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

Benjamin P. Geisler, MD, MPH,* Brent M. Egan, MD,† Joshua T. Cohen, PtID,‡ Abigail M. Garner, MS,* Ronald L. Akehurst, MFPHM,§ Murray D. Esler, MBBS, PtID,∥ Jan B. Pietzsch, PhD*

Menlo Park, California; Charleston, South Carolina; Boston, Massachusetts; Sheffield, United Kingdom; and Central Melbourne, Victoria, Australia

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 care (SoC) (p < 0.0001), from a baseline SBP of 178 ± 18 mm Hg (7). Beyond the surrogate
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 $\geq 160$ 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).
Patient characteristics. The modeled base case assesses the impact of RDN in a population similar to the Symplicity HTN-2 trial cohort (7). The mean baseline SBP was 178 mm Hg (95% confidence interval: 175 to 182 mm Hg), and the mean difference in SBP after 6 months of treatment was −32 mm Hg (−38 to −25 mm Hg). On average, members of the cohort were on 5 medications, had a mean age of 58 (55 to 61) years, were 43% female, had a diabetes mellitus prevalence of 34%, and a current smoker prevalence of 16%. Because the Symplicity HTN-2 trial did not report lipid levels, we used as a proxy 2005 to 2008 results from the National Health and Nutrition Examination Survey for patients whose blood pressure remained uncontrolled despite their use of 3 or more blood pressure medications (14). Lipid levels for this group were as follows: low-density lipoprotein 108 (103 to 114) mg/dl, HDL 53 (51 to 55) mg/dl, and total cholesterol 199 (191 to 206) mg/dl (Online Appendix). Unlike the National Health and Nutrition Examination Survey subpopulation or the Symplicity HTN-2 cohort, however, our simulated cohort was assumed not to include subjects with prior cardiovascular events, manifest CHD, or ESRD. We imposed this restriction on the simulated cohort to ensure predictive validity of the multivariate risk equations employed in the model. In a structural sensitivity analysis, we explored the impact of this assumption. Patients in both cohorts were assumed to be maintained on the antihypertensive medications from their baseline.

Using our base case cohort, we computed 10-year and lifetime probabilities of reaching one or several endpoints, with each endpoint separately reported. All simulations were conducted in TreeAge Pro (TreeAge Software, Williamstown, Massachusetts).

Analysis of uncertainty. We assessed uncertainty in multiple ways. First, we conducted one-way sensitivity analyses, varying all clinical input parameters by at least ±50% and cost and utility parameters over defined ranges, as described in Table 1 and in the Online Appendix. Second, we varied the baseline SBP value (mean 178 mm Hg). Third, we evaluated the following structural assumptions: 1) the assumed persistence of the blood pressure reduction after RDN (considering gradual effect size reduction over time); 2) the hypothetical possibility that the RDN procedure will have to be repeated to maintain treatment effect; and 3) the possibility that discomfort after the procedure substantially reduces utility for a short period of time (6 days at utility value of 0, equating to death). Fourth, we determined how large changes to individual assumptions must be to exceed the $50,000 per QALY willingness-to-pay threshold, which is sometimes used to categorize interventions as having either good value (ICER less than this threshold) or poor value (ICER in excess of $50,000 per QALY) (15).

Finally, we conducted a probabilistic sensitivity analysis (PSA). This involves randomly selecting values from known or estimated distributions for all input parameters, running the model, and repeating the process. We drew values from 54 distributions developed using primary data from the Symplicity HTN-2 study, the literature, and expert opinion (Online Appendix). The set of 5,000 results produced characterizes the probability distributions of outcomes resulting from the uncertainty around the input parameters.
Results

Model validation. Model-predicted relative risks (SBP of 120 mm Hg vs. 180 mm Hg) were similar to those predicted by the JNC7 model, except for the influence of increasing total cholesterol and of diabetes. For these cases, our model predicted more conservative relative risks associated with an SBP of 120 mm Hg (+12% risk difference; see Online Appendix). In comparisons with the NICE model, our model predicted an annual MI incidence of 0.39% and an annual stroke incidence of 0.73% for a combined cohort of men and women. The corresponding sex-specific incidence rates predicted by the UK NICE model were 0.45% (males) and 0.26% (females) for MI, and 0.70% (males) and 0.83% (females) for stroke. The results of validation attempts against placebo arms of RCT’s are outlined in the Online Appendix, along with their limitations. Clinical trial results were within the 95% credible intervals and projections showed a tendency to rather over-predict than under-predict.

Base case results. The model predicted that RDN would reduce each of the clinical event risks as compared to SoC. The smallest 10-year relative risks were obtained for MI, stroke, and ESRD (0.68, 0.70, and 0.72, respectively) whereas CHD and HF risk reductions were less substantial (0.78 and 0.79, respectively). Over 10 years, RDN reduced cardiovascular mortality by 30% and all-cause mortality by 15%. Over lifetime, risk reductions were less pronounced (Table 2). Reduced clinical event risks increased median survival from 17.07 to 18.37 years (an increment of 1.30 years) and quality-adjusted life expectancy from 12.07 to 13.17 QALYs (undiscounted: an additional 1.10 QALYs). Although RDN over lifetime reduced undiscounted costs by $1,769, it increased discounted costs by $2,013. This difference reflects the fact that RDN costs are incurred upfront while the resulting savings take place over a lifetime and hence are reduced when discounting procedures are applied. The discounted lifetime ICERs for RDN were $2,715 per life-year gained and $3,071 per QALY.
Uncertainty analyses. Model projections were relatively insensitive to plausible modifications of most input assumptions. The only input parameters that had a significant impact on the ICER were RDN-associated SBP reduction (effect size), baseline SBP, and costs for RDN therapy. In threshold analyses, the ICER exceeded the $50,000 per QALY willingness-to-pay threshold only when the SBP reduction after RDN was assumed to be no more than 11.1 mm Hg, substantially less than what has been observed in clinical trials (99% confidence interval: 22.8 to 40.5 mm Hg reduction). When baseline SBP was varied between 160 and 200 mm Hg, RDN was cost-saving between 160 and 172 mm Hg, and then gradually increased to $6,305 per QALY at 200 mm Hg. Structural sensitivity analyses assessed the effect of several additional scenarios. Under the hypothetical assumption that the treatment effect would decrease by 1 mm Hg annually, the projected ICER increased to approximately $13,300 per QALY. Threshold analysis revealed that SBP reduction would need to decrease by >3.0 mm Hg per year for ICER to exceed the $50,000 per QALY willingness-to-pay threshold. Assuming as many as 3 repeat procedures, 1 every 10 years, increased the ICER to $19,869 per QALY. Combinations of effect size reduction and repeat procedures are shown as 2-way sensitivity analyses in the Online Appendix. Assuming that patient utility is zero for the 6 days after the RDN procedure increased the ICER minimally to $3,135 per QALY. When modeling a cohort with prior cardiovascular events as per the baseline characteristics of the Symplicity HTN-2 study, the quality-adjusted life expectancy increased by 0.46 QALYs while costs increased by $1,270, resulting in an ICER of $2,732 per QALY (all values discounted). (See the Online Appendix for additional sensitivity analyses.)

The PSA for the examined cohort yielded a 95% credibility interval that ranged from cost saving to $31,460 per QALY. In all simulations, RDN improved health (i.e., incremental QALYs were >0), and in 21.1% of the simulations, RDN also decreased costs (i.e., was cost-saving). Ninety-seven percent of the simulation results were below a willingness-to-pay threshold of $30,000 per QALY, meaning that the PSA results indicate there is a 97% chance that the ICER is <$30,000 per QALY in the examined cohort. The results also indicate that there was a 99.6% probability that the ICER is less than the $50,000 per QALY threshold. (See Online Appendix for graphical PSA results.)

Discussion

Our results indicate that RDN might be cost-effective when compared to other, well-accepted medical treatments with an incremental cost-effectiveness ratio that is markedly below the commonly accepted threshold of $50,000 per QALY. Moreover, there might be an approximately 1 in 5 chance that RDN is cost-saving in the investigated cohort. Although RDN therapy represents an additional cost at time of treatment, it seems to offer great value over time.

According to our findings, RDN for resistant hypertension substantially reduces CVD and ESRD and increases survival. Cardiovascular endpoints decreased by 21% to 32% over 10 years and between 8% and 17% over lifetime. The more modest risk reductions observed over a lifetime might reflect the late-in-life contribution of events that were delayed by RDN but not fully prevented. These events may reflect the impact of other risk factors (e.g., diabetes, dyslipidemia, or smoking) that blood pressure reduction does not address. Because of these contributions, relative risk may differ across groups with different combinations of these and other risk factors. The JNC7 risk predictions, used in this paper to validate our model, also indicate that relative risks vary across groups with different cardiovascular risk factors.

External validation demonstrated that the simulation model-predicted relative risks for cardiovascular outcomes (SBP 120 mm Hg vs. 180 mm Hg) were similar to or slightly more conservative than the JNC7/Framingham-based predictions for 6 different hypothetical cohorts. In addition, projections by our model were similar to estimates from the NICE hypertension model except for stroke, the risk of which our model slightly under-predicted. Uncertainty analysis likewise suggests our findings are robust as...
plausible alternative assumptions did not substantially alter model projections.

As with most models evaluating long-term treatment effects, assumptions had to be made about the persistence of the therapeutic benefit. The Symplicity HTN-2 randomized controlled trial data reveal an initial reduction of 20 mm Hg 1 month after the RDN procedure, and of 32 mm Hg 6 months post-procedure (7). At the American College of Cardiology 61st Annual Scientific Session, the 12-month follow-up data from the HTN-2 trial and the 36-month data from the HTN-1 study were presented that indicate a sustained SBP reduction of 28 mm Hg and 33 mm Hg, respectively (16,17). Our base case assumption that this reduction persists indefinitely has not yet been confirmed, but seems reasonable given the observed growth in the treatment effect over time and literature suggesting that the effect of RDN is likely to persist or possibly even grow (18).

We also addressed this assumption in comprehensive sensitivity analyses, which showed that RDN remains cost-effective across a wide range of assumptions, including a fade-out of effect size of 2 mm Hg per year, or up to 3 repeat procedures with 5 years between each of them. Moreover, our model only reflects the beneficial impact of SBP reduction on cardiovascular and ESRD morbidity and mortality. Renal denervation is under investigation in other clinical settings, including increased insulin sensitivity (19), a further decreased risk for chronic kidney disease (20), and amelioration or stabilization of HF (21) and of sleep apnea (22); RDN is investigational in some of these comorbid subgroups and several trials are currently recruiting patients (Online Appendix). Omitting these potentially beneficial effects means that our results may understate the favorability of RDN’s clinical effectiveness, and therefore also its economic effectiveness.

Our model differs from other recently published decision-analytic hypertension models (13,23) in some important respects. First, it includes ESRD as an additional relevant endpoint for costs and life expectancy. ESRD was not an endpoint, for example, in the recently published hypertension model used for policy-making by NICE (13). Second, our model characterizes possible sequelae of CVD, including acute-phase and secondary events (23). Third, because our model uses the Framingham and other multivariate risk equations, differences in event probabilities between cohorts with different risk profiles can be modeled more accurately by explicitly taking into account relevant clinical input parameters such as lipid levels or underlying comorbid conditions such as atrial fibrillation or cardiomegaly/ventricular hypertrophy (13,23).

Despite this advantage, using results from an observational study rather than from an interventional study may reduce the magnitude of projected clinical benefits and hence the favorability of our cost-effectiveness estimates. Studies such as the Framingham Heart Study used here often use multivariate analyses to isolate the independent contribution of each factor to changes in risk while controlling for the others. For example, because the multivariate risk equation for MI suggests that LDL, HDL, and triglyceride levels strongly influence MI risk, controlling for these factors might reduce the residual predicted contribution of blood pressure to MI risk due to confounding, as some cardiovascular risk factors might be associated with each other.

In contrast, estimating the association between blood pressure and risk of reaching one of the clinical endpoints with evidence from interventional studies might yield a stronger estimate of this relationship, in part because these studies often use univariate regression analysis to estimate association measures. However, even among interventional studies of antihypertensive therapies, estimates of the relationship between blood pressure and the risk of reaching an endpoint vary (e.g., HF) (24). Finally, compared to observational studies, interventional studies have relatively limited follow-up (up to 5.5 years) (25) and, in some cases, a small sample size.

**Study limitations.** First, our model, by definition, represents CVD using a limited number of health states and transitions that may not always reflect the full spectrum of possible pathways of disease progression. Second, our model assumptions are based on office-based SBP measurements, which may imply larger SBP reductions than would be implied by ambulatory measurements. However, because most SBP measurements in the literature are based on office measurements, and the multivariate risk models use office-based SBP, this limitation is typical. Third, subjects in our dataset were mostly Caucasian. Therefore, these data may not be representative of the entire U.S. population. It is known, for example, that hypertension contributes about 15% to the difference in life expectancy between African Americans and Caucasians (26). Future clinical trials are likely to address this issue. Results of probabilistic sensitivity analyses for cohorts other than the one investigated here might differ in their proportions that are cost saving or cost-effective at given willingness-to-pay thresholds. Fourth, to facilitate implementation, we did not build into the model all possible combinations of primary disease and subsequent disease development. For example, the model accounts for the possibility that angina may be followed by MI or stroke, but not ESRD. The model included those pathways with the highest probability and hence reasonably approximates the disease process, but by omitting some pathways, it may underestimate the aggregate impact of elevated blood pressure. Fifth, because the current experience with RDN is relatively modest, adverse events that might occur after RDN have not been identified or included in this study except for a sensitivity analysis, which considered short-term reduced quality of life after the procedure (Online Appendix). Sixth, our model assumes the same health-related quality of life in the initial hypertension state for both RDN and SoC groups, although certain symptoms such as headaches or anxiety might improve in the former group after denervation treatment and resulting SBP decrease. Because our model effectively assumes that these potential improvements have no effect on quality of life, it conservatively understates aggregate societal benefits and,
therefore, underestimates the favorability of the ICER. Seventh, in the probabilistic sensitivity analysis we were unable to account for covariance between the input parameters as no such data were available to us. Finally, our analysis is based on the clinical findings of the Symplicity HTN-2 study, and assumes cost and effect size of the Symplicity system. Results are not readily transferable to other RDN systems. The Symplicity system is currently approved in Europe and other markets, but is investigational in the United States (NCT01418261).

Conclusions

Our results suggest that catheter-based RDN therapy is a cost-effective treatment strategy for resistant hypertension that might be more than an order of magnitude below the recognized threshold of $50,000 per QALY, depending on the durability of the treatment effect. Renal denervation might also be associated with substantial reductions in cardiovascular morbidity and mortality.

Acknowledgments

The authors are indebted to Michel Burnier, MD, Mark Caufield, FMEdSci, Mark A. Hlatky, MD, Peter J. Neumann, ScD, Neil R. Poulter, FMEdSci, Roland Schmieder, MD, and Hye-young Kang, PhD, for their helpful comments, which significantly improved this research.

Reprint requests and correspondence: Dr. Jan B. Pietzsch, Wing Tech Inc., 42808 Christy Street, Suite 230, Fremont, California 94025. E-mail: jpietzsch@wing-tech.com.

REFERENCES