Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number:	TER316
Topic:	Radiofrequency renal denervation for the treatment of resistant hypertension.
Summary of findings:	National Institute for Health and Care Excellence (NICE) interventional procedures guidance 418 (IPG418) evaluated the efficacy and safety of percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension (NICE 2012). It recommended that this procedure for renal denervation should only be used with special arrangements for clinical governance, consent, and audit or research. This topic exploration report identified one rapid assessment report, one Cochrane review, nine systematic reviews and one economic evaluation on radiofrequency renal denervation for the treatment of resistant hypertension. These varied in their overall objective and the treatments they compared renal denervation against. The main outcomes measured were 24-hour ambulatory and office systolic and diastolic blood pressure. A EUnetHTA (2013) report and two systematic reviews with metanalysis (Dahal et al. 2019, Silverwatch et al. 2021) reported renal denervation as a successful treatment to reduce 24-hour ambulatory and office blood pressure, whilst a Cochrane review (Coppolino et al. 2017) and one SR with metanalysis (Agasthi et al. 2019) reported non statistically significant reduction of both 24-hour ambulatory and office blood pressure. Some sources also highlighted that the available data regarding outcomes other than changes in blood pressure, such as overall and cardiovascular mortality, hospitalization and quality of life, were relatively scarce (Coppolino et al. 2017, EUnetHTA 2013, Silverwatch et al. 2021). One UK health economic study concluded that renal denervation for resistant hypertension might be cost-effective (Gladwell et al. 2014).

Introduction and aims

High blood pressure or hypertension is a very common condition affecting one in three adults in the UK. Higher levels of blood pressure (i.e., uncontrolled hypertension) might increase risks of cardiovascular disease, such as heart attack, stroke or other health issues. Lifestyle changes, such as diet and exercise, and antihypertensive medications might support a person with uncontrolled hypertension to keep their blood pressure at a safe level. Resistant hypertension refers to high blood pressure that remains uncontrolled and has not responded to lifestyle changes and optimal tolerated doses of three antihypertensive medications.

Renal denervation is an option to treat resistant hypertension and can be carried out via radiofrequency or ultrasound energy. In this report, we are only focusing on radiofrequency renal denervation therapy, which is a catheter-based procedure aiming to achieve blood pressure control. It involves radiotherapy ablation to burn the nerves in the renal arteries causing a reduction in the nerve activity, which decreases blood pressure. To date there are several renal denervation systems using radiofrequency, such as the Simplicity Spyral Renal Denervation (Medtronic) which is commercially available in Europe.

Health Technology Wales (HTW) researchers searched for evidence on the clinical and cost effectiveness of renal denervation for resistant hypertension treatment compared to usual care, which includes lifestyle interventions and/or a combination of antihypertensive medication.

Evidence overview

Guidance

In 2012, the National Institute for Health and Care Excellence (NICE) produced interventional procedures guidance (IPG418) on the efficacy and safety of percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension (NICE 2012). The IPG418 recommendations concluded that the existing evidence is from limited numbers of patients, but there is efficacy evidence both in the short and medium term. However, the IPG states that there is insufficient efficacy evidence in the long-term. The limited evidence available suggests a low incidence of serious periprocedural complications, but there is inadequate evidence on long term safety. Thus, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research (NICE 2012).

Health Technology Assessments (HTA)

We identified one rapid assessment by the European Network for health Technology Assessment (EUnetHTA) focusing on the safety and clinical effectiveness of renal denervation systems for treatment resistant hypertension (EUnetHTA 2013).

Regarding the safety of renal denervation, EUnetHTA (2013) included three randomised control trials (RCTs), three non-RCTs and sixteen case series. Similar to IPG418 (NICE 2012), the EUnetHTA (2013) report concluded that this procedure is safe in the short and medium term, but no conclusions were drawn on the likelihood of long-term complications due to inadequate follow-up lengths. In some studies, one of the main renal denervation complications was unwanted effects on post-procedure blood pressure, which can lead to hypotensive or hypertensive episodes requiring hospitalisation.

Regarding the clinical effectiveness of renal denervation, the EUnetHTA (2013) report included three systematic reviews, three RCTs and one non-RCT studies focusing on outcomes of overall mortality,

cardiovascular morbidity and blood pressure, as well as quality of life and patient satisfaction. According to EUnetHTA (2013), renal denervation appears to decrease blood pressure, thus patients expressed preference towards this procedure. Assessment of overall mortality and cardiovascular mortality remained inconclusive as the examined trials included a small number of participants.

Cochrane review

We identified one Cochrane review entitled 'Renal denervation for resistant hypertension' by Coppolino et al. (2017). They included 12 studies, four of which compared renal denervation to a sham procedure, one compared a proximal ablation to a complete renal artery denervation and seven compared renal denervation to usual or intensified antihypertensive therapy. Similarly to the HTA sources, Coppolino et al. (2017) found that there was no conclusive evidence that renal denervation improves cardiovascular morbidity and mortality in comparison to usual treatment. They also found that renal denervation did not reduce the ambulatory and office blood pressure when compared to usual therapy or sham. However, renal denervation was associated with an increased risk of episodes of very slow heart rate (i.e., bradycardia). Coppolino et al. (2017) reported that the quality of evidence was low for adverse events and cardiovascular outcomes and moderate for lack of effect on renal function and blood pressure, while data for all-cause mortality, fatal cardiovascular events, hospitalisation and quality of life were sparse or absent.

Systematic reviews

Based on the evidence identified above, we searched for evidence on the clinical effectiveness of renal denervation that was published between 2017 to present. We identified nine systematic reviews related to the clinical effectiveness of renal denervation for the treatment of resistant hypertension. In this report, we focus on the three most recent systematic reviews with metanalysis (Agasthi et al. 2019, Dahal et al. 2019, Silverwatch et al. 2021). The remaining six systematic reviews are provided in the literature search results below.

Two of the three most recent systematic reviews (Dahal et al. 2019, Silverwatch et al. 2021) are potentially partially applicable as they evaluated renal denervation in both uncontrolled and resistant hypertension (see Areas of Uncertainty below) compared to other treatment(s) or sham. The remaining systematic review (Agasthi et al. 2019) assessed the effect of renal denervation on blood pressure and renal function in resistant hypertension compared to medical therapy.

Overall, Dahal et al. (2019) and Silverwatch et al. (2021) reported that renal denervation significantly reduced the 24-hour and daytime ambulatory systolic and diastolic blood pressure in resistant hypertension compared to other treatments or sham. However, Agasthi et al. (2019) reported insignificant 24-hour ambulatory blood pressure benefits with renal denervation in resistant hypertension across all included studies, whilst a subgroup analysis of sham-controlled studies demonstrated a modest benefit in 24-hour ambulatory systolic blood pressure at six months with renal denervation.

Both Dahal et al. (2019) and Silverwatch et al. (2021) also reported that renal denervation significantly reduced the office diastolic blood pressure versus other treatment(s) or sham, while Agasthi et al. (2019) found non-significant reductions in the office diastolic blood pressure between renal denervation and medical interventions. Silverwatch et al. (2021) reported that renal denervation significantly reduced systolic office blood pressure, while Agasthi et al. (2019) and Dahal et al. (2019) found non-statistically significant reductions in the same metric when compared to other treatments or sham. Agasthi et al. (2019) also reported a non-statistically significant effect of renal denervation on renal function compared to medical therapy.

Additionally, Silverwatch et al. (2021) reported that there were insufficient data regarding overall and cardiovascular mortality as well as hospitalisation aligning with previous systematic reviews, including the Cochrane review by Coppolino et al. (2017) provided in this report. They also identified some concerns of bias for most the RCTs included in terms of outcome measurements, missing data outcomes and reported results selection (Silverwatch et al. 2021).

Economic evaluations

We identified one study (Gladwell et al. 2014) about the cost-effectiveness of renal denervation for resistant hypertension in the UK.

Gladwell et al. (2014) developed a Markov health-state economic model with a lifetime horizon. The model associated reductions in systolic blood pressure after renal denervation with reduced cardiovascular risks and renal complications. They concluded that renal denervation led to an improved health benefit over a patient's lifetime in comparison to antihypertensive medication only (12.77 vs. 12.16 discounted quality adjusted life years). They modelled additional lifetime costs per patient at £2,961 which were equivalent to an incremental cost per quality-adjusted life-year of £4,805.

Areas of uncertainty

Renal denervation has been the subject of previous health technology appraisal and economic evaluation, but the sources identified are several years old and may have been superseded by newer evidence. Furthermore, although these sources indicate that technology appraisal is feasible, the population/condition for any future appraisal needs to be carefully and clearly defined. Distinction between uncontrolled and resistant hypertension for renal denervation might be necessary. In this report, we focused on resistant hypertension as it refers to high blood pressure that cannot be brought under control by lifestyle and medication. This might influence the available evidence.

There is also lack of existing evidence synthesis regarding other outcomes beyond blood pressure. Although, there might be sources available to evaluate other outcomes such as cardiovascular morbidity and mortality, it is possible that they might not be as well-evidenced as blood pressure.

In addition to this, it is important to investigate what are the current and available care options for these patients in Wales. Thus, the most appropriate comparators need also to be carefully and clearly defined if appraisal proceeds. This might also influence the available evidence.

Although studies evaluating the cost effectiveness in the UK have been identified, if this topic proceeds to appraisal, an economic evaluation would be needed to clarify the cost effectiveness of this procedure in Wales and whether de novo economic modelling is feasible.

Literature search results

Health technology assessments and guidance

EUnetHTA. (2013). Renal denervation systems for treatment-resistant hypertension. Rapid assessment of other health technologies such as medical devices, surgical interventions or diagnostics WP5-SB-12. European Network for Health Technology Assessment. Available at: https://www.eunethta.eu/second-pilot-rapid-assessment-on-renal-denervation-systems-for-treatment-resistant-hypertension/ [Accessed 11 Oct 2021].

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Evidence reviews and economic evaluations

Agasthi P, Shipman J, Arsanjani R, et al. (2019). Renal Denervation for Resistant Hypertension in the contemporary era: A Systematic Review and Meta-analysis. Scientific reports. 9(1): 6200. https://doi.org/10.1038/s41598-019-42695-9

Coppolino G, Pisano A, Rivoli L, et al. (2017). Renal denervation for resistant hypertension. The Cochrane database of systematic reviews. 2: CD011499. https://doi.org/10.1002/14651858.CD011499.pub2

Dahal K, Khan M, Siddiqui N, et al. (2019). Renal denervation in the management of hypertension: A meta-analysis of sham-controlled trials. Cardiovascular revascularization medicine : including molecular interventions. 21(4): 532-7. https://doi.org/10.1016/j.carrev.2019.07.012

Kordalis A, Tsiachris D, Pietri P, et al. (2018). Regression of organ damage following renal denervation in resistant hypertension: a meta-analysis. Journal of Hypertension. 36(8): 1614-21. https://doi.org/10.1097/HJH.0000000000001798

Pappaccogli M, Covella M, Berra E, et al. (2018). Effectiveness of Renal Denervation in Resistant Hypertension: A Meta-Analysis of 11 Controlled Studies. High blood pressure & cardiovascular prevention : the official journal of the Italian Society of Hypertension. 25(2): 167-76. https://doi.org/10.1007/s40292-018-0260-5

Silverwatch J, Marti KE, Phan MT, et al. (2021). Renal Denervation for Uncontrolled and Resistant Hypertension: Systematic Review and Network Meta-Analysis of Randomized Trials. Journal of clinical medicine. 10(4): 1-14. https://doi.org/10.3390/jcm10040782

Vuignier Y, Grouzmann E, Muller O, et al. (2018). Blood Pressure and Renal Responses to Orthostatic Stress Before and After Radiofrequency Renal Denervation in Patients with Resistant Hypertension. Frontiers in cardiovascular medicine. 5: 42. https://doi.org/10.3389/fcvm.2018.00042

Wang S, Yang S, Zhao X, et al. (2018). Effects of Renal Denervation on Cardiac Structural and Functional Abnormalities in Patients with Resistant Hypertension or Diastolic Dysfunction. Scientific reports. 8(1): 1172. https://doi.org/10.1038/s41598-017-18671-6

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Gladwell D, Henry T, Cook M, et al. (2014). Cost Effectiveness of Renal Denervation Therapy for the Treatment of Resistant Hypertension in the UK. Applied Health Economics and Health Policy. 12(6): 611-22. https://doi.org/10.1007/s40258-014-0116-7

Mahfoud F, Mancia G, Schmieder R, et al. (2020). Renal Denervation in High-Risk Patients With Hypertension. Journal of the American College of Cardiology. 75(23): 2879-88. https://doi.org/10.1016/j.jacc.2020.04.036

Sardar P, Bhatt DL, Kirtane AJ, et al. (2019). Sham-Controlled Randomized Trials of Catheter-Based Renal Denervation in Patients With Hypertension. Journal of the American College of Cardiology. 73(13): 1633-42. https://doi.org/10.1016/j.jacc.2018.12.082

Date of search:	October 2021
Concepts used:	resistant hypertension; renal denervation