Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Renal denervation to treat people with resistant hypertension

Appraisal summary

Why did Health Technology Wales (HTW) appraise this topic?

High blood pressure (hypertension) is an important, treatable cause of premature morbidity and mortality. It is a major risk factor for stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline, and premature death. Lifestyle changes, smoking cessation and diet modification, play an important role in supporting people with hypertension to manage their blood pressure. There are also several medications that can be used to help control blood pressure.

For some people, these approaches are not sufficient to reduce hypertension to acceptable levels. This type of hypertension is referred to as resistant hypertension and it is associated with a high risk of negative outcomes. For this population, the National Institute for Health and Care Excellence (NICE) recommends that adherence to medication and home blood pressure is explored and that further medication and referral to specialist services may be needed. Additional treatments may therefore be beneficial.

What evidence did HTW find?

We identified a recent Cochrane systematic review that reported on the clinical effectiveness of renal denervation (ultrasound and radiofrequency) for the treatment of resistant hypertension. We also identified a further two relevant randomised controlled trials (RCTs) that were published after the systematic review and one longer-term follow-up of an included review. The evidence included in this report focuses on earlier iterations of renal denervation. We identified no studies that use newer treatment protocols with multi-electrode radiofrequency for resistant hypertension.

Evidence identified in the literature and an updated meta-analysis completed by HTW do not show significant improvements in systolic or diastolic 24-hour ambulatory blood pressure monitoring (ABPM) after renal denervation for resistant hypertension. Evidence on non-fatal cardiovascular events and hospitalisation is limited by the fact that studies are not powered or designed with long enough follow-ups to observe anticipated differences.

The economic analysis suggests that renal denervation was more effective but more costly than standard care. The resulting ICER of £233,841 per QALY is substantially higher than the threshold of £20,000 per QALY indicating that renal denervation is not cost-effective in comparison to standard care. This result contrasts with a previous UK analysis, which found renal denervation

to be cost effective. This difference is driven by the lower reduction in systolic blood pressure applied for patients treated with renal denervation in the HTW analysis.

There is a high level of uncertainty regarding whether the findings seen here would be replicated in newer treatment protocols as no evidence relating to these in the resistant hypertension population was identified. Newer approaches use a larger number of ablations in the main artery and branches, and it is possible that this approach would deliver improved benefits. Forthcoming trials may provide some evidence from sub-group analyses. However, additional larger trials focusing on this population may be needed.

What was the outcome of HTW's appraisal?

HTW is a national body working to improve quality of care in Wales. We collaborate with partners across health, social care, and industry to issue independent guidance that informs commissioning within Wales health and social care. We are supported by an Assessment Group, who ensure our work adheres to high standards of methodological and scientific rigour, and an Appraisal Panel, who consider evidence within the Welsh context and produce HTW guidance. More details on our appraisal process, the Assessment Group, and the Appraisal Panel can be found on the HTW website.

In this case, the HTW Assessment Group considered the evidence presented in this Evidence Appraisal Report. They concluded that due to the recent publication of NICE Interventional procedures guidance (IPG), it was not necessary or appropriate for HTW to produce guidance on this topic. Therefore, the Assessment Group recommended publication of the appraisal as an Evidence Appraisal Report only.

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question:

> What is the clinical and cost effectiveness of renal denervation for people with resistant hypertension when compared to standard care?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of identifying the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

High blood pressure (hypertension) is an important, treatable cause of premature morbidity and mortality. It is a major risk factor for stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline, and premature death (NICE 2022). It is estimated that around 700,000 people in Wales have high blood pressure (BHFC 2023); people of Black African or African-Caribbean family origin, people with diabetes, chronic kidney disease and people over the age of 65 are more likely to be represented in this population (BHF 2023). High blood pressure is one of the leading risk factors for premature death and disability in Wales, with half of all heart attacks and strokes being associated with high blood pressure (BHFC 2023). Lifestyle changes, smoking cessation and diet modification, play an important role in supporting people with hypertension to manage their blood pressure. There are also several medications that can be used to help control blood pressure.

However, for some people, these approaches are not sufficient to reduce hypertension to acceptable levels and the risk of negative outcomes remains high. International guidelines have defined resistant hypertension as a raised blood pressure (blood pressure 140/90 mmHg under appropriate conditions) despite treatment with at least three antihypertensive agents (one of which is usually a diuretic) at optimal or best tolerated doses (Myat et al. 2012). The NICE guideline for diagnosis and management of hypertension in adults (NG136) outlines that hypertension should be regarded as resistant if control is not achieved after three steps of treatment with ACE inhibitors, angiotensin receptor blocker (ARB) plus a Calcium Channel Blocker (CCB) and a thiazide-like diuretic (NICE 2022). Studies based in the UK and information provided by experts suggests that around 6 to 10% of people with hypertension do not gain control with antihypertensive drugs and alternative treatments may be needed for this population (Sinnott et al. 2017). This could mean 42,000 to 70,000 people in Wales have resistant hypertension. However, there is uncertainty around this figure.

For this population, NICE recommends that adherence to medication and home blood pressure monitoring is explored and this may then be followed by further medication or referral to specialist services if required. The guideline highlights that evidence on interventions for this group is limited. In Wales, experts have highlighted that a patient is referred to specialist services to rule out any secondary causes of resistant hypertension. It is important to note that this patient group is likely to consist of both people who have high adherence to recommended medication and are resistant to treatment despite this, and people who have lower adherence to recommended medications. For this latter group, NICE guidelines recommend that adherence is considered and addressed, and patients with low adherence should be judged as treatment-resistant and eligible for a different approach by their care team.

3. Health technology

Renal denervation therapy is a percutaneous catheter-based procedure aiming to achieve blood pressure control and may provide benefits for patients with resistant hypertension. The procedure is minimally invasive and is usually carried out under local anaesthetic. A catheter is inserted into the femoral artery through the groin and advanced to each renal artery. The catheter is connected to a generator that provides low-power radiofrequency or ultrasound to burn the nerves of the renal artery in several places. It is suggested that using renal denervation and ablation of nerves causes a reduction in nerve activity that can reduce blood pressure. This is proposed to be due to the role sympathetic signalling between the central nervous system and the kidneys plays in maintenance of high blood pressure.

A number of renal denervation systems are available using radiofrequency and ultrasound approaches. Experts highlighted that there have been major developments in the field that are linked to increasing knowledge and greater understanding of the anatomy and function of renal nerves and their links to hypertension. Earlier radiofrequency systems used single electrodes (e.g. Medtronic Symplicity) or multi-electrodes (e.g. St. Jude Medical EnlighHTN) to deliver a relatively small number of ablations. They also relied on clinicians delivering a series of single ablations to optimal parts of the artery. Newer systems use multi-electrodes (e.g. Medtronic Spyral) and treatment protocols have been updated to deliver a much larger number of ablations to the main artery and all accessible branches. For ultrasound (e.g. Recor Paradise), a common approach is to deliver four emissions to the main artery with at least one emission delivered proximal to branches. A cooling balloon provides protection to the arterial wall and allows targeting of the renal nerve.

NICE guideline (NG136) does not refer to renal denervation for people with resistant hypertension and recommends further attempts at control with medication or referral to specialist services (NICE 2022). NICE interventional procedures guidance from 2023 (IPG754) states that evidence on the long-term efficacy and safety of percutaneous transluminal renal sympathetic denervation is limited and recommends that sympathetic denervation of the renal artery only be used with special arrangements for clinical governance, consent, and audit or research (NICE 2023). NHS England has developed a commissioning policy for the use of renal denervation and states that there is not sufficient evidence to support routine commissioning (NHS England 2016). Experts highlighted that renal denervation is only being undertaken in clinical trial settings within Wales currently. The most recent position statement from the Joint UK Societies does not support routine use of renal denervation (RDN) and states additional clinical trial data is needed (Lobo et al. 2019).

4. Clinical effectiveness

A range of primary and secondary evidence was identified by the literature search. A recent Cochrane systematic review that reported on the clinical effectiveness of renal denervation (ultrasound and radiofrequency) for the treatment of resistant hypertension met our rapid review inclusion criteria and was considered the highest priority evidence (Pisano et al. 2021). We also identified and included three additional studies that were published after the latest search date in Pisano et al. (2021). The additional included studies were an RCT comparing ultrasound renal denervation and sham, an RCT comparing radiofrequency renal denervation and drug adjusted treatment and one longer term follow up from an earlier trial (Azizi et al. 2021, Bergland et al. 2021, Kario et al. 2022b).

More detail on the evidence identification and selection process is available in Appendix 3. None of the identified evidence, within either the Cochrane review or newer primary studies, used

newer treatment protocols for radiofrequency renal denervation within the treatment-resistant population. The study with the highest average number of ablations is well below current recommendations.

Pisano et al. (2021) conducted a systematic review and meta-analysis to examine the short- and long-term effects of renal denervation in individuals with resistant hypertension compared with standard care or sham. In total, 15 RCTs of 1,416 participants were included with study lengths ranging from three months to 24 months. Eligible participants were adults with refractory or resistant hypertension, defined by the presence of a clinic blood pressure above target despite the concomitant use of three or more antihypertensive drugs of different classes, including a diuretic. The review included four studies that compared renal denervation with sham procedure and 11 studies that compared renal denervation with standard or intensified antihypertensive therapy. Pisano et al. (2021) summarised treatment effects on available clinical outcomes and adverse events using random-effects meta-analyses. It was noted that for some outcomes (24-hour ABPM and office blood pressure) there were limitations regarding sample size, reporting and appropriateness of comparators, which may have had an influence on the findings. The authors assessed heterogeneity in estimated treatment effects using Chi^2 and I^2 statistics. Pisano et al. (2021) calculated summary treatment estimates as a mean difference (MD) or standardised mean difference (SMD) for continuous outcomes, and a risk ratio (RR) for dichotomous outcomes, together with their 95% confidence intervals (CI). Certainty of evidence was assessed using the GRADE approach. Further detail on the design and characteristics is available in Table 1.

Azizi et al. (2021) conducted a randomised, single blind trial comparing ultrasound renal denervation versus sham procedure. The trial was multicentre with 28 sites in the USA and 25 sites in Europe, including the UK. The trial included 136 participants aged 18 to 75 that were followed up for a period of two months. Eligible participants were switched to a once daily, fixed-dose, single-pill combination of a calcium channel blocker, an angiotensin receptor blocker, and a thiazide diuretic for four weeks before they were randomly assigned to receive ultrasound renal denervation (n=69) or a sham procedure (n=67). Azizi et al. (2021) reported outcomes on myocardial infarction, ischaemic stroke, hospitalisation, 24-hour ambulatory blood pressure and office blood pressure. Further detail on the design and characteristics is available in Table 2.

Another RCT that compared ultrasound renal denervation versus sham procedure was also identified. Kario et al. (2022b) conducted a multicentre single-blind sham-controlled trial that enrolled participants from Japan and South Korea between January 2017 and March 2020. Participants were defined as being treatment resistant despite a stable regimen of maximum tolerated dosages of at least three antihypertensive medications from different classes including a diuretic. A total of 143 participants were randomised to either ultrasound renal denervation (n=72) or sham procedure with a single triple pill (n=71) and were followed up over a three-month period. Standard-of-care antihypertensive medication remained unchanged up to the 3-month follow-up data collection. Kario et al. (2022b) reported outcomes on 24-hour ambulatory blood pressure and office blood pressure. The trial did not standardise medications or objectively measure medication adherence. Further detail on the design and characteristics is available in Table 2.

Bergland et al. (2021) conducted a single centre randomised controlled trial in Norway and compared radiofrequency renal denervation versus drug adjusted treatment. The study had a small sample size of 19 participants, with 9 in the renal denervation group and 10 in the adjusted drug treatment group. Participants were enrolled in the trial between August 2012 and June 2013 and were followed up at 6 months, 1 year, 3 years and 7 years. Data from the first follow up at 6 months was included in the Pisano et al. (2021) Cochrane review. For this review, we have included the most recent data from the seven years follow up. Adults aged 18 to 80, with treatment

resistant hypertension defined as an office systolic BP >140 mmHg, despite maximally tolerated doses of ≥3 antihypertensive drugs including a diuretic were included. The drug-adjusted group had their antihypertensive medication adjusted at baseline, 1 month and at 3 months and witnessed intake of drugs was performed at follow-up visits. Bergland et al. (2021) reported on changes in blood pressure for both groups. The study was stopped early for ethical reasons because renal denervation had uncertain BP-lowering effect however long-term follow up data were collected at seven years. Further detail on the design and characteristics is available in Table 2.

Following feedback from the HTW Assessment Group, the meta-analysis from the Cochrane systematic review was updated for outcomes on systolic and diastolic 24-hour ambulatory blood pressure. Further, following feedback from external experts on the development of renal denervation technology, details of the renal denervation system used in each of the studies reported in the Cochrane systematic review (Pisano et al. 2021) and primary studies (Azizi et al. 2021, Kario et al. 2022b) was extracted. This allowed us to conduct sensitivity analyses according to whether radiofrequency or ultrasound was used, and whether single or multi-electrode radiofrequency systems were used. As mentioned above, no studies using newer treatment protocols for radiofrequency renal denervation were identified in this population so sensitivity analyses rely on earlier studies using multi-electrode systems. Additional details on the methods of this meta-analysis are presented in Section 11 and all data tables and forest plots are available in Appendix 4.

4.1 Clinical outcomes

For this rapid review, we have focussed on the outcomes judged to be most important by Pisano et al. (2021) in the Cochrane review. We also extracted data for these outcomes from each of the RCTs (Azizi et al. 2021, Bergland et al. 2021, Kario et al. 2022b) where the relevant information was available. We have reported on the following outcomes below: non-fatal cardiovascular events (myocardial infarction, ischaemic stroke, unstable angina), hospitalisation, 24-hour ABPM, office ABPM, eGFR clearance and serum creatinine.

Experts highlighted that the highest priority outcome was 24-hour ABPM due to lower reliability of office-based testing and the need for larger samples and longer time periods to evidence improvements in cardiovascular events and hospitalisation. For this reason, HTW focused efforts to update pooled analysis on systolic and diastolic 24-hour ABPM. More detail on results for these outcomes is available in Table 3.

4.1.1 Non-fatal cardiovascular events (Myocardial infarction, ischaemic stroke, and unstable angina)

In a meta-analysis of four RCTs (742 participants) conducted by Pisano et al. (2021), there was no statistically significant difference in the rate of myocardial infarction between participants receiving renal denervation compared to sham or standard treatment (RR 1.31, 95% CI 0.45 to 3.84), with low heterogeneity reported (I^2=0%). In the RCT conducted by Azizi et al. (2021), the number of acute myocardial infarction events were reported as 1/69 (1%) for renal denervation and 0/67 for the control group in a two-month period.

For ischaemic stroke, Pisano et al. (2021) pooled data from five RCTs with a total 892 participants. Renal denervation showed little or no effect on the risk of ischaemic stroke compared to control (RR 0.98, 95% CI 0.33 to 2.95).. Low heterogeneity was reported for this outcome (I^2=0%). Similar

results were reported in the Azizi et al. (2021) RCT with no difference reported between the two groups; 0/69 events were reported for ultrasound renal denervation and 0/67 for sham procedure.

Pisano et al. (2021) also conducted a meta-analysis of three RCTs (270 participants) and found the renal denervation may have little or no effect on the risk of unstable angina compared to sham or standard therapy (RR 0.51, 95% CI 0.09 to 2.89) with no heterogeneity reported (I^2=0%).

It should be noted that Pisano et al. (2021) rated the quality of evidence for their above outcomes as low using GRADE, detailing that further research could very likely have an important impact on their confidence in the estimate of effect and is likely to change the estimate.

4.1.2 Hospitalisation

Pisano et al. (2021) included data on hospitalisation from three studies and used this to perform a meta-analysis. In a total of 743 participants, renal denervation was found to have little or no effect on the risk of hospitalisation compared to sham or standard treatment. The authors report the absolute effect standardised to 1,000 events and report that in pooled analysis there were the equivalent of 35 hospitalisations per 1,000 participants for renal denervation and 28 per 1,000 for sham or standard treatment (RR 1.24, 95% CI 0.50 to 3.11). One of the included RCTs reported that hospitalisations were due to atrial fibrillation episodes and in the other two RCTs, patients required hospitalisation to adjust antihypertensive medication.

Azizi et al. (2021) also reported no difference between the ultrasound renal denervation group (n=69) versus the sham procedure group (n=67), with zero hospital admissions recorded for either group in the two month follow up.

4.1.3 Systolic and Diastolic 24-hour ABPM (mmHg)

In an analysis conducted by HTW, ten RCTs with a total of 1,217 participants were pooled to examine differences in systolic 24-hour ABPM. The mean difference between the intervention and control group was -1.78mmHg (95% CI -4.06 to 0.5; I^2 = 15%) but this difference was not significant. Moiseeva et al. (2020) was removed from the primary analysis as it is reported only as an abstract, appears to be an outlier, and contributes a large amount of weight in random-effects analyses. When (Moiseeva et al. 2020) is included as a sensitivity analysis, the mean difference was -4.64 (95% CI -8.71 to -0.58) with a substantial increase in heterogeneity (I^2 = 74%). The quality of the evidence was given a moderate GRADE score by the Cochrane review authors.

In an analysis conducted by HTW, nine RCTs with 1,176 participants were pooled to examine differences in diastolic 24-hour ABPM. The mean difference between the intervention and control group was -1.26mmHg (95% CI -3.53 to 1.01; I^2 = 54%) but this difference was not significant. When (Moiseeva et al. 2020) was included as a sensitivity analysis, the difference was -2.93 (95% CI -5.81 to -0.05; I^2 = 75%). This was significant.

At a longer-term follow up of seven years, Bergland et al. (2021) reports non-significant differences in systolic 24-hour ABPM (p=0.33) and diastolic 24-hour ABPM (p=0.22) between the radiofrequency renal denervation group who then received drug adjustment (n=9) and the drug adjusted only group (n=10). This trial relies on a small number of participants due to recruitment stopping early for futility.

A series of sensitivity analyses were conducted to examine whether there is a differential effect between radiofrequency and ultrasound, and between single and multi-electrode radiofrequency. Results can be found in Appendix 4, Figures 4E to 4H. These analyses did not suggest differences according to these subgroups. As elsewhere in the report, it is important to note that newer

treatment protocols using multi-electrode radiofrequency were not identified and are therefore not included in these analyses.

Data tables and forest plots for all the above analyses are available in Appendix 4.

4.1.4 Systolic and Diastolic office BP (mmHg)

In a meta-analysis of nine RCTs (1,090 participants), Pisano et al. (2021) found that the mean systolic office BP in the renal denervation groups were on average 5.92 lower (95% CI -12.94 to 1.10) than for controls, however the difference was non-significant (p=0.10) and there was high heterogeneity (I^2=86%). The authors performed subgroup analyses and found that benefits on systolic office BP were evident in studies using a multi-electrode radiofrequency catheter (MD -5.10 mmHg, 95% CI -9.14 to -1.06) and heterogeneity was nullified (I^2=0%). Kario et al. (2022b) and Bergland et al. (2021) also reported no significant difference between the intervention and control groups for systolic office BP (mmHg) (p=0.51 and p=0.39 respectively). However, Azizi et al. (2021) reported a median between group difference of -0.7 (95% CI -13.0 to 0.0), favouring renal denervation.

For diastolic office BP, Pisano et al. (2021) pooled data from eight RCTs with a total of 1,049 participants. The authors found that renal denervation may reduce diastolic office BP when compared to sham or standard treatment MD -4.61 mmHg (95% CI -8.23 to -0.99). High heterogeneity was reported (I^2=77%). but this was completely nullified after excluding studies performing ablations with a single-electrode catheter system (I^2=0%). Pisano et al. (2021) reported the GRADE score as moderate for the evidence included for systolic and diastolic office BP.

The further three RCTs that we identified that were published after the Cochrane review found no significant difference in diastolic office BP between renal denervation groups and the control groups (Azizi et al. 2021, Bergland et al. 2021, Kario et al. 2022b). Azizi et al. (2021) reported a median between group difference of -4.0 (95% CI -9.0 to 0.0), favouring neither at two months follow up. Kario et al. (2022b) and Bergland et al. (2021) both report non-significant differences across groups.

4.1.5 eGFR or creatinine clearance (mL/min/1.73m^2)

In a meta-analysis of six RCTs (822 participants), Pisano et al. (2021) reported that renal denervation had little or no effect on renal function, as estimated by eGFR or creatinine clearance, as compared to control (-2.56 95% CI -7.53 to 2.42). The analysis showed moderate heterogeneity (I^2=50%). which was not further explored. Bergland et al. (2021) also reported longer-term outcomes for eGFR or creatinine clearance and found no significant difference (p=0.33) between renal denervation (n=9) and the adjusted drug treatment group (n=10).

4.1.6 Serum creatinine (mg/dL)

Pisano et al. (2021) also conducted a meta-analysis of five RCTs (721 participants), to analyse any differences in serum creatinine levels. The authors found that renal denervation may result in little or no difference over sham or standard treatment on serum creatinine levels (MD 0.03 mg/dL, 95% CI -0.06 to 0.13). The authors reported a moderate level of heterogeneity for this analysis (I^2=68%), which was not further explored as only five studies were included.

4.1.7 Adverse events

Pisano et al. (2021) systematically collected data on major adverse events from 11 RCTs. The authors reported that in one RCT, 36 serious adverse events were reported (n=24, 26% in the intervention group and n=12, 27% in the usual care group) and 17 periprocedural complications, including vascular (n=4), bleeding (n=8) and five other mild complications (back pain, groin pain and hypotension in the renal denervation group). Pisano et al. (2021) also reported that in another RCT minor symptoms such as headache, atypical chest pain, muscle convulsions and fatigue were recorded in five renal denervation patients and six sham patients, respectively. Two RCTs reported no periprocedural complications in either renal denervation or control arms and no study provided information on the occurrence of transient dizziness or anaemia.

Azizi et al. (2021) reported on procedural safety events for the renal denervation (n=69) group and the sham procedure group (n=67) within two months. No events were recorded in either group for death, clinically significant embolic events, any renal artery complication requiring intervention, acute renal injury, need for renal artery angioplasty or stenting or new onset renal artery stenosis greater than 50%. One event was recorded for major access site complications requiring intervention in the renal denervation group compared to none in the sham group. There were 12 safety events of procedure-related pain lasting more than two days recorded in the renal denervation group compared to 10 events in the sham group.

Kario et al. (2022b) reported on serious procedure/device-related adverse events within three months. One event each (1.4%) was recorded for vasospastic angina, puncture site, cellulitis, and postural dizziness in the renal denervation group (n=72) compared with none in the sham (n=71) group. One pyrexia event was recorded in the sham group (1.4%) compared to none in the renal denervation group. The most common specific clinical events were procedure related pain lasting for more than two days (e.g., back pain, puncture site pain, etc.), which occurred in six patients in each group.

Bergland et al. (2021) found no complications related to the renal denervation procedure and no adverse events related to the study participation for the drug adjusted control group over a seven-year period.

4.1.8 Quality of life

Only one RCT in the Pisano et al. (2021) Cochrane review reported data on quality of life (self-reported health status). After a six month follow up, the self-reported health status was 53.8 ± 22.3 in the control group and 75.0 ± 14.1 in the intervention group with higher scores indicating higher quality of life (baseline-adjusted between-group difference: 13.6; 95% CI -7.4 to 34.6; p= 0.28 favours neither).

Table 1. Systematic review and meta-analysis: Pisano et al. (2021)

Review	Design, search period	Number of studies	Patient characteristics	Interventions	Authors' Conclusions	Comments
Cochrane review by Pisano et al. (2021)	**Review period**: Up to November 2020. **Review purpose:** to evaluate the short- and long-term effects of renal denervation in individuals with resistant hypertension compared with standard care or sham. **Included study designs:** RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth, or other predictable methods) of individuals with resistant hypertension undergoing renal sympathetic denervation procedures.	**Number of studies:** 15 studies All 15 included studies were parallel-group RCTs with adult participants. **Length of studies**: from 3 to 24 months	**Population:** Adults (older than 18 years), with refractory or resistant hypertension, defined by the presence of a clinic blood pressure above target (higher than 140/90 mmHg, or higher than 130/80 mmHg in individuals with type 2 diabetes mellitus), despite the concomitant use of three or more antihypertensive drugs of different classes, including a diuretic.	**Intervention**: Any transcatheter renal sympathetic denervation procedures performed using contemporary percutaneous catheters compared with standard medical therapy or sham intervention. **Comparator:** 4 studies compared renal denervation with sham. 11 studies compared renal denervation with standard or intensified antihypertensive therapy.	In patients with resistant hypertension, there is low-certainty evidence that renal denervation does not improve major cardiovascular outcomes and renal function. Conversely, moderate-certainty evidence exists that it may improve 24h ABPM and diastolic office-measured BP.	Risk of bias assessed using GRADE. Most studies had unclear or high risk of bias for allocation concealment and blinding.
Abbreviations: RCT: Randomised controlled trial						

Table 2. Randomised controlled trials: design and characteristic

Study reference	Study Design	Participants	Interventions	Outcomes	Comments
Azizi et al. (2021)	Randomised single blind, sham controlled trial. **Randomisation:** participants were randomly assigned (1:1) to receive ultrasound renal denervation or a sham procedure. Multicentre (n=28, USA), (n=25, Europe) **Enrolment period:** 11 March 2016 to 13 March 2020 **Follow-up:** two months	**Number of participants:** Ultrasound renal denervation: (n=69), Sham procedure: (n=67) **Mean age:** Ultrasound renal denervation: 52.3 (7.5 SD)**,** Sham procedure: 52.8 (9.1 SD) **Inclusion criteria:** • Age ≥18 and ≤75 years at time of consent • Average seated office BP ≥140/90 mmHg at screening visit while on a stable regimen of at least 3 antihypertensive medications of different classes including a diuretic for at least 4 weeks prior to consent • Documented daytime ABP ≥135/85 mmHg after 4-week stabilisation period • Suitable renal anatomy compatible with the renal denervation procedure **Exclusion criteria:** • Ineligibility for treatment due to renal artery anatomy • Iliac/femoral artery stenosis • Type I diabetes mellitus or uncontrolled Type II diabetes • Secondary hypertension not including sleep apnoea • History of cerebrovascular events • History of cardiovascular events • Angina • Hypertensive drug contraindications • history of persistent or permanent atrial tachyarrhythmia • Active implantable medical device • Chronic oxygen support • Primary pulmonary hypertension • Limited life expectancy of <1 year • Night shift workers • Drug or alcohol dependency • Pregnancy	**Intervention**: The Paradise system ultrasound renal denervation (n=69) **Comparator:** Sham procedure (n=67)	**Primary outcome:** change in daytime ambulatory systolic blood pressure from baseline to 2 months.	Eligible patients were switched to a once daily, fixed-dose, single-pill combination of a calcium channel blocker, an angiotensin receptor blocker, and a thiazide diuretic four weeks before randomisation. The study had a large range of exclusion criteria, and it is possible that the trial population is not representative of people who would be likely to receive the intervention in the real world.

Study reference	Study Design	Participants	Interventions	Outcomes	Comments
Kario et al. (2022b)	Multicentre, randomised, single-blind, sham-controlled trial that enrolled patients from Japan and South Korea **Randomisation:** participants were randomly assigned (1:1) to receive ultrasound renal denervation or a sham procedure. **Enrolment period:** 12 January 2017 to 31 March 2020 **Follow up:** three months	**Number of participants:** Ultrasound renal denervation: (n=72), Sham procedure: (n=71) were included in the full analysis set **Mean age:** Ultrasound renal denervation: 50.7 (11.4 SD), Sham procedure: 55.6 (12.1 SD) **Inclusion criteria:** • Adults aged 20–75 years • Resistant hypertension (average seated office BP ≥ 150/90 mmHg) despite treatment with a stable regimen including maximum tolerated dosages of at least three antihypertensive medications from different classes (including a diuretic) • 24-hour ambulatory systolic BP (SBP) of ≥140 mmHg during a screening period of ~4–8 weeks prior to the procedure. • Suitable renal artery anatomy **Exclusion criteria:** • Patients with unsuitable renal artery anatomy • Chronic kidney disease (estimated glomerular filtration rate <40 mL/min/1.73 m2) • Secondary hypertension • Inadequately controlled diabetes mellitus • Inflammatory bowel disease • History of severe cardiovascular event • Other chronic conditions	**Intervention**: The Paradise system ultrasound renal denervation (n=72) **Comparator:** Sham procedure (renal angiogram only) (n=71)	**Primary outcome:** change in 24-hour ambulatory SBP from baseline at 3 months	Standard-of-care antihypertensive medication was to remain unchanged up to the 3-month follow-up data collection. However, the trial did not standardise medications or objectively measure medication adherence. There was missing ABPM data for both groups. (n=69) patients in the intervention group were included in the full analysis set and (n=67) patients in the control group were included in the full analysis set.

Study reference	Study Design	Participants	Interventions	Outcomes	Comments
Bergland et al. (2021)	Single-centre randomised controlled trial in Norway **Randomisation:** participants were randomised using block randomisation using a sealed envelope arranged in a fixed order **Enrolment period:** August 2012 to June 2013 **Follow-up:** seven years	**Number of participants:** Radiofrequency renal denervation (n=9), adjusted drug treatment (n=10) **Mean age:** Radiofrequency renal denervation 57.0 (10.9 SD), Adjusted drug treatment 62.7 (5.1 SD) **Inclusion criteria:** • Patients aged 18 to 80 years of age • normal renal arteries at computed tomography or MRI examination within 2 years before participation. • treatment resistant hypertension defined as office systolic BP (SBP) >140 mmHg, despite maximally tolerated doses of ≥3 antihypertensive drugs including a diuretic. • ambulatory daytime SBP >135 mmHg after witnessed intake of antihypertensive drugs **Exclusion criteria:** • Estimated glomerular filtration rate <45 mL/min per 1.73 m2 (MDRD formula) • urine albumin/creatinine ratio >50 mg/mmol • type 1 diabetes mellitus • Secondary hypertension • high serum aldosterone levels	**Intervention:** Radiofrequency renal denervation using Symplicity Catheter System **Comparator:** Drug-adjusted treatment - antihypertensive medication adjusted at baseline, 1 month, and at 3 months	**Primary outcome:** Blood pressure changes	The original trial was stopped early for ethical reasons because RDN had uncertain BP-lowering effect however long-term follow up data were collected at 3 and 7 years. The original trial with short-term outcomes was included in the Cochrane review. Small sample size. Witnessed intake of drugs was performed at follow-up visits immediately prior to all 24H ABPM measurements.
Abbreviations: ABPM: ambulatory blood pressure monitoring, BP: blood pressure, CI: confidence intervals, eGFR: estimated glomerular filtration rate, MD: mean difference, RCT: randomised controlled trial, RD: renal denervation					

Table 3. Renal Denervation compared to sham/standard treatment: summary of main outcomes

Outcome	Evidence source(s)	Number of studies, number of participants	Absolute effect	Relative effect
Myocardial infarction	Pisano et al. (2021)	4 RCTs, 742 participants in total	RD: 18/1000 Sham procedure/standard treatment: 14/1000	RR 1.31 (95% CI 0.45 to 3.84) p=0.62, favours neither
	Azizi et al. (2021)	1 RCT, 136 participants	Number of events: * RD: 1/69 Sham:0/67	NR
Ischaemic stroke	Pisano et al. (2021)	5 RCTs, 892 participants in total	RD: 14/1000 Sham procedure/standard treatment: 14/1000	RR 0.98 (95% CI 0.33 to 2.95) p=0.97, favours neither
	Azizi et al. (2021)	1 RCT, 136 participants	Number of events: * RD: 0/69 Sham:0/67	NR
Unstable angina	Pisano et al. (2021)	3 RCTs, 270 participants in total	RD: 11/1000 Sham procedure/standard treatment: 22/1000	RR 0.51 (95% CI 0.09 to 2.89) p=0.45, favours neither
Hospitalisation	Pisano et al. (2021)	3 RCTs, 743 participants in total	RD: 35/1000 Sham procedure/standard treatment: 28/1000	RR 1.24 (95% CI 0.50 to 3.11) p=0.64, favours neither
	Azizi et al. (2021)	1 RCT, 136 participants	Number of events: * RD: 0/69 Sham:0/67	NR
Systolic 24-hour ABPM (mmHg)	HTW analysis^	10 RCTs, 1217 participants in total	NR	MD: -1.78 (95%CI -4.06 to 0.5) p=0.13, favours neither
	Bergland et al. (2021)	1 RCT, 19 participants	**Baseline** RD: 149 Drug Adj: 151 **7 years** RD: 140 Drug Adj: 133	p=0.33, favours neither

Outcome	Evidence source(s)	Number of studies, number of participants	Absolute effect	Relative effect
Diastolic 24-hour ABPM (mmHg)	HTW analysis^	9 RCTs, 1176 participants in total	NR	MD: -1.26 (95%CI -3.53 to 1.01) p=0.28, favours neither
	Bergland et al. (2021)	1 RCT, 19 participants	**Baseline** RD: 89 Drug Adj: 85 **7 years** RD: 83 Drug Adj: 78	p=0.22, favours neither
Systolic office BP (mmHg)	Pisano et al. (2021)	9 RCTs, 1090 participants in total	NR	RD: The mean systolic office BP in the intervention groups were on average 5.92 lower (95%CI -12.94 to 1.10) Sham procedure/standard treatment: The mean systolic office BP ranged across control groups from 140 to 165.7 p=0.10, favours neither
	Azizi et al. (2021)	1 RCT, 136 participants	**At random assignment** RD: 155.6 Sham: 154.9 **At 2 months** RD: 147.1 Sham: 152.1	MD: -7.0 (95% CI -13.0 to 0.0) Adjusted p-value =0.037, favours RD
	Kario et al. (2022b)	1 RCT, 135 participants	NR	MD: -2.0 (95% CI NR) p=0.511, favours neither
	Bergland et al. (2021)	1 RCT, 19 participants	**Baseline** RD: 156 Drug Adj: 160 **7 years** RD: 155 Drug Adj: 146	p=0.39, favours neither
Diastolic office BP (mmHg)	Pisano et al. (2021)	8 RCTs, 1049 participants in total	NR	RD: The mean diastolic office BP in the intervention groups were on average 4.61 lower (95%CI -8.23 to 0.99)

Outcome	Evidence source(s)	Number of studies, number of participants	Absolute effect	Relative effect
				Sham procedure/standard treatment: The mean diastolic office BP ranged across control groups from 83.8 to 99.2 p=0.01, favours RD
	Azizi et al. (2021)	1 RCT, 136 participants	**At random assignment** RD: 101.4 Sham: 99.4 **At 2 months** RD: 96.6 Sham: 98.7	MeD: -4.0(95% CI -9.0 to 0.0) p-value =0.16, favours neither
	Kario et al. (2022b)	1 RCT, 135 participants	NR	MD: 0.1 (95% CI NR) p=0.946, favours neither
	Bergland et al. (2021)	1 RCT, 19 participants	**Baseline** RD: 91 Drug Adj: 88 **7 years** RD: 93 Drug Adj: 85	p=0.14, favours neither
eGFR or creatinine clearance (mL/ min/1.73m^2)	Pisano et al. (2021)	6 RCTs, 822 participants in total	NR	MD = -2.56 (95% CI -7.53 to 2.42) p=0.31, favours neither
	Bergland et al. (2021)	1 RCT, 19 participants	**Baseline** RD: 90.1 Drug Adj: 89.1 **7 years** RD: 76.3 Drug Adj: 66.9	p=0.33, favours neither
Serum creatinine levels (mg/dL)	Pisano et al. (2021)	5 RCTs, 721 participants in total	NR	MD=0.03 (95%CI -0.06 to 0.13) p=0.50, favours neither

P-values for Azizi et al. (2021) are adjusted for baseline scores; *Based on safety endpoints; ^see text for sensitivity analyses

Abbreviations: ABPM: ambulatory blood pressure monitoring, BP: blood pressure, CI: confidence intervals, eGFR: estimated glomerular filtration rate, MeD: unadjusted median between group difference, MD: mean difference, NR: not reported, RCT: randomised controlled trial, RD: renal denervation, RR: risk ratio

4.2 Ongoing trials

We identified several relevant trials listed on the clinical trials registry and reviewed ongoing trials listed in the Cochrane review (Pisano et al. 2021). However, these trials appear to have either been withdrawn, terminated or had not been updated for several years and have not published findings.

Experts highlighted that the SPYRAL HTN-ON Med trial was due to publish in late 2022 and includes a planned sub-group analysis for people in the treatment resistant population receiving three medications. However, subgroup analyses detailed in the published protocol do not appear to include this analysis (Böhm et al.). The trial aims to follow-up participants for 36 months but crossover from the sham to intervention arm will be allowed after six months. Details on this study are provided in Table 4. Experts also highlighted the TARGET BP I trial which examines use of an infusion of alcohol to achieve renal denervation (Mahfoud et al. 2021). This was considered out of scope as this approach was not included in the initial protocol and it is unclear if it will provide analyses for a resistant subgroup population.

Table 4. Ongoing Trials: design and characteristics

Study information	Status	Research questions & outcome measures
Registration: NCT02439775 **Country**: 11 countries, including four sites in the United Kingdom **Target recruitment:** 150 participants **Follow-up:** up to 36 months **Primary completion date:** October 2022	Active, not recruiting	The purpose of this study is to test the hypothesis that renal denervation decreases blood pressure and is safe when studied in the presence of up to three standard antihypertensive medications. **Population:** High blood pressure when receiving a medication regimen of one, two, or three antihypertensive medication classes **Intervention:** Symplicity Spyral multi-electrode renal denervation system **Comparator:** Sham Procedure **Relevant outcomes:** acute and chronic safety, change in blood pressure, cardiovascular events, hospitalisation, all-cause mortality

5. Economic evaluation

5.1 Health Economic Literature Review

Appendix 3 summarises the selection of articles for inclusion in the evidence review. The titles and abstracts of records identified in the search for this research question were screened and 11 health economic studies were deemed potentially relevant. The full texts of these studies were reviewed against the inclusion/exclusion criteria and eight studies were excluded from the review. Three studies were excluded as they were available as an abstract only (Kang et al. 2014, Naclerio et al. 2014, Tilden et al. 2014). Two studies were excluded as they presented reviews of existing economic literature review rather than de novo economic analyses (Mensa Sorato et al. 2020, SHTG 2014). One study was selectively excluded (Bulsei et al. 2018) because it presented a cost effectiveness analysis using 'cost per mmHg reduction in SBP' as the outcome rather than the preferred cost per quality adjusted life year (QALY). Another study was selectively excluded because it presented the same underlying model used in an included UK study but was less

applicable as it considered the healthcare perspective in the Netherlands (Henry et al. 2015). The final study was excluded because it was not an economic analysis (Cheng et al. 2021).

The three remaining economic studies were included in the review (Chowdhury et al. 2018, Dorenkamp et al. 2013, Gladwell et al. 2014). All three studies were cost-utility analyses which expressed effectiveness using QALYs and reported incremental cost effectiveness ratios (ICERs) to draw conclusions on cost effectiveness. The studies used Markov models to estimate the cost-effectiveness of renal denervation in comparison to standard care over a lifetime horizon. As there are no trials comparing hard clinical endpoints in patients treated with renal denervation and standard care, the models used SBP reductions as a surrogate endpoint. This data was combined with other published data and risk equations to drive differences in event rates.

One of the studies was directly applicable as it considered a UK NHS perspective (Gladwell et al. 2014). The other two studies were deemed to be only partially applicable to the decision context of NHS Wales as they considered healthcare systems in other countries. Dorenkamp et al. (2013) considered the perspective of the healthcare system in Germany while Chowdhury et al. (2018) considered an Australian healthcare perspective. All the studies adopt a risk model-based approach to estimate the longer-term impact following reductions in blood pressure. The series of Symplicity HTN trials inform the clinical evidence for each of the economic analyses.

Some potentially serious limitations were identified in the analyses. Most notably, there is uncertainty around the duration and size of the treatment effect with renal denervation. This uncertainty was partially explored within sensitivity analyses in the studies by varying the size of the SBP reduction or assuming that the procedure needs to be repeated to maintain the treatment effect. However, the variations explored in the analyses were somewhat conservative and therefore uncertainty remains.

Dorenkamp et al. (2013) used the earliest iteration of the Symplicity HTN trial series, Symplicity HTN 1 (Symplicity HTN-1 Investigators 2011). A sustained reduction of 20 mmHg following renal denervation was assumed in base-case analysis. The Systemic Coronary Risk Evaluation (SCORE) system was used to model relative transition risks. The modelled risk of cardiovascular disease was 2.2% lower in people treated with renal denervation. Renal denervation was found to have an ICER of €1,512 (£1,219) per QALY in men aged 50 and €1,560 (£1,257) per QALY in women aged 50. There was an increase in ICER at each age band up to the highest reported which was for women aged 90 with an ICER of €126,633 (£102,055). In probabilistic sensitivity analysis, there was a 95% probability of renal denervation being cost effective at a threshold of €25,000 per QALY up to the ages of 76 in men and 75 in women.

Gladwell et al. (2014) applied a reduction in SBP of 32mmHg based on the Symplicity HTN 2 trial (Esler et al. 2010). The renal denervation procedure was estimated to cost £4,500. Gladwell et al. (2014) used the Framingham cardiac risk model to estimate the decreased risk experienced by the renal denervation group. Renal denervation was found to be cost incurring with an increase to base case costs of £2,961 whilst increasing QALYs by 0.61. Renal denervation was estimated to be cost effective with an ICER of £4,805 per QALY. An alternative scenario considering a lower SBP (14.13 mmHg instead of 32 mmHg) resulted in the ICER increasing to £18,849 per QALY. Assuming that renal denervation is required every 10 years to maintain the treatment effect resulted in the ICER increasing to £14,312 per QALY. In probabilistic sensitivity analysis, RDN was found to have a 100% probability of being cost effective at a threshold of £20,000 per QALY.

The most recent economic evaluation was undertaken by Chowdhury et al. (2018) using the clinical results from the Symplicity HTN 3 trial (Bhatt et al. 2022). The modelled population consisted of individuals with treatment resistant hypertension aged less than 65 years. This cohort was chosen as the Symplicity HTN 3 trial showed that a blood pressure reduction was only observed in this patient group. The modelled blood pressure reduction of 5.7 mmHg for the renal denervation group reflects this patient group. Note that the overall effect size from the Symplicity

HTN 3 trial was 2.1 mmHg. Transition probabilities were estimated according to distributions observed in registry data with expected changes in blood pressure risk calculated according to the analysis by Ettehad et al. (2016). Ettehad et al. (2016) undertook a meta-analysis of the preventative effect of blood pressure lowering for cardiovascular disease. Dynamic risk transitions were applied according to the age-related cardiac trends. Chowdhury et al. (2018) concluded that renal denervation would be cost effective for people with treatment resistant hypertension if their ten-year cardiovascular risk score was equal to or above 13.2%. The reported ICER was $47,130(AUD) per QALY which is considered cost effective when compared to the $50,000 threshold but equates to £26,708 (1 AUD = 0.57 GBP: XE.com accessed April 2022) which wouldn't be considered cost effective according to the typical UK threshold of £20,000 per ICER.

The three included economic studies are reported in further detail in Table 5.

Table 5. Economic literature

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Gladwell et al. (2014) **Country:** United Kingdom (UK) **Type of economic analysis:** Cost-utility analysis **Perspective:** UK healthcare payer perspective covering direct health and social care costs. **Currency:** UK pound sterling (£) **Price year:** 2012 **Time horizon:** Lifetime **Discounting:** 3.5% per year **Potential conflict of interest:** Most of the authors (including lead author) were employees of a consultancy which was reimbursed by Medtronic Ltd to develop the model and prepare the	**Population** Patients with diagnosed resistant hypertension. The population was based on the inclusion criteria of the Symplicity HTN-2 trial. Patients had an average age of 58 years and 43% were female. The average baseline SBP was 178 mmHg, 34% had diabetes and 16% were smokers. Patients had an average of five prior medications for hypertension at baseline. It was assumed that patients had no prior cardiovascular events, manifest coronary heart disease (CHD), or evidence of underlying end-stage renal disease (ESRD). **Interventions** Catheter-based renal denervation (RDN) plus standard of care (SoC). **Comparator** SoC alone comprised of three or more antihypertensive medications. **Study design** Modified Markov health-state model with transition probabilities based on event history.	**Source of baseline and effectiveness data:** Baseline characteristics were based on the inclusion criteria of the Symplicity HTN-2 trial. Transition probabilities were calculated from multivariate risk equations from large-scale cohort studies, such as the Framingham Heart Study. Patients in the SoC arm were assumed to have a continual SBP of 178mmHg. Those treated with RDN were assigned a reduction in SBP of 32 mmHg, which was applied by six months in line with the Symplicity HTN-2 trial data. Mortality was split into disease specific mortality and overall mortality. Overall mortality was derived from standard life tables. Disease specific mortality was applied as either absolute risks from published regression equations or additional relative risks to underlying mortality data. **Source of resource use and cost data:** NHS Reference costs 2012 were used for most cost data. Additional costs were identified through a systematic literature review. Drug costs were based on prices listed in the British National	**Base case results (per patient)** **Costs** RDN: £11,770 SoC: £8,810 Incremental: £2,961 **Effectiveness** RDN: 12.77 QALYs SoC: 12.16 QALYs Incremental: 0.62 QALYs **ICER (cost per QALY)** £4,805 per QALY **Scenario analysis** Alternative scenarios were modelled using different estimates for the reduction in SBP with RDN and the duration of the treatment effect. Applying a lower SBP reduction based on the HTN-3 trial (14.13 mmHg instead of 32) resulted in the ICER increasing to £18,849 per QALY. Assuming that retreatment is required every 10 years to maintain the treatment effect resulted in the ICER increasing to £14,312 per QALY. While the ICER increase is substantial in both scenarios, the ICER is still below a threshold of £20,000 per QALY.	**Applicability** Directly applicable. **Limitations** Some potentially serious limitations were identified, as described below. • There is uncertainty around the duration and size of the treatment effect with RDN. This uncertainty is partially explored in sensitivity analysis, but conservative variations were applied. Thus, some uncertainty remains around these key aspects. • As there are no trials comparing hard clinical endpoints, the model uses an SBP reduction in combination with risk equations to estimate reductions in events. The reliability of the analysis therefore depends on the accuracy of the risk equations in predicting events. • There is some evidence to suggest that the Framingham risk equations may overestimate the risk of cardiovascular events. This could be a result of

Study details	Study population and design	Data sources	Results	Quality assessment
manuscript. One of the authors is an employee of Medtronic Ltd.		Formulary (BNF). The costs of the RDN procedure were sourced from data provided by the manufacturer. The RDN cost captures the HRG code associated with treatment as well as the cost of equipment. **Source of quality-of-life data:** Utility values for stroke, angina pectoris (AP), CHD and myocardial infarction (MI) were taken from a published economic model of statin treatment. ESRD utility was taken from a health-related quality of life review for patients with chronic renal disease. The quality of life impact of heart failure (HF) was sourced from a published sub-analysis of the FAIR-HF study, which considered patients with chronic heart failure and iron deficiency. All utilities were adjusted for the effects of age using a utility multiplier derived from the UK population norms for EQ-5D.	Thus, RDN would still be considered cost effective. **Sensitivity analysis** The impact of applying upper and lower values from a range around base case inputs was explored. Each input was varied independently in deterministic sensitivity analysis. The results showed that there were no changes that resulted in different conclusions (i.e. RDN was always cost effective). Variations in the reduction in SBP with RDN was found to have the greatest impact on the results. In probabilistic sensitivity analysis, RDN was found to have a 100% probability of being cost effective at a threshold of £20,000 per QALY.	disparities between the UK population and the US population, on which the equations were based or improvements in care since the equations were developed. • SBP was assumed to remain constant in the comparator arm. Notably, this included a scenario based on HTN-3 despite the study reporting a reduction of 11.23 mmHg in the comparator group (sham therapy). Therefore, the incremental effect of using RDN has been overestimated in the scenario analysis. • Patients were assumed to have no prior cardiovascular events, manifest CHD, or ESRD. Therefore, the modelled population may not reflect everyone with resistant hypertension.
Author and year: Dorenkamp et al. (2013) **Country:** Germany **Type of economic analysis:**	**Population** Patients with resistant hypertension. Baseline systolic blood pressure (SBP) was 160 mmHg or more despite compliance with at least three	**Source of baseline and effectiveness data:** Transition probabilities were based on German or North European registry data for cardiovascular disease (CVD) events. Incidence of ESRD was derived from	**Base case results (per patient)** Results were presented for men and women within various age groups. **Costs** RDN was never a cost-saving strategy. Costs ranged from	**Applicability** Partially applicable as it considered a non-UK perspective. **Limitations** Some potentially serious limitations were identified, as described below.

Study details	Study population and design	Data sources	Results	Quality assessment
Cost-utility analysis **Perspective:** Health care payer – German statutory health and nursing care insurance system. **Currency:** Euro (€) **Price year:** 2012 **Time horizon:** Lifetime **Discounting:** 3% per annum. **Potential conflict of interest:** Lead author received travel support from Medtronic for travel to meetings for the study or other purposes. Lead author and another author received lecture honoraria from Medtronic.	antihypertensive drugs (including one diuretic). Secondary causes of hypertension were excluded. The model considered cohorts of men and women at different ages. Results were presented for men and women at 50, 60, 70, 80, 85, and 90 years of age. **Interventions** Catheter-based renal denervation (RDN) plus standard of care (SoC). **Comparator** SoC consisting of antihypertensive regime consisting of metoprolol, ramipril, and torasemid at maximum dose. **Study design** Markov state-transition model	the German QuaSi-Niere renal registry. CVD event incidence for patients receiving RDN was adjusted upwards using the Systemic Coronary Risk Evaluation (SCORE) risk estimation system. RDN was associated with a sustained SBP reduction of 20mmHg based on data from Symplicity HTN-1. Relative risks declined by 2.2% per year for cardiovascular disease events and mortality to account for a decline in risk factors attributable to hypertension. Transition probabilities for secondary events within the first year following primary event were drawn from large registries or RCTs. Patients in symptomatic or asymptomatic health states were still at risk of CVD events using relative risks calculated by comparing the probabilities from registries and a range of RCTs with the incidences in the underlying population. **Source of resource use and cost data:** Cost data were sourced from 2012 version of the German Diagnosis Related Groups (G-DRG) system, German pharmaceutical price lists, and German fee schedules for doctors and outpatient visits.	€6,930 to €30,474 in the SoC arm and €10,729 to €32,349 in the RDN arm. Incremental costs varied from €1,732 to €3,799. Incremental costs were shown to rise as the age of the population increased. **Effectiveness** QALYs ranged from 3.11 to 15.75 in the SoC arm compared to 3.17 to 16.86 in the RDN arm. Incremental QALYs varied from 0.03 to 1.24. Younger patients at baseline were associated with a longer life expectancy and subsequently QoL, and incremental QALYs were also higher in the younger age groups. **ICER (cost per QALY):**. ICER values ranged from £1,512 to €126,633 (€1,512 to €62,417 in males and €1,560 to €126,633 in females). ICER results were generally more favourable in younger patients. When patients were aged 90 at baseline, there was a significant increase in the ICER. **Sensitivity analysis** In deterministic sensitivity analysis, the result was found to be most sensitive to changes	• There is uncertainty around the duration and size of the treatment effect with RDN. This uncertainty is partially explored in sensitivity analysis, but conservative variations were applied. Thus, uncertainty remains. • There are no trials comparing hard clinical endpoints in patients treated with RDN. Therefore, the model uses a surrogate endpoint of the reduction in SBP as the driver of differences in event rates. • It was assumed the treatment effect (20 mmHg reduction in SBP with RDN) would be maintained over the patient's lifetime. • No appropriate utility value following RDN found and so a value relating to PCI was used. • Results presented are broken down by male and female at different age groups however results are not provided for the overall cohort. • Model doesn't account for all possible combinations of health states nor for all diseases associated with hypertension.

Study details	Study population and design	Data sources	Results	Quality assessment
		Cost of RDN was based on G-DRG F54Z and included further costs in terms of periprocedural bleeding complications at a rate consistent with other percutaneous interventional procedures. Drug costs reflect the maximum amounts covered by German health insurance. It was assumed that four prescriptions were issued each year. **Source of quality-of-life data:** Utility values were derived from published literature (Stein et al., Neaser et al., Tsevat et al., Dorman et al., Young et al., Hornberger et al., Kroeker et al., Cohen et al.). No evidence was available on the procedural disutility of RDN. Therefore, a previously reported utility of 0.94 for percutaneous coronary interventions (PCI) was assigned to the one-year period following the RDN procedure.	in the SBP lowering effect related to RDN, the rate of RDN non-responders and RDN costs. RDN remained cost-effective in all alternative scenarios. Probabilistic sensitivity analysis was also conducted. The results showed that there was a 95% probability that RDN would remain cost-effective at a threshold of €25,000 per QALY up to an age of 76 in men and 75 in women.	
Author and year: Chowdhury et al. (2018) **Country:** Australia **Type of economic analysis:** Cost-utility analysis **Perspective:**	**Population** Patients with treatment resistant hypertension aged less than 65 years without initial CVD. **Interventions** Catheter-based RDN + SoC **Comparator** SoC comprised of full doses of	**Source of baseline and effectiveness data:** The SBP reduction in the RDN arm over and above SoC (5.7 mmHg) was based on data from the Symplicity HTN-3 trial. Cardiovascular risk was modelled to increase over time due to aging in both the RDN and SoC arms (by the same extent in each arm). Age-	**Base case results for 1,000 patients** **Costs** SoC: $26,273,976 RDN: $34,970,545 Incremental: $8,696,568 **Effectiveness** SoC: 11,216.9 QALYs RDN: 11,401.5 QALYs	**Applicability** Partially applicable as it considered a non-UK perspective. **Limitations** Some potentially serious limitations were identified, as described below. • The analysis considers best case scenarios only as

Study details	Study population and design	Data sources	Results	Quality assessment
Australian public health care system. **Currency:** Australian dollars ($) **Price year:** 2017 **Time horizon:** Lifetime **Discounting:** 5% per year **Potential conflict of interest:** The authors declared no conflict of interest.	three antihypertensive agents including a diuretic. **Study design** Markov model.	related trends were based on those observed for cardiovascular mortality among the Australian population. Expected changes to CVD risk from SBP reduction were based on data from a published meta-analysis by Ettehad et al. (2016). The proportional distribution of fatal and non-fatal CVD incidence was based on data from the "Reduction of Atherothrombosis for Continued health" registry. Proportional distribution of nonfatal incident MI and stroke were based on data from the Swedish Primary Care Cardiovascular Database. **Source of resource use and cost data:** Costs for inpatient management of nonfatal and fatal events, RDN and antihypertensive medications were drawn from published sources, such as the Pharmaceuticals Benefits Scheme (PBS) and the Medicare Benefits Schedule (MBS). It was assumed that both the RDN and SoC arm used three antihypertensive drugs continuously. RDN costs were based on a micro-costing exercise undertaken by Medtronic Ltd. and comprised a cost of catherization and material	Incremental: 184.5 QALYs **ICER (cost per QALY)** $47,130 per QALY (considered cost-effective by the authors based on a $50,000 per QALY threshold). Cost-effectiveness was achieved when initial 10-year cardiovascular risk was at least 13.2% **Scenario analysis** In a scenario analysis where the time horizon was reduced to 20 years, RDN was cost effective when the 10-year cardiovascular risk was at least 24.3%. In a scenario where RDN was repeated every 10 years, RND was cost effective when the 10-year cardiovascular risk was at least 61.1%. **Sensitivity analysis** In deterministic sensitivity analysis showed that results were highly sensitive to changes in the BP lowering effect of RDN in relation to SoC, the cost of RDN and participant's age. Probabilistic sensitivity analysis showed that there was an 85% probability that RDN would be cost-effective at a	results were only presented for the level of cardiovascular risk at which RDN becomes cost-effective. Results were not presented for a baseline assumed risk. Therefore, difficult to assess the impact of worse case scenarios, especially in relation to size and duration of treatment effect. • There are no trials comparing hard clinical endpoints in patients treated with RDN. Therefore, the model uses a surrogate endpoint of the reduction in SBP as the driver of differences in event rates. • Data from the Symplicity HTN-3 trial did not show statistical significantly reduced SBP in the RDN arm. • Reduction in SBP remained the same for all ages and was sustained over the model time horizon. • CVD health state comprised of MI and/or stroke rather than having events separated. • Patients were assumed to have no prior cardiovascular disease at baseline. Therefore, the modelled population may not reflect everyone with resistant hypertension.

Study details	Study population and design	Data sources	Results	Quality assessment
		costs, including resource used for screening. **Source of quality-of-life data:** Health state utility values were sourced from the published literature. A value for being 'alive without CVD' was based on a quality of life study in patients with hypertension. Quality of life values for nonfatal MIs, nonfatal strokes and the 'post-CVD event' health state were sourced from previous cost effectiveness studies.	threshold of $50,000 per QALY with an initial CVD risk of 13.2%.	• Assumed that all patients fully complied with medication, despite evidence suggesting otherwise.

AP: angina pectoris; BNF: British National Formulary; CHD: coronary heart disease; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; DSA: deterministic sensitivity analysis; ESRD: end-stage renal disease; GBP: Great British pounds; HF: heart failure; HRG: healthcare research group; HRQoL: health related quality of life; ICER: incremental cost-effectiveness ratio; MI: myocardial infarction; PSA: probabilistic sensitivity analysis; PCI: percutaneous coronary interventions; RCT: randomised controlled trial; RDN: renal denervation; SBP: systolic blood pressure; SoC: standard of care; QALY: quality-adjusted life year.

5.2 HTW Cost-utility analysis

The existing economic evidence base was considered insufficient to address the cost effectiveness of renal denervation. Therefore, HTW developed a cost-utility analysis to consider the cost effectiveness of renal denervation supported by standard care in comparison to standard care alone in the decision context of NHS Wales (see Appendix 6 for full details).

The analysis took the perspective of the UK NHS and personal social services (PSS). A lifetime horizon was considered to ensure that all relevant costs and outcomes were considered. Future costs and benefits were discounted at rate of 3.5% as recommended by the National Institute for Health and Care Excellence (NICE).

The modelling approach adopted was similar to that used in previous economic analyses considering renal denervation. QRISK3 was used to estimate the 10-year risk of cardiovascular events with standard care and renal denervation. QRISK3 was selected as the most applicable risk calculator to use for the analysis as it is widely used in NHS Wales. Baseline risk factors, such as age, sex, body mass index (BMI), diabetic status and systolic blood pressure were sourced from Bhatt et al. (2022).

A reduction in the risk of cardiovascular events was modelled for people treated with renal denervation based on a systolic blood pressure reduction of 1.78 mmHg. This matches the treatment effect estimated in the meta-analysis by Pisano et al. (2021). Note that this is a much more modest reduction than those utilised within previous economic assessments.

The cost of renal denervation was estimated to be £5,270 based on the value reported in Gladwell et al. (2014), inflated to 2021 prices. The estimated cost of treating cardiovascular events was sourced from the cost of relevant procedures within NHS Reference Costs 2020/21 (NHS England 2022). The cost of ongoing management following a cardiovascular event was sourced from an economic analysis conducted as part of NICE Guideline 136 (NG136) on the diagnosis and management of hypertension in adults (NICE 2022). The estimated increased risk of mortality and decrements in quality of life following cardiovascular events were also sourced primarily from the NG136 economic analysis (NICE 2022).

The base case results of the analysis are shown in Table 6. Treatment with renal denervation was found to be more effective but more costly than standard care. The ICER result of £233,841 is substantially higher than the threshold of £20,000 per QALY indicating that renal denervation is not cost effective.

Table 6. Base case results

Treatment strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Standard care	£6,524		16.31		
Renal denervation	£11,697	£5,173	16.33	0.02	£233,841

The model was found to be insensitive to the vast majority of variations considered in sensitivity analysis. In most scenarios, the conclusion of the analysis remained unchanged with renal denervation being more effective but more costly than standard care at an ICER value above the cost effectiveness threshold. However, unsurprisingly, the analysis was found to be very sensitive to the reduction in systolic blood pressure associated with renal denervation treatment. Notably, it was found that renal denervation would be cost effective when assuming a reduction in

systolic blood pressure of 32 mmHg. This reduction is equivalent to the reduction assumed in the analysis by Gladwell et al. (2014), in which renal denervation was found to be cost effective.

6. Organisational Considerations

At the time of the report, renal denervation is not routinely available in Wales for the treatment of resistant hypertension. HTW experts have reported that renal denervation is being used in Wales in a clinical trial setting.

HTW experts also noted that additional service requirements would need to be considered to implement renal denervation as the procedure would typically be undertaken in a catheterization lab (cath lab) but specialist services within general hospitals could be developed. Consideration should be given to the capacity of the service to absorb the impact of creating cath lab access that may require additional staffing and resources. HTW experts have reported that it is likely that a multidisciplinary team involving interventional radiologists, cardiologists and renal physicians would be the most appropriate in terms of stratifying/selecting the patients and delivering the renal denervation procedure. The requirement of a cath lab or specialist general hospital service to perform renal denervation may result in regional variations across Wales in accessing the procedure.

7. Patient issues

Health Technology Wales conducted a literature search for patient evidence, quality of life, patient experiences and opinions of people with resistant hypertension who undergo renal denervation.

Articles were found on patient preferences and decision making (3 studies).

Role of patient preferences in decision making

Kario et al. (2022a) conducted a web-based survey of patient preferences for renal denervation for hypertension treatment in Japan. The study was based on a Germany study that showed that a significant proportion of patients with elevated BP stated that they would prefer catheter-based RDN compared with ongoing antihypertensive drug therapy (Schmieder et al. 2019). The survey collected data on participant age, sex, area of residence, comorbidities, frequency of clinic visits for hypertension management, antihypertensive drug classes prescribed, total number of antihypertensive drugs taken per day, and the most recent home and office BP values, in addition to being asked: “I don’t want to undergo RDN”; “I’d rather not undergo RDN”; “I’d rather undergo RDN”; and “I want to undergo RDN”. Patients who chose either of the last two responses were defined as having a preference for RDN. Statistical analyses were performed using SAS 9.4.

Overall, their study reported 9.0 % wanted to undergo RDN and 22.6% would rather undergo RDN, bringing a total 31.6% expressing a preference for RDN. Patient preference for RDN did not vary significantly by the number of antihypertensive agents being taken, but a higher proportion of younger versus older patients had a preference for RDN. They did note significant differences in patient preference for RDN between patient subgroups based on home and office SBP values, with the highest preferences for RDN in those with more severe hypertension. There was also a significant relationship between poor adherence to antihypertensive medication and preference for RDN, with drug related side effects likely to increase patient preference for RDN and those who struggled to adhere to a medication regime preferring RDN. Those patients who experienced

side effects to their medication were more than 1.7 times more likely to prefer RDN compared to patients without side effects. People with heart failure was a significant predictor of preference for RDN.

The authors note that "should data continue to show that RDN has consistent and durable effects on BP in patients with hypertension, it would also have the advantage of not being dependent on daily actions performed by the patient", such as medication adherence. They also note than RDN has the potential to overcome the occurrence of drug-induced adverse events. The role of physicians is shown to be significant in patient preferences in this study as 87% of patients in our study stated that their doctor was the source of information they used to make a decision about RDN, therefore more research is needed to support physicians to provide their patients with robust data on which to make informed decisions.

This is echoed by Schmieder et al. (2021) in their study considering the relationship, and differences, between patient and physician perspectives of RDN. Like Kario et al. (2022a), Schmieder et al. (2021) note that RDN may be an attractive and effective option for patients with hypertension who cannot achieve control with other treatment methods, have elevated cardiovascular risk, and/or whose adherence is challenged by medication intolerance or other factors. The importance of the patient-provider relationship is becoming widely recognised by medical communities, but the basis for patient opinions toward treatment options maybe very different to that of their physicians. Schmieder et al. (2021) surveyed patients and physicians in both Western Europe and the United States to explore and compare patient and physician attitudes toward hypertension treatments, with particular focus on RDN. Patient perspectives were collected through in-depth interviews in person and by telephone, examination-room conversations and online surveys, as well as from interviews with treating physicians using a standardized questionnaire with space for open comments. Physicians were interviewed from the same countries as patients and were either preforming, or were interested in preforming, RDN. Data included demographics, time since diagnosis, BP level, duration of antihypertensive medication, self-reported degree of adherence, number of current medications, associated medical conditions, experience of side effects, knowledge of hypertension and associated risks, willingness to consider renal denervation and reasons for accepting or rejecting this option.

The results for physicians showed that referring cardiologists were more likely to recommend a patient for renal denervation with higher BP levels and greater number of current medications. Physicians expressed a need for support in the guidelines and the peer community, as well as more compelling data, to increase their likeness to recommend RDN and that patient concerns, such as to the invasiveness of the procedure, were obstacles to overcome in recommending RDN.

The results for patients found no link between BP level and willingness to consider treatment with renal denervation. Similarly, there was no obvious relationship between patients' current number of medications and their attitudes towards the renal denervation procedure. Patients who were yet untreated showed the highest preference for RDN, showing a preference for a one-time intervention. Patients who perceived high BP as a significant problem had a statistically higher preference for renal denervation than those who did not. Similarly to Kario et al. (2022a), patients who experienced side effects attributed to their BP medications also had a statistically higher preference for renal denervation than those who had not experienced side effects, as well as those with comorbidities. Physicians were again shown to be the main sources of information on treatments and a physician's recommendation was the single most important positive factor influencing patients' readiness to undergo RDN. The only difference between the findings from Europe and the United States was that 45% of patients in the US indicated a refusal to undergo renal denervation even if the procedure were recommended by their physician.

Schmieder et al. (2021) note that the differences in attitudes between patients and physicians are highly relevant and may have implications for both how treatment recommendations are

made by healthcare providers and received by patients. The authors note that patients most likely to prefer the renal denervation procedure had greater understanding of the risks associated with hypertension from either personal experience or health literacy, and thus had strong motivation to control their BP. They suggest that to resolve the tension between patient and physician attitudes to treatment, a dialogue between caregiver and patient is needed about the risks and benefits of various treatment approaches and patient preference. Patients' concerns in the United States, where renal denervation is not yet available, were stronger than in Europe, where the procedure has been an option for a few years and real-life experiences are available.

A similar study by Lin et al. (2020) surveying patients in Taiwan showed that drug intolerance is the most significant determinant of patient preference for RDN.

In addition to the HTW patient focused search, experts highlighted a survey-based study on patient preferences for therapies in hypertension, in particular focusing on medication and renal denervation. Schmieder et al. (2019) report on 1011 participants who were recruited by physicians across Germany and who had provided completed questionnaires. For participants who had hypertension but had not yet started medication, 61.7% reported they would prefer tablets and 38.2% reported they would opt for renal denervation. For participants who were already taking medication, 71.8% reported that they would rather take an additional tablet and 28.2% would prefer renal denervation. Preference for renal denervation increased if patients were younger, male, and had higher expectations of renal denervation's ability to reduce blood pressure.

8. Conclusions

The aim of this rapid review was to examine the clinical and cost effectiveness of radiofrequency and ultrasound renal denervation for people with resistant hypertension compared to standard care. We identified a recent Cochrane systematic review that reported on the clinical effectiveness of renal denervation (ultrasound and radiofrequency) for the treatment of resistant hypertension. We also identified a further two relevant RCTs that were published after the systematic review and one longer-term follow-up of a trial included in the Cochrane review. The included evidence focuses on earlier iterations of renal denervation and we identified no studies that use newer treatment protocols with multi-electrode radiofrequency for resistant hypertension.

Updated analyses that are based on the Cochrane systematic review and more recent trials do not show significant improvements in systolic or diastolic 24-hour APBM after renal denervation for resistant hypertension. Notably, we chose to exclude one study reported only as an abstract, and sensitivity analyses showed significant benefit after renal denervation only when this study is included. Analyses from the Cochrane systematic review and one of the more recent RCTs do not report significant reductions in systolic office BP. However, one of the newer trials does report significant reductions for this outcome. Sensitivity analyses for single vs. multi-electrode radiofrequency renal denervation do not show a difference in effect. However, as highlighted throughout the report, newer treatment protocols using a larger number of ablations with multi-electrodes were not identified for this population. The two trials available for ultrasound renal denervation are recently published and sensitivity analyses do not show an effect on either systolic or diastolic 24-hour ABPM.

Evidence on non-fatal cardiovascular events and hospitalisation is limited by the fact that studies are not powered or designed with long enough follow-ups to observe anticipated differences. Pisano et al. (2021) suggests that renal denervation has little or no effect on non-fatal cardiovascular events, myocardial infarction, ischaemic stroke, unstable angina or hospitalisation. However, these findings should be considered with reference to those limitations

and stronger evidence on reductions in blood pressure may be sufficient to assume a reduction in risk of these events over the longer term.

The economic analysis suggests that renal denervation was more effective but more costly than standard care. The resulting ICER of £233,841 per QALY is substantially higher than the threshold of £20,000 per QALY indicating that renal denervation is not cost-effective in comparison to standard care. This ICER result is much higher than the ICER of £4,805 per QALY reported in the previous UK cost effectiveness analysis by Gladwell et al. (2014). This stark difference is driven by the much more modest treatment effect applied in the HTW analysis. The HTW analysis assumed that renal denervation reduced systolic blood pressure by 1.78 mmHg whereas Gladwell et al. (2014) assumed it was reduced by 32 mmHg.

There is a high level of uncertainty regarding whether the findings seen here would be replicated in newer treatment protocols as no evidence relating to these in the resistant hypertension population was identified. Newer approaches use a larger number of ablations in the main artery and branches and it is possible that this approach would deliver improved benefits. Forthcoming trials may provide some evidence from sub-group analyses. However, additional larger trials focusing on this population may be needed.

9. Contributors

This topic was proposed by Medtronic.

The HTW staff and contract researchers involved in writing this report were:

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The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical and academic experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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10. References

Azizi M, Sanghvi K, Saxena M, et al. (2021). Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet. 397(10293): 2476-86. doi: https://dx.doi.org/10.1016/S0140-6736(21)00788-1

Bergland OU, Søraas CL, Larstorp ACK, et al. (2021). The randomised Oslo study of renal denervation vs. antihypertensive drug adjustments: efficacy and safety through 7 years of follow-up. Blood Pressure. 30(1): 41-50. doi: https://dx.doi.org/10.1080/08037051.2020.1828818

Bhatt DL, Vaduganathan M, Kandzari DE, et al. (2022). Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 trial. Lancet. 400(10361): 1405-16. doi: https://doi.org/10.1016/S0140-6736(22)01787-1

BHF. (2023). High blood pressure. British Heart Foundation. Available at: https://www.bhf.org.uk/informationsupport/risk-factors/high-blood-pressure [Accessed 14 Jun 2023].

BHFC. (2023). Wales factsheet. British Heart Foundation Cymru. Available at: https://www.bhf.org.uk/-/media/files/for-professionals/research/heart-statistics/bhf-cvd-statistics-wales-factsheet.pdf?rev=aac0954754d14efb8da6348599b7514a&hash=f609b99ec0e150a7f70845542cae77c7 [Accessed 14 Jun 2023].

Böhm M, Townsend RR, Kario K, et al. (2020). Rationale and design of two randomized sham-controlled trials of catheter-based renal denervation in subjects with uncontrolled hypertension in the absence (SPYRAL HTN-OFF MED Pivotal) and presence (SPYRAL HTN-ON MED Expansion) of antihypertensive medications: a novel approach using Bayesian design. Clinical Research in Cardiology. 109(3): 289-302. doi: https://doi.org/10.1007/s00392-020-01595-z

Brønnum-Hansen H, Jørgensen T, Davidsen M, et al. (2001). Survival and cause of death after myocardial infarction: the Danish MONICA study. Journal of Clinical Epidemiology. 54(12): 1244-50. doi: https://doi.org/10.1016/s0895-4356(01)00405-x

Bulsei J, Darlington M, Durand-Zaleski I, et al. (2018). How to perform a cost-effectiveness analysis with surrogate endpoint: renal denervation in patients with resistant hypertension (DENERHTN) trial as an example. Blood Pressure. 27(2): 66-72. doi: https://doi.org/10.1080/08037051.2017.1394160

CCEMG & EPPI-Centre. (2019). CCEMG - EPPI-Centre cost converter. v1.6. Campbell and Cochrane Economics Methods Group (CCEMG) and Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre). Available at: https://eppi.ioe.ac.uk/costconversion/ [Accessed 19 Dec 2023].

Cheng YY, Liu HX, Zhang M, et al. (2021). Computational modeling of catheter-based radiofrequency renal denervation with patient-specific model. 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2021: 4289-92. doi: https://doi.org/10.1109/EMBC46164.2021.9630677

Chowdhury EK, Reid CM, Zomer E, et al. (2018). Cost-effectiveness of renal denervation therapy for treatment-resistant hypertension: a best case scenario. American Journal of Hypertension. 31(10): 1156-63. doi: https://dx.doi.org/10.1093/ajh/hpy108

Danese MD, Gleeson M, Kutikova L, et al. (2016). Estimating the economic burden of cardiovascular events in patients receiving lipid-modifying therapy in the UK. BMJ Open. 6(8): e011805. doi: https://doi.org/10.1136/bmjopen-2016-011805

Dennis MS, Bamford JM, Sandercock PA, et al. (1989). Incidence of transient ischemic attacks in Oxfordshire, England. Stroke. 20(3): 333-9. doi: https://doi.org/10.1161/01.str.20.3.333

Dorenkamp M, Bonaventura K, Leber AW, et al. (2013). Potential lifetime cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension. European Heart Journal. 34(6): 451-61. doi: https://dx.doi.org/10.1093/eurheartj/ehs355

Esler MD, Krum H, Sobotka PA, et al. (2010). Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 376(9756): 1903-9. doi: https://doi.org/10.1016/s0140-6736(10)62039-9

Ettehad D, Emdin CA, Kiran A, et al. (2016). Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 387(10022): 957-67. doi: https://doi.org/10.1016/S0140-6736(15)01225-8

Gladwell D, Henry T, Cook M, et al. (2014). Cost effectiveness of renal denervation therapy for the treatment of resistant hypertension in the UK. Applied Health Economics & Health Policy. 12(6): 611-22. doi: https://dx.doi.org/10.1007/s40258-014-0116-7

Goodacre S, Nicholl J, Dixon S, et al. (2004). Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. BMJ. 328(7434): 254. doi: https://doi.org/10.1136/bmj.37956.664236.EE

Henry TL, De Brouwer BF, Van Keep MM, et al. (2015). Cost-effectiveness of renal denervation therapy for the treatment of resistant hypertension in The Netherlands. Journal of Medical Economics. 18(1): 76-87. doi: https://doi.org/10.3111/13696998.2014.978453

Kang HY, Suh HS, Kim HS, et al. (2014). Economic evaluation of catheter-based renal denervation for patients with resistant hypertension in Korea. Value in Health. 17(7): A762. doi: https://doi.org/10.1016/j.jval.2014.08.265

Kario K, Kagitani H, Hayashi S, et al. (2022a). A Japan nationwide web-based survey of patient preference for renal denervation for hypertension treatment. Hypertension Research. 45(2): 232-40. doi: https://doi.org/10.1038/s41440-021-00760-9

Kario K, Yokoi Y, Okamura K, et al. (2022b). Catheter-based ultrasound renal denervation in patients with resistant hypertension: the randomized, controlled REQUIRE trial. Hypertension Research. 45(2): 221-31. doi: https://dx.doi.org/10.1038/s41440-021-00754-7

Lavender M, Craig N, Kerr R, et al. (1998). Computer simulation to estimate the effectiveness of carotid endarterectomy. Journal of Health Services Research and Policy. 3(1): 6-11. doi: https://doi.org/10.1177/135581969800300104

Lin S-I, Li SH-W, Lan W-R, et al. (2020). Subtypes of patient preference for catheter-based hypertension therapy: a pilot study based on Taiwan consensus on renal denervation (RDNI2). Journal of the American College of Cardiology. 75(11): 3507. doi: https://doi.org/10.1016/S0735-1097(20)34134-6

Lobo MD, Sharp ASP, Kapil V, et al. (2019). Joint UK societies' 2019 consensus statement on renal denervation. Heart. 105(19): 1456-63. doi: https://doi.org/10.1136/heartjnl-2019-315098

Mahfoud F, Weber M, Schmieder RE, et al. (2021). Catheter-based alcohol-mediated renal denervation for the treatment of uncontrolled hypertension: design of two sham-controlled,

randomized, blinded trials in the absence (TARGET BP OFF-MED) and presence (TARGET BP I) of antihypertensive medications. American Heart Journal. 239: 90-9. doi: https://doi.org/10.1016/j.ahj.2021.05.015

Melsop KA, Boothroyd DB, Hlatky MA. (2003). Quality of life and time trade-off utility measures in patients with coronary artery disease. American Heart Journal. 145(1): 36-41. doi: https://doi.org/10.1067/mhj.2003.37

Mensa Sorato M, Davari M, Kebriaeezadeh A, et al. (2020). Cost-effectiveness of interventional therapies for management of treatment-resistant hypertension: systematic review of pharmacoeconomic studies. Journal of Pharmaceutical Health Services Research. 1(4): 307-19. doi: https://doi.org/10.1111/jphs.12384

Moiseeva A, Caraus A, Moscalu V, et al. (2020). Sympathetic renal denervation treatment in resistant hypertension: one-year follow-up. European Heart Journal. 41(Supplement_2): ehaa946.2785. doi: https://doi.org/10.1093/ehjci/ehaa946.2785

Myat A, Redwood SR, Qureshi AC, et al. (2012). Resistant hypertension. BMJ. 345: e7473. doi: https://doi.org/10.1136/bmj.e7473

Naclerio M, Corbo M, Beccagutti G. (2014). Renal denervation with the Symplicity catheter system for treatment-resistant hypertension: a budget impact analysis. Value in Health. 17(7): A480. doi: https://doi.org/10.1016/j.jval.2014.08.1387

NHS Digital. (2022). Health Survey for England, 2021 part 1: part 4 trends. Official statistics, National statistics, Survey. National Health Service. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/2021/part-4-trends [Accessed 19 Dec 2023].

NHS England. (2016). Renal denervation for resistant hypertension. Clinical Commissioning Policy 16004/P. National Health Service. Available at: https://www.england.nhs.uk/wp-content/uploads/2018/07/Renal-denervation-for-resistant-hypertension.pdf [Accessed 13 Jun 2023].

NHS England. (2022). National Cost Collection for the NHS 2020/2021. National Health Service. Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ [Accessed 10 Oct 2022].

NICE. (2006). Statins for the prevention of cardiovascular events. Technology appraisal guideline TA94. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/TA94 [Accessed 19 Dec 2023].

NICE. (2008). Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical guideline CG67. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/CG67 [Accessed 19 Dec 2023].

NICE. (2013). Unstable angina and NSTEMI: early management. [Original publication date: 24 Mar 2010; Last updated: 1 Nov 2013]. Clinical guideline CG94. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/CG94 [Accessed 19 Dec 2023].

NICE. (2014). Cardiovascular disease: risk assessment and reduction, including lipid modification Clinical guideline CG181. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/cg181 [Accessed 19 Dec 2023].

NICE. (2022). Hypertension in adults: diagnosis and management. [Original publication date: 28 Aug 2019; Last updated: 18 Mar 2022]. NICE guideline NG136. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ng136 [Accessed 12 Apr 2022].

NICE. (2023). Percutaneous transluminal renal sympathetic denervation for resistant hypertension. Interventional procedures guidance IPG754. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/ipg754 [Accessed 13 Jun 2023].

ONS. (2021). National life tables: Wales. Office for National Statistics. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetableswalesreferencetables [Accessed 19 Dec 2023].

Pisano A, Iannone LF, Leo A, et al. (2021). Renal denervation for resistant hypertension. Cochrane Database of Systematic Reviews. 11: CD011499. doi: https://dx.doi.org/10.1002/14651858.CD011499.pub3

Rosengren A, Wilhelmsen L, Hagman M, et al. (1998). Natural history of myocardial infarction and angina pectoris in a general population sample of middle-aged men: a 16-year follow-up of the Primary Prevention Study, Göteborg, Sweden. Journal of Internal Medicine. 244(6): 495-505. doi: https://doi.org/10.1111/j.1365-2796.1998.00394.x

Schmieder RE, Högerl K, Jung S, et al. (2019). Patient preference for therapies in hypertension: a cross-sectional survey of German patients. Clinical Research in Cardiology. 108(12): 1331-42. doi: https://doi.org/10.1007/s00392-019-01468-0

Schmieder RE, Kandzari DE, Wang TD, et al. (2021). Differences in patient and physician perspectives on pharmaceutical therapy and renal denervation for the management of hypertension. Journal of Hypertension. 39(1): 162-8. doi: https://doi.org/10.1097/HJH.0000000000002592

SHTG. (2014). What is the clinical and cost effectiveness of treatment with renal denervation for patients with resistant hypertension? Scottish Health Technologies Group. Available at: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/shtg_-_evidence_notes/evidence_note_54.aspx [Accessed 7 Mar 2022].

Sinnott S-J, Smeeth L, Williamson E, et al. (2017). Trends for prevalence and incidence of resistant hypertension: population based cohort study in the UK 1995-2015. BMJ. 358: j3984. doi: https://doi.org/10.1136/bmj.j3984

SSNAP. (2016). Cost and cost-effectiveness analysis. Technical report. National Guideline Centre & Sentinel Stroke National Audit Programme. Royal College of Physicians. Available at: https://www.strokeaudit.org/SupportFiles/Documents/Health-Economics/Health-economic-report-2016.aspx [Accessed 19 Dec 2023].

Stein JD, Brown GC, Brown MM, et al. (2002). The quality of life of patients with hypertension. Journal of Clinical Hypertension. 4(3): 181-8. doi: https://doi.org/10.1111/j.1524-6175.2002.00970.x

Symplicity HTN-1 Investigators. (2011). Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension. 57(5): 911-7. doi: https://doi.org/10.1161/hypertensionaha.110.163014

Tengs TO, Lin TH. (2003). A meta-analysis of quality-of-life estimates for stroke. Pharmacoeconomics. 21(3): 191-200. doi: https://doi.org/10.2165/00019053-200321030-00004

Tilden D, McBride M, Whitbourn R, et al. (2014). Cost effectiveness of catheter-based renal denervation for treatment resistant hypertension - an Australian payer perspective. Value in Health. 17(7): A762. doi: https://doi.org/10.1016/j.jval.2014.08.266

Tsevat J, Goldman L, Soukup JR, et al. (1993). Stability of time-tradeoff utilities in survivors of myocardial infarction. Medical Decision Making. 13(2): 161-5. doi: https://doi.org/10.1177/0272989x9301300210

Youman P, Wilson K, Harraf F, et al. (2003). The economic burden of stroke in the United Kingdom. Pharmacoeconomics. 21(Supplement 1): 43-50. doi: https://doi.org/10.2165/00019053-200321001-00005

11. Evidence review methods

We searched for evidence that could be used to answer the review question: What is the clinical and cost effectiveness of the renal denervation for people with resistant hypertension when compared to standard care?

The criteria used to select evidence for the appraisal are outlined in Appendix 1. These criteria were developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts and re-confirmed with HTW Assessment Group after expert review.

The systematic search followed HTW's standard rapid review methodology. A search was undertaken of Medline, Embase, CINAHL, KSR Evidence, Cochrane Library, the International Network of Agencies for Health Technology Assessment (INAHTA) HTA database, and Epistemonikos. Additionally, searches were conducted of key websites and clinical trials registries. The searches were conducted in February and March 2022 and an update search of Medline, Embase, CINAHL, KSR Evidence, Cochrane Library, and INAHTA HTA database was conducted on 28 September 2022. Appendix 2 gives details of the search strategy used for Medline. Search strategies for other databases are available on request. In Appendix 3 the PRISMA diagram summarises the selection of articles for inclusion in the review.

An additional search for patient-related literature was run on 7-8 April 2022. The full search report is available on request.

The HTW Assessment Group recommended that meta-analyses were updated to include data that are more recent. For all outcomes other than 24-hour systolic and diastolic ABPM, pooled data has been taken from the Pisano et al. review and methods for these pooled analyses are outlined in the Pisano et al. (2021) review. For 24-hour systolic and diastolic ABPM, HTW researchers broadly replicated the methods used by Pisano et al. and added data reported in studies that have been published more recently. Unlike the Pisano et al. (2021) review, the primary analysis reported for 24-hour systolic and diastolic ABPM excludes data from Moiseeva et al. (2020). This is because the study (Moiseeva et al. 2020) is reported as an abstract only and it adds substantial heterogeneity to the analyses, particularly for 24-hour systolic ABPM (from I^2 = 15% to I^2 = 74%), suggesting it is an outlier. Results including (Moiseeva et al. 2020) are also presented. HTW also conducted two sensitivity analysis according to whether radiofrequency or ultrasound was used, and when radiofrequency was used whether a single or multi-electrode was used. All analyses conducted by HTW are presented using random-effects and are robust to use of fixed effects. As noted elsewhere, no studies using newer treatment protocols with a multi-electrode were identified for this population.

The publication of this renal denervation evidence appraisal report was delayed until after publication of the NICE IPG754 on percutaneous transluminal renal sympathetic denervation for resistant hypertension (NICE 2023). Following publication of IPG754, it was decided by the HTW Assessment Group to publish this evidence appraisal report with no additional evidence. Therefore, the evidence contained in the report is current up to the date of the last search (28 September 2022), but the background references are current up to March 2023.

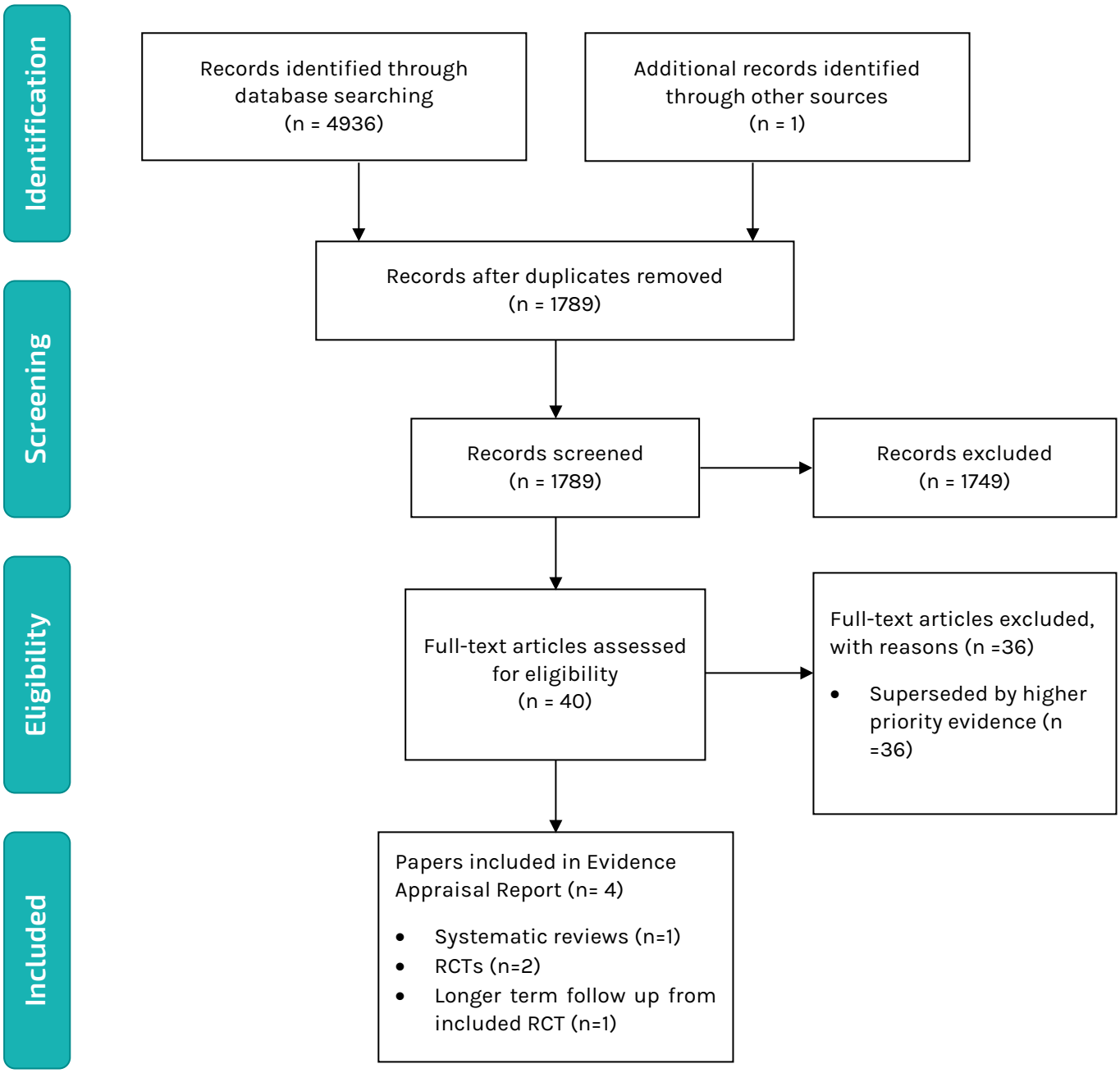
Appendix 1. Inclusion and exclusion criteria for evidence included in the review

	Inclusion criteria	Exclusion criteria
Population	People with resistant hypertension	People with uncontrolled hypertension where appropriate lifestyle interventions and antihypertensive treatment have not yet been trialled
Intervention	Renal denervation (ultrasound and radiofrequency)	
Comparison/ Comparators	Standard care (e.g., use of additional antihypertensives, including spironolactone or alpha- and beta-blockers and other specialist interventions). Sham procedures	
Outcome measures	Clinical outcomes (e.g., overall mortality cardiovascular mortality, cardiovascular morbidity including stroke, myocardial infarction, heart failure, blood pressure including changes in systolic and diastolic blood pressure, safety, adverse events) Patient-reported outcomes (e.g., health-related quality of life, patient satisfaction) Healthcare utilisation and economic outcomes	
Study design	We will prioritise the following study types, in the order listed: • Systematic reviews of randomised controlled trials. • Randomised controlled trials. We will also include evidence from lower priority sources where they relate to organisational issues, PPI and health economics.	
Search limits	Search date limits will be applied to include only evidence published after the literature search of the EUnetHTA review (2013).	
Other factors	Definitions of resistant hypertension are varied. We will use a broad definition of resistant hypertension to ensure all relevant studies are included. However, we will put particular focus on the NICE guideline definition of resistant hypertension (i.e. control is not achieved with lifestyle interventions and optimal tolerated doses of ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic)	

Appendix 2. Medline search strategy

Ovid MEDLINE(R) ALL <1946 to September 27, 2022>		
Hypertension		
1	exp Hypertension/	310339
2	(hypertension* or hyper-tension* or hypertensive or hyper-tensive).tw,kf.	492339
3	((rais* or high* or elevat* or increas*) adj3 (blood or arterial or systol* or diastol*) adj3 pressure*).tw,kf.	83971
4	((rais* or high* or elevat* or increas*) adj3 (arterial pressure or blood pressure or diastolic pressure or systolic pressure)).tw,kf.	82825
5	((rais* or high* or elevat* or increas*) adj3 (bp or dbp or sbp)).tw,kf.	23261
6	or/1-5	608822
Denervation		
7	Denervation/	14964
8	Autonomic Denervation/	445
9	Sympathectomy/	9802
10	Catheter Ablation/	37685
11	Radiofrequency Ablation/	2386
12	High-Intensity Focused Ultrasound Ablation/	2099
13	(denervat* or ablat* or sympathect* or neurotom* or neurectom*).tw,kf.	172574
14	((radiofrequency or radio-frequency or ultrasound or ultra-sound) adj2 (ablation? or catheter? or probe?)).tw,kf.	28280
15	or/7-14	192188
Renal		
16	Kidney/	288003
17	Renal Artery/	18530
18	(renal or kidney*).tw,kf.	981882
19	or/16-18	1050799
Renal denervation AND hypertension		
20	15 and 19	11408
21	6 and 20	3485
22	limit 21 to english language	3216
23	limit 22 to yr="2013 -Current"	1935

Appendix 3. Flow diagram outlining selection of relevant evidence



Appendix 4. Meta-analysis data tables and forest plots

Study or Subgroup	renal denervation Mean [mmHg]	SD [mmHg]	Total	sham/standard treatment Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI
SYMPLICITY HTN-3 2014	151.8	16	364	153.9	19.1	171	28.4%	-2.10 [-5.40, 1.20]
REQUIRE 2022	155.3	13.4	69	155	13.1	67	19.1%	0.30 [-4.15, 4.75]
RADIANCE-HTA TRIO 2021	135.2	16	69	140.5	18.7	67	12.5%	-5.30 [-11.16, 0.56]
DENER-HTN 2015	135.5	17.6	48	137.9	16.4	53	10.1%	-2.40 [-9.05, 4.25]
ReSET 2015	146.4	16.16	29	150	12.9	29	8.1%	-3.60 [-11.13, 3.93]
SYMPATHY	152	23.5	83	150.2	22.2	41	6.6%	1.80 [-6.67, 10.27]
Warchol 2014	140	14	28	144	19	24	5.7%	-4.00 [-13.20, 5.20]
Oslo RDN 2014	139	10.5	9	130	11.6	10	4.9%	9.00 [-0.94, 18.94]
HTN-JAPAN 2015	157.1	19.3	22	161.9	18.6	19	3.7%	-4.80 [-16.42, 6.82]
INSPIRED	139.7	23	6	158.2	17	9	1.1%	-18.50 [-40.00, 3.00]
Total (95% CI)			**727**			**490**	**100.0%**	**-1.78 [-4.06, 0.50]**

Heterogeneity: Tau² = 1.94; Chi² = 10.53, df = 9 (P = 0.31); I² = 15%
Test for overall effect: Z = 1.53 (P = 0.13)

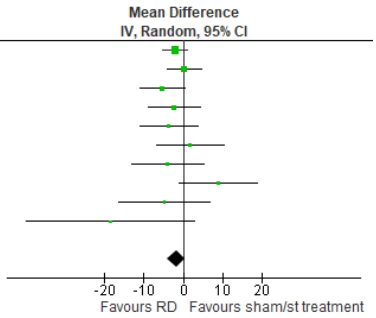


Figure 4A Renal denervation vs sham/standard therapy for systolic 24-hour ABPM

Study or Subgroup	renal denervation Mean [mmHg]	SD [mmHg]	Total	sham/standard treatment Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI
SYMPLICITY HTN-3 2014	151.8	16	364	153.9	19.1	171	11.6%	-2.10 [-5.40, 1.20]
REQUIRE 2022	155.3	13.4	69	155	13.1	67	10.9%	0.30 [-4.15, 4.75]
RADIANCE-HTA TRIO 2021	135.2	16	69	140.5	18.7	67	10.0%	-5.30 [-11.16, 0.56]
DENER-HTN 2015	135.5	17.6	48	137.9	16.4	53	9.4%	-2.40 [-9.05, 4.25]
Moiseeva 2020-B	145.4	11.6	25	166.96	14.2	25	9.0%	-21.56 [-28.75, -14.37]
ReSET 2015	146.4	16.16	29	150	12.9	29	8.8%	-3.60 [-11.13, 3.93]
Moiseeva 2020-M	145.4	11.6	25	158.64	17.95	25	8.2%	-13.24 [-21.62, -4.86]
SYMPATHY	152	23.5	83	150.2	22.2	41	8.1%	1.80 [-6.67, 10.27]
Warchol 2014	140	14	28	144	19	24	7.7%	-4.00 [-13.20, 5.20]
Oslo RDN 2014	139	10.5	9	130	11.6	10	7.2%	9.00 [-0.94, 18.94]
HTN-JAPAN 2015	157.1	19.3	22	161.9	18.6	19	6.2%	-4.80 [-16.42, 6.82]
INSPIRED	139.7	23	6	158.2	17	9	2.8%	-18.50 [-40.00, 3.00]
Total (95% CI)			**777**			**540**	**100.0%**	**-4.64 [-8.71, -0.58]**

Heterogeneity: Tau² = 34.10; Chi² = 42.89, df = 11 (P < 0.0001); I² = 74%
Test for overall effect: Z = 2.24 (P = 0.03)

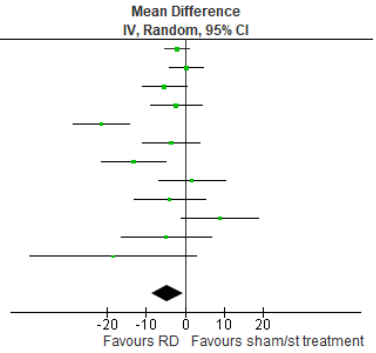


Figure 4B Renal denervation vs sham/standard therapy for systolic 24-hour ABPM, including Moiseeva et al. 2020

Study or Subgroup	renal denervation Mean [mmHg]	SD [mmHg]	Total	sham/standard treatment Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI
SYMPLICITY HTN-3 2014	83.1	13.7	364	87.4	14.6	171	17.6%	-4.30 [-6.90, -1.70]
REQUIRE 2022	91.3	9.3	69	89.4	9.4	67	15.9%	1.90 [-1.24, 5.04]
RADIANCE-HTA TRIO 2021	83.6	10.9	69	85.8	12	67	13.8%	-2.20 [-6.06, 1.66]
ReSET 2015	88.3	8.6	29	86.5	9.15	29	11.9%	1.80 [-2.77, 6.37]
DENER-HTN 2015	80.1	13	48	82.3	12	53	11.1%	-2.20 [-7.10, 2.70]
SYMPATHY	87.8	15.4	83	87.2	12.8	41	10.6%	0.60 [-4.53, 5.73]
Warchol 2014	80	10	28	86	10	24	9.9%	-6.00 [-11.45, -0.55]
Oslo RDN 2014	81	10	9	77	6	10	6.5%	4.00 [-3.52, 11.52]
INSPIRED	88.1	12.6	6	95.6	12.7	9	2.7%	-7.50 [-20.56, 5.56]
Total (95% CI)			**705**			**471**	**100.0%**	**-1.26 [-3.53, 1.01]**

Heterogeneity: Tau² = 5.83; Chi² = 17.28, df = 8 (P = 0.03); I² = 54%
Test for overall effect: Z = 1.09 (P = 0.28)

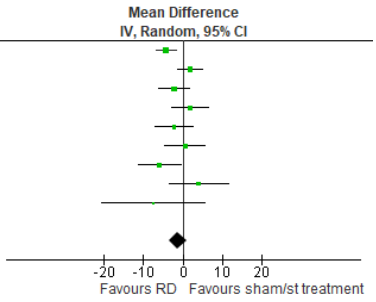


Figure 4C Renal denervation vs sham/standard therapy for diastolic 24-hour ABPM

Study or Subgroup	renal denervation Mean [mmHg]	SD [mmHg]	Total	sham/standard treatment Mean [mmHg]	SD [mmHg]	Total	Weight	Mean Difference IV, Random, 95% CI
SYMPLICITY HTN-3 2014	83.1	13.7	364	87.4	14.6	171	12.0%	-4.30 [-6.90, -1.70]
REQUIRE 2022	91.3	9.3	69	89.4	9.4	67	11.5%	1.90 [-1.24, 5.04]
RADIANCE-HTA TRIO 2021	83.6	10.9	69	85.8	12	67	10.8%	-2.20 [-6.06, 1.66]
Moiseeva 2020-B	89.36	2.3	25	101.04	10.65	25	10.3%	-11.68 [-15.95, -7.41]
ReSET 2015	88.3	8.6	29	86.5	9.15	29	10.0%	1.80 [-2.77, 6.37]
DENER-HTN 2015	80.1	13	48	82.3	12	53	9.6%	-2.20 [-7.10, 2.70]
SYMPATHY	87.8	15.4	83	87.2	12.8	41	9.4%	0.60 [-4.53, 5.73]
Warchol 2014	80	10	28	86	10	24	9.0%	-6.00 [-11.45, -0.55]
Oslo RDN 2014	81	10	9	77	6	10	7.0%	4.00 [-3.52, 11.52]
Moiseeva 2020-M	89.36	2.3	25	99.48	19.85	25	6.7%	-10.12 [-17.95, -2.29]
INSPIRED	88.1	12.6	6	95.6	12.7	9	3.6%	-7.50 [-20.56, 5.56]
Total (95% CI)			**755**			**521**	**100.0%**	**-2.93 [-5.81, -0.05]**

Heterogeneity: Tau² = 16.20; Chi² = 40.50, df = 10 (P < 0.0001); I² = 75%
Test for overall effect: Z = 1.99 (P = 0.05)

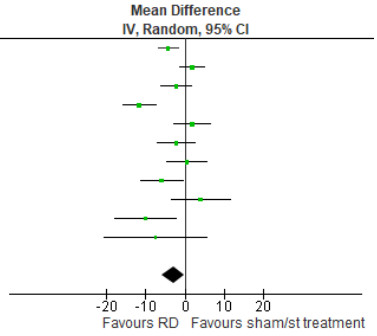


Figure 4D Renal denervation vs sham/standard therapy for diastolic 24-hour ABPM, including Moiseeva et al. 2020

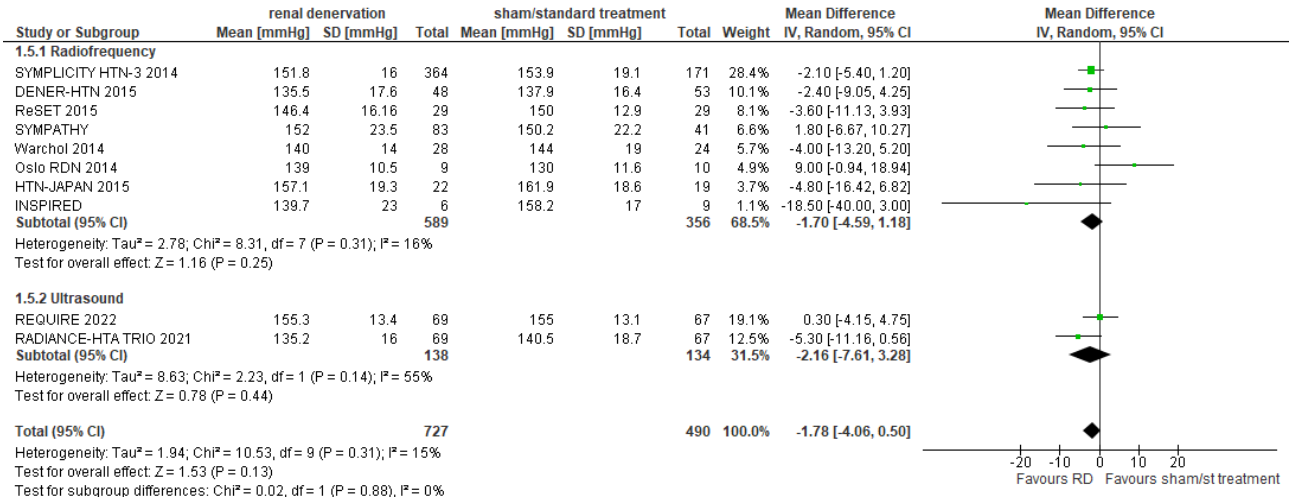


Figure 4E Sensitivity analysis for radiofrequency or ultrasound vs. sham/standard therapy for systolic 24-hour ABPM

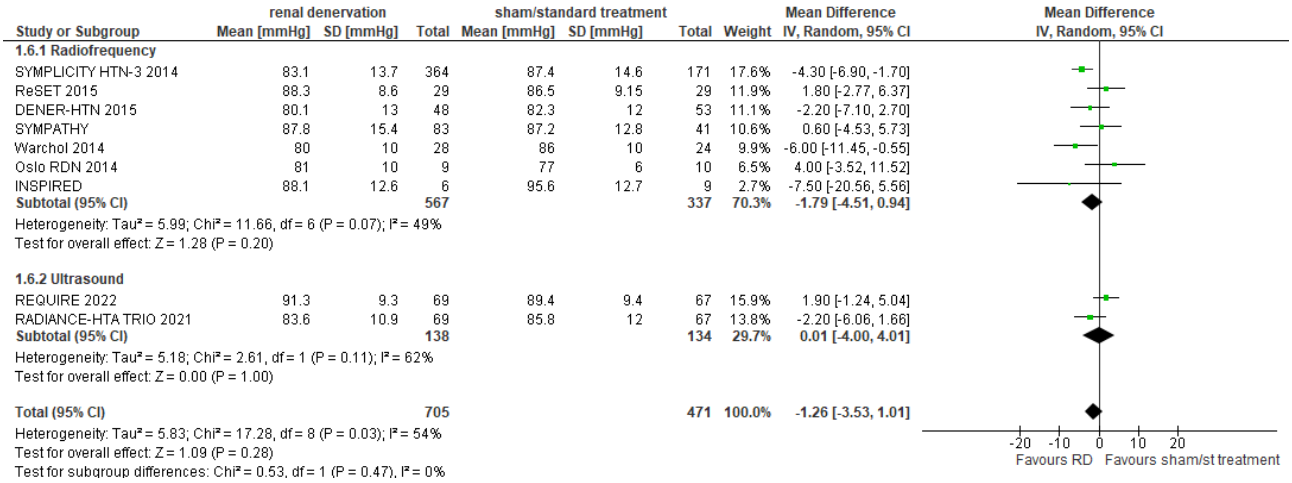


Figure 4F Sensitivity analysis for radiofrequency or ultrasound vs. sham/standard therapy for diastolic 24-hour ABPM

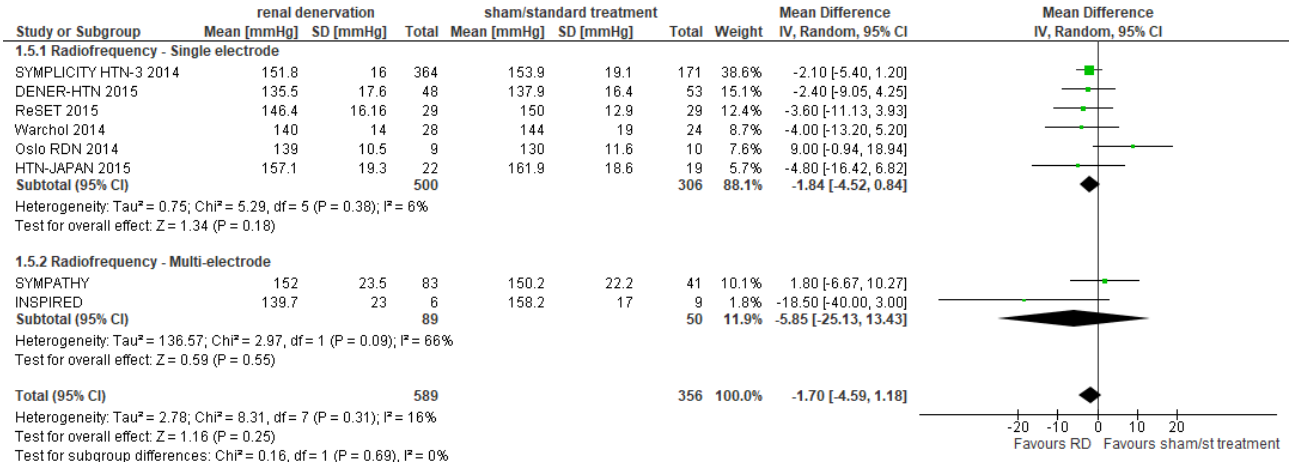


Figure 4G Sensitivity analysis for single or multi-electrode radiofrequency vs. sham/standard therapy for systolic 24-hour ABPM

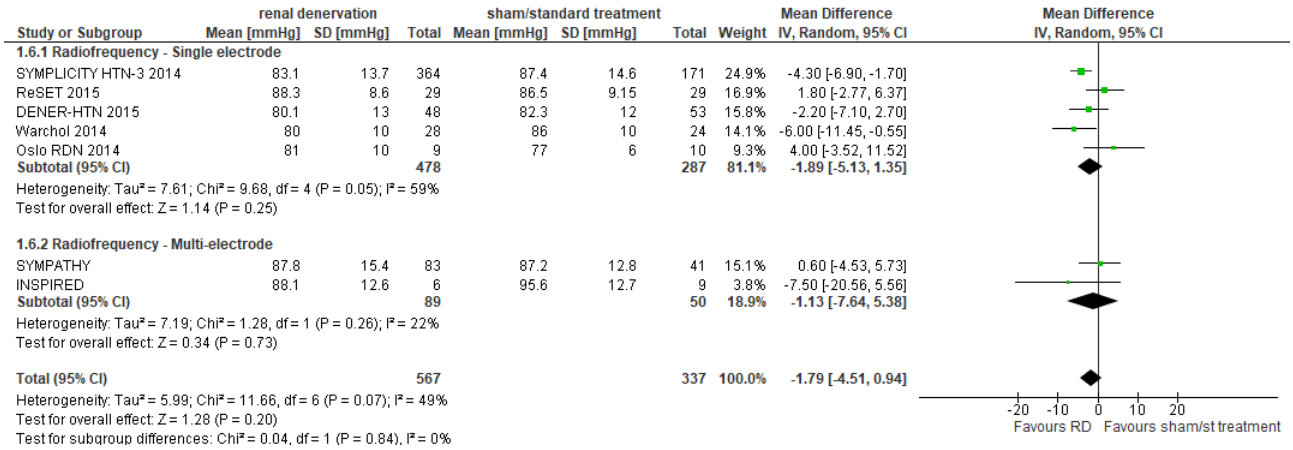


Figure 4H Sensitivity analysis for single or multi-electrode radiofrequency vs. sham/standard therapy for diastolic 24-hour ABPM

Appendix 5. HTW cost-utility analysis

1. Background and aims

The existing economic evidence base was considered insufficient to address the cost effectiveness of renal denervation. Two of the studies identified in the literature review were only partially applicable as they considered healthcare systems in other countries. One study was directly applicable as it considered a UK perspective, but some limitations were identified. In particular, there was uncertainty around the duration and size of the treatment effect with renal denervation and this uncertainty was not fully explored within sensitivity analysis. Therefore, HTW developed a cost-utility analysis to consider the cost effectiveness of renal denervation in the decision context of NHS Wales.

2. Methods

2.1 Model approach

A Markov model was constructed using Microsoft Excel to estimate the total costs and quality adjusted life years (QALYs) of the modelled treatment strategies. The analysis considered the cost effectiveness of renal denervation supported by standard care in comparison to standard care alone in people with treatment resistant hypertension.

The analysis took the perspective of the UK NHS and personal social services (PSS). A lifetime horizon was considered to ensure that all relevant costs and outcomes were considered. An annual cycle length was chosen as it was thought to reflect the level of granularity required. Future costs and benefits were discounted at rate of 3.5% as recommended by the National Institute for Health and Care Excellence (NICE).

The modelling approach adopted was similar to that used in previous economic analyses considering renal denervation. A risk prediction model was used to estimate the risk of cardiovascular events with standard care and with renal denervation. QRISK3 was selected as the most applicable risk calculator to use for the analysis as it is widely used in NHS Wales. QRISK3 estimates the risk of developing cardiovascular disease over the next 10 years based on risk factors, such as age, sex, body mass index (BMI), diabetic status and systolic blood pressure.

This approach allows for the surrogate endpoint of a reduction in systolic blood pressure to be used to drive differences in event rates. The modelled cardiovascular events are associated with decrements in quality of life, an elevated risk of mortality and treatment costs. Thus, the analysis approach enables costs and QALYs to be estimated over the expected lifespan of people treated with renal denervation and standard care in comparison to standard care alone.

2.2 Clinical data

2.2.1 Baseline demographics

The characteristics and risk factors used to inform the risk calculators were based on the baseline demographics from the Symplicity HTN 3 trial as reported by (Bhatt et al. 2022). Weighted averages were estimated for each input using the number of patients in the renal denervation and standard care arms of the trial.

The average age of the cohort was estimated to be 57.4 years old with 61% of the population estimated to be male and 39% estimated to be female. Systolic blood pressure at baseline was estimated to be 159.2 mmHg based on a weighted average value from both arms of the Symplicity HTN 3 trial at baseline (Bhatt et al. 2022). It was estimated that 45% of the population had type 2 diabetes with the remaining 55% having no diabetes (no one had type 1 diabetes). The average body mass index (BMI) of the population was estimated to be 34.1. BMI values were inputted into the risk equations as weight and height values. Based on values from the Health Survey for England 2021 (NHS Digital 2022), the average height for males was estimated to be 175.5cm while the average height for women was estimated to be 161.7cm. These height values were then used in conjunction with the BMI value to back-calculate an average weight of 99.8kg. All patients were assumed to be receiving blood pressure treatment, which further elevates their risk.

Where figures were not reported by Bhatt et al. (2022), the value was left blank with QRISK3 providing a standard estimation in its place. Note that QRISK3 requires that all values are inputted as integers and so values were rounded before being inputted (e.g. a systolic blood pressure value of 159 mmHg was inputted).

Cardiovascular risk was estimated by separately inputting risk factor profiles for diabetic females, non-diabetic females, diabetic males and non-diabetic males. The proportions listed above were then used to estimate a weighted average risk that applies for the whole population. Note that it was not possible to consider all possible permutations within this approach due to the multiplicity of risk factors. Most notably, it was not possible to accurately capture smoking status as the coexistence of risk factors is not known. For example, whether diabetic patients are also smokers. Furthermore, smoking status was simply reported as the proportion of current smokers by Bhatt et al. (2022) whereas QRISK3 has separate categories based on frequency of smoking. To capture the impact of the increased risk with smoking, alternative scenarios were modelled in sensitivity analysis (along with other alternative risk scenarios).

2.2.2 Estimated cardiovascular events

As noted in earlier sections, the analysis uses an estimated reduction in blood pressure with renal denervation to estimate subsequent reductions in cardiovascular events. In the base case analysis, the model used the 1.78 mmHg reduction in systolic blood pressure observed by the meta-analysis by Pisano et al. (2021). Note that this is a much more modest reduction than those utilised within previous economic assessments.

The estimated cardiovascular risk for the population was estimated for standard care as described in the section above. Cardiovascular risk was then re-estimated for the population receiving renal denervation supported by standard care by inputting a lower systolic blood pressure of 157 mmHg (accounting for rounding).

Table A1 shows the estimated cardiovascular risk at 10 years for people treated with standard care or renal denervation. Cardiovascular risk is presented separately for each of the risk profiles entered into QRISK3 (based on sex and diabetic status). It can be seen that the overall weighted average cardiovascular risk is 14.1% for people treated with standard care and 13.8% in people treated with renal denervation.

Table A1. Estimated cardiovascular risk at 10 years

Population	Estimated 10-year cardiovascular risk		
	Male	Female	Weighted average
Standard care			
No diabetes	12.7%	6.6%	10.3%
Type 2 diabetes	21.6%	14.1%	18.7%
Overall	16.7%	10.0%	**14.1%**
Renal denervation			
No diabetes	12.4%	6.5%	10.1%
Type 2 diabetes	21.2%	13.8%	18.3%
Overall	16.4%	9.8%	**13.8%**

2.2.3 Cardiovascular event proportions

QRISK3 provides an estimation of overall cardiovascular disease, which is a composite outcome encompassing myocardial infarction, coronary heart disease, ischaemic stroke, transient ischaemic attack and cardiovascular death. For the purpose of the economic evaluation, it was necessary to separate the overall risk into individual estimates for each event. This enables costs, mortality and quality of life implications to specified for each of the event types.

Events were separated following the approach adopted in an economic analysis conducted as part of NICE Guideline 136 (NG136) on the diagnosis and management of hypertension in adults (NICE 2022). NICE conducted a cost-effectiveness analysis on treatment initiation thresholds for people with stage one hypertension. QRISK2 was used to estimate events in the analysis and then the proportion of individual events were estimated using values used in previous NICE assessments. We applied the same values in the HTW analysis assuming that the underlying proportion of events is unlikely to change between QRISK2 and QRISK3.

Note that QRISK does not include the risk of heart failure or renal failure. Previous economic analysis have included these events within the analysis as it is possible that renal denervation may reduce the incidence of events through a reduction in blood pressure. We explored the possibility of incorporating heart failure risk by estimating risk using the Framingham risk model. However, the systolic blood pressure reduction of 1.78mmHG modelled in this analysis was not sufficient to reduce heart failure risk. This is because systolic blood pressure is inputted as categories in the Framingham risk model and the small reduction doesn't the categorisation. Therefore, the estimated risk of heart failure was predicted to be the same with standard care or renal denervation. We therefore decided to omit heart failure from the analysis as it would be equivalent in both arms and have no bearing on the cost effectiveness result.

We explored the possibility of incorporating renal failure using a separate risk calculator. However, we could not identify a suitable risk estimator. The Kidney Failure Risk model is often used for estimating renal failure, but it is not valid in patients with an estimated glomerular rate (eGFR) of more than 60. Based on the Symplicity HTN 3 trial, eGFR was estimated to be 73.2 in this population and therefore the Kidney Failure Risk model would not be applicable (Bhatt et al. 2022). Therefore, renal failure was also omitted from the analysis.

Table A2 details the estimated proportion of each event applied in the model.

Table A2. Estimated event proportions

Health state	Estimated proportion		
	Male	Female	Weighted average
Stable angina	32.8%	34.6%	33.5%
Unstable angina	7.1%	7.3%	7.2%
Myocardial infarction	17.2%	9.2%	14.1%
Transient ischemic attack	8.9%	9.5%	9.1%
Stroke	20.6%	28.8%	23.8%
Cardiovascular disease death	13.4%	10.6%	12.3%

The analysis assumes that patients can only experience one event per cycle. However, it is possible for patients to experience further events of the same type or different events in subsequent cycles. In some cases, this approach could confer an artificial benefit to patients as the cost and quality of life implications associated with an event may not be as severe as an event which has already been experienced. To prevent such a scenario occurring, it was assumed that patients could only progress to a different event state if the cost per QALY consequences were more severe than the previous event that had been experienced. In order to make this determination, the full cost and QALY implications of each event were estimated and a cost per QALY was calculated. The events were then ranked from least severe to most severe as follows, stable angina, unstable angina, transient ischemic attack, myocardial infarction and stroke.

Thus, patients that experience a stable angina event could transition to a different event state in subsequent cycle. However, patients that experience a stroke event could not transition to a different event state as stroke has the worst cost and QALY implications. Therefore, to transition out of this state would confer an artificial benefit to patients and underestimate the cost and QALY implications of the stroke event.

2.2.4 Mortality

Mortality is included in the model through two distinct approaches reflecting general mortality and event-related mortality. A standard age-adjusted life table with data from 2017-2020 in Wales was used to reflect baseline mortality rates for the population (ONS 2021).

Event specific mortality is applied in addition to the baseline risk using standardised mortality ratios (SMRs) for each event as shown in Table A3. SMRs were sourced from the economic analysis conducted as part of NICE NG136 on the diagnosis and management of hypertension in adults (NICE 2022). NICE sourced the SMRs from a variety of studies used within economic models in previous NICE guidelines. The original data sources that were cited by NICE are reported in Table A3.

It can be seen that the mortality risk is elevated after all cardiovascular events with the highest risk following stroke and myocardial infarction. Note that the elevated risk of mortality post-event exceeds the initial risk of cardiovascular-related death estimated within QRISK3. Therefore, the QRISK3 cardiovascular mortality estimate is only applied to patients that have yet to experience an event and it is applied in addition to the general mortality estimate.

Table A3. Mortality multipliers

Event	Standardised mortality ratio Mean (95% CI)	Source
Stable angina	1.95 (1.65-2.31)	Rosengren et al. (1998)
Unstable angina	2.19 (2.05-2.33)	NICE guideline 94 (NICE 2013)
Myocardial infarction	2.68 (2.48-2.91)	Brønnum-Hansen et al. (2001)
Transient ischemic attack	1.40 (1.10-1.80)	Dennis et al. (1989)
Stroke	2.72 (2.59-2.85)	Brønnum-Hansen et al. (2001)

2.3 Resource use and costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS and PSS were included. Where possible, all costs were estimated in 2021 UK prices (£). Historic costs were inflated to 2021 values using the Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) Cost Converter (CCEMG & EPPI-Centre 2019).

2.3.1 Renal denervation and standard care cost

Renal denervation was estimated to cost £4,500 in 2012 UK prices in the economic evaluation by Gladwell et al. (2014). We inflated this cost to 2021 prices, giving an estimated cost of £5,270 for renal denervation. Gladwell et al. (2014) estimated a monthly standard care cost of £5.80 based on the cost of anti-hypertensive drugs and a GP visit once per year. We inflated this cost to 2021 prices, giving an estimated cost of £81.51 per year.

2.3.2 Event costs

Table A4 details the initial cost and subsequent annual maintenance cost for each event.

The initial costs associated with treating and managing cardiovascular events were sourced from the 2020/21 NHS reference cost list (NHS England 2022). NHS reference costs lists different costs for events based upon comorbidity and complication (CC) scores. A weighted average cost per event was estimated using the reported frequency of events within each CC score.

The costs associated with ongoing treatment and maintenance following a cardiovascular event were sourced from the economic analysis conducted as part of NICE NG136 on the diagnosis and management of hypertension in adults (NICE 2022). NICE sourced the cost estimates from previous economic models developed for NICE guidelines or NICE Technology Assessment or other published economic models. The original data sources that were cited by NICE are reported in Table A4. NICE presented the event costs using a price year of 2016/17. We inflated costs to 2021 prices.

Table A4. Event costs

Health state	Treatment cost		Source
	Initial	Ongoing	
Stable angina	£2,052	£301	NHS reference costs 2020/21 (NHS England 2022) Danese et al. (2016)
Unstable angina	£2,052	£301	
Myocardial infarction	£3,067	£5,118	
Transient ischemic attack	£2,641	£647	
Stroke	£9,577	£5,716	NHS reference costs 2020/21 (NHS England 2022) SSNAP (2016)

2.4 Health-related quality-of-life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining life year estimates with quality-of-life values associated with being in a particular health state. Table A5 details the health-related quality of life values that were applied in the analysis.

Baseline quality of life was sourced from the economic analysis by Chowdhury et al. (2018), which reported a value of 0.98 for people receiving treatment for hypertension. Chowdhury et al. (2018) sourced this value from a quality-of-life study in patients with hypertension by Stein et al. (2002).

Quality-of-life values associated with cardiovascular events were sourced from the economic analysis conducted as part of NICE NG136 on the diagnosis and management of hypertension in adults (NICE 2022). The analysis used estimates that had been used in another economic model developed for NICE clinical guideline 181 (CG181) on cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (NICE 2014). The original data sources that were cited by NICE are reported alongside the relevant values in Table A5.

Table A5. Health-related quality of life values

Health state	Quality of life		Source
	Initial	Ongoing	
Baseline quality of life	0.980	0.980	Stein et al. (2002)
Stable angina	0.808	0.808	Melsop et al. (2003)
Unstable angina	0.770	0.770	Goodacre et al. (2004) NICE technology appraisal 94 (NICE 2006) NICE clinical guideline 67 (NICE 2008)
Myocardial infarction	0.760	0.880	Goodacre et al. (2004) NICE technology appraisal 94 (NICE 2006) Tsevat et al. (1993)
Transient ischemic attack	0.900	0.900	Lavender et al. (1998)
Stroke	0.628	0.628	Tengs & Lin (2003) Youman et al. (2003)

3. Results

3.1 Base case results

The base case results of the analysis are shown in Table A6, which details total and incremental costs and QALYs accrued over the treatment pathway with renal denervation supported by standard care and standard care alone. Treatment with renal denervation was found to be more effective than standard care due to a reduction in cardiovascular events. Renal denervation was also found to be more costly than standard care although it should be noted that the incremental cost is less than the cost of the procedure itself due to a reduction in event costs. The ICER result of £233,841 is substantially higher than the threshold of £20,000 per QALY indicating that renal denervation is not cost effective.

Table A6. Base case results

Treatment strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Standard care	£6,524		16.31		
Renal denervation	£11,697	£5,173	16.33	0.02	£233,841
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year;					

3.2 Sensitivity analysis

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run, and the new cost-effectiveness result is recorded. This is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the deterministic sensitivity analyses are presented in Table A7, which shows the ICER result (cost per QALY) for a range of different modelled scenarios.

The results show that the model was insensitive to the vast majority of variations considered in sensitivity analysis. However, the analysis was found to be very sensitive to the reduction in systolic blood pressure associated with renal denervation treatment. Notably, it was found that renal denervation was cost effective when assuming a reduction in systolic blood pressure of 32 mmHg. This reduction is equivalent to the reduction assumed in the analysis by Gladwell et al. (2014), in which renal denervation was found to be cost effective.

Table A7. Sensitivity analysis results

Modelled scenario	ICER (cost per QALY)
Base case	£233,841
Changes to baseline risk factors	
All male	£205,521
All female	£315,263
Non-diabetic	£284,870
Type 1 diabetes	£193,775
Type 2 diabetes	£196,128

Modelled scenario	ICER (cost per QALY)
All male	£205,521
Age = 55	£206,975
Age = 60	£253,382
Age = 65	£320,008
Age = 70	£418,855
Age = 75	£430,385
Ex-smoker	£204,718
Light smoker	£192,790
Moderate smoker	£194,403
Heavy smoker	£186,984
SBP treatment effects	
Upper CI - SBP increase of 0.50 mmHg	Dominated
Lower CI - SBP decrease of 4.06 mmHg	£127,746
32 mmHg reduction from Gladwell et al. (2014)	**£13,506**
20 mmHg reduction from Dorenkamp et al. (2013)	£22,649
5.73 mmHg reduction from Chowdhury et al. (2018)	£83,559
4.64 mmHg reduction from Moiseeva et al. (2020)	£96,812
Mortality multipliers	
Upper estimates	£222,905
Lower estimates	£245,627
Costs	
Renal denervation cost 50% lower	£114,727
Renal denervation cost 50% higher	£352,955
Event costs 50% lower	£234,290
Event costs 50% higher	£233,391
Post-event costs 50% lower	£235,613
Post-event costs 50% higher	£232,068
Quality of life	
Initial event QoL decrement 50% lower	£238,720
Initial event QoL decrement 50% higher	£229,157
Ongoing post-event QoL decrement 50% lower	£271,022
Ongoing post-event QoL decrement 50% higher	£205,631

4. Discussion

The analysis suggests that renal denervation supported by standard care is not cost effective in comparison to standard care alone with an ICER of £233,841 per QALY. This result is in stark contrast to the previous UK cost effectiveness analysis by Gladwell et al. (2014), which found renal denervation to be cost effective with an ICER of £4,805 per QALY. This difference is driven by the much more modest treatment effect applied in the HTW analysis. The HTW analysis assumed that renal denervation reduced systolic blood pressure by 1.78 mmHg whereas Gladwell et al. (2014) assumed it was reduced by 32 mmHg. This results in a much more substantial reduction in predicted cardiovascular events than in the HTW analysis.

This treatment effect and its subsequent impact on cardiovascular events remains the key uncertainty in economic analyses considering renal denervation. Clinical studies on renal denervation have focused on the surrogate endpoint of a reduction in systolic blood pressure. Therefore, economic analyses must use on risk calculators to estimate subsequent differences in event rates. Thus, this analysis is subject to the same limitation as much of the existing literature in that it is reliant upon the accuracy of the risk calculations.

We used QRISK3 as it is the most applicable to the UK setting. Indeed, it is widely used within UK clinical practice. However, as noted in a previous section, it does not capture all possible events. Most notably, this includes renal failure and heart failure. The omission of these events has the potential to underestimate the potential benefits of renal denervation as a reduction in blood pressure could lead to a reduction in heart and renal failure.

A further limitation with the QRISK3 approach was that the underlying algorithm was not publicly available. This meant that the estimated risk had to be calculated using the online tool rather than directly estimated within the model itself. As a result, it was not possible to undertake probabilistic sensitivity analysis as the estimated risk would not automatically update inline with variations in key input values (most notably, systolic blood pressure). Thus, uncertainty has not been fully explored within the analysis.

A final limitation with the QRISK3 approach is that it amalgamates all cardiovascular outcomes into a composite risk. Therefore, we had to make assumptions to estimate the proportion of risk attributed to each of the cardiovascular event types.