

Long-Term Effects of Arterial Stenting on Kidney Function for Patients with Ostial Atherosclerotic Renal Artery Stenosis and Renal Insufficiency

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Abstract. It is uncertain whether renal artery stent placement in patients with atherosclerotic renovascular renal failure can prevent further deterioration of renal function. Therefore, the effects of renal artery stent placement, followed by patency surveillance, were prospectively studied in 63 patients with ostial atherosclerotic renal artery stenosis and renal dysfunction (*i.e.*, serum creatinine concentrations of >120 $\mu\text{mol/L}$ (median serum creatinine concentration, 171 $\mu\text{mol/L}$; serum creatinine concentration range, 121 to 650 $\mu\text{mol/L}$). Pre-stent renal (dys) function was stable for 28 patients and declining for 35 patients (defined as a serum creatinine concentration increase of $\geq 20\%$ in 12 mo). The median follow-up period was 23 mo (interquartile range, 13 to 29 mo). Angioplasty to treat restenosis was performed in 12 cases. Five patients reached end-stage renal failure within 6 mo, and this was related to

stent placement in two cases. Two other patients died or were lost to follow-up monitoring within 6 mo, with stable renal function. For the remaining 56 patients, the treatment had no effect on serum creatinine levels if function had previously been stable; if function had been declining, median serum creatinine concentrations improved in the first 1 yr [from 182 $\mu\text{mol/L}$ (135 to 270 $\mu\text{mol/L}$) to 154 $\mu\text{mol/L}$ (127 to 225 $\mu\text{mol/L}$); $P < 0.05$] and remained stable during further follow-up monitoring. In conclusion, stent placement, followed by patency surveillance, to treat ostial atherosclerotic renal artery stenosis can stabilize declining renal function. For patients with stable renal dysfunction, the usefulness is less clear. The possible advantages must be weighed against the risk of renal failure advancement with stent placement.

Atherosclerotic renal artery stenosis causes hypertension and renal failure. Treatment via percutaneous transluminal angioplasty was originally designed to cure the hypertension (1). Studies have demonstrated a modest drug-sparing effect, but cures are rare (2). The introduction of arterial stent placement has led to considerable reductions in the rates of restenosis (3) but has not yielded superior BP control (3,4). Furthermore, with the use of modern antihypertensive drugs, angioplasty seems to offer little more benefit than antihypertensive treatment alone (5).

Renal failure attributable to atherosclerotic renal artery stenosis is increasingly being recognized as an important cause of renal insufficiency (6). It is even one of the leading conditions requiring renal replacement therapy among middle-aged and elderly populations (6,7). With an aging population, its prevalence can be expected to increase. Patients who require dial-

ysis because of atherosclerotic renal failure have poor prognoses (8). Therefore, the focus of treatment has shifted to the prevention of renal failure (5,9), but the usefulness of arterial stenting is uncertain. The group at risk to develop progressive ischemic nephropathy most likely includes patients in whom this process is already underway, *i.e.*, patients with increased serum creatinine concentrations. Stenting experience in this group is limited (4,10). Beneficial effects were reported for patients with progressive renal failure in one study, but follow-up periods were short and survival times were very short (11).

We prospectively studied the long-term effects of renal artery stent placement, followed by angiographic patency surveillance, for patients with ostial atherosclerotic renal artery stenosis and renal dysfunction. We investigated whether this policy would have a favorable effect on the course of renal function, specifically for patients exhibiting progressive renal dysfunction.

Materials and Methods

Patients

Between September 1992 and August 1997, we treated a total of 63 patients with ostial atherosclerotic renal artery stenosis and compromised renal function (serum creatinine concentration of >120 $\mu\text{mol/L}$) and hypertension (BP of $>160/95$ mmHg, with or without

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medication) with renal artery stents. Twenty-nine patients had been previously treated with percutaneous angioplasty. Ostial renal artery stenosis was defined as a $\geq 50\%$ reduction in the luminal diameter within the first 10 mm of the aortic lumen. Patients were selected on the basis of the finding that stenosis contributed to their renal dysfunction. This was established by positive captopril renographic findings or by a $\geq 20\%$ increase in plasma creatinine levels with the standardized use of an angiotensin-converting enzyme (ACE) inhibitor (12). Exclusion criteria were a history of cholesterol embolism, contraindications for anticoagulant medication, small size of the affected kidney (pole-to-pole distance of < 8 cm), $< 25\%$ function detected by renography, or a renal artery diameter of < 4 mm. Informed consent was obtained, and the studies was approved by the hospital committee for studies in humans.

Protocol

BP and serum creatinine levels were measured before the intervention. The patients continued to receive their regular medications, but ACE inhibitor administration was discontinued at least 2 wk before this assessment. Stent placement was performed as described by Rees (10). Heparin was administered (5000 IU, intravenously) during this procedure, and treatment was continued until adequate anticoagulation was achieved with the use of orally administered warfarin. Bilateral stenoses were treated in one session. After 3 mo, warfarin was replaced by aspirin (100 mg daily). Beginning in March 1997, warfarin was deleted from this regimen and patients received only 100 mg of aspirin daily, starting the day before the procedure, with heparin administration during the procedure. The procedure was considered successful if the residual stenosis was $< 50\%$ of the luminal diameter.

The patients attended the outpatient clinic at 1, 3, and 6 mo and every 6 mo thereafter, for measurement of BP and serum creatinine concentrations. For patients receiving an ACE inhibitor, administration was discontinued at least 2 wk before the 6-mo follow-up visit. At the other time points, ACE inhibitors were withheld only for patients with deterioration of renal function and serum creatinine concentrations measured without ACE inhibition were used for evaluation. Renal angiography was repeated at 6, 18, and 30 mo. When cholesterol embolism was suspected, angiography was replaced by spiral computed tomographic angiography. Angiography was also repeated if restenosis was suspected on a clinical basis, *i.e.*, in cases with an increase in diastolic BP of at least 15 mmHg with unchanged antihypertensive medication or an increase in serum creatinine levels of at least 20% that developed spontaneously or after the start of treatment with ACE inhibitors. Restenosis, defined as a reduction in the luminal diameter of $> 50\%$, was treated by angioplasty in the stent.

Definitions

The results of angiography were assessed in consensus readings by two experienced vascular radiologists. The diameter of the first normal segment distal to the stenosis was used for reference. Clinical success, as assessed during the most recent follow-up examination, was classified according to the guidelines of the Standards of Practice Committee of the Society of Cardiovascular and Interventional Radiology (13). In those guidelines, cure of hypertension is defined as a diastolic pressure of ≤ 90 mmHg without antihypertensive medication. Improvement is defined as a diastolic pressure that decreases below 90 mmHg or decreases by at least 15 mmHg with unchanged antihypertensive medication. Any other result is classified as a failure. Improvement in renal function is defined as a decrease in the serum creatinine concentration of at least 20%, and deterioration is defined

as an increase in the serum creatinine concentration of at least 20%. Any other result is defined as unchanged renal function.

Kidney Function before Treatment

For assessment of kidney function changes before stent placement, serum creatinine concentrations in the 1 yr preceding the procedure were compared. Only values measured without the use of ACE inhibitors were considered. Patients were considered to have declining renal function if serum creatinine levels had increased by at least 20% in the previous 12 mo. If serum creatinine measurements for 1 yr before the intervention were not available, increases in serum creatinine levels of $\geq 10\%$ in the previous 6 mo or $\geq 15\%$ in the previous 9 mo were considered to indicate deteriorating renal function. Patients with smaller increases or no changes in serum creatinine levels were considered to have stable function.

Statistical Analyses

Values are presented as medians and interquartile ranges (25 to 75%). Changes in serum creatinine concentrations before and after procedures were analyzed by comparisons of the slopes of plots of reciprocal serum creatinine concentrations *versus* time (in months). Statistical analyses were performed by using the Wilcoxon signed-rank test and Kaplan-Meier analysis (for survival times and renal function preservation). $P < 0.05$ was considered to indicate statistical significance.

Results

Patients

There was a propensity for the male gender (Table 1). Hypercholesterolemia, extrarenal atherosclerotic disease, and smoking were common. Unilateral artery stenosis, with a normal contralateral renal artery, was observed for only 24% of patients. The other patients had bilateral renal artery stenosis or contralateral occlusion. Thirty-six patients had hypercholesterolemia (serum cholesterol levels of > 6.5 mmol/L); 25 of these patients used a lipid-lowering drug and eight began using a statin soon after inclusion. During the course of the study, the national recommended cholesterol level above which statins are indicated for secondary prevention was decreased to 5.0 mmol/L, and eventually 10 more patients received lipid-lowering drug therapy.

Immediate Effects and Complications of Stent Placement

Sixty-one of the 63 patients underwent successful stenting of at least one renal artery. In one patient with unilateral disease, the stent was placed too distally and a second stent failed, leaving $> 50\%$ stenosis. In one patient with bilateral stenoses, an occlusion occurred during catheterization of the first kidney addressed, which required a surgical bypass. For three patients with bilateral ostial stenoses, stenting failed on one side. For the other 17 patients with bilateral disease, the procedure was effective on both sides. For seven of these patients, one of the arteries could be treated by conventional angioplasty because the stenosis was truncal rather than ostial.

The most common complication was local bleeding at the puncture site (Table 2). One patient required a blood transfusion. Immediate thrombosis of the stent occurred once and was

Table 1. Baseline clinical data^a

Parameter	No. of Patients (<i>n</i> = 63)
Gender (M/F)	40/23
Mean (range) age (yr)	66 (48–81)
Median (range) plasma creatinine concentration ($\mu\text{mol/L}$)	171 (121–650)
Median (quartile range) BP (mmHg)	
systolic	180 (161–204)
diastolic	100 (95–110)
Median (quartile range) no. of antihypertensive drugs taken	2 (1–3)
Diabetes mellitus	4 (6%)
Hypercholesterolemia	36 (57%)
Atherosclerotic disease	47 (75%)
cardial	31 (49%)
cerebral	12 (19%)
peripheral	34 (54%)
Smoking	
actual	34 (54%)
history	11 (17%)
Prior PTRA	23 (37%)
Type of stenosis	
unilateral	15 (24%)
bilateral	21 (33%)
in single kidney	1 (2%)
with contralateral occlusion	26 (41%)

^a PTRA, percutaneous transluminal renal angioplasty.

successfully resolved by selective intra-arterial streptokinase administration. Seven patients (11%) exhibited clinical signs of cholesterol embolism; for five of those patients (6%), plasma creatinine levels increased by at least 20% for >1 mo after the procedure. One patient became dialysis-dependent.

Long-Term Patency

Repeat angiography was performed for most available patients at 6 mo (54 of 56 patients, 96%), 18 mo (36 of 42

Table 2. Complications during the primary procedure

Complications	No. of Patients (<i>n</i> = 63)
Inguinal region bleeding	11 (17%)
Femoral artery aneurysm ^a	6 (10%)
Renal artery injury	4 (6%)
dissection	1
aneurysm	1
occlusion/thrombosis	2
Cholesterol embolism	7 (11%)
with renal dysfunction	5 (8%)

^a Arteriovenous fistula in one patient.

patients, 86%), and 30 mo (12 of 18 patients, 67%). The numbers of patients with newly detected restenosis ($\geq 50\%$) at these time points were ten (19%), seven (19%), and two (17%), respectively. Cumulatively, restenosis occurred in 19 cases. In 11 cases, the restenosis was successfully treated with conventional percutaneous transluminal angioplasty or with a second stent (*n* = 1). For one patient with a patent contralateral renal artery, nephrectomy was performed because of an aneurysm that had developed behind the stent. No action was taken in the other seven cases, because BP was well controlled and kidney function seemed stable, without deterioration, during standardized exposure to an ACE inhibitor.

Follow-up angiography was complicated by a temporary loss of renal function because of a cholesterol embolism in one patient. No permanent loss of renal function attributable to the angiography was observed.

Renal Function

Twenty-eight patients were classified as having stable renal dysfunction before stenting. Nine of those patients had unilateral disease. One became dialysis-dependent after 5 mo. One patient died at 6 mo, with end-stage renal failure. Of the remaining patients in this group, renal function improved for two, remained unchanged for 18, and declined for six. Serum creatinine levels were, by definition, stable in the period before the stent procedure and did not change in the 1 yr after the treatment (Table 3). The change in renal function, expressed as the change in $1/\text{serum creatinine concentration}$ per month, was -2.3 (-5.3 to 1.6) $\times 10^{-5}$ L/ μmol per mo before stent placement and -3.3 (-6.7 to 4.9) $\times 10^{-5}$ L/ μmol per mo in the subsequent 1 yr (*P* = 0.20, Wilcoxon signed-rank test) (Figure 1). At 12 mo, ACE inhibitors were used by 11 patients (42%) (for evaluation of kidney function during ACE inhibition, see above). During additional follow-up monitoring [median, 26 (14 to 42) mo], serum creatinine levels remained unchanged (Table 3).

Thirty-five patients, of whom six had unilateral disease, were considered to have deteriorating renal function before stent placement. Of these, one required dialysis 3 mo after stent placement and two others died within 6 mo, with predialysis serum creatinine levels. The stent placement did not clearly alter the rate of renal function decline for these three patients. One more patient died within 6 mo, and another was lost to follow-up monitoring at 4 mo, after experiencing a cerebrovascular accident. For these two subjects, the stent placement stabilized renal function. Of the remaining 30 patients in this group, kidney function improved for six, remained unchanged for 20, and declined for four. Serum creatinine levels, which by definition were increasing in the period before stent placement, had improved after 1 yr (Table 3). The decrease in renal function, *i.e.*, -29.0 (-41.2 to -17.1) $\times 10^{-5}$ L/ μmol per mo in the period before stenting, was reversed into improvement, 5.3 (-0.8 to 8.4) $\times 10^{-5}$ L/ μmol per mo (*P* < 0.001, Wilcoxon signed-rank test) (Figure 1). At 12 mo, ACE inhibitors were used by nine patients (30%), which was not significantly different from the percentage of patients using ACE inhibitors in the group with stable renal function [9 of 35 (30%) versus 11

Table 3. Serum creatinine concentrations before and after stent placement

Kidney Function before Stent Placement	Serum Creatinine Concentration (μM)			
	<12 Mo.	At Stent Placement	12 Mo after Stent Placement	Latest Follow-up Examination
Stable ($n = 26$)				
median	153	155	159	154
25–75%	131–175	130–180	132–212	129–212
Deteriorating ($n = 30$)				
median	132	182	154 ^a	157
25–75%	116–166	135–270	127–225	132–233

^a $P = 0.036$, compared with value at stent placement.

of 28 (42%). During additional follow-up monitoring [median, 23 (19 to 29) mo], one patient became dialysis-dependent after 27 mo. For the other patients, plasma creatinine levels remained stable (Table 3).

The cumulative number of patients who developed at least 20% decreases in renal function is presented in Figure 2. In 23 (13 to 36) mo, 15 of the 63 patients (24%) exhibited deterioration, and six of those patients reached end-stage renal failure. These latter patients exhibited a median baseline serum creatinine concentration of $326 \mu\text{mol/L}$ (range, 199 to $450 \mu\text{mol/L}$). For further analysis of whether increased baseline serum creatinine concentrations are associated with poor outcomes, patients were divided into two groups, *i.e.*, patients with mild renal failure (serum creatinine concentration of $\leq 300 \mu\text{mol/L}$) and patients with severe renal failure (serum creatinine concentration of $>300 \mu\text{mol/L}$). Baseline measurements indicated severe renal failure for ten patients, of whom five (50%) exhibited worsening of their renal function; this result was

significantly different from the outcomes for patients with mild renal failure (10 of 53 patients [19%]; $P < 0.05$). None of the 15 patients with unilateral stenosis experienced deterioration of renal function after stent placement; renal function improved for two patients, and no change in serum creatinine levels was observed for the remaining patients.

BP

Median baseline and follow-up systolic and diastolic BP values and the number of antihypertensive medications for all patients are presented in Table 4. Systolic and diastolic BP had decreased significantly by 6 mo after stent placement ($P < 0.001$), and this gain seemed to be durable. At the latest follow-up examination (at least 6 mo, *i.e.*, 56 patients), improvement or cure of hypertension was observed for 50% (28 of 56 patients) and 9% (5 of 56 patients) of patients, respectively.

Survival Rates

Twelve patients, one of whom was undergoing dialysis, died, after a median period of 9.5 mo (range, 4 to 42 mo). The Kaplan-Meier survival curve is shown in Figure 3. In eight cases, death could be attributed to a cardiovascular cause. No procedure-related death or death within 30 d of stent placement was noted.

Discussion

Our main finding is that renal artery stent placement, followed by monitoring and treatment for restenosis, stabilizes renal function for the majority of patients with atherosclerotic renal artery stenosis complicated by ischemic nephropathy. For patients for whom kidney function declined significantly in the 1 yr before treatment, this course could be reversed into improvement.

A recent meta-analysis demonstrated that, of 148 patients who underwent stent placement, mainly for treatment of atherosclerotic renal artery stenosis and renal failure (serum creatinine levels of $>133 \mu\text{mol/L}$), 74% responded with stable function or improvement of renal function (4). Data for the patients were collected from nine studies, and in most studies the follow-up period was <1 yr. We observed a similar rate (76%) of stable or improved renal function, however, with

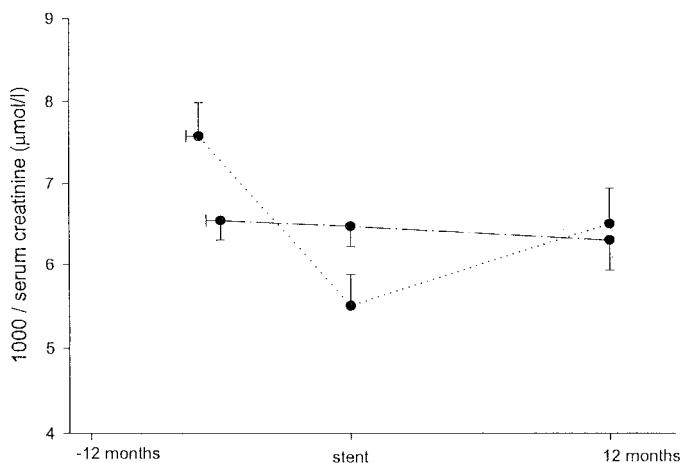
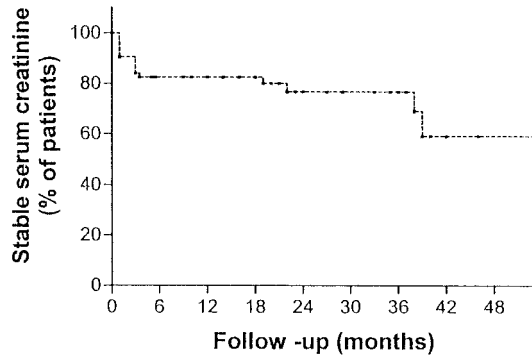


Figure 1. Reciprocals of serum creatinine levels before and after stent placement. Patients were divided on the basis of stable or deteriorating renal function in the 1 yr before stent placement. For patients with deteriorating renal function, the decreasing slope of the curve was reversed ($P < 0.001$) after stent placement. Seven patients who developed end-stage renal failure or were lost to follow-up monitoring within 6 mo were not included in this evaluation (.....●....., deteriorating ($n = 30$); —●—, stable ($n = 26$)).

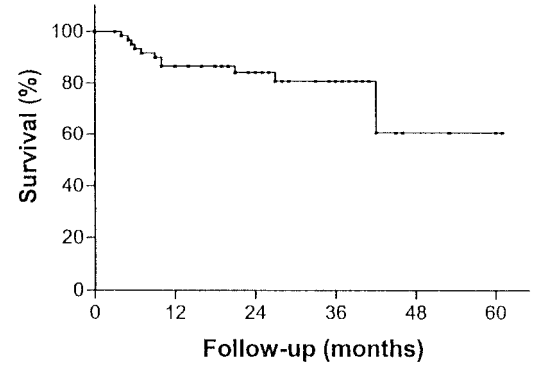


ESRD	:	5x		1x
Number of patients:		63	46	22
				13
				4

Figure 2. Kaplan-Meier curves for maintained renal function in all patients with atherosclerotic ostial renal artery stenosis and renal dysfunction who were treated with stent placement. Maintained renal function was defined as serum creatinine concentrations that did not increase above 120% of the serum creatinine levels at the time of stent placement. ESRD, number of patients who developed end-stage renal disease.

considerably longer follow-up periods. In this respect, it was probably important that monitoring and treatment of restenosis were essential parts of our policy.

To establish the clinical value of stent placement for patients with atherosclerotic renal artery stenosis and renal failure, we separately evaluated patients who had exhibited demonstrably declining renal function in the previous 1 yr. The observation that renal artery stent placement could retard progressive renal failure was recently reported by Harden *et al.* (11). Their study included 23 patients, but the follow-up period was only 8 mo. Pretreatment renal function (mean serum creatinine concentration, 257 $\mu\text{mol/L}$) was worse than in our study, and stent placement could not prevent 20% of their patients from rapidly becoming dialysis-dependent. Harden *et al.* (11) and others (4) have suggested that significantly increased serum creatinine levels are associated with poor outcomes. That association was confirmed in this study. The six patients who experienced progression to end-stage renal failure exhibited a median baseline serum creatinine level of 326 $\mu\text{mol/L}$ (range, 199 to 450



Number of patients:	63	52	30	16	5
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Figure 3. Kaplan-Meier survival curve for all patients with atherosclerotic ostial renal artery stenosis and renal dysfunction who were treated with stent placement.

$\mu\text{mol/L}$), which was well above the median for the whole group (171 $\mu\text{mol/L}$; range, 121 to 650 $\mu\text{mol/L}$). Furthermore, the percentage of patients with deterioration of renal function after stenting was twice as high for patients with baseline serum creatinine levels of $\geq 300 \mu\text{mol/L}$, compared with individuals with serum creatinine concentrations of $< 300 \mu\text{mol/L}$ (50 versus 19%, $P < 0.05$). The 2-yr survival rate for the Scottish population investigated (11), which was only 40% because of widespread cardiovascular disease, was also much lower than that for the population we studied. It is obviously difficult to study the long-term advantages of stenting for renal function control in a population with such a high cardiovascular risk. Our study of patients with clearly less cardiovascular risk demonstrates that stent placement, with subsequent arterial patency surveillance, can indeed stabilize previously declining renal function for years. In view of the progressive nature of ischemic renal failure (14,15), it is likely that, at least for some of those patients, the development of terminal renal failure can be postponed.

The reported rate of restenosis in the first 1 yr after stent placement in cases of ostial atherosclerotic renal artery stenosis varies between 0 and 39% and currently averages 10 to 15% (4). Data for later follow-up periods are scarce. Henry *et al.*

Table 4. BP at baseline and during follow-up monitoring

Parameter	Baseline	6 Mo	12 Mo	Latest Follow-up Examination	Wilcoxon Signed-Rank Test (Latest Follow-up Results Versus Baseline Results)
Systolic BP (mmHg)					
median	180	160	160	150	$P < 0.001$
25-75%	160-204	148-180	140-175	140-160	
Diastolic BP (mmHg)					
median	100	85	85	80	$P < 0.001$
25-75%	95-110	80-95	80-90	80-90	
No. of medications					
median	2	2	2	2	$P = 0.67$
25-75%	1-3	1-2	1-3	1-2	

(16) reported primary patency rates of 92% after 1 yr and 79% after 2 yr, suggesting undiminished development of restenosis in the second year. However, only 15 patients were monitored for 2 yr, and angiography was performed only when restenosis was suspected on the basis of ultrasound findings. Blum *et al.* (17) observed primary patency rates of 92% after 1 yr and 84% after 2 yr; 27 patients were monitored for 2 yr. We observed a somewhat higher restenosis rate, probably because we included more patients with bilateral disease. More importantly, those studies and our data indicate undiminished restenosis rates after the first 1 yr.

In their meta-analysis, Isles *et al.* (4) stated that most authors agree that restenosis is common enough to justify follow-up monitoring and reintervention. However, the reported experience with this follow-up policy in studies of meaningful duration is very limited (16–18). In our study, restenosis could be treated successfully with angioplasty, which confirms the general experience (10). We did not compare our policy with that of neglecting restenosis and thus cannot quantify how much surveillance for and treatment of restenosis contribute to the prevention of renal function decline. However, we presume that restenosis contributes to ischemic nephropathy as much as does primary stenosis. With this approach, we achieved the same preservation of renal function as observed by others in short-term studies. Duplex ultrasonography has emerged as a safe, inexpensive, sensitive tool for the assessment of restenosis of renal artery stents in the majority of the patients (19). We therefore recommend this method, instead of repeated angiography, for the follow-up monitoring of these high-risk patients for complications associated with the invasive procedure.

Whether and for which patients stenting will be cost-effective with the present policy can be answered only in randomized studies. Some points can be made. First, the complications of stenting and reinterventions must be considered in the evaluation. The most feared complication is widespread cholesterol embolism, which sometimes causes renal failure or even death. In this study, two patients developed end-stage renal failure, probably because of the stent placement. This risk is probably worse for patients with poorer pretreatment renal function (4,11). Second, it has been commonly noted that stenting and other methods of renal revascularization may decrease hypertension and the need for antihypertensive drugs (4,10,11). This effect was confirmed in this study. However, it may play no more than a secondary role, compared with renal failure prevention, in a cost-effectiveness study. Third, a favorable effect of arterial patency restoration may be much more difficult to demonstrate for patients with previously stable renal function. If, in correspondence to our data, the best result is that renal function remains stable after the procedure, whereas some patients experience accelerated renal function decline, we should obviously not subject such patients to the burden and risk of this treatment. However, the long-term natural course for these patients in relatively stable condition is uncertain, and a randomized study is required to determine whether stenting might still be useful for this group. Finally, ischemic nephropathy is a complex disease that also involves lipid abnormalities,

aging, endothelial dysfunction, hypertensive nephroangiosclerosis, areas of glomerular hypertension and segmental glomerulosclerosis, and interstitial fibrosis (20,21). The finding that stent placement can control the progression of renal failure clearly indicates the role of stenosis in this progression but obviously does not exclude the relevance of other contributing and possibly treatable factors. In this respect, it is of note that, during the study, almost 70% of the patients used statins, which were recently demonstrated to be able to ameliorate the progression of renal failure (22).

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