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NHS England

Clinical Commissioning Policy Proposition:

Renal denervation for Resistant Hypertension

Reference: NHS England A09X02/01

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Plain Language Summary

This policy proposition outlines NHS England's approach for the use of renal denervation for patients with resistant hypertension.

High blood pressure is not something that you can usually feel or notice. While the heart needs a level of pressure in the blood vessels to pump blood around the body to deliver energy and oxygen, if this pressure is too high, it puts extra strain on the arteries and heart. This can lead to serious conditions such as heart attack, heart failure, kidney disease, stroke, or dementia.

There are several ways to reduce blood pressure. For most patients, changes in lifestyle such as eating less salt or losing weight are enough to manage the risks. However, for others, medication may be required.

Resistant hypertension is defined as blood pressure that remains high despite treatment with three or more antihypertensive medications. It is an especially dangerous chronic condition because of its association with increased cardiovascular risk, including stroke, and heart attack as well as heart failure and kidney disease.

The renal nerves act to communicate information between the kidney and the brain and have a role in controlling blood pressure. Renal denervation is a clinical procedure where nerves in the patient's kidneys are deliberately damaged. There is clinical interest in renal denervation as a possible treatment for individuals with resistant hypertension.

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of renal denervation for resistant hypertension.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission renal denervation.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether renal denervation for resistant hypertension will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

Hypertension, also known as high blood pressure, is a chronic medical condition in which the blood pressure in the arteries is persistently elevated. This puts extra strain on the arteries and heart, which can lead to serious conditions such as heart attack, heart failure, kidney disease, stroke, or dementia.

There are several ways to reduce blood pressure. For most people, changes in lifestyle such as eating less salt or losing weight can be sufficient to reduce the risks. Some individuals however, will require medication with one or more antihypertensive medications.

There are a small number of people who will still not be able to reduce their blood pressure to normal levels (a "clinic" systolic blood pressure of <160 mm Hg). At the point where they have tried three or more of the conventional antihypertensive agents they will be diagnosed with resistant hypertension.

It is known that the renal nerves (sympathetic nerves) can be a main cause of hypertension when they become overactive. The renal denervation procedure inserts a device through the groin to deliver radiofrequency energy to deaden the nerves associated with the renal arteries. There is clinical interest as to whether renal denervation may be effective as a treatment option for individuals with drug-resistant hypertension.

3. Definitions

Resistant hypertension is defined as when an individual cannot control their blood pressure despite the use of at least three antihypertensive agents.

Renal denervation is a minimally invasive procedure during which a device is inserted through the groin to deliver radiofrequency energy to the nerves in the wall of the renal arteries; damaging (or ablating) these nerves may be a method to reduce blood pressure.

4. Aim and objectives

This policy proposition aims to define NHS England's commissioning position on renal denervation as part of the treatment pathway for adult patients with resistant hypertension.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with resistant hypertension.

5. Epidemiology and needs assessment

The 2010 Health Survey for England estimated that the prevalence of hypertension in adults of 16 years or older was 31.5% in men and 29.0% in women [1]. Diagnosis is, however, recognised as being complicated by several factors, not least because high blood pressure often does not have any symptoms and can only be established through a blood pressure check. Added to this, for some individuals, having health concerns may, in itself, cause the blood pressure to increase prior to examination which can lead to a misleading result. When seeking to establish resistant hypertension, it is also difficult to clearly evidence that individuals are taking their antihypertensive medications correctly.

It is known that there are a number of risk factors that increase the risk of high blood pressure, including:
a) age (risk increases significantly for those over the age of 65)
b) obesity
c) familial history
d) among individuals of African or Caribbean descent
e) diet – excess salt, caffeine, alcohol and not enough fruit and vegetables
g) low levels of exercise
h) smoking

Post hoc analyses of large scale trials of antihypertensive medications plus retrospective cross sectional observational studies point to a prevalence of resistant hypertension of 10-20% of the general hypertensive population [2].

Studies indicate that 5-10% of resistant hypertension patients have an underlying secondary cause for their elevated blood pressure—a prevalence significantly greater than that of the general hypertensive population [2].

Patients with resistant hypertension are almost 50% more likely to experience an adverse cardiovascular event compared with patients with blood pressure controlled by three or fewer antihypertensive agents [2].

6. Evidence base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of renal denervation for resistant hypertension.

This evidence review has sought to address the following research questions:

Research question 1: Is renal denervation clinically effective in patients with resistant hypertension (RH)?
Research question 2: Is renal denervation cost effective in patients with resistant hypertension (RH)?

In summary, the current evidence base is inconclusive for the clinical effectiveness of renal denervation (RDN) over current standard of care treatments for resistant hypertension with the more recent randomised control trial and meta-analysis indicating nil to modest impact of RDN on lowering blood pressure.

Question 1. Is renal denervation clinically effective in patients with resistant hypertension?

Early studies from 2010 onwards suggested that renal denervation (RDN) was a more clinically effective method of treatment than standard of care pharmacological interventions for patients with resistant hypertension (RH) (Bhatt et al., 2011, Esler et al., 2011). Meta-analyses based on such studies therefore found a significant effect in RH patients treated with RDN, which, added to the high levels of safety reported, resulted in general support for the use of this technology (Howard et al., 2013, Davis et al., 2013). More recently, Azizi et al., (2015) also showed a significant result in RDN patients against a control population that received stepped-care anti-hypertensive treatment).

The effectiveness of RDN was most recently challenged by the PRAGUE-15 trial (Rosa et al., 2015), which reported no significant benefits of RDN over an intensified pharmacological regimen including spironolactone. However, these RCTs were non-blinded, which made it difficult to ascertain the extent of the placebo effect (Jin et al., 2014). Therefore, SYMPLICITY HTN-3, a blinded RCT with a control group that received a placebo procedure (angiogram in lieu of renal denervation), was much anticipated.

In 2014, the 6-month results from the SYMPLICITY HTN-3 trial were published (Bhatt et al., 2014), and it reported that RDN produced insignificant reductions in both office and ambulatory systolic blood pressure. This data, however, was not immediately conclusive. Howard et al. (2013) concluded that even if results from this blinded RCT were to report lower blood pressure reductions than expected, a significant clinical impact would still be felt as long as blood pressure drops were in the region of 10 - 16 mm Hg.

Recently, the 12-month ambulatory blood pressures from the SYMPLICITY HTN-3 trial were published (Bakris et al., 2015). Ambulatory blood pressures are regarded as a more accurate measure compared to office blood pressure due to elimination of the white coat effect and averaging over 24 hours. The 6-month and 12-month results together paint an inconclusive story. Interestingly, the blinded trial produced no significant difference from the placebo - the difference in systolic blood pressure (SBP) reduction at 12 months was −2.39 mm Hg, which would itself suggest that the RDN procedure is not clinically effective (Bhatt et al., 2014, Bakris et al., 2015). However, unlike previous trials, patients in the placebo group actually responded to the control (placebo) procedure, with systolic blood pressure (SBP) drops of −11.74±25.94 mm Hg in the sham control group at 6 months (Bhatt et al., 2014). This could be due to the Hawthorne effect, where patient medication adherence is improved in both study arms (Kwok et al., 2014). Meanwhile, the RDN group registered an SBP drop of −14.13±23.93 mm Hg at 6 months (Bhatt et al., 2014) and 15.5 +/- 24.1 mm Hg at 12 months (Bakris et al., 2015). Although the differences were not significant between the RDN and placebo group the magnitude of the drop falls within the range that Howard et al. (2013) indicated would be clinically meaningful.

Siagian et al. (2014) stated that the limitations of SYMPLICITY HTN-3 trial included the regression-to-mean phenomenon, a lower baseline blood pressure than other studies in the past (159.1 mm Hg vs 180 mm Hg), and that there were no measurements taken to affirm the extent of the renal denervation and that the operators were inexperienced, although the authors of the study (Bhatt et al., 2014) claimed that operators who had operated five times

on patients did not produce better blood pressure results in the last operation compared to the first.

Patients in the SYMPLICITY HTN-3 trial also consumed higher amounts of the antihypertensive medication spironolactone (Kwok et al., 2014), which acts mechanistically similar to RDN (Pancholy et al., 2014). Such vasodilators have been shown to be a predictor for non-response in renal denervation procedures (Siagian et al., 2014). In addition, no urine test was taken to verify patient medication adherence, and results from this trial are only strictly applicable to catheters using the same radiofrequency-based technology found in the Simplicity catheters manufactured by Medtronic, and may not be directly translatable for ultrasound ablation catheters such as PARADISE (ReCor Medical, Ronkoma, New York) due to the unipolar nature of the SYMPLICITY system, which makes it more technically difficult to ensure circumferential ablation compared to more modern multipolar systems (Kwok et al., 2014).

Fadl et al., 2015 have reported a high quality meta-analysis of the data from 7 recently published randomized controlled trials (SYMPLICITY HTN-2 SYMPLICITY HTN-3 OSLO RDN PRAGUE-15 DENERHTN SYMPLICITY-FLEX SYMPLICITY HTN-Japan) which provides conclusive evidence that RDN is effective in a carefully selected patient sub-populations (stage I–II hypertension, low risk factor profile and evidence of sympathetic overactivity). The BP-lowering effect of RDN on top of continued or optimized antihypertensive drug treatment is modest, averaging 4.9 mmHg systolic and 3.5 mmHg diastolic on office measurement, and 2.8 mmHg systolic and 1.5 mmHg diastolic on 24 h ambulatory monitoring in the short term.

The current evidence base therefore fails to provide conclusive evidence in favour of RDN's clinical effectiveness over current standard of care treatments for resistant hypertension.

Question 2. Is renal denervation cost effective in patients with resistant hypertension?

There is only one paper in the literature search that provided evidence for the cost effectiveness of renal denervation in the context of resistant hypertension. Gladwell et al., 2014 concluded that RDN resulted in a greater health benefit to the patient compared to standard of care pharmacological intervention alone, extending QALYs from 12.16 to 12.77. This added health benefit came at a cost of £4805 per QALY. However, Gladwell et al., 2014 published their findings in the same year as the publication of SYMPLICITY HTN-3 trial results but were not able to include these results in their economic model. Given the reported lack of clinical effectiveness in SYMPLICITY HTN-3 (Bhatt et al., 2014, Bakris et al., 2015), the cost effectiveness of this treatment likely to impact the cost-effectiveness analysis. An updated model including results from this blinded RCT is needed before the cost effectiveness of RDN for RH can be accurately ascertained.

7. Documents which have informed this policy proposition

[1] Department of Health: Health Survey for England - 2010, Trend tables [NS]. Published date: 15 December 2011
[2] BMJ 2012; 345 doi: http://dx.doi.org/10.1136/bmj.e7473. Published date: 20 November

2012
[3] Hypertension in adults: diagnosis and management NICE guidelines [CG127] Published date: August 2011
[4] Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension NICE interventional procedure guidance [IPG418] Published date: January 2012
[5] Clinical Commissioning Policy Statement: Renal Denervation for Resistant Hypertension. April 2013. Reference: NHSCB/A09/PS/d

8. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).