

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1659 – Catheter-based renal denervation for uncontrolled elevated systolic blood pressure

Applicant: Medtronic Australasia Pty Ltd

Date of MSAC consideration: 23-24 November 2023

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of renal denervation (RDN) with a radiofrequency (RF) ablation catheter for the treatment of patients with specialist-confirmed treatment resistant hypertension (TRHTN) was received from Medtronic Australasia Pty Ltd by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of catheter-based RDN for the treatment of patients with TRHTN with uncontrolled elevated systolic blood (SBP; ≥ 150 mmHg) and/or elevated diastolic blood pressure (DBP; ≥ 110 mmHg) despite optimal medical management (OMM). MSAC considered that the evidence presented in the application did not demonstrate that RDN has superior clinical effectiveness compared to the comparator (OMM) in the proposed population. Based on the available evidence, MSAC noted that RDN resulted in a small reduction (< 5 mmHg) in SBP and DBP (recorded in an office setting) compared with sham procedures at 6 months in some patient subgroups. However, MSAC expressed concerns about the long-term sustainability of the blood pressure (BP) lowering effect considering potential influences from other factors such as anti-hypertensive medications and lifestyle changes. MSAC also noted the absence of direct evidence of reduction in cardiovascular events due to RDN. MSAC considered the cost-effectiveness of RDN was uncertain because the economic analysis applied reductions in office SBP from a small, post-hoc subgroup of a single trial, noting that in this specific subgroup, the degree of reduction in BP was not statistically significant and was further compounded by the uncertain longevity of the effect of RDN. The financial analysis was also considered to be highly uncertain and potentially underestimated. This was attributed to the potentially large pool of individuals with TRHTN meeting the eligibility criteria, along with the potentially higher number of providers capable of performing the proposed intervention than that estimated by the applicant.

MSAC considered that there may be a high clinical need for RDN in a specific subset of patients who have TRHTN (e.g., patients who are in 'hypertensive crisis' with > 180 mmHg SBP/ 120 mmHg DBP) who are on OMM with no other treatment alternatives as determined by a multidisciplinary team. However, MSAC considered that if this subpopulation was pursued, then a reapplication supported by evidence for the clinical effectiveness of RDN in this specific subpopulation would be required.

Consumer summary

This is an application from Medtronic Australasia Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of renal denervation with a radiofrequency ablation catheter for the treatment of patients with treatment-resistant hypertension.

Hypertension is a condition in which the blood pressure in the arteries is higher than normal. In most people, hypertension does not cause symptoms. However, if left untreated, persistent high pressure in the arteries causes damage, and can result in more serious conditions, including stroke, heart attack, heart failure, damaged arteries, kidney disease and dementia.

For many people, increasing daily physical activity, exercising, and lowering salt in the diet can reduce hypertension. If these lifestyle changes alone are not effective in lowering blood pressure, medicines called antihypertensives are needed. However, a small group of people take multiple antihypertensive medicines and still have high blood pressure. This is called treatment-resistant hypertension.

The heart, brain and kidneys send messages to nerves throughout the body to help regulate blood pressure. If the nerves near the kidneys are overactive, it can make the high blood pressure worse. In catheter-based renal denervation, a catheter (thin flexible tube) is inserted into an artery in the groin and guided to the arteries that supply blood to your kidneys. Once at the correct location, the catheter sends radiofrequency energy, which leads to concentrated heating to a particular place on the wall of the artery. The heat energy destroys the nerves near the arteries without damaging the arteries, potentially resulting in less nerve activity, relaxation of the arteries and a drop in blood pressure. This could be a treatment option for people with treatment-resistant hypertension.

MSAC considered renal denervation to have a similar safety profile to other procedures that involve the insertion of a catheter into the arteries that supply blood to the kidneys (e.g. imaging tests to look at the arteries in the kidneys). MSAC, however, considered it likely that renal denervation is less safe than the current standard of care (antihypertensive medicines). This is because renal denervation is a procedure that involves a catheter being inserted into the arteries. This procedure may cause unwanted events such as damage to blood vessels, bleeding, and infection. These kinds of complications cannot be caused by antihypertensive medications. MSAC noted that results from studies show a small drop in blood pressure after the renal denervation procedure. However, MSAC was uncertain whether this effect is long lasting and able to reduce the risk of developing more serious conditions such as stroke and heart attack. Therefore, MSAC was not convinced that renal denervation is more effective in improving a person's hypertension compared with the current standard of care. MSAC considered that renal denervation might have some benefit for patients who have very high blood pressure (patients who are in 'hypertensive crisis'). However, MSAC noted that this group of patients were not included in the recent studies of renal denervation, and therefore, more evidence will be needed to support this. MSAC did not consider renal denervation to be good value for money in the group targeted by this proposal. MSAC was also concerned that more people would access the treatment than predicted, which made the cost estimates very uncertain.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support MBS listing of renal denervation with a radiofrequency ablation catheter for the treatment of patients with treatment-resistant hypertension. MSAC did not consider renal denervation to be more effective than the current standard of care (optimal medical management). MSAC was also not convinced that renal denervation would be good value for money, and considered the estimates of the total financial impact to be highly uncertain.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from Medtronic Australasia Pty Ltd was requesting MBS listing of RDN with a RF ablation catheter for the treatment of patients with specialist-confirmed TRHTN.

MSAC noted that this is the first time it has considered this therapy. However, an MSAC application (application 1338) for catheter-based RDN for TRHTN was considered by PASC in April 2013 and again in August 2013. This application was withdrawn by the applicant prior to consideration by ESC or MSAC when a sham-controlled trial (SYMPPLICITY HTN-3) that used a first-generation device (SYMPPLICITY Flex with a single-electrode RF delivery system) did not confirm a significant antihypertensive effect compared with the sham control. MSAC noted that since then long-term data from the SYMPPLICITY HTN-3 trial and data from other randomised sham-controlled trials of RDN using a next generation multi-electrode catheter (SYMPPLICITY Spyril) have become available, contributing to the evidence base of the current application. MSAC noted that the SYMPPLICITY Spyril catheter is currently listed on the Australian Register of Therapeutic Goods (ARTG) and is now in use. MSAC noted that this application only included evidence relating to Medtronic RDN devices (SYMPPLICITY Flex and SYMPPLICITY Spyril). MSAC considered this inconsistent with the advice from PASC, that evidence from other manufacturers should also be considered. MSAC noted that this raised concerns regarding the generalisability of the evidence to other RDN devices given that the proposed MBS item is device agnostic.

MSAC noted that, in March 2023, the UK National Institute for Health and Care Excellence (NICE) recommended RDN for resistant hypertension only under special arrangements given the uncertainties relating to the long-term effectiveness and safety of the procedure¹. In November 2023, the US Food and Drug Administration (FDA) approved the SYMPPLICITY Spyril RDN system for use in patients with hypertension².

MSAC noted the applicant claimed that catheter-based intra-arterial RF ablation of renal sympathetic nerves addresses an unmet clinical need in people with TRHTN. This population is at increased risk of cardiovascular events, including death, and currently have limited further therapy options.

MSAC noted that the proposed population are those with TRHTN with elevated SBP ≥ 150 mmHg or elevated DBP ≥ 110 mmHg despite OMM (defined in the application as three or more antihypertensive medications, including a diuretic, at optimal tolerated doses) and at least one other defined cardiovascular risk factor. The proposed comparator is OMM. MSAC, however, did not consider the proposed population to consist entirely of patients with true TRHTN and noted the availability of a range of other alternative options for reducing BP in the proposed population, including additional pharmacotherapy and lifestyle changes.

MSAC agreed with the commentary that of the clinical evidence presented in the Applicant Developed Assessment Report (ADAR), only three sham controlled trials (SYMPPLICITY HTN-3, ReSET and SPYRAL HTN-ON MED) formed the key evidence base for RDN. MSAC noted that two of the key trials (SYMPPLICITY HTN-3 and ReSET) used the first generation SYMPPLICITY Flex device while the SPYRAL HTN-ON MED trial used the second generation SYMPPLICITY Spyril device. MSAC further noted that only a small subgroup of participants from the SPYRAL HTN-ON MED trial were on three or more antihypertensive medications, and therefore only a subpopulation of the SPYRAL HTN-ON MED trial aligned with the proposed population. MSAC

¹ National Institute for Health and Care Excellence (NICE) (2023) Percutaneous transluminal renal sympathetic denervation for resistant hypertension. Interventional procedures guidance [IPG754]. <https://www.nice.org.uk/guidance/ipg754>.

² US Food and Drug Administration (FDA) Premarket Approval (PMA) Number [P220026 - Symplicity Spyril™ Renal Denervation System](#), approved 17 November 2023.

agreed with the commentary that data from the SPYRAL HTN-OFF MED trial (a sham-controlled trial presented in the ADAR) should be considered supplementary evidence only as the study was not aligned with the PICO in terms of the population, intervention or comparator. MSAC also considered the Global SYMPLICITY registry data, which includes data for both first and second generation SYMPLICITY devices to be supplementary evidence. MSAC considered that the evidence base for the intervention was still evolving, with over 30 clinical trials currently in the active recruitment phase³.

MSAC noted that major adverse events (MAEs) related to RDN are rare, occurring in less than 1% of people. MAEs include dissection, embolic events, renal artery spasm, vascular complication at the femoral artery access site (e.g. haematoma and pseudoaneurysm), hypertensive crisis and issues related to the use of contrast agents (e.g. anaphylaxis and renal impairment). MSAC also noted the ADAR claimed that RDN has non-inferior safety compared to sham control, based on MAEs not being significantly more common in RDN than in the sham control arm. MSAC noted that the safety of RDN in comparison to OMM has not been evaluated in the existing studies. Despite this gap in evidence, MSAC considered that given RDN is a minimally invasive procedure linked to MAEs not observed with OMM, it would be conservative to assume that RDN has inferior safety compared to OMM.

MSAC noted that a reduction in measured BP is often used in trials as a surrogate for reduced cardiovascular disease (CVD) risk. MSAC noted that office SBP (OSBP) is often used as a standard clinically relevant measure, as it is easy to measure and is used in Australian guidelines. However, MSAC considered that 24-hour ambulatory measures were more accurate in capturing an individual's BP in everyday life. This was attributed to ambulatory measures being less susceptible to the white coat effect (a phenomenon where a patient's BP is falsely elevated in a health care setting) and the higher volume of BP readings obtained throughout a given time span.

For the comparative effectiveness assessment, MSAC considered that none of the meta-analyses of the key trials comparing RDN plus baseline medication compared to baseline medication alone yielded a statistically significant and clinically meaningful BP reduction (either OSBP, office DBP [ODBP], 24-hour ambulatory SBP [ASBP] or 24-hour ambulatory DBP [ADBP]) favouring RDN. MSAC noted that data for OSBP changes for RDN plus baseline medication compared to baseline medication alone were available for two of the key trials (SYMPLICITY HTN-3 and SPYRAL HTN-ON MED). MSAC noted that a meta-analysis conducted by the commentary of the SYMPLICITY HTN-3 and SPYRAL HTN-ON MED trials found a statistically significant reduction in mean OSBP at 6 months favouring the RDN intervention, but MSAC did not consider that on balance this mean OSBP reduction (-4.08 mmHg) was clinically meaningful.

In regards to the concept of clinically meaningful BP reduction, MSAC noted that consensus from the Hypertension Academic Research Consortium (HARC) indicated that a reduction in OSBP of ≥ 5 -10 mmHg, or a reduction in ODBP of ≥ 3 -5 mmHg, or a reduction in mean ASBP of ≥ 5 mmHg was generally considered to be clinically meaningful. However, other groups had suggested slightly higher thresholds. For example, the European Clinical Consensus Conference indicated that, for device-based therapies for hypertension, a reduction in OSBP of 10 mmHg, or a reduction in ASBP of 6-7 mmHg, was clinically meaningful.

MSAC noted that the meta-analysis from Ettehad et al (2016) proposed a linear relationship between the degree of SBP reduction and reduced CVD risk. According to this study, a 5 mmHg and 10 mmHg reduction in SBP reduced the risk of all-cause mortality by approximately 5% and 13% respectively. However, MSAC was not convinced that the relationship between SBP

³ ClinicalTrials.gov

reduction and reduced CVD risk was linear for SBP reductions less than 5 mmHg. MSAC considered the relationship between reduced CVD risks at a SBP reduction of less than 5 mmHg to be highly uncertain.

Regarding longevity of treatment effect, MSAC noted long term data from registries and sham-controlled trials up to 10 years. MSAC considered the durability of the RDN BP-lowering treatment effect encouraging, however raised uncertainty in the longevity of the treatment effect due to possible contributions from potential changes in anti-hypertensive medications and lifestyle changes, which may have been confounding factors. MSAC considered it plausible that RDN may result in a reduction in mortality and adverse cardiovascular events based on modest reductions in BP (as an accepted surrogate). However, there was no clear evidence for a reduction in cardiovascular mortality or other CVD-related events from the clinical trials up to 36 and 60 months.

MSAC noted the ADAR's clinical claim that RDN has superior effectiveness compared with sham procedures or no RDN. However, MSAC considered that the evidence presented in the application did not demonstrate that RDN has superior clinical effectiveness compared to the comparator (OMM) in the proposed population.

MSAC noted that the economic evaluation was a cost-utility analysis comparing RDN (plus OMM) with OMM alone. It used a Markov model that was initially developed for trials of RDN using the first-generation device. SBP was used as a predictor for cardiovascular events, with multivariate risk equations from large cohort studies used to calculate transition probabilities. MSAC noted that the ADAR base case only used data from the small subgroup of the SPYRAL HTN-ON MED trial that aligned with the PICO. This resulted in 46 patients in the RDN intervention arm and 32 patients in the sham control arm of the trial. MSAC noted that the mean OSBP reduction in this subgroup (-5.2 mmHg) reached the threshold for a clinically meaningful change as per the HARC consensus document, however noted that this reduction in BP was not statistically significant. The ADAR's base case incremental cost-effectiveness ratio (ICER) was **\$redacted**. The commentary proposed a revised base case using data from a meta-analysis of the SPYRAL HTN-ON MED subgroup together with the entire TRHTN population of SYMPLICITY HTN-3. This increased the patient numbers to 399 in the RDN treatment arm and 203 in the sham control arm. In this meta-analysis performed by the commentary, the mean between group difference in OSBP was -3.57 mmHg. MSAC noted that this reduction in BP was statistically significant, but MSAC did not consider this change to be clinically meaningful. MSAC noted that using the -3.57 mmHg treatment effect of RDN resulted in a revised base case ICER of **\$redacted**.

MSAC noted the ICERs generated from the sensitivity analyses conducted in the ADAR and by the commentary (see Table 16). MSAC noted that the sensitivity analysis results were most sensitive to model starting age, time horizon of the analysis, degree of BP reduction, the source of the relative risk used in the model and the cost of the RDN catheter. MSAC did not consider the modelled base case time horizon of 34.4 years appropriate given that there is no evidence of longevity of RDN treatment effect beyond 10 years. Reducing the time horizon to 15 years increased the ICER to **\$redacted** (see Table 16). MSAC noted that the sensitivity analysis results were relatively insensitive to costs (other than costs of the RDN catheter) and the utility values chosen. MSAC considered the cost-effectiveness of RDN uncertain because it was based on a non-statistically significant OSBP reduction from a small post-hoc subgroup of a single trial, further compounded by the uncertain durability of the RDN treatment.

MSAC noted that an epidemiological approach was used to estimate the total eligible population for the RDN procedure and capacity to deliver the service (both provider and infrastructure) were used to estimate utilisation and the financial implications of an MBS listing for RDN. The eligible patient population was estimated based on the number of adults prescribed antihypertensives

available through the Pharmaceutical Benefits Scheme (PBS). It also used published and unpublished data sources (including subgroup analyses from the Global SYMPLICITY Registry) to estimate the proportion of eligible patients who would undertake RDN. MSAC noted the ADAR assumptions regarding catheterisation laboratory capacity and interventional cardiologist capacity that would limit utilisation. Based on these assumptions, **redacted** people were estimated to seek RDN treatment in year 1, with only **redacted** of these predicted to receive RDN treatment due to capacity constraints. MSAC considered the assumptions about capacity constraints to be highly uncertain, as RDN would likely also be performed by providers other than interventional cardiologists and in settings other than private catheterisation laboratories. MSAC noted that a sensitivity analysis without supply constraints conducted by the commentary suggests a net cost to the MBS of over **\$redacted** in year 1. While MSAC acknowledged that this estimate is likely unrealistic in practice, MSAC considered it a reflection of the potentially high financial implications to the MBS based on the proposed eligible population for RDN.

MSAC noted that the ADAR estimated the net financial impact to the MBS to be **\$redacted** in year 1, increasing to **\$redacted** in year 6 assuming an MBS fee for RDN equivalent to MBS item 38287 (atrial chamber ablation). MSAC agreed with the Department and did not consider MBS item 38287 to be an equivalent procedure to RDN in terms of complexity and time taken for procedure and therefore did not consider it appropriate for the fee for RDN to be the same as MBS item 38287. MSAC considered MBS item 33527 to be a more appropriate fee comparison. MSAC noted the alternative financial impact analysis, based on aligning the RDN fee with the fee for MBS item 33527, resulted in a slightly reduced net impact to the MBS of **\$redacted** in year 1 to **\$redacted** in year 6.

MSAC noted that there were other cost factors not addressed. These included follow-up imaging costs (e.g. to monitor for renal artery stenosis), patient out-of-pocket costs, and cost of the RDN catheter (proposed to be **\$redacted**) if it is not approved for listing on Part C of the Prescribed List of Medical Devices and Human Tissue Products.

Overall, MSAC considered the financial impact to be uncertain, and that, under some plausible scenarios, it could be significantly higher than estimated in the ADAR. MSAC noted that the applicant also acknowledged that the financial estimates were highly uncertain, so offered to explore a risk-sharing arrangement. However, the Department advised that this could not be accommodated within the existing legislative framework for the MBS.

Overall, MSAC did not support public funding of RDN with an RF ablation catheter for the treatment of patients with specialist-confirmed TRHTN. MSAC considered the safety of RDN non-inferior to similar procedures including renal angiography, but inferior compared with OMM alone – the current standard of care. MSAC considered that based on the available evidence the treatment effect size of RDN in the short term to not be clinically meaningful in the proposed population. Although registry data are encouraging, MSAC noted that there is no proven long-term reduction in cardiovascular events due to RDN. Due to the reasons highlighted above, MSAC did not consider that RDN has superior clinical effectiveness compared with the comparator (OMM) in the proposed patient population. MSAC considered that the cost-effectiveness of RDN was uncertain because the economic analysis applied reductions in OSBP from a small, subgroup of a single trial that was not statistically significant and was further compounded by the uncertain longevity of the RDN effect. The financial analysis was also considered to be highly uncertain and potentially underestimated.

MSAC considered that there may be a high clinical need for RDN in a specific subset of patients who have TRHTN (e.g., patients who are in 'hypertensive crisis' with >180 mmHg SBP /120mmHg DBP) who are on OMM with no other treatment alternatives as determined by a multidisciplinary team. MSAC noted that this subpopulation was excluded from the recent

SPYRAL HTN-ON MED and SPYRAL HTN-OFF MED studies which used the second generation SYMPLICITY Spyral device included on the ARTG. MSAC considered that if this subpopulation were to be pursued, then a reapplication supported by evidence for the clinical effectiveness of RDN in this specific subgroup would be required.

4. Background

MSAC has not previously considered RDN for treatment of TRHTN or for any other indication. In 2012, Medtronic Australasia initiated an MSAC application for the listing of RDN for TRHTN based on evidence from an early proof-of-concept single-arm study (SYMPLICITY HTN-1) and an open randomised controlled study (SYMPLICITY HTN-2), in addition to other trials of RDN using RF ablation conducted in a TRHTN study population ([MSAC application 1338](#)). The Decision Analytic Protocol (DAP) was finalised in September 2013, and an MSAC submission was lodged in October 2013. However, just after submission, results from a single-blind, randomised, sham-controlled clinical trial (SYMPLICITY HTN-3) became available, which failed to confirm a significant beneficial effect of RDN on blood pressure (BP) compared with the sham procedure. As a consequence of the negative outcome of the SYMPLICITY HTN-3 trial, many programs for the development of various RDN devices were halted or suspended and MSAC application 1338 was withdrawn.

More recently, long term data from SYMPLICITY HTN-3 and other trials have become available, together with data from the Global SYMPLICITY Registry and recent randomised sham-controlled trials of RDN involving the next generation SYMPLICITY Spyral RDN system. Medtronic Australia therefore initiated a new MSAC application, acknowledging changes in updated treatment guidelines for managing hypertension (HTN) and potential changes in the population targeted for RDN.

Table 1 MSAC application history for renal denervation

Application	PASC/ ESC/ MSAC consideration
MSAC application 1338 – Catheter-based renal denervation for treatment-resistant hypertension	PASC April 2013 and August 2013 Application withdrawn after lodgment in October 2013
MSAC application 1659 – Catheter-based renal denervation for uncontrolled elevated systolic blood pressure	PASC April 2021 Lodgment of Applicant Developed Assessment Report (ADAR) June 2023

ESC = Evaluation Sub-committee; MSAC = Medical Services Advisory Committee; PASC = PICO Advisory Sub-committee
Source: Compiled by the commentary from Table 8 of MSAC 1659 ADAR.

5. Prerequisites to implementation of any funding advice

Regulatory approval status of RDN systems

RDN is a device-based therapy. The device system comprises a single use catheter and reusable RF ablation generator. Currently, there are two RDN systems listed on the Australian Register of Therapeutic Goods (ARTG):

- Medtronic Australasia’s second generation SYMPLICITY Spyral RDN multi-electrode catheter (ARTG ID 343930; effective date 21/09/2020) and SYMPLICITY system RF ablation generator (ARTG ID 198986; effective date 03/07/2012)

- Abbott Medical Australia's EnligHTN RF Ablation Catheter (ARTG ID 221818; effective date 31/03/2014), and EnligHTN system RF ablation generator (ARTG ID 198878; effective date 29/06/2012).

The Applicant Developed Assessment Report (ADAR) claimed that the EnligHTN system is not currently used in Australia and the EnligHTN trial program has been terminated.

The PICO Confirmation lists RDN systems that are no longer included on the ARTG ([MSAC 1659 PICO confirmation](#), Table A2). In addition to the predicate for SYMPLICITY Spyral (single electrode SYMPLICITY Flex), the withdrawn devices include RDN systems from Covidien (OneShot), St Jude, and Pacific Clinical Research Group Pty Ltd (Vessix Vascular V2 system, subsequently marketed by Boston Scientific).

Other RF RDN systems appear to be marketed in China (GL-06E15WA ablator and GL-6W ablation catheter), Korea (DENEX system) and Europe (Iberis system [Terumo]). Several systems are in development internationally, including the Netrod system (Shanghai Golden Leaf MedTec Co. Ltd, China) with a recently completed sham-controlled trial in patients with uncontrolled essential HTN (not yet published).

Funding provision for the single use catheter and generator

No RDN catheters are currently listed on the Prescribed List of Medical Devices and Human Tissue Products (PL). Medtronic is intending to apply for the inclusion of the SYMPLICITY Spyral RDN catheter on Part C. Advice on eligibility for the PL and a recommendation on whether or not to include the SYMPLICITY Spyral RDN catheter on Part C of the PL would fall within the remit of the Medical Devices and Human Tissue Advisory Committee (MDHTAC).

If not listed on the PL, treatment with RDN could result in significant out-of-pocket costs for patients. According to the ADAR, the cost of the SYMPLICITY Spyral catheter is **\$redacted** (per single-use catheter per treatment per lifetime). No justification for this cost was provided. The cost of the SYMPLICITY Spyral catheter is substantially higher than the PL Benefit for cardiac RF ablation catheters, which range from \$900 (non-irrigated) to \$3,700 (irrigated).

The cost applied to the economic evaluation for the SYMPLICITY RF ablation generator is **\$redacted**. This cost would be borne by the specialist centre providing the service (hospital or catheterisation laboratory). Likewise, it is assumed the centre providing the service would absorb the cost of additional consumable items (such as an introducer sheath, disposable guide catheter and dispersive electrodes).

6. Proposal for public funding

A new MBS listing is being requested for catheter-based RF RDN.

Catheter-based RDN is a minimally invasive therapeutic procedure using standard endovascular intervention techniques similar to those used in renal angioplasty or stenting. It is intended as a one-time treatment adjunct to existing standard-of-care medication therapy.

The proposed medical service is to be undertaken in specialist centres with appropriate catheterisation laboratory and emergency stenting facilities, in either the Public or Private setting, with the patient being admitted as an inpatient in hospital. Typically, a patient admitted early in the morning for their procedure would be permitted to go home in the afternoon. A patient admitted later in the day would generally be required to stay overnight.

The RDN procedure is typically performed under conscious sedation by a suitably qualified interventionalist (interventional cardiologist, interventional radiologist, interventional nephrologist, or vascular surgeon) with adequate experience in catheterisation and angioplasty of renal arteries as well as the necessary technical resources available for the management of any immediate complications that may occur.

With respect to the use of the SYMPLICITY Spyral, all operating healthcare professionals need to undergo a comprehensive training program that includes online training, web-based workshops and remote or onsite proctoring by Medtronic personnel. The training is provided by Medtronic, but it is not clear whether it is free of charge. The ADAR claims that most interventional cardiologists should be proficient in the procedure following training in 5-10 cases.

Description of the service

Immediately prior to RDN, an aortogram and selective renal angiogram is performed to determine patient suitability. According to the ADAR, approximately 5% of cases do not proceed past this step due to anatomical contraindications. In patients who are deemed suitable for RDN, sedation or analgesia is administered, and the RF catheter is percutaneously introduced via the femoral artery and advanced until the distal electrode reaches the renal artery at the established treatment zone.

Multiple angiographic imaging of the renal arteries is required to guide the RDN procedure and document the position of the catheter. Angiography is also performed at the end of each procedure to confirm the absence of damage to the renal artery.

The total procedure, including denervation of both kidneys, is estimated to take approximately 1.5-2 hours to complete. The number of ablations per renal artery (and therefore the time taken for the ablation component of the service) is dependent on the number and distribution of the RF electrodes. The average total number of ablation attempts per procedure in trials of SYMPLICITY Spyral was 47 (range 16-107). There is no simple and reliable method currently available to confirm successful RDN intra-procedurally.

Vascular closure devices are often used to assist haemostasis after RDN. Australian data from the Global SYMPLICITY Registry suggests closure devices are used in 69% of cases.

Patients are observed for 2 hours post procedure. Following the service, optimal medical management (OMM) should be continued with monitoring as usual and medication adjustments made as necessary to maintain optimal BP control and tolerability.

Proposed MBS item descriptor

The proposed wording for the proposed MBS item descriptor is provided in Table 2. The descriptor proposed in the ADAR is consistent with the descriptor in the PICO Confirmation, except that the term 'endovascular' has been omitted (the ADAR descriptor refers only to radiofrequency ablation).

The proposed wording does not specify the type of specialist who is required to confirm TRHTN, nor the trained interventionalist required to perform the procedure (i.e., a suitably qualified interventional cardiologist, interventional radiologist, interventional nephrologist or vascular surgeon), nor the appropriate setting/facility.

According to the clinical management algorithms, HTN specialists and general cardiologists are best placed to confirm TRHTN. The ADAR noted that investigation of medication compliance issues may involve a Home Medicines Review (HMR) or a pharmacy-based Medication Use

Review (MedsCheck). PASC considered that a HMR for optimising medication may not be an appropriate requirement for the service as they are frequently declined by patients.

MSAC may wish to consider whether patient selection for RDN should be decided by a multidisciplinary team, as per the advice in recent guidance released by the National Institute for Health and Care Excellence (NICE 2023)⁴ and the European Society of Cardiology Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (ESC/EAPCI, Barbato 2023)⁵.

Table 2 ADAR-proposed new MBS item for catheter-based radiofrequency renal denervation

Category 3 – THERAPEUTIC PROCEDURES
<p>MBS item XXXX</p> <p>Radiofrequency ablation of renal sympathetic nerves under image guidance (angiography) in adults ≥18 years of age with treatment-resistant hypertension confirmed by a specialist, with elevated systolic blood pressure ≥ 150 mm Hg or elevated diastolic blood pressure ≥110 mm Hg despite optimal medical management (using three or more antihypertensive drugs, including a diuretic, at optimal tolerated doses) and one or more of the following conditions:</p> <ul style="list-style-type: none"> • systolic blood pressure > 180mm Hg • previous myocardial infarction • previous stroke or transient ischemic attack (TIA) • diabetes • chronic kidney disease • atrial fibrillation • heart failure • peripheral arterial disease <p>Includes angiography. One service only. (Anaes.)</p>
Fee: \$2,298.35 Benefit: 75% = \$1,723.80

Source: Table 16 of MSAC 1659 ADAR+in-line commentary, updated by the commentary to reflect the ADAR-proposed MBS fee (at July 2023) and 75% Benefit for the inpatient service.

The indication proposed in the descriptor is consistent with the PICO but is not consistent with patients enrolled in randomised, sham-controlled trials of RDN. Patients with comorbidities or at very high cardiovascular (CV) risk were generally excluded from participation in clinical trials. However, real world evidence from the Global SYMPLICITY Registry provides some insights (with caveats) into the effectiveness and safety of RDN in high-risk patient subgroups.

The descriptor mentions ‘one service only’. MSAC may wish to consider amending to ‘applicable only once per lifetime’ to ensure that RDN is restricted to one service per lifetime.

Proposed fee for service

The proposed fee is based on MBS item 38287 [ABLATION OF ARRHYTHMIA CIRCUIT OR FOCUS or isolation procedure involving 1 atrial chamber] – Fee \$2,298.35 (as at 01 July 2023). The ADAR considers MBS item 38287 to be a reasonable benchmark for the procedure type

⁴ National Institute for Health and Care Excellence (NICE)(2023). *Interventional procedures guidance [IPG754]: Percutaneous transluminal renal sympathetic denervation for resistant hypertension.* <https://www.nice.org.uk/guidance/ipg754>

⁵ Barbato E et al. (2023) ‘Renal denervation in the management of hypertension in adults. A clinical consensus statement of the ESC Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (EAPCI)’, *European Heart Journal*, 44(15):1313-1330.

(catheter-based ablation) and time taken. The fee/benchmark was derived in consultation with key opinion leaders currently performing the RDN procedure.

The Department advised that comparison with MBS item 38287 (atrial chamber ablation) is inappropriate and that comparison with bilateral renal endarterectomy (MBS item 33527) is more suitable – Fee \$2,067.05 (75% Benefit \$1,550.30). The commentary presented the financial impact to the MBS using the ADAR-proposed fee and the alternate fee as per advice from the Department. The alternate fee has no material impact on cost effectiveness.

Of note, the service relating to MBS item 38287 (the benchmark service proposed in the ADAR) does not extend to intraoperative imaging during the cardiac ablation procedure (additional MBS items can be claimed for imaging). In contrast, the proposed item for RDN includes angiography at no additional fee.

It is unclear whether assessment of suitability for RDN using aortogram and selective renal angiogram is also intended to be captured in the proposed fee. This becomes relevant in cases where RDN does not proceed due to unsuitable renal anatomy. According to the PICO Confirmation, the MBS services associated with pre-RDN angiography include item 60027 and item 60075. These MBS costs would still apply if RDN does not proceed. The costs for these MBS services are not included in the ADAR economic evaluation or financial analysis.

In the pre-ESC response, the applicant noted that the costs of angiography required throughout the procedure (including immediately prior to the procedure) are included as part of the proposed fee. The applicant further clarified that patients deemed unsuitable for RDN after angiography will incur the MBS fee for angiography rather than that of RDN.

Any activities relating to the use of vascular closure devices during the RDN procedure would presumably be included within the proposed medical service (the time taken for vascular closure would not warrant the use of a separate MBS item).

The ADAR states that the RDN service is to be undertaken in specialist centres with the patient being admitted as an inpatient in hospital. As such, only the 75% Benefit is relevant.

7. Population

The population specified in the PICO Confirmation and the ADAR are patients with confirmed TRHTN (having tried OMM using three or more antihypertensive drugs, including a diuretic, at optimal tolerated doses), at greatest risk of cardiovascular disease (CVD) – meeting higher thresholds for elevated BP (systolic BP [SBP] ≥ 150 mmHg and/or diastolic BP [DBP] ≥ 110 mmHg) and having one or more additional specified CVD risk factors: SBP > 180 mmHg, previous myocardial infarction (MI), previous transient ischaemic attack (TIA) or stroke, diabetes mellitus, chronic kidney disease (CKD), atrial fibrillation (AF), heart failure (HF), peripheral arterial disease.

The diagnosis and onward management of patients with HTN mainly takes place in the primary health care setting. Current Australian guidelines (NHFA 2016)⁶ recommend that patients whose BP remains elevated above target on three antihypertensive drugs should be considered for referral to an HTN specialist or general cardiologist. Appropriate investigations should be

⁶ National Heart Foundation of Australia (2016) 'Guideline for the diagnosis and management of hypertension in adults', accessed 30 August 2023. <https://www.heartfoundation.org.au/bundles/for-professionals/hypertension>

undertaken to identify white coat HTN and secondary causes of HTN, including poor compliance to medication, and instigate OMM of the patient.⁷

If the patient remained hypertensive after ruling out and/or addressing other possible causes of HTN, they may then be considered to have TRHTN. Specialist confirmation of TRHTN is a prerequisite for accessing the proposed service.

8. Comparator

Currently, continued OMM, with a focus on treatment adherence, usually involving care advice of a specialist, remains the only option for patients with TRHTN.

The nominated comparator is therefore OMM without RDN (or with sham or no procedure in the clinical trial setting). This is consistent with the PICO Confirmation.

RDN is intended as a one-time treatment adjunct for patients with TRHTN, to be used in addition to OMM, defined as at least three antihypertensive medications, including a diuretic, at optimal tolerated doses. RDN is not intended to replace or substitute current practice.

Australian and international guidelines recommend that spironolactone may be used as an add-on (fourth) drug in some patients with TRHTN, under specialist advice. Although not consistent with the PICO, MSAC may wish to consider:

- whether spironolactone could be considered the main comparator for the assessment; there are at least two published open-label randomised trials directly comparing RDN (as add-on therapy) versus spironolactone (as add-on therapy) in patients with resistant HTN
 - DENERVHTA and PRAGUE-15 were excluded from the assessment but both trials found spironolactone to be more effective than RDN to reduce 24-hour ambulatory SBP
 - the authors of these excluded studies recommended that, if deemed well tolerated, spironolactone should be the fourth antihypertensive drug to prescribe in all patients with resistant HTN before considering RDN
- if spironolactone is not a suitable comparator, whether the eligibility criteria for RDN should be expanded to include previous failure or intolerance of, or contraindication to, mineralocorticoid receptor antagonists (i.e. aldosterone antagonists or potassium-sparing diuretics, such as spironolactone).

9. Summary of public consultation input

Consultation feedback was received from one consumer organisation, six health professional organisations and one individual (specialist). The seven organisations that submitted input were:

- Hearts4heart
- Australia and New Zealand Society of Nephrology – Committee of Interventional Nephrology (ANZSN CIN)
- Baker IDI Heart and Diabetes Institute

⁷ Current HTN guidelines from the European Society of Cardiology and European Society of Hypertension (ESC/ESH 2018) recommend that HTN be defined as resistant to treatment after failure of an appropriate therapeutic strategy, which should include a diuretic. The therapeutic strategy would typically involve an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) with a calcium channel blocker and a thiazide/thiazide-type diuretic,

- Dobney Hypertension Centre
- Hypertension Australia
- Interventional Radiology Society of Australasia (IRSA)
- Royal Australian and New Zealand College of Radiologists (RANZCR)

Of the eight consultation comments received, overall feedback from six were supportive of the proposal, while RANZCR was not supportive and IRSA offered provisional support, contingent on the 36 month follow-up data [of SPYRAL HTN-ON MED] being comparable to the long term follow up results of the [SPYRAL HTN-ON MED] pilot study.

Benefits

The feedback indicated the main benefits for RDN included:

- RDN provides an additional treatment option to help address an unmet clinical need for patients with uncontrolled and drug-resistant hypertension, who currently have no proven therapy options beyond further attempts to optimize lifestyle and pharmacotherapy.
- The potential to lower CV risk by lowering BP and reduce medication burden, subsequently lowering the risk of medication induced side effects and enhancing overall quality of life.
- The Dobney Hypertension Centre noted the European Society of Hypertension, a globally recognised peak body in hypertension management and treatment, recommend RDN as a treatment option for uncontrolled BP despite the use of antihypertensive drug combination therapy.
- The individual specialist stated that the procedure has a very low complication rate based on published literature.
- Feedback from the Dobney Hypertension Centre reported that patient feedback has been overwhelmingly positive with significant improvements in BP in most patients and frequent additional benefits in regard to physical and mental well-being.

Disadvantages/Implementation Issues

- ANZSN CIN and IRSA considered the selection of TRHTN patients as a critical factor in realising potential benefits from the proposed intervention, and equally importantly in preventing potential harm. The feedback raised concerns that the treatment may be provided to a large group of patients inappropriately with no perceivable benefit.
- Both ANZSN CIN and IRSA considered that all patients should be reviewed by a specialist/service dedicated to the treatment of resistant HTN to ensure medications, lifestyle and other factors are optimised, and have 24-hour ambulatory BP monitoring (ABPM) to exclude the 'white coat effect', which may contribute to 1/3 of apparent TRHTN. Similarly, the individual specialist emphasised that the proposed intervention be conducted exclusively after a multi-disciplinary consultation.
- IRSA considered that the procedure should be performed by an interventional specialist, which could include interventional cardiologists if suitably trained for renal interventions and able to perform renal angioplasty/stenting.
- ANZSN CIN noted that the efficacy of each individual treatment is difficult to measure as there is no tool to measure the success or otherwise of the procedure.
- ANZSN CIN considered that the proposed intervention might be less effective in patients with isolated systolic hypertension. ANZSN CIN noted that the intervention's efficacy in

the proposed treatment-resistant patient population with high cardiovascular risk is still under investigation, given that the SPYRAL HTN-ON MED trial is currently ongoing. ANZSN CIN considered the long-term efficacy of RDN for TRHTN is uncertain.

- RANZCR considered that the trials for RDN do not demonstrate a clinical benefit in terms of a reduction of adverse CV outcomes, which has been the standard for other therapeutic trials in HTN that have shaped current clinical practice guidelines.
- RANZCR also noted that while the RDN trials and registries indicate a modest ambulatory blood pressure reduction between 1-6 mmHg with RDN, the clinical significance of this has not been demonstrated (e.g. impact on myocardial infarction, strokes).

10. Characteristics of the evidence base

The ADAR restricted the clinical evidence base to randomised controlled trials (RCTs) of SYMPLICITY RDN devices. This is contrary to the advice provided by PASC in the PICO Confirmation that the evidence base should not be restricted to a device from one manufacturer only. The commentary noted there are relevant RCTs of RDN systems from other manufacturers (such as the EnligHTN system) that are not included in the ADAR. As these trials have not been assessed in the ADAR, it is unknown whether they would be material for decision making.

Note: beyond HTN, there are registered clinical trials of RDN for other morbidities characterised by sympathetic overactivity, including treatment of HF, CKD and AF.

The ADAR identified eight randomised trials in patients with uncontrolled HTN: four were sham-controlled (SYMPLICITY HTN-3, ReSET, SPYRAL HTN-ON MED, SPYRAL HTN-OFF MED) and four were open label (SYMPLICITY HTN-2, SYMPLICITY HTN-Japan, RDN OSA, DENER-HTN). The second generation SYMPLICITY Spyral device was used in two trials (SPYRAL HTN-ON MED and SPYRAL HTN-OFF MED); the other six trials used SYMPLICITY Flex (the predicate device).

Knowledge of treatment allocation is particularly confounding in therapeutic areas like HTN control, which are highly influenced by patient behaviour such as adherence to burdensome multi-pharmaceutical management regimens and the adoption of lifestyle factors (Figure 1 and Figure 2 illustrate this concern, showing larger treatment effects and wider confidence intervals in the open label trials than the sham-controlled trials). The commentary considered the four open trials to be supportive evidence only. The results from open trials were presented in the ADAR clinical evaluation; however, the ADAR overall clinical conclusions (summarised in GRADE tables) included evidence from the sham-controlled trials only.

Of the four sham-controlled trials, SYMPLICITY HTN-3 enrolled patients most closely resemble the proposed MBS population (severe TRHTN despite full tolerated, stable doses of at least three antihypertensive drugs of different classes, including a diuretic). The ADAR asserted that SYMPLICITY HTN-3 contained a number of important confounding factors that may have contributed to the lower-than-expected response in the RDN arm and more pronounced response in the sham control arm, leading to a treatment effect that was not statistically significant (refer to Section 10 of this Executive Summary for effectiveness results). The main factors highlighted in the ADAR were a lack of uniformity in the completeness and the pattern of denervation achieved with the first generation RDN device, operator inexperience, and variable patient and prescriber drug adherence behaviour. Nonetheless, the ADAR judged SYMPLICITY HTN-3 to be at low risk of bias and the commentary considered it the best available evidence to address the PICO.

The ADAR placed greater weight on the two second generation 'proof-of-concept' trials – SPYRAL HTN-ON MED and SPYRAL HTN-OFF MED – despite these trials enrolling patients with mild to

moderate uncontrolled HTN, who are at lower risk of CVD, and therefore less aligned with the PICO and proposed MBS populations. The SPYRAL trials were designed to overcome the perceived shortcomings of SYMPLICITY HTN-3. SPYRAL HTN-ON MED incorporated objective monitoring of adherence to prescribed antihypertensive medications. In both SPYRAL trials, RDN was performed by highly experienced operators using the second generation 4-electrode array catheter and a revised procedural technique that included the main renal artery and branches. Participants in SPYRAL HTN-ON MED and SPYRAL HTN-OFF MED were highly selected to reduce heterogeneity and more readily demonstrate a response to RDN. Treatment resistance was not required for study entry and patients with isolated systolic HTN or very severe systolic HTN were excluded.

The SPYRAL HTN-OFF MED trial investigated RDN as an alternative to, rather than an add-on to, pharmacological therapy. Subjects were either naïve to antihypertensive medication or had HTN after medication washout. Follow up was restricted to 3 months because it would not have been ethical to allow subjects with treatable uncontrolled HTN to remain untreated for a more protracted period. SPYRAL HTN-OFF MED was not aligned with the PICO in terms of the population, intervention nor comparator; as such, it was considered by the commentary to be supplementary evidence only.

The characteristics of the three sham-controlled trials that the commentary considered to be the key evidence base for RDN (SYMPLICITY HTN-3, ReSET and SPYRAL HTN-ON MED) are summarised in Table 3. The sham procedure in all three trials involved a renal angiogram without advancement of the RDN device into the artery. Additional steps were taken to further ensure blinding of the sedated patient (for example, delay in removal of the introducer sheath and a script to mimic a potential RDN procedure [SYMPLICITY HTN-3 and ReSET]; sensory isolation using blindfold and music and a lack of familiarity to the procedure and duration [SYMPLICITY HTN-3 and SPYRAL HTN-ON MED]). Patients in the sham control arms of SYMPLICITY HTN-3 and the SPYRAL HTN-ON MED Pilot cohort (N=80) were permitted to crossover to RDN after 6 months, with extended follow up to at least 36 months.

Enrolment in SYMPLICITY HTN-3 and ReSET was based on elevated SBP whereas enrolment in SPYRAL HTN-ON MED was based on elevated systolic and diastolic BP. While more than 99% of patients in SYMPLICITY HTN-3 were taking a diuretic at baseline, enrolment in ReSET was extended to patients who were intolerant of diuretics (15% of the trial population). In SPYRAL HTN-ON MED, the mean number of medication classes taken at baseline was 1.9 and only 43% of patients were taking a diuretic.

In terms of applicability to the Australian setting, the proportion of white/Caucasian participants was notably lower in SPYRAL HTN-ON MED (35% of study participants) compared with SYMPLICITY HTN-3 (72%) and ReSET (97%). The potential implications of this (if any) are not discussed in the ADAR.

Although the SPYRAL HTN-ON MED trial population is least representative of the PICO and proposed MBS population, none of the trials are entirely aligned. All three trials excluded patients with specific comorbidities that would put them at higher CVD risk. SPYRAL HTN-ON MED also excluded patients with an office SBP (OSBP) of 180 mmHg or higher.

In recognition of the applicability issues with the SPYRAL HTN-ON MED trial, the ADAR identified a subgroup of patients in this trial who received at least three antihypertensive medications at baseline, including a diuretic (see Table 3). Efficacy data from this subgroup are used exclusively in the ADAR base case economic model. Despite greater alignment with the PICO population, the commentary raises concerns about this subgroup: (i) it is not known whether subjects were truly treatment-resistant (patients were not required to receive maximal tolerated doses of antihypertensive medications at baseline); (ii) patients with systolic HTN or OSBP \geq 180 mmHg

were excluded from participation; and (iii) the RDN and sham control arms in this subgroup analysis are not necessarily balanced for baseline characteristics, placing this subgroup at high risk of bias.

Table 3 Features of the key sham-controlled trials of catheter-based, radiofrequency renal denervation (key trial status as determined in the commentary)

Trial ID Funding	N	Design/duration	Risk of bias	Patient population	PICO outcome(s)	Use in modelled evaluation
SYMPPLICITY HTN-3 Sponsored by Medtronic	535 (364 RDN + 171 sham control)	R (2:1 [treatment vs control]), MC, SB, sham-controlled 6 mo (60 mo extended F/U)	ADAR: Low Commentary: Unclear (some concerns)	Adults (aged 18-80 y) with TRHTN despite ≥3 anti-HT med classes, including a diuretic, at MTD OSBP ≥160 mmHg	Change from baseline in OSBP (6 mo) , ODBP, 24-h ASBP (6 mo) , 24-h ADBP Achievement of target OSBP (<140 mmHg) MAE (6 mo) and individual components CV death, stroke, MI, ESRD, hospitalisation for AF or HF (as chronic safety outcomes)	ADAR SA (as part of MA of all trials including open) and as part of MA for commentary revised base case
ReSET Independent study – Danish Heart Foundation	69 (36 RDN + 33 sham control)	R (1:1), DB, SC, sham-controlled 6 mo	ADAR: Low Commentary: Unclear (some concerns)	Adults (aged 30-70 y) with TRHTN despite ≥3 anti-HT meds, including a diuretic (if not intolerant) Daytime ASBP ≥145 mmHg	Change from baseline in 24-hr ASBP, 24-h ADBP AEs and complications, including death, MI, stroke	ADAR SA (as part of MA of all trials including open)
SPYRAL HTN-ON MED Sponsored by Medtronic	337 (206 RDN + 131 sham control) 80 Pilot cohort + 257 Expansion cohort	R (2:1 [treatment vs control]; 1:1 first 106 patients), MC, MN, SB, sham-controlled 6 mo (36 mo extended F/U of Pilot cohort)	ADAR: Low Commentary: Unclear (some concerns)	Adults (aged 20-80 y) with uncontrolled HTN despite 1-3 anti-HT med classes, at ≥50% recommended dosage ^a OSBP ≥150 and <180 mmHg, and ODBP ≥90 mmHg and mean 24-h ASBP ≥140 and <170 mmHg	Change from baseline in 24-h ASBP (6 mo) , 24-h ADBP, OSBP, ODBP Achievement of target OSBP (<140 mmHg) HRQoL MAE (1 mo) and individual components Mortality, ESRD, MI, stroke (as chronic safety outcomes)	ADAR SA (as part of MA of all trials including open)
SPYRAL HTN-ON MED subgroup ^b	80 (47 RDN + 33 sham control)	Post hoc subgroup 6 mo	ADAR: not assessed Commentary: High	Adults with uncontrolled HTN despite ≥3 anti-HT med classes, including a diuretic, at ≥50% recommended dosage ^a	Change from baseline in 24-h ASBP, OSBP	ADAR base case and as part of MA for commentary revised base case

ADAR = Applicant Developed Assessment Report; ADBP = ambulatory diastolic blood pressure; AE, adverse event; AF = atrial fibrillation; anti-HT = antihypertensive; ASBP = ambulatory systolic blood pressure; CV = cardiovascular; DB = double blind; ESRD = end stage renal disease; F/U = follow up; HF = heart failure; HRQoL = health-related quality of life; HTN = hypertension; MA = meta-analysis; MAE = major adverse events; MC = multicentre; med(s) = medication(s); MI = myocardial infarction; mmHg = millimetres of mercury; MN = multi-national; mo = month(s); MTD = maximum tolerated dose; ODBP = office diastolic blood pressure; OSBP = office systolic blood pressure; R = randomised; RDN = renal denervation; SA = sensitivity analysis; SB = single blind; SC = single centre; TRHTN = treatment-resistant hypertension; y = year(s).

^a <50% for thiazide-type diuretics in study sites in Japan, per standard of care

^b Post hoc subgroup analysis of SPYRAL HTN-ON MED with ≥3 antihypertensive medication classes, including a diuretic. The ADAR base case economic analysis used data from this subgroup alone. The commentary revised base case used data from a meta-analysis of SYMPPLICITY HTN-3 (all patients) and the SPYRAL HTN-ON MED subgroup.

Note: Primary powered endpoints are shown in bold text.

Source: Compiled for the commentary from Tables 19, 73, 147, 148, 149, 156 and 157 in MSAC 1659 ADAR-in-line commentary.

Table 4 summarises the characteristics of the additional evidence (randomised trials and observational studies) that was included in the ADAR to support the safety and effectiveness of RDN. The ADAR included real world evidence from an ongoing, open label, single-arm registry (Global SYMPLICITY Registry), which is funded by Medtronic and enrolls patients with uncontrolled HTN and/or conditions associated with sympathetic nervous system activation. Subgroup analyses of the registry were used to compare the two SYMPLICITY catheters and prove non-inferiority of the second generation Spyral catheter. Subgroup analyses were also conducted to interrogate patients within the registry from Australian sites.

Additional supplementary evidence for the long-term safety and/or effectiveness of RDN beyond 3 years was provided by several other published single-arm studies (Sesa-Ashton 2023; Al Ghorani 2023; Zeijen 2022). Published meta-analyses were included to support renal safety of RDN (Townsend 2020; Sanders 2017). No formal literature search was undertaken to identify these data sources; as such, the selection of studies may be at risk of bias.

Table 4 Features of additional primary studies provided for catheter-based, radiofrequency renal denervation (supplementary or supportive status as determined in the commentary)

Trial ID Funding	N	Design/ duration	Risk of bias	Patient population	PICO outcome(s)	Use in modelled evaluation
Randomised, sham-controlled						
SPYRAL HTN- OFF MED Sponsored by Medtronic	331 (166 RDN + 165 sham control) 80 Pilot cohort + 251 Pivotal study cohort	R (1:1), MC, MN, SB, sham- controlled, proof-of- concept trial 3 mo	ADAR: Low Commentary: Unclear (some concerns)	Adults (aged 20-80 y) with uncontrolled HTN in absence of anti-HT meds OSBP \geq 150 and <180 mmHg, and ODBP \geq 90 mmHg and mean 24-h ASBP \geq 140 and <170 mmHg	Change from baseline in 24- h ASBP (3 mo) , 24-h ADBP, OSBP, ODBP Achievement of target OSBP HRQoL MAE (1 mo) and individual components	ADAR SA (as part of MA of all trials including open)
Randomised, open label						
SYMPLICITY HTN-2 Sponsored by Ardian	106 (52 RDN + 54 control)	R (1:1), MC, MN, OL 6 mo (36 mo extended F/U)	ADAR: Moderate to high Commentary: High	Adults (aged 18-85 y) with TRHTN despite compliance with \geq 3 anti- HT meds OSBP \geq 160 mmHg (or \geq 150 mmHg in patients with T2DM)	Change from baseline in OSBP (6 mo) , ODBP, 24-h ASBP, 24-h ADBP Achievement of target OSBP AEs Composite CV endpoint	ADAR SA (as part of MA of all trials including open)

Trial ID Funding	N	Design/ duration	Risk of bias	Patient population	PICO outcome(s)	Use in modelled evaluation
SYMPPLICITY HTN-JAPAN Sponsored by Medtronic Japan	41 (22 RDN + 19 control)	R (1:1), MC, OL 6 mo (36 mo extended F/U)	ADAR: Moderate to high Commentary: High	Adults (aged 20-80 y) with TRHTN despite ≥3 anti-HT med classes, including a diuretic, at MTD OSBP ≥160 mmHg and mean 24-h ASBP ≥135 mmHg	Change from baseline in OSBP (6 mo) , ODBP, 24-h ASBP, 24-h ADBP MAE	ADAR SA (as part of MA of all trials including open)
RDN OSA (OSA-DENERV1) Independent grant funded study	60 (30 RDN + 30 control)	R (1:1), SC, OL, proof-of- concept trial 3 mo	ADAR: Moderate to high Commentary: High	Adults (aged 18-70 y) with TRHTN despite ≥3 anti-HT meds, including a diuretic, at full doses, coexisting with moderate- to-severe OSA OSBP ≥140 mmHg and mean daytime ASBP ≥135 mmHg	Change from baseline in OSBP (3 mo) , ODBP, 24-h ASBP, 24-h ADBP eGFR CV events	ADAR SA (as part of MA of all trials including open)
DENER-HTN Independent grant funded study	106 (53 RDN + 53 control)	R (1:1), MC, OL 6 mo (AEs to 48 mo)	ADAR: Moderate to high Commentary: High	Adults (aged 18-75 y) with resistant essential HTN despite ≥3 anti-HT med classes, including a diuretic, at MTD All patients switched to standardised triple anti- HT therapy Diurnal ASBP ≥135 mmHg and/or ADBP ≥85 mmHg after switching OSBP ≥140 mmHg and/or ODBP ≥90 mmHg	Change from baseline in 24-h ASBP, 24-h ADBP, OSBP, ODBP AEs, eGFR	ADAR SA (as part of MA of all trials including open)
Observational						
Global SYMPPLICITY Registry (GSR) Sponsored by Medtronic	Target enrolment >5,000 worldwide (ongoing) 2,466 with 3 y F/U	P, MC ^a , MN, OL, registry 36-mo data published	ADAR: not assessed	Adults (aged ≥18 y) with uncontrolled HTN and/or conditions associated with SNS activation who had undergone RDN with a SYMPPLICITY device (Flex or Spyral); eligibility for RDN as defined by local regulations	Change from baseline in 24-h ASBP, 24-h ADBP, OSBP, ODBP MAE, eGFR Subgroup analyses	ADAR base case (population characteristics)
Sesa-Ashton 2023	66 with long-term F/U	SC, OL Australia Mean F/U 8.8 ±1.2 y	ADAR: not assessed	Adults with TRHTN who had undergone RDN with SYMPPLICITY Flex as part of various clinical trials and had long-term F/U	Change from baseline in 24-h ASBP, 24-h ADBP, OSBP, ODBP AEs, eGFR	Not used
Al Ghorani 2023 (published letter)	39 (out of 107) with long-term F/U	P, SC, OL Germany Mean F/U 9.4 ±0.7 y	ADAR: not assessed	Adults with TRHTN who had undergone RDN with SYMPPLICITY Flex and had long-term F/U	Change from baseline in 24-h ASBP, 24-h ADBP eGFR	Not used

Trial ID Funding	N	Design/ duration	Risk of bias	Patient population	PICO outcome(s)	Use in modelled evaluation
Zeijen 2022	72	SC, OL, registry NLD Median F/U 3.5 y	ADAR: not assessed	Adults with TRHTN (on anti-HT meds or documented intolerance) who received RDN ^b within clinical study or compassionate use	eGFR Complications	Not used

ADAR = Applicant Developed Assessment Report; ADBP = ambulatory diastolic blood pressure; AE, adverse event; anti-HT = antihypertensive; ASBP = ambulatory systolic blood pressure; CV = cardiovascular; eGFR = estimated glomerular filtration rate; F/U = follow up; h = hour; HRQoL = health-related quality of life; HTN = hypertension; MA = meta-analysis; MAE = major adverse events; MC = multicentre; med(s) = medication(s); mmHg = millimetres of mercury; MN = multi-national; mo = month(s); MTD = maximum tolerated dose; NLD = The Netherlands; ODBP = office diastolic blood pressure; OL = open label; OSA = obstructive sleep apnoea; OSBP = office systolic blood pressure; P = prospective; R = randomised; RDN = renal denervation; SA = sensitivity analysis; SB = single blind; SC = single centre; SNS = sympathetic nervous system; T2DM = type 2 diabetes mellitus; TRHTN = treatment-resistant hypertension; y = year. a 196 active sites in 45 countries, including Australia.

b RDN was performed in the study using six different systems. RF was the predominant RDN method (~80% of subjects). SYMPLICITY Flex or Spyral was used in ~40% of subjects.

Note 1: Primary powered endpoints are shown in bold text.

Note 2: The commentary considers the open label trials to be supportive evidence while all other studies are considered supplementary.

Source: Compiled for the commentary from Tables 19, 147, 148, 150, 156 and 157 in MSAC 1659 ADAR+in-line commentary.

11. Comparative safety

Major adverse events (MAE)

Data for the primary safety measure – MAE (composite outcome) – were reported for SYMPLICITY HTN-3 and SPYRAL HTN-ON MED at 1, 3 and 6 months post procedure. The individual component events of the composite were also reported at these timepoints. Safety outcomes were not comprehensively reported in the publications relating to the ReSET trial; serious adverse events were infrequent in both arms in ReSET to 6 months.

Table 5 Results of the primary major adverse event (MAE) composite safety outcome

Study ID	RDN	Sham control	OR [95%CI]	RR [95% CI]	RD [95% CI]
	n/N (%)	n/N (%)	Result < 1 favours RDN		Result <0 favours RDN
1 month					
SYMPPLICITY HTN-3 ^a	4/362 (1.10%)	1/170 (0.59%)	1.89 [0.21, 17.02]	1.88 [0.21, 16.68]	0.01 [-0.01, 0.02]
SPYRAL HTN-ON MED	2/206 (0.97%)	1/131 (0.76%)	1.27 [0.11, 14.20]	1.27 [0.12, 13.89]	0.00 [-0.02, 0.02]
Meta-analysis	6/568 (1.06%)	2/301 (0.66%)	1.58 [0.31, 8.02] P=0.58	1.57 [0.31, 7.89] P=0.58	0.00 [-0.01, 0.02] P=0.53
			Heterogeneity: I ² =0%, P=0.81	Heterogeneity: I ² =0%, P=0.81	Heterogeneity: I ² =0%, P=0.81
6 months					
SYMPPLICITY HTN-3 ^a	13/359 (3.62%)	7/167 (4.19%)	0.86 [0.34, 2.19]	0.86 [0.35, 2.13]	-0.01 [-0.04, 0.03]
SPYRAL HTN-ON MED	2/204 (0.98%)	1/130 (0.77%)	1.28 [0.11, 14.23]	1.27 [0.12, 13.91]	0.00 [-0.02, 0.02]
Meta-analysis	15/563 (2.66%)	8/297 (2.69%)	0.90 [0.38, 2.17] P=0.82	0.91 [0.39, 2.11] P=0.82	0.00 [-0.02, 0.02] P=0.98
			Heterogeneity: I ² =0%, P=0.76	Heterogeneity: I ² =0%, P=0.77	Heterogeneity: I ² =0%, P=0.63

CI = confidence interval; OR = odds ratio; RR = risk ratio; RD = risk difference; RDN = renal denervation.

MAE was defined in all three trials as a composite of the following events: all-cause mortality; ESRD; significant embolic event resulting in end-organ damage; artery perforation or dissection requiring intervention; vascular complications; hospitalisation for hypertensive crisis/emergency not related to confirmed non-adherence with medications or new renal artery stenosis > 70%, confirmed by angiography within 6 months of randomisation (assessed at 6 months only).

^a Denominators have been amended to number of patients treated. Data are uncertain due to inconsistencies in Clinical Study Report. Source: Excerpt from Table 30 in MSAC 1659 ADAR+in-line commentary, incorporating commentary corrections.

Overall, reports of MAE (composite and individual component events) were infrequent and meta-analyses showed no statistically significant differences between the RDN and sham control arms. There were no occurrences of renal artery perforation or dissection requiring intervention or new cases of end stage renal disease (ESRD). Hospitalisation for hypertensive crisis or emergency was the most frequent of the individual component events reported in SYMPPLICITY HTN-3.

There were no statistically significant differences between the RDN and sham control arms in change in renal function during the randomised follow up period of the trials.

Longer term safety outcomes from trials

Where longer term safety follow up was available beyond completion of the randomised controlled period of the trials (SYMPPLICITY HTN-3 to 60 months; SPYRAL HTN-ON MED pilot to 36 months), the RDN procedure was found to be safe throughout, with no late-emerging complications. This assessment included outcomes that were classified as efficacy outcomes in the PICO (all-cause mortality, CV mortality, new onset ESRD, new MI, new stroke).

Cumulative event rates were not statistically different in patients who did and did not receive RDN. However, several safety outcomes in SYMPPLICITY HTN-3 were reported only in the group randomised to RDN: new ESRD; significant embolic events resulting in end-organ damage; and vascular complications requiring intervention (surgical repair, interventional procedure, thrombin injection, or blood transfusion). For each of these outcomes the number of events was low.

Longer term safety outcomes from other sources

Among 2,145 patients in the Global SYMPPLICITY Registry followed for 6 months, and 1,199 patients followed to 3 years, the incidence of CV death was 2.0% at 3 years and no long-term safety concerns were observed following the RDN procedure. The incidence of renal artery stenosis reported in the registry compares favourably with published information on the natural history of renal stenosis in hypertensive patients (although imaging was not requested systematically in all registry patients and therefore it may have been under-reported). Renal function, as assessed by the estimated glomerular filtration rate (eGFR), declined within the expected range for patients with uncontrolled HTN. However, the authors of publications from the registry noted that the observed safety profile should be regarded as being device specific. There is a need for continued long-term follow up of patients treated with the second generation SYMPPLICITY Spyrax catheter and the revised procedural techniques involving more distal renal vessel access.

Other observational studies with follow up to 10 years provided additional supplementary evidence for the safety profile of RDN, with no significant adverse effects on renal function over time – albeit with the caveats associated with long-term follow-up in single-arm studies. This evidence is not comparative and there is the potential for adverse effects on renal function to be masked by the ‘noise’ expected in a clinical area with substantial progression to CKD in many patients.

Safety conclusions

Overall, the commentary considered the randomised trials and the ADAR extended safety assessment (up to 10 years) support the general safety of the RDN procedure. The rates of adverse events in patients at high CV risk undergoing RDN were no more than would be expected for patients with this baseline comorbidity profile.

The commentary also noted that no significant increase in de novo renal artery stenosis or worsening kidney function was seen in long-term follow up beyond expected rates in patients with HTN and reduced kidney function. However, patients with severely reduced kidney function have not been satisfactorily investigated in the sham-controlled trials of RDN or the registry analyses. Therefore, renal safety of RDN can only be considered in patients with normal or mild-to-moderate reduced kidney function.

12. Comparative effectiveness

Clinical importance of changes in blood pressure

A relationship has been shown between BP reduction and reduced CVD risk, such that for each 10 mmHg or 5 mmHg drop in OSBP, there was an associated 13% and 5% decrease in all-cause mortality respectively, and an even greater reduction in other CV outcomes (Ettehad 2016)⁸. The ADAR asserted that pharmacological-induced reductions in SBP and DBP of ≥ 2 mmHg have been shown to significantly reduce the incidence of CVD in both hypertensive and normotensive individuals and are therefore considered clinically meaningful. However, the ADAR also cited

⁸ Ettehad D et al. (2016) ‘Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis’, *Lancet*, 387:957–967.

consensus from the Hypertension Academic Research Consortium (HARC; Kandzari 2022)⁹, which has advised that a reduction in OSBP of ≥ 5 -10 mmHg, or a reduction in office DBP (ODBP) of ≥ 3 -5 mmHg, or a reduction in mean 24-hour ambulatory SBP (ASBP) of ≥ 5 mmHg, are generally considered to be clinically meaningful. Other consensus groups have proposed slightly higher thresholds; for example, the European Clinical Consensus Conference (ECCC) for device-based therapies for HTN (Mahfoud 2017)¹⁰ considered a 10 mmHg reduction in OSBP or 6- 7 mmHg reduction in ASBP to be clinically meaningful.

The applicant's pre-ESC response stated that BP reductions are strongly associated with a continuous linear reduction in relative risk of major adverse cardiovascular events (MACE), with every 1 mmHg reduction in SBP correlating to a 2% relative risk reduction in MACE, independent of baseline BP and comorbidities. The applicant stated that this is consistent with the results of a meta-regression analysis of 55 randomised trials (> 265,000 patients), which demonstrate that even small BP reductions contribute to the reduced risk of death and cardiovascular events¹¹.

Change in office systolic blood pressure (OSBP)

For each BP outcome, the ADAR presented a meta-analysis including all randomised trials for which data were available, regardless of study design. In addition, where the availability of the data permitted, separate meta-analyses were presented grouping the trials by study design (second generation sham-controlled; first generation sham-controlled; open label trials). The ADAR acknowledged the RCT evidence base for RDN is heterogenous, including trials with differing designs, differing durations of follow-up, recruiting differing HTN populations and using different RDN device iterations. For these reasons, and as mentioned in Section 8 of this Executive Summary, the commentary focused on the best available evidence, which was the randomised, sham-controlled trials comparing RDN plus OMM with sham plus OMM.

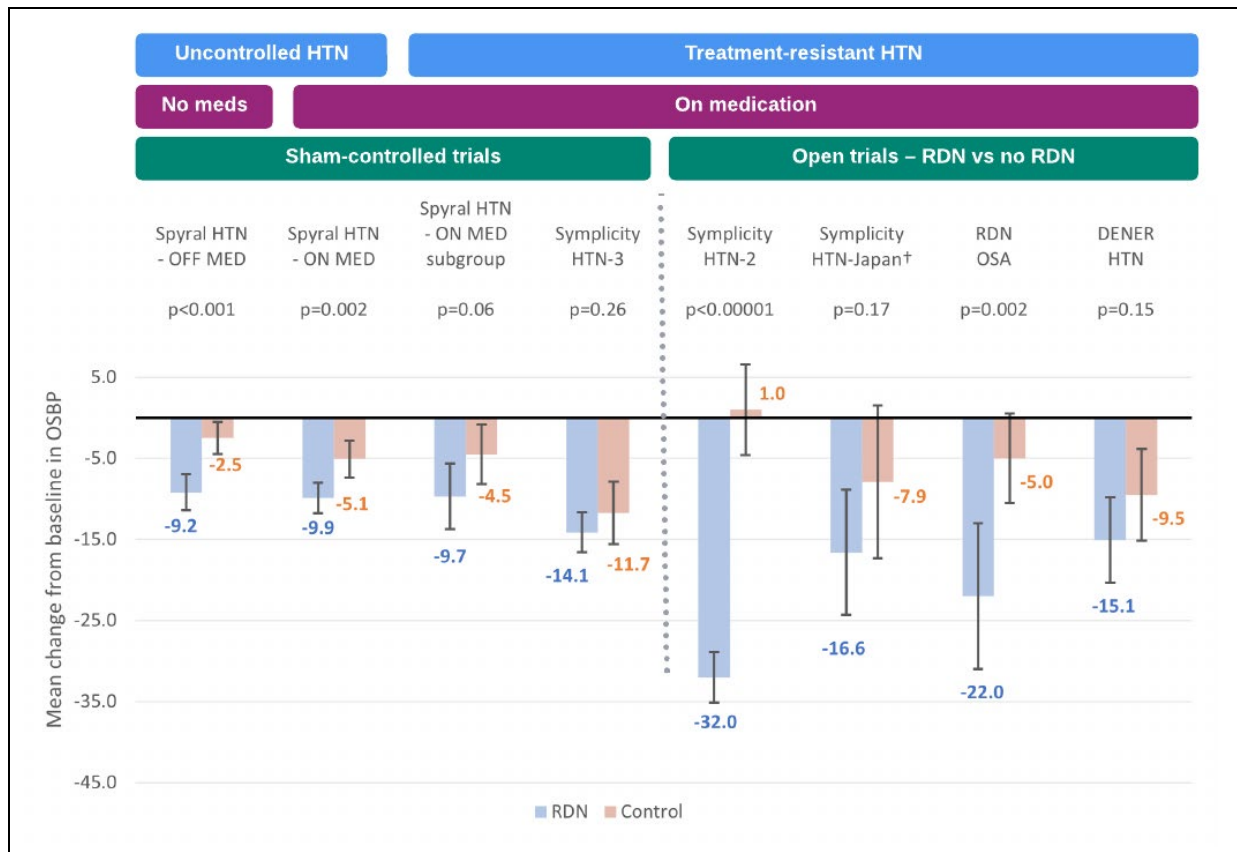
Figure 1 illustrates the importance of a control arm in studies of interventions in patients with HTN, where shifts from prior medical management imparted by the trial setting exerts substantial influence on the outcome. Across all seven trials included in the ADAR (ReSET did not report this outcome), OSBP reductions from baseline are notable in the control arms (with and without sham). The largest absolute reductions in OSBP (and the largest confidence intervals) are seen in the RDN arms of open trials, which have far greater scope than blinded trials for confounding due to patient behaviours.

⁹ Kandzari DE et al. (2022) 'Clinical trial design principles and outcomes definitions for device-based therapies for hypertension: A consensus document from the Hypertension Academic Research Consortium', *Circulation*, 145(11):847-863.

¹⁰ Mahfoud F et al. (2017) 'Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: state of the art and considerations for the future', *European Heart Journal*, 38(44):3272-3281.

¹¹ Ettehad D et al. (2016). "Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis." *Lancet* 387(10022):957-967.

Figure 1 Mean change from baseline in mean office SBP (mmHg) for RDN and control arms of randomised trials (open and sham-controlled) reporting this outcome



HTN = hypertension; meds = antihypertensive drugs; OSBP = office systolic blood pressure; RCT = randomised controlled trial; RDN = renal denervation; SBP = systolic blood pressure

† The sample sizes in this study were too small for a robust calculation of confidence intervals, so the ranges shown may not be accurate. Note: the bars indicate the 95% confidence interval around the mean for each arm. OFF-MED and RDN OSA report at 3 months. All other trials report at 6 months. For simplicity, the subgroup of the SPYRAL HTN-ON MED trial has been classified in the figure as a trial of patients with treatment-resistant HTN, although patients were not required to be treatment-resistant for study entry.

Source: Commentary Figure 2 in MSAC 1659 ADAR+in-line commentary, with addition of data from SPYRAL HTN-ON MED subgroup taken from Table 73 of MSAC 1659 ADAR+in-line commentary.

Of the three key trials selected by the commentary (SYMPPLICITY HTN-3, ReSET and SPYRAL HTN-ON MED), two reported mean change from baseline to 6 months in OSBP, and only one (SPYRAL HTN-ON MED) reported a statistically significant reduction compared with sham control (Table 6). When the two key trials reporting OSBP were meta-analysed, a statistically significant reduction in mean OSBP was observed; however, the mean reduction of 4.08 mmHg did not meet the threshold for a clinically meaningful change as proposed by the ECCC for device-based therapies for HTN, nor the HARC consensus document on clinical trial design principles and outcomes definitions for device-based therapies for HTN (noting that HARC is funded through grants from medical device manufacturers, including Medtronic).

Table 6 also shows the mean change from baseline in OSBP for the subgroup of SPYRAL HTN-ON MED who received at least three antihypertensive medications, including a diuretic. Despite this post hoc subgroup analysis showing no statistically significant difference between the RDN group (n=46) and the sham control group (n=32) for this outcome, the ADAR used these data exclusively in the base case economic analysis.

The commentary conducted a meta-analysis of SYMPPLICITY HTN-3 (all patients) and the SPYRAL HTN-ON MED subgroup taking at least three antihypertensive medications, including a diuretic,

which represents the best available evidence in terms of alignment with the PICO and proposed MBS population. This meta-analysis revealed a difference between RDN and sham control that was of borderline statistical significance ($P=0.05$), with a mean reduction in OSBP that is not clinically meaningful (3.57 mmHg).

For completeness, Table 6 also shows the mean change from baseline to 3 months in OSBP reported in the SPYRAL HTN-OFF MED trial (grey text) and the meta-analysis presented in the ADAR for all sham-controlled trials that reported change from baseline in OSBP.

Table 6 Change from baseline in mean office SBP (mmHg) in sham-controlled trials

Trial ID	Certainty (GRADE) ^a	RDN		Sham control		Difference [95% CI] P value
		n /N (%)	Change mean (SD)	n /N (%)	Change mean (SD)	
SYMPPLICITY HTN-3	-	353/364 (97.0%)	-14.13 (23.93)	171/171 (100%)	-11.74 (25.94)	-2.39 [-6.9, 2.1] P=0.26
SPYRAL HTN-ON MED all patients	-	199/206 (96.6%)	-9.9 (13.90)	126/131 (96.2%)	-5.1 (13.2)	-4.80 [-7.81, -1.79] P=0.002
SPYRAL HTN-ON MED subgroup ^a	-	46/47 (97.9%)	-9.7 (13.9)	32/33 (97.0%)	-4.5 (10.6)	-5.20 [-10.64, 0.24] P=0.06
Commentary Meta-analysis HTN-3 and HTN-ON MED all patients	⊕⊕⊖⊖ Low	552	-	297	-	-4.08 [-6.60, -1.56] P=0.001
Het: Tau ² = 0.00; Chi ² = 0.73, (P = 0.39); I ² = 0%						
Commentary Meta-analysis HTN-3 and HTN-ON MED subgroup ^b	⊕⊕⊖⊖ Low	399	-	203	-	-3.57 [-7.09, -0.04] P=0.05
Het: Tau ² = 0.00; Chi ² = 0.60, (P = 0.44); I ² = 0%						
SPYRAL HTN-OFF MED	-	156/166 (94.0%)	-9.2 (14.60)	150/165 (90.9%)	-2.5 (12.90)	-6.60 [-9.6, -3.5] P<0.001
ADAR Meta-analysis HTN-3, HTN-ON MED and HTN-OFF MED	⊕⊕⊖⊖ Low	708	-	447	-	-5.07 [-7.23, -2.91] P<0.00001
Het: Tau ² = 0.62; Chi ² = 2.39, (P = 0.30); I ² = 16%						

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; Het = heterogeneity; mmHg= millimetres of mercury; n = number analysed at endpoint, N = number randomised; RDN = renal denervation; SBP = systolic blood pressure; SD = standard deviation

^a GRADE Certainty of evidence as determined in the commentary. The ADAR considered the meta-analysis of the 3 trials to be 'Moderate'.

^b Post hoc subgroup of SPYRAL HTN-ON MED with ≥3 antihypertensive medications including a diuretic (Table 73 in MSAC 1659 ADAR).

Note 1: Statistically significant differences are shown in bold text.

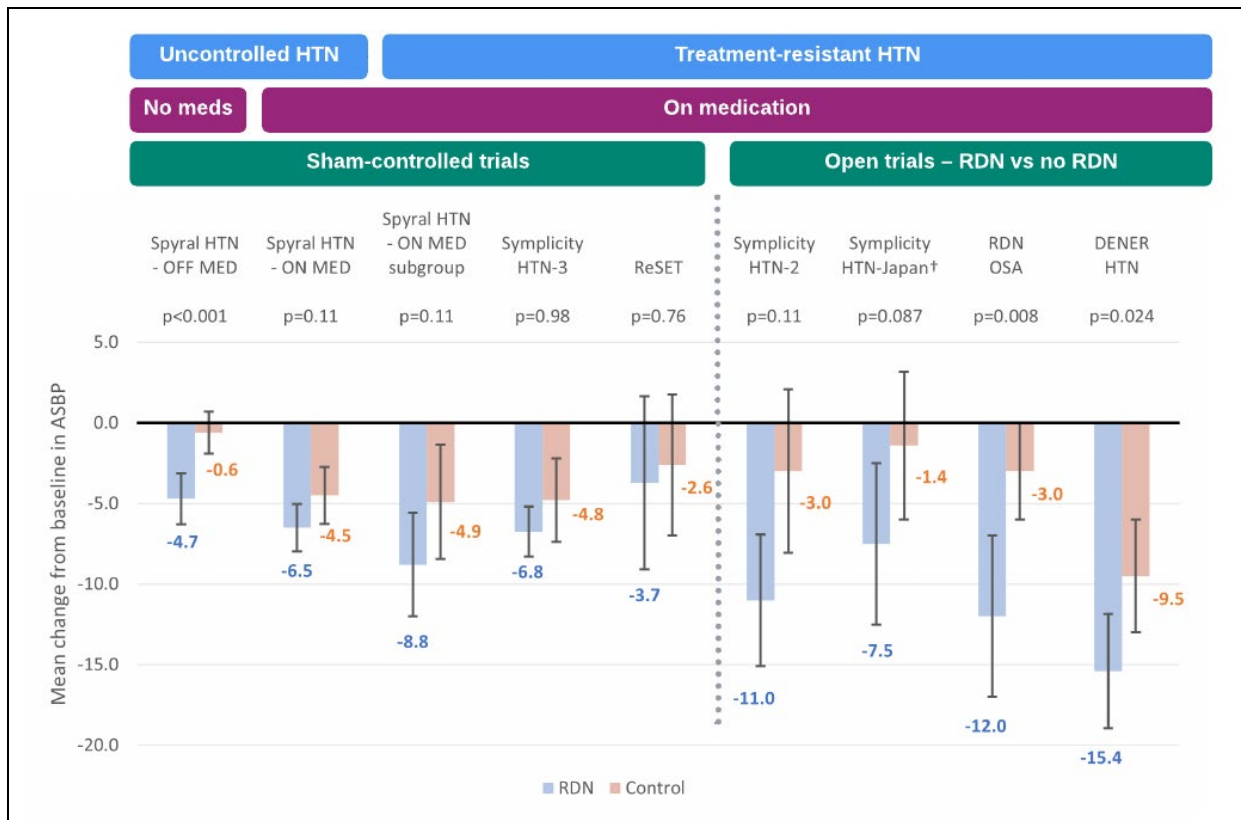
Note 2: SPYRAL HTN-OFF MED was considered supplementary evidence in the commentary and is shown in grey text. Follow up was 3 months in SPYRAL HTN-OFF MED and 6 months in SYMPPLICITY HTN-3 and SPYRAL HTN-ON MED.

Source: Compiled for the commentary from Table 48, Table 77 and Commentary Figure 11 in MSAC 1659 ADAR+in-line commentary.

Change in 24-hour ambulatory systolic blood pressure (ASBP)

Figure 2 illustrates sizeable reductions from baseline in 24-hour ASBP in the control arms of the eight trials reporting this outcome. The largest absolute reductions in ASBP are seen in the RDN arms of open trials.

Figure 2 Mean change from baseline in mean 24-hour ambulatory SBP (mmHg) for RDN and control arms of randomised trials (open and sham-controlled) reporting this outcome



ASBP = ambulatory systolic blood pressure; HTN = hypertension; meds = antihypertensive drugs; RCT = randomised controlled trial; RDN = renal denervation; SBP = systolic blood pressure

† The sample sizes in this study were too small for a robust calculation of confidence intervals, so the ranges shown may not be accurate. Note: the bars indicate the 95% confidence interval around the mean for each arm. OFF-MED and RDN OSA report at 3 months. All other trials report at 6 months. For simplicity, the subgroup of the SPYRAL HTN-ON MED trial has been classified in the figure as a trial of patients with treatment-resistant HTN, although patients were not required to be treatment-resistant for study entry.

Source: Commentary Figure 5 in MSAC 1659 ADAR+in-line commentary, with addition of data from SPYRAL HTN-ON MED subgroup taken from Table 72 of MSAC 1659 ADAR+in-line commentary.

Of the three key trials selected by the commentary (SYMPPLICITY HTN-3, ReSET and SPYRAL HTN-ON MED), all reported mean change from baseline to 6 months in 24-hour ASBP and none of the trials found a statistically significant reduction compared with sham control (Table 7). When the three trials were meta-analysed, a statistically significant reduction in mean 24-hour ASBP was observed, favouring RDN; however, the mean reduction of 1.92 mmHg did not meet the ECCO or HARC threshold for a clinically meaningful change. When the commentary restricted the meta-analysis to the two trials in patients with TRHTN (SYMPPLICITY HTN-3 and ReSET), the mean reduction in 24-hour ASBP was not statistically significant. Likewise, meta-analysis of SYMPPLICITY HTN-3, ReSET and the subgroup of SPYRAL HTN-ON MED resulted in a reduction in 24-hour ASBP that was not statistically significant.

Table 7 Change from baseline in mean 24-hour ambulatory SBP (mmHg) in sham-controlled trials

Trial ID	Certainty (GRADE) ^a	RDN		Sham control		Difference [95% CI] P value
		n /N (%)	Change mean (SD)	n /N (%)	Change mean (SD)	
SYMPPLICITY HTN-3	-	329/364 (90.4%)	-6.75 (15.11)	162/171 (94.7%)	-4.79 (17.3)	-1.96 [-5.0, 1.1] P=0.98
ReSET	-	35/36 (97.2%)	-3.7 (16.40)	33/33 (100%)	-2.6 (12.8)	-1.82 [-4.66, 1.03] P=0.21
SPYRAL HTN-ON MED all patients	-	192/206 (93.2%)	-6.5 (10.70)	116/131 (88.5%)	-4.5 (10.3)	-2.00 [-4.41, 0.41] P=0.11
SPYRAL HTN-ON MED subgroup ^a	-	45/47 (95.7%)	-8.8 (11.0)	30/33 (90.9%)	-4.9 (9.9)	-3.90 [-8.68, 0.88] P=0.11
Commentary Meta- analysis HTN-3 and ReSET	⊕⊕⊖⊖ Low	364	-	195	-	-1.82 [-4.66, 1.03] P=0.21
		Het: Tau ² = 0.00; Chi ² = 0.05, (P = 0.83); I ² = 0%				
Commentary Meta- analysis HTN-3, ReSET, HTN-ON MED all patients	⊕⊕⊖⊖ Low	556	-	311	-	-1.92 [-3.76, -0.08] P=0.04
		Het: Tau ² = 0.00; Chi ² = 0.06, (P = 0.97); I ² = 0%				
Commentary Meta- analysis HTN-3, ReSET, HTN-ON MED subgroup ^b	⊕⊕⊖⊖ Low	409	-	225	-	-2.36 [-4.81, 0.09] P=0.06
		Het: Tau ² = 0.00; Chi ² = 0.59, (P = 0.75); I ² = 0%				
SPYRAL HTN-OFF MED	-	140/166 (84.3%)	-4.7 (10.40)	134/165 (81.2%)	-0.6 (8.60)	-4.00 [-6.2, -1.8] P<0.001
ADAR Meta-analysis HTN-3, ReSET, HTN-ON MED, HTN- OFF MED	⊕⊖⊖⊖ Very low	696	-	445	-	-2.79 [-4.22, -1.37] P=0.0001
		Het: Tau ² =0.00 Chi ² = 2.21, (P = 0.53); I ² = 0%				

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; Het = heterogeneity; mmHg= millimetres of mercury; n = number analysed at endpoint, N = number randomised; RDN = renal denervation; SBP = systolic blood pressure; SD = standard deviation

^a GRADE Certainty of evidence as determined in the commentary. The ADAR considered the meta-analysis of the 4 trials to be 'Moderate'.

^b Post hoc subgroup of SPYRAL HTN-ON MED with ≥3 antihypertensive medications including a diuretic (Table 72 in MSAC 1659 ADAR).

Note 1: Statistically significant differences are shown in bold text.

Note 2: SPYRAL HTN-OFF MED was considered supplementary evidence in the commentary and is shown in grey text. Follow up was 3 months in SPYRAL HTN-OFF MED and 6 months in SYMPPLICITY HTN-3, ReSET and SPYRAL HTN-ON MED.

Source: Compiled for the commentary from Table 50, Table 77 and Commentary Figure 10 in MSAC 1659 ADAR+in-line commentary.

Change in office diastolic blood pressure (ODBP)

Of the three key trials selected by the commentary, two trials (SYMPPLICITY HTN-3 and SPYRAL HTN-ON MED) reported mean change from baseline to 6 months in ODBP. Neither reported a statistically significant reduction compared with sham control, although SPYRAL HTN-ON MED was borderline (Table 8). When the two trials were meta-analysed, a statistically significant reduction in mean ODBP was observed, favouring RDN; however, the reduction of 1.94 mmHg was not clinically meaningful.

The ADAR did not report this outcome for the subgroup of patients in SPYRAL HTN-ON MED who received at least three antihypertensive medications including a diuretic.

Table 8 Change from baseline in mean office DBP (mmHg) in sham-controlled trials

Trial ID	Certainty (GRADE) ^a	RDN		Sham control		Difference [95% CI] P value
		n /N (%)	Change mean (SD)	n /N (%)	Change mean (SD)	
SYMPPLICITY HTN-3	-	353/364 (97.0%)	-6.6 (11.90)	171/171 (100%)	-4.6 (13.60)	-2.00 [-4.39, 0.39] P=0.10
SPYRAL HTN-ON MED	-	199/206 (96.6%)	-5.2 (8.80)	126/131 (96.2%)	-3.3 (8.2)	-1.90 [-3.78, -0.02] P=0.053
Commentary Meta-analysis HTN-3 and HTN-ON MED	⊕⊕⊖⊖ Low	552	-	297	-	-1.94 [-3.42, -0.46] P=0.01
		Het: Tau ² = 0.00; Chi ² = 0.00, (P = 0.95); I ² = 0%				
SPYRAL HTN-OFF MED	-	156/166 (94.0%)	-5.1 (8.10)	150/165 (90.9%)	-1 (8.20)	-4.10 [-5.93, -2.27] P<0.0001
ADAR Meta-analysis HTN-3, HTN-ON MED, HTN-OFF MED	⊕⊖⊖⊖ Very low	708	-	447	-	-2.75 [-4.23, -1.27] P=0.0003
		Het: Tau ² =0.66 Chi ² = 3.25, (P = 0.20); I ² = 39%				

CI = confidence interval; DBP = diastolic blood pressure; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; Het = heterogeneity; mmHg= millimetres of mercury; n = number analysed at endpoint, N = number randomised; RDN = renal denervation; SD = standard deviation

^a GRADE Certainty of evidence as determined in the commentary. The ADAR considered the meta-analysis of the 3 trials to be 'Low'.

Note 1: Statistically significant differences are shown in bold text.

Note 2: SPYRAL HTN-OFF MED was considered supplementary evidence in the commentary and is shown in grey text. Follow up was 3 months in SPYRAL HTN-OFF MED and 6 months in SYMPPLICITY HTN-3 and SPYRAL HTN-ON MED.

Source: Compiled for the commentary from Table 49 and Table 77 in MSAC 1659 ADAR+in-line commentary.

Change in 24-hour ambulatory diastolic blood pressure (ADBP)

Of the three key trials selected by the commentary, none found a statistically significant reduction in mean 24-hour ADBP for RDN compared with sham control (Table 9). Meta-analysis also showed no statistically significant difference between groups in this outcome (except when data from the SPYRAL HTN-OFF MED supplementary trial was included in the meta-analysis).

Table 9 Change from baseline in mean 24-hour ambulatory DBP (mmHg) in sham-controlled trials

Trial ID	Certainty (GRADE) ^a	RDN		Sham control		Difference [95% CI] P value
		n /N (%)	Change mean (SD)	n /N (%)	Change mean (SD)	
SYMPPLICITY HTN-3	-	329/364 (90.4%)	-4.1 (9.20)	162/171 (94.7%)	-3.1 (10.10)	-1.00 [-2.85, 0.85] P=0.28
ReSET	-	35/36 (97.2%)	-1.7 (8.6)	33/33 (100%)	-2.6 (7.5)	0.90 [-2.93, 4.73] P=0.64
SPYRAL HTN-ON MED	-	192/206 (93.2%)	-4.4 (7.30)	116/131 (88.5%)	-3.4 (7.6)	-1.00 [-2.73, 0.73] P=0.26
Commentary Meta-analysis HTN-3 and ReSET	⊕⊖⊖⊖ Very low	364	-	195	-	-0.64 [-2.30, 1.02] P=0.45
		Het: Tau ² = 0.00; Chi ² = 0.77, (P = 0.38); I ² = 0%				
Commentary Meta-analysis HTN-3, ReSET, HTN-ON MED all patients	⊕⊖⊖⊖ Very low	556	-	311	-	-0.81 [-2.01, 0.38] P=0.18
		Het: Tau ² = 0.00; Chi ² = 0.85, (P = 0.65); I ² = 0%				

Trial ID	Certainty (GRADE) ^a	RDN		Sham control		Difference [95% CI] P value
		n /N (%)	Change mean (SD)	n /N (%)	Change mean (SD)	
SPYRAL HTN-OFF MED	-	140/166 (84.3%)	-3.7 (6.60)	134/165 (81.2%)	-0.8 (5.30)	-4.00 [-6.2, -1.8] P<0.001
ADAR Meta-analysis HTN-3, ReSET, HTN-ON MED, HTN- OFF MED	⊕⊕⊕⊕ Very low	696	-	445	-	-1.46 [-2.80, -0.11] P=0.03
Het: Tau ² =0.86 Chi ² = 5.72, (P = 0.13); I ² = 48%						

CI = confidence interval; DBP = diastolic blood pressure; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; Het = heterogeneity; mmHg= millimetres of mercury; n = number analysed at endpoint, N = number randomised; RDN = renal denervation; SD = standard deviation

^a GRADE Certainty of evidence as determined in the commentary. The ADAR considered the meta-analysis of the 3 trials to be 'Low'.

Note 1: Statistically significant differences are shown in bold text.

Note 2: SPYRAL HTN-OFF MED was considered supplementary evidence in the commentary and is shown in grey text. Follow up was 3 months in SPYRAL HTN-OFF MED and 6 months in SYMPPLICITY HTN-3, ReSET and SPYRAL HTN-ON MED.

Source: Compiled for the commentary from Table 51 and Table 77 in MSAC 1659 ADAR+in-line commentary.

Achievement of target systolic blood pressure (<140 mmHg)

Of the three key trials selected by the commentary, two trials reported the proportion of patients achieving target OSBP (<140 mmHg) at 6 months, and only SPYRAL HTN-ON MED reported a statistically significant difference, favouring the RDN arm (Table 10). However, the meta-analysis showed no statistically significant difference between groups in achievement of target OSBP.

The ADAR also included data for SPYRAL HTN-OFF MED, which showed no statistically significant difference between RDN and sham control for this outcome.

None of the sham-controlled trials reported the proportion of patients achieving target ODBP (<90 mmHg) or target mean 24-hour ASBP (<130 mmHg)/ADBP (<80 mmHg).

Table 10 Proportion of patients achieving target office SBP (<140 mmHg) at 6 months in key sham-controlled trials (selected by the commentary)

Trial ID	Certainty (GRADE) ^a	RDN	Control	OR [95% CI]	RR [95% CI]	RD [95% CI]
		n/N (%)	n/N (%)	Results >1 favours RDN		Results >0 favours RDN
SYMPPLICITY HTN-3	-	38/350 (10.9%)	22/169 (13.0%)	0.81 [0.46, 1.43]	0.83 [0.51, 1.36]	-0.02 [-0.08, 0.04]
SPYRAL HTN- ON MED	-	39/199 (19.6%)	8/126 (6.3%)	3.60 [1.62, 7.98]	3.09 [1.49, 6.39]	0.13 [0.05, 0.21] P=0.001
Commentary Meta-analysis HTN-3 and HTN-ON MED	⊕⊕⊕⊕ Moderate	77/549 (14.0%)	30/295 (10.2%)	1.66 [0.38, 7.21] P=0.50	1.56 [0.43, 5.72] P=0.50	0.05 [-0.10, 0.21] P=0.48
				Heterogeneity: I ² =89% (P=0.003)	Heterogeneity: I ² =89% (P=0.003)	Heterogeneity: I ² =91% (P=0.001)

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; mmHg= millimetres of mercury; OR = odds ratio; RD = risk difference; RDN = renal denervation; RR = risk ratio; SBP = systolic blood pressure

^a GRADE Certainty of evidence as determined in the commentary.

Note: Statistically significant differences are shown in bold text.

Source: Excerpt of Table 52 in MSAC 1659 ADAR+in-line commentary.

Achievement of a reduction in systolic blood pressure (5, 10, 15, 20 mmHg)

Although not a PICO outcome, the proportion of patients achieving a reduction in OSBP of at least 5, 10, 15 and 20 mmHg was reported in the ADAR. SYMPLICITY HTN-3 and SPYRAL HTN-ON MED were the only sham-controlled trials reporting these outcomes. In SYMPLICITY HTN-3, statistically significant differences were seen in the proportions of TRHTN patients achieving 5 and 10 mmHg reductions in OSBP, favouring RDN over sham control (approximately 10% higher proportion in the RDN arm). There were no statistically significant differences between arms for achievement of 15 or 20 mmHg reductions in OSBP. In SPYRAL HTN-ON MED, statistically significant differences were seen between arms for achievement of OSBP reductions of 10, 15 and 20 mmHg (not 5 mmHg).

Longer term blood pressure outcomes from trials

Long-term (three year) follow up on BP outcomes were presented in the ADAR for the SYMPLICITY HTN-3 trial and the SPYRAL HTN-ON MED Pilot cohort. Data were imputed (using last observation carried forward) for patients in the sham control group who crossed over to receive RDN after 6 months. The data showed that SBP and DBP reductions after RDN appeared to be maintained, if not progressively increased, over time.

The commentary noted that long-term trial follow-up data are useful for safety and for detecting any potential signals of poor durability. However, it may not be valid to attribute any observed sustained durability to RDN from such data because ongoing BP reductions will also be influenced by patient behaviour and medication changes (particularly for patients in SPYRAL HTN-ON MED who were not on OMM at baseline). The ADAR presented four different calculations of antihypertensive medication burden for patients in SPYRAL HTN-ON MED, all of which showed a gradual increase in medication burden over time, in both the RDN and the sham control arms, that could at least partly account for the maintenance in treatment effect.

The commentary asserted that the long-term data were consistent with, but do not establish, durability of effect. Furthermore, the long-term data do not represent an unbiased sampling – patients who may not have experienced sustained BP reductions after RDN may have been less inclined than others to persist in long-term follow up.

Longer term blood pressure outcomes from other sources

The ADAR presented longer term data from the Global SYMPLICITY Registry and several other single-arm observational studies as supplementary evidence for the durability of the RDN BP-lowering treatment effect. As for the long-term RCT follow up, the commentary noted that all observed BP improvements cannot be attributed to RDN – patients may have been subject to other ongoing factors that reduce BP (such as improved medical management, improved adherence to antihypertensive medication and changes in lifestyle) and it is not possible to account for these confounding factors in single cohort observational studies.

Incidence of cardiovascular disease

The incidence of CVD-related outcomes was reported in the clinical trials and the ADAR as chronic safety events. Data to 60 months were available from SYMPLICITY HTN-3 and to 36 months from SPYRAL HTN-ON MED; however, interpretation is limited by crossover after 6 months and dwindling patient numbers over time. In SYMPLICITY HTN-3, there were no statistically significant differences in individual CV-related events to 60 months between patients

who received RDN and those who did not (Table 11). New ESRD only occurred in patients allocated to RDN.

In SPYRAL HTN-ON MED, there was one CV death (sham control arm) and one stroke (RDN arm) by 36 months. The commentary speculates that the lower overall rate of CV-related events in the SPYRAL trial may be due to this population having hypertension of lower severity than the population in the SYMPLICITY HTN-3.

Table 11 Longer term cardiovascular disease outcomes reported in SYMPLICITY HTN-3

CVD-related event – n (%)	Allocated RDN N=364	Crossover group N=101	Combined RDN (allocated and crossover) N=465	Non crossover patients N=70
To 36 months	N=290	N=68	N=358	N=46
CV death	8 (2.76%)	4 (5.88%)	12 (3.35%)	2 (4.35%)
New ESRD	10 (3.45%)	0 (0.00%)	10 (2.79%)	0 (0.00%)
New stroke	17 (5.86%)	7 (10.29%)	24 (6.70%)	4 (8.70%)
New MI	17 (5.86%)	4 (5.88%)	21 (5.87%)	2 (4.35%)
Hospitalisation for HF	39 (13.4%)	3 (4.4%)	42 (11.7%)	6 (13.0%)
Hospitalisation for AF	14 (4.8%)	3 (4.4%)	17 (4.7%)	2 (4.3%)
To 60 months	N=154	NR	NR	N=27
CV death	12 (7.79%)	NR	NR	3 (11.11%)
New ESRD	11 (7.14%)	NR	NR	0 (0%)
New stroke	22 (14.29%)	NR	NR	4 (14.81%)
New MI	19 (12.34%)	NR	NR	2 (7.41%)
Hospitalisation for HF	42 (27.3%)	NR	NR	7 (25.9%)
Hospitalisation for AF	15 (9.7%)	NR	NR	4 (14.8%)

AF = atrial fibrillation; CV = cardiovascular; ESRD = end-stage renal disease; HF = heart failure; MI = myocardial infarction; NR = not reported; RDN = renal denervation

Source: Excerpt of Table 35 in MSAC 1659 ADAR+in-line commentary.

Health-related quality of life

Patient reported outcomes were available from SPYRAL HTN-ON MED, using the generic EQ- 5D- 3L health-related quality of life (HRQoL) instrument. There were no statistically significant differences between the RDN and sham control arms in terms of patient scoring at each item level (data not shown), with the exception of a statistically significant difference (P=0.042) between arms in the scoring of the mobility item at 6 months. Fewer patients in the sham control arm scored “no problems in walking about” and more patients scored “some problems walking about” compared to the patients in the RDN arm. The ADAR speculates that this may be a ‘chance’ finding. There was no difference between the treatment arms in terms of mean visual analogue scale (VAS) rating of ‘own health state today’ at baseline or at any time point during the available follow up.

Registry subgroup analyses to further address applicability concerns

The ADAR presented a series of subgroup analyses from the Global SYMPLICITY Registry to provide broader insights into the safety and effectiveness of RDN using Spyral (N=168) and Flex (N=1,070) devices, Australian patients (N=294), and a cohort that matched the proposed MBS

population (N=1,619). A backwards step-wise approach was then taken to compare each individual baseline component of the proposed MBS population (e.g. OSBP \geq 150 mmHg and/or ODBP \geq 110 mmHg vs $<$ 150 mmHg and/or $<$ 110 mmHg; \geq 3 antihypertensive medications vs $<$ 3 antihypertensive medications; MI vs no MI; AF vs no AF, etc.) to determine what effect each individual component was contributing to the overall result in the proposed MBS population.

Based on the subgroup analyses, the second generation Spyral catheter appeared to be non-inferior in safety and effectiveness compared with the Flex catheter. The analyses also showed that patients who matched the proposed MBS population criteria had a significantly greater reduction in SBP and DBP than the population who did not match the proposed MBS criteria – the caveat being that this latter cohort included heterogeneous patients, including a small proportion with conditions associated with sympathetic nervous system activation in the absence of uncontrolled HTN. The stepwise approach showed that the main driver of treatment effect was a patients' baseline SBP (the higher the baseline SBP, the greater the treatment effect). The number of antihypertensive medications and comorbidities did not appear to be drivers of treatment effect, with the exception that the RDN treatment effect may be lower in patients who have CKD.

These analyses provide supplementary evidence for the safety and effectiveness of RDN in the proposed MBS population; however, the commentary noted that subgroup analyses are not a substitute for direct evidence from well-conducted sham-controlled randomised trials in the target population.

Effectiveness conclusions

The ADAR concluded that the totality of the evidence demonstrated consistency of RDN treatment effect when considering absolute treatment effect, i.e. the within-patient change. However, the commentary refuted this conclusion, and pointed out that the evidence base clearly demonstrated a large sham effect imparted by the trial setting. It is not valid to infer that the absolute treatment effect measured in the intervention arms of the trials is a consequence of RDN alone; the Hawthorne effect and changes in clinical management and patient behaviour associated with the trial setting cannot be assumed to translate to the general clinical management setting. It is the commentary's view that the treatment effect size of RDN in the clinical setting is likely to approach, but not exceed, the clinically relevant thresholds described by the ECCC and HARC, although the effect may be stochastic, providing large benefits for an unidentified subset of patients.

Clinical claims

Effectiveness

The ADAR's clinical claim for RDN is as follows:

- The use of RDN results in **superior** effectiveness compared with either sham procedure or no RDN procedure.

Based on the best evidence available (i.e. sham-controlled trials in patients with uncontrolled or TRHTN on antihypertensive medication), the commentary considered that the clinical claims should be amended to:

- The use of RDN results in superior effectiveness in terms of statistically significant reductions at 6 months in OSBP, ODBP and ASBP compared with sham procedures; however, these reductions are **not clinically meaningful**
 - mean difference in OSBP was **4.08 mmHg**

- mean difference in 24-hour ASBP was **1.92 mmHg**.
- When the evidence is restricted to trials of patients with TRHTN (resembling the proposed MBS population), the use of RDN results in **non-inferior** effectiveness compared with sham procedures (i.e. no statistically significant reductions in OSBP, ODBP, ASBP, ADBP).
 - Addition of a subgroup from SPYRAL HTN-ON MED taking ≥ 3 medications, including a diuretic, resulted in superior effectiveness in terms of a statistically significant reduction in OSBP (but not 24-hour ASBP) compared with sham procedures; however, this reduction in OSBP was not clinically meaningful (mean difference in OSBP was **3.57 mmHg**).
- The use of RDN results in **non-inferior** effectiveness in terms of the proportion of TRHTN patients achieving target office SBP (<140 mmHg), compared with sham procedures.
- It is plausible that the use of RDN may result in a reduction in mortality and adverse CV events based on modest reductions in BP (as an accepted surrogate); however, there was **no clear evidence for a reduction in CV mortality or other CVD-related events** from the clinical trials presented in the ADAR with follow up to 36 and 60 months.

Safety

The commentary considered the ADAR's safety claim for RDN to be reasonable:

- The use of RDN results in **non-inferior** safety compared to similar procedures, including renal angiography, which was used as the "sham" procedure in the control arms of the blinded randomised controlled trials.

In addition, the commentary considered that the following claim can be made based on evidence from controlled open trials:

- As an endovascular intervention requiring femoral access and contrast agents, the use of RDN plus OMM may potentially result in **inferior** safety compared with OMM alone (though this cannot be confirmed because safety was not comprehensively reported in the open trials).

13. Economic evaluation

A cost-utility analysis was presented in the ADAR comparing RDN (plus OMM) to OMM (with or without sham procedure). The model used OSBP as a surrogate outcome for coronary heart disease (CHD) and CVD-related events, using multivariate risk equations from large-scale cohort studies (such as the Framingham Heart Study) to calculate transition probabilities to clinical endpoints (angina pectoris, stroke, MI, HF, ESRD, CV mortality and all-cause mortality).

The commentary noted that OSBP is a well-established surrogate for CVD and CV mortality; however, ambulatory measures are reported to be stronger predictors of CV events compared to office measures.¹² Furthermore, trials with extended follow up did not show a reduction in CVD-related events or CV mortality that could be attributed to RDN (although the trials were not powered for these endpoints).

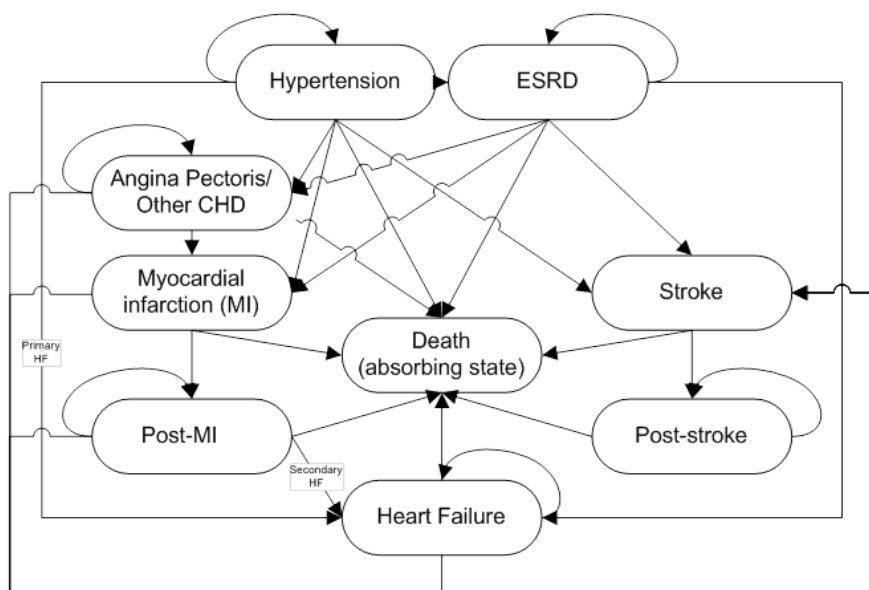
The ADAR base case economic analysis incorporated effectiveness data exclusively from a subgroup of the SPYRAL HTN-ON MED trial taking three or more antihypertensive medications at baseline, including a diuretic (refer to Section 8 of this Executive Summary for commentary on

¹² National Heart Foundation of Australia (2016) 'Guideline for the diagnosis and management of hypertension in adults', accessed 30 August 2023. <https://www.heartfoundation.org.au/bundles/for-professionals/hypertension>

this subgroup). As shown in Table 6, this subgroup showed a mean between-group difference in change from baseline in OSBP of - 5.2 mmHg, favouring RDN; however, the sample size was small (n=46 RDN and n=32 sham control) and the difference was not statistically significant. A revised base case was proposed in the commentary using data from a meta-analysis of the SPYRAL HTN-ON MED subgroup with the entire TRHTN population of SYMPLICITY HTN-3. In this meta-analysis, the mean between-group difference in OSBP was not clinically important (- 3.57 mmHg) and of borderline statistical significance (P=0.05). As such, the link from surrogate (OSBP) to modelled clinical endpoints is dubious.

The model structure is depicted in Figure 3 and the main components are described in Table 12. The modelling approach was based on a published study conducted by Medtronic (Geisler et al. 2012), but no specific justification was given in the ADAR for choosing this over other alternatives.

Figure 3 Model structure diagram



CHD = coronary heart disease; ESRD = end stage renal disease.
Source: Figure 88 in MSAC 1659 ADAR.

Table 12 Summary of the economic evaluation

Component	Description
Perspective	Australian health care system perspective
Population	Patients with TRHTN despite OMM (≥3 antihypertensive medications, used at optimal tolerated doses) and who also have one or more additional specified CVD risk factors
Prior testing	-
Comparator	OMM, with or without sham procedure
Type(s) of analysis	Cost-utility analysis
Outcomes	Life-years gained, QALYs
Time horizon	Lifetime
Computational method	Markov model
Generation of the base case	<ul style="list-style-type: none"> Modelled economic evaluation

Component	Description
	<ul style="list-style-type: none"> Background event risks derived from published risk equations (function of population characteristics) RDN Treatment benefit (in form of mean difference in OSBP [mmHg]) translated to relative risk of avoiding CHD, stroke, and HF events Events transformed to costs and QALYs Output expressed as cost per QALY gained of RDN relative to OMM
Health states	See Figure 3
Cycle length	1 month
Transition probabilities	Probability of AP/Other CHD, Probability of MI, Probability of Stroke, Probability of HF, Probability of entering ESRD, Probability of CV death, Probability of non-CV death
Discount rate	5% (MSAC guidelines Version 1.0)
Software	Microsoft Excel

AP = angina pectoris; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; ESRD = end-stage renal disease; HF = heart failure; MI = myocardial infarction; mmHg = millimetres of mercury; MSAC = Medical Services Advisory Committee; OMM = optimal medical management; OSBP = office systolic blood pressure; QALY = quality-adjusted life year; RDN = renal denervation; TRHTN = treatment-resistant hypertension

Source: Table 78 in MSAC 1659 ADAR+in-line commentary.

The ADAR results, along with the commentary revised base case, are provided in Table 13.

Table 13 Results of the stepped economic analysis

Step	Outcome	Costs included	Duration	IC	IE	ICER
1. Trial-based (overall population)	mmHg reduction SBP	RDN procedure + anti-HT meds	6 months	\$redacted	4.8	\$redacted
Commentary revised					4.08 ^a	\$redacted
2. Trial-based (MBS subgroup: ≥ 3 meds including a diuretic)	mmHg reduction SBP	RDN procedure + anti-HT meds	6 months	\$redacted	5.2	\$redacted
Commentary revised					3.57 ^b	\$redacted
3. Modelled evaluation (transform mmHg gained to RR of events, apply patient characteristics of SPYRAL HTN ON-MED MBS subgroup, transform events to mortality)	Combined event ^c avoided	RDN procedure + anti-HT meds	6 months	\$redacted	0.0037	\$redacted
4. Extrapolate to lifetime	Combined event ^c avoided	RDN procedure + anti-HT meds	34.4 years	\$redacted	0.1620	\$redacted
5. Transform events to treatment costs	Combined event ^c avoided	RDN procedure + anti-HT meds + event costs	34.4 years	\$redacted	0.1620	\$redacted
6. Transform events to QALYs	QALYs gained	RDN procedure + anti-HT meds + event costs	34.4 years	\$redacted	0.2795	\$redacted
Commentary revised						\$redacted ^b

anti-HT = antihypertensive; HTN = hypertension; IC = incremental cost; ICER = incremental cost-effectiveness ratio; IE = incremental effectiveness; MBS = Medicare Benefits Schedule; meds = medications; mmHg = millimetres of mercury; QALYs = quality-adjusted life years; RDN = renal denervation; RR = relative risk; SBP = systolic blood pressure

^a Derived from meta-analysis of SYMPLICITY HTN-3 and SPYRAL HTN-ON MED populations.

^b Derived from meta-analysis of SYMPLICITY HTN-3 and SPYRAL HTN-ON MED subgroup on ≥3 antihypertensive medication classes, including a diuretic.

^c Combined incidence of AP/Other CHD, MI, Stroke, HF, CV death.

Source: Derived from Table 110 in MSAC 1659 ADAR+in-line commentary.

The overall base case results are presented in Table 14, along with the commentary revised base case.

Table 14 Results of the economic evaluation

Item	RDN + OMM	OMM alone	Incremental
ADAR base case			
Total costs	\$redacted	\$redacted	\$redacted
QALYs	9.4429	9.1634	0.2795
ICER			\$redacted
Commentary revised base case			
Total costs	\$redacted	\$redacted	\$redacted
QALYs	9.3694	9.1634	0.2060
ICER			\$redacted

ADAR = Applicant Developed Assessment Report; ICER = incremental cost-effective ratio; OMM = optimal medical management; QALYs = quality-adjusted life years; RDN = renal denervation

Note: The commentary revised base case used a mean difference in OSBP of 3.57 mmHg (from SYMPLICITY HTN-3 and SPYRAL HTN-ON MED subgroup). All other model inputs were unchanged (MBS item fees were not updated because the impact on costs is immaterial). Source: Derived from Table 113 in MSAC 1659 ADAR+in-line commentary.

Key drivers of the results are provided in Table 15.

Table 15 Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Uncertain maintenance of treatment effect	High, as costs for RDN almost all up front
RR reduction in events by SBP	Varies by source selected	Favours either RDN or OMM depending on the source chosen
Cost of RDN catheter	Lower cost modelled as sensitivity analysis	Decreased the ICER

ICER = incremental cost-effectiveness ratio; OMM = optimal medical management; RDN = renal denervation; RR = relative risk; SBP = systolic blood pressure

Source: Compiled for the commentary from Section 3.3 in MSAC 1659 ADAR+in-line commentary.

Results were most sensitive to model starting age, SBP reduction, the source of the relative risk underpinning the analysis, and the time horizon of the analysis (with shorter than a lifetime horizon yielding higher ICERs). Results were relatively insensitive to the costs (other than that of the single use RDN catheter) and utility values chosen. See Table 16 for selected sensitivity analyses, calculated using the commentary revised base case.

Table 16 Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
ADAR base case	\$redacted	0.2795	\$redacted
Commentary revised base case	\$redacted	0.2060	\$redacted
Patient characteristics			
Baseline age (base case 65.6 years)			
55 years – ADAR	\$redacted	0.2869	\$redacted
55 years – Commentary revised	\$redacted	0.2337	\$redacted
75 years – ADAR	\$redacted	0.2356	\$redacted
75 years – Commentary revised	\$redacted	0.1480	\$redacted
Baseline SBP (base case 179.55 mmHg)			
150 mmHg – ADAR	\$redacted	0.2530	\$redacted
150 mmHg – Commentary revised	\$redacted	0.1868	\$redacted
175 mmHg – ADAR	\$redacted	0.2769	\$redacted
175 mmHg – Commentary revised	\$redacted	0.2041	\$redacted
200 mmHg – ADAR	\$redacted	0.2870	\$redacted
200 mmHg – Commentary revised	\$redacted	0.2124	\$redacted
Transformation of SBP benefit to RR of events (base case Thomopoulos 2014)			
Law (2009) – ADAR	\$redacted	0.2983	\$redacted
Law (2009) – Commentary revised	\$redacted	0.2060	\$redacted
Rahimi (2021) – ADAR	\$redacted	0.1567	\$redacted
Rahimi (2021) – Commentary revised	\$redacted	0.1273	\$redacted
Structural			
Time horizon (base case 34.4 years)			
15 years – ADAR	\$redacted	0.1595	\$redacted
15 years – Commentary revised	\$redacted	0.1184	\$redacted
20 years – ADAR	\$redacted	0.2194	\$redacted
20 years – Commentary revised	\$redacted	0.1625	\$redacted
30 years – ADAR	\$redacted	0.2755	\$redacted
30 years – Commentary revised	\$redacted	0.2033	\$redacted
Costs			
Reduced RDN catheter costs (base case \$redacted)			
\$3,700 – OSBP difference of 5.2 mmHg	\$redacted	0.2795	\$redacted
\$3,700 – Commentary revised	\$redacted	0.2060	\$redacted

ADAR = Applicant Developed Assessment Report; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year; RR = relative risk

Note: The commentary revised analyses used a mean difference in OSBP of 3.57 mmHg instead of 5.2 mmHg. All other model inputs were unchanged (MBS item fees were not updated).

Source: Excerpt from Table 114 in MSAC 1659 ADAR+in-line commentary.

14. Financial/budgetary impacts

Estimated use of the proposed technology

A predominantly epidemiological approach was taken to determine the expected extent of usage and associated financial implications of an MBS listing for RDN. The base case method of

calculating the patient population started with patients treated with antihypertensives from a 10% Pharmaceutical Benefits Scheme (PBS) sample of adults prescribed PBS antihypertensive medication, extrapolated to the rest of the adult population in Australia. Other published and unpublished data sources (including subgroup analyses from the Global SYMPLICITY Registry) were then used to determine the proportion of hypertensive patients who would ultimately be eligible (proposed MBS population) and may elect to receive RDN, taking private health insurance (PHI) status and patient preference (“demand”) into consideration.

A separate epidemiological method of calculating the budget impact was conducted in an additional sensitivity analysis, applying alternative sources to the total population of Australia. The ADAR claimed this triangulation approach provided greater certainty in the estimated pool of prevalent and incident patients who may potentially seek RDN treatment under the MBS.

The ADAR subsequently applied assumptions regarding organisational and infrastructure capacity constraints that would likely restrict the number of RDN procedures that can be performed each year. These assumptions regarding catheterisation laboratory capacity (**redacted**) and interventional cardiologist capacity (**redacted**) are highly uncertain. Furthermore, these assumptions do not take into consideration that RDN could also be performed by providers other than interventional cardiologists (notably, interventional radiologists, interventional nephrologists and vascular surgeons) and in settings other than private catheterisation laboratories. The ADAR claimed that over time the prevalent pool of eligible patients is expected to decrease until there is sufficient capacity to provide services to all incident patients seeking RDN.

The applicant’s pre-ESC response stated that the RDN procedure would only be performed by specialists who have undergone appropriate training. The Australian subgroup analysis of the GSR showed that 97% of procedures were performed by interventional cardiologists. The applicant further noted that catheterisation labs are better equipped to perform the RDN procedure and the RDN procedure would primarily be performed in the private sector due to the limited capacity of public hospitals to accommodate non-emergent procedures for private patients. Due to these reasons the applicant considered the RDN procedure to be likely limited to interventional cardiologists in private catheterisation laboratories in the short to medium term.

Table 17 Patients potentially seeking renal denervation

Parameter	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
Number of people potentially seeking RDN treatment (prevalence only)	redacted	redacted	redacted	redacted	redacted	redacted
Number of people potentially seeking RDN treatment (Yr 1: current prevalent cases and Yr 2-6: incidence)	redacted	redacted	redacted	redacted	redacted	redacted
Cath lab constraints	redacted	redacted	redacted	redacted	redacted	redacted
Patients potentially seeking RDN treatment (based on patient preference and cath lab capacity)	redacted	redacted	redacted	redacted	redacted	redacted
Interventional cardiologist capacity	redacted	redacted	redacted	redacted	redacted	redacted

cath = catheterisation; RDN = renal denervation

Source: Compiled for the commentary from Table 130, Table 131 and Table 132 in MSAC 1659 ADAR+in-line commentary.

Of concern, if interventional cardiologists and other providers are performing RDN at low volume, the treatment effect observed in the clinical trials may not translate to clinical practice. In the RDN trials using the SYMPPLICITY Spyral catheter, procedures were performed by highly experienced operators and employed advanced RF ablation techniques (more complete ablation with extension beyond the main renal artery into renal artery branch vessels).

Estimation of financial impact to the MBS

The financial implications to the MBS resulting from the proposed listing of RDN for TRHTN are summarised in Table 18. These estimates take into consideration the interventional cardiologist capacity restrictions discussed above. The number of services (starting from 2025) is based on a one-time procedure. The estimates in Table 18 deviate from those provided in the ADAR because they incorporate procedures that do not proceed to RDN due to unsuitable renal anatomy and MBS costs (75% Benefits) at 01 July 2023. Table 18 also shows the impact of aligning the proposed fee for RDN with the fee for MBS item 33527 (Department advice).

Table 18 Net financial implications of radiofrequency renal denervation to the MBS – assuming supply constraints

Parameter	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
Number of people who do not receive RDN (unsuitable anatomy) ^a	redacted	redacted	redacted	redacted	redacted	redacted
Number of people who receive RDN	redacted	redacted	redacted	redacted	redacted	redacted
Financial impact to the MBS of the proposed RDN service ^b	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Financial impact to the MBS of the proposed RDN service ^c	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Financial impact to the MBS of associated services ^d	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net financial impact to the MBS of the new listing for RDN^b	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net financial impact to the MBS of the new listing for RDN^c	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

MBS = Medicare Benefits Schedule; RDN = renal denervation

a Assumes 5% of eligible patients do not proceed to RDN due to unsuitable renal anatomy.

b Assumes MBS fee for RDN is equivalent to MBS item 38287 (proposed in ADAR). Incorporates imaging for RDN suitability.

c Assumes MBS fee for RDN is equivalent to MBS item 33527 (advised by Department). Incorporates imaging for RDN suitability.

d Includes items for anaesthesia (MBS item 21942) in all eligible patients. Includes items for imaging in patients who do not proceed with RDN (MBS item 60027, MBS item 60075).

Note: MBS costs relate to 75% Benefit at 01 July 2023.

Source: Compiled for the commentary from Table 133 and Table 134 in MSAC 1659 ADAR+in-line commentary.

Although highly unrealistic in practice, a sensitivity analysis without supply constraints suggested the net cost to the MBS could be in excess of \$redacted in Year 1. In acknowledgement that estimates are highly uncertain, Medtronic Australasia has offered their willingness to explore a risk-sharing arrangement.

Estimation of impact to other health budgets

RDN is intended as a one-time treatment adjunct, to be used in addition to current practice (OMM). That is, it is not intended to replace or substitute current practice. Since RDN is not intended to replace any medicines, an MBS listing for RDN for the treatment of TRHTN is not expected to impact the use of currently used therapies (“standard of care”).

The total cost of the RDN procedure (incorporating costs for the single use device, MBS services for the procedure and anaesthesia [75% Benefits], theatre and day admission) is estimated to be **\$redacted**. This excludes costs associated with renal imaging immediately prior to RDN (assumed to be captured in the MBS Fee) and capital equipment depreciation. The commentary also noted that costs for renal imaging at follow up timepoints post RDN (to monitor for renal stenosis) were not included but also acknowledged that it is unclear whether follow up imaging is undertaken in Australia.

The ADAR assumed that RDN catheters will be listed on Part C of the PL. The proposed device cost is **\$redacted**. If a PL listing is not achieved, the cost of the catheter could potentially be passed on to hospitals or patients. Patient out-of-pocket costs are not considered in the ADAR.

The expected net financial impact to PHIs is shown in Table 19, assuming supply constraints. The estimates assume day admission only for the RDN procedure.

Table 19 Net financial implications of radiofrequency renal denervation to private health insurers – assuming supply constraints

Parameter	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
Financial impact of PL Benefits payable for the proposed RDN service ^a	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Financial impact of theatre and hospital stay ^b	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net financial impact to PHIs	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

PHI = private health insurer; PL = Prescribed List; RDN = renal denervation

a Assumes 5% of eligible patients do not proceed to RDN due to unsuitable renal anatomy.

b Includes theatre fees (\$2,186.92) and accommodation costs (\$647.65) for all patients, including those who receive renal imaging but not RDN.

Note: Assumes single use RDN catheters will be listed on the PL at a Benefit of **\$redacted**.

Source: Derived from Table 136 in MSAC 1659 ADAR+in-line commentary.

Costs for consumable items typically used in endovascular procedures are not incorporated in the estimates, nor are costs associated with vascular closure devices (used in approximately 69% of procedures and available on the PL).

15. Other relevant information

The ADAR described the substantial cost of HTN in Australia primarily in terms of the heightened risk of developing CVD or CKD and the resultant impact on healthcare expenditure and lost productivity. The ADAR noted the greater prevalence of HTN in lower socioeconomic and remote

areas, and the disparity experienced by Indigenous Australians who have higher rates of HTN, with a lower age of onset, than non-Indigenous Australians. The ADAR considered the potential for RDN, in conjunction with OMM, to address this disparity. One unpublished Medtronic study interviewed 10 patients that were willing to try an interventional procedure in the Australian setting, and found 90% of the interviewed patients were extremely willing to undergo RDN if recommended by their physician. However, the scope of addressing such a prevalent issue with RDN is constrained by the limited capacity of catheterisation laboratories and potentially by the capacity/uptake of providers performing the procedure, making it likely this intervention would be restricted to those at extremely high clinical need.

The commentary noted that the high out-of-pocket costs (particularly if the RDN catheter is not listed on the PL) is likely to be a significant barrier for low socioeconomic and indigenous groups.

Remote residents will have to travel considerable distances to access this hospital-based service.

The commentary speculated that patients who undergo RDN may be less inclined to adhere to OMM, thereby accruing the cost of the RDN procedure but not the potential benefit of OMM and adjunctive RDN.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- Renal denervation (RDN) with radiofrequency (RF) ablation appears to have non-inferior safety compared to similar procedures, including renal angiography, which was used as the “sham” procedure in the control arms of the blinded RCTs. However, there are no data available for patients with severe renal dysfunction and therefore MSAC may wish to consider excluding these patients from the intervention.
- RDN appears to have superior effectiveness compared with both sham procedure or no RDN procedure. The between-group differences of -4.08 mmHg for 'change from baseline mean office systolic blood pressure (OSBP)' and -1.92 mmHg for 'change from baseline in mean 24-hour ambulatory systolic blood pressure (ASBP)' were statistically significant. The treatment effect size of RDN in the clinical setting is likely to approach, but not exceed, the clinically relevant thresholds described by the European Clinical Consensus Conference and the Hypertension Academic Research Consortium. However, according to other published literature, including a meta-regression analysis of 55 randomised trials, positive cardiovascular health outcomes have been demonstrated from systolic blood pressure (SBP) reductions of this magnitude.
- The service should be limited to “once per lifetime” in the MBS item descriptor. The descriptor should also reference the use of a multidisciplinary team to assess patient suitability for the procedure and restrict use to the intended population.

Economic issues:

- The economic model is informed by a small, post-hoc subgroup of a single trial. MSAC may wish to consider the appropriateness of this approach, given there are other larger trials available with populations that appear to better fit the proposed population.
- Although registry and open label data are encouraging, the long-term results cannot be attributed to the effectiveness of RDN with any certainty given the evolving nature of anti-hypertensive treatment for these patients. The ICER varies considerably depending on the time horizon used.

- The choice of relative risks (for avoiding chronic heart disease, stroke and heart failure events) from the literature used in the model highly impacts the ICER. MSAC may wish to consider the importance of this uncertainty.

Financial issues:

- The pool of potential recipients is large, and the budget analysis assumes that service provision will be restricted by capacity constraints. However, these assumptions are highly uncertain. MSAC may wish to consider the reasonableness of these assumptions in light of the applicant's offer to explore a risk-sharing arrangement.

ESC discussion

ESC noted that this application from Medtronic Australasia Pty Ltd requested Medicare Benefits Schedule (MBS) listing of renal denervation (RDN) with a radiofrequency (RF) ablation catheter for the treatment of patients with specialist-confirmed treatment-resistant hypertension (TRHTN). ESC considered that specialist confirmed TRHTN is distinct from uncontrolled hypertension (HTN).

ESC noted that the applicant had previously submitted an application seeking MBS listing of RDN for TRHTN ([MSAC application 1338](#)). ESC noted the previous application was withdrawn before being considered by MSAC because, shortly after submitting MSAC application 1338, results from a single-blind, randomised, sham-controlled clinical trial (SYMPPLICITY HTN-3) became available, which failed to confirm a significant beneficial effect of RDN on blood pressure (BP) compared with the sham procedure. As a consequence of the outcome of the SYMPPLICITY HTN-3 trial, many programs for the development of various RDN devices were halted or suspended and MSAC application 1338 was withdrawn. ESC noted that since then more data has become available: long-term data from SYMPPLICITY HTN-3 and other trials, data from the Global SYMPPLICITY Registry (GSR) and recent randomised sham-controlled trials of RDN involving the next-generation SYMPPLICITY Spyral RDN system.

ESC noted the consumer feedback from Hearts4heart, which supported the application. The feedback suggested that RDN was a viable option for patients resistant to anti-hypertensive medication, who have exhausted all other alternatives and emphasised that this procedure would increase the quality of life for these individuals.

ESC noted that the applicant developed assessment report (ADAR) stated that the RDN catheter costs \$**redacted** and is currently not listed on the Prescribed List of Medical Devices and Human Tissue Products (PL). ESC noted that if the cost of the RDN catheter is not covered by private health insurance (because the device is not on the PL), this could result in significant and likely prohibitive out-of-pocket costs for patients. ESC also noted that access to the service may be an issue for patients in rural or remote areas.

ESC noted the proposed MBS item descriptor and considered that:

- “Applicable only once per lifetime” was appropriate for this procedure to ensure that denervation of both kidneys is performed at the same time
- the renal angiogram should be included in the service (i.e. not billed separately)
- a multidisciplinary team should be a part of the patient suitability assessment process, and that this should be specified in the MBS item descriptor to restrict use of the proposed service to the intended population. This is consistent with the advice in recent guidance released by the National Institute for Health and Care Excellence (NICE 2023), and the European Society of Cardiology Council on Hypertension and the European Association of Percutaneous Cardiovascular Interventions (ESC/EAPCI, Barbato 2023)

- it should include wording to indicate that the procedure is an in-hospital service with an “assistance component”.

ESC noted that the proposed MBS item fee was \$2,218.50, which was equivalent to the fee for atrial chamber ablation (MBS item 38287). ESC noted the Department’s suggestion that this comparison is inappropriate and that comparison with bilateral renal endarterectomy (MBS item 33527) is more suitable (fee of \$2,067.05). ESC noted that this fee difference did not have a large impact on the economic or financial analysis.

ESC noted the clinical management algorithm. The RDN procedure is preceded by an aortogram and selective renal angiogram to determine patient suitability; about 5% of patients are not suitable due to anatomical contraindications. For the remaining 95% that do progress to RDN, between 16–107 (average of 47) ablations are required to denervate both kidneys (derived from the SYMPLICITY Spyral trials). The total procedure requires approximately 1.5-2 hours to complete. ESC noted that it is not possible to check whether the kidneys have been successfully denervated during the procedure itself.

ESC noted that the clinical evidence presented in the ADAR comprised data from eight randomised controlled trials (RCTs):

- four sham-controlled studies: SPYRAL HTN-OFF MED, SPYRAL HTN-ON MED, SYMPLICITY HTN-3, ReSET
- four open-label studies: SYMPLICITY HTN-2, SYMPLICITY HTN-Japan, RDN OSA and DENER-HTN.

ESC agreed with the commentary that the SYMPLICITY HTN-3, ReSET and SPYRAL HTN-ON MED sham-controlled trials, excluding SPYRAL HTN-OFF MED, are the key evidence base for RDN. Results of SPYRAL HTN-OFF MED were considered supplementary evidence due to lack of alignment with the PICO and proposed MBS population.

ESC noted that all RCTs presented in the ADAR had a 3 - 6 month follow-up window. Longer term data beyond the randomised trial period was available, with up to 36 months of follow-up for four of these studies (pilot cohort of SPYRAL HTN-ON MED, SYMPLICITY HTN-3, SYMPLICITY HTN-2 and SYMPLICITY HTN-Japan). In addition, up to 10 years of long-term follow-up data was provided by the GSR, and other observational cohort studies. ESC, however, raised concerns regarding the reliability of the long-term data due to potential sampling bias caused by loss to follow up and limitations associated with extended follow-up in single arm studies, particularly in HTN intervention studies where outcomes are influenced by patient behaviour and medication changes.

Regarding comparative safety, ESC noted that the rates of major adverse events (MAE) were similar for the RDN procedure versus the sham control at one month (1.06%, n=6/568 for RDN versus 0.66%, n=2/301 for sham) and six months (2.66%, n=15/563 for RDN versus 2.69, n=8/297 for sham) timepoints. ESC agreed with the commentary’s assessment that the rates of adverse events in patients at high cardiovascular (CV) risk undergoing RDN were no more than what would be expected for patients with the baseline comorbidity profile, and that no significant increase in *de novo* renal artery stenosis or worsening kidney function was seen in long-term follow up beyond the expected rates in patients with HTN and reduced kidney function. ESC considered that the safety of RDN was non-inferior to similar procedures including renal angiography, which was used as the sham procedure in the blinded RCTs. However, ESC noted that people with stage 3 kidney disease were not included in the safety studies and that patients with an estimated glomerular filtration rate (eGFR) of <40-45 mL/min were excluded in the key RCTs. As such, ESC agreed with the commentary’s conclusion that patients with severely reduced kidney function have not been satisfactorily investigated in either the sham-controlled trials of

RDN or the GSR analyses. Therefore, ESC considered that the renal safety of RDN can only be considered to be non-inferior in patients with normal or mild-to-moderate reduced kidney function. ESC also considered that MSAC may wish to consider whether the criteria for MBS funding should be amended to specify that patients must have an eGFR of at least 45 mL/min in order to exclude patients with severely reduced kidney function, ensuring consistency with the evidence base.

For the comparative effectiveness assessment, ESC agreed with the ADAR that a change in systolic BP (SBP) is a more sensitive indicator of cardiovascular risk and future outcomes compared to diastolic BP and is consistent with the National Heart Foundation of Australia guidelines¹³ for the management of HTN in which most of the evidence is based on SBP. ESC also agreed with the ADAR that the key primary clinical outcome of relevance is office-based SBP (OSBP) rather than 24-hour ambulatory SBP (ASBP). ESC noted that OSBP can give false elevated readings due to the stress some patients experience in a clinician's office (known as white coat HTN). However, ESC considered that the office-based measurement is more appropriate for the Australian context, noting that ambulatory blood pressure measurement is not reimbursed under the MBS for patients with diagnosed HTN and that the Australian clinical guidelines also acknowledge that most of the studies providing evidence for management and treatment of HTN are based on office-based measurements. ESC noted a meta-analysis of the SYMPLICITY HTN-3 and SPYRAL HTN-ON MED RCTs, which compared RDN plus baseline medication compared to baseline medication alone. This found that the mean between-group difference in OSBP between the treatment arms was -4.08 mmHg at 3–6 months, favouring RDN. However, ESC agreed with the commentary that the data that best aligned with the PICO population was the meta-analysis of the SPYRAL HTN-ON MED subgroup that aligned with the PICO, along with the entire TRHTN population of SYMPLICITY HTN-3. In this meta-analysis performed by the commentary, the mean between-group difference in OSBP was - 3.57 mmHg (P=0.05). ESC noted a meta-analysis of the SYMPLICITY HTN-3, SPYRAL HTN-ON MED and ReSET RCTs which compared changes in 24-hour ASBP in RDN plus baseline medication compared to baseline medication alone. The mean between-group difference in 24-hour ASBP between the treatment arms was -1.92 mmHg at 3–6 months, again favouring RDN.

ESC noted that the ADAR reported reduction in SBP appeared to be maintained at 36 months, and perhaps even further reduced, compared with SBP measurements at 3–6 months post-intervention. However, ESC noted that the medication burden for patients in SPYRAL HTN-ON MED RCT showed a gradual increase in medication burden over time in both the RDN and sham control arms. ESC agreed with the commentary that this could at least partly account for the maintenance in treatment effect. ESC also agreed with the commentary's assessment that the long-term data are consistent with, but do not establish, durability of effect. Furthermore, as noted earlier, the long-term data could represent biased sampling. As such, ESC considered the ADAR's claim that the reduction in SBP, after RDN, continues to reduce over time was uncertain.

ESC noted the ADAR reported that data from the GSR (at 36 months) suggested that, in patients who underwent RDN, there was a 26% (all patients) and 34% (TRHTN patients) relative risk reduction for major adverse CV events, compared with patients receiving only standard of care therapy. ESC also noted that the ADAR reported an analysis of the GSR data on time in therapeutic BP range that indicated a longer time in the target range after RDN was associated with a lower incidence of stroke, myocardial infarction and CV death.

ESC noted that the commentary queried whether the difference in OSBP and ASBP reduction between RDN and sham was clinically meaningful (i.e., a mean difference of -3.57 mmHg for the

¹³ Chew D et al. (2016). "National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Management of Acute Coronary Syndromes 2016." *Heart, Lung and Circulation* 25(9): 895-951.

change in OSBP from baseline between the RDN and sham group). ESC agreed with the commentary, that if the thresholds described by the European Clinical Consensus Conference and the Hypertension Academic Research Consortium were applied then, the treatment effect size of RDN in the clinical setting is likely to approach, but not exceed, the clinically relevant thresholds. However, ESC also noted and agreed with the applicant's pre-ESC response that other studies (including a meta-regression analysis of 55 randomised trials¹⁴) have demonstrated positive cardiovascular health outcomes from a SBP reduction of this magnitude. Overall, ESC considered the mean between-group difference in OSBP of - 3.57 mmHg to be clinically meaningful and that the available clinical evidence demonstrated that RDN has superior effectiveness compared to either sham procedure or no RDN procedure.

ESC noted that the economic model was a cost-utility analysis from an Australian healthcare system perspective. Inputs for the base case were background event risks derived from published risk equations (function of population characteristics); and RDN treatment benefit (in the form of mean difference in OSBP [mmHg]) translated to relative risk of avoiding chronic heart disease, stroke and heart failure (HF) events, which were transformed to costs and quality-adjusted life-years (QALYs). The output was expressed as cost per QALY gained from RDN relative to optimal medical management. Each health state was modelled as "initial" and then post-event health states that were split into a further two states for some conditions (for example, stroke, HF, and stroke plus HF). ESC considered this to be a complex, but appropriate, model. ESC sought clarification from the evaluation group regarding the issue raised in the commentary that the ADAR model was based on but deviated from the Geisler et al. (2012) model and that the deviation resulted in "dual-application" of treatment effect. The evaluation group clarified that in Geisler et al. (2012), the outcome incidence was calculated for the intervention and comparator groups through application of risk equations (with SBP as one variable within these), which were then used to calculate a relative risk for each outcome as reported in these authors' paper. The ADAR used relative risks from the literature, which were then multiplied by the baseline probabilities for optimal medical management group (except for ESRD where the approach was replicated from the Geisler et al. (2012) model). The probabilities for the optimal medical management group were derived from cohort-based risk equations as described in the ADAR. This clarification indicated that the concern for dual application of the SBP treatment effect is reduced, although the optimal medical management probabilities are affected by the baseline SBP.

ESC noted that the incremental cost-effectiveness ratio (ICER) presented in the ADAR was **\$redacted** per quality adjusted life year (QALY). ESC noted the data used to inform treatment efficacy of RDN in the ADAR's economic model was based on post-hoc subgroup of patients who met the PICO criteria from the SPYRAL HTN-ON MED RCT. A mean between group difference in OSBP of -5.20 mmHg from baseline was observed for this subgroup, favouring RDN. However, ESC agreed with the commentary that it was more appropriate to use the treatment effect (-3.57 mmHg mean between-group difference in OSBP) from the meta-analysis of the SPYRAL HTN-ON MED subgroup with the entire TRHTN population of SYMPLICITY HTN-3. ESC noted that using the -3.57 mmHg treatment effect for RDN increased the ICER to **\$redacted**/QALY. Using mean between-group difference in OSBP from SYMPLICITY HTN-3 alone (-2.39 mmHg) increased the ICER to **\$redacted**/QALY.

ESC noted the ICERs generated from the sensitivity analyses conducted in the ADAR and by the commentary (see Table 16). The key drivers of the model were SBP reduction, the model time horizon, starting age of the model population and the risk ratio source underpinning the analysis.

¹⁴ Ettehad D et al. (2016). "Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis." *Lancet* 387(10022):957-967.

ESC queried whether the modelled time horizon of 35 years was reasonable when the starting age of patients in the model was 65.6 years, and that reducing the time horizon to 30, 20 and 15 years increased the ICER to **\$redacted**, **\$redacted** and **\$redacted**, respectively (see Table 16). ESC noted that costs and utility values were largely unimportant drivers, aside from the cost of the RDN catheter (**\$redacted**). A lower RDN catheter cost of \$3,700 was modelled in the commentary's sensitivity analysis, which reduced the ICERs substantially (**\$redacted** – **\$redacted** /QALY, depending on the OSBP reduction used). ESC also noted that some intervention costs were potentially excluded, such as possible overnight stays, the possible use of heparin and use of closure devices. However, since costs were not a major driver of the model, ESC considered that these omissions may be insignificant for decision-making. ESC noted other minor issues raised by the commentary, including potentially overestimating the costs related to heart failure treatment, but, again, ESC noted that these costs were not major drivers of the model.

ESC noted that the ADAR estimated the utilisation and financial impact using an epidemiological approach. The ADAR assumed that 50% of eligible patients would want to access the intervention based on preference studies (tested in sensitivity analyses). ESC noted the ADAR also claimed that utilisation of this intervention would be limited by the number of interventional cardiologists able to perform the procedure and capacity of catheterisation laboratories. However, ESC agreed with the commentary's observation that this claim is uncertain and does not take into consideration that other providers could perform RDN and in settings other than private catheterisation laboratories.

ESC noted that the ADAR estimated the financial impact to the MBS ranged from **\$redacted** in year 1 to **\$redacted** in year 6 using the ADAR's proposed 75% rebate, and from **\$redacted** in year 1 to **\$redacted** in year 6 using the Department's suggested lower 75% rebate (i.e., equivalent to MBS item 33527 - bilateral renal endarterectomy). ESC noted the commentary also presented an alternative, although likely highly unrealistic, sensitivity analysis that explored the cost to the MBS if there were no supply constraints, which indicated the net costs to the MBS would be more than **\$redacted** in year 1. ESC highlighted that the largest budget impact would be to private health insurers due to the cost of the catheter (**\$redacted**) and hospital stays (about **\$redacted** in year 1 to **\$redacted** in year 6). ESC noted the ADAR stated the applicant is willing to explore a risk-sharing arrangement in acknowledgement of the uncertain utilisation estimates.

17. Applicant comments on MSAC's Public Summary Document

Medtronic Australasia is disappointed with MSAC's decision to not support public funding of its catheter-based RDN for the treatment of patients with True Resistant HTN (TRHTN) with uncontrolled elevated systolic blood (SBP; ≥ 150 mmHg) and/or elevated diastolic blood pressure (DBP; ≥ 110 mmHg) despite optimal medical management (OMM). Medtronic Australasia is of the firm belief that the evidence presented represents the best level evidence available for its RF-RDN technology however acknowledges the inherent limitations with conducting a sham controlled RCT in the hypertension device therapy area. We were pleased that MSAC considered that further defining the patient population to identify patients who may represent a higher clinical need for RDN and most likely to benefit from the intervention, may provide a way forward for RF-RDN. The current level of adoption of the Symplicity™ Spyral RF-RDN System by Interventional Cardiologists and referral physicians within Australia demonstrates the value of the technology. Medtronic Australasia continues to be fully committed to working with clinicians to support patient access to this important innovation in the treatment of resistant hypertension.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)