocardial infarction 0.68/0.85; all coronary heart disease 0.78/0.90; heart failure 0.79/0.92; end-stage renal disease 0.72/0.81). Median survival was 18.4 years for RDN versus 17.1 years for standard of care. The discounted lifetime incremental cost-effectiveness ratio was $3,071 per quality-adjusted life-year. Findings were relatively insensitive to variations in input parameters except for systolic blood pressure reduction, baseline systolic blood pressure, and effect duration. The 95% credible interval for incremental cost-effectiveness ratio was cost-saving to $31,460 per quality-adjusted life-year.

Conclusions The model suggests that catheter-based renal denervation, over a wide range of assumptions, is a cost-effective strategy for resistant hypertension that might result in lower cardiovascular morbidity and mortality. (J Am Coll Cardiol 2012;60:1271–7) © 2012 by the American College of Cardiology Foundation

Resistant hypertension is defined as elevated blood pressure despite full doses of 3 antihypertensive agents, including a diuretic. Hypertension is the most common risk factor for the development of cardiovascular disease (CVD) (1,2) and leads to long-term cardiovascular and renal consequences that present a substantial burden to health care systems (2). Resistant hypertension has been increasingly recognized as a clinically important problem and might affect 13% of the hypertensive population (3).

Recently, catheter-based renal denervation (RDN) treatment has been shown to be a viable therapeutic approach for resistant hypertension. This denervation reduces sympathetic renal and central tonus (4) and arterial blood pressure (5,6). The randomized controlled Symplicity HTN-2 trial confirmed a systolic blood pressure (SBP) reduction of 32 ± 23 mm Hg, compared with a change of +1 ± 23 mm Hg observed for standard of care (SoC) ($p < 0.0001$), from a baseline SBP of 178 ± 18 mm Hg (7). Beyond the surrogate

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Abbreviations and Acronyms

CHD = coronary heart disease
CVD = cardiovascular disease
ESRD = end-stage renal disease
HDL = high-density lipoprotein
HF = heart failure
ICER = incremental cost-effectiveness ratio
MI = myocardial infarction
NICE = National Institute for Clinical Excellence
PSA = probabilistic sensitivity analysis
QALY = quality-adjusted life-year
RCT = randomized controlled trial
RD = risk difference
RDN = renal denervation
SBP = systolic blood pressure
SoC = standard of care

endpoint SBP, no cardiovascular events, nor costs, have been evaluated as endpoints of clinical studies.

Our aim was, therefore, to develop a decision-analytic model to predict long-term cardiovascular consequences and to ultimately assess the cost-effectiveness based on the long-term clinical effectiveness of this novel treatment option compared to SoC alone.

Methods

We developed a state-transition (Markov) model to project the impact of treatment, defined to be SoC plus catheter-based RDN treatment with the Symplicity RDN system (Medtronic Ardian LLC, Mountain View, CA). We used the model to compare RDN plus the existing SoC—3 or more antihypertensive medications—to SoC alone. The model projects 7 clinical endpoints: stroke, myocardial infarction (MI), all coronary heart disease (CHD), heart failure (HF), end-stage renal disease (ESRD), cardiovascular mortality, and all-cause mortality.

We utilized multivariate risk equations from large-scale cohort studies, such as the Framingham Heart Study, to compute transition probabilities. Values for other input parameters were derived from systematic searches of literature catalogued in PubMed. Assumptions made in the base case analysis were assessed in deterministic, structural, and probabilistic sensitivity analyses.

Model structure and modeling framework. The Markov model, which had a cycle length of 1 month and half-cycle correction, included 34 health states to represent clinical disease progression. The same model structure was used for the 2 competing strategies. The model operates by taking the reductions in SBP observed in the randomized controlled trial (RCT) and applying associations, known from the published literature, between SBP and clinical events to estimate their number by type. The model follows a simulated cohort with hypertension but no prior cardiovascular events and tracks occurrence of stroke, MI, angina, HF, ESRD, and death. As illustrated in Figure 1, cohort members can reach more than one of these states. Patients with angina can experience a subsequent MI or stroke (we assumed a fixed proportion of stable vs. unstable angina). Heart failure can follow long-standing hypertension or be secondary to an MI. Patients with ESRD can subsequently reach other endpoints. All patients status post another, nonfatal clinical event could experience a stroke. In the MI and stroke states, disease-specific mortality rates are adjusted for 1 cycle to reflect increased mortality after the event; similarly, the health-state utility weight (utility) for MI is reduced for 6 months post-event.

All analyses were conducted using a life-time horizon except where otherwise indicated. Our outcome measures were clinical endpoint relative risks, median survival, and incremental cost-effectiveness ratio (ICER), defined as the incremental direct medical costs of treatment and consequences in 2010 U.S. dollars divided by the incremental health benefits expressed as quality-adjusted life-years (QALYs). From a societal perspective, we discounted both costs and health outcomes at 3% per year.

Input parameters. The estimated decrease in SBP after RDN and other baseline patient characteristics were based on results of the Symplicity HTN-2 trial (7); the baseline characteristics of patients with true resistant hypertension enrolled in this trial were similar to those in a registry of patients meeting resistant hypertension criteria (8), except for SBP: participants in HTN-2 had to have a baseline SBP of ≥160 mm Hg per inclusion criteria. All other input parameters were derived from systematic searches of the PubMed literature (Online Appendix). Cardiovascular event probabilities were obtained from the Framingham risk equations, except for the incidence of MI for which the PROCAM (Prospective Cardiovascular Münster Heart Study) risk equation was used. The ESRD incidence was estimated from the results of a more recent cohort study. Mortality rates were based on the most recent published estimates. Utilities were adjusted for different age groups by application of a multiplicative factor (9). Cost estimates were converted to 2010 U.S. dollars using the general consumer price index for the U.S. (10,11). Table 1 lists the key parameters (Online Appendix).

Model validation. The external validity of the model was assessed in several ways. First, the predicted 10-year relative risk of CHD for subjects with SBP 120 mm Hg were compared to subjects with SBP of 180 mm Hg for 6 combinations of risk factors analyzed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7): SBP, total cholesterol, high-density lipoprotein (HDL), smoking, diabetes mellitus, and left ventricular hypertrophy (Online Appendix) (12). For each combination of risk factors, we compared our simulated relative risk to the JNC7-reported relative risks. Second, the predicted MI and stroke incidences were computed for a cohort with an annual cardiovascular disease (CVD) risk of 2% and then compared to the corresponding projections generated by the U.K. National Institute for Clinical Excellence (NICE) hypertension model, which was recently used to inform guidelines for ambulatory blood pressure measurement (13). Third, attempts were made to compare model projections to event rates reported for the placebo arms of several large-scale hypertension RCTs (Online Appendix).