



Burchell, A. E., Chan, K., Ratcliffe, L. E. K., Hart, E. C., Saxena, M., Collier, D. J., ... Baumbach, A. (2016). Controversies Surrounding Renal Denervation: Lessons Learned From Real-World Experience in Two United Kingdom Centers. *Journal of Clinical Hypertension*, 18(6), 585-592. DOI: 10.1111/jch.12789

Peer reviewed version

License (if available):
Unspecified

Link to published version (if available):
[10.1111/jch.12789](https://doi.org/10.1111/jch.12789)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Wiley at <http://onlinelibrary.wiley.com/doi/10.1111/jch.12789/abstract>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/pure/about/ebr-terms.html>

THE CONTROVERSIES SURROUNDING RENAL DENERVATION: LESSONS LEARNT FROM REAL-WORLD EXPERIENCE IN TWO UK CENTRES

Running Title: Controversies in Renal Denervation

Authors:

*Amy E Burchell^{a,b} MA BMBCh MRCP, *Kenneth Chan^{c,d} MBBS MPharm, Laura EK Ratcliffe^{a,e} BSc MBBS MRCP, Emma C Hart^{a,e} BSc PhD, Manish Saxena^{c,d} MBBS, David J Collier^c MBBS PhD, Ajay K Jain^{c,f} BSc MRCP MD, Anthony Mathur^{c,f} MA MB BChir MRCP PhD, Charles J Knight^{c,f} MA BMBCh MD FRCP, Mark J Caulfield^{c,d} MB MD FRCP, Julian FR Paton^{a,e} BSc PhD, Angus K Nightingale^a MA BMBCh MD FRCP, †Melvin D Lobo^{c,d} MBChB PhD FRCP FBHS, †Andreas Baumbach^{a,b} MD FESC FRCP.

Affiliations:

- a. CardioNomics Research Group, Clinical Research & Imaging Centre-Bristol, Bristol Heart Institute, University Hospitals Bristol NHS Foundation Trust, University of Bristol, Bristol, BS2 8DX, UK.
- b. School of Clinical Sciences, University of Bristol, Bristol Royal Infirmary, Bristol, BS2 8HW, UK.
- c. William Harvey Heart Centre, NIHR Cardiovascular Biomedical Research Unit, Queen Mary University of London, London, UK.
- d. Barts Blood Pressure Clinic, Barts Health NHS Trust, London, UK.
- e. School of Physiology, Pharmacology & Neuroscience, Biomedical Sciences, University of Bristol, Bristol, BS8 1TD, UK.
- f. Department of Cardiology, London Chest Hospital, Barts Health NHS Trust, London, UK

* Joint first authors

† Joint last and corresponding authors

Conflicts of Interest and Source of Funding: Dr Burchell is funded by a University Hospitals Bristol NHS Foundation Trust Clinical Research Fellowship. Dr Lobo is supported by the Bart's Charity. The

Bristol NIHR Biomedical Research Unit for Cardiovascular Disease and Above and Beyond charity supported the renal denervation procedures performed in Bristol. Medtronic is supporting ongoing renal denervation research at the Bristol Heart Institute. Funding for renal denervation procedures at St Bartholomew's was provided by Medtronic as sponsor of Symplicity HTN-2 and also as provider of ablation catheters for use outside Symplicity HTN-2. Dr Lobo is a member of the Advisory Board and speaker bureau for Medtronic 2010-2012 and the Advisory Board and speaker bureau for St Jude Medical (2012-2015).

Dr Melvin Lobo

Department of Clinical Pharmacology

William Harvey Heart Centre,

Charterhouse Square

London, EC1M 6BQ, UK.

Email: m.d.lobo@qmul.ac.uk

Tel: (+44) 0207 882 3402

Fax: (+44) 0207 8823408

Prof Andreas Baumbach

CardioNomics Research Group

School of Clinical Sciences

University of Bristol

Bristol Royal Infirmary

Bristol, BS2 8HW, UK.

Email: Andreas.Baumbach@uhbristol.nhs.uk

Tel: (+44) 0117 342 6573

Fax: (+44) 0117 342 5968

Word count: 2698 (plus 498 in boxes)

No of Boxes: 2

No. of Tables: 2

No. of Figures: 5

Key Words:

Hypertension, renal nerves, sympathetic nervous system, blood pressure, kidney, renal denervation

Abstract

Renal denervation (RDN) is a therapy targeting treatment resistant hypertension (TRH). Symplicity HTN-1&2 reported response rates of >80%, however sham-controlled Symplicity HTN-3 failed to reach its primary blood pressure outcome. We address the current controversies surrounding RDN, illustrated with real-world data from two UK centres.

In our cohort 52% of patients responded to RDN; 13 ± 32 mmHg reduction in office systolic BP (oSBP) at six months (n=29, p=0.03). Baseline oSBP and number of ablations correlated with oSBP reduction (R=-0.47, p=0.01; R =-0.56, p=0.002).

In our experience RDN is an effective treatment for some patients with TRH, however individual responses are highly variable. Selecting patients for RDN is challenging; only 10% (33/321) of patients screened were eligible for our study. Medication alterations and non-adherence confound outcomes. Adequate ablation is critical and should impact on future catheter design/training. Markers of procedural success and improved patient selection parameters remain key research aims.

Introduction

Renal denervation (RDN) was developed as an endovascular ablation technique for patients with treatment resistant hypertension (TRH, blood pressure (BP) $\geq 140/90$ mmHg despite ≥ 3 anti-hypertensive medications). The procedure uses various energy modalities (such as radiofrequency (RF), ultrasound or cryotherapy) to disrupt the nerves innervating the kidney including both sympathetic efferent and sensory afferent nerves(1); when activated the latter can trigger reflex increases in sympathetic activity and arterial pressure(2). Initial proof of concept and safety studies (Symplicity HTN-1 and EnligHTN I) and a subsequent randomised controlled trial (RCT, Symplicity HTN-2) reported response (≥ 10 mmHg drop in office systolic blood pressure (oSBP)) rates of $\geq 80\%$ at 6 months post RDN(3-5). Significant reductions in oBP were maintained out to at least 24 months post denervation in all three of these studies ($-29/-14$ mmHg, $-29/-13$ mmHg and $-30/-11$ mmHg respectively)(6-8). However, most recently, the American sham-RCT (Symplicity HTN-3) failed to meet its primary outcome of a reduction in office BP at 6 months, prompting renewed discussion into the efficacy of RDN(9). In this review we will address the current controversies surrounding RDN and consider how real-world RDN outcomes can be put into perspective in light of the data from these large scale studies.

We will support this review with data from two UK centres, St Bartholomew's Hospital in London (Bart's) and the Bristol Heart Institute (BHI). These data illustrate the real-world clinical experience of RDN and highlight the variability in BP response, as well as some of the challenges involved in implementing a novel, invasive, irreversible and expensive therapy, in rigorously selected patients with TRH. The key findings from the cohort of our first 29 patients treated with RDN for TRH are described in Box 1; these lessons, which predict some of the problems that led to the failure of the large scale trial Symplicity HTN-3, will form the basis of our discussion.

Methods

321 patients were screened in order to recruit 29 patients with TRH from two British Hypertension Society-accredited Specialist Hypertension Clinics (Bart's: 11 patients, BHI: 18 patients) for RDN (see Figure 1). The subjects were enrolled between December 2009 and January 2011 in the Bart's cohort, and March 2012 and January 2013 in the BHI cohort. Prior to RDN, our patients were investigated for secondary causes of hypertension, white-coat hypertension (home and/or ambulatory blood pressure monitoring (ABPM)) and questioned about drug adherence (with observed tablet taking and subsequent ABPM at Bart's). Renal anatomy was determined prior to RDN using magnetic resonance or computerised tomography angiography and deemed suitable for ablation according to Joint British Society guidelines(10). RDN was performed via a 6 French femoral arterial sheath, under fluoroscopic guidance, using a Symplicity-Flex catheter (Medtronic, Inc., Santa Rosa, CA, USA). 4-7 discrete 8 watt RF ablations of 2 minutes duration each were administered within both renal arteries in a helical distribution. Patients were followed up with measures of office BP and ABPM at baseline, 1, 3, 6 and 12 months. The primary intent was to keep medications unchanged during follow-up, however medications could be changed at the discretion of the treating physician if clinically indicated. The study was approved by local ethics committees, and all patients provided written informed consent.

Statistics

Our data are presented as mean \pm standard deviation. Changes in physiological parameters have been assessed for significance using Student's t-test or 1-way ANOVA (with Bonferroni multiple comparison test) for continuous data with equal variances, Kruskal-Wallis test for continuous data with unequal variances, and Pearson chi-squared test for categorical data. Relationships between these parameters were evaluated using Pearson's correlation coefficient and linear regression (GraphPad Prism). A two-tailed p value of <0.05 was regarded as statistically significant.

Results and Discussion

Blood Pressure Outcomes

The response rate in our cohort was only 52% (15/29) at 6 months and 62% (13/21) at 12 months post RDN. Whilst there was a significant 13 ± 32 mmHg reduction in mean oSBP in our study cohort at six months following the procedure ($n=29$, $p=0.03$), this change is not of the magnitude seen in Symplicity HTN 1&2 (-22 ± 22 and -32 ± 23 mmHg respectively)(3, 5). Baseline patient characteristics for our cohort are summarised in Table 1 and mean oBP outcome data are shown in Figure 2. The BP responses were highly variable with some patients developing a clinically significant (≥ 10 mmHg, $n=15$) reduction in oSBP 6 months post RDN, whilst in others little BP effect ($n=7$) or an increase ($n=7$) was observed. Amongst the 15 patients who did respond to RDN the oSBP reduction at 6 months was robust (-38 ± 23 mmHg, $p<0.05$) and similar to that observed in Symplicity HTN-1&2(3, 5), furthermore by 12 months four patients had an oSBP reduction of >50 mmHg. These individual data are shown in Figure 3.

Our real-world data cannot replicate the findings of the Symplicity studies and are more reflective of the success rates seen in other European studies(11-13). The UK Renal Denervation Affiliation reports an oBP reduction of $22/9$ mmHg ($p<0.001$) in a cohort of 246 patients from 16 centres (14). The ALSTER and Heidelberg registries also report real-world data, with better response rates of 76% ($n=93$) and 73% ($n=63$) respectively(15, 16). Persu et al. report a response rate of 59.6% in their meta-analysis of 10 European expert RDN centres(17), and the Global Symplicity Register of 998 patients gives a response rate of 67%(18). These findings are more consistent with our 52% response rate and corroborate our clinical impression that whilst renal denervation is effective in some patients, it is not a panacea for all patients with poorly controlled hypertension.

13 patients in our cohort had ABPM data available at six months. There was a change in mean 24hr BP of $-12 \pm 21 / -7 \pm 14$ mmHg ($p=0.07/0.10$). Mean daytime BP changed by $-14 \pm 21 / -8 \pm 14$ mmHg ($p=0.04/0.07$) and mean night time BP by $-9 \pm 23 / -6 \pm 15$ mmHg ($p=0.23/0.53$)(Figure 4). The lack of ABPM data for all patients in our cohort is a clear limitation of the study. Our access to ABPM devices has now improved, however some patients (particularly those with the highest BP) continue to find high pressure cuff inflations during ABPM intolerable.

Mahfoud et al. compared the reduction in office and ambulatory BP in patients with resistant and pseudo-resistant hypertension following RDN; whilst both groups demonstrated a reduction in oBP, only those with true resistant hypertension demonstrated a significant reduction in 24hr ABPM of $-10.2/-4.9$ mmHg(19). The use of 24hr ABPM data as an outcome measure may also prove to better reflect the regression of end organ damage in these significantly hypertensive patients since nocturnal hypertension in particular correlates strongly with cardiovascular morbidity and mortality(20, 21). Ultimately BP is only a surrogate marker for the physical and economic burden inflicted by conditions such as stroke, myocardial infarction and chronic kidney disease(19, 22).

Predictors of Blood Pressure Response to Renal Denervation

The strongest positive predictor for a reduction in oSBP in the Symplicity HTN-3 study was a baseline oSBP of ≥ 180 mmHg(9, 23), a criterion which has previously been shown to correlate with BP reduction post RDN, as highlighted in the Global Symplicity and Heidelberg registry data(16, 18). We confirmed this significant correlation between baseline oSBP and the change in oSBP at 6 months ($R=-0.47$, $p=0.01$, Figure 5A) in our subjects.

Recent findings by Ewen et al. indicate that patients with isolated systolic hypertension (ISH) and therefore lower DBP, have a restricted response to RDN(24); this finding is supported by our data

with respect to baseline office and ambulatory DBP and ABPM outcomes (see figures 5B and C).

Conventionally a BP response to RDN has been arbitrarily defined as a reduction in oSBP of ≥ 10 mmHg(3). If our cohort is divided into RDN BP responders (n=15, oSBP reduction ≥ 10 mmHg), non-responders (n=7, change in BP -9 to +10 mmHg) and reverse responders (n=7, increase in oSBP > 10 mmHg), the key significant differences in baseline characteristics between these groups relate to the number of ablations the participants received (see Table 2). Our data demonstrate a significant correlation between both the number of ablations per artery and the total number of ablations for any given patient and the reduction in oSBP at 6 months (R=-0.56, p=0.002 and R=-0.55, p=0.002 respectively).

RDN Technique

One of the main critiques of Symplicity HTN-3 has been inadequate denervation due to operator inexperience/inadequate proctoring; there were 111 operators across 88 sites, of whom 31% contributed only 1 procedure and 23% contributed ≥ 5 procedures(9). This contrasts with the greater BP reductions seen in the Global Symplicity Registry in which 59% of operators performed > 15 procedures(18). Only 19/364 patients received per-protocol RDN in Symplicity HTN-3 and this, along with the confounding effects due to medication changes in 39% of the population, renders the trial difficult to interpret(9, 23).

In our cohort, reverse responders had significantly fewer ablations than responders and non-responders (see Table 2). It is possible that patients who only receive partial renal denervation may have an increase in BP due to unopposed action of the (usually inhibitory) reno-renal reflexes(25). Alternatively, partial denervation could cause sensitisation of those nerves that remain,

inflammation of the nerves, or growth of new nerves which could exacerbate the degree of hypertension(26, 27).

So how much denervation is required? In Symplicity HTN-1 a subset of patients underwent assessment with norepinephrine spillover, a validated technique for assessing regional sympathetic tone(28); a 47% reduction in sympathetic nerve activity (SNA) appeared sufficient to achieve a reduction in BP(3, 29). Further analyses by Esler et al. have shown that denervation following renal nerve ablation is highly variable between individuals and it is clear that the procedure is far more technically challenging than previously considered(29, 30). When the Symplicity catheter was first launched, operators were advised to prioritise ablation of the proximal superior aspect of the renal artery in order to target the highest density of renal nerves. However, review of novel anatomical human data indicates that the renal nerves accessible to intraluminal RF energy lie more distally in the renal artery adventitia(31); therefore operators following the earlier guidance may have been targeting the wrong part of the artery, resulting in inadequate denervation(32).

If the 'completeness' of denervation relates to procedural success, then a method for assessing the degree of renal nerve disruption achieved would be of significant clinical benefit and guide development of evolving catheter technologies. Techniques including direct electrical renal nerve stimulation, urinalysis for breakdown products of renal sympathetic nerve degradation (e.g. tyrosine hydroxylase) and measurement of reflex responses to afferent renal nerve stimulation with agents such as adenosine or bradykinin are under evaluation(33-35).

Patient Selection for Renal Denervation

In Symplicity HTN-2, 109 out of 190 (56%) patients screened were eligible for RDN. With tighter screening in Symplicity HTN-3 (including ABPM), of the 1441 patients assessed across 88 sites in the

United States, 561 (39%) were eligible for enrolment(5, 9). In our experience, meticulous screening of 321 patients referred to our Specialist Hypertension Clinics identified only 33 individuals (10%) with true TRH, suitable renal artery anatomy, and without significant excluding comorbidities (including eGFR <45 ml/min/1.73m² as per Symplicity HTN-2(5)) who were eligible for RDN (see Figure 1 and Table 1). This is consistent with estimates that 10-15% of patients with hypertension are genuinely treatment resistant once secondary causes of hypertension, pseudo-resistant hypertension and poor medication adherence are excluded(36, 37).

From our clinics, 184 of the 321 patients screened underwent renal magnetic resonance or computerised tomography (CT) angiography as part of their assessment for secondary hypertension; 20% of these patients (36/184) were anatomically ineligible for RDN including 8 cases of renal artery stenosis. This is a slightly higher anatomical exclusion rate than the 16% (30/190) of patients with ineligible anatomy in Symplicity HTN-2, but of a similar magnitude to the 20% (179/880) anatomical exclusion rate in Symplicity HTN-3(5, 9).

Medication Alteration and Adherence

There are important limitations with both our cohort and the Symplicity HTN studies surrounding the confirmation of adherence to medications and also changes in antihypertensive medication during the follow-up period(3, 5, 9).

In Symplicity HTN-2&3 there were medication changes in 23% and 39% of patients prior to 6 month follow-up respectively, however, the primary study outcomes were unaltered if patients with medication changes were removed from analyses(5, 9, 23). In our cohort, medications were changed in 59% (17/29) patients, however, there were no medication increases in patients who responded to RDN, and so, these drug changes would have blunted, rather than supplemented, any BP effect

seen. The standardised stepped-care antihypertensive medication regime used in the DENER-HTN study demonstrates that this issue can be well managed, although adequate patient support and infrastructure is required(38).

The run in period prior to RDN should also be considered; in Symplicity HTN-3 patients were only required to be on a stable drug regimen for two weeks prior to baseline assessments and it is therefore possible that medication changes could have influenced the data if there was an inadequate wash-in/wash-out period. An eight week period on stable medication should be required to ensure that any intervention is not confounded by a time-dependent drug effect(39).

Symplicity HTN-3 did not simply show a failure to alter BP, it demonstrated a significant reduction in oSBP in both RDN and sham groups (-14.13 ± 23.93 mmHg and -11.74 ± 25.94 mmHg respectively (both $p < 0.001$))(9). Of note, in Symplicity HTN-2 35% of control subjects had a ≥ 10 mmHg reduction in oSBP six months post RDN(5). This decrease in BP may be explained by an improvement in medication adherence. The phenomenon of a 'placebo' effect due to enrolment in a clinical study (also known as the Hawthorne effect) is well established(40) and it is likely that the 8 study contact points between screening and 6 month follow-up in Symplicity HTN-3 provided greater patient support than standard medical care(23).

Kandazari et al. highlight the significant reduction in oSBP in RDN vs sham patients amongst non-African American subjects in Symplicity HTN-3 (-15.2 vs -8.6 mmHg, $p=0.01$)(23). In fact, African American and non-African American subjects had similar oSBP responses 6 months after RDN (-15.5 and -15.2 mmHg respectively), and the difference in the oSBP outcomes lies in the sham arm of the study(23). Amongst the sham group, African American participants demonstrated a borderline significant greater reduction in oSBP than non-African American subjects (-17.8 vs -8.6 mmHg, $p=0.057$)(23, 41). Flack et al.'s recent multivariate analysis of Symplicity HTN-3 demonstrated that

African American race did not independently predict SBP outcomes in either the RDN or sham groups, however, in the sham group the interaction between African American race and being prescribed at least one antihypertensive medication three times per day was associated with a greater reduction in oSBP at 6 months(41). In the sham group there was also a trend towards a greater reduction in oSBP for patients living in the south/south-eastern regions of the USA(41); areas which have previously been associated with lower rates of medication adherence(42).

In Symplicity HTN-3 African American participants were taking a greater number of antihypertensive medications and had more complex medication regimes than non-African Americans(41). Individuals with complex drug regimens or who are prescribed a greater number of medications may be particularly likely to be non-adherent, and hence more vulnerable to a Hawthorne effect if enrolled in a clinical trial(43, 44). Hameed et al. addressed this issue by using directly observed medication administration with subsequent BP monitoring to confirm adherence prior to RDN(12). Their cohort achieved a response rate of 51% with an oBP reduction of -15/-6 mmHg ($p=0.01/0.2$) at 6 months, which is unlikely attributable to improved medication adherence. Given that at least 50% of patients with TRH are known to be non-adherent with their medications(45), more thorough assessment of medication adherence at screening, and during follow-up, should be mandatory in order to assess true drug resistance and establish any unreported changes in medication. Unfortunately, the best technique for assessing adherence, be it urine drug testing or observed tablet taking and ABPM, is yet to be established.

Conclusions

The failure of Symplicity HTN-3 to meet its primary BP outcome could condemn RDN to the history books. However, whilst individual responses vary considerably and real-world data cannot replicate the high success rates of earlier trials(18), and a Hawthorne effect amongst study participants must

be considered, there does appear to be a sub population of patients with TRH who respond to RDN. Whether this variability in outcome is due to inappropriate patient selection (including those with pseudo-resistant or non-sympathetically mediated hypertension), confounding drug titrations and adherence issues, or technical issues relating to incomplete denervation is yet to be clarified(46). Many of the controversies which now surround RDN could have been predicted from pre-existing real-world experience. The lessons detailed below (see Box 2) may help to identify those most likely to respond to RDN and evaluate the mechanisms underlying this intervention.

Acknowledgments

We would like to thank the Barts Charity, Bristol NIHR Cardiovascular Research Unit and the Bristol Above and Beyond charity for supporting this research.

References

1. Gulati V, White WB. Review of the state of renal nerve ablation for patients with severe and resistant hypertension. *J Am Soc Hypertens*. 2013;7(6):484-93.
2. Sobotka PA, Mahfoud F, Schlaich MP, Hoppe UC, Bohm M, Krum H. Sympatho-renal axis in chronic disease. *Clin Res Cardiol*. 2011;100(12):1049-57.
3. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373(9671):1275-81.
4. Worthley SG, Tsioufis CP, Worthley MI, Sinhal A, Chew DP, Meredith IT, et al. Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial. *Eur Heart J*. 2013;34(28):2132-40.
5. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet*. 2010;376(9756):1903-9.
6. Krum H, Schlaich MP, Sobotka PA, Bohm M, Mahfoud F, Rocha-Singh K, et al. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet*. 2014;383(9917):622-9.
7. Tsioufis CP, Papademetriou V, Dimitriadis KS, Kasiakogias A, Tsiachris D, Worthley MI, et al. Catheter-based renal denervation for resistant hypertension: Twenty-four month results of the

EnligHTN I first-in-human study using a multi-electrode ablation system. *Int J Cardiol.* 2015;201:345-50.

8. Esler MD, Bohm M, Sievert H, Rump CL, Schmieder RE, Krum H, et al. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPPLICITY HTN-2 randomized clinical trial. *Eur Heart J.* 2014;35(26):1752-9.

9. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med.* 2014;370(15):1393-401.

10. Mark Caulfield MdB, Trevor Cleveland, David Collier, John Deanfield, Huon Gray, Charles Knight, Melvin Lobo, Matthew Matson, Jon Moss, Neil Poulter, Iain Simpson, Charles Tomson, Bryan Williams. The Joint UK Societies Consensus on Renal Denervation for Resistant Hypertension 2011. Available from: <http://www.bhsoc.org/resources/bhs-statements/>.

11. Zuern CS, Eick C, Rizas KD, Bauer S, Langer H, Gawaz M, et al. Impaired cardiac baroreflex sensitivity predicts response to renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol.* 2013;62(22):2124-30.

12. Hameed MA, Pucci M, Martin U, Watkin R, Doshi S, Freedman J, et al. Renal Denervation in Patients With Uncontrolled Hypertension and Confirmed Adherence to Antihypertensive Medications. *J Clin Hypertens (Greenwich).* 2015 Oct 5. [Epub ahead of print]

13. Rohla M, Nahler A, Lambert T, Reiter C, Gammer V, Grund M, et al. Predictors of response to renal denervation for resistant arterial hypertension: a single center experience. *J Hypertens.* 2016 Jan;34(1):123-9.

14. Sharp A, Hameed A, Nightingale A, Martin U, Mark P, McKane W, et al. 8B.07: Results from the UK Renal Denervation Affiliation - 246 cases from 17 centres. *J Hypertens*. 2015;33 Suppl 1:e109.
15. Kaiser L, Beister T, Wiese A, von Wedel J, Meincke F, Kreidel F, et al. Results of the ALSTER BP real-world registry on renal denervation employing the Symplicity system. *EuroIntervention*. 2014;10(1):157-65.
16. Vogel B, Kirchberger M, Zeier M, Stoll F, Meder B, Saure D, et al. Renal sympathetic denervation therapy in the real world: results from the Heidelberg registry. *Clin Res Cardiol*. 2014;103(2):117-24.
17. Persu A, Jin Y, Azizi M, Baelen M, Volz S, Elvan A, et al. Blood pressure changes after renal denervation at 10 European expert centers. *J Hum Hypertens*. 2014;28(3):150-6.
18. Bohm M, Mahfoud F, Ukena C, Hoppe UC, Narkiewicz K, Negoita M, et al. First report of the Global SYMPPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. *Hypertension*. 2015;65(4):766-74.
19. Mahfoud F, Ukena C, Schmieder RE, Cremers B, Rump LC, Vonend O, et al. Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. *Circulation*. 2013;128(2):132-40.
20. Mancia G, Zanchetti A, Agabiti-Rosei E, Benemio G, De Cesaris R, Fogari R, et al. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. SAMPLE Study Group. Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation. *Circulation*. 1997;95(6):1464-70.

21. Hermida RC, Ayala DE, Mojon A, Smolensky MH, Portaluppi F, Fernandez JR. Sleep-time ambulatory blood pressure as a novel therapeutic target for cardiovascular risk reduction. *J Hum Hypertens*. 2014;28(10):567-74.
22. Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hashimoto J, et al. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. *Hypertension*. 2006;47(2):149-54.
23. Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. *Eur Heart J*. 2015;36(4):219-27.
24. Ewen S, Ukena C, Linz D, Kindermann I, Cremers B, Laufs U, et al. Reduced effect of percutaneous renal denervation on blood pressure in patients with isolated systolic hypertension. *Hypertension*. 2015;65(1):193-9.
25. Protasoni G, Golin R, Genovesi S, Zanchetti A, Stella A. Functional evidence of inhibitory reno-renal reflexes in spontaneously hypertensive rats. *Blood Press*. 1996;5(5):305-11.
26. Booth LC, Nishi EE, Yao ST, Ramchandra R, Lambert GW, Schlaich MP, et al. Reinnervation following catheter-based radio-frequency renal denervation. *Exp Physiol*. 2015;100(5):485-90.
27. Sakakura K, Tunev S, Yahagi K, O'Brien AJ, Ladich E, Kolodgie FD, et al. Comparison of histopathologic analysis following renal sympathetic denervation over multiple time points. *Circ Cardiovasc Interv*. 2015;8(2):e001813.

28. Meredith IT, Esler MD, Cox HS, Lambert GW, Jennings GL, Eisenhofer G. Biochemical evidence of sympathetic denervation of the heart in pure autonomic failure. *Clin Auton Res.* 1991;1(3):187-94.
29. Esler M. Illusions of truths in the Symplicity HTN-3 trial: generic design strengths but neuroscience failings. *J Am Soc Hypertens.* 2014;8(8):593-8.
30. Tzafiri AR, Keating JH, Markham PM, Spognardi AM, Stanley JR, Wong G, et al. Arterial microanatomy determines the success of energy-based renal denervation in controlling hypertension. *Sci Transl Med.* 2015;7(285):285ra65.
31. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, et al. Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol.* 2014;64(7):635-43.
32. Mahfoud F, Edelman ER, Bohm M. Catheter-based renal denervation is no simple matter: lessons to be learned from our anatomy? *J Am Coll Cardiol.* 2014;64(7):644-6.
33. Esler M. Renal denervation for treatment of drug-resistant hypertension. *Trends Cardiovasc Med.* 2015;25(2):107-15.
34. Gal P, de Jong MR, Smit JJ, Adiyaman A, Staessen JA, Elvan A. Blood pressure response to renal nerve stimulation in patients undergoing renal denervation: a feasibility study. *J Hum Hypertens.* 2015;29(5):292-5.
35. Katholi RE, Whitlow PL, Hageman GR, Woods WT. Intrarenal adenosine produces hypertension by activating the sympathetic nervous system via the renal nerves in the dog. *J Hypertens.* 1984;2(4):349-59.

36. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. *Hypertension*. 2011;57(6):1076-80.
37. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension*. 2011;57(5):898-902.
38. Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart 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;S0140-6736(14):61942-5.
39. Lobo MD, de Belder MA, Cleveland T, Collier D, Dasgupta I, Deanfield J, et al. Joint UK societies' 2014 consensus statement on renal denervation for resistant hypertension. *Heart*. 2015;101(1):10-6.
40. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol*. 2014;67(3):267-77.
41. Flack JM, Bhatt DL, Kandzari DE, Brown D, Brar S, Choi JW, et al. An analysis of the blood pressure and safety outcomes to renal denervation in African Americans and Non-African Americans in the SYMPPLICITY HTN-3 trial. *J Am Soc Hypertens*. 2015;9(10):769-79.
42. Couto JE, Panchal JM, Lal LS, Bunz TJ, Maesner JE, O'Brien T, et al. Geographic variation in medication adherence in commercial and Medicare part D populations. *J Manag Care Spec Pharm*. 2014;20(8):834-42.

43. Baggaly SA, Kemp RJ, Wang X, Magoun AD. Factors associated with medication adherence and persistence of treatment for hypertension in a Medicaid population. *Res Social Adm Pharm.* 2014;10(6):e99-112.

44. Marquez-Contreras E, Gil-Guillen VF, De La Figuera-Von Wichmann M, Franch-Nadal J, Llisterri-Caro JL, Martell-Claros N, et al. Non-compliance and inertia in hypertensive Spaniards at high cardiovascular risk: CUMPLE study. *Curr Med Res Opin.* 2014;30(1):11-7.

45. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens.* 2013;31(4):766-74.

46. Schlaich MP, Esler MD, Fink GD, Osborn JW, Euler DE. Targeting the sympathetic nervous system: critical issues in patient selection, efficacy, and safety of renal denervation. *Hypertension.* 2014;63(3):426-32.

Real-world findings from the Bart's/BHI renal denervation cohort

1. Despite rigorous patient selection, using similar inclusion criteria, we could not reproduce the response rate of >80% seen in the first two Symplicity studies; the response rate in our cohort was only 52% at 6 months (n=29)(4,5).
2. Baseline oSBP predicts an individual patient's response (≥ 10 mmHg reduction in oSBP) to RDN; patients with an oSBP of >177 mmHg being most likely to respond.
3. Previous studies have reported outcome data as a mean reduction in oBP, but this does not tell the full story. The individual patient response to RDN is highly variable and responders, non-responders and even reverse responders (with an increase in oBP after RDN) can be identified. Reverse responders had fewer ablations points than both responders and non-responders in our cohort, a finding that highlights the importance of operator experience and has significant implications for the development of novel RDN catheters.
4. Identifying appropriate patients for RDN is a challenge. From our specialist hypertension clinics, 321 patients were screened to identify only 33 (10 %) individuals with TRH who were eligible for RDN. 20% of these patients (36/184) were anatomically ineligible for RDN, including 8 cases of renal artery stenosis.
5. Despite our aim to keep medications unchanged during the first six months of follow-up, 17/29 (59%) patients had changes to their drug regimens during this period; challenges in controlling medications and confirming medication adherence in real-world clinical situations make BP outcome data more difficult to interpret.

Box 1: Findings from the Bart's/BHI renal denervation cohort. Following rigorous screening, 29 patients underwent renal denervation using a Symplicity Flex catheter with baseline and outcome measures of office and ambulatory blood pressure. oSBP: office systolic blood pressure, RDN: renal denervation, TRH: treatment resistant hypertension.

Clinical implications for future studies of renal denervation

- The magnitude and rate of response to RDN in the real-world is not as high as in Symplicity HTN-1&2, and future trials should be powered accordingly.
- ABPM at baseline and study endpoints should be mandatory, and the relationship between white-coat effect and response to RDN further addressed.
- Blood pressure is a marker for hypertensive disease and data for hard endpoints based on target organ damage (e.g. left ventricular hypertrophy, excretory renal function, albuminuria, stroke, myocardial infarction) are required to support the efficacy of RDN.
- RDN is consistently most effective in those patients with severe treatment resistant hypertension (oSBP >160 mmHg). A greater understanding of the mechanisms underlying RDN should be established before this therapy is offered to the broader hypertensive population.
- Hypertension is an umbrella term and may cover a range of pathologies. Patients with white-coat effect or isolated systolic hypertension represent subgroups with different underlying physiology and therefore potentially different susceptibility to RDN.
- Adequate ablation is critical and should impact on operator training and catheter design; BP outcomes can only be interpreted if we know that adequate denervation has been achieved. On-table markers of procedural success are required.
- The extent of renal denervation required to reduce blood pressure is yet to be established, and the possibility that inadequate denervation could exacerbate hypertension must be considered.
- Medication changes and adherence issues confound BP outcomes; every attempt should be made to standardise and monitor adherence to concurrent pharmacotherapy during RDN trials.

Box 2. Clinical implications for future studies of renal denervation. RDN: renal denervation, oSBP: office systolic blood pressure, ABPM: ambulatory blood pressure monitoring.

	Baseline (n=29)
Demographics	
Age (years)	55.4 ± 12.9
Male gender	14 (48%)
Body mass index (kg/m ²)	30.2 ± 4.3
Risk factors and target organ damage	
eGFR (ml/min/1.73m ²)	74 ± 18
Type II diabetes	5 (17%)
Hypercholesterolaemia	7 (24%)
Rheumatoid arthritis	2 (7%)
Coronary artery disease	8 (28%)
Cerebrovascular disease	9 (31%)
Antihypertensive treatment	
No. of antihypertensive drugs	5.2 ± 1.7
ACEi/ARB	23 (79%)
Calcium channel blockers	21 (72%)
Diuretics	22 (76%)
Aldosterone antagonists	13 (45%)
Beta-blockers	18 (62%)
Alpha-blockers	18 (62%)
Direct renin inhibitors	6 (21%)
Centrally acting agents	12 (41%)
Direct vasodilators	4 (14%)
Office blood pressure and heart rate measurements	
SBP (mmHg)	188 ± 20
DBP (mmHg)	104 ± 21
PP (mmHg)	84 ± 20
Heart rate (bpm)	82 ± 18
ABPM Data	
Daytime SBP (mmHg, n=18)	171 ± 19
Daytime DBP (mmHg, n=18)	101 ± 18
Night time SBP (mmHg, n=16)	157 ± 23
Night time DBP (mmHg, n=16)	89 ± 21
24hr SBP (mmHg, n=16)	168 ± 19
24hr DBP (mmHg, n=16)	99 ± 20
24hr heart rate (bpm, n=16)	76 ± 12

Table 1. Patient baseline characteristics. We present baseline demographic data for our cohort, including ABPM data excluding white-coat hypertension for 18/29 patients. The remaining 11 patients were assessed for pseudo-resistant hypertension using home blood pressure monitoring or ABPM assessment in primary care prior to enrolment in our study. Data shown as mean ± standard deviation. eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, PP: pulse pressure, ACEi: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blockers, bpm: beats per minute.

	Responders (n=15)	Non Responders (n=7)	Reverse Responders (n=7)	P=
Response to RDN				
at 6 months				
Δ oSBP	-38 \pm 23 [-49,-26] ^{*†}	1 \pm 4.4 [-4.2,2.2] [*]	26 \pm 10 [18,34] [†]	<0.0001
Δ oDBP	-11 \pm 19 [-20,-1]	-3 \pm 12 [-12,5]	5 \pm 16 [-6,17]	0.12
Baseline Parameters				
Age (years)	59.9 \pm 12.1	49.6 \pm 9.0	51.4 \pm 15.5	0.14
Male gender	9 (60%)	3 (43%)	2 (29%)	0.37
Body mass index (kg/m ²)	29.7 \pm 2.6	32.1 \pm 5.1	29.8 \pm 6.5	0.52
eGFR (ml/min/1.73m ²)	77 \pm 13	72.4 \pm 17.8	68.6 \pm 25.9	0.55
No. of antihypertensives	4.9 \pm 1.6	5.9 \pm 2.0	5.0 \pm 1.8	0.49
No. of ablations per artery	5.6 \pm 0.6 [†]	5.5 \pm 0.8 [#]	4.4 \pm 0.8 ^{†#}	0.003
Total number of ablations	11.0 \pm 1.2 [†]	11.0 \pm 1.5 [#]	8.9 \pm 1.7 ^{†#}	0.008
oSBP (mmHg)	192 \pm 17	186 \pm 14	180 \pm 30	0.41
oDBP (mmHg)	101 \pm 21	105 \pm 21	109 \pm 24	0.69
Heart rate (bpm)	79 \pm 18	86 \pm 17	90 \pm 20	0.49

Table 2. Difference in office BP outcomes and baseline parameters between BP responders (reduction in oSBP \geq 10 mmHg), non-responders (change in oSBP between -9 and +10 mmHg) and reverse responders (increase in oSBP >10 mmHg). Significant differences between subgroups for each parameter as indicated ($p < 0.05$): *Responders vs Non Responders, †Responders vs Reverse Responders, #Non Responders vs Reverse Responders. oSBP: office systolic blood pressure, oDBP: office diastolic blood pressure, bpm: beats per minute. Data shown as mean \pm SD [CI]. P values from 1 way ANOVA with Bonferroni multiple comparison test for continuous data and Pearson chi-squared test for categorical data.

Figure 1. Patient screening pathway prior to renal denervation. All patients identified via Specialist Hypertension Clinic. eGFR; estimated glomerular filtration rate (units ml/min/1.73m²)

Figure 2. Change in mean office systolic and diastolic blood pressure 1, 3, 6 and 12 months post renal denervation (RDN). SBP: systolic blood pressure, DBP: diastolic blood pressure. *p = 0.03, **p = 0.002.

Figure 3. Change in office systolic blood pressure (oSBP) for individual patients at 1, 3, 6 and 12 months post renal denervation (RDN). Patients grouped by oSBP outcome at 6 months post RDN: A. Responders (reduction in oSBP \geq 10 mmHg), B. Non-responders (change in oSBP between -9 and +10 mmHg), C. Reverse responders (increase in oSBP >10 mmHg).

Figure 4. Change in blood pressure parameters for the 13 patients with ambulatory BP data at baseline and 6 months post renal denervation. SBP: systolic blood pressure, DBP: diastolic blood pressure. *p = 0.04

Figure 5. A. Correlation between baseline office SBP and the change in office SBP (primary outcome measure) at 6 months post renal denervation. In the 13 patients with available ambulatory BP data: B. Correlation between baseline office DBP and the change in mean 24hr SBP at 6 months post renal denervation, C. Correlation between baseline daytime DBP and the change in mean 24hr SBP at 6 months post renal denervation. oSBP: office systolic blood pressure, oDBP: office diastolic blood pressure, R: Pearson's correlation coefficient.