ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Renal artery sympathetic nerve radiofrequency denervation

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Abstract

Background: Arterial hypertension is one of the most common chronic diseases in the western world, affecting more than 25% of the adult population.

Aim: The aim of this study was to assess changes in arterial blood pressure (BP) levels in hypertensive patients, after ablation of nerve terminals in renal arteries, using radiofrequency energy during 24 months of follow-up.

Methods: Thirty-two patients with diagnosed resistant hypertension (20 men and 12 women) underwent percutaneous catheter-based renal denervation of nerve terminals in renal artery walls. Mean BP value before ablation was [mm Hg]: systolic 174.92, diastolic 99.73 and pulse pressure 75.19. After procedure reduction value of BP was reported [mm Hg]: systolic 146.78; diastolic 87.14, pulse pressure 59.64 at 24-month follow-up ($p < 0.05$ for all).

Results: 30% of patients had systolic BP ≤ 140 mm Hg, 67% had diastolic BP ≤ 90 mm Hg, and optimum BP values ≤ 140/90 mm Hg were observed in 30% of patients.

Conclusions: In our cohort of patients, percutaneous renal artery ablation procedure effectively reduces systolic, diastolic BP and pulse pressure. No adverse events during 24 months of follow-up were noted. These results were comparable with available data from SIMPLICITY I and II trials.

Key words: hypertension, resistant hypertension, renal artery ablation

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INTRODUCTION

There is an increasing prevalence of arterial hypertension — nearly 26% of the world's adult population (nearly one billion people) suffer from arterial hypertension [1]. High blood pressure (BP) is the main risk factor for cardiovascular disease, renal failure, stroke, and myocardial infarction [2, 3]. Unfortunately, improvement in hypertension awareness, treatment, and control is not optimal [4]. Recent data have confirmed that only 74.9% of patients with arterial hypertension undergo treatment. In this group of patients, hypertension is well-controlled only in 52.5% of patients, suggesting that in up to a half of patients BP is uncontrolled [3].

Resistant hypertension is defined as BP that remains above the goal despite concurrent use of three antihypertensive medications (including diuretic) in optimal doses. Resistant hypertension is a severe clinical problem because it is difficult to treat and occurs in 10–12% of hypertensive patients [5–8]. Due to that fact new therapeutic options are needed. One of the effective and safe therapeutic methods for reduction of a high BP is percutaneous renal sympathetic denervation (RN). SYMPLICITY HTN-1 and SYMPLICITY HTN-2 studies testing this method proved significant reduction in BP levels without major adverse outcomes [9–13]. However, the SYMPLICITY HTN-3 study did not confirm those findings, due to a specific patient subset attending the study (for example African American).

The aim of this study was to assess changes in arterial BP levels in hypertensive patients after ablation of nerve terminals

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Table 1. Inclusion/exclusion criteria

1. Renal artery anomalies:
a. Haemodynamically significant renal artery stenosis (over 50%) by visual assessment
b. Atherosclerotic lesion or stenosis within the artery which may potentially, according to the operator, add additional hazard to patient safety during artery catheterisation
c. Haemodynamically or physiologically significant stenosis that may be responsible for arterial hypertension
d. Prior renal artery stenting or angioplasty
e. Patients with more than one renal artery at one side
2. Suspicion of secondary hypertension or diagnosed secondary hypertension regardless of the underlying cause (including one associated with administered drugs)
3. Patients with a history of coronary artery disease manifested by myocardial infarction, unstable angina or stroke in the previous six months
4. Patients with significant valvular disease
5. Type 1 diabetes
6. Patients with implantable cardioverter-defibrillator or pacemaker
7. Patients requiring breathing support
8. Patients suffering from a disease or taking drugs that potentially influence the effectiveness of the therapy (e.g. peripheral atherosclerosis, aortic aneurysm, bleeding disorders, thrombocytopenia, anaemia, arrhythmia, alcohol abuse, drug addiction)
9. Patients who plan pregnancy or are pregnant

in renal arteries (denervation) as well as procedure safety in two years of follow-up of patients in the Polish population.

METHODS

All patients were the part of the HTN-1 and HTN-2 studies. Adult patients with resistant arterial hypertension, who met all inclusion/exclusion criteria (Table 1) were eligible for this study. Basically, we included patients with diagnosed arterial hypertension resistant to pharmacological treatment. The presence of resistant arterial hypertension was defined as mean brachial artery seated systolic pressure above 160 mm Hg during out-patient department visits, despite historical compliance with at least three antihypertensive drugs (including a diuretic) in optimal doses.

Blood pressure measurement was performed in accordance with Joint National Committee 7 guidelines [14]. Measurements were performed each time by the same person, sitting, in triplicate, and then averaged.

Four weeks before renal denervation mean BP systolic value was above 160 mm Hg. Also, four weeks before procedure and during the entire study no modification of pharmacotherapy was allowed. Patient compliance with medication was strictly verified by interview and patient diary. In case of pharmacotherapy modification, patients were excluded from the follow-up analysis. Obesity was defined as waist circumference > 102 cm in men, > 88 cm in women.

The technique of renal denervation has recently been described [10–13]. After standard femoral vascular access, the SIMPLICITY catheter (Ardian Inc., USA, currently Medtronic Inc., USA) was introduced into each renal artery. During the procedure, a standard dose of unfractionated heparin was used. Six radiofrequency ablations at 8 W with duration up to 120 s each were performed in both renal arteries. Applied energy, tip temperature, and impedance were monitored by catheter system in response to a predetermined algorithm during the procedure.

Follow-up visits were performed at one, three, six, nine, 12, 18, and 24 months after the procedure. BP (systolic, diastolic, pulse pressure) measurements were performed (according to the methodology described earlier), as well as blood count, electrolytes, urea, creatinine and urine, and a physical exam including orthostatic BP measurements.

During the entire study major adverse events (death, stroke, myocardial infarction) or other outcomes associated with the procedure were monitored.

Before the study, written informed consent was obtained from all patients. The study was approved by the Institutional Bioethics Committee (two separate ethics committee approvals since the patients attended in the SYMPLICITY HTN-1 and SYMPLICITY HTN-2 studies).

Statistical analysis

For statistical analysis, we assessed continuous variables between groups, including the BP, with Student's two-sample t test. All statistics analyses were performed with Statistica (StatSoft). Statistical significance was set at $p = 0.05$. All tests were two-tailed.

RESULTS

Thirty-two patients (20 men and 12 women) were included into the study. Baseline characteristics are presented in Table 2. Pre-procedure antihypertensive medications are presented in

Table 2. Baseline characteristics

Patient numbers	32 (20 men, 12 women)
Age (mean) [years]	31–76 (56.75)
Weight (mean) [kg]	74–145 (94.91)
Height (mean) [cm]	159–184 (169)
Body mass index (mean) [kg/m^2]	23.36–46.81 (33.21)
Risk factors:	
Hypercholesterolaemia	19 (59%)
Diabetes mellitus	11 (34%)
Abdominal obesity (WC > 102 cm in men, 88 > cm in women)	9 (28%)
Current smoking	2 (6%)
Cardiovascular disease:	
Heart failure (mean), NYHA grade	1–3
Angina pectoris	7 (22%)
Coronary artery disease	8 (25%)
Myocardial infraction	5 (16%)
Valvular disease	2 (6%)
Cardiomyopathy	2 (6%)
Ventricular arrhythmia	1 (3%)
Other disease:	
Renal insufficiency	2 (6%)
Asthma	1 (3%)
Chronic obstructive pulmonary disease	1 (3%)
Gastric ulcer	3 (9%)

NYHA — New York Heart Association scale; WC — waist circumference

Table 3. Pre-procedure antihypertensive medications

Medications	N	%
Beta-blockers:	25	81%
acebutolol	1	3%
betaxolol	10	32%
bisoprolol	10	32%
carvedilol	1	3%
metoprolol	1	3%
nebivolol	1	3%
sotalol	1	3%
ACEI:	19	61%
captopril	3	10%
lisinopril	1	3%
cilazapril	1	3%
enalapril	2	6%
perindopril	1	3%
quinapril	6	19%
ramipril	4	13%
trandolapril	1	3%
ARB:	19	61%
candesartan	10	32%
losartan	2	6%
telmisartan	3	10%
valsartan	4	13%
amlodipine	10	32%
doxazosin	3	10%
clonidine	1	3%
rilmenidine	2	6%
nitrendipine	12	39%
dilitazem	3	10%
Diuretics:	46	–
chlortalidone	4	13%
spironolactone	13	42%
furosemide	11	35%
torasemide	7	23%
hydrochlorothiazide	5	16%
indapamide	4	13%
amiloride	2	6%

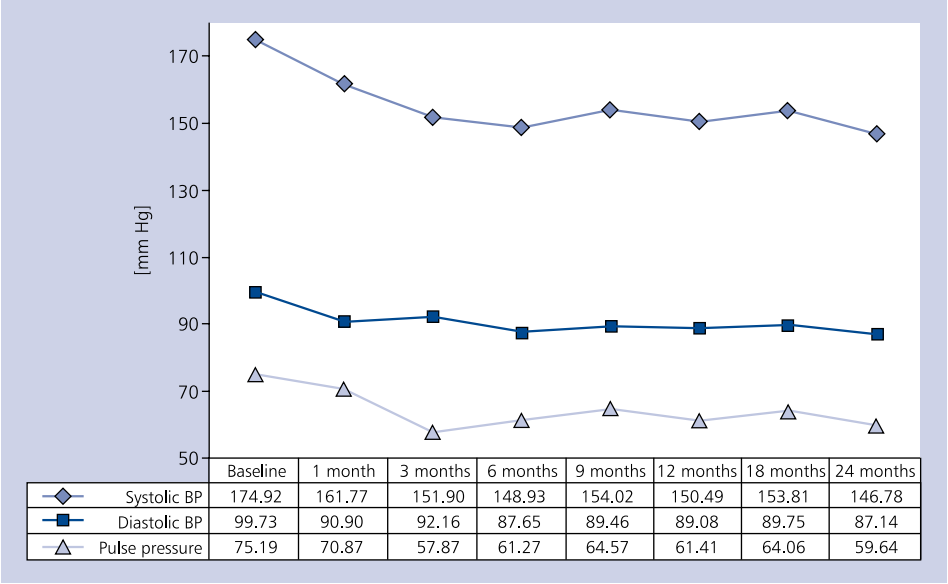
ACEI — angiotensin-converting-enzyme inhibitors; ARB — angiotensin II receptor antagonists; beta-blockers — beta adrenergic receptor antagonists

Table 3. Patients' ages ranged from 31 to 76 years (mean value 56.75 years), and body mass index ranged from 23.36 to 46.81 kg/m^2 (33.21 kg/m^2). The hypertension risk factors were: hypercholesterolaemia was diagnosed in 19 patients, diabetes mellitus type 2 in 11 patients, and obesity (waist circumference > 102 cm in men, > 88 cm in women) was present in nine patients. The co-existing cardiovascular disease included: seven patients had coronary artery disease, two patients had valvular disease, two patients had cardiomyopathy, and one patient had ventricular arrhythmia. One patient had asthma, one had chronic obstructive pulmonary disease, and three patients had gastric ulcer. Only two patients were diagnosed with chronic renal insufficiency according to elevated creatinine and urea in blood serum (third grade according to classification, which means eGFR 30–59 mL/min/1.73 m^2). No patient had symptoms of peripheral artery disease. Patients ranged by New York Heart Association classification from 1 to 3.

The mean value of three measurements of BP before ablation was: systolic from 162 to 212 mm Hg (mean value 174.92 mm Hg), diastolic from 82 to 121 mm Hg (mean value 99.7 mm Hg), pulse pressure from 54 to 100 mm Hg (mean value 75.2 mm Hg). The heart rate ranged from 60 to 98 bpm (mean value 72.3 bpm) (Table 2).

Periprocedural

According to the protocol, six radiofrequency ablations at 8 W lasting up to 120 s each were performed in both renal



	Baseline	1 month	3 months	6 months	9 months	12 months	18 months	24 months
Systolic BP	174.92	161.77	151.90	148.93	154.02	150.49	153.81	146.78
Diastolic BP	99.73	90.90	92.16	87.65	89.46	89.08	89.75	87.14
Pulse pressure	75.19	70.87	57.87	61.27	64.57	61.41	64.06	59.64

Figure 1. Mean systolic, diastolic blood pressure (BP), and pulse pressure at baseline and one, three, six, nine, 12, 18, and 24 months after the procedure. All results are statistically significantly ($p < 0.05$)

arteries in each patient. No complications related to vascular access site or other adverse events like vascular, renal, or cardiovascular complications were noted. Visceral pain at the time of energy delivery was managed mostly with supplemental intravenous opioids. The one prolonged postoperative in-hospital stay was not related to the procedure, and all 32 patients were discharged home.

One year after the procedure

One year after the procedure, 30 patients showed up for follow-up visit. Three patients modified significantly the prescribed antihypertensive treatment and were excluded from the one year analysis. All other patients remained compliant with baseline pharmacotherapy.

The mean value of systolic BP for the 27 patients ranged from 111 to 203 mm Hg (mean value 150.49 mm Hg) and was 24.42 mm Hg lower than baseline, ($p < 0.05$). The mean value of diastolic BP for the 27 patients ranged from 63 to 117 mm Hg (mean value 89.08 mm Hg) and was 10.65 mm Hg lower than baseline before the ablation procedure, $p < 0.05$. The pulse pressure decreased to 61.41 mm Hg (mean value) from baseline 75.19 mm Hg, $p < 0.05$. Systolic, and diastolic BP and pulse pressure were statistically significantly lower than at baseline. The highest mean BP reduction was: systolic 77.33 mm Hg, diastolic 45 mm Hg ($p < 0.05$).

The mean values of heart rate ranged from 60 to 121 bpm (mean value 77.36 bpm) during the one-year follow-up. The mean heart rate was 5.05 bpm higher than that measured before the procedure (statistically not significant). No complications related to the ablation procedure nor adverse events were noted. The weight one year after the procedure ranged from 58 to 140 kg (mean value 90.52 kg) and was not statistically different from the mean value before the procedure.

One year after the procedure in 30% (eight patients) systolic BP was ≤ 140 mm Hg and in 52% (14 patients) diastolic BP was ≤ 90 mm Hg. Optimum BP value ≤ 140/90 mm Hg was observed in 19% of all patients.

Additionally, all patients had a computed tomography (CT) scan performed to check for the renal artery lesions postoperatively. None of the patients who had a CT scan performed in 6–12 months of follow-up had significant lesions in renal arteries diagnosed. Two patients had up to 30% lesions in their renal arteries, but these lesions were already diagnosed during the preoperative angiography. No progress of any of these lesions was found in one-year follow-up.

Two years after the procedure

Two years after the procedure, 27 patients were seen in follow-up. All patients remained compliant with baseline pharmacotherapy. There were no reports of adverse clinical events related to the procedure or BP changes. Another five patients had substantial modification of medication or those not compliant to pharmacotherapy, so they were excluded from the study according to the protocol approved by the Ethical Committee.

The mean value of systolic BP for the 27 patients ranged from 117 to 192 mm Hg (mean value 146.78 mm Hg) and was 28.14 mm Hg lower than baseline, $p < 0.005$. The mean value of diastolic BP for the 27 patients ranged from 71 to 110 mm Hg (mean value 87.14 mm Hg) and was 12.59 mm Hg lower than baseline before the ablation procedure, $p < 0.005$. The pulse pressure decreased to 59.64 mm Hg (mean value) from baseline 75.19 mm Hg (Fig. 1), $p < 0.05$. Systolic, diastolic

BP, and pulse pressure were statistically significantly lower than at baseline. The highest mean BP reduction was: systolic 83 mm Hg, diastolic 49.67 mm Hg.

The mean values of heart rate ranged from 57 to 121 bpm (mean value 82.96 bpm) during the two years of follow-up. The mean heart rate was 9.81 bpm higher than that measured before the procedure. All these results were statistically significant ($p < 0.005$).

Two years after the procedure, in 30% (eight patients) systolic BP was ≤ 140 mm Hg and in 67% (18 patients) diastolic pressure was ≤ 90 mm Hg. Optimum BP values ≤ 140/90 mm Hg were observed in 30% of all patients.

DISCUSSION

These long-term results are consistent with previous reports [11, 13]. Radiofrequency renal nerve ablation is an effective treatment in reducing the level of BP in patients with arterial hypertension resistant to pharmacotherapy. In the carefully selected group of patients from Poland, systolic, diastolic, and pulse pressure were statistically significantly lower two years after the procedure. Also, the complete group of SYMPLICITY HTN-1 patients after two years follow-up showed that mean systolic and diastolic BP remained lowered ($p < 0.001$) [9].

Radiofrequency renal sympathetic denervation is a safe and effective treatment option for patients with drug-resistant hypertension. In the first clinical trials, the SIMPLICITY I (two-year follow-up) showed mean systolic BP reduction of 30 mm Hg and diastolic BP of 14 mm Hg, and the SIMPLICITY II (one-year follow-up) showed mean systolic BP reduction of 28.1 mm Hg and diastolic BP of 9.7 mm Hg ($p < 0.001$). After one year observation, both trials showed that durable BP reduction was present in 84% of patients [9, 10]. It suggests, that radiofrequency renal ablation may reduce the total cardiovascular risk in patients with resistant hypertension according to the cardiovascular risk observed in non-resistant hypertension patients. The obvious BP lowering, especially the pulse pressure, can reflect future risk benefit for these patients; however, it is still too early to estimate the overall outcome of adverse events such as death, stroke, and myocardial infarction in long-term observation in this small study. Nonetheless, the patients enrolled had exhausted alternative therapy, and RN provided a calculable benefit in this cohort. The current reports do not report serious adverse events of the RN, but few minor complications are noted: pseudoaneurysms in the access site, rapid onset hypotonia, urinary tract infections, paraesthesia, and pain, all self-limited complications [12]. It should be emphasised that meta-analysis supports a 13% reduction of mortality for every 10 mm Hg reduction of systolic BP [15]. In our group, the BP reduction was persistent in two years of follow-up.

To date, no long-term vascular or renal complications have been identified in large cohorts, or in our group of patients. Also, no new reports of renal failure, renal artery stenosis, syncope, or other vascular or cardiovascular adverse events were noted during two years of follow-up in the Polish sample.

The study, which was conducted to confirm the positive role of RN was called SYMPLICITY HTN-3; however, the results did not demonstrate sufficient effectiveness of this procedure in lowering BP [16]. The study showed no significant reduction in BP monitoring, both office measurement and 24-h ambulatory blood pressure monitoring (AMBP), in the population of patients who underwent RN compared with the control group (a placebo sham operated group, who received only arteriography of renal arteries). The results of SYMPLICITY HTN-3 were critically analysed, especially since the reverse results of the Global Simplicity Registry and the first meta-analysis of European studies were published [17]. All of this questioned denervation of the renal arteries as a step forward in the treatment of resistant hypertension. Also, our current analysis is at odds with the results of the SYMPLICITY HTN-3 study.

There are many hypotheses trying to explain the reasons for the discrepancy between study results. The simplest is that in SYMPLICITY HTN-3 patients improved the compliance both in terms of lifestyle changes and pharmacotherapy. However, it seems that the main reason for the negative results of SYMPLICITY HTN-3 was probably the different patient population including 25% African Americans, who showed in subgroup analysis that they did not respond to renal denervation [18].

It is also believed that in some cases, the procedure was not effective because of poor catheter construction (the system has been changed now) and little experience of the operators. In all discussions, it is also emphasised that the crucial point of successful RN is proper patient selection and exclusion of patients who simply do not take hypertensive drugs [19]. Our patient population was very carefully selected from individuals with drug resistant hypertension confirmed for years. Also, all patients without proper compliance were excluded from the study.

Based on the HTN-3 study and other known studies on RN, we can estimate that this method can be effective in a population of Caucasians, under the age of 60 years, without renal insufficiency, and with resistant hypertension treated obligatorily with four antihypertensive drugs, including aldosterone antagonist. In addition, renal denervation should be performed with more technologically advanced catheters than those used in the study HTN1-3 [19].

Additional positive effects of RN should support the positive role of this method in advanced patient care. Witkowski et al. [20] suggested that renal sympathetic denervation may be a potentially useful option for patients with comorbid resistant hypertension, glucose intolerance, and obstructive sleep apnoea. Schlaich et al. [21] performed renal denervation in obese and hypertense women with polycystic ovary syndrome

(PCOS). In this study, renal denervation caused a reduction in both BP and insulin resistance, which are important therapeutic targets in PCOS patients. Improvement of glucose tolerance has also been confirmed by other authors [22, 23]. Renal denervation in patients with arterial hypertension also led to improvement of cardiac diastolic function, reduction of left ventricular mass [24], and reduction of augmentation index [25] in hypertension patients. Another group of patients in whom renal denervation can be a potential therapeutic option are haemodialysis patients with resistant or difficult to control hypertension. Performed studies showed that renal denervation significantly reduces BP in haemodialysis patients [26, 27]. Unfortunately, in our group of patients, this kind of sub-analysis was not performed.

Another study performed on a Polish population is the Polish Renal Denervation registry [28]. In this study at 12-month follow-up the mean 24-h systolic BP change was –8.3 mm Hg at six months and –4.6 mm Hg at 12 months. This registry, similarly to our findings, demonstrated moderate BP decrease after RN; however, in both studies the selection of the patients was performed very carefully. Findings from both studies suggest that in the Polish patient population RN can be effective.

Renal sympathetic denervation, as a new method of hypertension treatment, deserves attention because there is enough data suggesting it can significantly lower BP in a carefully selected group of patients, and this effect is persistent in two years of follow-up.

Limitations of the study

This is a non-randomised, single-arm study with a relatively small patient sample size, which does not allow us to come to definitive conclusions for the general Polish population.

The study is a sub-analysis of two Polish cohorts of the SYMPLICITY I and SYMPLICITY II studies. Patients who were not compliant were excluded from the study, but we were not able check other patients' compliance. As was already mentioned, six applications per artery (according to the protocol) was probably not sufficient to reach perfect results of RN. Probably better catheter construction, which facilitates the electrode apposition and energy delivery into the arterial wall, will also eliminate the problems observed in unexperienced operators, associated with difficult anatomy of the artery, and decrease the total time of the procedure.

CONCLUSIONS

Renal sympathetic denervation is a safe and effective therapeutic treatment reducing the level of BP in patients with arterial hypertension resistant to pharmacotherapy. After two years of the procedure, no new or late complications or unexpected adverse events were noted in the Polish cohort of patients. The significant BP reduction after two years of follow-up was confirmed, with the BP below 140/90 mm Hg in 30% of cases and diastolic BP below 90 mm Hg in 67%.

Conflict of interest and financial support: *All the procedures were performed in the SYMPLICITY HTN-1 and SYMPLICITY HTN-2 studies, so the whole study was sponsored by Medtronic. The authors received a study fee for conducting the clinical trial.*

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Ablacja zakończeń nerwowych w tętnicy nerkowej prądem o wysokiej częstotliwości

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Streszczenie

Wstęp: Nadciśnienie tętnicze jest jedną z najbardziej powszechnych chorób przewlekłych w krajach zachodnich i dotyczy więcej niż 25% dorosłej populacji.

Cel: Celem pracy była ocena zmian ciśnienia tętniczego (BP) u pacjentów z nadciśnieniem tętniczym po ablacji zakończeń nerwowych w tętnicach nerkowych z zastosowaniem prądu o wysokiej częstotliwości w 24-miesięcznej obserwacji.

Metody: Trzydziestu dwóch pacjentów z rozpoznanym nadciśnieniem opornym (20 mężczyzn i 12 kobiet) poddano przezskórnej denerwacji zakończeń nerwowych w ścianie tętnic nerkowych. Średnia wartość ciśnienia krwi przed ablacją wynosiła [mm Hg]: 174,92 (skurczowe), 99,73 (rozkurczowe), a ciśnienie tętna — 75,19. Po 24 miesiącach obserwacji stwierdzono zmniejszenie wartości ciśnienia tętniczego [mm Hg]: skurczowe — 146,78; rozkurczowe — 87,14, ciśnienie tętna — 59,64.

Wyniki: Wszystkie wyniki były statystycznie znamienne. U 30% pacjentów zanotowano wartość skurczowego BP ≤ 140 mm Hg, u 67% osób rozkurczowe BP wynosiło ≤ 90 mm Hg, natomiast optymalne wartości ciśnienia krwi (≤ 140/90 mm Hg) stwierdzono u 30% pacjentów po 24 miesiącach od ablacji tętnic nerkowych.

Wnioski: W grupie badanych chorych przezskórna ablacja tętnicy nerkowej skutecznie obniżyła skurczowe i rozkurczowe BP oraz ciśnienia tętna. Nie stwierdzono istotnych zdarzeń niepożądanych w ciągu 24-miesięcznej obserwacji. Wyniki badań polskiej grupy pacjentów nie odbiegają w żaden sposób od wyników uzyskanymi w badaniach SIMPLICITY I i II.

Słowa kluczowe: nadciśnienie tętnicze, ablacja tętnic nerkowych

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