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Sympathetic Response and Outcomes Following Renal Denervation in Patients With Chronic Heart Failure: 12-Month Outcomes From the SYMPPLICITY HF Feasibility Study

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Disclosures

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Authors' Contributions

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ABSTRACT

Background: Heart failure (HF) is associated with chronic sympathetic activation. Renal denervation (RDN) aims to reduce sympathetic activity by ablating the renal sympathetic nerves. We investigated the effect of RDN in patients with chronic HF and concurrent renal dysfunction, in a prospective, multicenter, single-arm feasibility study.

Methods and Results: Thirty-nine patients with chronic systolic HF (left ventricular ejection fraction [LVEF] <40%, New York Heart Association class II-III,) and renal impairment (estimated glomerular filtration rate [eGFR; assessed with Modification of Diet in Renal Disease equation] <75 mL/min/1.73 m²) on stable medical therapy were enrolled. Mean age was 65±11 years; 62% had ischemic HF. The average number of ablations per patient was 13±3. No protocol-defined safety events were associated with the procedure. One subject experienced a renal artery occlusion that was possibly related to the denervation procedure. Statistically significant reductions in N-terminal prohormone brain natriuretic peptide (NT-proBNP; 1530±1228 vs 1428±1844 ng/mL, $P=0.006$) and 120-minute glucose tolerance test (11.2±5.1 vs 9.9±3.6, $P=0.026$) were seen at 12 months, but there was no significant change in LVEF (28±9% vs 29±11%, $P=0.536$), 6-minute walk test (384±96 vs 391±97 m, $P=0.584$), or eGFR (52.6±15.3 vs 52.3±18.5 mL/min/1.73 m², $P=0.700$).

Conclusions: RDN was associated with reductions in NT-proBNP and the 120-minute glucose tolerance test in HF patients 12 months after RDN treatment. There was no deterioration in other indices of cardiac and renal function in this small feasibility study.

Key Words: Sympathetic nervous system, chronic kidney disease, renal impairment.

HIGHLIGHTS

- RDN was associated with reductions in NT-proBNP and the 120-minute glucose tolerance test in HF patients with renal dysfunction 12 months after treatment.
- No deterioration in other indices of cardiac and renal function 12 months after RDN treatment was observed.
- No serious adverse events were adjudicated as related to the device, procedure, or therapy. There was one renal artery occlusion that was possibly related to the denervation procedure.

ABBREVIATIONS

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HF = heart failure

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

MSNA = muscle sympathetic nerve activity

NT-proBNP = N-terminal prohormone brain natriuretic peptide

RDN = renal denervation

Heart failure (HF) and chronic kidney disease (CKD) represent a significant and growing global health issue. Excessive sympathetic nervous system activation is the main contributor to the development and progression of both disease states. By blocking the function of beta-adrenergic receptors, beta blockers shield the heart from the excessive sympathetic activation, allowing a later recovery of autonomic balance with major mortality benefits. However, alternative options are required to supplement current therapeutic regimens. Renal sympathetic denervation (RDN) reduces renal sympathetic activity by modulating the sympathetic reflexes to the kidney.¹ Animal models of HF have shown that surgical RDN improves both ventricular and renal function.² Little is known about the effect of RDN in human HF³ or renal disease.⁴ We report 12-month outcomes from the first feasibility study of RDN in patients with both HF and renal insufficiency. The primary aims were to evaluate the safety of RDN with the Symplicity Flex™ catheter and to investigate the physiologic response to RDN for the treatment of HF and renal impairment.

Methods

The Renal Denervation in Patients With Chronic Heart Failure & Renal Impairment (Symplicity HF, NCT01392196) feasibility trial was a prospective, multicenter, open-label, single-arm study that enrolled patients with chronic systolic HF and renal impairment. Inclusion criteria included left ventricular ejection fraction (LVEF) estimated by means of echocardiography, magnetic resonance, ventricular angiography <40%, New York Heart Association [NYHA] Class II-III, and renal impairment expressed by an estimated glomerular filtration rate (eGFR, assessed by means of the Modification of Diet in Renal Disease [MDRD] equation) of 30 to 75 mL/min/1.73 m². Unless intolerant, patients received optimal guideline-recommended doses of HF

medications. Exclusion criteria included hemodynamically significant renal artery stenosis, previous renal artery intervention, main renal artery <4 mm in diameter or <20 mm in treatable length, or multiple renal arteries in which the main renal artery was estimated to supply <75% of the kidney.

RDN was performed using the Symplicity Flex single-electrode catheter system (Medtronic, Santa Rosa, California). The protocol mandated application of 4 to 6 treatments to each main renal artery, starting at the distal end and extending toward the ostium while rotating the tip of the catheter 90° between applications. A proctor was present at each case. Details of the denervation procedure have been previously described.¹

Renal artery duplex ultrasound and echocardiography outcomes were evaluated by core laboratories (VasCore and Mayo Echo Core Lab, respectively). Safety outcomes were determined by an independent clinical events committee, and an independent data monitoring safety committee evaluated safety throughout the trial. A proof-of-concept substudy investigated renal and cardiac norepinephrine spillover and muscle sympathetic nerve activity (MSNA) using microneurography; renal blood flow, using mercaptoacetyl triglycine nuclear imaging; and pulmonary wedge pressure, using a pulmonary catheter.^{5,6}

Institutional ethics approval and written informed consent from study subjects were obtained. The study complied with the Declaration of Helsinki.

Statistical Analysis

The trial was designed as a feasibility study to assess the safety and physiological consequences of RDN. The sample size (40) was chosen to minimize the number of subjects with chronic HF who were exposed to RDN while providing preliminary safety and performance information

before proceeding to a clinical trial. The substudy sample size was limited to 10 as it was a proof-of-concept investigation. Descriptive statistics were used because there were no powered primary or secondary endpoints or prespecified hypotheses. All initial analyses were performed according to the intention-to-treat principle. For patient characteristics, continuous parameters were summarized using mean, standard deviation, and number of values. Nominal parameters were summarized as counts and percentages. Ad hoc comparisons between baseline and 12-month measurements were performed using the paired *t* test, the McNemar test, or the Wilcoxon signed rank test for non-normally distributed data, which were identified by use of the Shapiro-Wilk test. *P* values <0.05 were considered statistically significant. Results for all patients with data available at each time point are presented. Paired data are also reported for measures with statistically significant differences between baseline and 12-month values. Measures of sympathetic activity were summarized using mean, standard deviation, and number of values at baseline, 6 months, and 12 months. Because of the limited number of patients in this substudy, no comparisons are reported. Analyses were performed using SAS software version 9.1 or later (SAS Institute, Cary, North Carolina).

Results

Study patient population

A total of 39 subjects, from 8 study sites located in Europe and Australia, were included in the analysis. The 12-month follow-up results of all these 39 subjects were available for reporting data in the present study. The mean age was 65±11 years; 87% were male. Sixty-two percent had ischemic heart failure. The mean body mass index (BMI) of all subjects was 31±6 kg/m². The majority of subjects were New York Heart Association (NYHA) class II (68%) and the

remaining were NYHA III (32%); mean LVEF was $28\pm 9\%$. Approximately half of the subjects had a history of myocardial infarction (51%) or implantable cardioverter-defibrillator/cardiac resynchronization therapy devices (49%), 54% of the subjects had renal insufficiency (eGFR <60), and 51% had diabetes mellitus type 2.

Renal Denervation Procedure

Bilateral renal nerve ablation was performed per protocol in all subjects; 4 to 20 radiofrequency ablation treatments per patient were performed (mean 13 ± 3).

Safety Data

One death (2.6%, cardiovascular related) and 1 myocardial infarction (2.6%) had occurred by 12 months. There were 12 hospitalizations for decompensated HF in 8 patients (20.5%). One subject experienced a renal artery occlusion evident on a nuclear flow scan that did not meet the protocol definition of stenosis due to absence of a confirmatory renal angiogram. Six subjects (15.4%) had a rise in creatinine of 25% to 50%. No other major adverse events were observed.

Cardiac and Renal Physiologic Response

Statistically significant reductions in NT-proBNP and glucose tolerance at 120 minutes were seen at 12 months; however, other markers of change in cardiac function did not reach statistical significance (Table 1). No changes in renal physiologic response were observed at 12 months compared with baseline (Table 1, Figure 1). There were no changes observed in 6-minute walk distance, quality of life, body mass index, or glycemic control (Table 1). A reduction in use of mineralocorticoid receptor antagonists was seen (67% to 55%, $P=0.046$).

Figure 1: Change in eGFR from baseline through 12 months of follow-up.

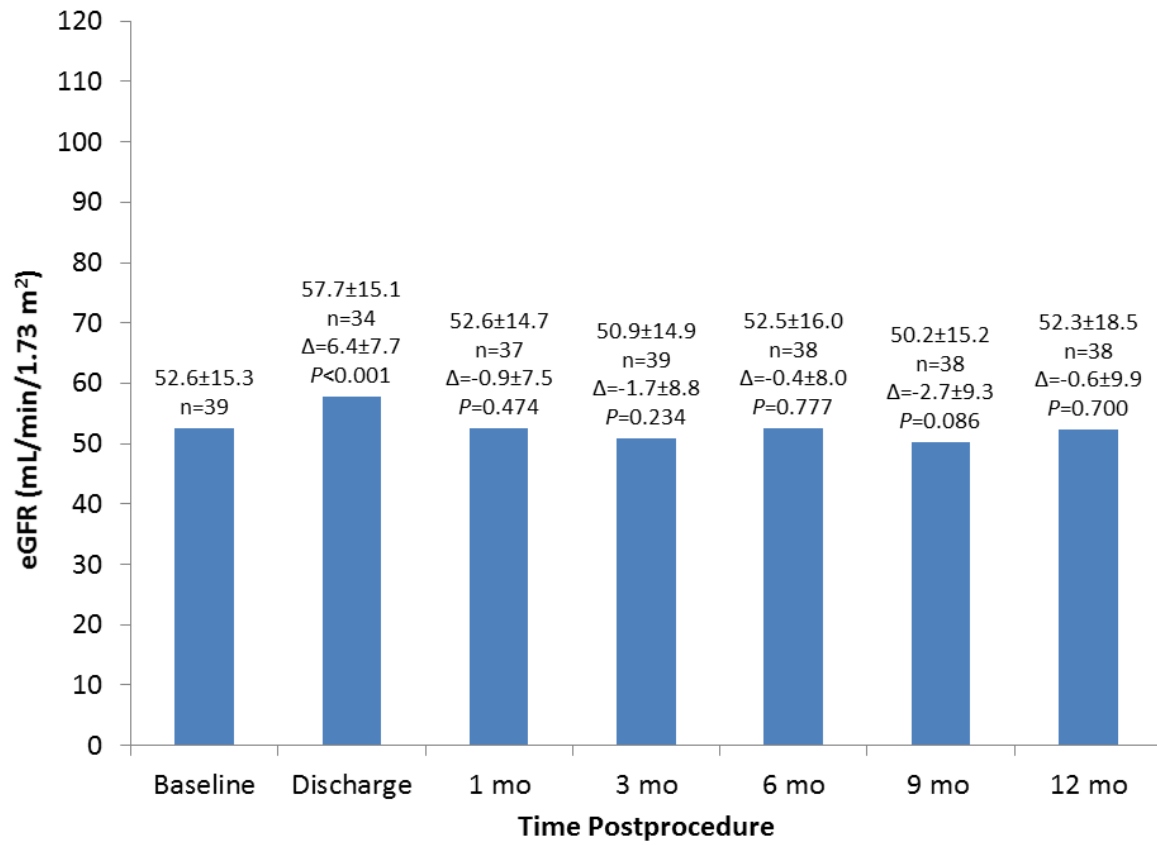


Table 1: Baseline characteristics and 12-month outcomes

	Baseline (N=39)	12 Months (N=38)	12-Month Change (N=38)	P vs Baseline
Body mass index, kg/m ²	31±6	31±6	0.1±1.5	0.673 ^a
Heart rate, bpm	69±10	69±9	-0.1±9.6	0.972 ^a
Office blood pressure, mmHg				
Systolic	123±20	122±19	-1±18	0.669 ^b
Diastolic	75±12	74±11	-1±12	0.323 ^b
Medication use				
ACEi/ARB	92%	87%	-6%	0.157 ^c
Beta-blocker	97%	97%	0%	NA ^c
MRA	67%	55%	-11%	0.046 ^c
Functional tests				
6-min walk test, m	384±96 (N=39)	391±97 (N=34)	-6±60 (N=34)	0.584 ^a
MLHF score	1.7±1.1 (N=38)	1.6±1.1 (N=38)	-0.2±0.6 (N=37)	0.160 ^b
Blood/serum tests				

NT-proBNP, ng/L	1899±1818 (N=29)	1466±1782 (N=29)	-102±1006 (N=27)	0.006 ^{b,d}
Fasting c-peptide, nmol/L	1.9±1.0 (N=21)	1.8±0.9 (N=19)	0.2±0.9 (N=15)	0.361 ^a
Fasting glucose levels, mmol/L	6.7±2.6 (N=32)	7.0±2.7 (N=37)	0.2±2.3 (N=31)	0.271 ^b
Glucose tolerance test ^e				
0 min	6.5±2.1 (N=32)	6.2±1.7 (N=30)	-0.3±1.4 (N=25)	0.538 ^b
60 min	11.8±4.0 (N=26)	11.5±3.4 (N=21)	0.5±2.9 (N=18)	0.799 ^b
120 min	11.2±5.1 (N=29)	9.9±3.6 (N=25)	0.5±2.0 (N=21)	0.026 ^{b,f}
Hemoglobin A1c, %	6.4±1.1 (N=38)	6.5±1.4 (N=32)	0.1±0.9 (N=32)	0.377 ^b
Renal function				
eGFR, mL/min/1.73 m ²	52.6±15.3 (N=39)	52.3±18.5 (N=38)	-0.6±9.9 (N=38)	0.700 ^a
Echocardiographic results				
LVEF, %	28±9 (N=34)	29±11 (N=37)	1±9 (N=33)	0.536 ^b
LV mass, g	290±100 (N=27)	269±107 (N=28)	-17±86 (N=24)	0.274 ^b
Interventricular septal thickness at diastole, mm	10.1±2.6 (N=27)	9.2±2.1 (N=31)	-0.6±2.2 (N=25)	0.208 ^b

24-h urine studies				
Creatinine, mmol/24 h	10.8±4.8 (N=30)	12.5±6.7 (N=28)	1.4±6.7 (N=28)	0.633 ^b
Creatinine clearance, mL/s	1.5±1.7 (N=23)	1.5±1.6 (N=29)	-0.4±1.7 (N=20)	0.268 ^b
Protein, g/L	0.1±0.2 (N=32)	2.2±10.1 (N=35)	2.4±10.9 (N=30)	0.684 ^b

Baseline and 12-month analyses included all data available at each time point for each parameter; N values are provided within the body of the table. Twelve-month change and *P* value calculations included only patients with data available at both baseline and 12 months.

^a*P* value calculated using the paired *t* test.

^b*P* value calculated using the Wilcoxon signed rank test.

^c*P* value calculated using the McNemar test.

^dMean baseline and 12-month NT-proBNP values of the patients includes in the paired analysis (N=27) were 1530±1228 and 1428±1844, respectively.

^eBlood glucose level was tested 120 min after fast oral intake of 75 g glucose.

^fMean baseline and 12-month 120-min glucose tolerance values of the patients in the paired analysis (N=21) were 9.8±4.5 and 10.3±3.6, respectively.

ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; EF, ejection fraction; eGFR, estimated glomerular filtration rate; LV, left ventricular; MLHF, Minnesota Living With Heart Failure questionnaire; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal prohormone brain natriuretic peptide.

Sympathetic Activity

The 6-month change in renal and cardiac norepinephrine spillover was -243 ± 306 and -8 ± 17 , respectively. The 6- and 12-month changes in MSNA were -10 ± 11 bursts/min and -5 ± 4 bursts/min, respectively (Table 2).

Table 2: Sympathetic activity at baseline, 6 months, and 12 months

	Baseline	6 Months	6-Month change	12 Months	12-Month change
Renal NE spillover, ng/min	515±209 (N=6)	277±92 (N=5)	-243±306 (N=5)	322±45 (N=2)	-48±188 (N=2)
Cardiac NE spillover, ng/min	31±11 (N=5)	25±19 (N=4)	-8±17 (N=4)	30±2 (N=2)	-10±9 (N=2)
MSNA, bursts/min	59±8 (N=5)	50±18 (N=5)	-10±11 (N=5)	55±11 (N=5)	-5±4 (N=5)
MSNA, bursts/100 heartbeats	89±17 (N=5)	76±29 (N=5)	-12±12 (N=5)	84±20 (N=5)	-5±6 (N=5)

Analyses included all patients at each time point for each parameter; N values are provided within the body of the table. NE, norepinephrine; MSNA, muscle sympathetic nerve activity.

DISCUSSION

We present a prospective, single-arm feasibility study of RDN therapy in patients with systolic HF and renal dysfunction. The RDN procedure appears to be safe and well tolerated. Statistically significant reductions in NT-proBNP and 120-minute glucose tolerance were seen. No other significant changes in indices of cardiac or renal function were demonstrated following RDN at 1-year follow-up. No serious adverse events were adjudicated as related to the device, procedure, or therapy.

The serious adverse events observed in this trial likely reflect the severity of HF in these patients. Elevated NT-proBNP is an independent predictor of mortality in HF,⁷ and death, myocardial infarction, and HF hospitalization are not unexpected in this group; however, RDN as a contributor cannot be excluded. The renal artery occlusion observed in 1 subject may relate to the RDN procedure, to progression of pre-existing atherosclerosis, occlusion from cardiac or vascular emboli, and/or thrombosis due to the hypercoagulable state. Rates of renal artery stenosis in other studies with this system have been low,⁸ and this is the first report of renal artery occlusion.

Preclinical trials in animal models have suggested beneficial effects of RDN on HF associated with high sympathetic tone.⁹ Several prospective trials have shown reduced LV mass in non-selected hypertensive patients^{10,11} following RDN therapy, suggesting a potential benefit for HF patients. Trials of RDN in HF have had mixed results. Seven HF subjects studied using the same first-generation single-electrode RDN system had no change in LVEF at 6 months.³ A prospective, randomized single-center study of 25 HF patients with preserved EF¹² did not detect improvements in endpoints compared with controls. However, a study in 60 HF patients with reduced EF found significant improvements in LVEF, 6-minute walk distance, NYHA class, and

NT-proBNP with RDN compared with controls.¹³ Few data exist on whether RDN confers benefits in patients with CKD. In 15 patients with stage 3 or 4 CKD (mean eGFR 31 mL/min/1.73 m²), no significant alterations in kidney function were seen following the procedure.¹⁴

Although statistically significant changes in markers of sympathetic response could not be reliably determined in the substudy because of the low number of patients, there was a 47% decrease in renal norepinephrine spillover, a 26% decrease in cardiac norepinephrine spillover, and a 17% reduction in MSNA bursts/min at 6 months. These changes may be potential signals of a sympatholytic effect of RDN that the study was not powered to detect.

The 12-month clinical course for HF is usually one of decline¹⁵; thus, the lack of deterioration may suggest a clinical effect of RDN. A biochemical improvement in HF was observed 12 months following RDN in this study; however, the 7% reduction in NT-proBNP level at 12 months did not reach the 25% threshold currently regarded as a clinically meaningful improvement.¹⁶ The reduction in MSNA bursts/min values post-RDN is not dissimilar to that described by Hering et al.¹⁷ in hypertensive patients, perhaps suggesting that partial denervation may have been achieved.

Conversely, the lack of changes in tested clinical variables might relate to insufficient extension of therapy delivery with the adopted RDN technique. In the SYMPPLICITY protocol, the lesions were distributed only in the main renal artery from the ostium to the first major bifurcation, and no treatments were applied distal to the main bifurcation of the renal artery. Recent investigations have challenged the efficacy of this relatively conservative “first-generation” therapy approach to consistently achieve appropriate nerve destruction,^{18,19} and there is now convincing data from human studies to indicate that distal artery and branch treatment

appears significantly more potent than main artery denervation.^{20,21} A recent human cadaver histological analysis reported that the renal nerve fibers are much closer to the vessel lumen near the distal end of the main trunk of the renal artery, thereby making nerves in the proximal portion relatively less susceptible to radiofrequency energy damage as compared to the distal portion.¹⁸ Unfortunately, there is no reliable method to assess the completeness of denervation in the catheterization laboratory. Confirmation of effective RDN has been tested by electrical stimulation of the renal artery target area before and after RDN,²² but confirmatory data that this test predicts success of denervation are unavailable.

The major limitation of this trial is its small sample size. As this was a feasibility trial, it included no sham control group, which has been shown to be important in assessing RDN.⁸ The multielectrode Symplicity Spyral™ RDN catheter is currently being tested with sham controls in the SPYRAL HTN Global Clinical Trial Program (NCT02439749, NCT02439775), and a further trial in systolic HF is ongoing (NCT01639378). Additional studies may be warranted to evaluate the potential for RDN to provide benefit in patients with HF and/or renal dysfunction once an optimal RDN procedure is determined.

Conclusion

RDN was associated with small reductions in NT-proBNP and 120-minute glucose tolerance at 12 months in patients with HF. There was no deterioration in other indices of cardiac or renal function following RDN. This was a small feasibility trial of patients with HF and renal dysfunction with limited data on physiological responses. No adverse events were adjudicated as related to RDN; however, 1 renal artery occlusion occurred that was possibly related to RDN.

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REFERENCES

1. 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;373:1275-81. doi: 10.1016/S0140-6736(09)60566-3.
2. Sobotka PA, Krum H, Bohm M, Francis DP, Schlaich MP. The role of renal denervation in the treatment of heart failure. *Curr Cardiol Rep* 2012;14:285-92. doi: 10.1007/s11886-012-0258-x.
3. Davies JE, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, et al. 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. doi: 10.1016/j.ijcard.2012.09.019.
4. Schlaich MP, Bart B, Hering D, Walton A, Marusic P, Mahfoud F, et al. Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease. *Int J Cardiol* 2013;168:2214-20. doi: 10.1016/j.ijcard.2013.01.218.
5. Meredith IT, Eisenhofer G, Lambert GW, Dewar EM, Jennings GL, Esler MD. Cardiac sympathetic nervous activity in congestive heart failure. Evidence for increased neuronal norepinephrine release and preserved neuronal uptake. *Circulation* 1993;88:136-45.
6. Schlaich MP, Kaye DM, Lambert E, Sommerville M, Socratous F, Esler MD. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation* 2003;108:560-5. doi: 10.1161/01.CIR.0000081775.72651.B6.

7. Kirk V, Bay M, Parner J, Krogsgaard K, Herzog TM, Boesgaard S, et al. N-terminal proBNP and mortality in hospitalised patients with heart failure and preserved vs. reduced systolic function: data from the prospective Copenhagen Hospital Heart Failure Study (CHHF). *Eur J Heart Fail* 2004;6:335-41.
8. 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;370:1393-401.
9. Dai Z, Yu S, Zhao Q, Meng Y, He H, Tang Y, et al. Renal sympathetic denervation suppresses ventricular substrate remodelling in a canine high-rate pacing model. *EuroIntervention* 2014;10:392-9. doi: 10.4244/eijv10i3a65.
10. Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Bohm M, et al. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *J Am Coll Cardiol* 2012;59:901-9. doi: 10.1016/j.jacc.2011.11.034.
11. Schirmer SH, Sayed MM, Reil JC, Ukena C, Linz D, Kindermann M, et al. Improvements in left ventricular hypertrophy and diastolic function following renal denervation: effects beyond blood pressure and heart rate reduction. *J Am Coll Cardiol* 2014;63:1916-23. doi: 10.1016/j.jacc.2013.10.073.
12. Patel HC, Rosen SD, Hayward C, Vassiliou V, Smith GC, Wage RR, et al. Renal denervation in heart failure with preserved ejection fraction (RDT-PEF): a randomized controlled trial. *Eur J Heart Fail* 2016;18:703-12. doi: 10.1002/ejhf.502.
13. Chen W, Ling Z, Xu Y, Liu Z, Su L, Du H, et al. Preliminary effects of renal denervation with saline irrigated catheter on cardiac systolic function in patients with heart failure: a

- prospective, randomized, controlled, pilot study. *Catheter Cardiovasc Interv* 2016 May 3. [E-pub ahead of print].
14. Hering D, Mahfoud F, Walton AS, Krum H, Lambert GW, Lambert EA, et al. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol* 2012;23:1250-7. doi: 10.1681/asn.2011111062.
 15. Watson RD, Gibbs CR, Lip GY. ABC of heart failure. Clinical features and complications. *BMJ* 2000;320:236-9.
 16. Januzzi JL, Troughton R. Are serial BNP measurements useful in heart failure management? Serial natriuretic peptide measurements are useful in heart failure management. *Circulation* 2013;127:500-7; discussion 8. doi: 10.1161/CIRCULATIONAHA.112.120485.
 17. Hering D, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW, et al. Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. *Hypertension* 2013;61:457-64. doi: 10.1161/HYPERTENSIONAHA.111.00194.
 18. 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;64:635-43. doi: 10.1016/j.jacc.2014.03.059.
 19. Mahfoud F, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D, et al. Impact of lesion placement on efficacy and safety of catheter-based radiofrequency renal denervation. *J Am Coll Cardiol* 2015;66:1766-75. doi: 10.1016/j.jacc.2015.08.018.
 20. Pekarskiy SE, Baev AE, Mordovin VF, Semke GV, Ripp TM, Falkovskaya AU, et al. Denervation of the distal renal arterial branches vs. conventional main renal artery

- treatment: a randomized controlled trial for treatment of resistant hypertension. J Hypertens 2017;35:369-75. doi: 10.1097/HJH.0000000000001160.
21. Schlaich MP. Renal Sympathetic Denervation: A Viable Option for Treating Resistant Hypertension. Am J Hypertens 2017. doi: 10.1093/ajh/hpx033.
 22. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, et al. 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. doi: 10.1016/j.jacc.2012.05.036.