

Original Paper

Renal Artery Stenting Associated With Improvement in Renal Function and Blood Pressure Control in Long-Term Follow-Up

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Key Words

Renal artery stenting • Renal function • Blood pressure

Abstract

Background/Aims: Clinical benefits of percutaneous treatment of renal artery stenosis (RAS) remain controversial. The aim of this study was to evaluate the effects of renal artery stenting on kidney function and blood pressure (BP) control in the long-term follow-up. Additionally angiographic follow up was performed in selected subgroup of patients. **Methods:** The study was designed as international registry of 265 consecutive patients with RAS treated with renal artery stenting. The primary end-point of the study was the change in renal function and blood pressure at long-term follow-up as compared with baseline values. Evaluation of the renal function was based on estimated glomerular filtration rate (eGFR) with the use of the modification of diet in renal disease (MDRD) formula. **Results:** All patients had clinical follow-up at the median time of 23.8 (interquartile range: 3-90) months during ambulatory visits. At follow-up eGFR improved in 53.9% of patients. These patients had lower pre-procedural systolic BP, more severe lesion type at baseline and lower diameter stenosis in control angiography. At follow up visits, SBP improvement was observed in 77.4% of patients. The average number of anti-hypertensive medications before the procedure and at follow up did not change significantly (2.70 ± 1.0 vs 2.49 ± 0.9 , $p=0.1$). Restenosis rate based on control angiography performed at median time of 15 months was 12%. **Conclusion:** The results of the

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study suggest that interventional treatment of RAS may preserve renal function and improve blood pressure control at long-term follow-up.

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Introduction

Renal artery stenosis (RAS) is the most common cause of secondary hypertension, which affects 1-5% of hypertensive patients [1-4]. In 90% of patients RAS is caused by atherosclerosis. Significant stenosis contributes to poor control of hypertension, deterioration of renal function, left ventricle hypertrophy and heart failure. The goal of renal artery revascularization is to preserve renal function, improve the blood pressure (BP) control and prevent cardiovascular complications of hypertension. In atherosclerotic RAS percutaneous interventions, including balloon angioplasty and renal artery (RA) stenting proved to be safe minimally invasive treatment, which may improve BP control and preserve renal function. Results of several single center studies evaluating clinical effects of RAS have shown benefits, however other clinical trials (ASTRAL, STAR) [5, 6] have shown no significant improvement when compared with medical therapy. Nevertheless in patients with significant RA stenosis producing compromised perfusion, angioplasty with stenting might still contribute to preserved renal function. Therefore, an all-comer registry with long-term follow-up of patients with significant atherosclerotic RAS treated with stenting was undertaken. The aim of the registry was to evaluate renal function and BP control after percutaneous renal artery revascularization. In a subset of patients a control RA angiography was performed in order to evaluate the rate of restenosis and progression of atherosclerosis.

Patients and Methods

The study was designed as an international registry of 265 consecutive patients enrolled in two clinical centers located in Ustron (American Heart of Poland, Poland) and at San Antonio (Endovascular and Heart Institute, San Antonio, TX, USA) between 2001 and 2009. Patients were eligible for the study if they had $\geq 50\%$ de novo RA atherosclerotic stenosis and at least one of the following: (1) poorly controlled hypertension (mean systolic blood pressure (SBP) of $\geq 160\text{mmHg}$) on at least three anti-hypertensive medications including diuretic, (2) impairment of renal function ($\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$), (3) unexplained congestive heart failure or recurrent acute pulmonary oedema. Absolute contraindication for double antiplatelet therapy (active gastrointestinal bleeding, recent haemorrhagic stroke, allergy to aspirin or thienopyridines), previous RAS and fibromuscular dysplasia were considered to be exclusion criteria.

Procedural data

All procedures were performed by femoral approach under local anesthesia with 6-8F arterial sheaths. Baseline angiography with Judkins right angiographic catheter was performed and the target RA was then selectively engaged with the 6-7F guiding catheter. Angioplasty procedures with the use of balloon expandable stents were performed according to standard interventional techniques. Pre-dilatation was carried out when critical ($>90\%$) or calcified stenosis was diagnosed. In patients with bilateral stenoses, both lesions were treated during single procedure. The procedural success was defined as residual percent diameter stenosis of less than 30% as measured by quantitative vessel angiography (QVA) system. Before the procedure dual antiplatelet therapy (DAT) was started with loading dose of 300 mg aspirin (in patients who were already on aspirin, the maintenance dose was used) and either ticlopidine (500 mg) or clopidogrel (300-600 mg) according to the operators practice at the time of the procedure. Then, the standard dose of ticlopidine (2 x 250mg daily) or clopidogrel (75 mg daily) was continued for the following 4-6 weeks. Aspirin was advised indefinitely. Immediately before the intervention, a bolus (100 units/kg) of unfractionated heparin was administered intravenously. Quantitative evaluation of angiographic images acquired at baseline and during control angiography was performed with the use of quantitative vessel analysis software (QAngio XA Software version 7.1.14.0; Medis Medical Imaging Systems). Analyzed parameters included: minimal lumen

diameter (MLD) of the reference segment and target lesion, reference vessel diameter (RVD), lesion length, acute gain (AG) and late lumen loss (LL). The reference segment was defined as the nearest to the lesion, visually normal segment of the RA on angiography. Acute gain was calculated as a difference between MLD measured after the procedure and MLD analyzed before the procedure. Late lumen loss was calculated as a difference between MLD acquired immediately after the procedure and MLD at follow-up. Percent diameter stenosis (%DS) at follow-up was calculated using the following formula: $[1 - (\text{MLD}/\text{RVD})] \times 100\%$. Restenosis was defined as a reduction in the luminal diameter of $\geq 50\%$.

Follow-up

Clinical follow-up. Baseline clinical data including patient demographics, comorbidities, laboratory tests, ambulatory BP measurements, number and types of anti-hypertensive medications, indications for the procedure and complications were collected from the medical notes and hospital information system.

The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine level using the modified "Modification of Diet in Renal Disease" (MDRD) formula. Renal dysfunction was categorized as severe for patients with $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$, moderate for patients with eGFR between 30 to 60 mL/min/1.73 m^2 , and none for patients with $\text{eGFR} > 60 \text{ mL/min/1.73 m}^2$.

The follow-up clinical outcomes were collected in all patients at the median time of 23.8 months (interquartile range 3-90) during ambulatory visits; the data included information on blood pressure (BP), oral anti-hypertensive treatment, serum creatinine and any adverse clinical events (including cardiac and non-cardiac death, myocardial infarction, stroke, or repeat revascularization).

Angiographic follow-up. The follow-up renal angiography was performed in one third of patients enrolled to the study (95 of 265) at the median time of 15 months after percutaneous transluminal renal angioplasty (PTRA) (IQR: 3-24). The decision in order to perform control angiography was made based on clinical indications and local practice of centers participating in the study. In addition, the very long-term telephone follow-up (median 7.85 years) was performed in a subgroup of 207 patients treated in Ustron, Poland.

End-points. The primary end-point of the study was the change in renal function and blood pressure at long-term follow-up as compared with baseline values. The prognostic parameters of renal function improvement and optimal pressure control were identified. Secondary outcomes were: ambulatory blood pressure, change of creatinine levels, number of anti-hypertensive drugs, rate of Major Adverse Cardiac and Cerebrovascular Events (MACCE; composite of death, acute myocardial infarction, stroke) and all-cause mortality. Additionally, in subpopulation of patients who underwent control angiography the recurrence of RA stenosis and angiographic variables associated with the clinical outcome were evaluated. All adverse events were analyzed by Clinical Events Committee.

Statistical Analysis

Statistical analysis was performed using MedCalc Software (v.11.0.1, Belgium). The data with normal distribution were expressed as means \pm standard deviations, whereas non-normally distributed data were expressed as median and interquartile range. Qualitative data were expressed as numbers and percentages. Normality of data distribution was verified with Shapiro-Wilk test. The parametric variables between the groups were compared using the unpaired Student t test while U-Mann-Whitney test was used for non-normally distributed data. The chi-square test or Fisher exact test was used for comparison of nonparametric variables. Statistical differences between clinical data related to tested procedures were analyzed using the Wilcoxon (quantitative data) and McNemar's or chi-square tests (qualitative data). Survival curves were estimated using Kaplan-Meier analysis. The Cox proportional hazard model incorporating most significant variables was used for multivariate analysis of independent risk factors influencing long-term outcomes, while logistic regression was used for independent predictors of short-term outcomes. In addition, receiver operating characteristic (ROC) analysis was performed to find the optimal cut-off point to predict the response of renal function after stenting. A p-value < 0.05 was considered statistically significant.

Results

Baseline data
Baseline demographic features of the patients enrolled in the study are described in table 1. A total of 265 patients were enrolled to the study. The mean age of all the patients was 69.0 years, and 53% of the patients were male. Diabetes mellitus was present in 28.5% of patients. Coronary artery disease (CAD) was

Table 1. Demographic data and medications used in the study (n=265 patients)

| | |
|--|-----------------------|
| Age, median (IQR) | 69,0 (63,0 - 74,0) |
| Male, n(%) | 143 (53) |
| Diabetes Mellitus, n(%) | 75 (28,5) |
| Dyslipidemia, n(%) | 101 (38,3) |
| Current smoker, n(%) | 42 (16,1) |
| Peripheral artery disease, n(%) | 84 (31,6) |
| Carotid artery disease, n(%) | 52 (19,5) |
| Coronary artery disease, n(%) | 238 (89,5) |
| Baseline systolic blood pressure, median(IQR) | 160,0 (145,0 - 171,3) |
| Baseline diastolic blood pressure, median(IQR) | 86,0 (80,0 - 95,0) |
| Baseline creatinine level, median(IQR) | 1,2 (1,0 - 1,4) |
| eGFR ml/min/1,73m ² , median(IQR) | 54,7 (43,4 - 67,0) |
| Number of anti-hypertensive drugs at baseline, mean±SD | 2,7±1,0 |
| Anti-hypertensive drugs at baseline: | |
| • ACE or ARB, n (%) | 231 (87,1) |
| • Beta blockers, n(%) | 233 (87,9) |
| • Ca-blockers, n(%) | 140 (52,8) |
| • Thiazide, n(%) | 127 (47,9) |
| • Aldosterone antagonists, n(%) | 39 (14,7) |
| • Alpha blockers, n(%) | 21 (7,9) |

Table 2. Procedural data

| | Baseline | After PTR | Angiographic follow-up * |
|--------------------|---------------------|---------------------|--------------------------|
| RD (mm) | 6,10 (5,24 - 6,57) | 5,82 (5,07 - 6,79) | 5,96 (5,25 - 6,87) |
| MLD (mm) | 2,39 (1,87 - 2,98) | 4,30 (3,84 - 4,96) | 4,21 (3,63 - 4,81) |
| % DS (%) | 70,0 (58,79 - 80,0) | 7,55 (3,77 - 12,90) | 10,68 (4,97 - 24,63) |
| Lesion length (mm) | 10,63 ± 4,04 | NA | NA |
| AG (mm) | NA | 1,99 (1,16 - 2,68) | NA |
| LLL (mm) | NA | NA | 0,34 (-0,15 - 1,28) |
| Restenosis | NA | NA | 11 (12,0%) |

NA = not applicable; * Concerns subgroup of 95 patients who underwent control angiography at the median time of 15 months after PTR

present in 89.5% of patients and peripheral artery disease (PAD) in 31,6% of them. Pre-procedural mean systolic blood pressure (SBP) was 160 mmHg and diastolic (DBP) was 86mmHg. Creatinine level and mean eGFR at baseline were 1.2 and 54.7 mL/min/1.73m² respectively. The average number of anti-hypertensive drugs per patient was 2.7±1. Eighty seven percent of patients were treated with an ACE inhibitors or angiotensin II receptor blockers, 87,9% of patients were treated with beta-blockers, 52,8% of patients received calcium channel blockers, 47,9% patients received thiazide diuretics, 14,7% of patients received aldosterone antagonist and only 7,9% of patients received alpha receptor inhibitors (table 1).

Procedural data

All procedural characteristics are presented in table 2. The pre-procedural median of diameter stenosis was 70,0% (58,8-80,0%). Distribution of percent diameter stenosis (%DS) in treated arteries is presented on figure 1. Of all lesions 73% were categorized as ostial with the median distance 0,00 (0,00-2,7) mm from the aortic lumen. Of all patients who underwent stenting, bilateral renal artery stenosis was observed in 14 (5,2%) patients. The most frequently used stents included: Corynthian (Cordis Vascular) in 30.9% of cases and Herculink+ (Abbott Vascular) in 18,7% of cases. The average diameter and length of implanted stents were 5,52±1,0 mm and 14,70±2,7 mm. The mean maximal inflation pressure was 14,37±4,22 atm. The procedural and angiographic success rate was 100% with residual

stenosis of $5,1 \pm 8,7\%$. There were three cases (1,4%) of edge dissection. There were no severe procedure-related complications or in-hospital major cardiovascular events.

Clinical outcomes

All patients had clinical follow-up at the median time of 23.8 (ICQ:3-90) months during ambulatory visits. Median eGFR before the procedure for the whole treated population was 54,65 (43,40-67,00) ml/min/1,73m². After the procedure eGFR increased to 61,40 (48,65-72,35) ml/min/1,73m² (Figure 2). The improvement in renal function defined as the increase in eGFR compared with baseline values was achieved in 53,9% of patients. Renal function did not change in 15,5% of patients while in 30,6% patients continued to deteriorate. In the overall patients population the median of serum creatinine concentration decreased significantly from 1,2 (1,00-1,40) mg/dl at baseline to 1,10 (0,90-1,30) mg/dl ($p < 0,01$) at follow-up (Figure 3). At follow up visits, SBP improvement

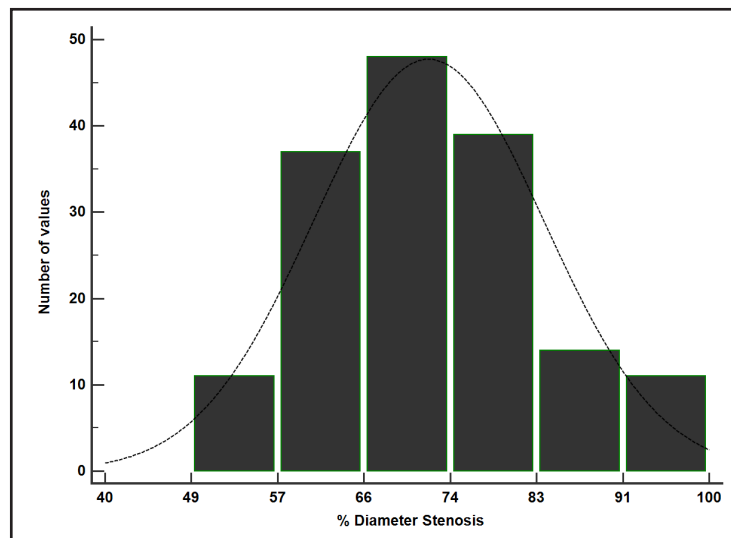


Fig. 1. Distribution of stenosis severity at baseline.

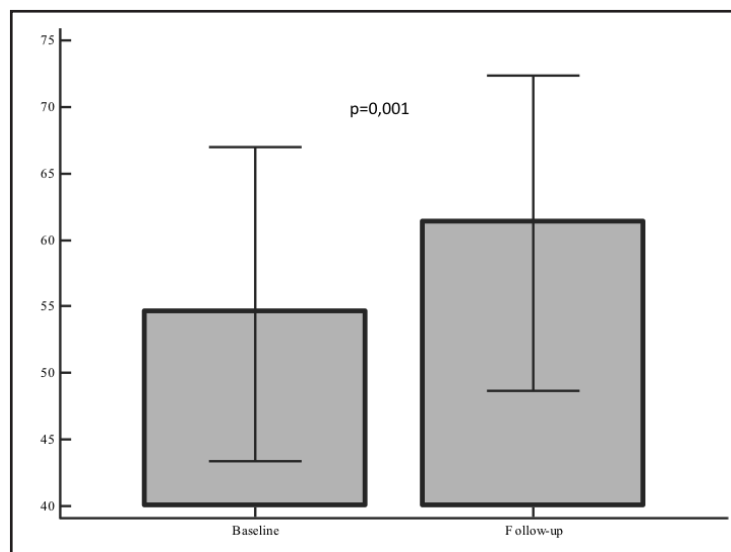


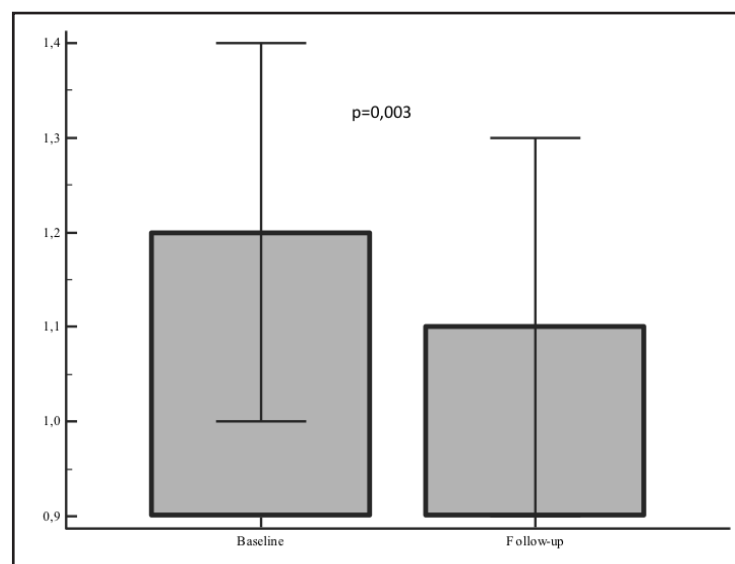
Fig. 2. eGFR before PTRa and at follow-up for the whole treated population (median and IQR).

was observed in 77,4% of patients while DBP improvement in 68,2% of patients. The SBP was reduced from 160,00 (145,00-171,25) mmHg to 135,00 (125,00-146,00) mmHg and DBP from 86,00 (80,00-95,00) mmHg to 75,00 (70,00-80,00) mmHg; $p < 0,01$ (Figure 4 and 5). Patients in whom eGFR or blood pressure improved or remained unchanged had lower pre-procedural SBP, more severe lesion type at baseline (longer lesion with higher diameter stenosis) and lower diameter stenosis in control angiography as compared to patients in whom renal function deteriorated (table 3). The multivariate analysis revealed the following independent determinants for the response of renal function after stenting: pre-procedural %DS, pre-procedural eGFR and creatinine level, pre-procedural SBP, male gender and peripheral artery disease. In addition, all patients in whom eGFR improved at follow-up had significantly lower maximal BP ($p < 0,01$; figure 6). The average number of anti-hypertensive medications before the procedure and at follow up did not change significantly ($2,70 \pm 1,0$

Table 3. The comparison of clinical and procedural characteristics for patients in whom renal function improved or preserved compared with patients in whom renal function deteriorated

| | Patients in whom renal function improved or preserved | Patients in whom renal function deteriorated | p |
|------------------------------|---|--|--------|
| | n=143 (69,4%) | n=63 (30,6%) | |
| % DS baseline | 72,04± 12,65 | 57,19± 19,01 | <0,01 |
| % DS control | 13,07± 16,59 | 23,94± 24,72 | 0,03 |
| Lesion length | 11,33± 4,25 | 9,31±3,59 | 0,04 |
| eGFR baseline | 53,46±16,61 | 67,44±26,93 | 0,0001 |
| eGFR control | 64,61± 20,68 | 52,24±20,64 | 0,002 |
| Creatinine levels - baseline | 1,20(1,00-1,47) | 1,00(0,90 - 1,20) | 0,0006 |
| Creatinine levels - control | 1,00(0,90-1,20) | 1,20(1,02 - 1,60) | 0,0001 |
| SBP baseline | 153,00(140,00-170,00) | 160,00 (150,00 - 180,00) | 0,024 |

Fig. 3. Creatinine before PTRa and at follow-up for the whole treated population (median and IQR).



vs. $2,49 \pm 0,9$, $p=0,1$). At baseline, one anti-hypertensive drug was applied to 7.3% of patients; two to 37.4%, three to 35.1%, four to 16.0%, five to 1.9%, and six drugs were given to 1.5% of patients. At the follow up visit, 1.7% of patients did not require anti-hypertensive treatment; one drug was used by 9.7% of patients, two by 42.4%, three by 33.1%, four by 11.4% and five by 1.7% of patients. The number of anti-hypertensive drugs did not influence the occurrence of blood pressure improvement ($p=0,4$). The frequency of MACCE rate was 21.7%, death occurred in 11.4%, myocardial infarction in 3.3% and stroke in 2.7% of patients. In extended follow-up performed in 207 patients (median 7,85 years; 28-3983 days) the MACCE rate was 26,1%, death 18.1%, stroke

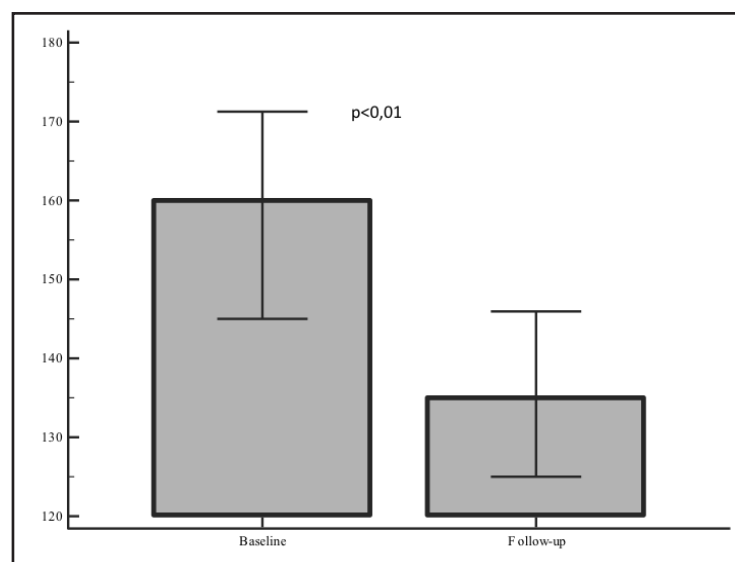


Fig. 4. Systolic blood pressure before PTRa and at follow-up for the whole treated population (median and IQR).

4.5% and myocardial infarction 6.4%. Kaplan-Meier survival probability estimates of eleven years was 69% (Figure 7), while MACCE free and restenosis free survival were 60.2% (Figure 8) and 92.7%, respectively.

Angiographic follow-up

The follow-up renal angiography was performed in 95 patients (36%) at the median time of 15 months after PTRE (IQR: 3-24). Angiographic control revealed restenosis, which occurred in 11 (12%) cases. The median late lumen loss at this time point was 0,34mm (-0,15 - 1,28). The ROC analysis demonstrated that the value of 67.4% was the optimal cut-off point to predict the response of renal function after stenting (AUC: 0,74; 95% CI 0,54 to 0,83; $p < 0,01$).

Discussion

Our study aimed to evaluate if RA stenting leads to improvement of renal function based on eGFR changes and blood pressure control in the long-term follow-up. We found that at median time of 23.8 months eGFR improved in

53,9% of patients while SBP decreased in 77,4%. We did not observe any significant changes in the number of anti-hypertensive medications before the procedure and at follow up. All patients in whom eGFR improved at follow-up benefited from renal stenting with significantly lower maximal BP. These results need to be interpreted in the context of recently published randomized, controlled clinical trials, including ASTRAL [5] and STAR [6] that assessed the usefulness of RA stenting with respect to kidney function and found no significant advantage of this therapy. Although in the ASTRAL the daily drug dosage was reduced, no significant difference in blood pressure was found. However, these two trials had some limitations that could significantly influence the results. In the ASTRAL trial patients with RAS were included if the need for revascularization was uncertain in the opinion of clinician (pa-

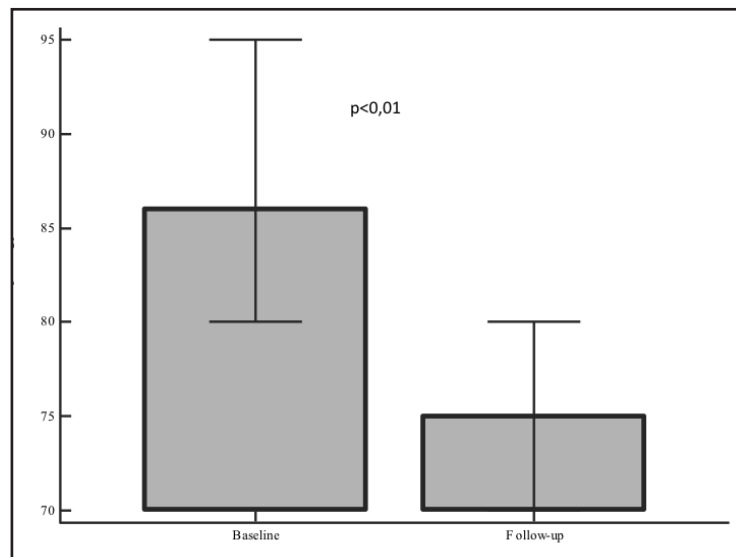


Fig. 5. Diastolic blood pressure before PTRE and at follow-up for the whole treated population (median and IQR).

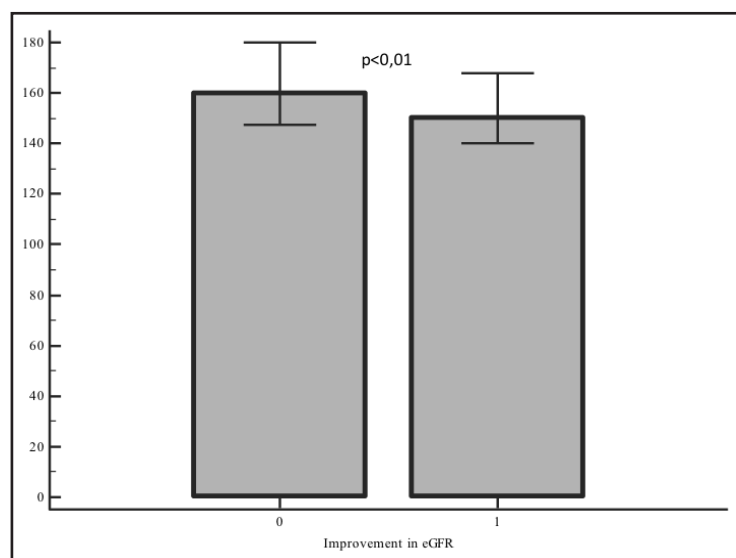


Fig. 6. No change (0) or eGFR improvement (1) vs SBP max at follow-up (median and IQR).

tients with high likelihood of benefit from stenting were excluded), many of patients had borderline renal stenosis, minimal or no hypertension or normal renal function. In the STAR trial only 140 patients were enrolled making this study underpowered to detect a $\geq 20\%$ decrease in creatinine clearance. In another randomized CORAL trial it was shown that although renal-artery stenting reduced systolic pressure of 2mmHg it did not confer a significant benefit with respect to the prevention of clinical events. The other previously published randomized studies that tested influence of renal artery angioplasty and stenting on blood pressure control were also inconclusive as they were small, not adequately powered for clinical outcomes and stents were rarely used [7-9]. These results are in contrast to our registry and to many other prospective multicenter registries, which reported that renal artery stenting improves or stabilizes renal function and reduces systolic and diastolic blood pressures with excellent safety profile [10-13]. Unfortunately,

due to the nature of registries these results cannot be widely accepted. In our study we identified renal artery stenosis of 67.4% as the optimal cut-off value to predict the response of renal function and blood pressure control after stenting. In addition, we showed that patients who improved at follow-up had more severe lesion types at baseline (longer lesion with higher diameter stenosis). In most previous studies stenosis severity was assessed mainly by visual estimate of angiography or by non-invasive techniques thus, many patients with borderline or even with non-significant stenosis were included to the study. In the STAR trial 33% of patients included in the study had only mild RAS defined as 50-70%. In the ASTRAL trial 41% of patients had stenosis of less than 70%. This may at least partially explain the lack of effectiveness of renal stenting procedures [14]. Similarly to coronary territory borderline stenosis in the range between 50-70% may require additional diagnostics including pressure gradient in order to check significance of ischemia. Leeser et al showed that

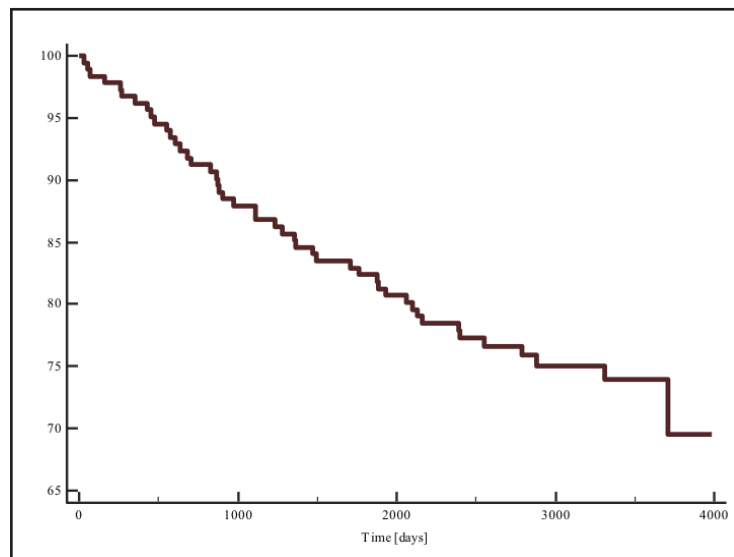


Fig. 7. Death.

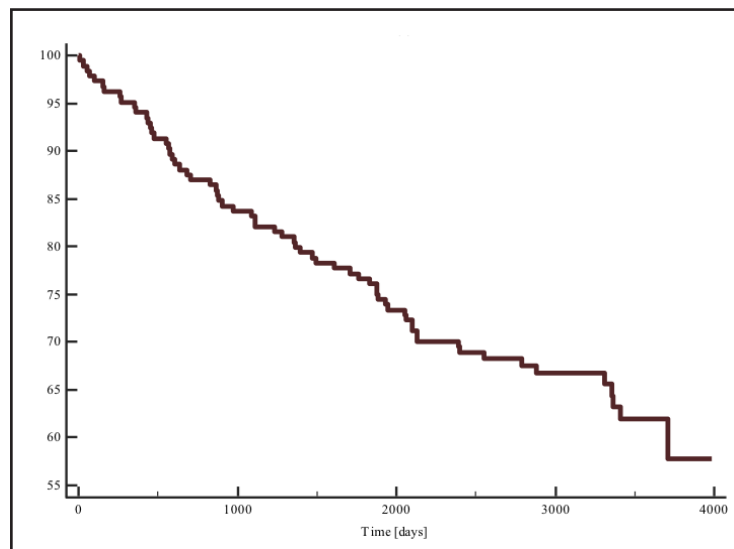


Fig. 8. MACCE.

hyperemic systolic gradient in renal arteries measured by a pressure guidewire after a 30 mg bolus dose of papaverine of >21mmHg was identified as haemodynamically significant and predicted sustained improvement in blood pressure at 12 months [15]. This finding has been reflected recently by ACC/AHA, which defined significant RAS among others as stenosis of 50% to 70% diameter by visual estimation with a peak translesional gradient of at least 20 mm Hg or a mean gradient of at least 10 mm Hg. Other criteria include angiographic stenosis of at least 70% diameter or stenosis greater than 70% diameter by intravascular ultrasound measurement. Another important finding of our study is that patients in whom eGFR improved had significantly worse parameters of renal function at baseline with lower pre-procedural systolic blood pressure. In previously published trials majority of patients had normal or near-normal renal function as measured by serum creatinine, which could be responsible for non-benefit of revascularization on renal function. In contrary, the long-term presence of undiagnosed severe RAS, which leads to renal hypoperfusion, parenchyma fibroses and finally to renal atrophy will not be able to respond to interventional treatment even in the presence of documented renal ischemia, as described previously [14]. For this reason, in patients with significant RAS and decreased renal function in whom compensatory mechanisms are capable to maintain lower arterial pressures interventional procedures may still be valuable. Previous studies have shown that renal artery stenosis is closely related to adverse cardiovascular events [16]. All patients included in our study had high percentage of coronary artery disease (89.5%), relatively high systolic blood pressure at baseline (160mmHg) and eGFR lowered on average to 54.7%. Although these patients could be classified as “high-risk”, the Kaplan-Meier survival probability estimates of eleven years was 69%, showing their good clinical outcomes, which may be related to optimal medical and interventional treatment of both renal and coronary arteries. In the previous report of PJ Conlon et al. significantly shorter 4-year survival rate of 65% of patients with RAS detected at the time of coronary angiography was similar to our study at eleven years [8]. The decision to perform intervention in a patient with RAS should be also taken on the basis of previous experience in order to avoid technical failure and complications. In our study all procedures were performed in two experienced clinical centers performing almost 30 renal artery percutaneous interventions per year. This has led to very high procedural and angiographic success rate of 100%, with only minor procedural issues like 1.4% of margin dissections. We did not find any in-hospital major cardiovascular events. Similarly, angiographic control performed at the median time of 15 months after PTRR revealed restenosis, which occurred only in 11 (12%) cases. This study has several limitations. First of all, the main limitation was the nonrandomized design of the study. Secondly, we did not measure other clinical and angiographic parameters, which as shown in previous reports, could further influence the findings of our study including proteinuria, kidney diameters, renal resistive index, translesional gradient etc [14]. Finally, we have noted that the average number of medications was 2.7, which is less than recommended by most guidelines for acceptable medical therapy to treat resistant hypertension.

Conclusions

The results of our registry suggest that interventional treatment of RAS may preserve renal function and improve blood pressure control at long-term follow-up however, further studies are warranted.

Disclosure Statement

The authors report no financial relationships or conflicts of interest regarding the content herein.

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