EuroIntervention 2014;10:21-23

From SYMPLICITY HTN-3 to the Renal Denervation Global Registry: where do we stand and where should we go?

Atul Pathak[1]*, MD; Sebastian Ewen[2], MD; Jean Fajadet[3], MD; Benjamin Honton[3], MD; Felix Mahfoud[2], MD; Jean Marco[4], MD; Markus Schlaich[5], MD; Roland Schmieder[6], MD; Konstantinos Tsioufis[7], MD; Christian Ukena[2], MD; Thomas Zeller[8], MD

1. Université de Toulouse Paul Sabatier, CHU de Toulouse, Service de Pharmacologie Clinique, Unité de Pharmacologie Cardiovasculaire et Autonome, INSERM 1048, Toulouse, France; 2. Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; 3. Cardiovascular Unit of the Clinique Pasteur, Toulouse, France; 4. PCR, Toulouse, France; 5. Neurovascular Hypertension & Kidney Disease and Human Neurotransmitters Laboratories, Baker IDI Heart & Diabetes Institute and Faculty of Medicine, Nursing & Health Sciences, Monash University, Melbourne, Victoria, Australia; 6. University Hospital Erlangen, Nephrology and Hypertension, Erlangen, Germany; 7. First Cardiology Clinic, University of Athens, Hippokration Hospital, Athens, Greece; 8. Universitaets-Herzzentrum Freiburg – Bad Krozingen, Klinik für Kardiologie und Angiologie II, Bad Krozingen, Germany

We read with interest the paper by Bhatt et al[1] published in the New England Journal of Medicine. In summary, the blinded SYMPLICITY HTN-3 trial did not show a significant difference in the reduction of systolic blood pressure (BP) in patients with resistant hypertension six months after renal denervation (RDN) as compared with a sham control. The primary safety endpoint of the trial was met. Herein, we are aiming not to discuss the potential weaknesses of the trial and how these may have impacted on the results, but rather to address the question as to whether this trial is informative and what it can teach us, whether it should impact on clinical decision making, how the trial may help clinicians or investigators to enhance their knowledge about appropriate patient selection for RDN, and whether it may provide a glimpse into the future development of RDN.

What have we learned from patients phenotypes in this trial?

As in many other studies, in SYMPLICITY HTN-3 one has to recognise that patients with true resistant hypertension represent a challenging population. According to epidemiological data, the prevalence of resistant hypertension among patients with hypertension in industrialised countries is approximately 10%[2,3]. However, proper selection of patients with true resistant hypertension in RDN trials has shown that the prevalence might be even lower if anatomical feasibility for RDN is taken into account[4]. Accordingly, the high screening failure in SYMPLICITY HTN-3 is not surprising and indicates the strict inclusion and exclusion criteria, with strict protocols for up-titration of medication. Whether the investigated patient population represents a real-world situation or whether it is rather artificial needs to be discussed. The systematic use of 24-hour ambulatory BP monitoring (ABPM) was an important design feature overcoming known limitations of office BP measurements alone. Unfortunately, thus far only the mean 24-hour ABPM data have been presented and it would be interesting to analyse other parameters of 24-hour ABPM. For example, almost 44% of patients were diabetic. These patients, when suffering from autonomic neuropathy, are known to display both orthostatic hypotension and also supine hypertension. Patients with obstructive sleep apnoea (OSA) syndrome usually present with nocturnal hypertension or non-dipper/reverse dipper phenotype and the prevalence of OSA amongst patients with resistant hypertension may be as high as 70%. Further, BP variability in this study could be used as an indirect measure to assess autonomic modulation and as a potential

Corresponding author: Service de Pharmacologie Clinique, Fédération des Services de Cardiologie, Faculté de Médecine/CHU de Toulouse, INSERM 1048, Université de Toulouse Paul Sabatier, 31432 Toulouse, France. E-mail: atul.pathak@univ-tlse3.fr

DOI: 10.4244/EIJV10I1A4

biomarker predicting response to RDN[5]. The authors should be encouraged to use their ABPM data to perform extensive assessment of BP phenotype, which may have an impact on RDN results.

What have we learned about RDN and sympathetic modulation?

While the vast majority of patients considered for RDN will have high sympathetic activity, this may not be the case in all. Despite the use of sophisticated non-invasive or invasive techniques (norepinephrine spillover, muscle sympathetic nerve activity, heart rate variability [HRV], plasmatic or urinary metabolites of sympathetic pathway), no definitive study has yet been able to identify the right biomarker to detect and predict elevated sympathetic activity or the optimal candidate for RDN. However, two recent studies have assessed potential biomarkers for RDN. Zuern et al suggested that cardiac baroreflex sensitivity (BRS) may be a predictor of response to RDN[6]. Dörr et al found that RDN responders had significantly higher serum levels of sFLT-1, ICAM-1, and VCAM-1 compared to the non responders group[7]. In the subgroup analyses of SYMPLICITY HTN-3, Afro-Americans (AA) were shown to have low renin levels and one out of two had genetic polymorphisms in the beta-1 adrenergic receptor gene, which provides evidence for the differences in pathophysiology of hypertension[8]. From antihypertensive drug trials, it is well known that AA respond differently to antihypertensive drugs, e.g., ACE inhibitors and angiotensin receptor blockers are less effective, whereas vasodilators are quite potent in lowering BP in this population[8]. Interestingly, in SYMPLICITY HTN-3 one quarter of the recruited patients were AA. A subgroup analysis revealed that AA had a substantially more pronounced sham response compared to non-AA (–17.8 mmHg versus –8.6 mmHg). In the RDN groups, AA and non-AA response was almost exactly the same. Further investigations are clearly needed to understand these results.

Are there some technical issues, or was renal denervation effective in this trial?

One reason why the trial could be neutral is that although the interventionists were experienced operators, the majority were unfamiliar with the specific RDN procedure. Looking at site experience, among 88 centres, 364 procedures have been performed by 111 operators, with 31% having performed only one procedure. As with any procedure, a learning curve can be postulated and the question arises as to whether this may have impacted on the degree of denervation achieved and, thereby, on BP results. The overall number of complete ablations was lower compared to other trials and the rate of notches following RDN was very low (60% had 0-1 notches). Additionally, further analysis of the results of different proctors would be interesting, to investigate whether there was a difference between operators who performed one or more than five procedures. Furthermore, there is no intraprocedural marker to confirm that RDN was successfully achieved in SYMPLICITY HTN-3. In SYMPLICITY HTN-1[9], a significant reduction in kidney norepinephrine spillover was measured in the first 10 patients to confirm a successful treatment; however, these patients were treated with a different catheter system and clearly the denervation achieved, on average a 47% reduction in renal noradrenaline spillover, is far from being complete. In most published RDN studies and even in those with limited BP lowering effects, heart rate significantly decreased after the procedure, partly BP independent. In SYMPLICITY HTN-3, heart rate remained unchanged in patients undergoing RDN, which might be a sign of unsuccessful RDN. The study underlines the need to develop biomarkers predicting response of effectiveness of the procedure. Finally, new technological developments and refinements (multi-electrode approach, stability of the device, other energy source such as ultrasound ablation or cryoablation) could help to improve the reproducibility with which substantial renal denervation can be achieved and thereby outcomes.

Is there a difference in effectiveness and safety when renal denervation is performed in real-world settings?

The Global SYMPLICITY Registry[10] is the first and largest dataset of patients treated with RDN. This open-label, multicentre study aimed to examine the safety and effectiveness of the procedure, and outcomes presented are for the first 1,000 consecutively enrolled patients at six months. There were five adverse events attributed to the procedure, including four vascular access-site complications (0.34%) and one renal artery dissection that was treated. There were also nine hospitalisations for hypertensive emergency (1.0%), eight for atrial fibrillation (0.9%), eight strokes (0.9%), six hospitalisations for new onset heart failure (0.7%), five heart attacks (0.6%), four deaths (0.4%) and two cases of new onset end-stage kidney disease (0.2%) that were considered unrelated to the procedure. In addition to the favourable safety profile, office systolic BP showed a significant drop at six months of 11.9 mmHg for all patients and of 19.8 mmHg for patients with baseline office pressure values greater than or equal to 160 mmHg. Ambulatory systolic BP dropped significantly at six months (–7.9 mmHg for all patients with pressures 140 or higher compared to –9.2 mmHg for the subset of patients with BP greater than or equal to 160 mmHg). This data set confirms previously published data about the safety of the procedure and indicated that RDN lowers BP in that open-label real-world registry.

Is a sham procedure a clinically meaningful control arm?

A sham procedure controlled study is the purest scientific approach to evaluate a new invasive therapy. In drug studies, placebo is an established control arm which could even be used in daily practice to replace active agents if being found equally effective to true drugs. However, a sham procedure, as used in the SYMPLICITY HTN-3 study, cannot be used in clinical daily practice because it would be unethical to expose a patient to general anaesthesia or sedation for simply performing a diagnostic renal angiogram. Even if RDN was not superior as compared to the sham procedure it did lower BP significantly in resistant hypertensive patients with no treatment alternative left. Thus, considering the potential risks of persistent resistant hypertension, one could argue that it would be

unethical to withhold from a patient a proven BP-lowering treatment option which might prevent life-threatening complications of resistant hypertension, even if this treatment modality is not more effective than a sham procedure. Perhaps not dissimilar to the experience with baroreflex activation therapy, it will be important to assess the longer-term BP effects of RDN vs. sham control with the possibility that any effect in the sham arm may gradually vanish, whereas the BP-lowering effect of RDN may be sustained, as demonstrated in both SYMPLICITY HTN-1 and HTN-2.

Involvement of patients in future research projects?

RDN might represent a possibility for non-compliant patients or for patients who do not take pills (non-adherent, non-persistent). Indeed, Jung et al[11] recently reported that non-adherence to drug treatment affects up to 50% of patients with difficult to control hypertension. Before we give the patient the choice, further studies in that interesting area are needed.

Renal denervation effects beyond blood pressure reduction?

There is growing evidence which is derived from animal and human studies that RDN might exert multiple pleiotropic effects beyond a pure reduction of BP and heart rate. Positive effects after renal sympathetic denervation have been described in glucose metabolism[12,13], obstructive sleep apnoea[14,15], reduction of left ventricular mass index, improvements of left ventricular ejection fraction and parameters of diastolic dysfunction in echo[16] and MRI[17] substudies, antiarrhythmic effect including atrial fibrillation[18,19] and ventricular arrhythmias[20], and chronic heart failure[21]. These small, preliminary studies are interesting but require further investigations to assess the potential utility of RDN in these disease states with increased sympathetic activity.

Conflict of interest statement

A. Pathak has received research grants, speaker honoraria and consultancy fees from Medtronic, St. Jude Medical, Covidien, ReCor Medical. F. Mahfoud was investigator of the Symplicity HTN-1 and HTN-2 trials and is supported by Deutsche Hochdruckliga and Deutsche Gesellschaft für Kardiologie and has received research grants, speaker honoraria and consultancy fees from Medtronic/Ardian, St. Jude Medical, Boston Scientific, and Cordis. M. Schlaich is supported by an NHMRC Research Fellowship and has received consulting fees, and/or travel and research support from Medtronic, Abbott, Novartis, Servier, Pfizer and Boehringer-Ingelheim. R. Schmieder is a member of the speakers' bureau or has received honoraria from AstraZeneca, Berlin Chemie AG, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Medtronic, Novartis, Servier, Takeda Pharmaceuticals and Terumo. He has acted as a consultant for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Medtronic, Novartis and Servier, and has received grant or research support (awarded to the University Hospital, University Erlangen/Nürnberg) from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Bundesminesterium für Bildung und Forschung, Daiichi Sankyo, Novartis and Medtronic. K. Tsioufis has received travel expenses from Medtronic and a research grant and honoraria fees from St. Jude Medical and is co-principal investigator of the ENLIGHTN I study. C. Ukena has received scientific support and speakers honoraria from Medtronic, St. Jude Medical, and Covidien. T. Zeller is an advisor for Medtronic, ReCor, Boston Scientific and receives study grants from St. Jude Medical, Medtronic, ReCor, Boston Scientific. The other authors have no conflict of interest to declare.

References

The references can be found in the online version of this paper.

Online data supplement

References

1. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med.* 2014;370:1393-401.
2. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. *Hypertension.* 2011;57:1076-80.
3. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, Oliveras A, Ruilope LM. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension.* 2011;57:898-902.
4. Savard S, Frank M, Bobrie G, Plouin PF, Sapoval M, Azizi M. Eligibility for renal denervation in patients with resistant hypertension: when enthusiasm meets reality in real-life patients. *J Am Coll Cardiol.* 2012;60:2422-4.
5. Tsioufis C, Papademetriou V, Worthley M, Chew D, Sinhal A, Meredith I, Malaiapan Y, Worthley S. Differential impact of renal sympathetic denervation on indexes of short-term blood pressure variability in patients with resistant hypertension. *J Am Coll Cardiol.* 2014;63(12_S):A1307.
6. Zuern CS, Eick C, Rizas KD, Bauer S, Langer H, Gawaz M, Bauer A. Impaired cardiac baroreflex sensitivity predicts response to renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol.* 2013;62:2124-30.
7. Dörr O, Liebetrau C, Möllmann H, Gaede L, Troidl C, Rixe J, Hamm C, Nef H. Soluble fms-Like Tyrosine Kinase-1 and Endothelial Adhesion Molecules (Intercellular Cell Adhesion Molecule-1 and Vascular Cell Adhesion Molecule-1) as Predictive Markers for Blood Pressure Reduction After Renal Sympathetic Denervation. *Hypertension.* 2014;63:984-90.
8. Johnson JA. Ethnic differences in cardiovascular drug response: potential contribution of pharmacogenetics. *Circulation*. 2008;118:1383-93.
9. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet.* 2009;373:1275-81.
10. Böhm M, Mahfoud F, Ukena C, Hoppe UC, Narkiewicz K, Negoita M, Ruilope L, Schlaich M, Schmieder R, Whitbourn R, Williams B, Zeymer U, Zirlik A, Mancia G. Effect of renal denervation in a real world population of patients with uncontrolled hypertension - The Global SYMPLICITY Registry. ACC Washington DC 2014; Late Breaking Clinical Trials.
11. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens.* 2013;31:766-74.
12. Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, Hoppe UC, Vonend O, Rump LC, Sobotka PA, Krum H, Esler M, Böhm M. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation*. 2011;123:1940-6.
13. Schlaich MP, Straznicky N, Grima M, Ika-Sari C, Dawood T, Mahfoud F, Lambert E, Chopra R, Socratous F, Hennebry S, Eikelis N, Böhm M, Krum H, Lambert G, Esler MD, Sobotka PA. Renal denervation: a potential new treatment modality for polycystic ovary syndrome? *J Hypertens.* 2011;29:991-6.
14. Witkowski A, Prejbisz A, Florczak E, Kadziela J, Sliwinski P, Bielen P, Michalowska I, Kabat M, Warchol E, Januszewicz M, Narkiewicz K, Somers VK, Sobotka PA, Januszewicz A. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension.* 2011;58:559-65.
15. Linz D, Hohl M, Nickel A, Mahfoud F, Wagner M, Ewen S, Schotten U, Maack C, Wirth K, Böhm M. Effect of renal denervation on neurohumoral activation triggering atrial fibrillation in obstructive sleep apnea. *Hypertension.* 2013;62:767-74.
16. Schirmer SH, Sayed MM, Reil JC, Ukena C, Linz D, Kindermann M, Laufs U, Mahfoud F, Böhm M. Improvements of left-ventricular hypertrophy and diastolic function following renal denervation - Effects beyond blood pressure and heart rate reduction. *J Am Coll Cardiol.* 2013 Nov 25. [Epub ahead of print].
17. Mahfoud F, Urban D, Teller D, Linz D, Stawowy P, Hassel JH, Fries P, Dreysse S, Wellnhofer E, Schneider G, Buecker A, Schneeweis C, Doltra A, Schlaich MP, Esler MD, Fleck E, Böhm M, Kelle S. Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multicentre cardiovascular magnetic resonance imaging trial. *Eur Heart J.* 2014 Mar 6. [Epub ahead of print].
18. Linz D, Mahfoud F, Schotten U, Ukena C, Neuberger HR, Wirth K, Böhm M. Effects of electrical stimulation of carotid baroreflex and renal denervation on atrial electrophysiology. *J Cardiovasc Electrophysiol.* 2013;24:1028-33.
19. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, Shirokova N, Karaskov A, Mittal S, Steinberg JS. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol.* 2012;60:1163-70.
20. Ukena C, Bauer A, Mahfoud F, Schreieck J, Neuberger HR, Eick C, Sobotka PA, Gawaz M, Böhm M. Renal sympathetic denervation for treatment of electrical storm: first-in-man experience. *Clin Res Cardiol.* 2012;101:63-7.
21. Davies JE, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, Hamady M, Hughes AD, Sever PS, Sobotka PA, Francis DP. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. *Int J Cardiol.* 2013;162:189-92.