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Joint UK societies' 2019 consensus statement on renal denervation

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EXECUTIVE SUMMARY/ABSTRACT

Improved and durable control of hypertension is a global priority for healthcare providers and policymakers. There are several lifestyle measures that are proven to result in improved blood pressure (BP) control. Moreover, there is incontrovertible evidence from large scale randomised controlled trials (RCTs) that antihypertensive drugs lower BP safely and effectively in the long-term resulting in substantial reduction in cardiovascular morbidity and mortality. Importantly, however, evidence is accumulating to suggest that patients neither sustain long-term healthy behaviours nor adhere to lifelong drug treatment regimens and thus alternative measures to control hypertension warrant further investigation. Endovascular renal denervation (RDN) appears to hold some promise as a non-pharmacological approach to lowering BP and achieves renal sympathectomy using either radiofrequency energy or ultrasound-based approaches. This treatment modality has been evaluated in clinical trials in humans since 2009 but initial studies were compromised by being non-randomised, without sham control and small in size. Subsequently, clinical trial design and rigour of execution has been greatly improved resulting in recent sham-controlled RCTs that demonstrate short-term reduction in ambulatory BP without any significant safety concerns in both medication-naïve and medication-treated hypertensive patients. Despite this, the joint UK societies still feel that further evaluation of this therapy is warranted and that RDN should not be offered to patients outside of the context of clinical trials. This document reviews the updated evidence since our last consensus statement from 2014 and provides a research agenda for future clinical studies.

antihypertensive drug treatment regimens.² Of late, there has been increasing focus on interventional measures to combat uncontrolled hypertension and a variety of novel technologies are currently being evaluated in clinical trials.³ These include sympathomodulatory approaches such as renal denervation (RDN), baroreflex activation therapy and endovascular baroreflex modulation: of these RDN has been the focus of greatest interest and research and our consensus statement is limited to consideration of this therapeutic approach.

Initial studies using radiofrequency (RF) RDN indicated some promise for the therapy in patients with resistant hypertension (RHTN) leading to a joint UK societies (JUKS) 2012 consensus statement recommending that RDN be considered as an additional component of the National Institute for Health and Care Excellence (NICE) hypertension treatment algorithm at step 5.⁴⁻⁶ This meant that RDN would only be considered as a 'standard of care' invasive approach to treat RHTN in patients who had failed to respond to conventional pharmacological measures and who were managed by hypertension experts. In the UK, plans were in place to cautiously adopt RDN via the 'commissioning through evaluation' approach that had been successfully utilised in the case of transcatheter aortic valve replacement therapy in order to prevent widespread uptake of a potentially expensive and not yet fully tested therapy for which the long-term risks were not established. However, these plans were halted following the publication of the SYMPPLICITY HTN-3 randomised controlled study which failed to show a benefit of RF RDN over sham therapy in patients with RHTN.⁷

The publication prompted the JUKS to reconvene to produce a 2014 consensus statement which placed a moratorium on the use of RDN in routine clinical practice in the UK until further favourable evidence had emerged.⁸ The consensus statement outlined a number of failings of the clinical studies of RDN to date, as well as making a series of recommendations for future studies. These recommendations were reiterated and expanded on in international guidance derived from the European Clinical Consensus Conferences with both documents taking into account recent research findings which gave greater detail of renal nerve microanatomy in humans,

BACKGROUND AND SCOPE OF THE CONSENSUS STATEMENT

High blood pressure (BP) is the most important risk factor for cardiovascular (CV) disease globally and a major threat to society's well-being, despite improved awareness and treatment of uncontrolled hypertension.¹ While lifestyle modification and pharmacotherapy are effective in improving BP control and lowering the risk of CV events, there is increasing recognition that patients may not be able to sustain healthy behaviour in the long term nor do they always maintain persistent adherence to



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improved technical approaches for RDN and meticulous attention to rigorous trial design and execution in order to eliminate medication instability, BP variability and procedural inadequacy while mandating use of blinded end points (ambulatory systolic blood pressure (ASBP)).^{9,10} This led to new and improved clinical trials of RDN utilising input from experts in the field to lead on both the design and execution of the studies in collaboration with commercial sponsors. Several of these proof-of-principle studies have now been presented and published and they demonstrate the short-term efficacy and safety of endovascular RDN performed using RF or ultrasound (US) energy; JUKS now consider the new evidence that they provide.

SPYRAL STUDY PROGRAMME

Early RDN studies were performed using a unipolar catheter (Symplicity Flex; Medtronic, Galway, Ireland) delivering 4–6 focal ablation points per renal artery with RF energy. Subsequently, Medtronic iterated the design of the catheter to provide circumferential ablation while appreciating the newly established distribution of periarterial renal nerves.¹¹ Furthermore, the procedural approach was refined to ensure RF energy was applied more distally in the renal artery including branch/accessory artery denervation.^{12–14} The newly evolved Spyral multielectrode RF catheter (Medtronic, Galway, Ireland) paired with the Symplicity G3 RF RDN generator (Medtronic, Minneapolis, MN, USA) was put to the test in the SPYRAL study programme which initiated a global, multicentre approach to studying RDN in hypertensive patients.¹⁵

SPYRAL HTN-OFF MED

This multicentre, prospective, randomised, controlled, single-blind study of RDN recruited patients from 21 centres in the USA, Europe, Australia and Japan.¹⁶ The design was a non-powered proof-of-concept trial with prespecified analyses at 40, 60, 80 and 100 patients as it was felt that the reduction in BP and variability of the ASBP primary endpoint were not known in this hitherto untested patient group with mild-to-moderate hypertension. Patients between the age of 20 and 80 years were selected with office systolic blood pressure (SBP) of 150–180 mm Hg and office diastolic blood pressure (DBP) \geq 90 mm Hg. The study participants were also required to have 24 hours mean ASBP of 140–170 mm Hg at initial screening and following a medication washout period of 3–4 weeks. Evaluation of medication usage was undertaken using tandem high-performance liquid chromatography (HPLC) and mass spectroscopy of urine and plasma samples by an independent laboratory. Patients who fulfilled inclusion criteria underwent a renal angiogram to ensure anatomical enrolment criteria were met and then were randomised on a 1:1 basis to RDN versus sham therapy. Great efforts were made to ensure adequate blinding of patients including use of conscious sedation, sensory isolation (with blindfolding and

music) and successful blinding was confirmed with the use of an established blinding index.¹⁷

The Symplicity SPYRAL catheter was used to provide circumferential four quadrant RF RDN undertaken by a single operator in each trial centre (to minimise procedural variability) and with proctoring. All accessible renal arteries, branches and accessory arteries in a size range of 3–8 mm were targeted according to detailed prespecified treatment plans that were agreed between operators and expert proctors, who were present to ensure a standardised treatment approach within each procedure.

Patients were required to remain off antihypertensive medication for a period of 3 months following randomisation. In all 353 patients were enrolled of whom 80 were randomised to RDN (n=38) or sham (n=42); baseline clinical characteristics did not differ significantly between the groups. In the RDN group, patients received on average 43.8 ± 13.1 ablations in total with the majority of ablations directed to the branch vessels (25.9 ± 12.8) as compared with the main arteries (17.9 ± 10.5). This represents four times the number of ablations delivered to each patient in Symplicity HTN-3. Despite great care being taken to ensure medication stability throughout the study, three patients in the RDN group and five patients in the control group were found to be taking antihypertensive medication at baseline according to the results of drug testing. Overall compliance with the requirement to be off medication throughout the study was 85%.

The first interim analysis at 3 months postrandomisation showed a significant reduction in both office and ambulatory BP (ABP) in the RDN group: 24 hours ASBP -5.5 mm Hg (95% CI -9.1 to -2.0 ; $p=0.0031$), 24 hours ambulatory DBP (ADBP) -4.8 mm Hg (-7.0 to -2.6 ; $p<0.0001$), office SBP -10.0 mm Hg (-15.1 to -4.9 ; $p=0.0004$) and office DBP -5.3 mm Hg (-7.8 to -2.7 ; $p=0.0002$)¹⁶ (figure 1). There were no significant changes in the sham group and thus the mean difference between the groups favoured RDN for both office and 24 hours ABP (ABP) reduction from baseline with baseline-adjusted analyses also confirming these findings. Marked heterogeneity of BP response was noted in both treatment and sham control groups and more than half of the RDN group exhibited reduction in 24 hours ASBP of >10 mm Hg. Importantly, no major procedural or clinical safety events were noted in either group throughout the 3 months.

Figure 1 24 hours ambulatory systolic blood pressure reduction in Spyral HTN-OFF MED and HTN-ON MED, RADIANCE-HTN SOLO and SYMPPLICITY HTN-3 randomised clinical trials. Data shown as mean \pm SEM. Δ , change from baseline; ASBP, ambulatory systolic blood pressure; RDN, renal denervation.

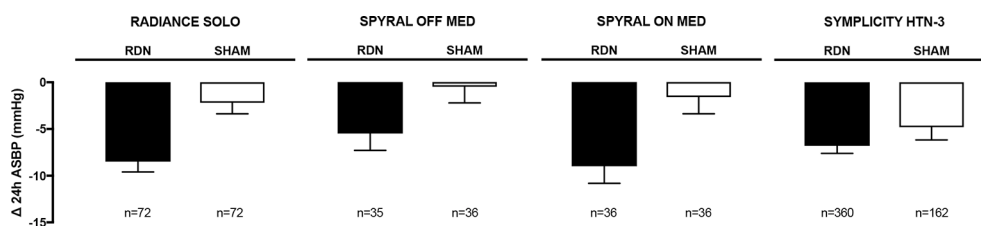


Figure 1 24 Hour ambulatory systolic blood pressure reduction in Spyral HTN-OFF MED and HTN-ON MED, RADIANCE-HTN SOLO and SYMPPLICITY HTN-3 randomized clinical trials. Data shown as mean \pm SEM. (Δ =change from baseline; ASBP=Ambulatory systolic blood pressure; RDN=renal denervation).

SPYRAL HTN-ON MED

In this global multicentre randomised sham-controlled study, the investigators aimed to assess the safety and efficacy of RF RDN in patients between the ages of 20 and 80 years with mild-to-moderate hypertension already on treatment with 1-to-3 standard antihypertensive medications.¹⁸ BP enrolment criteria were the same as for SPYRAL HTN-OFF MED with the intention to exclude patients with isolated systolic hypertension. Drug adherence was monitored through use of HPLC and mass spectroscopy of urine and plasma samples at baseline and follow-up visits, complemented by observed tablet taking prior to ambulatory blood pressure monitoring at each visit. Patients who met all the inclusion criteria were randomly assigned to either RDN or sham in a 1:1 ratio after a renal angiogram with similar efforts to blind patients and assessors as in SPYRAL HTN-OFF MED, with maintenance of blinding for up to 12 months following randomisation.

Patients were treated with RDN or underwent sham control procedure exactly as described in the SPYRAL HTN-OFF MED section and returned for office follow-up visits at 1, 3 and 6 months. Antihypertensive medication changes were not allowed for 6 months following randomisation unless escape criteria were met. From a total of 467 screened and enrolled patients, the investigators reported a prospectively planned interim analysis on the first 80 patients randomly assigned to RDN (n=38) or sham control (n=42). Clinical characteristics and mean office and ABP parameters did not differ between the groups. There were no differences in either the number of antihypertensives prescribed between the groups nor in the distribution of the classes of antihypertensive medications. Patients treated with RDN received 45.9 ± 13.7 ablations in total with 19.3 ± 8.9 ablations in the main arteries and 26.6 ± 11.7 ablations in the branches.

There were no powered end points in this study and analysis was undertaken on an intention-to-treat basis. Effective masking of patients to randomisation allocation was achieved and demonstrated through the use of a blinding index at 3 and 6 months follow-up. The change in ABP was significantly greater at 6 months in the RDN group than the sham control group: for 24 hours ASBP (difference -7.4 mm Hg, -12.5 to -2.3 ; $p=0.0051$) and 24 hours ADBP (difference -4.1 mm Hg, -7.8 to -0.4 ; $p=0.0292$) (figure 1). Furthermore, significantly greater changes in the RDN group compared with the sham group were seen for office SBP (difference -6.8 mm Hg, 95% CI -12.5 to -1.1 ; $p=0.0205$) and office DBP (difference -3.5 mm Hg, -7.0 to -0.0 ; $p=0.0478$). Differences in 24 hours ASBP and ADBP were not significant between the groups at 3-month follow-up and a progressive trend in reduction in office and ABP was demonstrated from 3 to 6 months. In this study, assessment of adherence to antihypertensive drugs revealed some surprising findings with non-prescribed antihypertensives being detected in 10%–15% of all patients at each timepoint. In addition, adherence with prescribed therapy was only ~60% with highly variable patient adherence at all timepoints. There were insufficient numbers of patients in each group for a meaningful per protocol analysis which would have excluded patients meeting escape criteria and non-adherent patients. Once again, this study demonstrated the safety of RF RDN with no procedural or clinical events through 6 months of follow-up.

RADIANCE SOLO STUDY

A novel RDN platform utilising US energy to thermally ablate the renal sympathetic nerves has recently been developed

(Paradise RDN System; ReCor Medical, Palo Alto, CA, USA).¹⁹ The technology consists of an ablation catheter with a low-pressure water-filled cooling balloon containing a ceramic US transducer delivering radial energy and an automated customised power generator. The design permits circumferential ablation at a depth of 1–6 mm with reduced endothelial damage in contrast to RF ablation (depth 0–4 mm) with concomitant local endothelial destruction. Also, in contrast to RF energy catheters, the Paradise System is currently intended for use in the main renal arteries and large accessory vessels (>4 mm diameter) only.

The RADIANCE SOLO study was an international multicentre single blind randomised sham-controlled trial undertaken in US and European centres aiming to evaluate the safety and efficacy of the Paradise System in non-medicated patients with primary hypertension.²⁰ Similar to the SPYRAL programme studies, this was an off-medication trial partnered with a study in patients with RHTN taking a fixed combination triple antihypertensive (RADIANCE TRIO) which is still recruiting patients (ClinicalTrials.gov Identifier: NCT02649426). However, both SOLO and TRIO studies were independently powered for their primary endpoints, based on the incremental BP-lowering effects seen with RDN in the DENER-HTN study. The SOLO study enrolled men and women between the ages of 18 and 75 years with either uncontrolled hypertension taking 0–2 antihypertensive drugs or with controlled hypertension taking 1–2 drugs. During a 4-week run-in period, any participants taking antihypertensive medications were required to wash out these medications. At the end of the run-in period, all patients were required to meet ABP criteria (daytime BP $\geq 135/85$ and $<170/105$ mm Hg) prior to randomisation, on no prescribed antihypertensive medications.

Patients were randomised 1:1 to receive either RDN or sham control with patients, assessors and follow-up visit physicians remaining blinded to treatment allocation for 6 months postrandomisation. Efforts were made to maintain blinding through the use of periprocedural sensory masking and this was successful according to the results of the Bang and James blinding indices. In total, 803 patients were enrolled of whom 633 were excluded mostly due to failure to meet BP criteria. Ultimately, 170 patients proceeded to renal angiography of whom 146 met the anatomical criteria for randomisation: 74 were allocated to RDN and 72 to sham control. There were no significant differences in baseline characteristics between the groups. Per protocol denervation required a minimum of two US activations per renal artery and a maximum of three per vessel. Those randomised to treatment with US RDN in SOLO received an average of 5.4 (SD 1.0) US emissions in total, bilaterally. There was no difference between the groups in postprocedure pain. The reduction in daytime ASBP was greater in the RDN group (-8.5 mm Hg, SD 9.3) than in the sham control group (-2.2 mm Hg, SD 10.0; baseline-adjusted difference between groups: -6.3 mm Hg, 95% CI -9.4 to -3.1 , $p=0.0001$) (figure 1). Per protocol analysis suggested that the small numerical sham BP differences were observed principally in those patients who had restarted medications and not in the group who remained off meds in the sham arm. Secondary endpoint analysis demonstrated significant reductions in office and home SBP and DBP in the RDN group compared with the sham group. No major adverse events were reported in either group.

OTHER EVIDENCE THAT SUGGESTS RDN MAY BE BENEFICIAL FOR RHTN Sham-controlled studies

To date, 1113 patients have been studied in randomised sham-controlled trials of RDN using either RF or US technologies (table 1). Of these studies only the aforementioned SPYRAL programme and RADIANCE-HTN SOLO study and

Table 1 Randomised sham-controlled trials of renal denervation in humans

Study name and (year) ClinicalTrials.gov Identifier	No of patients	Experimental design	Hypertension phenotype	Denervation technology and number of ablations	Primary BP endpoint	Change in primary EP (mm Hg) p for baseline-adjusted treatment difference
RADIANCE HTN-SOLO ²⁰ (2018) NCT02649426	146	Multicentre RCT: single blind (participant) Sham: renal angiogram	Combined mild–moderate systolic–diastolic HTN: off meds	PARADISE balloon cooled US catheter 5 US emissions per patient	Daytime ASBP reduction at 8 weeks	RDN –8.5 SHAM –2.2 p=0.0001
REDUCE-HTN: REINFORCE ²¹ (2018) NCT02392351	51	Multicentre RCT: single blind (participant) Sham: renal angiogram	Mild–moderate systolic HTN: off meds	Vessix balloon catheter, helical bipolar RF electrodes 14 ablations per patient	24 hours ASBP reduction at 8 weeks	RDN –5.3 SHAM –8.5 p=0.08 (interim analysis)
SPYRAL ON MED ¹⁸ (2018) NCT02439775	80	Multicentre RCT: single blind (participant) Sham: renal angiogram	Combined mild–moderate systolic–diastolic HTN: on meds	SPYRAL multielectrode RF catheter 46 ablations per patient	24 hours ASBP reduction at 6 months	RDN –9.0 SHAM –1.6 p=0.006
SPYRAL OFF MED ¹⁶ (2017) NCT02439749	80	Multicentre RCT: single blind (participant) Sham: renal angiogram	Combined mild–moderate systolic–diastolic HTN: off meds	SPYRAL multielectrode RF catheter 44 ablations per patient	24 hours ASBP reduction at 3 months	RDN –5.5 SHAM –0.5 p=0.04
WAVE IV ³⁸ (2016) NCT02029885	81	Multicentre RCT: double blind, Sham: diagnostic US	Mild–moderate systolic HTN: on meds	External low intensity focused US, 14 US emissions per artery	Office SBP reduction at 6 months	RDN –12.9 SHAM –22.7 p=0.13 (interim analysis)
RESET ³⁹ (2016) NCT01459900	69	Single centre RCT: double blind, Sham: renal angiogram	Mild–moderate systolic HTN: on meds	Unipolar Symplicity Flex RF catheter 10 ablations per patient	Daytime ASBP reduction at 3 months	RDN –6.2 SHAM –6.0 p=0.95
RDN in mild resistant HTN ⁴⁰ (2015) NCT01656096	71	Single centre RCT: double blind, Sham: renal angiogram	Mild systolic HTN: on Meds	Unipolar Symplicity Flex RF catheter 11 ablations per patient	24 hours ASBP reduction at 6 months	RDN –7.0 SHAM –3.5 p=0.15
Symplicity HTN3 ⁷ (2014) NCT01418261	535	Multicentre RCT: single blind (participant) Sham: renal angiogram	Moderate–severe systolic HTN: on meds	Unipolar Symplicity Flex RF catheter 11 ablations per patient	Office SBP reduction at 6 months	RDN –14.1 SHAM –11.3 p=0.26

The term resistant hypertension has not been used as these trials did not apply the current definition of resistant hypertension as inclusion criteria.³⁵ ASBP, ambulatory systolic blood pressure; HTN, hypertension; RCT, randomized controlled trial; RF, radiofrequency; SBP, systolic blood pressure; US, ultrasound.

the REDUCE HTN: REINFORCE trial (ClinicalTrials.gov Identifier: NCT02392351) were conceived in accordance with updated recommendations for design of clinical trials of RDN in the wake of the negative SYMPLICITY HTN3 study.

The REDUCE HTN: REINFORCE study used a bipolar RF over-the-wire low-pressure balloon catheter with 4–8 helically spaced, simultaneously activated electrodes (depending on catheter size) to achieve circumferential denervation with no more than two 30 s applications per artery. Following a 4-week washout period, non-medicated patients between the ages of 18 and 75 years with office SBP between 150 and 180 mm Hg (and ASBP of 135–170 mm Hg) were randomised to RDN or control in a 2:1 ratio and no medication changes were allowed prior to the primary endpoint at 8 weeks.²¹ The study was terminated prematurely on the basis of futility following an interim analysis instigated by slow enrolment, which showed that the primary end point could not be met. Although there were no procedural or clinical safety concern and despite the fact that follow-up of the 51 enrolled patients showed significant office and ASBP reduction at 6 months in treated patients compared with controls, the sponsor (Boston Scientific) has to date not indicated if it will continue with its RDN programme.

Randomised controlled trials without sham procedure

There have been 10 randomised controlled trials (RCTs) of RDN to date, mostly designed and initiated prior to SYMPLICITY HTN3, half of which were small in size (<100 patients) and 2 of which were prematurely terminated (table 2). Of these, the DENERHTN study, an investigator-led trial funded by the French Ministry of Health, was one of the earlier RCTs to show the efficacy of RF RDN in patients with RHTN despite using the original ablation procedure with patients receiving a median number of six ablations in the right renal artery and five in the left.²² The study was also important in demonstrating that a standardised approach to managing medications using a triple antihypertensive regimen at the outset (indapamide

1.5 mg, ramipril 10 mg or irbesartan 300 mg, amlodipine 10 mg daily), followed by a standardised stepped care antihypertensive regimen, could be used in both RDN and control groups to effectively ensure that both cohorts were equally and stably medicated throughout the study. The same investigators went on to later report a high prevalence of non-adherence to anti-hypertensive drugs in DENERHTN (50% in both cohorts) despite very close scrutiny from investigators throughout the study although this did not influence the primary endpoint outcome.²³

The RADIOSOUND-HTN trial was the first study to investigate the efficacy of RDN using different procedural approaches and technologies.²⁴ Patients with RHTN were randomised in a 1:1:1 ratio to receive RF RDN to the main renal arteries (RFM-RDN) or RF RDN to the main renal arteries, side branches and accessories (RFB-RDN) or endovascular US RDN to the main renal arteries (USM-RDN). RF ablation was performed using the Symplicity Spyral catheter and US ablation was undertaken using the Paradise RDN system. In total 120 patients were enrolled with a mean daytime ABP 153/86±12/13 mm Hg. Of these, 39 were randomised to RFM-RDN, 39 to RFB-RDN and 42 to USM-RDN. At 3 months, daytime ASBP reduction was similar between the USM-RDN and RFB-RDN groups but was significantly greater in the USM-RDN group than in the RFM-RDN group (–13.2±13.7 vs –6.5±10.3 mm Hg, mean difference –6.7 mm Hg, global p=0.038 by ANOVA, adjusted p=0.043). Although this was a single centre study, the treatment effects were similar to those reported in the previously described SPYRAL and SOLO studies and once again no safety signal was observed. The study findings confirm earlier data that suggest that RF RDN targeting both main renal artery and branches is required to achieve more complete renal sympathectomy as measured by reduction in renal norepinephrine tissue content and renal cortical axon density.¹² Clearly further studies are now required to compare the efficacy and cost effectiveness of US and RF RDN.

Table 2 Randomised trials of renal denervation in humans without sham

Study name and (year) ClinicalTrials.gov Identifier	No of patients	Experimental design	Hypertension phenotype	Denervation technology and No of ablations	Primary BP endpoint	Change in primary EP (mm Hg) p for baseline-adjusted treatment difference
RADIOSOUND ²⁴ (2018) NCT02920034 RF vs US RDN	120	Single centre three arm randomised trial: single blind	Moderate systolic HTN: on meds	SPYRAL multielectrode RF catheter: 17/35 ablations per patient (RFM-RDN/RFB-RDN) PARADISE balloon cooled US catheter: 6 ablations per patient	Daytime Mean ASBP reduction at 3 months	RFM-RDN -6.5 RFB-RDN -8.3 US -13.2 p only significant for US vs RFB-RDN
RDN OSA ⁴¹ (2018) NCT01366625 RDN vs standard pharmacotherapy in patients with moderate to severe OSA	60	Single centre RCT: open label, blinded endpoint evaluation	Moderate systolic HTN: on meds Moderate-severe OSA	Unipolar Symplicity Flex RF catheter 12 ablations per patient	Office SBP reduction at 3 months	RDN -22.0 Control -5.0 p=0.002
INSPIRED ⁴² (2017) NCT01505010 RDN vs standard pharmacotherapy	15	Three centre RCT: open label, blinded endpoint evaluation	Combined mild-moderate systolic-diastolic HTN: on meds	Enlightn multielectrode RF catheter 8-24 ablations per patient	24 hours ASBP reduction at 6 months	RDN -21.7 Control 0.7 p=0.018
SYMPATHY ⁴³ (2017) NCT01850901 RDN vs standard pharmacotherapy	139	Multicentre RCT: open label, blinded endpoint evaluation	Moderate-severe systolic HTN: on meds	Enlightn multielectrode or Symplicity Flex RF catheters 15 ablations per patient	Daytime Mean ASBP reduction at 6 months	RDN -6.0 Control -7.9 p=0.625
DENERVHTA ⁴⁴ (2016) NCT02039492 RDN vs spironolactone	24	Three centre RCT: open label, blinded endpoint evaluation	Moderate-severe systolic HTN: on meds	Unipolar Symplicity Flex RF catheter: 8-12 ablations per patient	24 hours ASBP reduction at 6 months	RDN -5.7 Control -23.6 p=0.01
PRAGUE-15 ⁴⁵ (2015) NCT 01560312 RDN vs optimised pharmacotherapy	106	Multicentre randomised trial, open label, blinded endpoint evaluation	Moderate systolic HTN: on meds	Unipolar Symplicity Flex RF catheter: 11 ablations per patient	24 hours ASBP reduction at 6 months	RDN -8.8 Control -8.1 p=0.87
DENER-HTN ⁴² (2015) NCT01570777 RDN vs optimised pharmacotherapy	106	Multicentre RCT: open label, blinded endpoint evaluation	Moderate-severe systolic HTN: on meds	Unipolar Symplicity Flex RF catheter: 11 ablations per patient	Daytime Mean ASBP reduction at 6 months	RDN -15.8 Control -9.9 p=0.03
HTN JAPAN ⁴⁶ (2015) NCT01644604 RDN vs standard pharmacotherapy	41	Multicentre randomised trial, open label, blinded endpoint evaluation	Severe systolic HTN: on meds	Unipolar Symplicity Flex RF catheter: 11 ablations per patient	Office SBP reduction at 6 months	RDN -16.6 Control -7.9 p=0.169 Early termination due to Symplicity HTN-3 result
RDN OSLO ⁴⁷ (2013) NCT01673516 RDN vs optimised pharmacotherapy	20	Single centre RCT, open label, blinded endpoint evaluation	True treatment resistant HTN	Unipolar Symplicity Flex RF catheter: 8 ablations per artery	Office SBP reduction at 6 months	RDN -8.0 Control -28.0 p=0.08 Early termination (ethical reasons)
Symplicity HTN-2 ⁵ (2010) NCT00888433 RDN vs standard pharmacotherapy	106	Multicentre RCT: open label, blinded endpoint evaluation	Severe systolic HTN	Unipolar Symplicity Flex RF catheter: 8-12 ablations per patient	Office SBP reduction at 6 months	RDN -32 Control 1 p=0.0001

ASBP, ambulatory systolic blood pressure; HTN, hypertension; RCT, randomised controlled trial; RF, radiofrequency; RFB-RDN, radiofrequency renal denervation to main renal artery, branches and accessories; RFM-RDN, radiofrequency renal denervation to main renal artery; SBP, systolic blood pressure; US, ultrasound.

Non-randomised studies (registries)

A number of registry studies of RDN exist with >4000 patients enrolled and treated to date utilising different ablation technologies but with the majority of patients in each being treated with RF RDN using the unipolar Symplicity catheter and the original proximal renal artery procedural approach. Importantly, none of these registries has identified either a procedural or a renovascular safety signal, although renovascular surveillance has been less rigorously scrutinised than in the randomised clinical trials. JUKS have limited consideration to the largest three of these non-randomised studies.

The Global Symplicity Registry (GSR) is a multicentre study which has provided valuable data on the efficacy and safety of RF RDN in >2500 patients with uncontrolled hypertension in a real world setting.²⁵ Initial reports demonstrating clinically meaningful office and ABP (and heart rate) reduction at 6 and 12 months are now published as well as data indicating an attenuated effect of RDN in patients with isolated systolic hypertension.²⁶⁻²⁸ Another report from this registry has shown that at 12 months after treatment, RDN was associated with a significant improvement in health-related quality of life measures and in particular reduction in anxiety/depression.²⁹ More recently, GSR data have been presented at the European Society of

Cardiology 2018 meeting demonstrating durable office and 24 hours ASBP reduction (16 and 9 mm Hg, respectively) out to 3 years following treatment (*manuscript in press, European Heart Journal*).

In the UK Renal Denervation Affiliation study, investigators reported the effect of RDN in 253 patients with uncontrolled hypertension from 18 UK centres.³⁰ Eighty-one per cent of patients were treated with the Symplicity Flex catheter. Mean follow-up duration was 11 months for office BP which fell by 22/9 mm Hg and 8.5 months for daytime ABP which fell by 12/7 mm Hg, with reduced response noted in the lowermost quartile of starting BP. The fall in BP was independent of medication changes and aldosterone antagonist use did not affect response.

In Sweden, 252 hypertensive patients treated with RDN between 2011 and 2015 were followed up in a national registry for up to 36 months.³¹ More than 90% of patients were treated with RF RDN of which 60% had Symplicity Flex and utilised the older procedural technique of proximal main renal artery denervation. Despite this, significant reductions in office and 24 hours mean ASBP (15 and 8 mm Hg, respectively) were noted at 6 months and persisted at 36 months follow-up without change in antihypertensive medications. No significant safety

Table 3 Research agenda to determine the role of renal denervation in clinical practice

Research priority	Considerations
Pivotal studies and additional registry data to determine role of RDN in treatment of hypertension	<ul style="list-style-type: none"> ▶ It is critical to understand the effect of RDN in patients both on and off medications and given that current studies have been small in size, larger scale sham-controlled clinical trials (with powered endpoints) are needed with rigorous evaluation of medication usage. ▶ Using ABP for endpoints is mandatory but office BP should also be collected and home BP where possible (with strict patient instructions to avoid using home BP data to adjust their medication regimens). ▶ It may be difficult to recruit patients without the promise of a cross-over opportunity. ▶ An outcome trial would be desirable, though there would be considerable challenges to achieving this and the cost would be enormous.
Establish the durability/safety of the different RDN technologies	<ul style="list-style-type: none"> ▶ Longer term follow-up to determine procedural, renal artery and renal safety is necessary as well as to determine durability of effect. ▶ The possibility of functional renal nerve regrowth can be assessed.⁴⁸ ▶ Are there differences between the energy modalities in terms of efficacy/safety/durability?
Is RDN cost-effective?	<ul style="list-style-type: none"> ▶ Modelling cost-effectiveness will require larger datasets and hopefully as these begin to emerge, the cost of the RDN procedure may have started to diminish due to market forces/competing technologies.
What is the mechanism of action?	<ul style="list-style-type: none"> ▶ This remains to be clarified and the role of afferent/efferent renal sympathetic signalling and selective afferent/efferent sympathectomy should be addressed.⁴⁹
Which patients are best responders?	<ul style="list-style-type: none"> ▶ Heterogeneity of response is observed with all drug and device therapy—what does this mean and can true responders/non-responders be defined? ▶ Even partial responders may benefit significantly from RDN if there are no other treatment options.
Can procedural markers of success be defined and will they be of value?	<ul style="list-style-type: none"> ▶ Novel technologies are providing insights into how to achieve successful ablation procedure through renal nerve mapping but presently add considerably to time spent on the table in the catheter lab and their value is undetermined.⁵⁰
Of interest, not critical for hypertension indication	
Is RDN useful for other sympathetically mediated diseases?	<ul style="list-style-type: none"> ▶ Conditions such as heart failure, obstructive sleep apnoea and chronic kidney disease are all characterised by increased sympathetic signalling and may respond to RDN.
Is lowering of BP the best biomarker of a successful RDN procedure?	<ul style="list-style-type: none"> ▶ If an RDN procedure does not lower BP by a clinically significant amount, it remains of interest to understand if there may be other benefits (eg, regression of LVH, improved glycaemic parameters, reduction in arterial stiffness).^{51–54}

BP, blood pressure; LVH, left ventricular hypertrophy; RCT, randomised clinical trial; RDN, renal denervation.

concerns arose and renal function remained stable throughout follow-up.

THE US FOOD AND DRUG ADMINISTRATION PERSPECTIVE ON DEVICE THERAPY OF HYPERTENSION

The US Food and Drug Administration (FDA) convened an advisory panel in Washington (05/12/2018) comprising FDA members, device manufacturers and clinicians, to discuss the approval process and requirements for device-based therapies for hypertension.³² While this panel meeting was not focused on data review, its main objective was to clarify the path forward for device therapies of hypertension including RDN. The discussants agreed on the following points:

1. It is appropriate to study RDN in further clinical trials utilising both the ‘off’ meds and ‘on’ meds study design. A RDN registry (with evaluation of renal function) and postmarketing evaluation would also be critical to determine long-term safety, clinical outcomes and provide an opportunity to examine subgroups.
2. Sham control remains the most rigorous way to study RDN unless clinically impossible. However, cross-over studies were not felt to be helpful given the possibility of confounding.
3. It is critical to continue to focus on safety: procedural, revascular and renal function safety comparisons between groups (active therapy and sham control) and to a performance goal.
4. To determine efficacy, ABP should remain the endpoint for clinical studies, with recommendation that a 5–7 mm Hg decrease in ASBP is meaningful and that 12-month durability of BP lowering efficacy should be demonstrated.
5. Reduction in medication burden was felt to be clinically meaningful and also addressed an area of unmet need: the importance of accruing data on patients’ preferences for

treatment of their long-term condition with drug/non-drug therapy.

THE JUKS UPDATED PERSPECTIVE ON RDN

The SPYRAL and RADIANCE study programmes to date have provided encouraging data to suggest that RDN may have a role in the treatment of hypertension. Moreover, these trials have shown the value of collaboration between hypertension specialists, interventionalists and industry to design high quality, rigorously executed clinical trials which have moved the field forward and rekindled enthusiasm for RDN in the clinical community. However, these studies have limitations: they are of short duration, included a small number of patients, and longer term follow-up has not been published as yet. In addition, the studies reported considerable heterogeneity in the response to RDN, leaving open the question of which patients may be best responders to the therapy. Finally, at present, it is unclear which technology may be best for RDN, with RF and US systems appearing more or less similar in efficacy and ongoing trials of chemical ablation systems are not published yet.

To date, the NICE has not updated the guidance originally produced in 2012 regarding RDN (IPG418) which deemed that there were insufficient data to support the routine use of RDN but that patients could be offered the procedure in the context of audit/research with a firm recommendation for data collection and publication of outcomes in all patients treated with RDN.³³ In July 2016, NHS England decided that RDN would not be routinely commissioned due to lack of clinical effectiveness on the basis of the Symplivity HTN-3 outcome and secondary lack of cost effectiveness data.³⁴ Subsequently, the 2018 European Society of Cardiology-European Society of Hypertension (ESC-ESH) guideline for the management of arterial hypertension mandated that routine use of any device therapy for hypertension was not recommended outside the context of clinical trials

(class II recommendation, grade B level of evidence).³⁵ It is worth pointing out that the most recent studies from the SPYRAL and RADIANCE programmes were not considered at the time of the European guidelines writing and that in July 2018, the ESH Working Group on interventional treatment of hypertension published a position paper that followed the recommendation of the 2018 ESC-ESH guideline and outlined further research questions to be addressed.³⁶

Having considered the evidence reviewed earlier in this document, the JUKS also have concluded that there are insufficient data at present to suggest that RDN should be considered routine standard of care in the management of hypertension in adults and that additional clinical trials data are required. There are several important areas of research that should be considered as next steps and a research agenda has been defined (table 3). It is important to recognise that the use of interim analyses in both SPYRAL studies may have led to overestimation of effect size (type I error) and such an approach is strongly discouraged for future studies.³⁷ The recent focus on patient preference for non-drug treatments should also be considered in the design of future studies. The latter should act as a stimulant to those who look after patients with hypertension to consider referring their patients to centres undertaking RCTs of the therapy.

CONCLUSIONS

Hypertension remains a global health issue and better means to diagnose, treat and control hypertension in the long term are urgently required. Increasing evidence indicates that many patients struggle to maintain healthy lifestyles and are non-adherent to pharmacological measures to control BP in the long term. Although further research is needed on the best ways to ensure compliance, such individuals might therefore choose to have a device treatment, if proven durably safe and effective, in preference to lifelong drug therapy. The JUKS concludes that there is insufficient evidence to recommend routine use of RDN for hypertension at the present time and that use of RDN should remain restricted to clinical trials. However, we support the ongoing clinical trials programmes from the different device manufacturers across the spectrum of RDN technologies and strongly encourage clinicians who look after patients with hypertension to inform their patients about these studies which are recruiting participants who are on or off medications in order to inform future practice*.

*Active RDN clinical trial programmes with details of local recruiting centres are listed below:

Ablative Solutions Ltd. <https://clinicaltrials.gov/ct2/show/NCT02910414>

Medtronic: <https://clinicaltrials.gov/ct2/show/NCT02439749>

ReCor Medical: <https://clinicaltrials.gov/ct2/show/NCT03614260>

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REFERENCES

- 1 Forouzanfar MH, Liu P, Roth GA, *et al*. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990–2015. *JAMA* 2017;317:165–82.
- 2 Carey RM, Muntner P, Bosworth HB, *et al*. Prevention and Control of Hypertension: JACC Health Promotion Series. *J Am Coll Cardiol* 2018;72:1278–93.
- 3 Lobo MD, Sobotka PA, Pathak A. Interventional procedures and future drug therapy for hypertension. *Eur Heart J* 2017;38:1101–11.
- 4 Caulfield M, de Belder M, Cleveland T, *et al*. Joint UK Societies' Consensus Summary Statement on Renal Denervation for Resistant Hypertension. 2011 <http://www.bhsoc.org/docs/Joint-UK-Societies-Summary-on-Renal-Denervation.pdf>.

- 5 Esler MD, Krum H, Sobotka PA, *et al.* Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010;376:1903–9.
- 6 Krum H, Schlaich M, Whitbourn R, *et al.* Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009;373:1275–81.
- 7 Bhatt DL, Kandzari DE, O'Neill WW, *et al.* A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;370:1393–401.
- 8 Lobo MD, de Belder MA, Cleveland T, *et al.* Joint UK societies' 2014 consensus statement on renal denervation for resistant hypertension. *Heart* 2015;101:10–16.
- 9 Mahfoud F, Böhm M, Azizi M, *et al.* Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design. *Eur Heart J* 2015;36:2219–27.
- 10 Mahfoud F, Schmieder RE, Azizi M, *et al.* Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: state of the art and considerations for the future. *Eur Heart J* 2017;38:3272–81.
- 11 Sakakura K, Ladich E, Cheng Q, *et al.* Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol* 2014;64:635–43.
- 12 Mahfoud F, Tunev S, Ewen S, *et al.* Impact of Lesion Placement on Efficacy and Safety of Catheter-Based Radiofrequency Renal Denervation. *J Am Coll Cardiol* 2015;66:1766–75.
- 13 Tzafiriri AR, Keating JH, Markham PM, *et al.* Arterial microanatomy determines the success of energy-based renal denervation in controlling hypertension. *Sci Transl Med* 2015;7:285ra65.
- 14 Tzafiriri AR, Mahfoud F, Keating JH, *et al.* Innervation patterns may limit response to endovascular renal denervation. *J Am Coll Cardiol* 2014;64:1079–87.
- 15 Kandzari DE, Kario K, Mahfoud F, *et al.* The SPYRAL HTN Global Clinical Trial Program: Rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications. *Am Heart J* 2016;171:82–91.
- 16 Townsend RR, Mahfoud F, Kandzari DE, *et al.* Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet* 2017;390:2160–70.
- 17 James KE, Bloch DA, Lee KK, *et al.* An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation--a VA cooperative study. *Stat Med* 1996;15:1421–34.
- 18 Kandzari DE, Böhm M, Mahfoud F, *et al.* Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018;391:2346–55.
- 19 Mauri L, Kario K, Basile J, *et al.* A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: The RADIANCE-HTN and REQUIRE clinical study designs. *Am Heart J* 2018;195:115–29.
- 20 Azizi M, Schmieder RE, Mahfoud F, *et al.* Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018;391:2335–45.
- 21 Weber M, Kirtane AJ, Weir MR, *et al.* Six Month Results of the REDUCE HTN: REINFORCE Study of Renal Denervation for the Treatment of Hypertension. *TCT2018*. San Diego, USA, 2018.
- 22 Azizi M, Sapoval M, Gosse P, *et al.* Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015;385:1957–65.
- 23 Azizi M, Pereira H, Hamdidouche I, *et al.* Adherence to Antihypertensive Treatment and the Blood Pressure-Lowering Effects of Renal Denervation in the Renal Denervation for Hypertension (DENERHTN) Trial. *Circulation* 2016;134:847–57.
- 24 Fengler K, Rommel KP, Blazek S, *et al.* A Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients With Resistant Hypertension (RADIO SOUND-HTN). *Circulation* 2019;139:590–600.
- 25 Böhm M, Mahfoud F, Ukena C, *et al.* Rationale and design of a large registry on renal denervation: the Global SYMPLICITY registry. *EuroIntervention* 2013;9:484–92.
- 26 Böhm M, Mahfoud F, Ukena C, *et al.* First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. *Hypertension* 2015;65:766–74.
- 27 Böhm M, Ukena C, Ewen S, *et al.* Renal denervation reduces office and ambulatory heart rate in patients with uncontrolled hypertension: 12-month outcomes from the global SYMPLICITY registry. *J Hypertens* 2016;34:2480–6.
- 28 Mahfoud F, Bakris G, Bhatt DL, *et al.* Reduced blood pressure-lowering effect of catheter-based renal denervation in patients with isolated systolic hypertension: data from SYMPLICITY HTN-3 and the Global SYMPLICITY Registry. *Eur Heart J* 2017;38:ehw325.
- 29 Kindermann I, Wedegärtner SM, Mahfoud F, *et al.* Improvement in health-related quality of life after renal sympathetic denervation in real-world hypertensive patients: 12-month outcomes in the Global SYMPLICITY Registry. *J Clin Hypertens* 2017;19:833–9.
- 30 Sharp AS, Davies JE, Lobo MD, *et al.* Renal artery sympathetic denervation: observations from the UK experience. *Clin Res Cardiol* 2016;105:544–52.
- 31 Völz S, Spaak J, Elf J, *et al.* Renal sympathetic denervation in Sweden: a report from the Swedish registry for renal denervation. *J Hypertens* 2018;36:151–8.
- 32 FaD A. Circulatory system devices panel meeting: clinical evaluation of anti-hypertensive devices. 2018.
- 33 Excellence NIHaC. Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. 2012.
- 34 England N. Clinical Commissioning Policy: Renal denervation for resistant hypertension. 2016.
- 35 Williams B, Mancia G, Spiering W, *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European heart journal* 2018;2018:603–98.
- 36 Schmieder RE, Mahfoud F, Azizi M, *et al.* European Society of Hypertension position paper on renal denervation 2018. *J Hypertens* 2018;36:2042–8.
- 37 Pocock SJ, Clayton TC, Stone GW. Challenging Issues in Clinical Trial Design: Part 4 of a 4-Part Series on Statistics for Clinical Trials. *J Am Coll Cardiol* 2015;66:2886–98.
- 38 Schmieder RE, Ott C, Toennes SW, *et al.* *J Hypertens* 2018;36:e21.
- 39 Mathiassen ON, Vase H, Bech JN, *et al.* Renal denervation in treatment-resistant essential hypertension. A randomized, SHAM-controlled, double-blinded 24-h blood pressure-based trial. *J Hypertens* 2016;34:1639–47.
- 40 Desch S, Okon T, Heinemann D, *et al.* Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. *Hypertension* 2015;65:1202–8.
- 41 Warchol-Celinska E, Prejbisz A, Kadziela J, *et al.* Renal denervation in resistant hypertension and obstructive sleep apnea: randomized proof-of-concept Phase II Trial. *Hypertension* 2018;72:381–90.
- 42 Jacobs L, Persu A, Huang QF, *et al.* Results of a randomized controlled pilot trial of intravascular renal denervation for management of treatment-resistant hypertension. *Blood Press* 2017;26:321–31.
- 43 de Jager RL, de Beus E, Beefink MM, *et al.* Impact of medication adherence on the effect of renal denervation: the SYMPATHY Trial. *Hypertension* 2017;69:678–84.
- 44 Oliveras A, Armario P, Clarà A, *et al.* Spironolactone versus sympathetic renal denervation to treat true resistant hypertension: results from the DENERVHTA study - a randomized controlled trial. *J Hypertens* 2016;34:1863–71.
- 45 Rosa J, Widimský P, Toušek P, *et al.* Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension* 2015;65:407–13.
- 46 Kario K, Ogawa H, Okumura K, *et al.* SYMPLICITY HTN-Japan - First Randomized Controlled Trial of Catheter-Based Renal Denervation in Asian Patients -. *Circ J* 2015;79:1222–9.
- 47 Fadl Elmula FE, Hoffmann P, Larstorp AC, *et al.* Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension* 2014;63:991–9.
- 48 Singh RR, McArdle ZM, Ludica M, *et al.* Sustained decrease in blood pressure and reduced anatomical and functional reinnervation of renal nerves in hypertensive sheep 30 months after catheter-based renal denervation. *Hypertension* 2019;73:718–27.
- 49 Fudim M, Sobotka AA, Yin YH, *et al.* Selective vs. Global Renal Denervation: a case for less is more. *Curr Hypertens Rep* 2018;20:37.
- 50 Tsioufis KP, Feyz L, Dimitriadis K, *et al.* Safety and performance of diagnostic electrical mapping of renal nerves in hypertensive patients. *EuroIntervention* 2018;14:e1334–42.
- 51 Saxena M, Shour T, Shah M, *et al.* Attenuation of Splanchnic Autotransfusion Following Noninvasive Ultrasound Renal Denervation: a novel marker of procedural success. *J Am Heart Assoc* 2018;7.
- 52 Mahfoud F, Schlaich M, Kindermann I, *et al.* Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation* 2011;123:1940–6.
- 53 Mahfoud F, Urban D, Teller D, *et al.* Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multi-centre cardiovascular magnetic resonance imaging trial. *Eur Heart J* 2014;35:2224–31.
- 54 Ott C, Franzen KF, Graf T, *et al.* Renal denervation improves 24-hour central and peripheral blood pressures, arterial stiffness, and peripheral resistance. *J Clin Hypertens* 2018;20:366–72.