High Number of Ablation Points in Renal Sympathetic Denervation for Uncontrolled Hypertension

Chien-Lung Huang, MD[1], Tien-Ping Tsao, MD[1], Ching-Hwa Hsu, RN, NP, MSN[1,2], Wei-Hsian Yin, MD, PhD, FESC[1,3]

[1]*Division of Cardiology, Heart Center, Cheng Hsin General Hospital, Taipei, Taiwan*
[2]*School of Nursing, National Yang-Ming University, Taipei, Taiwan*
[3]*School of Medicine, National Yang-Ming University, Taipei, Taiwan*

Abstract

Catheter-based renal sympathetic denervation (RDN) is in clinical trial for the treatment of hypertension. It may also be effective for the treatment of hypertensive chronic kidney disease (CKD). We report a 68-year-old male patient with moderate hypertension. The patient was non-adherent and intolerant to antihypertensive medication due to severe impotence. RDN was performed to treat all bilateral upper and lower polar arteries since the minimum required diameter was present. Atotal of 153 (70 left- and 83 right side) points were ablated effectively. No immediate complications arose. There was no significant deterioration of renal function in the three month follow-up period. Our case report shows that RDN was beneficial in for treatment of hypertension and improvement of renal function in hypertensive CKD.

Keywords: renal sympathetic denervation, renal function, hypertension

Introduction

Device-based renal denervation has been setting the stage for alternative or complementary blood pressure lowering strategy in patients with uncontrolled hypertension.[1] Sympathetic over-activity plays an important role in the pathophysiology of hypertension and associated comorbidities, and renal denervation is designed to disrupt both efferent and afferent sympathetic nerves and modulate central sympathetic outflow and renal physiology. Despite the lack of efficacy compared with antihypertensive therapy alone, asshown in the Symplicity HTN-3 trial, an indication of the efficacy of renal denervation has persisted, prompting additional exploratory and preclinical studies, which have motivated further studies. Three sham-controlled, randomized studies demonstrated clinically meaningful blood pressure reduction with renal denervation in hypertensive patients in conjunction with prescribed antihypertensive medications.[2-4] A recent meta-analysis of renal denervation trials with < 10% unplanned changes in antihypertensive medications during the follow-up periods showed consistent and statistically significant reduction in

Address for correspondence: Wei-Hsian Yin, MD, PhD, FESC
Professor, School of Medicine, National Yang-Ming University, Taipei, Taiwan; Division of Cardiology, Heart Center, Cheng Hsin General Hospital; No. 45, Cheng Hsin Street, Bei-Tou, Taipei 11220, Taiwan
Tel: +886-2-2826-1242; E-mail: yinwh@pchome.com.tw

both office and ambulatory blood pressure in the renal denervation group compared to the control group.[5] Furthermore, the Global SYMPLICITY Registry was developed to characterize safety and efficacy outcomes with renal denervation among broader populations through 3 years.[6] In recently published results among 1,742 patients with average 24-h systolic ambulatory blood pressuremeasurement (ABPM) of 154 ± 18 mmHg, the reduction in systolic office (-16.5 ± 28.6 mmHg) and ambulatory blood pressure (-8.0 ± 20 mmHg) was maintained through 3 years, representing not only a statistically significant decrease but also one deemed clinically important by societal consensus. In addition, the investigators described an annualized decline in the estimated glomerular filtration rate (eGFR) and a very low incidence of renal artery stenosis (0.1%) that were overall consistent with predicted estimates.[7] However, the long-term safety results of renal denervation, particularly with approaches using main and branch renal artery ablations, require further evidence.

Recently published consensus statementson renal denervation for the management of arterial hypertension from the Taiwan Hypertension Society and Taiwan Society of Cardiology, suggest renal denervation as a legitimate alternative antihypertensive strategy. The statements further delineate 5 subgroups of hypertensive patients who stand to benefit the most from renal denervation, as follows: Resistant hypertension, Patients with blood pressure-mediated vasculature or organ damage, those Non-adherent to antihypertensive medications, those Intolerant to antihypertensive medications, and those with Secondary causes treated but hypertension still uncontrolled. These patients have been dubbed "RDN i2", i.e. preferred candidates for renal denervation.[7]

This case study reports the short-term renal outcome from a moderately hypertensive patient who suffered from some severe side effects of antihypertensive medications, who expressed strong preference for renal denervation for blood pressure management, and who was subsequently treated with a high number of ablation points forrenal denervation in March 2018.

Case Report

Our patient was a 68-year-old male who sought care for the first time in our hospital due to poor control of BP levels in Mar 2017. Relevant family history included his father on renal replacement therapy. The patient was a smoker, but did not ingest major quantities of salt, alcoholic beverages, or other substances or drugs that could interfere with BP or anti-hypertensive medications. An initial physical examination revealed a BP of 171/81 mmHg.

After multiple treatments with combined anti-hypertensive medicines (Bisoprolol 5 mg 0.5# QD, Trichlormethiazide 2 mg QD, Amlodipine 5mg QD, Olmesartan 20 mg QD), his BP was almost within the normal limit, < 140/90 mmHg, in May 2017. However, poor compliance was later noted, even under single pill combination therapy (Amlodipine 5 mg/Olmesartan 40 mg 1# QD), and at one point he even stopped our medicineand received Chinese herb therapy from Aug 2017 to Oct 2017. He also complained of the side effect of severe impotence since beginning anti-hypertensive drug administration. His BP fluctuated from Nov 2017 to Apr 2018, around 135/80 ~ 165/100 mmHg. After thorough discussion with the patient, he asked for renal denervation therapy in Mar 2018.

Complementary tests revealed: haematocrit: 39.6%; haemoglobin: 12.7 g/dL; glycemia: 130 mg/dL; creatinine: 1.18 mg/dL; uric acid: 7.9 mg/dL; total cholesterol: 172 mg/dL; triglycerides: 119 mg/dL; HDL cholesterol: 39 mg/dL; LDL cholesterol: 108 mg/dL; sodium: 140 mmol/L; and potassium: 4.1 mmol/L. Urinary sediments were normal. An electrocardiogram revealed sinus rhythm with signs of left ventricular hypertrophy, while his renal MRA showed evidence of two main left renal arteries supplying the left kidney and two right main renal arteries supplying the right kidney. Bilateral adrenal glands are normal in this MR examination (Figure 1).

RDN was performedvia the right femoral artery. We decided to treat all the bilateral upper and lower polar arteries since the minimum required diameter was attained (Figure 2a, 2b, 3a, 3b). A total of 153 points (70 on the left and 83 on the right) were ablated effectively and recorded by Medtronic staff. (Figure 4a, 4b; Supplement: RDN worksheet). The evolution of BP values following the procedure is described in the Figure 5. However, due to the patient'spersonal problems, he refused ambulatory blood pressure monitoring (ABPM), and only office BP and home BP were recorded. Three months after the procedure, office BP values had decreased by around 11 mmHg under Amlodipine 5 mg/Valsartan 80 mg half pill once daily, with no significant modification in heart rate. No immediate complications arose, despite the high total of 153 renal artery points to be ablated for both renal arteries. There was no significant deterioration of renal function duringthe three month follow-up period (Figure 6).

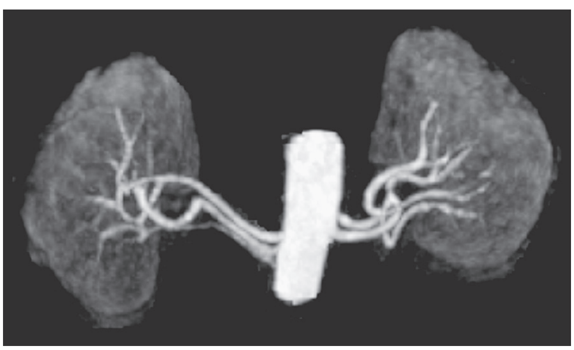


Figure 1. MRA of renal arteries.

Discussion

According to the recommendations of the Taiwan Hypertension Society and Taiwan Society of Cardiology, renal denervation is a legitimate alternative antihypertensive strategy. Our patient was non-adherent and intolerant to the antihypertensive medications due to severe impotence.

According to research presented at 2014 ESC Congress by Dr. Linda Schmiedel from Germany,[8] renal denervation seems to be more successful at reducing blood pressure when it includes accessory renal arteries, however, controversy remains over the best ablation strategy for renal denervation, namely, is it true that "the more, the better?" Our case report contributes

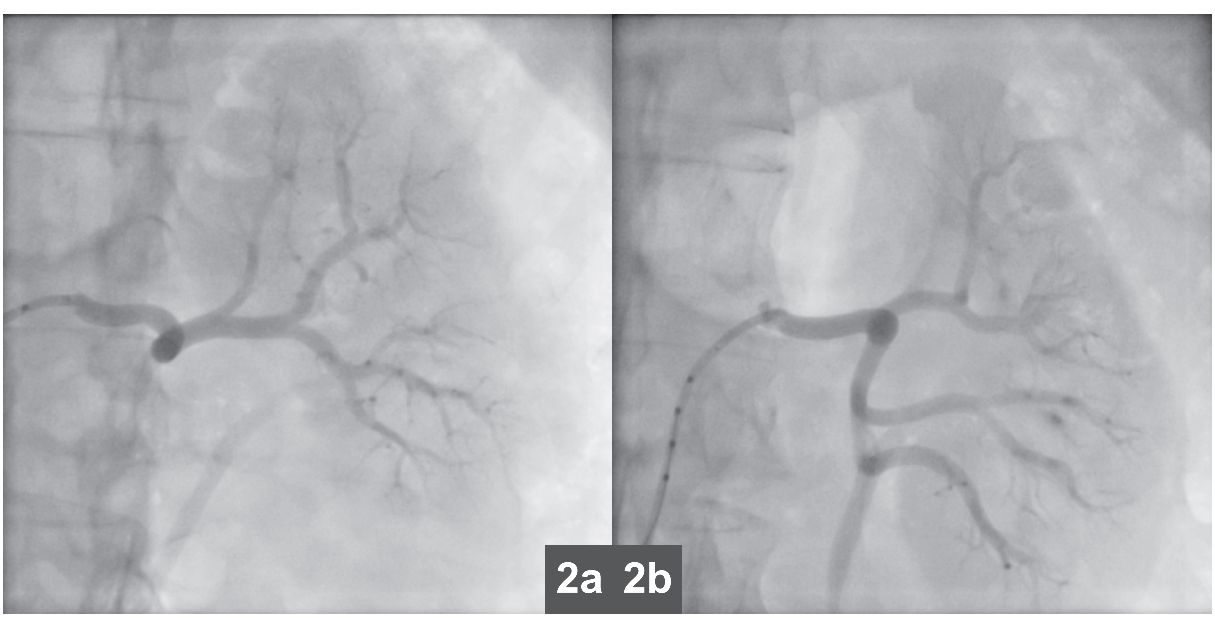


Figure 2. Two left main renal arteries by angiography. (2a. left superior; 2b. left inferior)

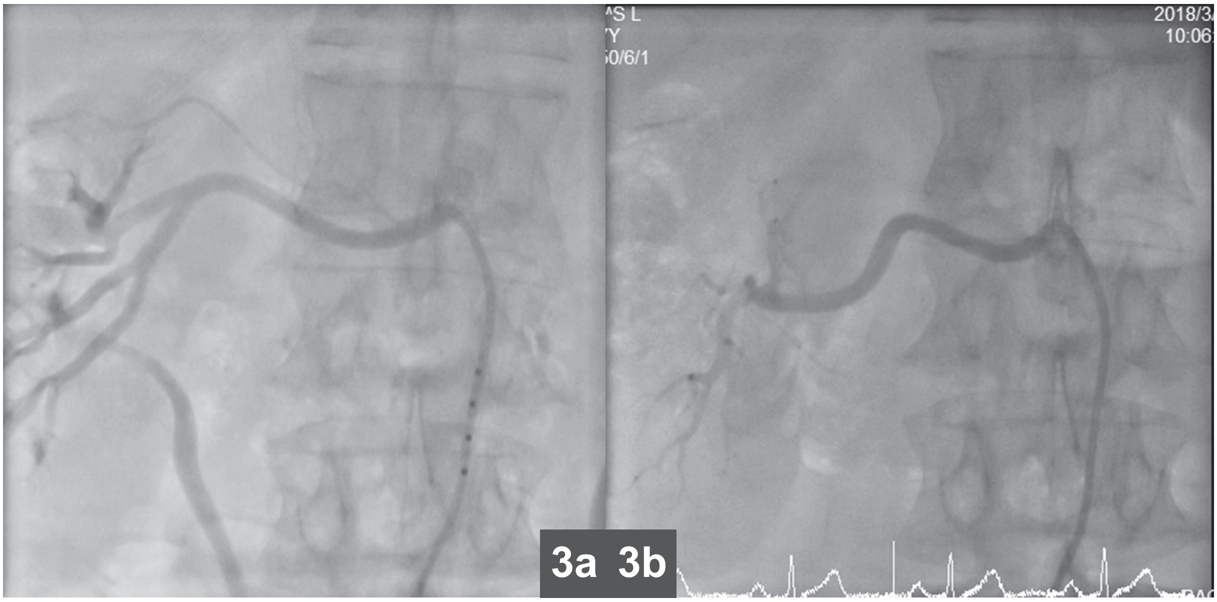


Figure 3. Two right main renal arteries by angiography. (3a. right superior; 3b. right inferior)

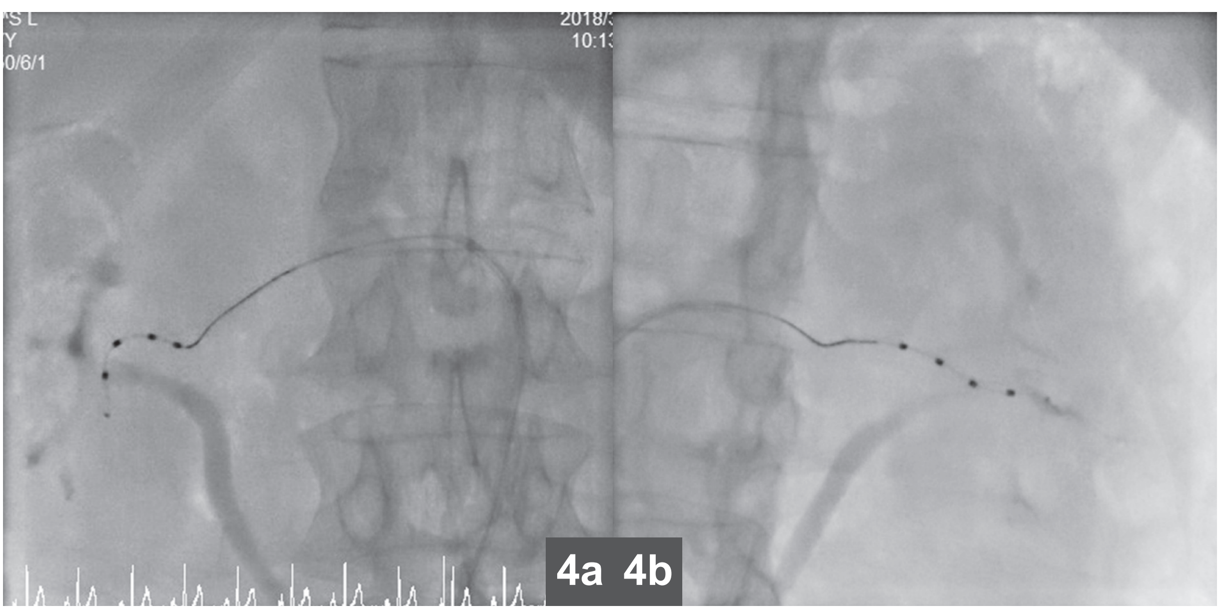


Figure 4. Ablation procedures. (4a. for one of the right renal arteries; 4b. for one of the left renal arteries)

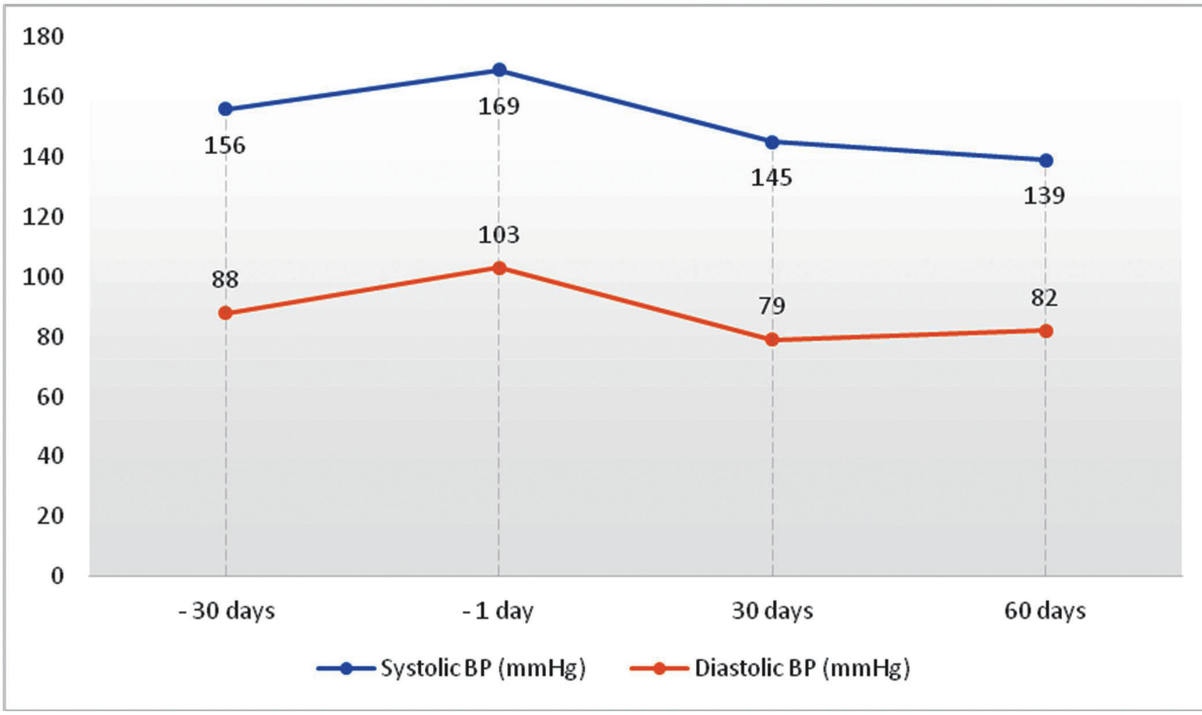
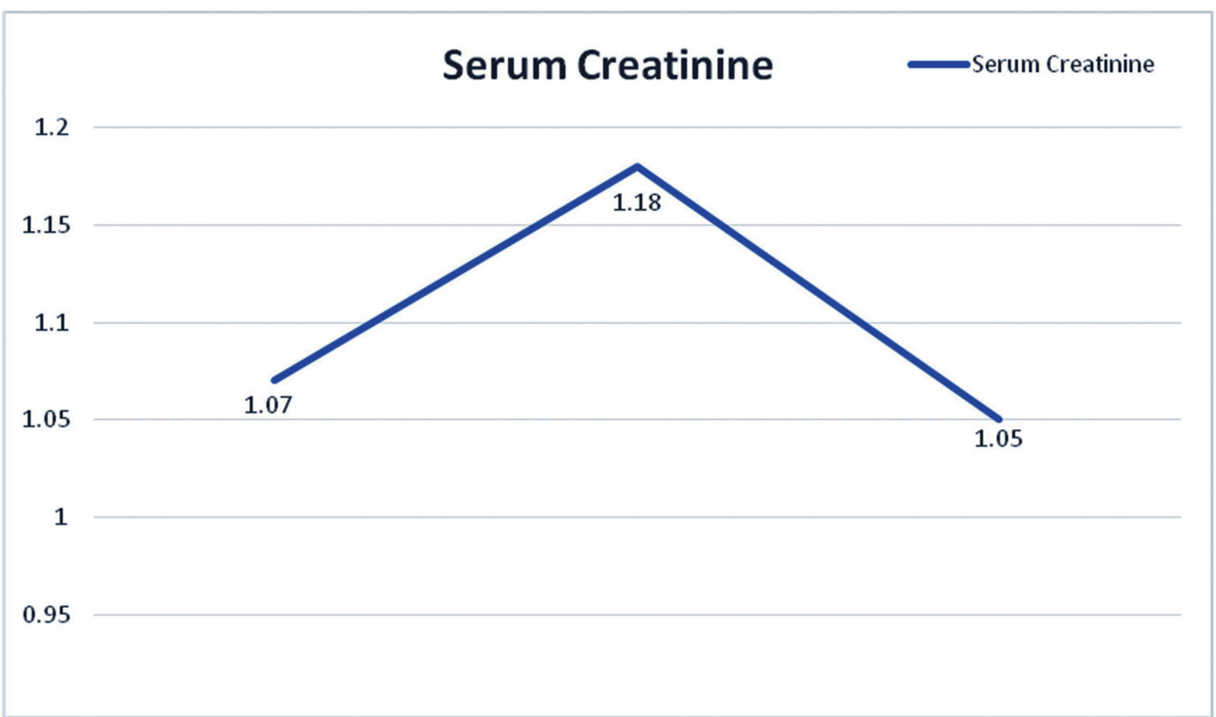


Figure 5. Blood pressure (BP) level during the follow up period.



Date	2017/04/13	2018/03/27 (pre-RDN)	2018/07/09 (post-RDN)
Cr. (mg/dL)	1.07	1.18	1.05

Figure 6. Serum creatinine level.

to the established safety data of RDN, since our patient experienced no increased occurrence of vascular spasm or deterioration of renal outcome, despite the use of 153 ablation points. To the best of our knowledge, this is the highest number of ablation points used for RDN. Our short-term result is in line with previous reports showing a renal protective action of RDN during follow-up. However, some renal artery stenosis has been reported post-RDN.[9] It is well known that the development of atherosclerotic lesions after endothelial injury can progress slowly and may take years to become clinically apparent. Thus, long-term renal safety data are still needed for these patients.

Additionally, it is reasonable to assume that renal artery stenosis could be reliably identified prior to RDN by MR or CT renal angiography for the visualization of bilateral renal artery anatomy whenpreparing forextensive ablation of both renal arteries, including all main trunks and main branches.

Based on the above, the notion arises that proper location as well as increased number of ablation points during an RDN procedure can result in more complete interruption of the renal sympathetic nerves, and thus in improved BP reduction. Along these lines, in the present study, the number of distal ablations were related to better ambulatory systolic BP reduction but not to office BP.[1] In the SYMPLICITY HTN-3 trial, BP response increased with increasing number of ablations delivered, and the successful delivery of circumferential quadrant ablations.[5,6] The difference in the mean number of ablations attempted (energy application) per artery between SYMPLICITY HTN-1 and SYMPLICITY HTN-3 was almost four, suggesting a "dose-response" dependency between the number of ablation attempts and the efficacy of RDN. Additionally, only a small proportion of patients in SYMPLICITY HTN-3 had successful ablation across all four quadrants of the renal artery. In these patients, complete four-quadrant ablation in both renal arteries was associated with a higher office systolic BP drop of 24.3 mm Hg. In the present study, there is a lack of data on four-quadrantablation assessment and this limits the ability to address the confounding impact of incomplete ablation as perceived with a 360-degree interruption of nerves in the renal arteries.[1] Consequently, the design of new studies addresses this issue by promoting a "more is better" approach to RDN ablation strategy in each renal artery.[6,7]

Conclusion

Hypertension is a global health issue and better tools and methods 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 strategy to control BP in the long term. Although further research is needed on the best ways to ensure compliance, such individuals might benefit from having the choice of receiving a device treatment, such as RDN, if proven durably safe and effective, in preference to lifelong drug therapy.[10]

Reference

1. 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(9671):1275-81.
2. 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(10108):2160-70.
3. Kandzari DE, Bohm 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. The *Lancet* 2018; 391(10137):2346-55.
4. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, interna-

tional, single-blind, randomised, sham-controlled trial. *The Lancet* 2018;391(10137):2335-45.

5. Liu LY, Lin PL, Liao FC, et al. Effect of radiofrequency-based renal denervation: The impact of unplanned medication change from a systematic review and meta-analysis. *Acta Cardiol Sin* 2019; 35(2):144-52.
6. Boehm M, Mahfoud F, Ukena C, et al. Rationale and design of a large registry on renal denervation: the Global SYMPLICITY registry. *EuroIntervention* 2013;9(4):484-92.
7. Mahfoud F, Böhm M, Schmieder R, et al. Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry. *Eur Heart J* 2019. (in press)
8. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm 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.
9. Kaltenbach B, Id D, Franke JC, et al. Renal artery stenosis after renal sympathetic denervation. *J Am Coll Cardiol* 2012;60:2694-5.
10. Lobo MD, Sharp ASP, Kapil V, et al. Joint UK societies' 2019 consensus statement on renal denervation. *Heart* 2019;105:1456-63.