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Original article

Cost-effectiveness of renal denervation therapy for the treatment of resistant hypertension in The Netherlands

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Abstract

Objectives:
Safety and efficacy data for catheter-based renal denervation (RDN) in the treatment of resistant hypertension have been used to estimate the cost-effectiveness of this approach. However, there are no Dutch-specific analyses. This study examined the cost-effectiveness of RDN from the perspective of the healthcare payer in The Netherlands.

Methods:
A previously constructed Markov state-transition model was adapted and updated with costs and utilities relevant to the Dutch setting. The cost-effectiveness of RDN was compared with standard of care (SoC) for patients with resistant hypertension. The efficacy of RDN treatment was modeled as a reduction in the risk of cardiovascular events associated with a lower systolic blood pressure (SBP).

Results:
Treatment with RDN compared to SoC gave an incremental quality-adjusted life year (QALY) gain of 0.89 at an additional cost of €1315 over a patient's lifetime, resulting in a base case incremental cost-effectiveness ratio (ICER) of €1474. Deterministic and probabilistic sensitivity analyses (PSA) showed that treatment with RDN therapy was cost-effective at conventional willingness-to-pay thresholds (€10,000–80,000/QALY).

Conclusion:
RDN is a cost-effective intervention for patients with resistant hypertension in The Netherlands.

Introduction

Hypertension is an important worldwide public-health challenge due to both the prevalence and concomitant risks of cardiovascular and kidney disease[1,2]. The prevalence of hypertension is predicted to increase by ~24% by 2025 in developed countries[3], and has been identified as the leading risk factor for mortality[4]. Furthermore, it has been shown to be a key risk factor for a range of cardiovascular events including: stroke, myocardial infarction (MI), heart failure (HF), and peripheral arterial disease. Hypertension also heightens the risk of renal abnormalities, the most severe of which is end-stage renal disease (ESRD)[5]. The increase in prevalence and the associated consequences of hypertension will result in a considerable economic burden[6,7].

Despite numerous safe and effective pharmacological interventions for hypertension, a significant percentage of patients (10–30%[5,8,9]) have resistant hypertension, a condition where blood pressure remains above the goal range in spite of optimal medical treatment with three or more different anti-hypertensive

therapies (one being a diuretic at maximal recommended or maximal tolerated dose). For these patients, conventional pharmacological treatment fails to control blood pressure adequately and, thus, treatment options for this sub-group of patients are limited. Furthermore, patients with resistant hypertension have an increased risk of cardiovascular events of ~50% compared to patients with controlled blood pressure over 5 years[10].

Catheter-based sympathetic renal denervation (RDN) is an innovative procedure-based approach that disrupts afferent and efferent nerves and lowers blood pressure by using radio frequency[11]. A randomized controlled trial, Symplicity HTN-2, was undertaken with 106 patients to assess the comparative efficacy of the RDN procedure in combination with maintaining previous medical treatment (standard of care, SoC) compared to SoC alone[12]. Patients enrolled in the Symplicity HTN-2 trial had a mean baseline SBP of 178 ± 18 mmHg and results showed a mean decrease in office SBP of 32 ± 23 mmHg at 6 months for patients treated with RDN, compared to mean increase in office SBP of 1 ± 21 mmHg for patients treated with SoC[12]. A related single-armed study with a follow-up of 36 months found that the substantial reduction in office SBP following RDN therapy persisted for the full duration of the study[13].

There have been several estimations of the cost-effectiveness of RDN therapy in Europe and the US[14–16] based on HTN-2 findings in which RDN seems to be an efficient therapeutic option for patients with resistant hypertension. However, no such estimation exists in the Dutch healthcare setting, which is based on compulsory basic health insurance regulated by the Zorginstituut Nederland (institution of care for The Netherlands). In this type of system, it is desirable to evaluate the cost-effectiveness of a therapy over a patient's lifetime in order to fully incorporate the incremental costs and health gains associated with that treatment, which is particularly important for a chronic condition such as hypertension. In this paper, we consider the cost-effectiveness (cost per life-year gained (LYG) and cost per quality-adjusted life year gained (QALY)) of RDN therapy for patients with resistant hypertension in The Netherlands compared to SoC.

Methods

Study design

An existing cost-effectiveness model was used[16], which was based on data from the HTN-2 trial[12] and examined the cost-effectiveness of RDN in the UK. The model had two arms; one followed patients who were treated with RDN and SoC and the other followed patients treated with SoC alone. The model was a transition-state Markov model with seven clinical end-points; stroke, MI, coronary heart disease (CHD), HF, ESRD, cardiovascular mortality, and all-cause mortality.

In total, the model had 34 uniquely defined health states that allowed for patients to be categorized as having up to two types of cardiovascular events; primary and secondary (e.g. MI post ESRD; see Figure 1). The risk of subsequent events, particularly mortality, was therefore different between patients who had one or more cardiovascular events. Time-dependent health states were also included in the model (post-stroke, post-MI, and HF Year 1 and Year 2) to allow different risks to be applied

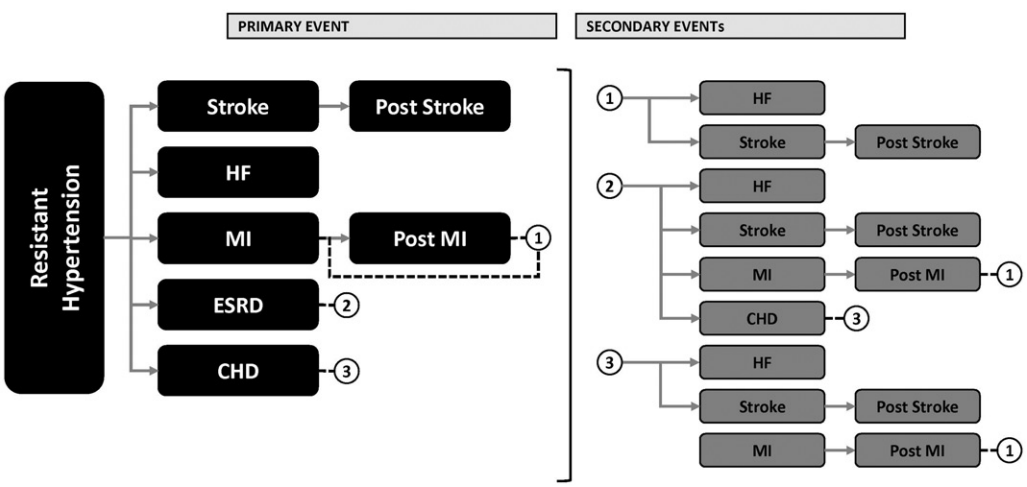


Figure 1. Model diagram. CHD, coronary heart disease; ESRD, end-stage renal disease; HF, heart failure; MI, myocardial infarction.
Non-cardiovascular death was applied at each cycle based on the general mortality rate (for patients with hypertension) and modelled ESRD mortality (ESRD state). Cardiovascular death was applied at each cycle based on the published data for CHD, stroke, MI and mortality.
At each cycle of the model, patients could have either remained in their current health state or experienced a new cardiovascular or non-cardiovascular event or death and moved to a new state.

and, thus, allow the rate of subsequent events to vary according to the time since the primary event.

The model used a cycle length of 1 month and followed patients over a lifetime horizon to evaluate the economic impact of RDN therapy. As 1 month is a relatively long cycle length, results were half cycle corrected assuming that, on average, patients experience an event half way through the cycle. Clinical inputs and patient characteristic such as baseline SBP, age and gender were taken from the Symplicity HTN-2 trial (Table 1), as described by Gladwell *et al.*[16] All patients were assumed to have a mortality risk of one upon reaching the age of 100. The difference in rates of cardiovascular events on each arm was driven by the reduction in SBP shown in the Symplicity HTN-2 trial of 32 mmHg (based on 90% responder rate), which was applied to the RDN arm of the model.

The model was adapted to the Dutch setting with country-specific costs, utility, and mortality data from published literature where possible. Results were derived using a Dutch payer perspective to include only healthcare costs.

Table 1. Patient characteristics.

Patient characteristics	*n* (range)
Age (years)	58 (45–70)[12]
Sex (% female)	43[12]
Diabetes mellitus (%)	34
Current smoker (%)	16[15]
LDL (mmol/l)	3.54 (2.5–5.17)[15]
HDL (mmol/l)	1.40 (1.03–1.55)[15]
Triglycerides (mmol/l)	1.64 (0.56–2.26)[15]
Baseline SBP (mmHg)	178 (173–183)[12]
Treatment effect (mmHg reduction)	32 (25–39)[12]

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

The outcomes of the model were costs, LY, and QALYs. In line with the Zorginstituut Nederland guidelines for pharmacoeconomic research[17], costs and benefits (LYs and QALYs) were discounted at 4.0% and 1.5% per annum, respectively.

Transition probabilities

The Dutch model used the same approach as undertaken in the UK model to estimate cardiovascular and non-cardiovascular event probabilities (Table 2). The Framingham risk equations were used to estimate the underlying transition probabilities based on a range of patient characteristics (see supplementary content) for stroke, HF, and CHD. The incidence of MI was estimated using PROCAM risk equations[18] and the probability of ESRD was predicted using the results of a recent cohort study[19]. Mortality rates for each of the health states were taken from the UK model and were based on recent estimates from the literature (Table 2). Background mortality rates that apply to patients in all health states were based on data published by Statistics Netherlands[20].

Costs

A manual review of the literature was conducted via PubMed and general internet searching to gather data on the costs and resource use for each clinical end-point. A summary of the costs applied to each health state in The Netherlands is given in Table 3. The cost of initial unstable angina pectoris (AP), initial HF, initial MI and acute stroke are applied as one-off costs as patients spend one cycle only in these health states before moving onto the time-dependent tunnel states (unstable AP; MI; HF

Table 2. Model inputs.

Patient characteristics	Parameter, *n* (Range)
Stroke incidence	Exponential (SBP, age, sex, CVD, LVH, DM, smoking, AF)[34,35]
AP/CHD incidence	Weibull (SBP, age, sex, menopausal status (♀), TC, HDL, TG (♀), DM, smoking, medications, alcohol)[36,37]
MI incidence	Exponential (SBP, age, TG, HDL, LDL, DM, γ-GT, smoking)[18]
Primary HF incidence	Exponential (SBP, age, sex, DM, LVH, cardiomegaly, vital capacity, heart rate, CHD, valve disease)[38]
Secondary HF incidence	0.12% for AP; 0.18% post MI, 23.1% in the first 30 days[39]
ESRD incidence	Rate with HRs (SBP, diabetes)[40,41]
Stroke mortality	12.6% (Month 1) HR = 2.3 (Months 2+) applied to general mortality RR = 2.27–2.99 post-MI applied to stroke mortality RR = 2.19 post-HF applied to stroke mortality[42]
MI mortality	1.5–29.5% depending on age (Month 1); applies a constant death risk (2.2–3.5%) based on SBP with a RR (1.00–2.46) for age (Months 2+)[43–45]
HF mortality	4–6% (Month 1); 1.2–1.5% (Months 2–12); 0.7% (Months 13+); with a RR = male 0.29–2.48; female 0.39–3.28 applied based on age stratified regression[43,46]
ESRD mortality	Age-stratified regression (0.24–1.27% per month)[19]

AF, atrial fibrillation; AP, angina pectoris; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; ERA-EDTA, European Renal Association–European Dialysis and Transplantation Association; ESRD, end-stage renal disease; γ-GT, gamma-glutamyl transferase; HDL, high-density lipoprotein; HF, heart failure; HR, hazard ratio; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MI, myocardial infarction; RR, relative risk; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Table 3. Cost and utility inputs.

Health state	Cost in 2012 Euros (Range*)	Utility (range†)
Stable AP/CHD	€9.78 (€7.95, €11.78) per month[23,47,48]	0.82 (0.64–0.95)[25]
Initial unstable AP/CHD	€3983 (€3240, €4800) per event[25]	0.64 (0.51–0.76)[25]
Unstable AP/CHD	€12.61 (€10.26, €15.20) per month[23,47,48]	0.82 (0.64–0.95)[25]
ESRD patient without diabetes	€3680 (€2994, €4435) per month[49]	0.72 (0.6–0.83)[50]
ESRD patient with diabetes	€3680 (€2994, €4435) per month[49]	0.72 (0.60–0.83)[50]
Initial HF	€4413 (€3590, €5318) per event[51]	0.68 (0.62–0.80)[52]
HF Year 1	€35.22 (€28.65, €42.45) per month[23,47,53]	0.68 (0.62–0.80)[52]
HF Year 2	€22.75 (€18.51, €27.42) per month[23,47,53]	0.68 (0.62–0.80)[52]
SoC	€16.71 (€13.59, €20.14) per month[23,24,47]	1.00[54–55]
RDN therapy	€6574 (€5349, €7923) per event (source: Medtronic cost estimation 2012)	N/A
Initial MI	€3983 (€3240, €4800) per event[56]	0.76 (0.72–0.79)[57] (first 6 months)
Post-MI	€94.41 (€76.82, €113.79) per month[58]	0.88 (0.80–0.96)[59] (after 6 months from initial MI)
Acute stroke	€9663 (€7862, €11,647) per event[58]	0.72 (0.57–0.85)[60]
Post-stroke Year 1	€781 (€635, €941) per month[58]	0.72 (0.57–0.85)[60]
Post-stroke Year 2	€781 (€635, €941) per month[58]	0.72 (0.57–0.85)[60]

AP, angina pectoris; CHD, coronary heart disease; ESRD, end-stage renal disease; HF, heart failure; MI, myocardial infarction; NICE, National Institute of Health and Care Excellence; NL, The Netherlands; RDN, renal denervation, SoC, standard of care. Utility for death is 0. Utility values were adjusted for age using the age-dependent multipliers from Kind *et al.*[26], which give utility values for the average member of the population at each age. UK-specific utility multipliers were used in the absence of such data for the Dutch population.

*Upper and lower bounds were calculated for costs assuming a gamma distribution with a standard error of 10% of the mean deterministic value.

†Where possible 95% confidence intervals were used for upper and lower bound values according to a beta distribution; where this was not possible upper and lower bounds were calculated assuming standard error equal to 10% of the deterministic (mean) value.

Year 1; MI; post-stroke). The tunnel states were included to capture changes in costs, quality-of-life, and risk in a given health state over time. For example, costs of a heart failure are higher in the first year than in subsequent years. The inflation indices from the Dutch Central Office For Statistics[21] were used to inflate costs to 2012 prices, where necessary.

In order to fully capture the cost of pharmaceuticals dispensed in The Netherlands, a 'Pharmacy fee' (€5.67 average to August 2012[22]) was incurred when a patient collected their prescription from a pharmacy. Patients were assumed to do so every 90 days, giving a monthly 'Pharmacy fee' of €1.89 added to each drug cost. In addition to this, any initial prescription was assumed to take place with a general practitioner, costing €29.74 for the first prescription and €14.87 for each prescription thereafter[23], giving a monthly prescription cost of €6.19 [Year 1: (€29.74 + (3*€14.87))/12); Subsequent years: (4*€14.87)/12 = €4.96]. Costs shown in Table 3 include pharmacy, prescription and hospital costs.

The cost of SoC was calculated based on the treatment guidelines for cardiovascular risk management in patients over the age of 70 from the Dutch Society of General Practitioners[24]. Given the patient groups mentioned in the guideline and the starting age of patients in the model this was deemed most appropriate. SoC treatments are hydrochlorothiazide (12.5 mg once daily), amlodipine (5 mg once daily), perindopril (4 mg once daily), and simvastatin (20 mg once daily)[24]. The cost of anti-hypertensive medication was applied to all health states on both arms of the model, with the exception of death, in line with the Symplicity HTN-2 protocol[12]. The cost of the RDN procedure was estimated at €6573 based on a micro-costing exercise undertaken by Medtronic Ltd., and was applied as a one-off cost in the first cycle of the intervention arm. The cost estimation included both the procedure and material costs and the screening phase resources.

Utilities

Health-related quality-of-life (HRQoL) was captured in the model by assigning utility weights to each of the following health states (stroke; MI, HF, AP/CHD (stable & unstable), ESRD, and death).

Utility values were identified by a manual search of the literature via Pubmed and general internet searching, shown in Table 3. Where Dutch-specific utility values were not available, the UK values were used (hypertension, HF, ESRD, MI after first 6 months) from Gladwell *et al.*[16].

In the UK model, the utility value assigned to the MI state was varied over time, with a lower value of 0.76 applied in the first 6 months post-MI event to capture the lower HRQL in the months following the event. A higher utility value of 0.88 was applied from Month 7 onwards in the MI health state. The application of a lower

utility value in the first 6 months was also applied in The Netherlands model. Eefting *et al.*[25] estimated the HRQoL for patients who had experienced an MI receiving off-pump surgery and stenting for angioplasty. At baseline and after 6 months' treatment with stenting and surgery gave very similar values and, thus, the average of the two values were used as Dutch-specific utility data in the model. This resulted in values of 0.644, 0.751, 0.836, and 0.825 for patients with AP in months 1, 2–6, 7–12, and 13 onwards post-event, respectively. In order to convert the utility values as measured by Eefting *et al.* to values that could be used in the Dutch model, the utility value for the first month was used for acute AP/Initial CHD and a weighted average was taken from the three remaining utility values and used for the AP/other CHD health states. The utility values were weighted by the average time spent in the AP/CHD health state (97 months). Therefore the utility for AP/CHD for the Dutch model was calculated as follows: $(5*0.751 + 6*0.836 + (97 - 5 - 6)*0.825)/97 = 0.822$.

Where more than one event had occurred (e.g., stroke post-HF) the lowest utility value was applied (HF). Utility values were adjusted for age using the age-dependent multipliers from Kind *et al.*[26], which give utility values for the average member of the population at each age. UK-specific utility multipliers were used in the absence of such data for the Dutch population.

Sensitivity analysis

All inputs in the economic model were averages and, therefore, had distributional properties. Given this, parameter uncertainty was estimated by assigning relevant distributions to each input according to standard health economic practice. Deterministic (one-way) sensitivity analysis was performed to assess the robustness of the model results when varying parameter values. In-one way sensitivity analysis, each parameter is varied to the upper and lower bounds and the incremental cost-effectiveness ratio (ICER) value is recorded at each point. Where possible, 95% confidence intervals were used for upper and lower bound values; where this was not possible upper and lower bounds were calculated assuming standard error equal to 10% of the deterministic (mean) value. The ten most influential parameters in terms of ICER variation are presented as a tornado diagram.

A probabilistic sensitivity analysis (PSA) was also performed on the model to estimate the sensitivity of the RDN cost-effectiveness results given the level of uncertainty around parameter inputs. In the PSA, Monte Carlo simulation methods were used to sample values from the plausible ranges and distributions of each parameter simultaneously over 5000 iterative samples. This gives 5000 unique outcomes with a different combination of parameter values for each sample. Results were compiled and displayed as a cost-effectiveness plane and a cost-effectiveness acceptability curve.

Scenario analysis

In order to undertake the analysis, a number of assumptions concerning the treatment effect of RDN therapy were necessary. In the base case the mean reduction in office SBP of 32 mmHg shown in the Symplicity HTN-2 trial[12] was assumed to be sustained over a patient's lifetime. However, in the absence of clinical data on the long-term treatment effect, a scenario analysis was conducted assuming a waning in the treatment effect of 1 mmHg per year requiring re-treatment after 10 years to maintain a SBP within the normal range. In the base case analysis, it was assumed that the average treatment age was 58, taken from the Symplicity HTN-2 trial[12]. Additional scenario analyses were conducted around the age of a patient at initial treatment to determine how the cost-effectiveness of RDN therapy varies with age.

A third scenario was also considered using the recently published results from HTN-3[27]. HTN-3 is the first sham controlled study of RDN therapy, with patients randomly assigned to either RDN plus SoC or sham plus SoC. Results showed a mean reduction in SBP from baseline of 14.13 mmHg (± 29.93) for patients receiving RDN plus SoC compared to 11.74 mmHg (± 25.94) for the sham arm[27]. This suggested a smaller treatment effect than previously reported studies with more mature clinical data, including HTN-2 and HTN-1. However, this is only an interim reported data-set, and, as a sham effect would be time limited and as patients would not be offered a sham procedure in clinical practice, we considered a scenario based on a reduction in SBP of 14.13 mmHg for the RDN plus SoC arm compared to no expected SBP change on the SoC arm. This was deemed a more relevant comparison to real-world practice SoC.

Results

Base case

The base case results indicate that treatment with RDN therapy results in a substantial increase in QALYs (0.89) over a patient's lifetime at an incremental discounted cost of €2600. This resulted in an ICER which is substantially below the bandwidth of thresholds used in The Netherlands of €10,000–€80,000 per QALY gained[28]. Furthermore, the incremental gain in QALYs for patients receiving RDN therapy is greater than the incremental gain in LYs (0.89 QALY, 0.78 LYs/patient discounted; 1.20 QALYS, 1.09 LYs/patient undiscounted; Table 4)

Table 4. Results.

Base case results: Treatment	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	Cost per QALY	Cost per LY
Discounted								
Standard of care	€20,861	15.13	16.87	—	—		—	
Renal denervation	€23,461	16.02	17.65	€2600	0.89	0.78	€2914	€3335
Undiscounted								
Standard of care	€38,226	17.74	19.98	—	—		—	
Renal denervation	€38,190	18.94	21.07	−€36	1.20	1.09	−€30	−€33
Breakdown of cost results (undiscounted)								
End state	Standard of care			Renal denervation			Incremental costs	
Cost								
Hypertension (renal denervation)				€6,574			€6574	
Hypertension (background medication)	€2,530			€2,911			€381	
Angina pectoris/Coronary heart disease	€899			€872			−€26	
Myocardial infarction	€3,498			€3,054			−€444	
Heart failure	€1,344			€1,257			−€88	
Stroke	€28,443			€22,110			−€6332	
End-stage renal disease	€1,512			€1,411			−€101	
Total:	€38,226			€38,190			−€36	
Utility								
Hypertension	12.327			14.127			1.800	
Angina pectoris	1.639			1.613			−0.026	
Myocardial infarction	1.307			1.162			−0.146	
Heart failure	0.658			0.646			−0.011	
Stroke	1.786			1.374			−0.412	
End-stage renal disease	0.024			0.022			−0.002	
Total	17.741			18.944			1.203	

LY, life year; QALY, quality-adjusted life year.

indicating patients are not only living longer (reduced mortality) but also have reduced morbidity.

As with the UK RDN model by Gladwell *et al.*[16], the additional health benefit stems from the reductions in the risk for cardiovascular events, resulting in patients spending less time in severe health states with low HRQoL. In particular, results show patients receiving RDN therapy spend on average 4.94 and 1.75 fewer months in the stroke and MI health states, respectively (Table 4). Due to the structure of the model, patients who do not transition to more severe cardiovascular health states remain in the hypertension health state where HRQoL is maximized with a utility value of 1.

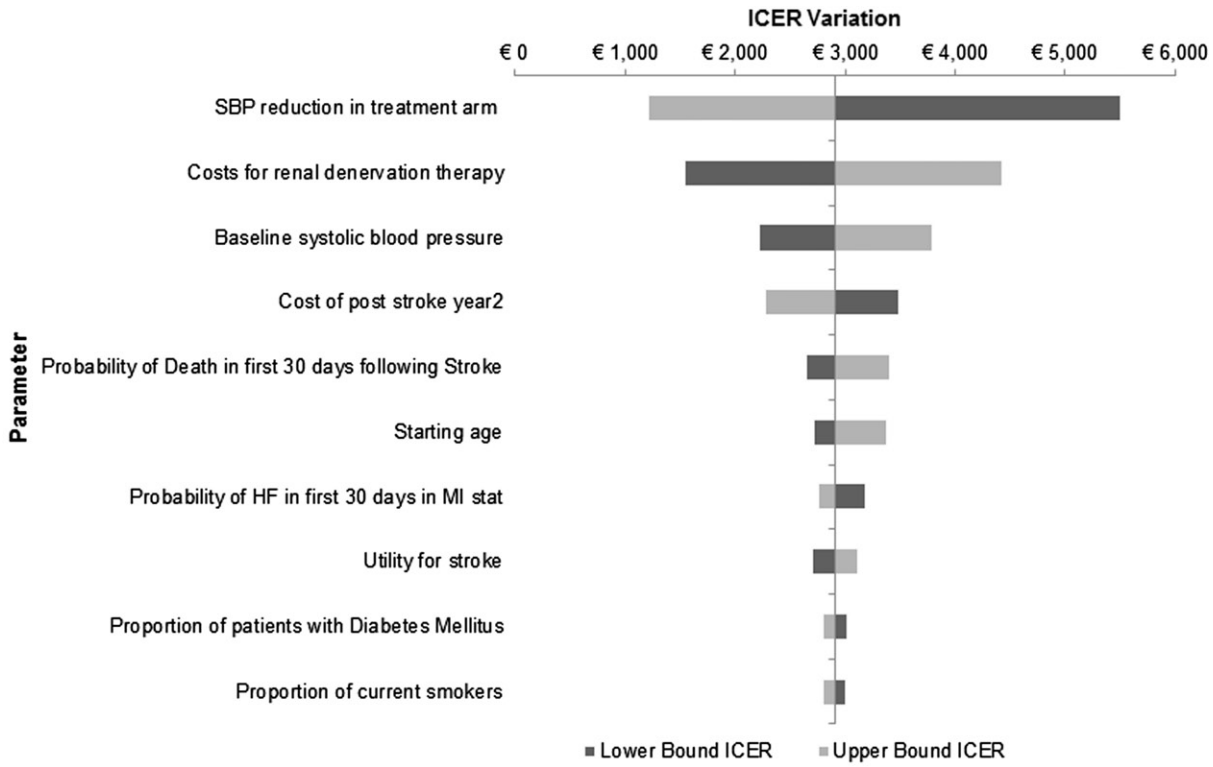
The additional cost of providing RDN (estimated at €6574 per procedure) is almost completely offset by cost savings due to reduced cardiovascular events over a patient's lifetime. The cost of RDN is not completely offset due to the discounting rate applied to costs, and patients having more cardiovascular events later in life (incremental cost RDN €2600; Table 4). Where there is no discounting, results show the cost of RDN is completely offset and is a cost saving treatment by €36. The greatest cost saving comes from the reduction in strokes (−€6332 undiscounted) which accounts for 74% of the total cost on the SoC arm and 58% of total costs on the RDN arm (Table 4).

Sensitivity analysis

As with previous cost-effectiveness models for RDN[14–16], the treatment effect is shown to have the greatest effect on the ICER, ranging from being a cost-saving treatment option to €5512/QALY between the upper and lower bounds of the treatment effect, respectively (Figure 2). The second and third most influential parameter is the cost of the RDN procedure and the baseline SBP, respectively, which are both key inputs in the economic model. The cost of the RDN procedure is a substantial up-front cost, meaning it is not subject to discounting and, therefore, cost-offsets experienced in the future must be relatively large. Baseline SBP defines the relative treatment effect.

When the model was run in a PSA, results over 10,000 iterations showed that the ICER values remained well below €10,000/QALY, as shown on the cost-effectiveness plane (Figure 3).

The expected (mean probabilistic) value is €3075/QALY, which is very close to the base case value of €2914 The corresponding cost-effectiveness acceptability curve (Figure 4) demonstrates the probability that RDN and SoC is cost-effective compared with SoC alone for a range of threshold values from €0–€12,000. For willingness-to-pay thresholds exceeding €12,000/QALY the probability that RND is cost-effective was equal to 1.



Parameter Name	Distribution	LB	LB ICER	U B	UB ICER
SBP reduction in treatment arm	Normal	25	€ 5,512	39	€ 4,308
Costs for RDN therapy	Gamma	€ 5,349	€ 1,541	€ 7,923	€ 2,886
Baseline SBP	Normal	173	€ 2,222	183	€ 1,565
Cost of post stroke year 2	Gamma	€ 635	€ 3,492	€941	€ 1,214
Probability of death in first 30 days following stroke	Beta	0.009	€ 2,644	0.363	€ 760
Starting age	Triangular	55	€ 2,715	61	€ 659
Probability of HF in first 30 days in MI stat	Beta	0.009	€ 3,187	0.363	€ 436
Utility for stroke	Beta	0.57	€ 2,708	0.85	€ 409
Proportion of patients with diabetes mellitus	Beta	0.218	€ 3,026	0.473	€ 224
Proportion of current smokers	Beta	0.074	€ 3,012	0.271	€ 216

Figure 2. One-way sensitivity analysis tornado diagram. HF, heart failure; ICER, incremental cost-effectiveness ratio; LB, Lower bound; MI, myocardial infarction; QALYs, quality-adjusted life years; RDN, renal denervation; SBP, systolic blood pressure; UB, Upper bound. An ICER greater than zero indicates costs and QALYs greater than zero; an ICER less than zero indicates costs less than zero and QALYs greater than zero.

Scenario analysis

Deterministic sensitivity analysis showed the treatment effect and the cost of RDN therapy to be the two most influential parameters in the model. Therefore, a scenario was considered where the long-term treatment effect wanes over time by 1 mmHg per year, resulting in patients requiring re-treatment with RDN therapy after 10 years to maintain a SBP within the normal range. Results indicate, even with this steady reduction in the treatment effect, RDN therapy remains cost-effective with an ICER value of €9056 (see Table 5).

Scenario analyses conducted around the patient age at treatment indicated that the ICER for RDN falls below €10,000/QALY up to the age of 75. This is due to the fact that the upfront cost of RDN therapy is offset to a lesser degree as older patients have an increased risk of severe events, such as stroke, as age increases. As would

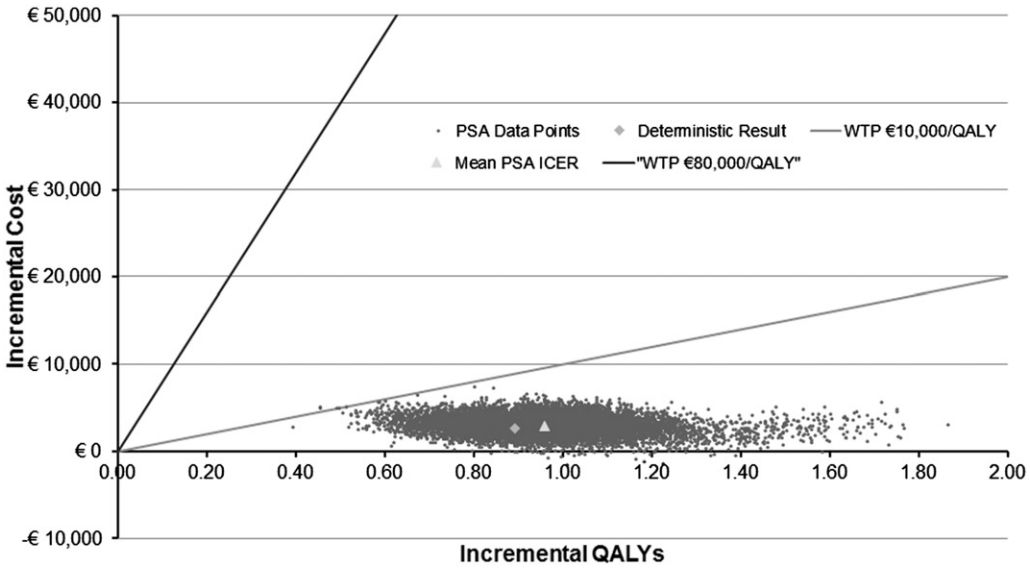


Figure 3. PSA–cost-effectiveness plane. ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

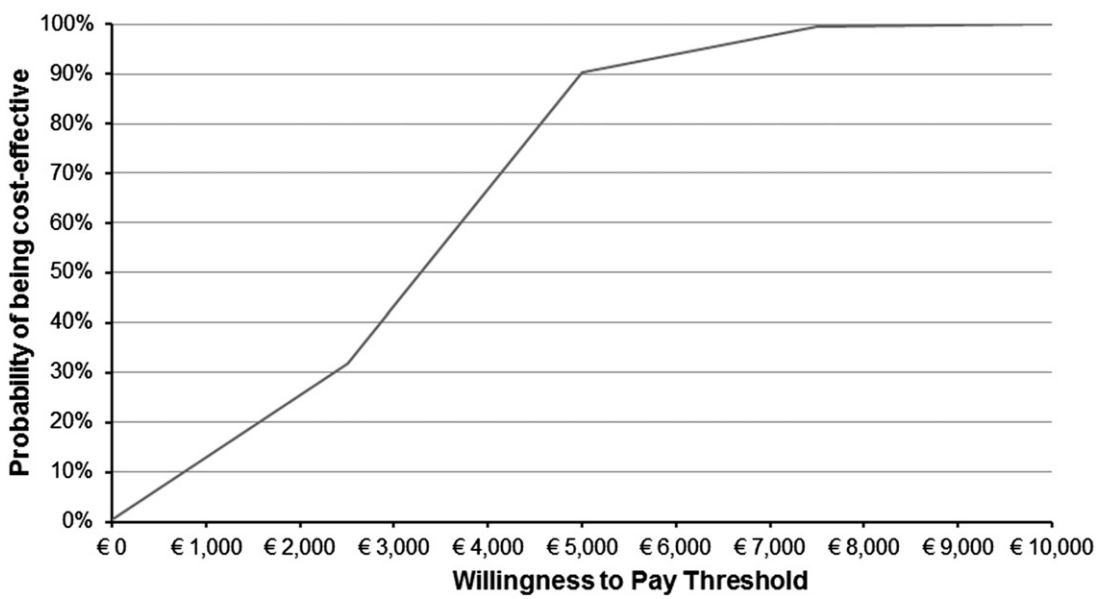


Figure 4. PSA–cost-effectiveness acceptability curve. PSA, probabilistic sensitivity analysis.

be expected, using an average reduction in SBP from HTN-3 of 14.23 mmHg increased the ICER compared to the base case analysis. However, even with this reduced efficacy RDN still falls well within the band of acceptable cost-effectiveness thresholds used in The Netherlands with an ICER of €17,270. In absolute terms, the incremental cost under this scenario compared to the base case results is an additional €5166 per patient. This increase in cost is mostly due to the cost of the RDN procedure, as well as patients receiving RDN plus SoC living longer and, therefore, utilizing more healthcare resources over their lifetime.

Discussion

Results from the economic model strongly indicate that RDN is cost-effective for the treatment of resistant hypertension at the conventional threshold levels used by Zorginstituut Nederland (€10,000–80,000)[28]. The mean

Table 5. Scenario analysis, discounted results.

Scenario One: Waning of treatment effect (−1 mmHg per year)								
Treatment	Total costs	Total QALYs	Total LYs	Incremental costs	Incremental QALYs	Incremental LYs	Cost per QALY	Cost per LY
Standard of care	€20,861	15.13	16.87					
Renal denervation	€27,055	15.81	17.46	€6,194	0.68	0.59	€9,056	€10,488

Scenario Two: Cost-effectiveness of RDN therapy according to patient age at treatment				
Age at treatment	Treatment	Costs	QALYs	ICER (Cost per QALY)
50	SoC	£22,900	18.66	
	RDN + SoC	£25,016	19.56	£2,370
55	SoC	£21,772	16.67	
	RDN + SoC	£24,153	17.60	£2,552
60	SoC	£20,157	14.11	
	RDN + SoC	£22,926	14.97	£3,209
65	SoC	£18,089	11.79	
	RDN + SoC	£21,341	12.60	£4,026
70	SoC	£15,393	9.46	
	RDN + SoC	£19,243	10.15	£5,619
75	SoC	£12,527	7.65	
	RDN + SoC	£16,984	8.25	£7,502
80	SoC	£9,949	5.96	
	RDN + SoC	£14,893	6.37	£12,036
85	SoC	£7,651	4.49	
	RDN + SoC	£12,985	4.74	£21,393

Scenario Three: Treatment effect from Symplicity HTN-3								
Treatment	Total costs	Total QALYs	Total LYs	Incremental Costs	Incremental QALYs	Incremental LYs	Cost per QALY	Cost per LY
Standard of care	€20,861	15.13	16.87					
Renal denervation	€26,027	15.43	17.12	€5,166	0.30	0.26	€17,270	€20,114

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; RDN, renal denervation; SoC, standard of care.

probabilistic and deterministic ICERs of €2914/QALY and €3075/QALY, respectively, are in line with findings from Gladwell *et al.*[16], Dorenkamp *et al.*[14], and Geisler *et al.*[15], who estimated base case ICERs of £5887 in the UK, €2642 (men) and €2323 (women) in Germany, and $3071 in the US, respectively. Treatment with RDN reduces the risk of cardiovascular events and, thus, the time spent in all severe disease states within the model. This reduction in more severe events under treatment with RDN leads to both a reduction in morbidity, yielding higher utility scores while alive, and a decrease in the associated mortality. Furthermore, one-way sensitivity analysis showed that RDN therapy remains cost-effective at the 95% confidence intervals for the treatment effect (25 mHg, 39 mmHg) with ICERs below €10,000/QALY[28].

The cost of SoC in the model was estimated using the treatment guidelines for cardiovascular risk management[24], with patients receiving four pharmacological treatments. It is recognized that these guidelines were developed for patients with non-resistant hypertension and, as such, may under-estimate the absolute pharmacological burden of the patient population analysed here. However, due to the structure of the model with all patients on each arm receiving the same anti-hypertensive medication, this is not likely to impact the cost-effectiveness results. In fact, there is the possibility that the current model structure may over-estimate the cost of pharmacological interventions on the RDN arm because patients may reduce their medications following RDN. However, in the absence of Dutch data on treatment patterns before and after RDN therapy, the model uses the conservative assumption that all patients remain on the same treatments following RDN therapy. One ongoing study in RDN therapy at the University Medical Center Utrecht (UMCU) is collecting patient level data on pharmacological use prior to RDN therapy and at 6 months post-RDN which may provide data for future cost-effectiveness analyses.

In general, due to the relatively short duration of trials, economic models are necessary to extrapolate the findings and predict results for a patient's lifetime. Consequently, the results are heavily reliant on the predictive equations used in the model. In particular, the Framingham risk equation was used to estimate the probabilities of most cardiovascular events (except for MI where the PROCAM risk equation was used). There is some evidence to suggest that the Framingham risk equations, which are based on a US population, over-estimate the

risk of cardiovascular events in European populations[29], although the underlying reason for this is unclear. This disparity may be due to differences in the levels of CHD risk in the Framingham population and the European population, or it may be due to the improved care and treatment for patients with hypertension over the last decade. Conversely, the hypertensive population under consideration in this model has increased risk of cardiovascular events compared to the general Dutch population, as the patients in the model have resistant hypertension. The true predictive power of the Framingham risk equations in this resistant hypertension population is, therefore, unknown.

There is some uncertainty around the duration and size of the treatment effect from RDN therapy given the lack of long-term data and recent results from Symplicity HTN-3; this first sham controlled randomized single-blind phase III study of RDN[27]. Results from HTN-3 were incorporated into the model through scenario analysis, using a reduction in SBP of 14.23 mmHg as shown in the trial for patients receiving RDN plus SoC in the economic model. The reduction in baseline SBP of 11.74 mmHg shown on the sham arm was not used to represent SoC in the economic model, as patients in the real-world clinical setting would not be offered a sham procedure and, thus, any economic analysis of this scenario would offer little value. Furthermore, the economic model was not designed to incorporate additional costs associated with a sham procedure and, therefore, would under-estimate the cost-effectiveness of RDN.

HTN-3 is the first RDN trial not to reach the primary efficacy end-point, however the primary safety end-point was met, demonstrating that RDN is a safe treatment for patients with resistant hypertension. This deviation in results compared with previous trials is thought to arise from a variety of confounding factors. One potential factor is patient behavior; those enrolled in the study were closely monitored as part of the trial protocol, which may have resulted in patients modifying their lifestyle and drug adherence. In addition, there were a number of other differences between Symplicity HTN-3 and previous trials, including: a greater number of trial sites, which led to procedural variability; differences in the requirement for maximum tolerated doses; and differences in case proctoring. Results from Symplicity HTN-3 are in the preliminary stages, and further data for the planned 5-year follow-up period may offer a fuller picture of the efficacy of RDN therapy. Further analysis of the cost-effectiveness of RDN therapy using the final Symplicity HTN-3 study results could be valuable; however, it is worth noting that, despite this uncertainty, the reduction in SBP shown in HTN-3 is a significant reduction compared to most statin therapies, which typically give a reduction in SBP of ~1.45–2.2 mmHg[30–32].

It is worth noting that the reduction in treatment effect of 1 mmHg per annum, used in the scenario analysis, is a somewhat arbitrary value due to absence of long-term clinical data when the model was originally designed[15]. However, since the development of the original model, further data have become available on the duration of the treatment effect from the 3-month follow-up of the Symplicity HTN-1 trial[13]. Results from this follow-up study indicate that there is a sustained treatment effect (or possible increase in treatment effect) over the first few years following intervention; therefore, this scenario gives a conservative estimate of the cost-effectiveness of RDN therapy.

A Netherlands-specific randomized controlled trial (SYMPATHY ClinicalTrials.gov NCT01850901) is also underway. This study will estimate SBP reduction, as well as collect patient and procedure level data to identify predictors of effect and define characteristics in patients that are likely to respond, allowing analysis of the effectiveness of RDN in several pre-stratified sub-groups. Future economic analyses should also be informed by the Symplicity HTN-3 and SYMPATHY trial data when analyzed at appropriate follow-up time points of 2 years and beyond.

As part of the RDN procedure, screening is required to assess the eligibility of patients for treatment. This is included in the micro-costing of RDN treatment on a patient level, but it does not account for the fact that, on average, four patients are screened for every one successful patient moving on to treatment. The cost of RDN therapy may, therefore, be under-estimated in the current model. However, as RDN therapy for the treatment of resistant hypertension becomes standard of care, it may become easier to identify eligible patients and, thus, reduce the burden of screening over time. The necessity for screening with RDN therapy has resulted in an increase in the identification of secondary causes of hypertension. Verloop *et al.*[33] reported that 14 underlying causes of hypertension were detected in 181 patients screened for RDN therapy that otherwise may not have been discovered. As with the additional costs of screening, the potential benefits are not captured in the economic model and, thus, the effect on results is uncertain.

Dutch guidelines for pharmacoeconomic research state that the evaluation should be performed and reported from a societal perspective, in which all costs and benefits are included, irrespective of who bears them[17]. This analysis was conducted from the perspective of the healthcare payer and, thus, does not include any indirect or non-medical costs or benefits. Results are, therefore, comparable to previous published estimates in the UK, Germany, and the US, but are limited in the true reflection of the real world impact of RDN. However, given RDN therapy reduces the number of cardiovascular events, especially stroke, which is associated with substantial indirect medical costs

(e.g., informal care costs) and direct non-medical costs (e.g., productivity losses), it is likely that the inclusion of societal benefits would improve the cost-effectiveness of RDN therapy.

For some parameters no Netherlands-specific data were available. In particular, five of the eight utility values used were based on UK data. However, while this limitation is acknowledged, deterministic sensitivity analysis did not indicate any single utility value to be a key driver of the ICER value. Furthermore, base case results indicate that RDN therapy is highly cost-effective in The Netherlands healthcare setting and any variation in utility values, within plausible ranges, is unlikely to change the results sufficiently such that the reimbursement decision would change.

There are a variety of analyses that could be conducted to strengthen the economic analysis such as incorporating data on the long-term treatment effects from two of the Symplicity trials (HTN-2 and HTN-3). Furthermore, a particularly relevant analysis would be to use results from the SYMPATHY to incorporate Netherlands-specific data into the model to further analyse the economic and clinical implications for the introduction of RDN therapy in The Netherlands.

Conclusion

Treatment with RDN therapy offers a safe and effective alternative to standard therapy and has been shown to be cost-effective in The Netherlands, and thus is an effective use of healthcare resources compared to the care currently received by patients with resistant hypertension.

Transparency

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