

Denervation of the renal arteries — what next?

Katarzyna Kostka-Jeziorny¹, Andrzej Tykarski¹, Stefan Grajek²

¹Department of Hypertension, Angiology, and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland

²Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland



Katarzyna Kostka-Jeziorny, MD, PhD, graduated in medicine from the Jagiellonian University Medical College in Krakow and currently works at the Department of Hypertension, Angiology, and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland. She became a specialist in internal medicine in 2011 and a specialist in hypertensiology in 2013. Assistant Professor, Head of Laboratory of Functional Diagnostics of Arteries in the Department of Hypertensiology, Angiology, and Internal Medicine, and Coordinator of the study “RDN-Pol Registry” in Poznan. Her scientific research interests include resistant hypertension, renal denervation, hyperuricaemia in hypertension, central blood pressure, and chronotherapy of hypertension.

She is a member of European Society of Hypertension, European Society of Cardiology, American Society of Hypertension, and ‘Club 30’ of the Polish Cardiac Society. She is the co-author of 2015 Guidelines for the Management of Hypertension Recommendations of the Polish Society of Hypertension.



Professor **Andrzej Tykarski**, MD, PhD, Head of the Chair and Department of Hypertension, Angiology, and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland. He graduated in medicine from the Poznan University of Medical Sciences, Poland in 1982, and obtained his PhD from the same University in 1988. He is currently Professor of Internal Medicine in the Poznan University of Medical Sciences, and the Head of the Chair and Department of Hypertension, Angiology, and Internal Medicine. He was the Dean of the Medical Faculty (2005–2012), Vice-President of Poznan University of Medical Sciences (2012–2016) and in 2016 was elected President. His research has been focused on the haemodynamics of hypertension, renal function in renovascular and essential hypertension, and the role of uric acid and hyperuricaemic drugs in hypertension.

Recently, much of his activity is related to 24-h ambulatory blood pressure monitoring and chronotherapy. He was the Polish regional coordinator of several trials including SCOUT, ADVANCE, RELYPSA, and NAVIGATOR. He is the Polish national coordinator of the TECOS trial. Professor Tykarski has published over 200 papers mainly in the areas of hypertension and cardiovascular disease. He was the Editor-in-Chief of “*Nadciśnienie Tętnicze*” (“Arterial Hypertension”) (2004–2014) — the official journal of the Polish Society of Hypertension. He is on the editorial board of 11 Polish and international journals. From 2003 to 2015 he was a Wielkopolska Area consultant in clinical management of hypertension. He is a member of the Scientific Council of the Polish Society of Hypertension. He was a member (2003, 2008, 2011) and coordinator (2015) of the Task Force for the Management of Arterial Hypertension of the Polish Society of Hypertension, preparing the Polish Guidelines for the Management of Arterial Hypertension. He is former Secretary (1998–2000) and Vice-President (2002–2004) of the Scientific Council of the Polish Society of Hypertension and current President of the Polish Society of Hypertension.

Address for correspondence:

Katarzyna Kostka-Jeziorny, MD, PhD, Department of Hypertension, Angiology, and Internal Diseases, Poznan University of Medical Sciences, ul. Długa 1/2, 61–848, Poznań, Poland, e-mail: kostkajeziorny@gmail.com

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Professor **Stefan Grajek**, MD, PhD, Professor of Cardiology, Head of the First Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland. He graduated in medicine from the Poznan University of Medical Sciences, in 1970, and obtained his PhD from the same University in 1979. He is a specialist in cardiology, hypertensiology, and internal medicine. His research has been focused on coronary disease, percutaneous coronary intervention, percutaneous transluminal renal artery angioplasty and stenting, resistant arterial hypertension, and renal denervation. He was the Polish regional coordinator of several trials including GUSTO IV, GUSTO V, ASSENT-4, and STREAM. He is on the editorial board of many Polish and international journals. He is a co-author of the 2015 Guidelines for the Management of Hypertension Recommendations of the Polish Society of Hypertension. Professor Grajek has published over 700 papers, mainly in the areas of cardiovascular disease, coronary intervention, and arterial hypertension.

INTRODUCTION

Arterial hypertension (AH) is one of the most common disorders of the cardiovascular system. Throughout years of investigation, more and more effective substances were introduced to antihypertensive therapy, including newly developed therapeutic schemes. Despite such advancement in therapeutic strategy, a group of patients remains afflicted with resistant AH and it seems to be resistant to antihypertensive medication even in maximum doses.

In Poland the estimated proportion of patients with resistant AH is between 12% and 13% of the total population treated for hypertension. Data suggests a low frequency of this phenomenon; however, statistics estimating the frequency of AH in groups of patients admitted to reference centres suggest a 10-fold increase [1, 2]. A patient with resistant hypertension, as opposed to a patient after a successful treatment of hypertension with good control of blood pressure (BP) values, can be characterised by faster development of complications within the organs. Consequently, the cardiovascular risk is considerably higher.

Denervation of the renal arteries is designed for patients with truly resistant AH. According to the regulations of PTNT 2015/ESC/ESH 2013, refractory AH is defined by BP \geq 140/90 mm Hg while taking three different antihypertensive drugs (including a diuretic), appropriately and fully dosed [3, 4]. Nevertheless, according to the position of the ESH from 2012 concerning the denervation treatment, a classification for patients who additionally were ingesting mineralocorticoid receptor blocker [5] was suggested. Validation of that claim was found in the Simplicity-3 study, which demonstrated a better antihypertensive effect in patients afflicted with resistant hypertension, who were given the aforementioned group of medications. Equally interesting results were presented by the PATHWAY study, which did not directly deal with renal denervation (RDN) but instead with the optimal antihypertensive therapy of patients afflicted with resistant hypertension [6]. 335 patients with resistant hypertension were treated with angiotensin converting en-

zyme inhibitor (ACEI)/sartan + diuretic + calcium channel blocker (CCB), with added spironolactone 25–50 mg, bisoprolol 5–10 mg, or doxazosin 4–8 mg. The highest reduction in systolic and diastolic blood pressure was observed in the spironolactone group. More importantly, among the patients qualified for the study, i.e. 325, only 15 of the patients proved to be truly resistant to therapy, and theoretically this is the group for which an invasive AH treatment could be considered. Williams, the main researcher in the PATHWAY study, suggested redefining refractory AH, claiming that it should be defined as uncontrolled BP values during the antihypertension therapy using a combination of ACEI/sartan + CCB + diuretic + spironolactone.

INCONCLUSIVE RESULTS AND POST-SIMPLICITY-3 DISAPPOINTMENT

Renal arteries denervation has a solid theoretical background, so it is safe to expect an effective AH treatment. The first results of the Simplicity-HTN1 and HTN2 studies have pointed towards strong positive outcomes.

The first results obtained after the first 45 denervation procedures were published in the acclaimed "Lancet" (2009) magazine [7]. The patients underwent radiofrequency ablation of the renal arteries of the sympathetic nervous system from July 2007 to October 2008 with the observation period of 12 months. The success of the treatment was evaluated based on controlling the noradrenaline release after the denervation procedure. The average arterial pressure value before joining the trial was 177/101 mm Hg. The patients were ingesting an average of approximately 4.7 antihypertension medications. The average reduction in the renal noradrenaline was 47%. The arterial BP measurements after the ablation were lower than the results prior to the ablation by $-14/-10$ mm Hg, $-21/-10$ mm Hg, $-22/-11$ mm Hg, $-24/-11$ mm Hg, and $-27/17$ mm Hg in the first, third, sixth, ninth, and twelfth month of observation, respectively. Another interesting observation was the re-establishment of the day and night arterial pressure rhythm, together with a reduction

in BP values at night. Prior to joining the trial, the majority of patients did not experience a physiological drop in their pressure at night (non-dipper syndrome). In the extended Simplicity-HTN1 study of 137 patients, a significant drop in arterial pressure was observed over the observation period of 12 months. The average reduction of systolic (SBP)/diastolic (DBP) BP amounted to 20/10 mm Hg, 24/11 mm Hg, 25/11 mm Hg, and 23/11 mm Hg after one, three, six and 12 months, respectively. The effect of the denervation procedure was retained 18 and 24 months after the treatment [8].

Simplicity-HTM2, a randomised clinical trial, included 106 patients around 48 ± 12 years old [9]. The patients were randomly assigned to two groups: the denervation group ($n = 52$) and the control group ($n = 54$). The average arterial pressure amounted to 178/98 mm Hg despite antihypertensive treatment with approximately 5.3 drugs. Compared to the control group, a considerable reduction in SBP was observed in each observation point. Six months post-denervation, a reduction of 32/12 mm Hg in the arterial pressure was noted. Home BP measurements showed that the average decrease of the arterial pressure in the treatment group was 20 mm Hg for SBP and 12 mm Hg for DBP, compared to an average drop of 2 mm Hg and no DBP drop in the control group. The sympathetic nerve ablation in the area of catheterised renal arteries caused a sustained reduction of arterial BP without serious negative side effects in patients with refractory arterial blood pressure.

There has been declining interest in the denervation of the renal arteries, as well as in its significance as the ultimate treatment of resistant AH, after publication of the results of the randomised clinical trial Simplicity-HTN3 [10]. The patients qualified for the clinical trial were included randomly, in the ratio of 2:1, respectively, into the treatment group and the control (sham) group, the latter having only been subject to an angiography.

Out of 1441 patients initially qualified for the trial, 535 were eventually included further and randomly assigned to either the treatment group or the control group. There were no significant differences between the two samples. The afflicted patients were treated with five antihypertensive agents, four of which were ingested in the maximum tolerated doses.

After six months of the observation period, there were no statistically significant differences both in primary and secondary endpoint. In-office measurements showed an average reduction of 14.13 ± 23.93 mm Hg in SBP in the treatment group and a reduction of 11.74 ± 25.94 mm Hg in the sham group. Average decrease of SBP in 24-h ambulatory blood pressure (ABPM) amounted to 6.75 ± 15.11 mm Hg in the denervation group and 4.79 ± 7.25 mm Hg in the sham group, which constituted a 1.96 mm Hg difference between groups. After dividing the sample population into smaller groups based on factors such as diabetes, sex, race, obesity, treatment with aldosterone receptor blocker, the

glomerular filtration rate (GFR), age, and the alteration of medication types during the trial, some sub-groups exhibited considerable differences in the decrease of SBP. In the conducted sub-analysis it was demonstrated that the denervation treatment is more effective in Caucasian patients under the age of 65 years without chronic renal failure. However, it is worth noting that even then the decrease was insignificant at below 10 mm Hg.

After surprising results that were contradictory to the ones obtained in previous studies, a wave of criticism of the Simplicity-3 trial arose together with a search for the plausible causes of its failure. Firstly, the focus was turned to the issue of antihypertensive therapy. There was an assumption present in two groups, necessary due to ethical reasons, which stated that the applied anti-hypertension medication should not be altered throughout the trial with the exception of a situation in which it would be necessary from a clinical point of view. That situation has occurred in 40% (!) of patients, more frequently in the sham group. It is worth noting that in the sub-group analysis, the alteration did not negatively influence the outcome, as long as the intensity of the pharmacological treatment in the denervation group was not unknowingly diminished. Moreover, the patients in the American Simplicity HTN-3 trial were treated differently than in Europe, as 40% of them were given medication with a direct vasodilation effect, more popular in the United States, although they are known to be predictors of a worse response to RDN. The percentage was twice as high as in previous Simplicity trials.

Another criticism of the trial's methodology was directed towards the more frequent use of aldosterone receptor blocker in the sham group. Taking into account the sub-group analysis showing a much higher antihypertensive effect among the patients ingesting aldosterone receptor blockers, this disproportion could have diluted the RDN effect. Despite the results of the sub-group analysis of the patients using the aldosterone receptor blocker not being statistically significant due to a low sample size.

The cause of the negative results of the Simplicity HTN-3 trial could be atypical for a European population sample. Over 25% of the sample were Afro-American, who in the sub-group analysis did not react to RDN treatment. The cause of that was a considerably higher reduction in arterial pressure among Afro-Americans in the sham group compared to the Caucasian or the Asian race (-17.8 mm Hg vs. 8.6 mm Hg). This difference may be due to an ameliorated compliance or a better reaction to the vasodilation medications that were included before randomisation among Afro-Americans. It is worth remembering that AH among Afro-Americans is usually characterised with hypervolaemia and low activity of renal plasma. Taking that into account, the results of the Simplicity HTN-3 trial are not fully representative for the European population.

Another, more serious, technical cause of the negative results of the trial is the scarce experience of the researchers performing the RDN procedure. The group of 535 patients were recruited in 88 health centres, and 364 denervation procedures were performed by 111 surgeons (!). Due to the fact that the procedure was not previously registered in the United States, this type of procedure was a first for the majority of the surgeons.

In another randomised trial PRAGUE-15, it was demonstrated that the RDN is not as successful in reducing BP values as adding spironolactone [11]. This prospective, randomised, open, and multi-centre study investigated the effectiveness of the RDN procedure compared to the intensification of the pharmacological treatment using spironolactone (if it was tolerated) in patients with truly resistant AH. 106 patients were randomly assigned to the group being treated invasively ($n = 52$) or the intensification of pharmacological treatment group ($n = 54$). The benchmark SBP value in the first group amounted to 159 ± 17 mm Hg and 155 ± 17 mm Hg in the second group, and the average number of applied antihypertensive medications was 5.1 and 5.4, respectively. After six months a considerable decrease in SBP values was recorded in 24-h measurements of ABPM (-8.6 [95% confidence level: $-11.8, -5.3$] mm Hg, $p < 0.001$ in the denervation group compared to -8.1 renal innervation [95% confidence level: $-12.7, -3.4$] mm Hg; $p = 0.001$ in the spironolactone group). A reduction in the DBP values was also observed (-12.4 [95% confidence level: $-17.0, -7.8$] mm Hg, $p < 0.001$ in the denervation group compared to -14.3 [95% confidence level: $-19.7, -8.9$] mm Hg, $p < 0.001$ in the spironolactone group). There were no significant differences between BP value reductions between groups. However, a significant increase in creatinine concentration in the blood serum and a simultaneous drop in the clearance of creatinine were both observed in the group treated pharmacologically. The aforementioned results confirmed the safety of the RDN treatment.

In the randomised trial DENERHTN it was demonstrated that in the patients afflicted with resistant arterial hypertension, despite being treated with a medication inhibiting the renin-angiotensin-aldosterone system, CCB, and a thiazide-like diuretic, performing the denervation procedure is more effective in terms of hypertension that adding more antihypertensive medication, including spironolactone [12]. This trial included 101 qualified patients (48 in the denervation group and 53 in the control group). After six months of observation, a greater reduction of SBP values in ABPM in the hours of activity -5.9 mm Hg (-11.3 to -0.5 ; $p = 0.03$) was found. The difference was obtained in patients who in both groups ingested a similar amount of antihypertensive medication and had similar adherence levels as well as a similar safety profile.

In studying the effectiveness of the RDN, an initiative of the Simplicity system's producer — Global Simplicity Registry

— cannot be omitted. Eventually, the database is supposed to collect information on the denervation procedures of at least 5000 patients from around 200 centres around the world. The registry gathers not only the results of the treatment of refractory AH, but also the effect of the RDN procedure on conditions related to hyperactivity of the immune system (insulin resistance, OSA, chronic renal disease).

In 2015, "Hypertension" published the first report of the registry [13]. The study's aim was to evaluate the safety profile and the effectiveness of RDN using the Simplicity's system in patients with uncontrolled AH. This global database is a prospective, open, and multi-centre study. In-house and 24-h ABPM values were analysed, as well as benchmark values of systolic arterial pressure in-house and in ABPM with values after the ablation of the renal arteries after six months. Other values analysed were those of glycaemic and renal function parameters. The trial included only patients who fully complied with the definition of resistant hypertension, in addition to a systolic arterial pressure of ≥ 160 mm Hg and ≥ 135 mm Hg in ABPM. The results of 998 patients were analysed, including 323 with severe AH. The average SBP values shown by home BP measurements amounted to 163.5 ± 24.0 mm Hg in the entire group and 179.3 ± 16.5 mm Hg in the severe hypertension group. The benchmark SBP values in ABPM amounted to 151.5 ± 17.0 mm Hg and 159.0 ± 15.6 mm Hg in respective groups. After six months, for all patients, the reduction in SBP and ABPM values was -11.6 ± 25.3 and -6.6 ± 18 mm Hg, respectively ($p < 0.001$ for both). In the group with severe hypertension, the reaction amounted to -20.3 ± 22.8 mm Hg and -8.9 ± 16.9 mm Hg ($p < 0.001$ for both). The decrease was significant; however, a greater reduction was obtained in patients with very high SBP values.

Finally, we obtained results of the first Polish registry RDN-POL [14]. Forty-four patients with true resistant hypertension (23 men, mean age 52.3 years) with daytime SBP in ABPM ≥ 135 mm Hg, on ≥ 3 antihypertensive agents, including diuretic, underwent RDN and completed 12-month follow-up. Mean reductions of office SBP/DBP were $-23.8/-10.0$ mm Hg, $-12.5/-4.6$ mm Hg, and $-12.6/-6.1$ mm Hg at three, six, and 12 months, respectively (all significant except diastolic at six months). Diabetes was the only predictor of office SBP reduction at six months (odds ratio 9.6; 95% confidence interval: 1.4–66.5, $p < 0.05$). Mean 24-h SBP change was -8.3 mm Hg at six months and -4.6 mm Hg at 12 months. The RDN-POL Registry demonstrated moderate BP decrease after RDN. The predictors of BP reduction were diabetes, 2-h glucose and baseline office SBP. Analysis of ABPM responders indicates a probable positive impact of RDN on glycaemic control. The results of the study proving positive effects of the renal arteries ablation treatment, which are non-hypertension related, should not be neglected.

THE EFFECT ON GLYCAEMIC

In 2011 “Circulation” published a paper on the effect of renal arteries denervation on insulin resistance in patients with resistant AH [15]. Fifty-five patients were included in the trial according to commonly accepted qualification criteria. In patients from the denervation group, apart from the arterial pressure drop (SBP $[-28 \pm 2$ mm Hg; $p < 0.001$] and DBP $[-10 \pm 2$ mm Hg; $p < 0.001$]), the glucose concentration on an empty stomach dropped from 118 ± 3.4 mg/dL to 108 ± 3.8 mg/dL ($p = 0.039$). On the other hand, in the control group the change was not statistically significant. The insulin concentration dropped from 20.8 ± 3.0 μ IU/mL to 9.3 ± 2.5 μ IU/mL ($p = 0.006$), which was followed by a reduction of the peptide C concentration from 5.3 ± 0.6 ng/mL to 3.0 ± 0.9 ng/mL ($p = 0.002$). The sensitivity to insulin, which was measured by the HOMA-IR and ISQUICKI indicators, increased slightly after the renal artery denervation. The HOMA-IR indicator dropped from 6.0 ± 0.9 to 2.4 ± 0.8 ($p = 0.001$) and the ISQUICKI indicator showed an increase from 0.32 ± 0.01 to 0.36 ± 0.01 ($p = 0.001$). In patients with diagnosed diabetes ($n = 13$), the denervation treatment significantly decreased the glucose, insulin, and peptide C concentration on an empty stomach, and the insulin sensitivity improved after three months.

THE EFFECT ON THE PARAMETERS OF OBSTRUCTIVE SLEEP APNEA

The relation between AH and obstructive sleep apnoea (OSA) is especially strong in patients with refractory hypertension resistant to treatment. In the investigation of the patients with badly controlled arterial pressure using three different kinds of antihypertensive medication, previously unsuspected OSA was found in 83% of the patients [16]. Moreover, it was confirmed that the greater the lack of breath at night, the higher the probability of being resistant to hypertension treatment.

In 2011, “Hypertension” published a Polish study that evaluated the effect of RDN in patients with refractory AH coinciding with OSA [17]. Ten patients participated in the study: seven males and three females. The average age was 49.5 years, and the observation period was six months. The RDN resulted in a reduction of SBP and DBP by 34/13 mm Hg after six months of treatment ($p < 0.01$), significant reduction in glucose blood concentration, and a lower index of apnea-hypopnea: 16.3/h vs. 4.5/h ($p = 0.059$).

The study shows that RDN can be a modern method to treat resistant AH and obstructive apnoea, especially in patients with metabolic disorders. It also showed the positive effect of renal ablation BP, glucose metabolism, and sleep apnoea reinforcing the significance of activating the sympathetic nervous system in the development of risk factors of the cardiovascular system.

THE EFFECT ON THE SYMPTOMS OF HEART FAILURE

The REACH (REnal Artery Denervation in Chronic Heart Failure) pilot results have been published, and the study's aim was to assess the safety of applying renal artery ablation procedures in patients with chronic heart failure (HF) [18]. The procedures were performed on seven patients aged approximately 69 years, with systolic HF, who were undergoing optimal pharmacological therapy. In accordance with previous expectations, it was proven that the procedure is safe; there were no complications after the procedures, in the post-operation period, or during the six-month observation period. Arterial pressure after six months of observation dropped by approximately 7.1 ± 6.9 mm Hg for SBP and 0.6 ± 4.0 mm Hg for DBP. Those reductions proved to be statistically insignificant, but more importantly no hypertension or fainting episodes were recorded, and it is worth bearing in mind that the initial arterial pressure in that group was normal. The procedure did not affect kidney functions, and furthermore it decreased the subjective symptoms of HF and improved the patients' condition measured by a six-minute walk. We are currently waiting the results of the main part of the REACH study. In current observations, 100 HF patients with New York Heart Association II–IV type of condition with a left ventricular ejection fraction $< 40\%$, with estimated GFR > 35 mL/min, currently undergoing optimal HF therapy will be studied. The study will assess the effect of the denervation treatment on HF symptoms, physical activity tolerance, arterial pressure, arrhythmia episodes, and chemical receptor sensitivity.

CONCLUSIONS

According to the “Catheter-based renal sympathetic denervation for the treatment of resistant arterial hypertension in Poland — experts consensus statement”, although published before obtaining the Simplicity HTN-3, PRAGUE-15 and DENERHTN results, the prerequisite of the treatment is a clinical value of SBP ≥ 160 mm Hg (an average of three measurements), ingesting at least three fully dosed antihypertensive medications, including a diuretic. Since the Simplicity HTN-3 trial it is believed that patients qualified for ablation should take a dose of aldosterone receptor blocker. Currently, until the long-term effectiveness of RDN treatment is assessed, it is suggested that the qualifications for the procedures are performed by hypertension-specialised centres and the procedure itself should be conducted by an experienced invasive cardiologist.

Conflict of interest: participation in “RDN-POL Registry”; lectures for Medtronic.

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