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Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function

A Randomized Trial

Liesbeth Bax, MD, PhD; Arend-Jan J. Woittiez, MD, PhD; Hans J. Kouwenberg, MD; Willem P.T.M. Mali, MD, PhD; Erik Buskens, MD, PhD; Frederik J.A. Beek, MD, PhD; Branko Braam, MD, PhD; Frans T.M. Huysmans, MD, PhD; Leo J. Schultze Kool, MD, PhD; Matthieu J.C.M. Rutten, MD; Cornelius J. Doorenbos, MD, PhD; Johannes C.N.M. Aarts, MD; Ton J. Rabelink, MD, PhD; Pierre-François Plouin, MD; Alain Raynaud, MD; Gert A. van Montfrans, MD, PhD; Jim A. Reekers, MD, PhD; Anton H. van den Meiracker, MD, PhD; Peter M.T. Pattynama, MD, PhD; Peter J.G. van de Ven, MD, PhD; Dammis Vroegindewij, MD, PhD; Abraham A. Kroon, MD, PhD; Michiel W. de Haan, MD, PhD; Cornelis T. Postma, MD, PhD; and Jaap J. Beutler, MD, PhD*

Background: Little is known about the efficacy and safety of renal artery stenting in patients with atherosclerotic renal artery stenosis (ARAS) and impaired renal function.

Objective: To determine the efficacy and safety of stent placement in patients with ARAS and impaired renal function.

Design: Randomized clinical trial. Randomization was centralized and computer generated, and allocation was assigned by e-mail. Patients, providers, and persons who assessed outcomes were not blinded to treatment assignment.

Setting: 10 European medical centers.

Participants: 140 patients with creatinine clearance less than 80 mL/min per 1.73 m² and ARAS of 50% or greater.

Intervention: Stent placement and medical treatment (64 patients) or medical treatment only (76 patients). Medical treatment consisted of antihypertensive treatment, a statin, and aspirin.

Measurements: The primary end point was a 20% or greater decrease in creatinine clearance. Secondary end points included safety and cardiovascular morbidity and mortality.

Results: Forty-six of 64 patients assigned to stent placement had the procedure. Ten of the 64 patients (16%) in the stent placement group and 16 patients (22%) in the medication group reached the primary end point (hazard ratio, 0.73 [95% CI, 0.33 to 1.61]).

Serious complications occurred in the stent group, including 2 procedure-related deaths (3%), 1 late death secondary to an infected hematoma, and 1 patient who required dialysis secondary to cholesterol embolism. The groups did not differ for other secondary end points.

Limitation: Many patients were falsely identified as having renal artery stenosis greater than 50% by noninvasive imaging and did not ultimately require stenting.

Conclusion: Stent placement with medical treatment had no clear effect on progression of impaired renal function but led to a small number of significant procedure-related complications. The study findings favor a conservative approach to patients with ARAS, focused on cardiovascular risk factor management and avoiding stenting.

Primary Funding Source: Dutch Kidney Foundation, Bayer, Cordis, and Pfizer.

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www.annals.org

For author affiliations, see end of text.

Clinicaltrials.gov registration number: NCT00150943.

* For a list of investigators, sites, and organization of the STAR (STent placement and blood pressure and lipid-lowering for the prevention of progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery) Trial, see the **Appendix** (available at www.annals.org).

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Current guidelines on treatment of atherosclerotic renal artery stenosis (ARAS) to preserve renal function state that stent placement is a reasonable treatment strategy for patients with bilateral disease or a solitary functioning kidney, whereas it may be considered an option for patients with unilateral stenosis (1). Evidence for the clinical benefit of renal artery stenting is scarce, and controlled studies do not support use of this procedure (2, 3).

The natural history of ARAS is characterized by progression with loss of renal function (4–6). Patients with ARAS are considered high risk because their absolute cardiovascular risk exceeds the need for renal replacement therapy (7). Impaired renal function in these patients is assumed to be caused not only by reduced blood flow to the kidney but also by loss of microvascular renal perfusion and renal fibrosis (8). These conditions are driven by hypertension, hyperlipidemia, diabetes mellitus, and smoking. Intervention studies have mainly focused on relieving the stenosis, which results in stabilization or improvement of renal function in most patients (3). No studies have addressed how aggressive medical therapy might affect the intrarenal component of the disease.

The number of percutaneous renal artery interventions is increasing rapidly (9, 10). Although there are no controlled trials supporting this strategy, serious morbidity and death have been reported as complications of stenting (2, 3, 11, 12). We therefore designed a randomized trial to

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Appendix

Appendix Table

Conversion of graphics into slides

assess the efficacy and safety of stent placement plus medical management compared with medical treatment alone in patients with renal impairment and ARAS.

METHODS

Study Design

We performed a randomized trial involving 10 centers (9 in the Netherlands and 1 in France) in which patients were randomly assigned to undergo renal artery stent placement combined with medical treatment or medical treatment only. Patients were monitored for 2 years. Data were collected in each participating center and gathered at the trial coordination center (University Medical Center Utrecht, Utrecht, the Netherlands). The trial was monitored by an independent data and safety monitoring board. A planned interim analysis was performed after 70 patients had been included and followed for 2 years. A statistically significant between-group difference in the primary end point was the stopping rule. The study protocol was approved by the local institutional review board at each participating site. Written informed consent was obtained from each participant.

Participants

We recruited patients from the departments of internal medicine and nephrology at the participating sites. Eligibility criteria were impaired renal function, ostial ARAS detected by various imaging studies, and stable blood pressure.

Impaired renal function was defined as an estimated creatinine clearance less than 80 mL/min per 1.73 m² according to the Cockcroft and Gault formula, based on the mean of 2 fasting serum creatinine values measured within 1 month of each other.

Ostial ARAS was defined as a reduction in the luminal diameter of the renal artery of 50% or more within 1 cm of the aortic wall in the presence of atherosclerotic changes in the aorta, detected by computed tomographic angiography, magnetic resonance angiography, or digital subtraction angiography performed as part of routine clinical care by the patients' physicians. Unilateral stenosis was defined as unilateral ostial stenosis with either a truncal stenosis or no stenosis in the contralateral artery. Bilateral ostial stenosis was defined as ostial stenosis on both sides, unilateral ostial stenosis with contralateral occlusion, or solitary kidney with ostial stenosis. All angiograms were evaluated by 2 experienced radiologists at the coordination center.

Participants were required to have blood pressure controlled while receiving a stable medication dosage in the month before inclusion, if possible without angiotensin-converting enzyme inhibitors or angiotensin II-receptor antagonists. The target blood pressure was less than 140/90 mm Hg.

Exclusion criteria were renal size less than 8 cm, renal artery diameter less than 4 mm, estimated creatinine clearance less than 15 mL/min per 1.73 m², diabetes mellitus

Context

Renal stents are commonly used to treat renal artery stenosis.

Contribution

In this randomized trial, medical treatment of renal artery stenosis was compared with medical treatment plus stenting. Patients who underwent stenting experienced no clear benefits, and several experienced complications, including 2 procedure-related deaths.

Caution

The study was underpowered to provide a definitive estimate of efficacy.

Implication

In this sample, stenting of stenosed renal arteries provided no clear benefit and caused harm, suggesting that patients with renal artery stenosis should be treated with medical therapy alone.

—The Editors

with proteinuria (>3 g/d), and malignant hypertension. Details of the protocol are described elsewhere (13).

Randomization

Eligible patients underwent random assignment at the coordination center. We used a centrally administered, computer-generated permuted block randomization scheme using blocks of 3, stratified according to participating site and unilateral or bilateral stenosis. We communicated assignments by e-mail and mail to the investigators at the site, who subsequently informed the patients of their allocation, initiated medication, and scheduled angiography (for those in the stent group) within 2 weeks of randomization. Study personnel were unaware of the permuted block size.

Medication Group

Patients assigned to receive medication only were given treatment for atherosclerotic risk factors. Hypertension was treated with diuretics, calcium antagonists, β -blockers, and α -blockers, followed by angiotensin-converting enzyme inhibitors, angiotensin II-receptor antagonists, and increasing doses of diuretics if first-line antihypertensive treatment failed. Target blood pressure was less than 140/90 mm Hg. Patients were given 10 mg of atorvastatin titrated to 20 mg as tolerated regardless of lipid levels (13); aspirin, 75 to 100 mg/d; and smoking cessation counseling.

Patients could undergo angiography and stent placement if necessary for refractory hypertension (blood pressure >180/100 mm Hg and mean blood pressure >160/95 mm Hg during 24-hour ambulatory monitoring while receiving the maximum dose of all classes of antihypertensive agents), malignant hypertension, and pulmonary edema (13).

Stent Group

Patients in the stent group received the same medical treatment as patients in the medication group. A Palmaz-Corinthian IQ/Palmaz-Genesis stent (Johnson & Johnson Medical, Miami Lakes, Florida) was placed in every ostial stenosis, according to a standardized protocol (14). Truncal stenoses were treated by balloon angioplasty. Renal artery interventions were performed by interventional radiologists with at least 10 years of experience with the procedures. Technical success was defined as a residual stenosis less than 50%. Patients allocated to stenting began receiving aspirin, 75 to 100 mg/d, the day before admission. During follow-up, re-intervention was allowed when restenosis was suspected on the basis of a 20% or greater decrease in renal function or if patients had refractory or malignant hypertension or pulmonary edema. Ostial stenoses were treated with stent placement, and truncal and in-stent stenoses were treated with balloon angioplasty.

Follow-up

Patients were followed up at 1 and 3 months and every 3 months thereafter for 2 years. Fasting serum creatinine and 3 sitting blood pressures were measured at every visit. Total cholesterol, high- and low-density lipoprotein cholesterol, and triglyceride levels were recorded at 1, 3, and 6 months and every 6 months after. All centers were monitored yearly for quality control of the data.

End Points

The primary end point was worsening of renal function, defined as a 20% or greater decrease in estimated creatinine clearance compared with baseline, based on 2 repeated measurements. This was the definitive end point in the medication group. In the stent group, patients who reached the end point underwent imaging to exclude restenosis of the renal artery. If no restenosis occurred, the end point was reached. If restenosis had occurred, re-intervention was performed, and the primary end point was reached if the reduction in creatinine clearance of 20% or greater persisted 1 month after re-intervention.

Secondary end points were procedural complications, changes in blood pressure, incidence of refractory or malignant hypertension and pulmonary edema, cardiovascular morbidity and mortality, and total mortality. Complications were considered periprocedural if they occurred within 30 days of treatment. Cardiovascular morbidity and mortality were independently evaluated by the clinical event committee according to a preexisting protocol (15).

Statistical Analysis

The sample size calculation was based on an expected reduction in the incidence of progressive renal failure, defined as serum creatinine levels that increased by at least 20% in the previous 12 months, from 50% in the medication group to 20% in the stent group, with a power of 90% (16). To detect this difference at a significance level of 5%, we needed to recruit 140 patients (13).

Between-group differences in patient characteristics were evaluated by using chi-square tests for discrete variables, the *t* test for continuous variables with normal distribution, and the Wilcoxon rank-sum test for variables that were not normally distributed. A 2-sided *P* value less than 0.05 was considered statistically significant.

Outcomes were compared when patients reached the primary end point or at 2 years and were analyzed according to the intention-to-treat principle. In our primary analysis, patients who died or who were lost to follow-up were censored. Because renal failure and death are probably related, we also compared groups by using a composite outcome of the trial's primary end point and death, in which patients who were lost to follow-up were censored. We used an estimated Kaplan–Meier survival curve to characterize the cumulative incidence of the primary end point and the composite outcome of primary end point and death and used the log-rank test to compare the groups. Crude hazard ratios (with 95% CIs) comparing the stent group with the medication group (reference) for each end point were obtained from Cox proportional hazards regression models. Log-minus-log plots were used to evaluate the proportional hazards assumption. No violation was detected. To assess the modifying effect of the type of stenosis, the statistical significance of the product term of type of stenosis and randomization was determined. Because a considerable proportion of patients in the stent group received medical treatment only, we also performed a by-protocol analysis. All data were analyzed using SPSS, version 15.0 (SPSS, Chicago, Illinois).

Role of the Funding Source

The study was funded by the Dutch Kidney Foundation, Bayer, Cordis, and Pfizer. The funders had no role in the study design, collection, analysis and interpretation of data, writing of the report, or the decision to submit the manuscript for publication. However, they approved the design and organization of the trial.

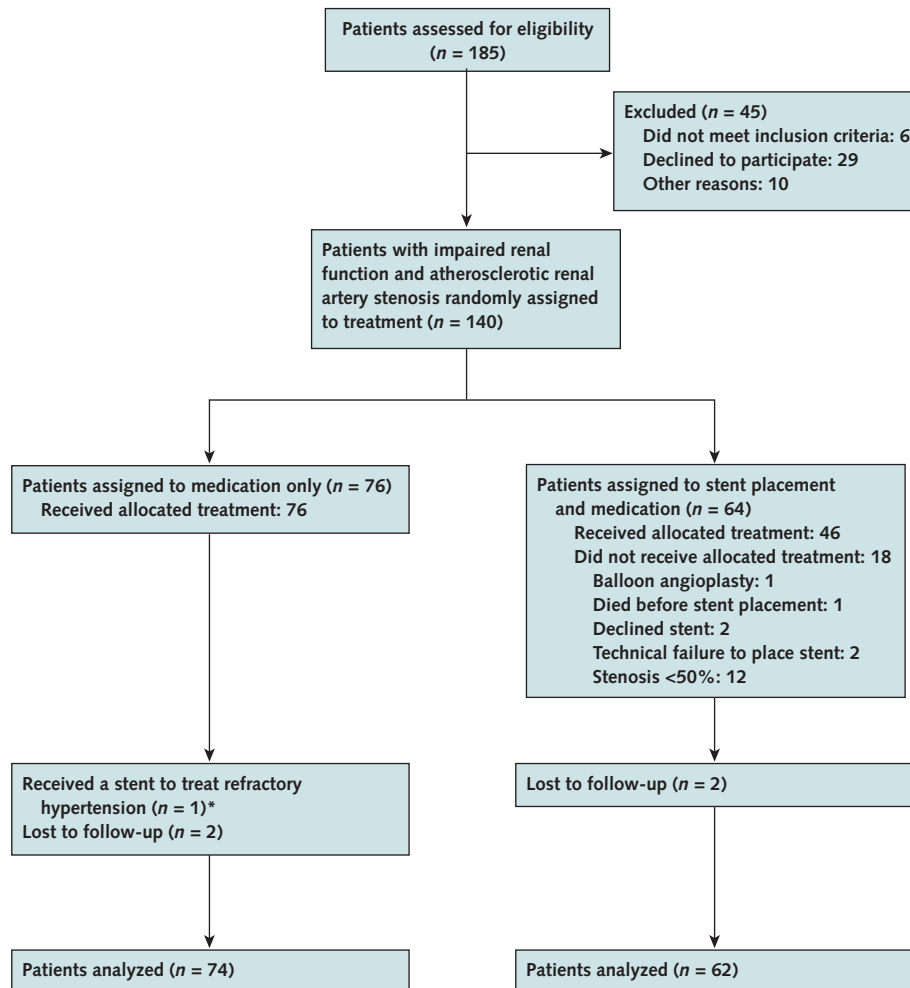
RESULTS

Patients

Figure 1 shows the study flow. Between June 2000 and December 2005, 140 patients were randomly assigned to medical treatment only ($n = 76$) or medical treatment with additional stent placement ($n = 64$) and were followed for 2 years. The number of patients in each group differed slightly because randomization was stratified by center and type of stenosis.

In the medication group, all patients received the allocated treatment. In the stent group, a stent was placed in 46 patients, all of whom had residual stenosis less than 20%. Eighteen patients in the stent group did not receive the assigned treatment after randomization (12 had ARAS <50% at the time of the procedure, 2 had technical failure to place the stent, 2 declined stenting, 1 had balloon angioplasty, and 1 died before the procedure). These pa-

Figure 1. Study flow diagram.



* Included in analysis.

tients were analyzed as if they had received the stent (intention-to-treat).

Patient Characteristics

The groups did not differ in baseline patient characteristics, including renal function, severity and type of renal artery stenosis, and imaging study used to detect the stenosis (Table 1).

Primary End Point

Sixteen patients (22%) in the medication group and 10 (16%) in the stent group (2 of whom did not receive a stent at the beginning of the trial) reached the primary end point (hazard ratio, 0.73 [95% CI, 0.33 to 1.61]) (Table 2). The primary end point was reached in both groups at a mean of 10 months (SD, 7). Five of the 10 patients in the stent group had repeated angiography before reaching the end point (3 had no stenosis, 1 had restenosis treated by stenting, and 1 had restenosis treated with balloon angio-

plasty). No procedural complications occurred in these patients, and all had persistence of decline in renal function (>20% decrease in creatinine clearance) 1 month after repeated angiography. Angiography was not repeated in the other 5 patients because of concurrent end-stage cancer (2 patients); end-stage renal disease before re-intervention (2 patients); and renography demonstrating normal kidney perfusion, suggesting a patent stent (1). Event-free survival did not statistically significantly differ between the groups (log-rank $P = 0.44$) (Figure 2). Type of stenosis (unilateral or bilateral) was not a statistically significant effect modifier ($P = 0.41$). The by-protocol analysis comparing the 90 patients who received medical treatment only with the 50 patients who received renal artery intervention plus medical treatment had the same result (17 [19%] primary events vs. 9 [18%] primary events; hazard ratio, 0.9 [CI, 0.4 to 2.0]).

Table 1. Participant Characteristics at Baseline

Characteristic	Medication Group (n = 76)	Stent Group (n = 64)
Mean age (SD), y	67 (9)	66 (8)
Men, n (%)	45 (59)	43 (67)
Vascular history, n (%)		
Any vascular disease	59 (78)	54 (84)
Diabetes mellitus	18 (31)	16 (30)
Cerebrovascular disease	18 (31)	15 (28)
Heart failure	7 (12)	5 (9)
Abdominal aortic aneurysm	9 (15)	7 (13)
Peripheral arterial disease	30 (51)	26 (48)
Coronary artery disease	32 (54)	23 (43)
Current or past smoking	52 (68)	46 (72)
Current smoking	15 (20)	20 (31)
Renal function		
Mean serum creatinine level (SD)		
μmol/L	145 (51)	154 (60)
mg/dL	1.6 (0.58)	1.7 (0.68)
Mean estimated creatinine clearance (SD), mL/min per 1.73 m ²	46 (16)	45 (15)
Blood pressure		
History of hypertension, n (%)	73 (96)	63 (98)
Mean systolic blood pressure (SD), mm Hg	163 (26)	160 (25)
Mean diastolic blood pressure (SD), mm Hg	82 (12)	83 (13)
Antihypertensive drugs		
Mean number of drug categories (SD)	2.9 (1.0)	2.8 (1.0)
Treatment, n (%)		
ACE inhibitors	23 (30)	21 (33)
Angiotensin II–receptor antagonists	18 (24)	17 (27)
Laboratory data		
Mean total cholesterol level (SD)		
mmol/L	5.1 (1.0)	4.9 (1.2)
mg/dL	197 (38)	189 (46)
Mean HDL cholesterol level (SD)		
mmol/L	1.2 (0.4)	1.2 (0.4)
mg/dL	46 (15)	46 (15)
Mean LDL cholesterol level (SD)		
mmol/L	3.1 (0.9)	2.8 (1.3)
mg/dL	119 (35)	108 (50)
Mean triglyceride level (SD)		
mmol/L	1.8 (1.2)	2.2 (1.6)
mg/dL	159 (106)	195 (142)
Mean glucose level (SD)		
mmol/L	6.2 (2.0)	5.9 (1.6)
mg/dL	112 (36)	106 (29)
Median proteinuria (IQR), g/d	0.14 (0.08–0.36)	0.19 (0.1–0.5)
Previous renal artery intervention, n (%)	8 (11)	7 (11)
Balloon angioplasty, n (%)	7 (9)	6 (9)
Stent, n (%)	1 (1)	1 (2)
Test used to evaluate stenosis, n (%)		
Computed tomographic angiography	24 (32)	23 (36)
Magnetic resonance angiography	39 (51)	35 (55)
Angiography	13 (17)	6 (9)
Type of ostial stenosis, n (%)		
Unilateral	41 (54)	32 (50)
Bilateral	35 (46)	32 (50)
Occlusion or shrunken kidney	11 (31)	14 (44)
Single kidney	3 (8)	1 (3)
Degree of stenosis of the most affected kidney		
50%–70%	24 (32)	22 (34)
70%–90%	35 (46)	20 (31)
>90%	17 (22)	22 (34)

ACE = angiotensin-converting enzyme; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.

Secondary End Points

The groups did not significantly differ in blood pressure control and cardiovascular morbidity and mortality (Table 2) or in the incidence of the composite outcome of worsening renal function and death (Figure 2). Procedure-related deaths occurred only in the stent group. Time until death during follow-up was similar in both groups: a mean of 12 months (SD, 8) for the medication group and 10 months (SD, 10) for the stent group. Three patients in the medication group developed therapy-refractory hypertension; of these patients, 1 did not receive a stent because of a kidney smaller than 8 cm, 1 did not receive a stent because of technical failure, and 1 received a stent successfully. One patient in the medication group had pulmonary edema combined with a 20% decrease in creatinine clearance.

Complications

Two patients in the stent group died of procedure-related causes within 30 days after stent placement. In 1 of the patients, embolization of a perforated renal artery was required. The patient subsequently developed pulmonary edema, needed mechanical ventilation, and died of a massive ischemic stroke 3 days later. The second patient had perforation of a renal artery branch. The artery was embolized, but despite re-intervention the patient went into hypovolemic shock, experienced the acute respiratory distress syndrome, and died of multiorgan failure after 1 week. These adverse events occurred at different centers and with different providers.

The most common complications after stent placement were minor and mainly consisted of hematoma at the puncture site (11 patients [17%]). In 1 of these patients, secondary infection in the groin required surgical reconstruction. The patient thereafter developed end-stage renal failure, pulmonary edema, and heart failure and died 6 months after the procedure. In 2 other patients, stent placement was complicated by false aneurysm of the femoral artery. Injury to the kidney or renal artery occurred in 5 patients; however, this was never associated with loss of renal function and additional intervention was never required. These complications also occurred at different centers and with different providers. Minor side effects of medication were reported in 15 patients in the medication group and 4 in the stent group.

One patient in the stent group who had repeated angiography required permanent dialysis after cholesterol embolism. No stenosis was found in this patient on repeated angiography, and therefore no intervention was performed. In another patient, repeated angiography was complicated by groin hematoma.

Patient Characteristics During Follow-up

The groups did not significantly differ in patient characteristics at the time of reaching the primary end point or 2-year follow-up (Appendix Table, available at www.annals.org), except for slightly higher total cholesterol and low-density lipoprotein cholesterol levels in the medication group despite a slightly higher dosage of statin.

Table 2. Primary and Secondary End Points

End Point	Medication Group (n = 74)*	Stent Group (n = 62)*	Crude Hazard Ratio (95% CI)†
Primary end point, n (%)‡			
Unilateral or bilateral stenosis	16 (22)	10 (16)	0.73 (0.33–1.61)
Unilateral stenosis only	8 (20)	3 (9)	0.48 (0.13–1.81)
Bilateral stenosis only	8 (23)	7 (22)	0.95 (0.34–2.61)
Secondary end points, n (%)			
Therapy-refractory hypertension	3 (4)	0	–
Malignant hypertension	0	0	–
Pulmonary edema	1 (1)	0	–
Cardiovascular morbidity			
Heart failure	3 (4)	1 (2)	0.39 (0.04–3.71)
Coronary artery disease	3 (4)	3 (5)	1.16 (0.23–5.73)
Peripheral arterial disease	7 (9)	4 (6)	0.67 (0.20–2.28)
Cerebrovascular disease	1 (1)	0	–
Abdominal aortic aneurysm	0	0	–
All-cause mortality			
Overall deaths	6 (8)	5 (8)	0.99 (0.30–3.24)
Cardiovascular mortality	4 (5)	2 (3)	0.59 (0.11–3.25)
Periprocedural mortality§	0	2 (3)	–
Primary end point or death, n (%)	22 (30)	15 (24)	0.81 (0.42–1.56)

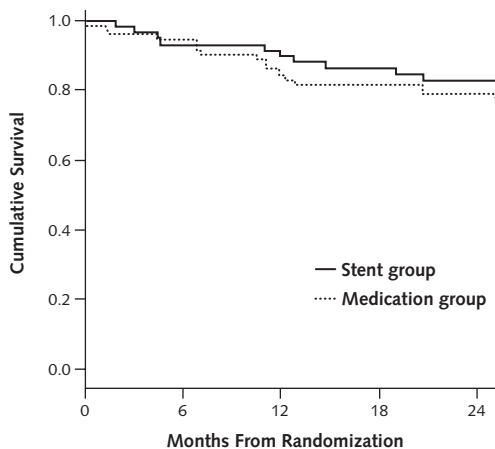
* 2 patients in each group were lost to follow-up at 2 years.

† The medication group is the reference group.

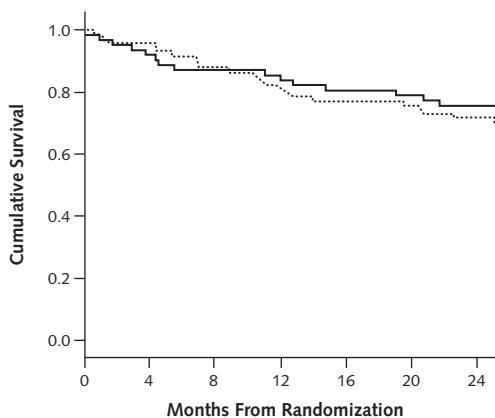
‡ The primary end point was a $\geq 20\%$ decrease in estimated creatinine clearance compared with baseline. In the stent group, the primary end point was reached if the $\geq 20\%$ reduction in creatinine clearance persisted 1 month after re-intervention.

§ Death within 30 days after start of treatment.

Figure 2. Survival curves for the primary end point (top) and the primary end point plus death (bottom) during 2 years of follow-up.



Patients remaining, <i>n</i>		0	6	12	18	24
Medication group	76	68	60	57	53	
Stent group	64	54	52	50	46	



Patients remaining, <i>n</i>		0	6	12	18	24
Medication group	76	68	60	57	53	
Stent group	64	54	52	50	46	

The analysis was censored by death and loss to follow-up.

DISCUSSION

In patients with impaired renal function and ARAS, we found no statistically significant difference in progression of renal failure over 2 years in those treated with stenting and medication compared with those treated with medication only. However, the confidence bounds around our hazard estimate are compatible with both efficacy and harm, so the finding is inconclusive. A considerable number of stent-related complications occurred, including 2 procedure-related deaths, 1 death secondary to an infected hematoma and 1 case of deterioration of renal function resulting in dialysis, suggesting that renal stenting for

ARAS may cause more harm than benefit in a community setting.

Revascularization of the renal artery to preserve renal function is based on the assumption that ischemia contributes to renal insufficiency and that correction of the stenosis and restoration of renal perfusion will stabilize or improve renal function. The ultimate goal is to prevent or delay the need for renal replacement therapy. Having retrieved no results on a MEDLINE PubMed search for trials published from 1990 through 2008 comparing stent placement with medical treatment for ARAS and impaired renal function, we believe that ours is the first controlled trial of whether revascularization can preserve renal function. Our data show a small benefit on the primary end point of stent placement compared with medication only (16% vs. 22%) that was inconclusive given the wide CIs around the estimate of effect. The fact that renal function may progress despite successful revascularization underscores the complex cause of ischemic nephropathy with an important intrarenal (parenchymal) component strongly affected by risk factors for atherosclerosis. These results are in accordance with the preliminary public report of the ASTRAL (Angioplasty and STent for Renal Artery Lesions) trial (17), which found no clinically worthwhile benefits associated with revascularization on any of the outcomes that were studied. A search of ClinicalTrials.gov for ongoing clinical trials evaluating the effects of revascularization on renal function suggests that several trials of revascularization for ARAS are ongoing or recently completed, with publication of results pending (18, 19).

The number and time frame of deaths were similar in the 2 groups. Two procedure-related deaths (3%) occurred, even though our interventional radiologists had extensive experience (more than 10 years) with renal stenting. Previous intervention studies among patients with ARAS treated specifically for renal failure have shown 30-day all-cause mortality rates of 0% to 10% (16, 20–26). In studies with a prospective design, the procedure-related mortality rate was 0% to 3.6%, and the rate of need for dialysis within 30 days after stent placement was 0% to 4% (16, 20, 23). These proportions are similar to those in our trial.

Our study had a lower rate of primary events than anticipated, which reduced the power of the trial to detect a difference between groups. One explanation could be that cardiovascular risk management has improved in recent years, with the newer antihypertensives and lipid-lowering drugs that were used in both study groups. Statins have been shown to reduce proteinuria in patients with chronic kidney disease (27) and to reduce loss of kidney function in patients with cardiovascular disease (28). When we designed our trial 10 years ago, few studies were available on the natural course of renal function in patients with ARAS, and those that were available included patients with renovascular hypertension with generally better renal function. Schreiber and colleagues (4) demonstrated that 38% of the patients had a 20% deterioration of renal func-

tion after a mean of 52 months, and Dean and associates (29) showed progressive renal failure in 46% of patients after 44 months. The only study at the time in patients with impaired renal function specifically showed that 55% of the patients had decreasing renal function (>20%) in the year before intervention (16). In our power calculation, we therefore considered an event rate of 50% in 2 years for the medication group. An important implication of this lower event rate is that a very large sample would need to be studied to demonstrate a clinically significant difference with use of the stent, but only a small proportion of patients would benefit from it at the expense of serious complications and high costs. These considerations reinforce our impression that although our findings were inconclusive with respect to efficacy, they nevertheless provide valuable evidence that the balance between the potential advantages and disadvantages does not favor stent placement.

In terms of blood pressure, studies comparing balloon angioplasty of the renal artery and medical therapy in patients with renovascular hypertension have suggested a small beneficial effect in the intervention group (30, 31). In our patients with ARAS and renal dysfunction, blood pressure improved from baseline in both groups. However, systolic and diastolic blood pressures did not differ between the groups, and equal numbers of antihypertensive drugs were given.

Our study has limitations. First, a considerable number of patients had stenoses less than 50% at inclusion. In addition, by randomly assigning patients on the basis of results of noninvasive diagnostic tests, we introduced the possibility that patients with false-positive imaging studies would be enrolled. However, at the time that we designed our protocol, noninvasive imaging with computed tomographic angiography and magnetic resonance angiography were believed to be very reliable. A meta-analysis by Vasbinder and coworkers (32) demonstrated that both imaging techniques had a high diagnostic performance compared with angiography. Later evidence suggested a lower accuracy for diagnosing ARAS (33). However, we must have included some patients who had stenoses of less than 50% in both groups. The dropout rate of 3% (compared with the planned 10%) must have compensated in part for the dilution of power. Neither the intention-to-treat analysis nor the by-protocol analysis demonstrated a beneficial effect of additional stent placement.

In conclusion, we believe that this is the first trial comparing stent placement plus medication with medication only in patients with impaired renal function and ARAS. We found no statistically significant difference in progression of renal failure over 2 years in the 2 groups, although our findings are compatible with both efficacy and harm and are therefore inconclusive. A considerable number of stent-related complications occurred, including 2 procedure-related deaths. Thus, our findings favor a conservative therapeutic approach to patients with ARAS, fo-

cused on cardiovascular risk factor management without stenting.

From University Medical Center Utrecht and Julius Center for Health Sciences and Primary Care, Utrecht, Twenteborg Hospital Almelo, Almelo, University Medical Center Groningen, Groningen, University Medical Center Nijmegen, Nijmegen, Jeroen Bosch Hospital, 's-Hertogenbosch, Deventer Hospital, Deventer, University Medical Center Leiden, Leiden, Academic Medical Center Amsterdam, Amsterdam, Erasmus Medical Center Rotterdam and Maastad Hospital, Rotterdam, and University Hospital Maastricht, Maastricht, the Netherlands; University of Alberta Hospital, Edmonton, Alberta, Canada; and European Hospital Georges Pompidou, Paris, France.

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Reproducible Research Statement: *Study protocol:* Available from Dr. Beutler (e-mail, j.beutler@jzbz.nl) or Dr. Mali (e-mail, w.mali@umcutrecht.nl). *Statistical code:* Not available. *Data set:* Available from Dr. Beutler (e-mail, j.beutler@jzbz.nl) after obtaining agreement of the steering committee.

Requests for Single Reprints: Liesbeth Bax, MD, PhD, Department of Radiology (E01.132), University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Bax, Mali, and Beek: Department of Radiology (E01.132), University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.

Dr. Woittiez: Department of Internal Medicine, Twenteborg Hospital Almelo, Zilvermeeuw 1, 7609 PP Almelo, the Netherlands.

Dr. Kouwenberg: Department of Radiology, Twenteborg Hospital Almelo, Zilvermeeuw 1, 7609 PP Almelo, the Netherlands.

Dr. Buskens: Department of Epidemiology, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands.

Dr. Braam: Division of Nephrology, Department of Medicine, University of Alberta Hospital, 11-107 Clinical Sciences Building, Edmonton, Alberta T6G 2B7, Canada.

Dr. Huysmans: University Medical Center Nijmegen, Department of Nephrology, Geert Grooteplein-Zuid 10, 6525 GA Nijmegen, the Netherlands.

Dr. Schultze Kool: Department of Radiology, University Medical Center Nijmegen, Geert Grooteplein-Zuid 10, 6525 GA Nijmegen, the Netherlands.

Dr. Rutten: Department of Radiology, Jeroen Bosch Hospital, Nieuwstraat 34, 5211 NL 's-Hertogenbosch, the Netherlands.

Dr. Doorenbos: Department of Internal Medicine, Deventer Hospital, Nico Bolkesteinlaan 75, 7416 SE Deventer, the Netherlands.

Dr. Aarts: Department of Radiology, Deventer Hospital, Nico Bolkesteinlaan 75, 7416 SE Deventer, the Netherlands.

Dr. Rabelink: Department of Nephrology, University Medical Center Leiden, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands.

Dr. Plouin: Department of Internal Medicine, European Hospital Georges Pompidou, 20 rue Leblanc, 75908 Paris Cedex 15, France.

Dr. Raynaud: Department of Radiology, European Hospital Georges Pompidou, 20 rue Leblanc, 75908 Paris Cedex 15, France.

Dr. van Montfrans: Department of Internal Medicine, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.

Dr. Reekers: Department of Radiology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.

Dr. van den Meiracker: Department of Internal Medicine, Erasmus Medical Center, Dr. Molewaterplein 50-60, 3015 GE Rotterdam, the Netherlands.

Dr. Pattynama: Department of Radiology, Erasmus Medical Center, Dr. Molewaterplein 50-60, 3015 GE Rotterdam, the Netherlands.

Dr. van de Ven: Department of Internal Medicine, Maasstad Hospital, Olympiaweg 350, 3078 HT Rotterdam, the Netherlands.

Dr. Vroegindewij: Department of Radiology, Maasstad Hospital, Olympiaweg 350, 3078 HT Rotterdam, the Netherlands.

Dr. Kroon: Department of Internal Medicine, University Hospital Maastricht, P. Debyelaan 25, 6229 HX Maastricht, the Netherlands.

Dr. de Haan: Department of Radiology, University Hospital Maastricht, P. Debyelaan 25, 6229 HX Maastricht, the Netherlands.

Dr. Postma: Department of Internal Medicine, University Medical Center Nijmegen, Geert Grooteplein-Zuid 10, 6525 GA Nijmegen, the Netherlands.

Dr. Beutler: Department of Internal Medicine, Jeroen Bosch Hospital, Nieuwstraat 34, 5211NL 's Hertogenbosch, the Netherlands.

Author Contributions: Conception and design: L. Bax, A.J.J. Woittiez, W.P.T.M. Mali, E. Buskens, F.T.M. Huysmans, T.J. Rabelink, P.F. Plouin, C.T. Postma, J.J. Beutler.

Analysis and interpretation of the data: L. Bax, W.P.T.M. Mali, E. Buskens, F.J.A. Beek, F.T.M. Huysmans, T.J. Rabelink, C.T. Postma, J.J. Beutler.

Drafting of the article: L. Bax, W.P.T.M. Mali, T.J. Rabelink, J.J. Beutler.

Critical revision of the article for important intellectual content: L. Bax, A.J.J. Woittiez, H.J. Kouwenberg, W.P.T.M. Mali, E. Buskens, F.J.A. Beek, F.T.M. Huysmans, L.J. Schultze Kool, M.J.C.M. Rutten, C.J. Doorenbos, J.C.N.M. Aarts, T.J. Rabelink, P.F. Plouin, A. Raynaud, G.A. van Montfrans, J.A. Reekers, A.H. van den Meiracker, P.M.T. Pattynama, P.J.G. van de Ven, D. Vroegindewij, A.A. Kroon, M.W. de Haan, C.T. Postma, J.J. Beutler.

Final approval of the article: L. Bax, A.J.J. Woittiez, H.J. Kouwenberg, W.P.T.M. Mali, E. Buskens, F.J.A. Beek, B. Braam, F.T.M. Huysmans, L.J. Schultze Kool, M.J.C.M. Rutten, C.J. Doorenbos, J.C.N.M. Aarts, T.J. Rabelink, P.-F. Plouin, A. Raynaud, G.A. van Montfrans, J.A. Reekers, A.H. van den Meiracker, P.M.T. Pattynama, P.J.G. van de Ven, D. Vroegindewij, A.A. Kroon, M.W. de Haan, C.T. Postma, J.J. Beutler. Provision of study materials or patients: A.J.J. Woittiez, H.J. Kouwenberg, B. Braam, F.T.M. Huysmans, L.J. Schultze Kool, M.J.C.M. Rutten, C.J. Doorenbos, J.C.N.M. Aarts, P.F. Plouin, A. Raynaud, G.A. van Montfrans, J.A. Reekers, A.H. van den Meiracker, P.M.T. Pattynama, P.J.G. van de Ven, D. Vroegindewij, A.A. Kroon, M.W. de Haan, C.T. Postma, J.J. Beutler.

Statistical expertise: E. Buskens.

Obtaining of funding: W.P.T.M. Mali, E. Buskens, J.J. Beutler.

Administrative, technical, or logistic support: L. Bax, F.J.A. Beek.

Collection and assembly of data: L. Bax, F.J.A. Beek.

APPENDIX: STAR TRIAL INVESTIGATORS, SITES, AND ORGANIZATION

Investigators and Sites

L. Bax, W.P.T.M. Mali, E. Buskens, F.J.A. Beek, H.A. Koomans, G.B. Braam, B.C. van Jaarsveld (University Medical Center Utrecht, Utrecht, the Netherlands [trial coordination center]); J.J. Beutler, M.J.C.M. Rutten (Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands); A.J.J. Woittiez, J.J. Kouwenberg (Twenteborg Hospital, Almelo, the Netherlands); C.T. Postma, F.T.M. Huysmans, L.J. Schultze Kool, T. Thien, F.B.M. Joosten (University Medical Center Nijmegen, Nijmegen, the Netherlands); C.J. Doorenbos, J.C.N.M. Aarts (Deventer Hospital, Deventer, the Netherlands); P.F. Plouin, A. Raynaud, M. Azizi, A. la Batide Alanore (European Hospital Georges Pompidou, Paris, France); G.A. van Montfrans, J.A. Reekers (Academic Medical Center Amsterdam, Amsterdam, the Netherlands); A.H. van den Meiracker, P.M.T. Pattynama, J. Deinum (Erasmus Medical Center, Rotterdam, the Netherlands); P.J.G. van de Ven, D. Vroegindewij (Maasstad Hospital, Rotterdam, the Netherlands); A.A. Kroon, P.W. de Leeuw, J.M.A. van Engelshoven, M.W. de Haan (University Hospital Maastricht, Maastricht, the Netherlands).

Organization

Steering committee: J.J. Beutler (*Chair*), T.J. Rabelink, W.P.T.M. Mali, E. Buskens, P.F. Plouin, C.T. Postma. *Safety and data monitoring committee:* P. de Jong, J.J.P. Kastelein, R.A. Manoliu, M. Boers. *Clinical end point committee:* F.L.J. Visseren, C.A. Gaillard, M.J.M. Cramer.

Appendix Table. Patient Characteristics at Primary End Point or 2-Year Follow-up

Characteristic	Medication Group (n = 68)*	Stent Group (n = 57)†	P Value‡
Renal function			
Mean serum creatinine level (SD)			0.37
μmol/L	168 (76)	156 (69)	
mg/dL	1.9 (0.86)	1.8 (0.78)	
Mean estimated creatinine clearance (SD), mL/min	46 (19)	50 (22)	0.29
Blood pressure§			
Mean systolic blood pressure (SD), mm Hg	155 (26)	151 (23)	0.40
Mean diastolic blood pressure (SD), mm Hg	79 (11)	77 (12)	0.44
Blood pressure on target, n (%)	20 (29)	18 (32)	0.95
Medication use			
Mean number of antihypertensive drug categories (SD)	2.9 (1.1)	2.6 (1.4)	0.30
ACE inhibitors, n (%)	21 (31)	21 (37)	0.48
Angiotensin II-receptor antagonists, n (%)	24 (35)	14 (25)	0.196
Atorvastatin or other statin, n (%)	63 (93)	48 (84)	0.24
Mean dose of atorvastatin (SD), mg	23 (13)	19 (9)	0.078
Receiving a lipid-lowering drug, n (%)	63 (93)	51 (89)	0.53
Receiving antiplatelet or anticoagulant therapy, n (%)	58 (85)	48 (84)	0.87
Laboratory data			
Mean total cholesterol level (SD)			0.011
mmol/L	4.4 (1.0)	4.0 (0.9)	
mg/dL	169 (38)	154 (35)	
Mean HDL cholesterol level (SD)			0.187
mmol/L	1.2 (0.4)	1.1 (0.3)	
mg/dL	46 (15)	42 (12)	
Mean LDL cholesterol level (SD)			0.003
mmol/L	2.5 (0.8)	2.0 (0.6)	
mg/dL	96 (31)	77 (23)	
Mean triglyceride level (SD)			0.51
mmol/L	1.9 (1.1)	2.0 (1.0)	
mg/dL	168 (97)	177 (88)	
Median proteinuria (IQR), g/d	0.15 (0.09–0.6)	0.16 (0.1–0.3)	0.92
Current smoking, n (%)	18 (27)	15 (26)	0.99

ACE = angiotensin-converting enzyme; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.

* At 2 years, 2 patients were lost to follow-up and 6 patients had died.

† At 2 years, 2 patients were lost to follow-up and 5 patients had died.

‡ Chi-square test for discrete variables and *t* test for continuous variables.

§ Target blood pressure was <140/90 mm Hg.

|| The systolic and diastolic blood pressures improved in both groups compared with baseline, with use of the same number of antihypertensive drugs. The mean change in systolic blood pressure was -9.0 mm Hg (*P* = 0.013) in the medication group and -9.5 mm Hg (*P* = 0.021) in the stent group; the mean respective changes in diastolic blood pressure were -3.9 mm Hg (*P* = 0.011) and -6.9 mm Hg (*P* = 0.001).