

# Effectiveness of Management Strategies for Renal Artery Stenosis: A Systematic Review

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**Background:** Atherosclerotic renal artery stenosis is increasingly common in an aging population. Therapeutic options include medical treatment only or revascularization procedures.

**Purpose:** To compare the effects of medical treatment and revascularization on clinically important outcomes in adults with atherosclerotic renal artery stenosis.

**Data Sources:** The MEDLINE database (inception to 6 September 2005) and selected reference lists were searched for English-language articles.

**Study Selection:** The authors selected prospective studies of renal artery revascularization or medical treatment of patients with atherosclerotic renal artery stenosis that reported mortality rates, kidney function, blood pressure, cardiovascular events, or adverse events at 6 months or later after study entry.

**Data Extraction:** A standardized protocol with predefined criteria was used to extract details on study design, interventions, outcomes, study quality, and applicability. The overall body of evidence was then graded as robust, acceptable, or weak.

**Data Synthesis:** No study directly compared aggressive medical therapy with angioplasty and stent placement. Two randomized

trials compared angioplasty without stent and medical treatments. Eight other comparative studies and 46 cohort studies met criteria for analysis. Studies generally had poor methodologic quality and limited applicability to current practice. Overall, there was no robust evidence. Weak evidence suggested no large differences in mortality rates or cardiovascular events between medical and revascularization treatments. Acceptable evidence suggested similar kidney-related outcomes but better blood pressure outcomes with angioplasty, particularly in patients with bilateral disease. Improvements in kidney function and cure of hypertension were reported among some patients only in cohort studies of angioplasty. Available evidence did not adequately assess adverse events or baseline characteristics that could predict which intervention would result in better outcomes.

**Limitations:** The evidence from direct comparisons of interventions is sparse and inadequate to draw robust conclusions.

**Conclusions:** Available evidence does not clearly support one treatment approach over another for atherosclerotic renal artery stenosis.

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**R**enal artery stenosis is defined as narrowing of the renal artery lumen. Atherosclerosis, which usually involves the ostium and proximal third of the main renal artery and the perirenal aorta, accounts for 90% of cases of renal artery stenosis (1). Atherosclerotic renal artery stenosis is increasingly common in aging populations, particularly elderly people with diabetes, hyperlipidemia, aortoiliac occlusive disease, coronary artery disease, or hypertension. Atherosclerotic renal artery stenosis is a progressive disease that may occur alone or in combination with hypertension and ischemic kidney disease (1). Although the prevalence of atherosclerotic renal artery stenosis is poorly defined, it may vary from 30% among patients with coronary artery disease identified by angiography (2) to 50% among elderly people or those with diffuse atherosclerotic vascular diseases (3). In the United States, 12% to 14% of patients in whom dialysis is initiated have been found to have atherosclerotic renal artery stenosis (4).

Most authorities consider blood pressure control, preservation or salvage of kidney function, and prevention of flash pulmonary edema to be important treatment goals for patients with atherosclerotic renal stenosis. Treatment options include medication alone or revascularization of the stenosed artery or arteries. Combination therapy with multiple antihypertensive agents, often including angiotensin-converting enzyme inhibitors or angiotensin-receptor block-

ers, calcium-channel blockers, and  $\beta$ -blockers, is frequently prescribed. Some clinicians also use statins to decrease low-density lipoprotein cholesterol levels and antiplatelet agents, such as aspirin or clopidogrel, to reduce the risk for thrombosis. The current standard for revascularization in most patients is percutaneous transluminal angioplasty with stent placement across the stenosis. Angioplasty without stent placement is less commonly used. Revascularization by surgical reconstruction is generally done only in patients with complicated renal artery anatomy or in those who require pararenal aortic reconstructions for aortic aneurysms or severe aortoiliac occlusive disease.

The American College of Cardiology and the American Heart Association recently published guidelines for management of patients with peripheral arterial disease,

See also:

## Print

Editors' Notes . . . . . 902

## Web-Only

Appendix Table

CME quiz

Conversion of figure and tables into slides

**Context**

Is medical therapy as effective as revascularization for atherosclerotic renal artery stenosis?

**Contribution**

This systematic review found no trials that compared aggressive medical therapy and angioplasty with stent in adults with atherosclerotic renal artery stenosis. Some evidence suggested similar kidney outcomes but better blood pressure outcomes with angioplasty, particularly in patients with bilateral renal disease. Weak evidence suggested no large differences in mortality or cardiovascular events between medical and revascularization treatments. No evidence directly compared adverse event rates between treatments.

**Implications**

Available evidence comparing benefits and harms of modern treatments for atherosclerotic renal artery stenosis is sparse and inconclusive.

—The Editors

including renal artery stenosis (5, 6). Although these guidelines provide recommendations about which patients should be considered for revascularization, considerable uncertainty remains about which intervention provides the best clinical outcomes. Among patients treated with medical therapy alone, experts are concerned about the risk for deterioration of kidney function and worsening cardiovascular morbidity and mortality. Revascularization procedures may provide immediate improvement in kidney function and blood pressure, but they are invasive interventions that could result in substantial morbidity or death, and because of the risk for restenosis the durability of their benefits is questioned.

Although evidence regarding the optimal management of atherosclerotic renal artery stenosis appears uncertain, a Medicare claims analysis found that the rate of percutaneous renal artery revascularization has rapidly increased between 1996 and 2000, with the number of interventions increasing from 7660 to 18 520 (7). To determine which patients, if any, with atherosclerotic renal artery stenosis would most benefit from angioplasty with stent placement, as opposed to continued aggressive medical treatment, the National Institutes of Health has sponsored the large, multicenter Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial. Participants are currently being enrolled in the trial, and results should be reported in 2010. Meanwhile, the Agency for Healthcare Research and Quality, under Section 1013 of the Medicare Modernization Act, commissioned a review asking key questions related to the effectiveness of aggressive medical therapy compared with renal artery angioplasty with stent placement. However, because no published evidence directly compared angioplasty with stent placement and aggressive

medical treatment with currently available drugs, the review covered direct comparisons of revascularization, including angioplasty with or without stent placement and surgery, and various medical regimens and indirect comparisons of angioplasty (with stent placement) and surgical interventions, various medical therapies, and natural history (8).

**METHODS****Data Sources and Selection**

To identify articles relevant to several key questions, we searched the MEDLINE database from inception to 6 September 2005 for studies involving adults with atherosclerotic renal artery stenosis. The **Figure** shows the search and selection process. The full technical report (available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm)) provides a more detailed description of the study methods. We also reviewed reference lists of related systematic reviews, selected narrative reviews, and primary articles, and we invited domain experts to provide additional citations. We combined search terms for renal artery stenosis, renal hypertension, and renal vascular disease, and we limited the search to English-language articles of studies in adult humans that had relevant research designs. We included peer-reviewed primary studies of adult patients treated for atherosclerotic renal artery stenosis and excluded studies that evaluated patients with renal artery stenosis in the setting of a transplanted kidney, renal artery aneurysm requiring repair, aortic disease requiring invasive intervention, or concurrent cancer or patients who had had previous surgical or angioplasty interventions for renal artery stenosis. We included only studies that reported outcomes of interest (mortality rate, kidney function, blood pressure, and cardiovascular events) at 6 months or more after the initial intervention. We excluded studies in which more than 20% of patients had renal artery stenosis due to other causes. We categorized studies according to whether they evaluated medical treatment, angioplasty, or surgical revascularization or were natural history studies, and by whether they directly compared interventions.

We used different eligibility criteria for studies of different interventions, based on the varying number of studies available for each intervention and the relevance of the intervention to current practice. We included all direct comparisons of medical treatment with angioplasty and all uncontrolled (cohort) studies of medical treatment that had at least 10 patients in each group, regardless of study design. For angioplasty, surgical, or natural history studies, we included only those in which at least some patients were recruited in 1993 or later, after the publication of the Fifth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. These guidelines marked a substantial change from previous guidelines in treatment recommendations for hypertension, including more aggressive blood pressure targets (9). In addition, at



**Table 1. Summary of Reviewed Studies**

Study Type	Intervention	Studies, <i>n</i>	Quality, <i>n</i>			Applicability, <i>n</i>			Participants, <i>n</i>	Years of Intervention
			Good	Fair	Poor	High	Moderate	Low		
Randomized trials	Angioplasty with stent placement versus medical therapy	0								
Randomized trials	Angioplasty without stent placement or combination of angioplasty with and without stent placement versus medical therapy	2*		2			1	1	103	1992–1995‡
Comparison studies†	Revascularization versus medical therapy	8*		2	6	1		7	597	1981–2003‡
Cohort studies	Medical treatment	4		1	3		1	3	83	Not reported
Cohort studies	Natural history	8		3	5		3	5	721	1970–1998‡
Cohort studies	Angioplasty with stent placement	21		10	11	2	14	5	3368	1989–2002‡
Cohort studies	Angioplasty with and without stent placement	4		3	1	1	2	1	427	1993–1999
Cohort studies	Surgical revascularization	4			4			4	921	1980–2004
Studies that reported adverse events		37							5378	

\* One study had both a randomized and nonrandomized component.

† Combination angioplasty and surgery or surgery versus medical therapy (randomized or nonrandomized study), or angioplasty versus medical therapy in a nonrandomized study.

‡ Some studies did not report the intervention years.

## RESULTS

### What Is the Evidence That Medical Therapy Is More or Less Effective than Revascularization (Angioplasty with or without Stents) for Adults with Atherosclerotic Renal Artery Stenosis? What Adverse Events and Complications Have Been Associated with These Treatments?

Available evidence was neither adequate nor sufficiently applicable to current practice to clearly support one treatment approach over another for the general population with atherosclerotic renal artery stenosis. Only 2 randomized trials directly compared angioplasty and medical treatment alone (Table 1). Weak evidence based on few study participants suggested no large differences in mortal-

ity rates or cardiovascular events between patients treated medically only and those receiving angioplasty (Table 2). Randomized, controlled trials; other comparative studies; and cohort studies reported similar overall changes in kidney function after angioplasty as with medical therapy alone. However, improved kidney function over time after the intervention was reported among some patients only in cohort studies of angioplasty. Acceptable evidence showed that combination antihypertensive treatment decreased blood pressure substantively but that angioplasty may result in better blood pressure control, particularly in people with bilateral disease. Cure of hypertension (achievement of blood pressure control without medication) was reported only among several patients treated with angio-

**Table 2. Effects of Renal Artery Revascularization versus Medical Treatment Alone on Clinical Outcomes**

Outcomes	Strength of Evidence	Studies (Participants), <i>n</i>			Conclusions
		Randomized Trials	Other Comparative Studies	Cohort Studies	
Death	Weak	1 (55)	4 (381)	30 (4646)	No large difference in mortality up to about 5 years between revascularization and medical treatment
Kidney function	Acceptable	2 (103)	7 (428)	34 (4916)	No substantial difference in kidney function; improvements in kidney function were reported in cohort studies only among patients receiving revascularization
Blood pressure	Acceptable	2 (103)	8 (597)	34 (4275)	Some evidence that blood pressure may be lowered more after angioplasty than with medical treatment alone, particularly among patients with bilateral disease (range, no difference to 26/10 mm Hg lower after angioplasty); cure of hypertension was reported in cohort studies only among patients receiving revascularization
Cardiovascular events	Weak	1 (55)	1 (52)	3 (560)	No large differences found in comparative studies up to about 4 years
Adverse events	Weak	2 (103)	4 (323)	31 (4906)	Evidence does not support meaningful conclusions about relative adverse events or complications from angioplasty compared with medical treatment

plasty. Available evidence did not adequately assess net harm due to adverse events and complications of medical treatment or angioplasty, but important complications after revascularization occur in a small percentage of patients and all drugs have associated adverse events.

Almost two thirds of the studies that we reviewed were of poor methodologic quality; none was deemed to be of good quality. More than half of the studies had limited applicability to patients commonly seen in practice or to modern management strategies. All studies implicitly or explicitly included only patients with generally stable blood pressure, kidney function, and cardiovascular status. Thus, they were not applicable to patients with acute decompensation due to progressive atherosclerotic renal artery stenosis. No study directly compared angioplasty with stent placement and “aggressive” medical treatment with currently available antihypertensive, antiplatelet, and lipid-lowering agents.

#### **Characteristics of Reviewed Studies**

Overall, we reviewed 55 studies (Table 1). Nine studies (in 11 publications) directly compared medical treatment with revascularization (Table 3) (10–20). Of these, 2 randomized trials compared angioplasty without stent placement with medical treatment (10, 11). A third randomized trial compared angioplasty without stent placement at the start of the trial with angioplasty delayed by 3 months in half of the remaining patients and medical treatment alone in the other patients (12–14). The remaining 7 comparative studies (including 1 of a nonrandomized subgroup from a randomized trial [10]) compared multiple types of revascularization with a variety of medical treatment for a wide range of durations (6 months to 7 years).

Twenty-five prospective cohort studies that each included at least 30 patients who received angioplasty primarily after 1993 reported “long-term” outcomes 6 months or more after angioplasty (21–45). Four cohort studies evaluated angiotensin-converting enzyme inhibitors or “triple therapy” (treatment with 3 classes of antihypertensive agents) (46–49). An additional 8 natural history studies evaluated cohorts of patients who usually received some medical treatment that was not clearly described (18, 50–56). Long-term outcomes of interest were reported for 4 surgical cohorts that each included at least 100 patients who received angioplasty mostly after 1993 (57–60). Thirty-seven studies reported on adverse events (10–14, 16, 17, 21, 22, 24, 25, 27, 29–36, 39–46, 49, 57–65).

#### **Mortality Rate in Studies at Least 6 Months in Duration**

One small randomized, controlled trial of angioplasty versus medical treatment (55 patients) (10), 4 other comparative studies (10, 17–19), and 30 cohort studies of various interventions reported on mortality (18, 22–30, 32–36, 39, 41–44, 47, 49, 51, 52, 55–60). About half of the studies reported mortality data at 2 years or less. Seven

studies (primarily surgical studies) reported mortality data for patients followed for at least 5 years (17, 19, 51, 57–60). Studies were generally too small to detect anything but large differences in mortality rates, and no large differences in mortality rates were found. Mortality rates greater than 40% within 6 years occurred mostly in studies of patients with high-grade stenosis (>75%) or bilateral disease.

#### **Kidney Function Outcomes**

The 2 randomized, controlled trials of angioplasty versus medical treatment (10, 11) and the 7 other studies that directly compared revascularization and medical treatment (10, 12–18, 20) mostly found no clinically or statistically significant differences in kidney-related outcomes. Among 22 cohort studies of angioplasty (18 with stent placement, 4 with or without stent placement), 2 reported statistically significant improvements in kidney function (25, 37), 2 reported statistically significant deterioration (34, 39), and 18 reported no statistically significant changes (21–24, 26–28, 30, 32, 33, 35, 36, 38, 40–42, 44, 45). Within these studies, 8% to 51% of patients were categorized as having improved kidney function and up to 31% had worsened kidney function. Mean changes in kidney function were generally small; the largest improvement found was a mean increase in glomerular filtration rate from baseline (0.9 mL/s [54 mL/min]) of 0.13 mL/s (8 mL/min) over 3 to 23 months (37). Among 3 surgical cohort studies, kidney function improved in 43% of patients in 1 study and worsened in 10% to 28% across the studies (58–60). In comparison, 2 cohort studies of medical treatment (47, 49) and 7 cohort studies of natural history (18, 50–55) reported progressive decreases in kidney function.

#### **Blood Pressure Outcomes**

The 2 randomized trials of angioplasty versus medical treatment (10, 11), the 8 other comparative studies (10, 12–20), all 25 angioplasty cohort studies (21–45), all 4 medical cohort studies (46–49), 3 natural history cohort studies (18, 53, 56), and 2 surgical cohort studies (58, 59) reported blood pressure outcomes. Both trials of angioplasty versus medical treatment and most of the other comparative studies found some evidence of greater improvement in blood pressure after angioplasty than medical treatment. Plouin and colleagues (11) found that both systolic and diastolic blood pressures were reduced by 6 mm Hg more after angioplasty than medical treatment alone, but only the change in diastolic blood pressure was statistically significant. In addition, after angioplasty, patients required almost half as many antihypertensive drugs. Webster and associates (10) found that among patients with bilateral disease, a substantially greater, statistically significant reduction in blood pressure occurred after angioplasty than with medical treatment alone (net decrease, 26/10 mm Hg); however, no statistically significant difference

**Table 3. Direct Comparisons of Angioplasty or Surgery and Medical Treatment for Renal Artery Stenosis\***

Author, Year (Reference)	Study Design	Intervention	Patients with Renal Artery Stenosis (Patients with Atherosclerotic Renal Artery Stenosis), n	Mean Blood Pressure, mm Hg	Mean Glomerular Filtration Rate, mL/s (mL/min)	Mean Serum Creatinine Concentration $\mu\text{mol/L}$ (mg/dL)	Mean Degree of Stenosis (Patients with Bilateral Stenosis), %
<b>Angioplasty versus medical treatment</b>							
Webster et al., 1998 (10)	Randomized trial	Angioplasty, no stent placement	12 (12)	190/99	NR	182 (2.1)	>50 (100)
		2 or 3 agents (atenolol, bedrofluazide, calcium-channel blockers)‡	16 (16)	190/101	NR	148 (1.7)	
		Angioplasty, no stent placement	13 (13)	189/105	NR	138 (1.6)	>50 (0)
		2 or 3 agents (atenolol, bedrofluazide, calcium-channel blockers)‡	14 (14)	182/99	NR	168 (1.9)	
Plouin et al., 1998 (11)	Randomized trial	Angioplasty, with or without stent placement	23 (23)	165/98	1.2 (73)	—	>60 (0)
		Multiple drug regimens	25 (25)	165/96	1.2 (73)	—	
<b>Angioplasty versus medical treatment or delayed angioplasty</b>							
Krijnen et al., 2004 (12); van Jaarsveld et al., 2000 (13, 14)		Angioplasty, no stent placement	56 (56)	179/104	1.1 (67)	—	76 (23)
		Multiple drug regimens (28 patients) or delayed angioplasty (22 patients)	50 (50)	180/103	1.0 (60)	—	72 (22)
<b>Angioplasty versus medical treatment</b>							
Webster et al., 1998 (10)	Nonrandomized, prospective	Angioplasty, no stent placement	28 (28)	196/109	NR	169 (1.9)	>50 (NR)
		2 or 3 agents (bedrofluazide, calcium-channel blocker)	51 (51)	197/103	NR	144 (1.6)	
Taylor et al., 1989 (15)	Nonrandomized, prospective	Angioplasty, no stent placement	5 (NR)	160/96	NR	NR	>60 (NR)
		No revascularization, 0–3 drugs	15 (NR)	174/100	NR	NR	
Englund and Brown, 1991 (16)	Nonrandomized, retrospective	Angioplasty, no stent	21 (Study unclear whether 19, 20, or all 21 patients had atherosclerotic renal artery stenosis)	165/96	NR	341 (3.9)	NR
		Unspecified drugs	17 (17)	185/101	NR	332 (3.8)	NR
Pizzolo et al., 2004 (17)¶	Retrospective	Angioplasty, with or without stent	63 (63)	168/95	NR	129 (1.5)	~88 (30)
		Multiple drug regimens**	37 (37)	159/91	NR	127 (1.4)	~79 (27)
<b>Angioplasty versus surgery or medical treatment</b>							
Pillay et al., 2002 (18)	Nonrandomized, prospective	Various procedures ††	12 (NR)	86 (diastolic)	NR	150 (1.7)	>50 (100)
		Unspecified drugs	21 (NR)	90 (diastolic)	NR	110 (1.2)	
Johansson et al., 1999 (19)	Nonrandomized, prospective	Various procedures‡‡	105 (~91)	179/91	1.0 (61)	—	50 (NR)
		Unspecified drugs	64 (~56)	NR	NR	NR	
<b>Surgery versus medical treatment</b>							
Uzzo et al., 2002 (20)§§	Randomized trial	Surgery	25 (25)	NR	NR	NR	75 (NR)
		Unspecified drugs	27 (27)	NR	NR	NR	

\* NR = not reported; Rx = prescriptions.  
 † Among participants with both unilateral and bilateral renal artery stenosis, congestive heart failure occurred in 9% of those who received angioplasty and 13% of those who received medical treatment alone, and stroke occurred in 4% and 13%, respectively. Myocardial infarction occurred in 4% of patients who received angioplasty and in an unclear proportion of those who received medical treatment alone.  
 ‡ Alternatively, patients received furosemide, methyl dopa, or prazosin. Angiotensin-converting enzyme inhibitors were not allowed.  
 § Target diastolic blood pressure < 95 mm Hg; if necessary, atenolol (50 mg), furosemide (40 mg), or enalapril (10 mg) was used.  
 ¶ Twenty-two of 50 patients assigned to medical therapy received angioplasty at 3 months because of persistent hypertension or deterioration of kidney function. These patients were originally assigned to receive amlodipine, 10 mg (plus atenolol, 50 mg if > 40 years of age), or enalapril, 20 mg (plus hydrochlorothiazide, 25 mg if > 40 years of age), or if neither regimen was tolerated, atenolol, 100 mg (plus hydrochlorothiazide, 25 mg if > 40 years of age).

Table 3—Continued

Location of Stenosis (Percentage of Patients)	Years in Which Patients Were Enrolled	Mean Study Duration (Range)	Results		Study Quality	Applicability of Results
			Blood Pressure	Kidney Function		
Ostial (46)	NR	NR (3–54 months)	Decrease, 34/11 mm Hg	Creatinine increase, 10 $\mu\text{mol/L}$ ; 8% developed "renal failure" <sup>††</sup>	Fair	Moderate
			Decrease, 8/1 mm Hg ( $P < 0.005$ [net]); total Rx change not significant (net)	Creatinine increase, 4 $\mu\text{mol/L}$ ; not significant (net); 7% developed "renal failure" <sup>††</sup>		
Ostial (52)			Decrease, 2/2 mm Hg	Creatinine increase, 8 $\mu\text{mol/L}$		
			Decrease, 10/2 mm Hg (not significant [net]); total Rx change not significant (net)	Creatinine change, 0 $\mu\text{mol/L}$ ; not significant (net)		
Ostial (39)	1992–1999	6 months	Decrease, 14/8 mm Hg; total Rx at end, 1.0	No patient had worsened kidney function; increase in creatinine clearance, 0.06 mL/s	Fair	Low
			Decrease, 7/1 mm Hg ( $P = \text{not significant}/0.04$ [net]); total Rx at end, 1.8 ( $P = 0.009$ [net])	1 of 19 patients had worsened kidney function; increase in creatinine clearance, 0.01 mL/s (not significant [net])		
NR	1993–1998	1 year	Decrease, 19/12 mm Hg; total Rx decrease, 0.8	Worsened in 4%; increase in creatinine clearance, 0.05 mL/s	Moderate	High
			Decrease, 17/7 mm Hg (not significant [net]); total Rx decrease, 0.1 ( $P = 0.10$ [net])	Worsened in 12%; increase in creatinine clearance, 0.03 mL/s (not significant [net])		
Ostial (63)	NR	3–54 months	Decrease, 13/11 mm Hg; total Rx decrease, 0.5 (not significant [net])	Creatinine increase, 13 $\mu\text{mol/L}$	Moderate	Low
			Decrease, 12/6 mm Hg; total Rx increase, 0.3 ( $P = 0.01$ [from baseline])	Creatinine increase, 5 $\mu\text{mol/L}$ (not significant [net])		
NR	NR	6.5 months (1–21 months)	Decrease, 23/6 mm Hg; total Rx decrease, 1; no data on change in blood pressure status	Creatinine decrease, 44 $\mu\text{mol/L}$ (including 7 patients who had surgery)	Poor	Low
		13 months (7–20 months)	Decrease, 24/20 mm Hg; total Rx change, 0; 20% had unchanged blood pressure	Creatinine increase, 88 $\mu\text{mol/L}$ ( $P < 0.01$ [net])		
NR	1981–1988	NR	Decrease, 9/5 mm Hg; total Rx decrease, 1; no patient cured of hypertension	Creatinine increase, 93 $\mu\text{mol/L}$	Poor	Low
NR	NR	16 months (NR)	Decrease, 24/12 mm Hg (not significant [net]); total Rx change, 0 (not significant [net]); no patient cured of hypertension	Creatinine increase, 61 $\mu\text{mol/L}$ (not significant [net])		
NR	1996–2002	28 months (1–60 months)	0% cured of hypertension, 57% improved, 43% unchanged	82% improved, 18% worse	Poor	Low
NR			0% cured of hypertension, 29% improved, 71% unchanged	52% improved, 48% worse		
NR	1994–1998	2.5 years (>2 years)	Decrease, 15 mm Hg; total Rx increase, 0.03	Creatinine increase, 53 $\mu\text{mol/L}$ ( $P = 0.01$ [from baseline]); 1 patient required dialysis	Poor	Low
			Decrease, 6 mm Hg (not significant [net]); total Rx increase, 0.13 (not significant [net])	No creatinine change (not significant [from baseline]); no patient required dialysis		
NR	1983–1984 and 1988–1994	7.1 years (NR)	53% cured of hypertension at 1 year	NR	Poor	Low
			NR	NR		
NR	NR	6.2 years (up to 7 years)	No difference in "blood pressure control" (not significant)	No difference in dialysis-free survival or change in glomerular filtration rate (not significant)	Poor	Low

¶ Entry criteria differed markedly for patients receiving angioplasty and those receiving medical therapy. Patients receiving angioplasty had primary evaluation for resistant hypertension or unexplained azotemia. Patients receiving conservative therapy had angiographic evaluation for other causes, primarily lower-extremity arteriopathy. Endovascular therapy not considered for this latter group.

\*\* Target blood pressure  $\leq 140/90$  mm Hg. The most frequently used classes of drugs were angiotensin-converting enzyme inhibitors (62% of patients), diuretics (62%), calcium antagonists (49%), and  $\beta$ -blockers (30%).

†† Among 12 patients, "9 [had] angioplasties (1 failure) and 1 [had] bilateral stent. 4 kidneys had . . . surgery."

‡‡ Eighty-eight patients had angioplasty and 17 had reconstructive surgery or nephrectomy.

§§ The stopping point (diastolic blood pressure  $> 100$  mm Hg during treatment or worsening kidney function [including need for dialysis] or occurrence of an atherosclerotic cardiovascular event or death) was reached in 68% of patients after surgery and 67% of those receiving medical treatment (not statistically significant).

was found in blood pressure among patients with unilateral disease. Among the cohort studies, medical treatment or natural history (mostly medical treatment alone) resulted in decreases of 20 to 50 mm Hg in systolic blood pressure and 8 to 42 mm Hg in diastolic blood pressure, whereas in studies of angioplasty with stent placement, patients had decreases of 6 to 32 mm Hg in systolic blood pressure and 0 to 17 mm Hg in diastolic blood pressure after revascularization. Almost all studies of angioplasty with stent placement reported that some patients (up to 18%) were cured of hypertension.

### Cardiovascular Outcomes

In a trial of 55 patients randomly assigned to angioplasty without stent or antihypertensive treatment alone, Webster and associates (10) found no differences in event rates for congestive heart failure, stroke, or myocardial infarction across 54 months of follow-up. Similarly, in a trial of 52 patients receiving surgical revascularization or medical treatment alone, near-identical percentages of participants had a stopping point event that included cardiovascular events (20). The reporting of cardiovascular outcomes in cohort studies (47, 56, 58) was inadequate to allow cross-study comparisons. No study of medical interventions reported cardiovascular outcomes.

### Adverse Events and Restenosis Rates

Adverse events were reported in 37 studies, including the 2 randomized trials of angioplasty and medical treatment and 1 retrospective comparative trial (10–14, 16, 17, 21, 22, 24, 25, 27, 29–36, 39–46, 49, 57–65). Rates of adverse events between interventions were not directly compared. Adverse events reported in angioplasty studies included death by 30 days in up to 3% of patients, transient deterioration of kidney function in 1% to 13%, renal artery or parenchymal injury in up to 5%, and periprocedural cardiovascular events in up to 3%. Other adverse events reported were hemorrhage, hematomas, and renal artery occlusion. Seventeen studies of angioplasty with stent placement showed restenosis rates that ranged from 10% to 21% during follow-up of 3 to 40 months (22, 23, 26–31, 33–35, 37–41, 43). Only Ramos and colleagues (37) noted a statistically significantly higher rate of restenosis among patients who had undergone stent placement for ostial lesions compared with those with nonostial lesions (27% vs. 8%). Adverse events related to blood pressure medications (angiotensin-converting enzyme inhibitors,  $\beta$ -blockers, and hydralazine) included orthostatic hypotension, central nervous system symptoms, digestive symptoms, the Raynaud phenomenon, and various other symptoms.

### What Baseline Characteristics, Including Diagnostic Tests, Are Associated with Improved or Worse Outcomes When Treating with Either Medical Therapy Alone or Angioplasty?

The studies of diagnostic tests were inadequate to determine whether any such tests may predict long-term out-

comes or guide best treatment approaches (Table 4). Weak evidence suggests that patients with bilateral disease may preferentially benefit from angioplasty over medical treatment alone. A variety of other clinical factors may be predictive of poorer outcomes with angioplasty or medical treatment alone; however, evidence is insufficient to suggest whether other factors can assist in decisions about preferred treatment.

Webster and associates (10) found different relative effects of angioplasty and medical treatment according to whether patients had unilateral or bilateral disease. Patients with bilateral stenosis had much larger, statistically significant decreases in blood pressure after angioplasty than with medical treatment, in contrast to patients with unilateral stenosis, who had similar changes in blood pressure regardless of the type of intervention (Table 3). The Dutch Renal Artery Stenosis Intervention Cooperative Study, which compared early revascularization with delayed or no revascularization, found a similar difference in diastolic blood pressure reduction but not in creatinine clearance (12–14). A single trial comparing surgical revascularization with medical treatment reported that among patients with an elevated serum creatinine concentration (177 to 354  $\mu\text{mol/L}$  [2 to 4 mg/dL]), those who had surgical procedures were less likely to die or have uncontrollable hypertension than were those treated medically ( $P = 0.01$ ; no other data reported) (20). This was in contrast to their overall finding of no difference in outcomes between interventions. No other associations were reported between baseline factors and relative difference in outcomes based on treatment choice.

Among the reviewed studies, 4 diagnostic tests have been evaluated to determine their value in predicting outcomes in patients with atherosclerotic renal artery stenosis; however, each test was evaluated in only 1 study. The Dutch Renal Artery Stenosis Intervention Cooperative Study found that neither the captopril test nor renography (scintigraphy) predicted kidney function, blood pressure, or dose of antihypertensive drugs after angioplasty or medical treatment (12–14). Two cohort studies disagreed on the predictive value of baseline resistance index greater than 80%. In one study, patients with an elevated resistance index were most likely to benefit in terms of kidney function and blood pressure control after angioplasty with stent placement (44), whereas in another study, patients with an elevated resistance index were more likely to have worsening kidney function and less likely to have improved blood pressure or reduced use of antihypertensive medication after surgery or angioplasty with or without stenting (36). One natural history study reported that nonspiral flow on magnetic resonance angiography predicted statistically significantly worse kidney function outcomes (54).

Acceptable evidence, primarily from cohort studies, showed that poorer kidney function (17, 19, 26, 30, 34–38, 41, 44, 58–60) or concomitant cardiovascular disease (17, 19, 28, 34, 35, 44, 58) predicted higher mortality

**Table 4. Baseline Factors as Predictors of Treatment Outcomes**

Baseline Factor	Treatment	Strength of Evidence	Studies (Participants), n (n)			Conclusions
			Randomized Trials	Other Comparative Studies	Cohort Studies	
Diagnostic tests	Revascularization	Weak		1 (106)	2 (354)	Captopril testing and renography (scintigraphy) did not predict outcomes after angioplasty (1 study); disagreement about whether elevated resistance index predicted outcomes after angioplasty (2 studies)
	Medical treatment	Weak			1 (45)	Nonspiral flow on magnetic resonance angiography predicted progression of kidney function worsening
Bilateral disease (vs. unilateral disease)	Revascularization versus medical treatment	Weak	1 (55)	1 (106)		Greater blood pressure improvement and possibly better kidney function after angioplasty compared with medical treatment, in contrast to patients with unilateral disease
	Revascularization	Weak			7 (1999)	Disagreement about whether patients with bilateral disease had a reduced mortality rate or better kidney and blood pressure outcomes
	Medical treatment	Weak			2 (116)	No difference in kidney outcomes, but higher mortality rate with bilateral disease
Baseline kidney function	Revascularization versus medical treatment	Weak		1 (52)		Among patients with elevated serum creatinine concentrations, surgical revascularization resulted in a lower mortality rate than did medical treatment alone
	Revascularization	Acceptable		2 (269)	12 (2246)	Poorer kidney function predicted a higher mortality rate, poorer clinical outcomes (including cardiovascular events), and poorer blood pressure control after angioplasty; studies disagreed about whether baseline kidney function predicted improvements in kidney function after angioplasty
	Medical treatment	Weak		1 (52)	1 (26)	Poorer kidney function predicted higher mortality and dialysis rates but not changes in blood pressure
Baseline percent stenosis	Revascularization	Weak	1 (55)	2 (185)	2 (471)	Disagreement about whether the percentage of stenosis predicted blood pressure or kidney outcomes after angioplasty
	Medical treatment	Weak	1 (55)	1 (52)	1 (362)	Reduced survival, but no effect on blood pressure or kidney function
Baseline cardiovascular disease	Revascularization	Acceptable		2 (269)	5 (1454)	Patients with cardiovascular disease had increased mortality rates and worse kidney function after angioplasty
	Medical treatment	Weak		2 (269)	1 (362)	Disagreement about whether cardiovascular disease predicts death
Demographic characteristics	Revascularization	Weak	1 (55)	3 (348)	2 (561)	Disagreement about whether outcomes differed by sex or age of patients
	Medical treatment	Weak	1 (55)	3 (348)	1 (362)	Disagreement about whether outcomes differed by sex or age of patients
Stent placement	Revascularization	Weak			2 (269)	No difference in blood pressure and kidney outcomes between patients who had stents placed and those who did not

rates and poorer clinical outcomes among patients who had angioplasty (with or without stent placement). Evidence was weak owing to sparseness of data or disagreement among studies on other baseline factors and outcomes (Table 4), including the presence of bilateral disease among patients having revascularization (25, 27, 34, 37, 39, 40, 45) or among those enrolled in natural history studies (55, 56); the degree of kidney function (20, 51) and cardiovascular disease (17, 19, 52) in patients enrolled in medical treatment studies; and percentage of artery stenosis (17, 19,

28, 34, 35, 44, 52, 58), age, and sex (10, 17, 19, 34, 35, 52), regardless of intervention or type of study.

#### What Treatment Variables Are Associated with Improved or Worse Outcomes of Renal Artery Angioplasty with Stent Placement, Including Periprocedural Medications, Type of Stent, Use of Distal Protection Devices, or Other Adjunct Techniques?

No study that met eligibility criteria reported analyses of whether periprocedural interventions, such as different

drugs or different approaches, affected complications or long-term outcomes in patients undergoing revascularization. Two prospective cohort studies reported no difference in blood pressure and kidney-related outcomes between patients who had stents placed and those who did not (Table 4) (21, 42).

## DISCUSSION

Overall, the evidence is not sufficiently robust to determine the comparative effectiveness of angioplasty (with or without stenting) and medical treatment alone. Only 2 randomized trials with long-term outcomes and a third randomized trial that allowed substantial crossover of treatment after 3 months directly compared angioplasty and medical treatment. However, no randomized trial evaluated angioplasty with stent placement, the revascularization technique that is currently most commonly used. Furthermore, the randomized trials did not evaluate enough patients or did not follow patients for a sufficient duration to allow definitive conclusions to be made about clinical outcomes, such as mortality and cardiovascular or kidney failure events.

Some acceptable evidence from comparison of medical treatment and angioplasty suggested no difference in long-term kidney function but possibly better blood pressure control after angioplasty, an effect that may be limited to patients with bilateral atherosclerotic renal artery stenosis. The evidence regarding other outcomes is weak. Because the reviewed studies did not explicitly address patients with rapid clinical deterioration who may need acute intervention, our conclusions do not apply to this important subset of patients.

Although use of angioplasty to improve blood flow to the kidneys holds appeal, the treatment of atherosclerotic renal artery stenosis is probably considerably more complicated. The challenge lies in the substantial overlap between etiologic factors of aortorenal vascular disease and parenchymal kidney disease. The disease conditions that result in atherosclerotic narrowing of the renal arteries, namely diabetes mellitus, dyslipidemia, and elevated blood pressure, are also independently associated with direct kidney injury. Thus, in many cases, revascularizing the renal artery fails to improve hypertension or kidney function, which may be mediated not only by macrovascular atherosclerotic renal artery stenosis but also by underlying microvascular kidney disease. Further evaluation of the role of atherosclerotic renal artery stenosis in hypertension and kidney dysfunction is needed to determine whether intervention should be directed toward improving kidney perfusion through angioplasty with stent placement or more aggressively targeting the underlying factors of parenchymal kidney disease with combination medical therapy.

The ongoing CORAL trial is enrolling patients with atherosclerotic renal artery stenosis with at least 60% narrowing and systolic hypertension for which they are receiv-

ing 2 or more antihypertensive medications (66). Patients with advanced chronic kidney disease (serum creatinine concentration  $\geq 265 \mu\text{mol/L}$  [ $\geq 3.0 \text{ mg/dL}$ ]), those with very small kidneys, and certain patients with cardiovascular disease are being excluded. This trial, whose results are expected to be reported in 2010, will probably address many of the deficiencies in current evidence about revascularization versus medical treatment alone. It also might provide useful evidence about the value of different diagnostic tests to determine which intervention would be best for individual patients; whether particular baseline characteristics could suggest which intervention would be best; the value of co-interventions at the time of angioplasty; the value of alternative methods of performing angioplasty with stent placement or of using different types of stents; and the effect of different combinations of antihypertensive medications with other interventions, such as lipid-lowering and antiplatelet drugs. However, if no further trials of sufficient size and duration are done, the findings of the CORAL trial may be applied to patients with less or more severe atherosclerotic renal artery stenosis than those included in the trial. This potentially incorrect extrapolation may result in inappropriate treatment of patients, misallocated resources, and worse patient outcomes. Given the limitations in the quality and applicability to current practice of published studies, it is unclear whether the differences between participants in the published studies and those being enrolled in the CORAL trial will help with extrapolation of the results to patients who were not eligible for the CORAL trial.

Another lesson from our review is that researchers should consider how to improve and standardize definitions of atherosclerotic renal artery stenosis and severity of disease. These considerations should be based on how these definitions and classifications might be associated with clinical outcomes. The CORAL trial and other studies of atherosclerotic renal artery stenosis should use the current suggested methods for estimating kidney function, including preferential use of estimated glomerular filtration rate and stage of chronic kidney disease over serum creatinine concentration alone. The community of clinicians and professional organizations involved in performing renal artery angioplasty should also consider how to improve procedural techniques with the goal of improving clinical outcomes. The methods to achieve these goals may require quality improvement and other types of studies.

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**Note:** The full report is available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

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**Appendix Table. Study Quality, Applicability, and Strength of Evidence Ratings**

Rating category quality	Explanation
Good	Studies that have the least bias and results that are considered valid. Studies that mostly adhere to the commonly held concepts of high quality including the following qualities: a formal randomized, controlled design; clear description of the sample, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; < 20% dropout rate; clear reporting of dropouts; and no obvious bias.
Fair	Studies are susceptible to some bias that is not sufficient to invalidate the results. They do not meet all the criteria in the "Good" category because they have some deficiencies, but none likely to cause major bias. The studies may be missing information, making it difficult to assess limitations and potential problems.
Poor	Studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.
<b>Applicability</b>	
High	The sample is representative of the target population and includes at least 30 persons. It should be sufficiently large to cover a range of severity of atherosclerotic renal artery stenosis, including percent stenosis, percentage of patients with bilateral stenosis, blood pressure, and kidney function. The mean values of these variables should be at least broadly similar to the mean for the typical patient receiving treatment for atherosclerotic renal artery stenosis. In addition, the intervention should be applicable to currently used interventions, including angioplasty with stent placement and/or antihypertensive drugs currently in common use.
Moderate	The sample is representative of a relevant subgroup of the target population but not the entire population, or interventions used were similar to those of primary interest to this review (e.g., angioplasty without stent placement). Limitations include such factors as narrow age range, inclusion of patients without atherosclerotic renal artery stenosis, atypically high blood pressure, or serum creatinine concentration.
Low	Sample is representative of a narrow subgroup of patients only, and is of limited applicability to other subgroups (e.g., a study of a surgical intervention or mostly from the early 1980s when angiotensin-converting enzyme inhibitors, calcium antagonists, and beta-blockers were either not or rarely used).
<b>Strength of body of evidence</b>	
Robust	There is a high level of assurance with validity of the results for the question based on at least two high-quality studies with long-term follow-up of a relevant population. There is no important scientific disagreement across studies in the results for the question.
Acceptable	There is a good to moderate level of assurance with validity of the results for the question based on fewer than two high-quality studies or in high-quality studies that lack long-term outcomes of relevant populations. There is little disagreement across studies in the results for the question.
Weak	There is a low level of assurance with validity of results for the question based on either moderate- to poor-quality studies or on studies of a population that may have little direct relevance to the question. There could be disagreement across studies in the results for the question.