



Aalborg Universitet

AALBORG UNIVERSITY  
DENMARK

## Renal Artery Stenting in Consecutive High-Risk Patients With Atherosclerotic Renovascular Disease

*A Prospective 2-Center Cohort Study*

Reinhard, Mark; Schousboe, Karoline; Andersen, Ulrik B.; Buus, Niels Henrik; Rantanen, Jesper Moesgaard; Bech, Jesper Nørgaard; Mafi, Hossein Mohit; Langfeldt, Sten; Bharadwaz, Arindam; Hørlyck, Arne; Jensen, Mogens Kærsgaard; Jeppesen, Jørgen; Olsen, Michael Hecht; Jacobsen, Ib Abildgaard; Bibby, Bo Martin; Christensen, Kent Lodberg

*Published in:*

Journal of the American Heart Association

*DOI (link to publication from Publisher):*

[10.1161/JAHA.121.024421](https://doi.org/10.1161/JAHA.121.024421)

*Creative Commons License*

CC BY-NC-ND 4.0

*Publication date:*

2022

*Document Version*

Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

*Citation for published version (APA):*

Reinhard, M., Schousboe, K., Andersen, U. B., Buus, N. H., Rantanen, J. M., Bech, J. N., Mafi, H. M., Langfeldt, S., Bharadwaz, A., Hørlyck, A., Jensen, M. K., Jeppesen, J., Olsen, M. H., Jacobsen, I. A., Bibby, B. M., & Christensen, K. L. (2022). Renal Artery Stenting in Consecutive High-Risk Patients With Atherosclerotic Renovascular Disease: A Prospective 2-Center Cohort Study. *Journal of the American Heart Association*, 11(7), e024421. [e024421]. <https://doi.org/10.1161/JAHA.121.024421>

### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

ORIGINAL RESEARCH

# Renal Artery Stenting in Consecutive High-Risk Patients With Atherosclerotic Renovascular Disease: A Prospective 2-Center Cohort Study

Mark Reinhard , MD, PhD; Karoline Schousboe , MD, PhD; Ulrik B. Andersen, MD; Niels Henrik Buus , MD, PhD, DMSc; Jesper Moesgaard Rantanen , MD, PhD; Jesper Nørgaard Bech , MD, PhD; Hossein Mohit Mafi, MD; Sten Langfeldt, MD; Arindam Bharadwaz , MD, EBIR; Arne Hørlyck , MD; Mogens Kærsgaard Jensen, MD; Jørgen Jeppesen , MD, DMSc; Michael Hecht Olsen , MD, PhD, DMSc; Ib Abildgaard Jacobsen, MD, DMSc; Bo Martin Bibby , MSc, PhD; Kent Lodberg Christensen , MD, DMSc

**BACKGROUND:** The aim of this study was to prospectively evaluate the effects of renal artery stenting in consecutive patients with severe atherosclerotic renal artery stenosis and high-risk clinical presentations as defined in a national protocol developed in 2015.

**METHODS AND RESULTS:** Since the protocol was initiated, 102 patients have been referred for revascularization according to the following high-risk criteria: severe renal artery stenosis ( $\geq 70\%$ ) with true resistant hypertension, rapidly declining kidney function, or recurrent heart failure/sudden pulmonary edema. At baseline, the mean 24-hour ambulatory systolic blood pressure was 166.2 mm Hg (95% CI, 162.0–170.4), the defined daily dose of antihypertensive medication was 6.5 (95% CI, 5.8–7.3), and the estimated glomerular filtration rate was 41.1 mL/min per 1.73m<sup>2</sup> (95% CI, 36.6–45.6). In 96 patients with available 3-month follow-up data, mean 24-hour ambulatory systolic blood pressure decreased by 19.6 mm Hg (95% CI, 15.4–23.8;  $P < 0.001$ ), the defined daily dose of antihypertensive medication was reduced by 52% (95% CI, 41%–62%;  $P < 0.001$ ), and estimated glomerular filtration rate increased by 7.8 mL/min per 1.73m<sup>2</sup> (95% CI, 4.5–11.1;  $P < 0.001$ ). All changes persisted after 24 month follow-up. Among 17 patients with a history of hospitalization for acute decompensated heart failure, 14 patients had no new episodes after successful revascularization.

**CONCLUSIONS:** In this prospective cohort study, we observed a reduction in blood pressure and antihypertensive medication, an increase in estimated glomerular filtration rate, and a decrease in new hospital admissions attributable to heart failure/sudden pulmonary edema after renal artery stenting.

**REGISTRATION:** URL: <https://clinicaltrials.gov>. Identifier: NCT02770066.

**Key Words:** atherosclerotic renal artery stenosis ■ atherosclerotic renovascular disease ■ flash pulmonary edema ■ rapid loss of kidney function ■ renal revascularization ■ resistant hypertension

Randomized clinical trials have failed to demonstrate benefits of renal artery stenting in addition to medical therapy in patients with atherosclerotic renal artery stenosis,<sup>1–3</sup> but these trials have significant limitations. The main limitation of these trials is that patients with the most severe forms of renovascular

Correspondence to: Mark Reinhard, MD, PhD, Department of Renal Medicine and The Clinic of Hypertension, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, and Department of Clinical Medicine, Aarhus University, Palle Juul-Jensens Boulevard 82, 8200 Aarhus N, Denmark. Email: [m.reinhard@dadlnet.dk](mailto:m.reinhard@dadlnet.dk)

Supplemental Materials for this article are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.024421>

For Sources of Funding and Disclosures, see page 14.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: [www.ahajournals.org/journal/jaha](http://www.ahajournals.org/journal/jaha)

## CLINICAL PERSPECTIVE

### What Is New?

- In this prospective cohort study of well-defined high-risk patients with severe atherosclerotic renal artery stenosis established after the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial was published, we observed a reduction in blood pressure, an improvement in kidney function, and a decrease in new hospital admissions attributable to heart failure/sudden pulmonary edema after revascularization.
- To increase the validity of our results, we performed 24-hour ambulatory blood pressure monitoring after nurse-administered medication to ensure patient adherence and included prestudy results on ambulatory blood pressure monitoring and kidney function to reduce the risk of regression to the mean.

### What Are the Clinical Implications?

- In carefully selected patients with severe atherosclerotic renal artery stenosis and high-risk clinical presentations, renal artery stenting may be beneficial, but this should be confirmed in randomized clinical trials.
- Our findings are in favor of the current US guideline from the Society for Cardiovascular Angiography and Interventions, which recommends renal artery stenting in patients with hemodynamically significant atherosclerotic renal artery stenosis when there is concomitant cardiac destabilization syndromes, resistant hypertension, or progressive ischemic nephropathy, as compared with the more restrictive European guideline.

## Nonstandard Abbreviations and Acronyms

<b>ABPM</b>	ambulatory blood pressure monitoring
<b>CORAL</b>	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
<b>KDIGO</b>	Kidney Disease: Improving Global Outcomes
<b>PTRA</b>	percutaneous transluminal renal angioplasty

disease were excluded or not enrolled.<sup>4,5</sup> Accordingly, a recent comparative effectiveness review of renal artery stenosis management strategies commissioned by the Agency for Healthcare Research and Quality found that results from the randomized trials had limited applicability to many patients for whom renal

artery stenting is recommended, particularly those who present with pulmonary edema or rapidly declining kidney function.<sup>5,6</sup> In the newest US guidelines from the Society for Cardiovascular Angiography and Interventions from 2017, renal artery stenting is considered appropriate for hemodynamically significant atherosclerotic renal artery stenosis (visual stenosis  $\geq 70\%$  or  $\geq 50\%$  with a resting translesional mean gradient  $\geq 10$  mm Hg) when there is concomitant cardiac destabilization syndromes (recurrent heart failure, sudden pulmonary edema, or acute coronary syndrome), resistant hypertension, or progressive ischemic nephropathy in patients with bilateral disease or a solitary functioning kidney.<sup>4,7</sup> These recommendations are in agreement with the conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on the Heart, Kidney, and Vasculature held in February 2020.<sup>8</sup> In comparison, the European guideline from 2017 is less specific and more conservative and states that angioplasty may be considered in selected patients with significant atherosclerotic renal artery stenosis and recurrent heart failure or sudden pulmonary edema (class IIb Level of Evidence C) and in rare cases of acute oligo-anuric kidney failure in patients with bilateral renal artery disease without significant kidney atrophy.<sup>9</sup>

After the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial was published in 2014,<sup>2</sup> the 3 Danish centers offering percutaneous transluminal renal angioplasty (PTRA) agreed on following a common prospective study protocol limiting PTRA to patients with high-risk clinical and radiological features of renovascular disease in a proof-of-concept study. Thus, the aim of the study was to prospectively evaluate the effects of renal artery stenting on blood pressure (BP), estimated glomerular filtration rate (GFR), and heart failure/pulmonary edema recurrences in a group of well-defined patients with true resistant hypertension, rapidly declining kidney function, or recurrent heart failure/sudden pulmonary edema and with severe renal artery stenosis assessed by both visual estimation ( $>70\%$  stenotic) and functional evaluation with Doppler ultrasound and renography.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Design

The DAN-PTRA (NCT02770066) study is a prospective, single-arm cohort study developed in 2015 by the 3 PTRA performing centers in Denmark. Two of the 3 centers adhered to the protocol in January 2015

and November 2016, respectively, and from then on included all patients consecutively referred for PTRAs with stent placement according to the national study criteria. Together, the 2 centers covered  $\approx 3.1$  million of the 5.7 million inhabitants in Denmark. The study was performed in accordance with the Declaration of Helsinki. The study was reported to the Central Denmark Region Committees on Health Research Ethics and to the Danish Data Protection Agency. All patients provided written informed consent. No funding was provided.

## Study Participants

To be eligible for renal artery stenting, patients were required to present with at least 1 of the following high-risk clinical syndromes: (1) resistant hypertension with average 24-hour ambulatory systolic BP  $\geq 130$  (mostly  $\geq 150$ ) mm Hg despite  $\geq 3$  antihypertensive drugs including a diuretic, if tolerated, and each prescribed at optimal doses,<sup>7</sup> (2) rapidly declining kidney function with a reduction in estimated GFR of  $>5$  mL/min per  $1.73\text{m}^2$  per year, or (3) hospital admissions with acute decompensated heart failure ( $\geq 2$  hospitalizations for heart failure or  $\geq 1$  hospitalizations for sudden, “flash” pulmonary edema) with no obvious explanations such as nonadherence, left ventricular ejection fraction  $<40\%$ , or valvular heart disease. In addition, computed tomographic or magnetic resonance angiography should demonstrate a stenosis of  $\geq 70\%$  reduction of the luminal diameter in at least 1 projection. Furthermore, Doppler ultrasound and renography with and without captopril were performed to assess the hemodynamic significance of the stenoses. PTRAs were not performed if the length of the affected kidney was  $<7$  cm.

Before referral for renal artery revascularization, each patient was discussed at a multidisciplinary meeting that, depending on the center, could involve the following disciplines: nephrology, cardiology, vascular interventional radiology, and vascular surgery. Patients with bilateral disease but only 1 functioning kidney were initially referred for revascularization of the functioning kidney, but if the response was poor, the patient was subsequently evaluated for removal of the nonfunctioning kidney. Before angioplasty, patients not already receiving antiplatelet therapy were started on indefinite treatment with aspirin 75 mg/day. In addition, patients were advised to take lipid-lowering drugs indefinitely and received counseling regarding smoking cessation, diet, and physical activity. Follow-up visits after renal artery stenting were planned after 3, 12, 24, 36, 48, and 60 months and included 24-hour ambulatory blood pressure monitoring (ABPM) after nurse-administered medication, reassessment of kidney function, and Doppler ultrasound (if performed at the given center).

Captopril renography was repeated after 24 months unless the patient had a solitary functioning kidney.

## Ambulatory Blood Pressure Monitoring after Nurse-Administered Medication

To improve the study validity, patient adherence to antihypertensive treatment was ensured by nurse-administered medication before 24-hour ABPM at baseline and at all follow-up visits. According to this procedure, patients brought their medication packages to the clinic and were asked about their medication habits, and the medication was checked and administered from the original packaging by a nurse (witnessed drug intake) immediately before the ABPM. ABPM was routinely performed with the oscillometric method (using either Spacelabs 90217, Spacelabs Healthcare, Hawthorne, WA; or Takeda TM-2430, A&D Company Ltd., Tokyo, Japan) or in patients aged  $>80$  years or with known supraventricular arrhythmia with the auscultatory method using DiaSys Integra II (Novacor, Rueil-Malmaison, France). Measurement interval was  $\leq 60$  minutes both day and night. The defined daily dose of antihypertensive medication was calculated according to the World Health Organization Collaborating Center for Drugs Statistics Methodology Defined Daily Dose system to compare the use of different types of antihypertensive drugs.<sup>10</sup>

## Kidney Function

Estimated GFR was calculated with use of the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.<sup>11</sup> Available data on kidney function (plasma creatinine and urine albumin-creatinine ratio) 3, 12, and 24 months before angioplasty were collected retrospectively. If the urine albumin-creatinine ratio was missing at a given time point but the patient had a negative urine dipstick, the latter was used and set to be equivalent to a urine albumin-creatinine ratio of 29 mg/g (upper reference limit of a normal urine albumin-creatinine ratio).

## Doppler Ultrasound

Doppler ultrasound was performed by a few experienced operators and mostly included indirect parameters (pulsatility index and resistance index) in the evaluation of hemodynamically significant stenosis/restenosis.<sup>12,13</sup> Doppler ultrasound was performed at baseline and at each follow-up visit.

## Renography

Renography was performed with  $^{99\text{m}}$ technetium-mercapto-acetyl-triglycine or  $^{99\text{m}}$ technetium-diethylenetriaminepentaacetic acid. Captopril renography

was carried out 60 minutes after 25 mg of captopril had been administered orally. Baseline renography was carried out after the patients had discontinued treatment with angiotensin-converting enzyme inhibitor (ACEi) and angiotensin-receptor blocker (ARB) for 5 to 10 days (according to local guidelines). Renograms were classified according to the consensus report on ACEi renography in low or intermediate/high probability for renovascular hypertension.<sup>14</sup> The following was classified as intermediate/high probability for renovascular hypertension: relative function of 1 kidney  $\leq 30\%$  or increased excretion time  $\geq 11$  minutes ( $\geq$  grade 2 renogram) with no change between baseline and captopril renography or an improvement in split kidney function of  $\geq 5\%$  or a decrease in time to peak activity of at least 5 minutes (change  $\geq 1$  renogram grades) on the affected side on baseline renography compared with captopril renography.<sup>14–16</sup>

### Description of Stenoses

All noninvasive imaging and invasive angiographic findings were evaluated and described independently by 2 experienced radiologists, and stenoses were classified as  $<70\%$ ,  $70\%$  to  $79\%$ ,  $80\%$  to  $89\%$ ,  $\geq 90\%$ , or occlusion.

### Renal Artery Stenting

PTRA with stent placement was performed via retrograde femoral or brachial approach with the use of different sheaths, guidewires, and balloon-expandable stents according to local team policy.

### Outcomes

The primary outcome measure was changes in 24-hour ambulatory BP from baseline to 24 months after renal artery stenting in patients with 24-hour ambulatory average systolic BP  $\geq 150$  mm Hg at baseline. Secondary outcome measures included changes in 24-hour ambulatory BP from baseline to 24 months after renal artery stenting in patients with 24-hour ambulatory average systolic BP  $\geq 130$  mm Hg at baseline, changes in defined daily doses of antihypertensive medication, changes in kidney function, periprocedural events (events  $\leq 30$  days after PTRA), and clinical events during follow-up. Since only 4 patients had 24-hour ambulatory average systolic BP  $<130$  mm Hg at baseline, we chose to include all patients in the secondary outcome measure analysis of BP changes after renal artery stenting. Clinical events matched clinical end points in the CORAL trial (death from any cause, death from cardiovascular or renal causes, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive kidney insufficiency, and permanent renal-replacement therapy) and the same definitions were used.<sup>2</sup>

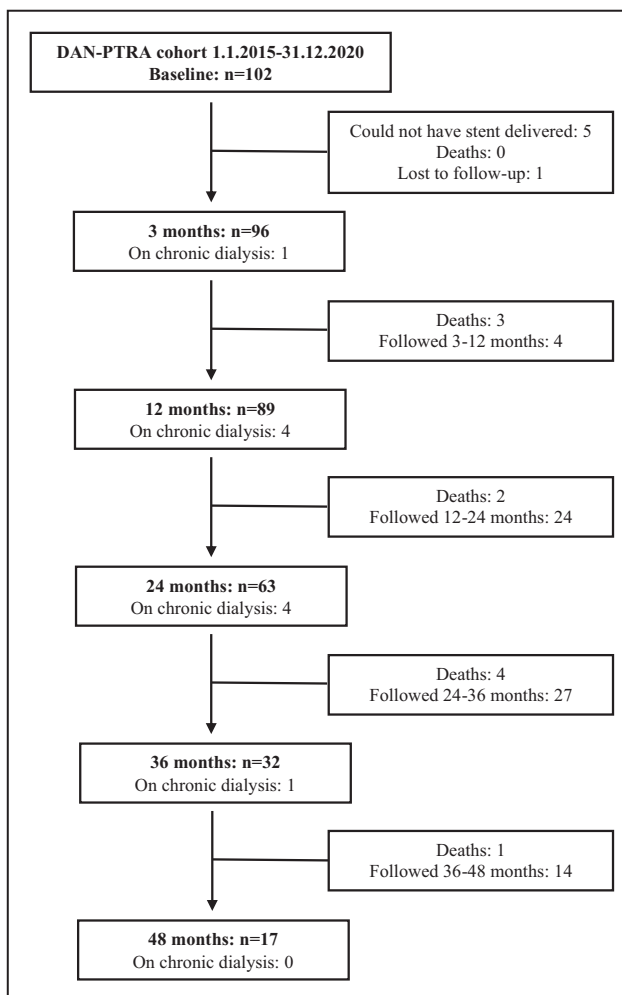
### Statistical Analysis

Categorical data are expressed as proportions and changes from baseline analyzed using McNemars test. Summary statistics for continuous variables are presented as means with standard deviations for variables with normal distribution or medians with ranges for skewed variables. Changes from baseline were analyzed using multivariate repeated measurements ANOVA. Model validation was performed by comparing observed and expected within-subject SDs and correlations and by inspecting quantile-quantile plots of the residuals. Prestudy and baseline systolic and diastolic 24-hour ambulatory BP measurements were compared with the paired *t*-test. Model validation was performed by inspecting Bland-Altman plots and quantile-quantile plots of the differences. Results are presented as means or geometric means (after back-transformation of means of log-transformed data) with 95% CI, as appropriate. Before log transformation, the defined daily dose of antihypertensive medication was set to 0.1 for patients not taking any antihypertensive medication after revascularization to avoid missing values. The conclusions were the same whether the defined daily dose was 0 or set to either 0.1 or 0.5 before log transformation. If patients needed dialysis before the PTRA procedure, the estimated GFR was set to 10 mL/min per  $1.73\text{m}^2$ . If patients started permanent renal-replacement therapy during follow-up, the estimated GFR was also set to 10 mL/min per  $1.73\text{m}^2$ , whereas the patients were excluded from further analyses regarding BP and antihypertensive treatment. Univariate and multivariable linear regression models were used to assess the relationship between potential predictors of the changes in 24-hour ambulatory systolic BP and estimated GFR at 3-month follow-up after PTRA. Predictors were listed according to potential clinical significance and findings from previous studies.<sup>12,17,18</sup> The predictor variables included in the models were chosen by assessing their likely clinical significance, but the number of missing values was also taken into account. Several of the diagnostic predictor variables had missing values, and therefore both basic multivariable regression models including variables with no missing values (age, sex, body mass index, diabetes, 24-hour ambulatory systolic BP, rapidly declining kidney function, recurrent heart failure/sudden pulmonary edema, and discontinuation of ACEi or ARB because of a  $\geq 30\%$  increase in estimated GFR) and extended multivariable regression models with the addition of variables with missing values (urine albumin-creatinine ratio, Doppler ultrasound, renography, degree of stenosis, and performance of bilateral renal artery stenting) were considered. *P* values  $<0.05$  were considered statistically significant. Data were analyzed using Stata version 16.1 (Lakeway Drive, TX).

## RESULTS

### Study Cohort

From January 2015 to January 2021, a total of 102 patients were referred for PTRA with stent placement according to the common national criteria (Figure 1). Baseline characteristics are shown in Tables 1 and 2. In total, 95 of the 102 patients suffered from resistant hypertension, of whom 36 patients had no additional clinical indication for angioplasty. Only 3 of the 36 patients with resistant hypertension as the sole indication for renal artery stenting had baseline 24-hour ambulatory systolic BP <150 mm Hg. In 5 patients, angioplasty was not possible because of total occlusion of the renal artery. The remaining 97 patients were successfully revascularized on at least 1 side and followed for a median of 24.4 months (interquartile range, 13.3–36.2) during which 5 patients started permanent renal-replacement therapy and 10 patients died.



**Figure 1.** Flowchart for patients referred for angioplasty.

### Stenting and Periprocedural Events

All PTRA procedures in the study included stent placement. Only 3 of the stented arteries were <70% stenotic and these arteries were stented in conjunction with contralateral stenting of a >70% renal artery stenosis (Table 2). In 10 patients referred for renal artery stenting on both sides, revascularization was possible on only 1 side. In 14 patients, revascularization was performed subacutely in conjunction with hospitalization for pulmonary edema, severe hypertension, or acute kidney injury that was refractory to medical therapy. There were 12 procedure-related complications but no procedure-related deaths. Four patients experienced either dissection, rupture, or thrombosis of the renal main or branch arteries, which in 1 case resulted in a reduction in estimated GFR from 38 to 18 mL/min per 1.73m<sup>2</sup>, although, surprisingly, estimated GFR slowly increased and returned to baseline level at 24-month follow-up. Two patients had embolism to the kidneys, but this did not affect the kidney function. Two patients who were treated subacutely because of refractory pulmonary edema developed respiratory failure during the procedure, and both patients recovered at the intensive care unit. Four patients developed either femoral or brachial artery pseudoaneurysms located at puncture sites. The observed rate of serious periprocedural events was similar to the event rate observed in the CORAL trial (Table S1).<sup>2</sup>

### Quality of BP Measurements

A total of 397 BP measurements were available for analysis. Of these measurements, 374 (94%) were performed with a standard cuff-based oscillometric or auscultatory device and 10 (3%) with a cuffless SOMNOtouch NIBP device (Somnomedics GmbH, Randersacker, Germany), and 96% of these measurements were performed after nurse-administered medication. The cuff-less SOMNOtouch NIBP device was used only for 24-hour ABPM if the patient could not accept use of the standard cuff-based method. Twelve BP measurements in 8 patients (3%) were made with either automated office BP or home BP measurements because ABPM could not be performed. Automated office BP was recorded with the BpTRU device (BpTRU Medical Devices Ltd., Coquitlam, BC, Canada) set to measure 6 times with an interval of 5 minutes and with the patient resting quietly and alone. The result was the mean of the last 5 measurements. Finally, 1 patient was treated in the intensive care unit with intravenous antihypertensive drugs and hemodialysis before subacute renal artery stenting and baseline BP was calculated as the mean of the 24-hour invasive BP measurements in the intensive care unit before angioplasty.

**Table 1. Baseline Characteristics of the Study Participants (N=102)**

Characteristics	
Age, y	69.2 (62.5–76.3)
Female sex	52 (51.0)
Body mass index, kg/m <sup>2</sup>	26.2 (22.8–30.1)
Ambulatory blood pressure readings, mm Hg	
24-h systolic ABPM	166.2±21.6
24-h diastolic ABPM	82.3±12.3
Daytime systolic ABPM	168.0±21.3
Daytime diastolic ABPM	84.6±12.8
Nighttime systolic ABPM	161.9±25.0
Nighttime diastolic ABPM	77.6±12.7
Duration of antihypertensive treatment, y	10 (2–20)
Number of antihypertensives	4.0±1.3
Defined daily dose of antihypertensives	6.3 (4.3–9.0)
Estimated GFR,* mL/min per 1.73 m <sup>2</sup>	39.7 (23.5–54.0)
Estimated GFR* <60 mL/min per 1.73 m <sup>2</sup>	82 (80.4)
Urine albumin-creatinine ratio, mg/g	61 (17–396)
Single kidney function	
Anatomical single kidney	6 (5.9)
Functional single kidney	17 (16.7)
Missing data	10 (9.8)
Medical history and risk factors	
Diabetes (all type 2)	20 (19.6)
History of ischemic heart disease	27 (26.5)
History of cerebrovascular disease	17 (16.7)
History of heart failure	17 (16.7)
History of malignancy	11 (10.8)
Current or former smoker	84 (82.4)
Lipid-lowering drug use	87 (85.3)

Data are mean±SD or median (interquartile ranges) for continuous variables and number (%) for categorical variables. ABPM indicates ambulatory blood pressure monitoring; and GFR, glomerular filtration rate.

\*The estimated GFR was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula.

## Ambulatory Blood Pressure and Antihypertensive Medication

Both systolic and diastolic BP decreased significantly after renal artery stenting (Figure 2 and Table 3). At 3-month follow-up, 24-hour ambulatory systolic BP after witnessed drug intake was reduced by 19.6 mm Hg (95% CI, 15.4–23.8;  $P<0.001$ ) and 24-hour ambulatory diastolic BP by 8.4 mm Hg (95% CI, 6.3–10.4;  $P<0.001$ ) compared with baseline, and the reductions persisted throughout the follow-up period. Of the 97 successfully treated patients, 60 patients had a meaningful decrease in 24-hour ambulatory systolic BP of at least 10 mm Hg (13 had a BP reduction between 10 and 19 mm Hg, 18 had a BP reduction between 20 and 29 mm Hg, and 29 had a BP reduction ≥30 mm Hg) from baseline to 3-month follow-up. Of

**Table 2. Indications for Angioplasty and Results of Baseline Investigations (N=102)**

Indications for angioplasty	
Resistant hypertension	95 (93.1)
Decline in estimated GFR of ≥5 mL/min per 1.73 m <sup>2</sup> per year*	63 (61.8)
Recurrent heart failure/sudden pulmonary edema	20 (19.6)
Subacute angioplasty† performed in	14 (13.7)
Doppler ultrasound	
Performed in	82 (80.4)
Size of right kidney, cm	10.1±1.7
Size of left kidney, cm	9.9±1.9
No signs of stenosis	12 (11.8)
Signs of unilateral stenosis	56 (54.9)
Signs of bilateral stenosis	14 (13.7)
Missing	20 (19.6)
Resistance index ≥0.8 in successfully treated kidneys (n=112)‡	13 (11.6)
Resistance index <0.8 in successfully treated kidneys (n=112)‡	67 (59.8)
Resistance index missing in successfully treated kidneys (n=112)‡	32 (28.6)
Renography	
Low probability of renal artery stenosis	12 (11.8)
Intermediate/high probability of renal artery stenosis	75 (73.5)
Missing	15 (14.7)
Imaging before angioplasty	
Computed tomographic angiography	93 (91.2)
Magnetic resonance angiography	5 (4.9)
No imaging before angioplasty	4 (3.9)
Identified renal arteries	204
Bilateral disease§	53 (52.0)
Angiographic findings	
Bilateral disease§	55 (53.9)
Bilateral renal artery stenting	15 (14.7)
Number of renal artery stentings	113
Renal artery stenosis <70%¶	3 (2.7)
Renal artery stenosis 70%–79%	22 (19.5)
Renal artery stenosis 80%–89%	32 (28.3)
Renal artery stenosis ≥90%	46 (39.8)
Nonassessable	10 (8.8)

Data are mean±SD for continuous variables and number (%) for categorical variables.

GFR indicates glomerular filtration rate.

\*The estimated GFR was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula.

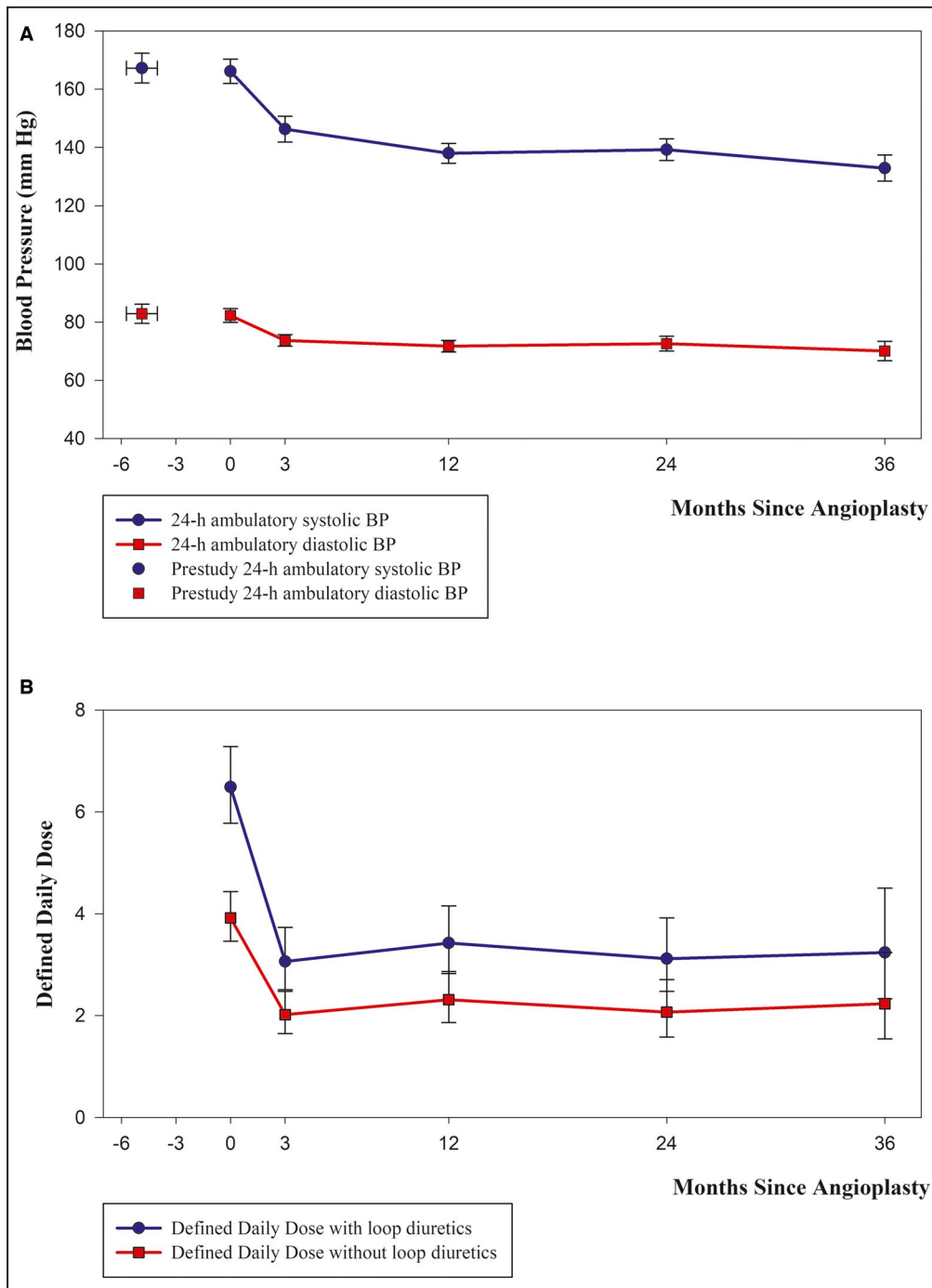
†In 14 patients, revascularization was performed subacutely in conjunction with hospitalization for pulmonary edema, severe hypertension, or acute kidney injury refractory to medical therapy.

‡A total of 97 patients had renal artery stenting performed and in 15 cases on both sides resulting in 112 treated kidneys.

§Bilateral disease was defined as stenosis of ≥70% of the diameter of at least 1 artery supplying each kidney.

||In 1 patient, 2 renal arteries supplying the same kidney were stented.

¶Stenting performed in conjunction with stenting of a stenosis of ≥70% of the artery supplying the other kidney.



**Figure 2. 24-h ambulatory blood pressure (BP) and antihypertensive medication.**

**A**, Mean values for 24-h ambulatory systolic and diastolic BP; and **(B)** geometric mean values for the Defined Daily Dose of antihypertensive medication with and without loop diuretics included. In **(A)** the results of prestudy ambulatory blood pressure monitoring for 55 patients are shown as a dotted circle for mean systolic BP and as a dotted square for mean diastolic BP. Error bars are 95% CIs.

the remaining 37 patients, 35 patients had a reduction of <10 mm Hg, and 2 patients had no follow-up data because one started chronic dialysis and the other was lost to follow-up. Within a subgroup of 55 patients with available prestudy 24-hour ambulatory BP measured on average  $4.9 \pm 3.2$  months before baseline,

there was no significant difference between prestudy and baseline 24-hours ambulatory BP (difference in the systolic BP of 1.2 mm Hg (95% CI,  $-4.5$  to  $6.8$ ;  $P=0.68$ ) and in the diastolic BP of 0.6 mm Hg (95% CI,  $-2.3$  to  $3.5$ ;  $P=0.67$ )) (Figure 2). With regard to the primary outcome measure, 81 patients had ambulatory systolic



**Table 3. Baseline Values and Changes from Baseline Are Derived From Multivariate Repeated Measurements ANOVA**

Parameter	No. of patients*	Baseline values and changes from baseline (95% CI) <sup>†</sup>		P value
24-h ambulatory BP, full cohort				
Systolic BP, mm Hg		Mean changes from baseline		
Baseline	102	166.2	(162.0 to 170.4)	
3 mo	95	-19.6	(-23.8 to -15.4)	<0.001
12 mo	85	-28.2	(-33.7 to -22.7)	<0.001
24 mo	59	-25.7	(-30.8 to -20.6)	<0.001
Diastolic BP, mm Hg		Mean changes from baseline		
Baseline	102	82.3	(79.9 to 84.7)	
3 mo	95	-8.4	(-10.4 to -6.3)	<0.001
12 mo	85	-10.6	(-13.1 to -8.2)	<0.001
24 mo	59	-9.2	(-11.7 to -6.8)	<0.001
24-h ambulatory BP, subgroup with 24-h ambulatory systolic BP ≥150 mm Hg at baseline				
Systolic BP, mm Hg		Mean changes from baseline		
Baseline	81	174.0	(170.4 to 177.6)	
3 mo	75	-22.9	(-28.2 to -17.7)	<0.001
12 mo	66	-35.8	(-41.6 to -30.0)	<0.001
24 mo (primary outcome measure)	46	-32.2	(-37.9 to -26.4)	<0.001
Diastolic BP, mm Hg		Mean changes from baseline		
Baseline	81	84.3	(81.6 to 86.9)	
3 mo	75	-9.5	(-12.0 to -6.9)	<0.001
12 mo	66	-13.1	(-15.9 to -10.3)	<0.001
24 mo (primary outcome measure)	46	-11.3	(-14.0 to -8.6)	<0.001
Antihypertensive medications				
Defined daily dose of antihypertensives including loop-diuretics		Geometric mean ratios (ref. baseline)		
Baseline	102	6.5	(5.8 to 7.3)	
3 mo	95	0.48	(0.38 to 0.59)	<0.001
12 mo	85	0.55	(0.45 to 0.68)	<0.001
24 mo	59	0.50	(0.40 to 0.64)	<0.001
Number of antihypertensives		Mean changes from baseline		
Baseline	102	4.0	(3.7 to 4.2)	
3 mo	95	-1.0	(-1.3 to -0.7)	<0.001
12 mo	85	-0.7	(-1.0 to -0.4)	<0.001
24 mo	59	-0.9	(-1.3 to -0.5)	<0.001
Estimated GFR, full cohort				
Estimated GFR, <sup>†</sup> mL/min per 1.73 m <sup>2</sup>		Mean changes from baseline		
-24 mo	84	19.7	(15.7 to 23.8)	<0.001
-12 mo	91	12.0	(8.4 to 15.7)	<0.001
-3 mo	101	3.3	(0.8 to 5.7)	0.009
Baseline	102	41.1	(36.6 to 45.6)	
3 mo	96	7.8	(4.5 to 11.1)	<0.001
12 mo	89	5.3	(2.1 to 8.5)	0.001
24 mo	63	7.2	(3.2 to 11.2)	0.001
Estimated GFR, subgroup with rapid decline in estimated GFR at baseline				
Estimated GFR, <sup>†</sup> mL/min per 1.73 m <sup>2</sup>		Mean changes from baseline		
-24 mo	50	30.4	(25.6 to 35.1)	<0.001
-12 mo	55	19.2	(14.3 to 24.1)	<0.001

(Continued)

Downloaded from <http://ahajournals.org> by on April 21, 2022

**Table 3. Continued**

Parameter	No. of patients*	Baseline values and changes from baseline (95% CI) <sup>†</sup>		P value
-3 mo	62	6.1	(2.7 to 9.5)	0.001
Baseline	63	29.9	(25.7 to 34.0)	
3 mo	59	12.5	(7.9 to 17.0)	<0.001
12 mo	53	8.8	(4.7 to 13.0)	<0.001
24 mo	33	12.8	(7.5 to 18.1)	<0.001
Albuminuria				
Urine albumin-creatinine ratio <sup>‡</sup>		Geometric mean ratios (ref. baseline)		
-24 mo	56	0.47	(0.31 to 0.71)	0.001
-12 mo	73	0.57	(0.41 to 0.79)	0.001
-3 mo	79	1.11	(0.88 to 1.41)	0.38
Baseline (mg/g)	95	66.9	(46.5 to 96.3)	
3 mo	83	1.13	(0.79 to 1.62)	0.51
12 mo	83	0.57	(0.40 to 0.82)	0.003
24 mo	59	0.68	(0.44 to 1.05)	0.08

Data are mean at baseline and mean changes from baseline (95% CI) for ambulatory blood pressure, number of antihypertensives, and estimated GFR and geometric mean at baseline and geometric mean ratios (95% CI) for the defined daily dose of antihypertensives and for the urine albumin-creatinine ratio. BP indicates blood pressure; and GFR, glomerular filtration rate.

No. of patients\* = †If a patient started permanent renal-replacement therapy during follow-up, the estimated GFR was set to 10 mL/min per 1.73m<sup>2</sup> and the patient was excluded from further analyses regarding BP and antihypertensive treatment.

Baseline values and changes from baseline (95% CI)<sup>†</sup> = †Using a paired t-test to calculate the changes in the same patients over time led to only minor changes in the results and did not change the conclusions.

Estimated GFR, ‡ mL/min per 1.73 m<sup>2</sup> = †The estimated GFR was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula.

Urine albumin-creatinine ratio<sup>‡</sup> = ‡A total of 584 urine albumin-creatinine ratios were available for the analysis and, of these, 21 (18 before baseline and 3 after baseline) were assigned a value of 29 mg/g because the ratio was not measured but the patient had a negative urine dipstick at the given time point.

BP  $\geq$ 150 mm Hg at baseline, and in this subgroup the 24-hour ambulatory systolic BP was reduced by 32.2 mm Hg (95% CI, 26.4–37.9;  $P$ <0.001) from baseline to 24-month follow-up (Table 3).

At 3-month follow-up, the defined daily dose of antihypertensive medication with loop diuretics included was reduced by 52% (95% CI, 41%–62%;  $P$ <0.001), and when loop diuretics were excluded from the analysis, the reduction was 48% (95% CI, 36%–58%;  $P$ <0.001) compared with baseline and the reductions persisted through follow-up (Figure 2 and Table 3). The observed reduction in the defined daily dose of antihypertensive medication corresponded to a significant reduction ( $P$ <0.001) in the number of antihypertensives used from 4.0 (95% CI, 3.7–4.2) at baseline to 3.0 (95% CI, 2.7–3.2) at 3-month follow-up (Table 3). The proportions of patients treated with the different classes of antihypertensives at baseline and last follow-up visit are shown in Table 4. Of note, the proportion of patients treated with either an ACEi or an ARB increased significantly from 40.6% at baseline to 71.9% at last follow-up visit, whereas the use of most other drug classes decreased significantly. Importantly, however, only 7 of the 62 patients who were not taking an ACEi/ARB at baseline had never been treated with these drug classes. In the remaining 55 patients, treatment with ACEis/ARBs was discontinued for a median of 5.0 months (interquartile range, 2.1–10.3) before PTRAs for the following reasons:

increase of  $\geq$ 30% in P-creatinine ( $n$ =41); hyperkalemia ( $n$ =2); suspicion, evaluation, or a diagnosis of renal artery stenosis ( $n$ =11); or angioedema ( $n$ =1). According to the hospital records, treatment with an ACEi/ARB was given for a median of 24.9 months (interquartile range, 4.1–95.9) before it was discontinued, but this may underestimate the true duration of the treatment because treatment with these drug classes were often started by the patient's general practitioner before it was registered in the hospital system.

### Kidney Function Before Stenting

Data on plasma creatinine 3, 12, and 24 months before renal artery stenting were collected retrospectively and were available for 99% of the patients at -3.0 months (95% CI, -3.2 to -2.9), for 89% at -12.0 months (95% CI, -12.5 to -11.5), and for 82% at -24.5 months (95% CI, -25.2 to -23.8). From -24 months to baseline, estimated GFR decreased by overall 19.7 mL/min per 1.73m<sup>2</sup> (95% CI, 15.7–23.8;  $P$ <0.001) and in the subgroup of patients with rapidly declining kidney function at baseline by 30.4 mL/min per 1.73m<sup>2</sup> (95% CI, 25.6–35.1;  $P$ <0.001). The urine albumin-creatinine ratio before renal artery stenting was available for 77% of the patients at -3.7 months (95% CI, -4.1 to -3.3), for 72% at -11.8 months (95% CI, -12.6 to -10.9), and for 55% at -25.2 months (95% CI, -26.6 to -23.9) and increased

**Table 4. Use of Antihypertensive Medication at Last Visit Compared With Baseline**

Antihypertensive medication	Proportion at baseline, %	Proportion at last visit, %	Difference, % (95% CI)		P value
ACEI/ARB	40.6	71.9	31.3	(20.1 to 42.4)	<0.001
Alpha blockers	36.5	12.5	-24.0	(-35.7 to -12.2)	<0.001
Alpha and beta blockers	19.8	12.5	-7.3	(-14.3 to -0.3)	0.02
Beta blockers	61.5	41.7	-19.8	(-31.5 to -8.1)	0.001
Calcium channel blockers	87.5	66.7	-20.8	(-32.3 to -9.4)	<0.001
Diuretics	93.8	80.2	-13.5	(-23.1 to -4.0)	0.003
Thiazides	34.4	17.7	-16.7	(-27.6 to -5.8)	0.002
Loop diuretics	64.6	54.2	-10.4	(-22.1 to 1.2)	0.06
Potassium-sparing agents <sup>§</sup>	28.1	24.0	-4.2	(-15.6 to 7.3)	0.43
Centrally acting agents <sup>†</sup>	14.6	1.0	-13.5	(-22.0 to -5.1)	<0.001
Direct vasodilators <sup>‡</sup>	8.3	3.1	-5.2	(-11.6 to 1.1)	0.06

McNemars test was used to compare proportion at baseline with proportion at last visit. ACEI indicates angiotensin-converting enzyme inhibitor; and ARB, angiotensin receptor blocker.

Potassium-sparing agents\* = \* Spironolactone, eplerenone, or amiloride.

Centrally acting agents<sup>†</sup> = †Methyldopa or moxonidine.

Direct vasodilators<sup>‡</sup>= ‡Hydralazine or minoxidil.

significantly by a factor of 2.1 (95% CI, 1.4–3.2,  $P<0.001$ ) from -24 month to baseline (Figure 3 and Table 3).

### Kidney Function After Stenting

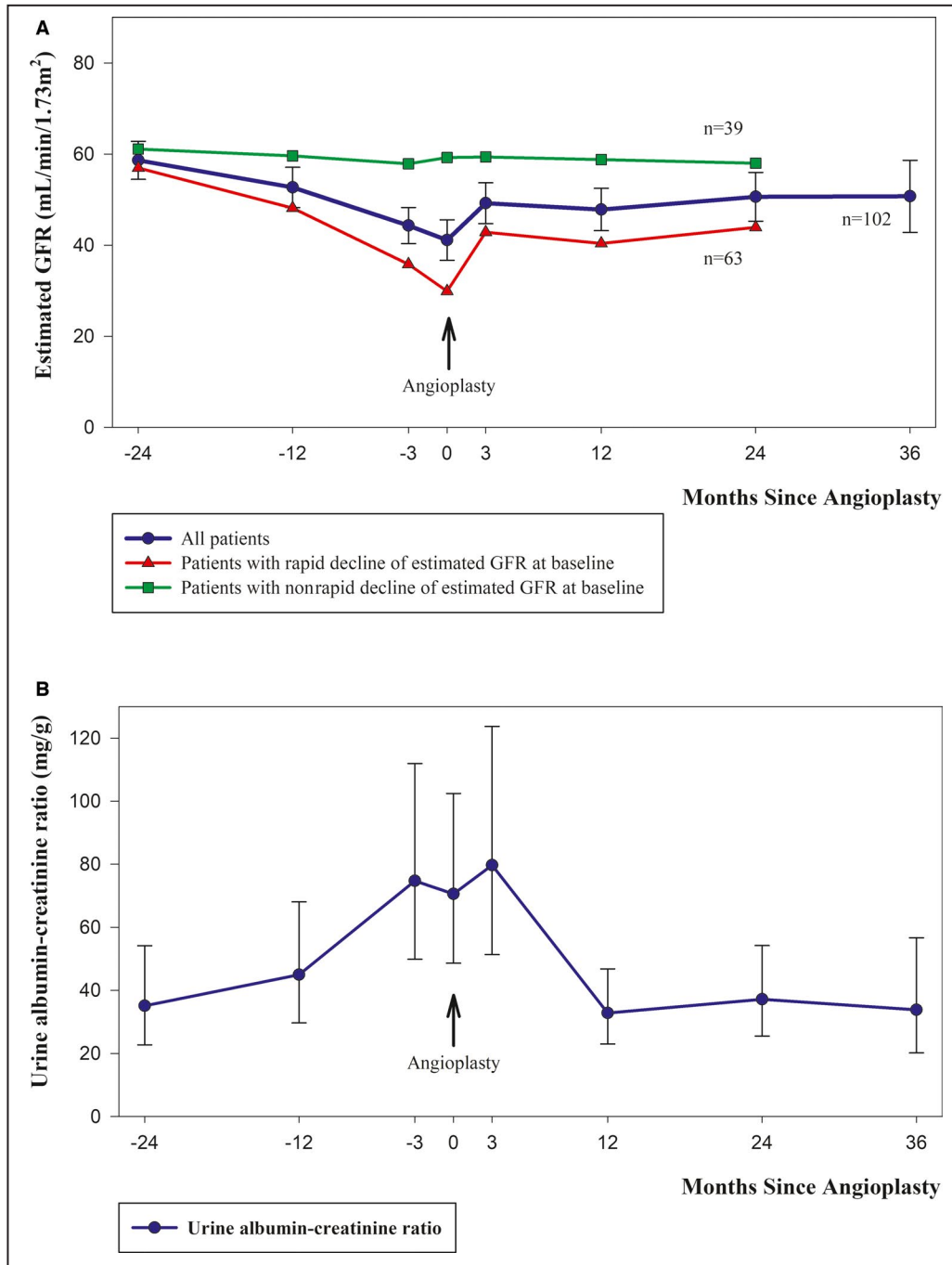
At 3-month follow-up after renal artery stenting, the mean estimated GFR had increased significantly by overall 7.8 mL/min per 1.73m<sup>2</sup> (95% CI, 4.5–11.1;  $P<0.001$ ) and in the subgroup of 63 patients with rapidly declining kidney function at baseline by 12.5 mL/min per 1.73m<sup>2</sup> (95% CI, 7.9–17.0;  $P<0.001$ ), and the observed changes persisted throughout the follow-up period. Four patients required dialysis before renal artery stenting because of acute kidney injury, and 2 patients with successful renal artery stenting regained kidney function, whereas 2 patients with unsuccessful renal artery stenting continued on chronic dialysis. Among the 63 patients with rapidly declining kidney function at baseline, 59 patients had successful revascularization, and among these patients, the estimated GFR at last follow-up after a median of 23.9 months (interquartile range, 12.2–36.8) was reduced by >5 mL/min per 1.73m<sup>2</sup> in 8 patients, of whom 3 had started chronic dialysis; was unchanged (deviated by ≤5 mL/min per 1.73m<sup>2</sup> from baseline value) in 24 patients; and had increased by >5 mL/min per 1.73m<sup>2</sup> in 27 patients. The urine albumin-creatinine ratio decreased significantly after renal artery stenting and was reduced by 43% (95% CI, 18%–60%;  $P=0.003$ ) at 12-month follow-up compared with baseline. In 32 patients who were treated for unilateral renal artery stenosis, captopril renography 24 months after revascularization showed that kidney function on the treated side had increased significantly by 13% (95% CI, 7%–20%;  $P<0.003$ ) compared with captopril renography at baseline.

### Recurrent Heart Failure/Sudden Pulmonary Edema

Twenty patients with a history of recurrent heart failure or sudden, “flash” pulmonary edema, were referred to renal artery stenting. In 3 of these patients, renal artery stenting was not possible because of total renal artery occlusion. Of the successfully treated patients, 14 (82%) patients had no new hospital admissions because of congestive heart failure during follow-up, whereas 3 patients continued to have episodes of heart failure/pulmonary edema and suffered from progressive loss of kidney function, leading to chronic dialysis in 2 patients.

### Predictors of Changes in 24-Hour Ambulatory Systolic BP and Estimated GFR After PTR

Univariate and multivariable linear regression analyses for changes in systolic BP and estimated GFR after PTR are presented in Tables S2 and S3. The analyses revealed several interesting findings but should be interpreted with caution since there were missing values in the extended analyses and the 95% CIs were in general rather wide. In the univariate and multivariable models for change in 24-hour ambulatory systolic BP at 3-month follow-up, increasing 24-hour ambulatory systolic BP at baseline and discontinuation of ACEI/ARB because of an increase of ≥30% in P-creatinine were associated with a favorable BP response, whereas increasing age was associated with an unfavorable BP response (Table S2). In the similar models for change in estimated GFR at 3-month follow-up, female sex, increasing 24-hour ambulatory systolic BP, rapidly declining kidney function, recurrent heart



**Figure 3. Estimated glomerular filtration rate (GFR) and urine albumin-creatinine ratio.**  
**A,** Mean values for estimated GFR for all patients and for the subgroups of patients with rapidly declining kidney function and nonrapidly declining kidney function before renal artery stenting. The mean values for estimated GFR for the subgroups are shown until 24 months because of sparse data thereafter. **B,** Geometric mean values for the urine albumin-creatinine ratio. Error bars are 95% CIs.

failure/sudden pulmonary edema, and angiographic stenosis  $\geq 90$  were the most important factors associated with a favorable response in estimated GFR after PTRAs, whereas a resistance index  $\geq 0.8$  with Doppler ultrasound was associated with an unfavorable response in the multivariable model (Table S3).

### Clinical Events

Among the 97 patients with successful renal artery stenting, 17 patients had at least 1 clinical event during follow-up (only the first event in each category was included). The clinical events were stroke (n=3), acute myocardial infarction (n=2), hospitalization for

congestive heart failure (n=5), reduction of estimated GFR  $\geq 30\%$  and not on permanent renal-replacement therapy (n=2), permanent renal-replacement therapy (n=5), and death (n=10). Causes of death were cardiovascular (n=1), cancer (n=4), infection (n=4), and a perforated peptic ulcer (n=1). The 5 patients requiring permanent renal-replacement therapy during follow-up were started on dialysis after 2, 149, 186, 295, and 472 days, respectively. The patient who started chronic dialysis only 2 days after renal artery stenting underwent subacute revascularization because of refractory heart failure and acute kidney injury, but kidney function did not improve. In comparison, the 5 patients with unsuccessful but otherwise uncomplicated angioplasty had a poor prognosis. Four patients died within 6 months from a renal cause (n=1), infection (n=2), and an unknown cause (n=1), and 1 patient with a baseline estimated GFR of 12 mL/min per 1.73m<sup>2</sup> started chronic hemodialysis after 37 days. Four of the 5 patients were referred for subacute renal artery stenting because of treatment-refractory heart failure/pulmonary edema or acute kidney failure.

### Reangioplasty and Contralateral Nephrectomy After Primary Renal Artery Stenting

Elective reangioplasty with stent placement was performed successfully in 4 patients with restenosis after a median of 12.5 months (interquartile range, 10.1–24.1). Acute reangioplasty was performed in 1 patient who became anuric on the day after removal of a nonfunctioning kidney because of development of an in-stent thrombosis in the renal artery to the remaining kidney. Reangioplasty was performed 2 days after the nephrectomy, and the patient needed temporary hemodialysis but regained kidney function, although estimated GFR decreased from  $\approx 45$  to 30 mL/min per 1.73m<sup>2</sup>.

Five patients with a solitary functioning kidney and a poor response to renal artery stenting were subsequently referred to nephrectomy on the contralateral side in an attempt to improve BP control. Three of these nephrectomies were complicated by an incisional hernia, an intra-abdominal hematoma requiring blood transfusion, and, as already mentioned, an in-stent thrombosis in the contralateral renal artery, respectively.

## DISCUSSION

In this prospective cohort study of patients with severe atherosclerotic renal artery stenosis and well-defined high-risk clinical presentations, we observed a reduction in BP and antihypertensive medication, an increase in estimated GFR, and a decrease in new hospital

admissions because of heart failure/sudden pulmonary edema after renal artery stenting. Three months after revascularization, mean 24-hour ambulatory systolic BP after witnessed drug intake was reduced by  $\approx 20$  mm Hg, and 60 of 97 successfully treated patients had a meaningful decrease in 24-hour ambulatory systolic BP of at least 10 mm Hg (including 29 patients with a decrease  $\geq 30$  mm Hg), although the mean number of antihypertensive medications was reduced. In the CORAL trial, mean systolic BP declined in the stent group by 16.6 mm Hg and in the medical therapy-only group by 15.6 mm Hg, but in that trial, the number of antihypertensive medications was increased equally in both groups.<sup>2</sup> Patients with severe renovascular hypertension are generally poor responders to antihypertensive treatment. To evaluate the validity and reproducibility of the baseline ambulatory BP measurements, we included prestudy 24-hour ambulatory BP results available for 55 patients and found no significant difference between prestudy and baseline results. Taken together, renal artery stenting in this selected patient population was associated with improved BP control and tolerance to blockage of the renin-angiotensin system. A similar effect of renal artery stenting on ABPM in patients with true resistant hypertension has recently been reported in a retrospective single-center study.<sup>17</sup> Baseline predictors for favorable systolic BP response after successful revascularization were increasing systolic BP and a history of discontinuation of an ACEi/ARB because of a  $>30\%$  increase in P-creatinine, whereas increasing age predicted an unfavorable response.

In up to 12% of patients with kidney failure, the attributable cause may be progressive ischemic nephropathy caused by atherosclerotic renal artery stenosis.<sup>4</sup> Our study included data on kidney function from 24 months before renal artery stenting, and our observations suggest that revascularization may change the natural course of ischemic kidney injury in patients with severe renal artery stenosis. Thus, in 85% of successfully treated patients with rapidly declining kidney function at baseline, the estimated GFR was unchanged or had improved at last follow-up compared with baseline. Furthermore, captopril renography 24 months after renal artery stenting showed a significant improvement of the kidney function on the treated side. Finally, we observed a significant decrease in albuminuria after renal artery stenting. Taken together, our observations suggest that renal artery stenting can stabilize and even increase estimated GFR in patients with rapidly declining kidney function. This conclusion concurs with a recently published retrospective study of the effect of renal artery stenting in patients with rapidly deteriorating kidney function.<sup>19</sup> and Baseline predictors for favorable response in kidney function after successful revascularization included severity of clinical

presentation at baseline (increasing systolic BP, rapidly declining kidney function, and recurrent heart failure/sudden pulmonary edema) and angiographic stenosis  $\geq 90\%$ . Of interest, a resistance index  $\geq 0.8$  was associated with an unfavorable response in estimated GFR after PTR, which is in agreement with a previous study.<sup>12</sup>

Among the patients with a history of recurrent heart failure or sudden pulmonary edema before renal artery stenting, 82% of the successfully treated patients had no new hospital admissions for congestive heart failure in the follow-up period. The beneficial effect of renal artery stenting in this particular group of high-risk patients is supported by other nonrandomized trials.<sup>19,20</sup> Although our results concur with a number of nonrandomized trials on high-risk patients with severe atherosclerotic renal artery stenosis,<sup>5,6</sup> they are not in accordance with the 3 largest randomized clinical trials.<sup>1-3</sup> Compared with these trials, the patients in our study had more severe renal artery stenoses and more severe clinical presentations. This may also explain why patients in the CORAL trial tolerated treatment with ARB (candesartan), whereas treatment with ACEis/ARBs in this study was discontinued in 55 of 62 patients not taking these drugs at baseline, mostly because of an increase of at least 30% in P-creatinine ( $n=41$ ). Although the fraction of patients treated with an ACEi/ARB increased from 41% at baseline to 72% during follow-up, it is unlikely that this alone should explain the observed reduction in BP as the proportion of patients treated with an ACEi/ARB at 3-month follow-up had only increased by 14% (95% CI, 3%–24%;  $P=0.01$ ) compared with an overall reduction in the defined daily dose of antihypertensive medications of 52%.

Clinical events were defined using the same criteria as in the CORAL study,<sup>2</sup> but patients were followed for a median of 24 months in this study compared with 43 months in the CORAL study. Among the 97 successfully treated patients, there were 10 cardiovascular events in 8 patients (the first event in each of the following categories was included: stroke, acute myocardial infarction, and hospitalization for congestive heart failure), 5 (5%) patients started permanent renal-replacement therapy, and 10 (10%) patients died from any cause. Among the total number of participants in the CORAL study ( $n=931$ ), there were 194 cardiovascular events, 24 (3%) patients started permanent renal-replacement therapy, and 139 (15%) patients died from any cause during follow-up. Considering the shorter follow-up in the present study, the clinical event rate seemed higher than observed in the CORAL study, but patients in the present study had higher BP (daytime ambulatory systolic BP 168 mm Hg versus office BP 150 mm Hg in the CORAL study) and lower estimated GFR (40 mL/min per 1.73m<sup>2</sup> versus 58 mL/min per 1.73m<sup>2</sup> in the CORAL study). In a more comparable retrospective study

including patients with high-risk presentations ( $n=467$ ), 155 (33%) patients had a cardiovascular event (only 1 event per participant was included), 18% reached end-stage kidney disease, and 55% died during a median follow-up of 46 months.<sup>20</sup> Finally, as previously noted, 5 patients in the present study with unsuccessful but otherwise uncomplicated angioplasty had a very poor prognosis, as 4 patients died within 6 months and 1 patient started chronic hemodialysis 37 days after the attempt of revascularization.

Taken together, it seems plausible that some of the discrepancy between nonrandomized and randomized studies may be explained by patient selection, as recently pointed out in a comparative effectiveness review by the Agency for Healthcare Research and Quality.<sup>5</sup>

The major limitation of this prospective study is the absence of a control group. However, it may not be possible to include patients with the most severe renovascular syndromes in randomized clinical trials and avoid crossover between groups, since these patients are often relatively refractory to medical therapy and guidelines already recommend renal artery stenting for these patients.<sup>7</sup> To increase the quality and reproducibility of our results, we performed 24-hour ambulatory BP monitoring after nurse-administered medication to ensure patient adherence to prescribed medication. Furthermore, we included prestudy results of 24-hour ambulatory BP monitoring and kidney function to reduce the risk of regression to the mean and to demonstrate a true effect of renal artery stenting on BP control and on kidney function.

If we knew with certainty that alternative therapies would never produce similar results, our data would provide an approach to identify the patients that might benefit from the procedure, despite the severity of their atherosclerotic morbidity/mortality and the unavoidable presence of procedural complications. This would require a randomized comparison of PTR versus noninvasive management in a population with these high-risk characteristics. Until such a trial is available, our findings can serve to support current recommendations in the US guideline from the Society for Cardiovascular Angiography and Interventions from 2017<sup>7</sup> and in the KDIGO conference report from 2021.<sup>8</sup>

## ARTICLE INFORMATION

Received November 15, 2021; accepted February 21, 2022.

### Affiliations

Department of Renal Medicine and The Clinic of Hypertension, Aarhus University Hospital, Denmark (M.R., N.H.B.); Department of Clinical Medicine, Aarhus University, Denmark (M.R., N.H.B., K.L.C.); Department of Endocrinology/Steno Diabetes Center Odense and The Clinic of Hypertension, Odense University Hospital, Denmark (K.S., I.A.J.); Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet, Glostrup, University of Copenhagen, Glostrup, Denmark (U.B.A.); Department of Nephrology, Aalborg University Hospital, Denmark (J.M.R.); Department of Medicine, University

Clinic in Nephrology and Hypertension, Godstrup Regional Hospital, Denmark (J.N.B.); Department of Radiology (H.M.M., S.L., A.B., A.H.) and Department of Vascular Surgery (M.K.J.), Aarhus University Hospital, Aarhus N, Denmark; Department of Medicine, Amager Hvidovre Hospital Glostrup, University of Copenhagen, Glostrup, Denmark (J.J.); Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark (J.J.); Department of Internal Medicine, Holbaek Hospital, Denmark (M.H.O.); Centre for Individualized Medicine in Arterial Diseases (CIMA), Department of Regional Health Research, University of Southern Denmark, Odense C, Denmark (M.H.O.); Department of Biostatistics, Aarhus University, Denmark (B.M.B.); and Department of Cardiology and The Clinic of Hypertension, Aarhus University Hospital, Denmark (K.L.C.).

### Acknowledgments

The authors are indebted to the patients for participating. We also thank Ninna Lundorf, Line Lanstorp, Eva Madsen, Lene Schlamovitz, and Karin Hansen for the skilled performance of nurse-administered medication before ambulatory blood pressure monitoring, which was of utmost importance for the interpretation and validity of the results in the present study.

### Sources of Funding

None.

### Disclosures

Dr Olsen reports grants from Novo Nordic Foundation outside the submitted work. The remaining authors have no disclosures to report.

### Supplemental Material

Table S1–S3

## REFERENCES

- Bax L, Woittiez AJ, Kouwenberg HJ, Mali WP, Buskens E, Beek FJ, Braam B, Huysmans FT, Schultze Kool LJ, Rutten MJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med.* 2009;150:840–841. doi:10.7326/0003-4819-150-12-200906160-00119
- Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, Cohen DJ, Matsumoto AH, Steffes M, Jaff MR, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med.* 2014;370:13–22. doi:10.1056/NEJMoa1310753
- Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, Baigent C, Carr S, Chalmers N, Eadington D, Hamilton G, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med.* 2009;361:1953–1962. doi: 10.1056/NEJMoa0905368
- Prince M, Tafur JD, White CJ. When and how should we revascularize patients with atherosclerotic renal artery stenosis? *JACC Cardiovasc Interv.* 2019;12:505–517. doi:10.1016/j.jcin.2018.10.023
- Raman G, Adam GP, Halladay CW, Langberg VN, Azodo IA, Balk EM. Comparative effectiveness of management strategies for renal artery stenosis: an updated systematic review. *Ann Intern Med.* 2016;165:635–649. doi:10.7326/m16-1053
- Balk EM, Raman G, Adam GP, Halladay CW, Langberg VN, Azodo IA, Trikalinos TA. Renal Artery Stenosis Management Strategies: An Updated Comparative Effectiveness Review. Comparative Effectiveness Review No. 179. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2012-00012-I.) AHRQ Publication No. 16-EHC026-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2016. Available at: [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm). Accessed March 14, 2022.
- Klein AJ, Jaff MR, Gray BH, Aronow HD, Bersin RM, Diaz-Sandoval LJ, Dieter RS, Drachman DE, Feldman DN, Gigliotti OS, et al. SCAI appropriate use criteria for peripheral arterial interventions: an update. *Catheter Cardiovasc Interv.* 2017;90:E90–E110. doi:10.1002/ccd.27141
- Hicks CW, Clark TWI, Cooper CJ, de Bhaillis ÁM, De Carlo M, Green D, Malyszko J, Miglinas M, Textor SC, Herzog CA, et al. Artherosclerotic renovascular disease: a KDIGO (Kidney Disease: Improving Global Outcomes) controversies conference. *Am J Kidney Dis.* 2022;79:289–301. doi:10.1053/j.ajkd.2021.06.025
- Aboyans V, Ricco J-B, Bartelink M-L, Björck M, Brodmann M, Cohnert T, Collet J-P, Czerny M, De Carlo M, Debus S, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO), The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J.* 2018;39:763–816. doi:10.1093/eurheartj/ehx095
- WHO Collaborating Centre for Drug Statistics Methodology. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Available at: [https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/). Accessed March 14, 2022.
- Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604–612. doi:10.7326/0003-4819-150-9-200905050-00006
- Radermacher J, Chavan A, Bleck J, Vitzthum A, Stoess B, Gebel MJ, Galanski M, Koch KM, Haller H. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med.* 2001;344:410–417. doi:10.1056/nejm200102083440603
- Zeller T, Bonvini RF, Sixt S. Color-coded duplex ultrasound for diagnosis of renal artery stenosis and as follow-up examination after revascularization. *Catheter Cardiovasc Interv.* 2008;71:995–999. doi:10.1002/ccd.21525
- Taylor A, Nally J, Aurell M, Blaufox D, Dondi M, Dubovsky E, Fine E, Fommei E, Geyskes G, Granerus G, et al. Consensus report on ACE inhibitor renography for detecting renovascular hypertension. Radionuclides in Nephrourology Group. Consensus Group on ACEI Renography. *J Nucl Med.* 1996;37:1876–1882.
- Johansson M, Jensen G, Aurell M, Friberg P, Herlitz H, Klingenstierna H, Volkman R. Evaluation of duplex ultrasound and captopril renography for detection of renovascular hypertension. *Kidney Int.* 2000;58:774–782. doi:10.1046/j.1523-1755.2000.00226.x
- Stratigis S, Stylianou K, Kyriazis PP, Dermizaki E-K, Lygerou D, Syngelaki P, Stratakis S, Koukouraki S, Parthenakis F, Tsetis D, et al. Renal artery stenting for atherosclerotic renal artery stenosis identified in patients with coronary artery disease: does captopril renal scintigraphy predict outcomes? *J Clin Hypertens (Greenwich).* 2018;20:373–381. doi:10.1111/jch.13160
- Courand P-Y, Dinic M, Lorthioir A, Bobrie G, Grataloup C, Denarié N, Soulat G, Mousseaux E, Sapoval M, Azizi M, et al. Resistant hypertension and atherosclerotic renal artery stenosis: effects of angioplasty on ambulatory blood pressure. A retrospective uncontrolled single-center study. *Hypertension.* 2019;74:1516–1523. doi:10.1161/hypertensionaha.119.13393
- Mishima E, Suzuki T, Ito S. Selection of patients for angioplasty for treatment of atherosclerotic renovascular disease: predicting responsive patients. *Am J Hypertens.* 2020;33:391–401. doi:10.1093/ajh/hpaa016
- Vassallo D, Ritchie J, Green D, Chrysochou C, Kalra PA. The effect of revascularization in patients with anatomically significant atherosclerotic renovascular disease presenting with high-risk clinical features. *Nephrol Dial Transplant.* 2018;33:497–506. doi:10.1093/ndt/gfx025
- Ritchie J, Green D, Chrysochou C, Chalmers N, Foley RN, Kalra PA. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. *Am J Kidney Dis.* 2014;63:186–197. doi: 10.1053/j.ajkd.2013.07.020

# **SUPPLEMENTAL MATERIAL**



**Table S1. Comparison of angiographic complications between the present study (DAN-PTRA) and the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial.**

Angiographic complications per vessel treated		
	DAN-PTRA	CORAL
Dissection/rupture/occlusion/wire perforation of renal artery	4/113 (3.5%)	19/495 (3.8%)
Distal embolization	2/113 (1.8%)	6/495 (1.2%)
Pseudoaneurysm formation	4/113 (3.5%)	1/495 (0.2%)

**Table S2. Baseline predictors of change in 24-h ambulatory systolic blood pressure at 3-month follow-up after renal artery stenting in the univariate, basic multivariable and extended multivariable linear regression analyses.**

Predictor variables	No. of patients	Change in 24-h ambulatory systolic BP at 3-month follow up					
		Univariate linear regression		Basic multivariable linear regression (n=95)		Extended multivariable linear regression (n=57)	
		Coefficient of regression (95% CI)	<i>P</i> value	Coefficient of regression (95% CI)	<i>P</i> value	Coefficient of regression (95% CI)	<i>P</i> value
Age (years)	95	0.48 (0.06 to 0.90)	0.025	0.50 (0.14 to 0.87)	0.007	0.57 (0.06 to 1.08)	0.03
Woman	95	6.5 (-2.1 to 15.1)	0.14	7.2 (-0.4 to 14.7)	0.06	1.4 (-9.8 to 12.6)	0.80
BMI (kg/m <sup>2</sup> )	95	0.05 (-0.80 to 0.90)	>0.9	-0.39 (-1.20 to 0.41)	0.33	-1.5 (-2.8 to -0.2)	0.03
Diabetes type II	95	5.3 (-5.5 to 16.1)	0.33	5.6 (-3.9 to 15.2)	0.25	18.0 (1.3 to 34.7)	0.04
24-h ambulatory systolic BP	95	-0.46 (-0.63 to -0.28)	<0.001	-0.44 (-0.61 to -0.27)	<0.001	-0.42 (-0.69 to -0.16)	0.003
Rapid decline in estimated GFR	95	-3.8 (-12.7 to 5.0)	0.40	-3.9 (-11.8 to 4.0)	0.33	-6.2 (-18.6 to 6.2)	0.32
Recurrent heart failure/sudden pulmonary edema	95	-7.0 (-18.5 to 4.4)	0.23	-1.3 (-12.5 to 10.0)	0.82	-1.4 (-17.9 to 15.1)	0.87

ACEi/ARB discontinued due to $\geq 30\%$ increase in P-Creatinine	95	-11.4 (-20.1 to -2.8)	0.01	-9.3 (-17.6 to -1.0)	0.03	-11.4 (-24.7 to 1.9)	0.09
log urine albumin-creatinine ratio (mg/g)	89	-0.82 (-3.3 to 1.6)	0.50			-1.8 (-4.6 to 0.9)	0.19
Doppler ultrasound with signs of renal artery stenosis	75	-5.4 (-19.2 to 8.5)	0.44			-1.2 (-18.5 to 16.2)	0.89
Resistance index $\geq 0.8$ of treated kidneys	69	11.8 (-2.6 to 26.2)	0.11			5.9 (-12.2 to 24.1)	0.51
Renography with moderate-high risk of renal artery stenosis	82	-6.1 (-18.9 to 6.7)	0.35			-0.23 (-15.1 to 14.7)	>0.9
Stenosis $\geq 90\%$ of at least one stented renal artery	87	-6.9 (-15.9 to 2.1)	0.13			-6.3 (-18.7 to 6.0)	0.31
Bilateral renal artery stenting performed	95	-0.48 (-12.4 to 11.4)	>0.9			-17.0 (-32.3 to -1.7)	0.03

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CI, confidence interval; and GFR, glomerular filtration rate.

**Table S3. Baseline predictors of change in estimated GFR at 3-month follow-up after renal artery stenting in the univariate, basic multivariable and extended multivariable linear regression analyses.**

Predictor variables	No. of patients	Change in estimated GFR at 3-month follow up							
		Univariate linear regression		Basic multivariable linear regression (n=96)			Extended multivariable linear regression (n=57)		
		Coefficient of regression (95% CI)	P value	Coefficient of regression (95% CI)	P value	Coefficient of regression (95% CI)	P value		
Age (years)	96	-0.15 (-0.48 to 0.17)	0.36	-0.29 (-0.57 to -0.01)	0.04	-0.04 (-0.41 to 0.32)	0.81		
Woman	96	8.2 (1.8 to 14.5)	0.01	6.8 (1.0 to 12.6)	0.02	6.9 (-1.1 to 14.9)	0.09		
BMI (kg/m <sup>2</sup> )	96	-0.63 (-1.3 to 0.00)	0.05	0.11 (-0.52 to 0.73)	0.73	0.44 (-0.49 to 1.4)	0.35		
Diabetes type II	96	-0.4 (-8.3 to 8.2)	>0.9	-0.3 (-7.7 to 7.1)	>0.9	-1.5 (-13.4 to 10.4)	0.80		
24-h ambulatory systolic BP	96	0.25 (0.11 to 0.39)	0.001	0.19 (0.06 to 0.33)	0.004	0.18 (-0.01 to 0.37)	0.06		
Rapid decline in estimated GFR	96	11.5 (5.2 to 17.9)	<0.001	9.8 (3.7 to 16.0)	0.002	6.2 (-2.7 to 15.0)	0.17		
Recurrent heart failure/sudden pulmonary edema	96	14.8 (6.7 to 22.8)	<0.001	6.4 (-2.1 to 14.9)	0.14	13.0 (1.2 to 24.7)	0.03		

ACEi/ARB discontinued due to $\geq 30\%$ increase in P-Creatinine	96	10.0 (3.6 to 16.5)	0.003	4.6	(-1.8 to 11.0)	0.16	0.9 (-8.5 to 10.4)	0.84
log urine albumin-creatinine ratio (mg/g)	90	0.48 (-1.2 to 2.2)	0.57				0.68 (-1.30 to 2.65)	0.49
Doppler ultrasound with signs of renal artery stenosis	76	7.1 (-2.9 to 17.1)	0.16				0.5 (-11.9 to 12.9)	>0.9
Resistance index $\geq 0.8$ of treated kidneys	70	-4.6 (-15.2 to 5.9)	0.38				-14.7 (-27.7 to -1.8)	0.03
Renography with moderate-high risk of renal artery stenosis	82	9.7 (0.6 to 18.8)	0.04				6.9 (-3.8 to 17.5)	0.20
Stenosis $\geq 90\%$ of at least one stented renal artery	87	7.0 (0.0 to 14.0)	0.05				8.4 (-0.4 to 17.2)	0.06
Bilateral renal artery stenting performed	96	-4.3 (-13.3 to 4.7)	0.35				-2.1 (-13.0 to 8.8)	0.70

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CI, confidence interval; and GFR, glomerular filtration rate.