Comparative Effectiveness Review

Number 5

Comparative Effectiveness of Management Strategies for Renal Artery Stenosis

This report is based on research conducted by the Tufts-New England Medical Center Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0022). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strengths and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Executive Summary

Background

Renal artery stenosis (RAS) is defined as the narrowing of the lumen of the renal artery. Atherosclerosis accounts for 90 percent of cases of RAS. Atherosclerotic RAS (ARAS) is a progressive disease that may occur alone or in combination with hypertension and ischemic kidney disease. The prevalence of ARAS ranges from 30 percent among patients with coronary artery disease to 50 percent among the elderly and those with diffuse atherosclerotic vascular diseases. In the United States, 12 to 14 percent of new patients entering dialysis programs have been found to have ARAS.

Most authorities consider the goals of therapy to be improvement in uncontrolled hypertension, preservation or salvage of kidney function, and improvement in symptoms and quality of life. Treatment alternatives include medications alone or revascularization of the stenosed renal artery or arteries. Combination therapy with multiple antihypertensive agents, usually including angiotensin converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), calcium channel blockers, and/or beta blockers, is frequently prescribed with a goal of normalizing blood pressure. Some clinicians also recommend statins to lower low density lipoprotein (LDL) cholesterol and antiplatelet agents, such as aspirin or clopidogrel, to reduce 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 employed. Revascularization by surgical reconstruction is generally used only for patients with complicated renal artery anatomy or for patients 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 the management of patients with peripheral arterial disease, including renal artery stenosis. These guidelines provide recommendations about which patients should be considered for revascularization; however, there remains considerable uncertainty on which intervention provides the best clinical outcomes. Among patients treated with medical therapy alone, there is the risk of deterioration of kidney function, with worsening morbidity and mortality. Renal artery revascularization may provide immediate improvement in kidney function and blood pressure; however, as with all invasive interventions, it may result in substantial morbidity and mortality in some patients.

Placement of renal artery stents can resolve dissections, minimize stenosis recoil and restenosis, and correct translesional pressure gradients. The evidence for durability of benefit is unclear; the majority of published studies on stent placement in ARAS had followup duration of less than 2 years. Comparison among studies on the effect of revascularization on hypertension and kidney function is limited because of differences in medical therapy, target blood pressure, and criteria for improvement.

Considerable controversy remains regarding optimal strategies for evaluation and management of patients with ARAS. The evidence supporting benefit of aggressive diagnosis and treatment remains unclear. Meanwhile, a Medicare claims analysis found that the rate of

percutaneous renal artery revascularization rapidly increased from 7,660 interventions in 1996 to 18,520 in 2000.

To determine which patients with ARAS, if any, 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. This trial is currently enrolling subjects and plans to report results in 2010. Meanwhile, the Agency for Healthcare Research and Quality (AHRQ) has commissioned a review of the evidence on the effectiveness of renal artery angioplasty with stent placement vs. aggressive medical therapy. This review was commissioned under Section 1013 of the Medicare Modernization Act, which calls for comparative effectiveness reviews on medications and devices. AHRQ requested that the Tufts-New England Medical Center Evidence-based Practice Center (Tufts-NEMC EPC) conduct a review of the literature on the comparative effectiveness of management strategies for renal artery stenosis.

This report summarizes the evidence evaluating the effect and safety of angioplasty with stent placements and medical therapies in the treatment of ARAS, particularly after long-term followup. The key questions and principal definition of terms were determined with the assistance of a technical expert panel.

Key questions addressed in this report are:

1. For patients with atherosclerotic renal artery stenosis in the modern management era (i.e., since JNC-5 in 1993[a]), what is the evidence on the effects of aggressive medical therapy (i.e., antihypertensive, antiplatelet, and antilipid treatment) compared to renal artery angioplasty with stent placement on long-term clinical outcomes (at least 6 months), including blood pressure control, preservation of kidney function, flash pulmonary edema, other cardiovascular events, and survival?

   1a. What are the patient characteristics, including etiology, predominant clinical presentation, and severity of stenosis, in the studies?

   1b. What adverse events and complications have been associated with aggressive medical therapy or renal artery angioplasty with stent placement?

2. What clinical, imaging, laboratory, and anatomic characteristics are associated with improved or worse outcomes when treating with either aggressive medical therapy alone or renal artery angioplasty with stent placement?

3. 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?

[a] JNC-5 is the 5th Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The JNC-5 guidelines, issued in 1993, marked a substantial change from previous guidelines in treatment recommendations for hypertension, including more aggressive blood pressure targets. The guidelines were issued around the same time that ACE inhibitors began to be used more routinely for patients with severe hypertension.

Conclusions

Key Question 1: Clinical outcomes–Angioplasty with stent vs. aggressive medical therapy

There is no published evidence directly comparing angioplasty with stent placement and "aggressive" medical treatment with currently available drugs for ARAS (Table A**)**. Therefore, this review covers direct comparisons of angioplasty with or without stent and various medical regimens, and indirect comparisons between angioplasty with stent, surgical interventions, various medical therapies, and natural history. All the studies reviewed either implicitly or explicitly included only patients with generally stable blood pressure, kidney function, and cardiovascular status. Patients with acute decompensation due to progressive ARAS were not included. Therefore this review does not pertain to this important class of patients.

Overall, the evidence does not currently support one treatment approach over the other for the general population of people with ARAS (Table B). Notably, almost two-thirds of the studies were of poor methodological quality and more than half were of limited applicability to the population of interest. A very limited evidence base directly compares angioplasty without stent placement and medical treatment. While there was a benefit in blood pressure after angioplasty, particularly in patients with bilateral disease, there was no difference in kidney function outcomes. Possibly there were no differences in mortality and cardiovascular event rates, although studies generally included too few patients and were of too short a duration to make definitive assessments regarding these clinical event outcomes. Comparison of adverse events and complications across the various interventions is difficult. However, it is clear that various complications after revascularization do occur in a small percentage of patients, and each of the antihypertensive drugs has associated adverse events.

Description of reviewed studies

No study directly compared angioplasty with stent placement to aggressive medical therapy (Table A). Two randomized controlled trials directly compared angioplasty without stent placement to medical treatment, with outcomes primarily reported at 6 and 12 months. A third randomized trial compared angioplasty without stent placement at the start of the trial to angioplasty delayed by 3 months in half of the remaining patients and medical treatment alone in the other patients. The remaining seven comparative studies (one of which was a nonrandomized subgroup of one of the randomized trials) compared multiple types of revascularization to a variety of medical treatments for a wide range of durations–from about 6 months to 7 years–in both prospective and retrospective studies.

Hundreds of studies of cohorts of patients receiving angioplasty, both prospective and retrospective, have been published since 1980. Of these, the 25 prospective studies that analyzed at least 30 patients who received angioplasty mostly after 1993 and reported long-term ($\geq$ 6 months) outcomes of interest were reviewed. Few studies specifically evaluated the effect of medical treatments that are currently common in patients with ARAS. Only four cohort studies evaluated ACE inhibitors or "triple therapy," treatment with three classes of antihypertensive agents. An additional eight natural history studies evaluated cohorts of patients who mostly received medical treatment (although for the most part this is not clear). Four surgical cohorts

analyzed at least 100 patients who received angioplasty mostly after 1993 and reported long-term outcomes of interest. Thirty-seven of these studies reported on adverse events.

Mortality (study duration 6 months or greater, Table B)

One small randomized controlled trial of angioplasty (without stent) vs. medical treatment, 3 other comparative studies, and 31 cohort studies of various interventions reported mortality data. Although studies were generally too small to detect any but large differences in mortality rates, no differences in mortality were found between interventions, up to about 5 years. Very high mortality rates, over 40 percent within 6 years, occurred mostly in studies of patients with either high-grade stenosis (>75 percent) or bilateral disease.

Weak evidence suggests no difference in mortality rates with medical treatment alone or with angioplasty.

Kidney function (Table B)

The two randomized controlled trials of angioplasty vs. medical treatment and the seven other studies with direct comparisons between revascularization and medical treatment mostly found no clinical or statistically significant differences in kidney outcomes. Among 17 cohort studies of angioplasty with stent, improved kidney function ranged from 8 to 51 percent. There were small to modest changes in creatinine clearance (–2 to +8 mL/min) or serum creatinine (–0.1 to +0.2 mg/dL). Only a single cohort study of medical treatment reported change in serum creatinine over an average of 1.5 years, an increase of 0.3 mg/dL. Seven natural history studies found similar increases in serum creatinine or progressive decreases in kidney function.

Overall, cohort studies of angioplasty with stent placement found changes in kidney function similar to those found in the medical and natural history studies. However, only in the studies of angioplasty with stent placement were some patients reported to have improved kidney function. This implies that, at least in a subset of patients with ARAS, kidney function is more likely to improve after angioplasty with stent placement than with continued medical treatment.

There is acceptable evidence that overall there is no difference in kidney outcomes between patients treated medically only and those receiving angioplasty. However, improvements in kidney function were reported only among patients receiving angioplasty.

Blood pressure control (Table B)

Two trials of angioplasty vs. medical treatment, 7 other comparative studies, all 25 angioplasty studies, all 4 medical studies, 2 natural history studies, and 2 surgical cohort studies reported blood pressure outcomes. Both trials and most of the other comparative studies found some evidence of greater blood pressure improvement after angioplasty than with medical treatment, although the benefit of angioplasty may be limited to patients with bilateral disease. The cohort studies generally found better blood pressure control among patients treated medically alone than among those who received revascularization. However, almost all cohort studies of angioplasty with stent placement reported that some--up to 18 percent of patients--were cured of hypertension (generally defined as maintaining blood pressure control without medication).

Across all studies of angioplasty with stent placement, blood pressure fell after revascularization between 6-32/0-17 mm Hg. Among the medical and natural history studies, blood pressure generally decreased by 20-50/8-42 mm Hg with combinations of multiple antihypertensive drugs. It is not possible to draw conclusions about the relative effect of the different interventions on blood pressure measurements.

There is acceptable evidence that combination antihypertensive treatment results in large decreases in blood pressure. There is also acceptable evidence that angioplasty is more likely than medical treatment alone to result in better blood pressure control, including cure of hypertension.

Cardiovascular outcomes (Table B)

One trial of angioplasty vs. medical treatment and a comparative study of surgery and medical treatment reported cardiovascular outcomes. In the angioplasty trial, no differences were found in event rates for congestive heart failure, stroke, or myocardial infarction, regardless of intervention, for up to 54 months of followup. In the surgery trial, near-identical rates of a combined outcome of atherosclerotic cardiovascular event, death, diastolic hypertension, or worsening kidney function were found for surgery and medical treatment. The reporting of cardiovascular outcomes in cohort studies was inadequate to allow cross-study comparisons. No study of medical interventions reported cardiovascular outcomes.

There is weak evidence suggesting similar rates of cardiovascular events between interventions; however, it is likely that the studies were too small to detect different rates of cardiovascular events.

Restenosis rate (after angioplasty with stent placement only)

A total of 17 studies of angioplasty with stent placement evaluated restenosis rates during followup of 3 to 40 months; rates ranged from 10 to 21 percent. Only one study noted a statistically significantly higher rate of restenosis among those who had undergone stent placement for ostial lesions compared to those with nonostial lesions.

Adverse events (including 30-day mortality, Table B)

Adverse events were reported in 37 studies, including both angioplasty trials and one retrospective comparative trial. No direct comparisons were made of differences in adverse event rates between interventions. Adverse events reported in 16 angioplasty studies included 30-day mortality in up to 3 percent of patients, transient deterioration of kidney function in 1 to 13 percent, renal artery or parenchymal injury in up to 5 percent, and periprocedural cardiovascular events in up to 3 percent. Other adverse events reported included hemorrhage and hematomas, and renal artery occlusion. Medical studies did not report mortality within 30 days of being followed. Adverse events related to blood pressure medications (ACE inhibitors, beta blockers, and hydralazine) included orthostatic hypotension, central nervous system symptoms, digestive symptoms, Raynaud's phenomenon, and others.

The evidence does not adequately assess the net harms due to adverse events and complications of medical treatment or angioplasty.

Key Question 2: Baseline predictors of outcomes (Table B)

Among the studies reviewed, the value of diagnostic tests either for predicting long-term outcomes or for helping determine the best treatment is unclear. A variety of indicators of the severity of ARAS and of health problems, such as poorer kidney function, worse blood pressure, and coexisting cardiovascular disease, predict poorer outcomes in patients with ARAS. The reviewed studies did not report any indicators that may predict improved outcomes.

Randomized controlled trials of angioplasty vs. medical treatment

Neither trial directly analyzed whether any baseline predictors, including diagnostic tests, would predict relative outcomes between interventions. However, in one trial patients with bilateral stenosis had larger decreases in blood pressure after angioplasty than with medical treatment, in contrast to patients with unilateral disease.

Other direct comparisons

Another randomized trial, comparing early vs. either delayed or no revascularization, found that in contrast to patients with unilateral disease, patients with bilateral disease had better improvement in diastolic blood pressure, but not in creatinine clearance. Captopril test, renogram, recent hypertension, and stenosis >80 percent were not predictors of either worse outcome overall or of which intervention would result in better outcomes.

Angioplasty and comparative studies that combined interventions for analyses

Worse baseline kidney function was associated with increased mortality, poor clinical outcomes, and relatively worse blood pressure after revascularization. A history or markers of some cardiovascular diseases were associated with increased mortality, poor clinical outcomes, and relatively worse kidney function after revascularization.

Age and beta blocker or diuretic use at baseline were not significant predictors of mortality or other clinical outcomes. Baseline captopril test, renogram, arterial norepinephrine, and ACE genotype were generally not associated with outcomes. The association between baseline predictors and outcomes was uncertain for several factors, including baseline kidney function as a predictor of followup kidney function, baseline cardiovascular disease as a predictor of blood pressure effect, percent stenosis before angioplasty, bilateral vs. unilateral ARAS, and sex.

Cross-study (indirect) comparisons

No conclusions could be reached from noncomparative studies regarding which patients might have better outcomes with or without revascularization.

Natural history studies

Associations between baseline variables and outcomes in natural history studies are generally weak, since each association was analyzed by one or two studies only. Among the studies, worse kidney function, higher grade stenosis, various markers of cardiac disease, and older age were

associated with higher mortality or dialysis. Patients with nonspiral blood flow in the renal arteries had significant progression in kidney impairment, while those with spiral flow did not.

Key Question 3: Treatment variables as predictors of outcomes after angioplasty (Table B)

Two prospective cohort studies found no difference in blood pressure and kidney outcomes between patients who had stents placed and those who did not. However, no study that met eligibility criteria reported analyses of whether other periprocedural interventions, such as different drugs or different approaches, affected either complications or long-term outcomes.

Populations studied compared to the ongoing CORAL trial

The CORAL trial is enrolling patients with ARAS ≥ 60 percent and systolic hypertension who are on two or more antihypertensive medications. Those with advanced chronic kidney disease (serum creatinine ≥ 3.0 mg/dL) or very small kidneys (<7 cm), as well as certain patients with cardiovascular disease, are being excluded. The two published randomized controlled trials that compare angioplasty to medical treatment alone used somewhat different eligibility criteria, suggesting that patients with a different severity of ARAS are being enrolled in CORAL. One trial used similar criteria for percent stenosis, but only in patients with unilateral disease; blood pressure and kidney function criteria were narrower, indicating that, on average, hypertension and kidney disease were less severe. The other trial included patients with lower grade stenosis (>50 percent) but did not exclude patients with more severe hypertension and included patients with more severe kidney disease. Among the remaining studies that compared revascularization to medical treatment and the noncomparative cohort studies, there were a wide range of eligibility criteria, such that patients with stenosis as low as 50 percent were commonly included, and patients with either more or less severe blood pressure and kidney function than those in the CORAL trial were often included. Across studies, there was no clear evidence that differences in eligibility criteria were predictive of outcomes–except possibly that patients with bilateral disease had greater improvement after angioplasty compared to those with unilateral disease. It was evident, by comparing mortality rates or change in kidney function across studies, that the severity of disease of enrolled patients differed among studies, although, eligibility criteria, including percent stenosis, blood pressure, kidney function, and others, were not clearly associated with overall outcomes. Furthermore, the evidence does not adequately address how differences in eligibility criteria may affect the comparison between angioplasty and medical treatment.

Remaining Issues

In comparison with the CORAL trial, for which patients are currently being enrolled, the two published randomized controlled trials comparing angioplasty to medical treatment alone differed either in whether patients with bilateral disease were included or the severity of hypertension and kidney disease allowed. Other studies also varied widely in their eligibility criteria. Combining the criteria, studies could not be classified adequately based on their severity

of ARAS. Overall, with the possible exception of inclusion of patients with bilateral or unilateral disease, the eligibility criteria (or the severity of disease) of the published studies were not predictive of outcomes in a manner that would be applicable to patients who are not being enrolled in the CORAL trial.

There are additional topics of interest that the CORAL trial may be able to evaluate, primarily through post hoc analyses, but that may require additional studies to address adequately. These include the value of different diagnostic tests to determine which intervention would be best for individual patients; other baseline characteristics as predictors of relative outcomes; the value of cointerventions at the time of angioplasty, alternative methods of performing angioplasty with stent placement, or alternative types of stents; and the effect of different combinations of antihypertensive medications with other interventions such as lipid lowering and antiplatelet drugs.

The challenge of treating ARAS to achieve the targeted outcomes of improved blood pressure control and preservation of kidney function lies in the significant overlap between etiologic factors of aortorenal vascular disease and parenchymal kidney disease. While diabetes mellitus, dyslipidemia, and elevated blood pressure are associated with atherosclerotic narrowing of the renal arteries and consequent worsening of blood pressure and kidney function, they are independently associated with direct kidney injury. In a great many cases, overcoming the renal artery lesion fails to improve hypertension or kidney function, which may be mediated not only by ARAS but also by underlying kidney disease. Systematically evaluating the role of ARAS in hypertension and kidney dysfunction will assist in determining 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.

Additional randomized controlled trials would be required to address the issues that will not be covered by the CORAL trial. Without such trials, there is the risk that the findings of the CORAL trial will be broadened to be considered applicable to patients with less or more severe ARAS than those patients included in the CORAL trial.

In addition, the ARAS research community should consider how to improve and/or standardize definitions of ARAS and severity of disease. These considerations should be based on how these definitions and the disease severity scale would correlate with clinical outcomes. The CORAL trial and other studies of ARAS should use the current suggested methods for estimating kidney function, including preferential use of estimated glomerular filtration rate (GFR) over serum creatinine, and stage of chronic kidney disease. The community of clinicians and professional organizations involved in performing renal artery angioplasty should consider how to improve procedural techniques and minimize variations in techniques and clinical outcomes across the clinicians performing the interventions, as clinically warranted. This may require quality improvement and other types of studies.

As the reviewed studies did not explicitly address the population of patients who may need acute intervention because of rapid clinical deterioration, the conclusions of this review do not apply to these patients.

Table A. Summary of Reviewed Studies

Study type and intervention	No. of studies	Quality			Applicability			No. of subjects	Intervention years
		Good	Fair	Poor	High	Moderate	Low		
Randomized trial of angioplasty with stent vs. medical therapy	0							--	--
Randomized trial of angioplasty without stent or combination of angioplasty with and without stent vs. medical therapy	[2]2		2			1	1	103	1992-95 and no data [3]
Comparison studies of revascularization vs. medical therapy [1]	[2]8		2	6	1		7	597	1981-2003 and no data[3]
Cohort studies of medical treatment	4		1	3		1	3	83	No data
Cohort studies of natural history	8		3	5		3	5	721	1970-98 and no data[3]
Cohort studies of angioplasty with stent only	21		10	11	2	14	5	3,368	1989-2002 and no data[3]
Cohort studies including angioplasty with and without stent	4		3	1	1	2	1	427	1993-99
Cohort studies of surgical revascularization	4			4			4	921	1980-2004
Studies that reported adverse events	37							5,378	1980-2005 and no data[3]

[1] Combination angioplasty and surgery or surgery vs. medical therapy, either randomized or nonrandomized, or angioplasty vs. medical therapy in a non-randomized study.
[2] One study had both a randomized and nonrandomized component.
[3] Some studies did not report the intervention years.

Table B. Summary of Comparative Data in Treatments of Renal Artery Stenosis

Key Questions	Strength of evidence	Summary/conclusion/comments
Key Question 1: Comparisons		
Angioplasty with or without stent vs. medical treatment	N/A	• 2 RCTs evaluated long-term outcomes comparing angioplasty without stent placement to various medical treatments; 6 nonrandomized prospective or retrospective studies compared angioplasty (with or without stent) or surgical revascularization to various medical treatments. • 20 prospective cohorts that met criteria evaluated angioplasty with stent placement; 4 cohort studies evaluated angioplasty with or without stents. • Studies that compared stent placement to no stent placement found no difference in outcomes. • 3 cohort studies evaluated different antihypertensive medical treatments; no studies evaluated anti-hyperlipidemia or lipid-lowering drugs; 8 cohort studies evaluated the natural history of patients with RAS, on various management regimens.
Mortality	Weak	• 1 RCT, 3 nonrandomized comparative studies, and 31 cohort studies of various interventions suggest no difference in mortality up to about 5 years between revascularization and medical treatment.

Key Questions	Strength of evidence	Summary/conclusion/comments
Kidney function	Acceptable	• 2 RCTs found no difference in kidney outcomes, mostly at 6 and 12 months. • Among 7 other comparative studies, most found no difference in kidney outcomes, although 2 found some supporting evidence for better kidney function after angioplasty (with or without stent). • The cohort studies mostly support the conclusion that kidney outcomes are similar with either angioplasty or medical treatment, although improvements in kidney function were reported only among the angioplasty cohort studies.
Blood pressure	Acceptable	• The 2 RCTs both found some evidence of greater blood pressure improvement after angioplasty than with medical treatment, although this relative effect may be limited to patients with bilateral disease. • Most other comparative studies found larger blood pressure reductions among patients having revascularization than medical treatment alone, although the difference was often clinically small and statistically nonsignificant. However, 2 studies found larger reductions in blood pressure among patients treated without revascularization, although the differences were not statistically significant. • Among cohort studies, larger reductions in blood pressure were found among medical treatment or natural history studies than in angioplasty studies, although the effect of pre-angioplasty antihypertensive medication use cannot be corrected for. Only in cohort studies of angioplasty were patients cured of hypertension, no longer requiring medication to maintain normal blood pressure.
Cardiovascular	Weak	• 1 RCT found similar rates of cardiovascular events at 3 to 54 months of followup after angioplasty or with continued medical treatment. • Reporting of cardiovascular outcomes was too sparse among studies to make meaningful indirect comparisons.
Adverse events	N/A	• The evidence does not support meaningful conclusions about relative adverse events or complications from angioplasty compared to medical treatment.
Key Question 2: Baseline predictors of outcomes		
Angioplasty with or without stent vs. medical treatment	Weak	• In one RCT, patients with bilateral disease had larger decreases in blood pressure after angioplasty compared with medical treatment, in contrast to patients with unilateral disease.
Angioplasty	N/A	• 5 comparative studies and 15 cohort studies analyzed baseline variables as possible predictors of outcomes. Most of the comparative studies, however, did not distinguish between interventions in these analyses.

Baseline kidney function	Acceptable	o	The 10 studies that evaluated baseline kidney function generally found that poorer kidney function (with a wide range of definitions) predicted higher mortality, poorer clinical outcomes including cardiovascular events, and/or poorer blood pressure control. However, among 4 studies, 2 found that kidney function after angioplasty improved more among patients with worse baseline kidney function, 1 found no difference in effect among patients with different baseline kidney function, and 1 found less improvement in kidney function among patients with worse baseline kidney function.
Key Questions	**Strength of evidence**		**Summary/conclusion/comments**
Baseline RAS severity	Weak	•	4 studies evaluated baseline percent stenosis. The studies were heterogeneous in their analyses and their conclusions. 1 found a borderline increase in mortality among patients with >70% stenosis. 1 found that higher percent stenosis was associated with higher blood pressure after revascularization. 1 found no association with either kidney function or diastolic blood pressure. 1 found that patients with higher grade stenosis had greater benefits in their kidney function than patients with lower grade stenosis.
		•	11 studies evaluated whether bilateral vs. unilateral RAS was a predictor of outcomes. The studies were heterogeneous in their analyses and their conclusions. 2 found bilateral disease was associated with increased mortality, but 2 found no association (although 1 of these did find an association with a combined poor clinical outcome). Among 7 studies, most found no association with either change in kidney function or blood pressure, but 2 found that patients with bilateral disease had better improvement in blood pressure, and 1 found better improvement in kidney function than patients with unilateral disease.
Baseline cardiovascular disease	Acceptable	•	Among 6 studies, a range of cardiovascular measures, including history of disease, were found to be associated with increased risk of death, new cardiovascular events, or decreased likelihood of improvement in kidney function after revascularization. 2 studies, though, found that some baseline cardiovascular factors, including history of myocardial infarction, CHF, or hyperlipidemia, or reduced ejection fraction, did not predict increased mortality.
Diagnostic tests	Weak	•	3 diagnostic tests were evaluated by 4 studies. The captopril test, renogram, and unilateral renin secretion were not associated with differential outcomes in blood pressure, kidney function, or mortality. 2 studies evaluated a resistance index of over 80%; 1 found that these patients had worse kidney and blood pressure outcomes and 1 found that they had better changes in both kidney function and blood pressure levels.
Demographics	Weak	•	Among 5 studies evaluating age, 1 found that older patients had higher followup blood pressure, 1 that they had lower followup blood pressure, and 3 found that after adjustment for other predictors, age was not associated with poor clinical outcomes.
		•	Among 3 studies evaluating sex, 2 found that men had worse outcomes than women, but 1 found no difference after adjustment for other predictors.
Medical treatment	N/A	•	No study evaluated potential predictors of outcomes.
Natural history	N/A	•	4 natural history studies examined various predictors, 2 of which performed multivariate analyses.
Baseline	Weak	•	1 study found that lower baseline GFR was independently associated

kidney function			with higher mortality or dialysis.
Baseline RAS severity	Weak	o	2 studies found that higher grade stenosis was independently associated with higher mortality (1 by multivariate, 1 univariate analysis); 1 study found that bilateral disease was not associated with kidney disease prognosis.
Baseline cardiovascular disease	Weak	•	1 study found that various markers of cardiac disease predicted mortality in patients with coronary artery disease and RAS.
Key Questions	**Strength of evidence**		**Summary/conclusion/comments**
Diagnostic tests	Weak	•	1 study found that patients with nonspiral blood flow in the renal arteries had significant progression in kidney impairment, while those with spiral flow did not.
Demographics	Weak	•	1 study found that older age predicted mortality in patients with coronary artery disease and RAS.
Key Question 3: Effect of periprocedural interventions on outcomes			
Angioplasty with or without stent	Weak	•	2 studies found no difference in blood pressure and kidney outcomes between patients who had stents placed and those who did not.
Other interventions	N/A	•	No study that met eligibility criteria reported analyses of whether other periprocedural interventions, such as different drugs or different approaches, affected either complications or long-term outcomes.

Abbreviations: CHF = congestive heart failure; GFR = glomerular filtration rate (or creatinine clearance); N/A = not applicable; RAS = renal artery stenosis; RCT = randomized controlled trial.

Chapter 1. Introduction

Background

Renal artery stenosis (RAS) is defined as the narrowing of the lumen of the renal artery. Atherosclerosis accounts for 90 percent of cases of RAS and usually involves the ostium and proximal third of the main renal artery and the perirenal aorta.[1] RAS is becoming increasingly common because of atherosclerosis in an aging population; in addition, there is an increased prevalence of atherosclerotic RAS (ARAS) among elderly with diabetes, hyperlipidemia, aortoiliac occlusive disease, coronary artery disease, and hypertension. ARAS is a progressive disease that may occur alone or in combination with hypertension and ischemic kidney disease.[1] The prevalence of ARAS in the general population remains poorly defined, although the prevalence may vary from 30 percent among patients with coronary artery disease (CAD) identified by angiography[2] to 50 percent among elderly or those with diffuse atherosclerotic vascular diseases.[3] In the United States 12 to 14 percent of new patients entering dialysis programs have been found to have ARAS.[4]

Optimal strategies for evaluating patients suspected of having RAS remain unclear. Patients with moderate to high risk atherovascular diseases who present with uncontrolled hypertension or unexplained abnormal kidney function tests are generally evaluated for RAS.[1,5,6] A reduction in estimated glomerular filtration rate (GFR) of at least 30 percent from baseline following angiotensin converting enzyme (ACE) inhibitor or angiotensin-receptor blockers (ARB) therapy is a clinical clue suggestive of RAS.[7] A variety of physiological studies to assess the renin-angiotensin system and perfusion studies to assess renal blood flow are available. However, the clinical clues can be nonspecific and physiologic studies have limited usefulness in ARAS, especially, among the elderly. The initial evaluation relies on imaging techniques such as duplex ultrasonography, magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and radionuclide renal scanning. The success rates of these noninvasive imaging techniques depend on operator's experience, body habitus, the presence of bowel gas, and may be less reliable visualizing distal segments of renal arteries. Currently, catheter angiography remains the reference standard for the evaluation of the degree of stenosis in RAS.

Most authorities consider the goals of therapy to be improvement in uncontrolled hypertension, preservation or salvage of kidney function, and improvement in symptoms and quality of life. Treatment alternatives include medications alone or revascularization of the stenosed renal artery or arteries. Combination therapy with multiple antihypertensive agents, usually including ACE inhibitors or ARBs, calcium channel blockers, and or beta blockers, are frequently prescribed with a goal of normalizing blood pressure. Some clinicians also recommend statins to lower low density lipoprotein (LDL) cholesterol and antiplatelet agents, such as aspirin or clopidogrel, to reduce 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 employed. Revascularization by surgical reconstruction is generally used for only patients with complicated renal artery anatomy or for patients 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 the management of patients with peripheral arterial disease, including RAS.[8,9] These guidelines provide recommendations about which patients should be considered for revascularization; however, there remains considerable uncertainty on which intervention provides the best clinical outcomes. Among patients treated with medical therapy alone, there is the risk for deterioration of kidney function with worsening morbidity and mortality. Renal artery revascularization may provide immediate improvement in kidney function and blood pressure; however, as with all invasive interventions, it may result in substantial morbidity and mortality in some patients.

ACE inhibitors and ARBs are effective in controlling renovascular hypertension in 86 to 92 percent of these patients, but the loss of kidney function due to reduction in transcapillary filtration pressure can result in acute or chronic kidney disease.[1] Indications and timing of revascularization for ARAS are topics of considerable debate. The American Heart Association lists three clinical criteria for revascularization: 1) hypertension (accelerated, refractory, or malignant), 2) renal salvage, and 3) cardiac disturbance syndromes (recurrent "flash" pulmonary edema or unstable angina with significant RAS).[10] This must be weighed against the morbidity and mortality risks of revascularization.

Placement of renal artery stents can resolve dissections, minimize stenosis recoil and restenosis, and correct translesional pressure gradients. The evidence for durability of benefit is unclear; the majority of the published studies on stent placement in ARAS had followup duration of less than two years. Comparison among studies on the effect of revascularization on hypertension and kidney function is limited because of differences in medical therapy, target blood pressure, and criteria for improvement.[1] The American College of Cardiology and the American Heart Association recently published guidelines for the management of patients with peripheral arterial disease, including renal artery stenosis.[8,9] Nevertheless, considerable controversy remains regarding optimal strategies for evaluation and management of patients with ARAS; the evidence supporting a benefit of aggressive treatment remains unclear.

Meanwhile, a Medicare claims analysis found that the rate of percutaneous renal artery revascularization has rapidly increased between 1996 and 2000 with the number of renal artery interventions increasing from 7,660 to 18,520. However, there is marked disparity in use across geographical regions.[11] Therefore, the Agency for Healthcare Research and Quality (AHRQ) is commissioning an expedited review of the evidence on the effectiveness of renal artery angioplasty with stent placement versus aggressive medical therapy. This review was commissioned under Section 1013 of the Medicare Modernization Act, that instructs to conduct comparative-effectiveness reviews on medications and devices. AHRQ has requested the Tufts-New England Medical Center Evidence-based Practice Center (Tufts-NEMC EPC) to conduct a review of the literature on the Comparative Effectiveness of Management Strategies for Renal Artery Stenosis.

Scope and Key Questions

This report summarizes the evidence evaluating the effect and safety of angioplasty (with or without stents, or surgical revascularization) and medical treatments in the treatment of ARAS, particularly after long-term followup. Key questions addressed in this report are:

1. For patients with atherosclerotic renal artery stenosis in the modern management era (i.e., since JNC-5 in 1993*), what is the evidence on the effects of aggressive medical therapy (i.e., antihypertensive, antiplatelet, and antilipid treatment) compared to renal artery angioplasty with stent placement on long-term clinical outcomes (at least 6 months) including blood pressure control, preservation of kidney function, flash pulmonary edema, other cardiovascular events, and survival?

   1a. What are the patient characteristics, including etiology, predominant clinical presentation, and severity of stenosis, in the studies?

   1b. What adverse events and complications have been associated with aggressive medical therapy or renal artery angioplasty with stent placement?

2. What clinical, imaging, laboratory and anatomic characteristics are associated with improved or worse outcomes when treating with either aggressive medical therapy alone or renal artery angioplasty with stent placement?

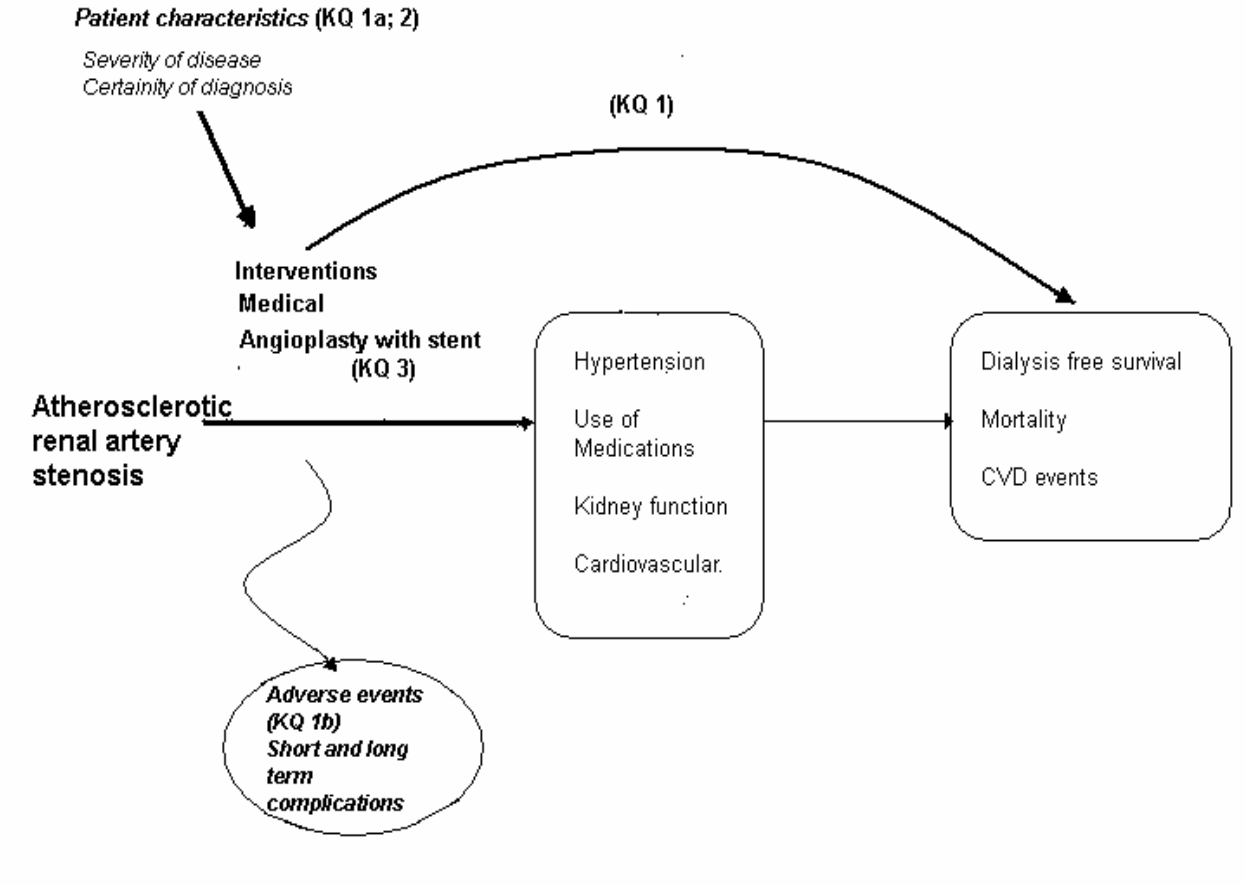
3. What treatment variables are associated with improved or worse outcomes of renal artery angioplasty with stent placement, including periprocedural medications, type of stent, use of distal protection devices, or other adjunct techniques?

*5th Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (1993). These guidelines marked a substantial change from previous guidelines in treatment recommendations for hypertension, including more aggressive blood pressure targets. This time point also marks when ACE inhibitors began to be used more routinely for patients with severe hypertension.

Analytic Framework

We applied the analytic framework depicted in Figure 1 to answer the key questions in the evaluation of the treatment modalities for ARAS. This framework addressed relevant clinical outcomes. It also examined clinical predictors that affected treatment outcomes. While evidence from high quality randomized controlled trials was preferred, these data were rare, so nonrandomized and uncontrolled studies were used to augment the evidence.

Figure 1. Analytic framework for evaluating the effectiveness and safety of treatments for renal artery stenosis.



Arrows depict studies sought to address key questions formulated in this report
Abbreviation: KQ, key question.

Types of Participants

The population of interest for this report is adults with ARAS that is of sufficient severity to warrant aggressive management, either due to resistant hypertension, evidence of kidney damage, or the high likelihood of poor outcomes. Because of the variety of techniques used to diagnose and define RAS, the definitions used by study authors were accepted. Where possible this review is limited to studies of patients with a high proportion of ARAS (as opposed to fibromuscular dysplasia and other diseases). In addition, only studies of revascularization where the large majority of patients had only procedures to correct ARAS (as opposed to aortic disease or renal artery aneurysm) were included.

Types of Interventions

The primary interventions of interest are angioplasty with stent placement and aggressive medical treatment, as defined in the key questions. However, given the state of the evidence, this review also covers angioplasty without stent placement, surgical revascularization, any medical

treatment, and so-called "natural history" studies where a variety of generally undefined strategies are employed.

Types of Outcome Measures

The primary outcomes of interest include long-term (6 months or more) mortality, kidney function, hypertension, cardiovascular disease, and related outcomes, in addition to adverse events and complications (including 30-day mortality).

Types of Studies

The ideal study to answer the key questions would be a randomized controlled trial directly comparing the primary interventions of interest. However, given the paucity of randomized trials and of nonrandomized comparative studies, this review evaluates studies of cohorts of patients who received one treatment (or one set of treatments) without a control group. In addition, because of continued changes in management of hypertension and of RAS over the past 20 years or more, older noncomparative studies of patients enrolled prior to the publication of JNC-5 (as described above and in the Methods section) in 1993 were not reviewed.

CORAL Trial

A randomized, multicenter clinical trial sponsored by National Institutes of Health (NIH), the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial contrasts the effect of renal artery stent placement with optimum medical therapy (including antihypertensive drugs, a statin, and aspirin) and clopidogrel (an antiplatelet agent) to optimum medical therapy alone in patients with hemodynamically significant ARAS and systolic hypertension.[12]

The first line antihypertensive treatment will be either an ARB (candesartan) alone or with hydrochlorothiazide. Study eligibility criteria continue to evolve. The latest agreed upon criteria (Rundback JH. Personal communication, Jun 4, 2006) include adults with ARAS ≥ 60 percent and systolic hypertension on two or more antihypertensive medications. Those with high stage kidney disease (serum creatinine ≥ 3.0 mg/dL) at enrollment, very small kidneys (<7 cm), as well as certain patients with cardiovascular disease are being excluded. Other eligibility criteria apply.

The trial started in April 2004 and plans to follow approximately 2,200 North American patients at up to 100 clinical sites for the occurrence of a composite cardiovascular and kidney endpoint, including cardiovascular or kidney-related death, myocardial infarction, hospitalization for congestive heart failure, stroke, doubling of serum creatinine level, and need for renal replacement therapy. The study is expected to last about 3 to 5.5 years. This study is to be completed in 2010 and no results are available at this time.

Chapter 2. Methods

Technical Expert Panel

This report on the comparison of aggressive medical therapy to angioplasty with stenting for the management of atherosclerotic renal artery stenosis (ARAS) is based on a systematic review of the literature. The Tufts-NEMC EPC held teleconferences with a Technical Expert Panel (TEP) formed for this project. The TEP served in an advisory capacity for this report, helping to refine key questions, identify important issues, and define parameters for the review of evidence. The TEP included nephrologists, a vascular surgeon, an interventional radiologist, and the task order officer from AHRQ.

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the key questions. We searched MEDLINE® (1966-September 6, 2005) for English language studies of adult humans to identify articles relevant to each key question. We also reviewed reference lists of related systematic reviews and selected narrative reviews and primary articles. In electronic searches, we combined terms for renal artery stenosis (RAS), renal hypertension, and renal vascular disease, limited to adult humans, and relevant research designs (see Appendix A for complete search strategy). We invited TEP members to provide additional citations. We did not search systematically for unpublished data.

Study Selection

We assessed titles and/or abstracts of citations identified from literature searches for inclusion, using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria. Results published only in abstract form are not included in our reviews because adequate information is not available to assess the validity of the data and these reports have generally not been peer-reviewed.

Population and Condition of Interest

We included studies of adults (≥ 18 years) with RAS, as defined by the study authors, whether unilateral, bilateral, or in patients with a solitary functioning kidney. Where possible, we focused on studies of patients with ARAS. We thus excluded studies of fibromuscular dysplasia, arteritis-associated RAS, acute embolic stenosis, and other nonatherosclerotic stenosis. However,

we included studies with mixed populations so long as at least 80 percent of subjects with RAS had atherosclerotic disease. Studies that that did not report how many patients had ARAS were generally included unless we inferred that many patients did not have ARAS. Studies that included less than 80 percent subjects with ARAS, but that reported results separately for the subgroup of subjects with ARAS were included.

We excluded studies that evaluated patients with RAS in the setting of a transplanted kidney, renal artery aneurysms (requiring repair), aortic disease requiring invasive intervention, or concurrent cancer (including renal cell carcinoma). We also excluded studies of patients who had previous surgical or angioplasty interventions for RAS.

Interventions of Interest

The primary interventions of interest were "aggressive medical therapy" – defined as antihypertensive drugs, antilipid (lipid lowering) drugs, and antiplatelet drugs – and angioplasty with stent placement. There was consensus among the TEP members that the currently accepted invasive intervention for ARAS in the large majority of patients in the United States is angioplasty with stent. However, it was recognized that the large majority of the published evidence on angioplasty for RAS includes a wide variety of specific interventions and that limiting the review to analyses of patients who received only angioplasty with stent would be insufficient to assess the topic.

In addition, because of the known limitations and heterogeneity of the literature base, and to elicit a better understanding of the effect of a range of interventions for RAS, it was decided to broaden the interventions of interest to include both "natural history" studies that include patients receiving any intervention (or none) and studies of surgical interventions. However, in order to focus on those surgical studies that evaluated patients for whom a choice between medical treatment or angioplasty would be considered, we excluded studies of patients who required surgery for related conditions, such as aortic revascularization or valvular repair. Similarly, we excluded studies of surgical procedures that are not comparable to angioplasty, such as endarterectomy, renal ablation or nephrectomy, and revascularization of an occluded atrophic kidney (which is not generally feasible by angioplasty).

Comparators of Interest

Given the known paucity of comparative studies, we included both uncontrolled and controlled studies, with any comparator.

Outcomes of Interest

With the TEP, we analyzed clinical and surrogate outcomes of greatest interest regarding the comparison of medical and angioplasty interventions. It was agreed that given the chronicity of the disease process, only long-term outcomes and adverse effects were of interest. For the purposes of this report, "long-term" was defined as at least 6 months, although it was agreed with the TEP that results at 12 months or more are of greater interest.

Outcomes of interest included:

- Mortality due to all causes
- Change in kidney function
    - Need for renal replacement therapy
    - Categorization into "improved," "stable," or "worsened" kidney function or similar categories, as defined by the study authors
    - Change in glomerular filtration rate (GFR), creatinine clearance, or serum creatinine
- Change in blood pressure control
    - Hypertensive crises and other hypertension-related clinical events
    - Categorization into "improved," "stable," or "worsened" hypertension, or similar categories, as defined by the study authors
    - Change in the number of antihypertensive medications used
    - Change in blood pressure
- Restenosis after angioplasty with stent placement, as defined by authors
- Flash pulmonary edema or congestive heart failure events
- Other cardiovascular events, including
    - Cardiac events
    - Cerebrovascular disease events
    - Peripheral vascular disease events
- Adverse events, including, but not restricted to
    - In-hospital and 30-day postprocedure deaths
    - Major and minor peri- and postprocedure events
    - Major and minor drug-related adverse events

For questions 2 and 3 we also included subgroup and regression analyses that compared preintervention patient and intervention characteristics and outcomes of interest. These included,

but were not limited to, patient demographics; clinical, imaging, laboratory, and anatomic characteristics of the RAS; and treatment variables such as periprocedural medications, type of stent, use of distal protection devices, or other adjunct techniques. We extracted details from studies that reported analyses on the likelihood of outcomes based on the presence of patient or procedure related variables (e.g., that compared death rates among patients with high or low kidney function), but we extracted only the reported statistical significance of analyses that compared mean values of the variables in patients with dichotomized outcomes (e.g., that reported mean age of those who lived and those who died). These latter analyses were not considered to be sufficiently helpful for a clinician making a decision of which intervention to recommend to a given patient.

When outcomes were reported at multiple time points, we included those that occurred at 6 months, 12 months, and each subsequent year, so long as there were at least 10 subjects being evaluated.

Years of Intervention of Interest

The TEP had numerous discussions regarding the applicability of the literature to American patients in 2006 and after. It was noted that there continue to be many changes and advances in the management of patients with RAS. In particular the successful control of patients' blood pressure has improved greatly with the introduction of the angiotensin converting enzyme (ACE) inhibitors starting in the early 1990s, and subsequently angiotensin receptor blockers (ARBs). In addition, with the publication of the Fifth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-5) in 1993, greater emphasis was placed on attempting to achieve lower blood pressure levels than earlier sets of recommendations. In addition, it was recognized that there have been major shifts in the types of procedures that patients are receiving for ARAS. In particular, surgical intervention is currently rare, except in the setting of coexisting conditions such as aortic or renal artery aneurysm. In addition, the placement of stents is becoming more common. Furthermore, there continue to be advances and shifts in the diagnostic tools for determining the severity of ARAS.

Given these changes in diagnosis and treatment of ARAS, it was determined that older studies are of limited applicability to making decisions concerning ARAS in the modern era. A threshold at 1993 was chosen because 1) this was the year of publication of JNC-5; 2) it was the approximate time when ACE inhibitors and subsequently ARBs began to be commonly used; and 3) this coincided with the timeframe when placement of stents became more common and surgical intervention became less common. Thus, with exceptions enumerated below, studies published in or before 1993 or that included subjects whose interventions all occurred prior to 1993 were excluded.

Study Designs of Interest

Given the known sparseness of randomized, or even nonrandomized, comparative trials it was agreed to include uncontrolled single arm cohort studies (also known as pre-post studies). Initially, the plan was to include only prospective studies that evaluated at least 30 subjects in order to both minimize the bias related to retrospective analyses and to set a minimum level of power and applicability. However, eligibility criteria were broadened for several specific topics, as enumerated below, due to sparseness of data.

Specific Eligibility Criteria for Different Topics

Comparative studies. For studies that compared either a specific medical intervention or natural history to either angioplasty or surgery, we included studies of any study design, whether prospective or retrospective, so long as at least 10 subjects were evaluated. For studies that compared medical treatment to angioplasty, we included studies regardless of enrollment date. For studies of either natural history or surgery, that were of lessened applicability due to the interventions used, only studies that included patients whose interventions occurred in 1993 or later were eligible. Any comparative study that failed to meet eligibility criteria was also examined to determine whether individual cohorts of subjects (e.g., the natural history arm alone) may be eligible for other sections of the review.

Angioplasty studies. The large majority of available articles on ARAS reported on cohorts of subjects who received angioplasty. Given the large number of studies, only cohort studies of angioplasty with stent placement were eligible. Studies in which only some patients received stents were included, but studies of only angioplasty without stent placement were excluded. It was further agreed to limit these studies based on the minimal quality criteria of prospective studies with at least 30 patients evaluated, at least some of whom had the procedure performed in 1993 or later. In addition, because the primary questions of interest pertain to patients with ARAS who have not had a previous invasive intervention, we excluded studies in which more than 20 percent of the subjects had a previous procedure.

Medical intervention and "natural history" studies. Studies of specific medical interventions were separated from studies that evaluated patients who received a mix of interventions. These latter, natural history, studies usually described the interventions poorly, if at all. While an attempt was made to distinguish studies of a variety of only medical treatments from those that followed people regardless of intervention (including angioplasty, surgery, or both), this was not always feasible. For medical intervention studies, we included only prospective studies of antihypertensive, antilipid, or antiplatelet medications with at least 10 subjects who received treatment at any date. For natural history studies, we included both prospective and retrospective studies with at least 10 patients, at least some of whom were followed in 1993 or later.

Surgery studies. Studies of surgical interventions of any study design, whether prospective or retrospective, were included. To be eligible, surgical studies had to include at least some patients who had their procedure in 1993 or later. Prospective studies with at least 10 subjects and retrospective studies with at least 100 subjects were eligible.

Data Extraction

Items extracted included first author, year, country, setting, funding source, study design, inclusion, and exclusion criteria, including study definitions of RAS and ARAS (see Appendix B for a sample data extraction form). For randomized controlled trials (RCTs), we recorded the method of randomization, allocation concealment, blinding, and whether results were reported on

an intention-to-treat basis. Specific population characteristics included demographics such as age and sex, blood pressure, mean percent renal artery stenosis, percent of subjects with bilateral stenosis, and kidney function. Details regarding angioplasty techniques, including type of stent, surgical techniques, and/or medical interventions were also extracted.

For each outcome of interest, baseline, followup, and change from baseline data were extracted, including information of statistical significance. For most outcomes, only data from the last reported time point were included. Mortality data from all 6-month intervals from baseline and the final value were extracted. When outcome data were reported as overall outcomes, without a specific time point, the mean or median time of followup was used. All adverse event data were extracted.

For studies that reported any analyses of any predictors of outcomes (related to Key Questions 2 and 3), full data were extracted for each predictor of interest when analyses were performed from the perspective of the predictor (e.g., sex as a predictor of death). Multivariable analyses were preferred over univariate analyses. When analyses were performed from the perspective of the outcomes (e.g., average baseline age of those who died and survived), only the statistical significance of the association was extracted.

Quality Assessment

We assessed the methodological quality of studies based on predefined criteria. We used a 3-category grading system (A, B, C) to denote the methodological quality of each study. This grading system has been used in most of the previous evidence reports from the Tufts-NEMC EPC as well as in evidence-based clinical practice guidelines.[13,14] This system defines a generic grading system that is applicable to varying study designs including RCTs, nonrandomized comparative trials, cohort, and case-control studies. For RCTs, we mainly considered the methods used for randomization, allocation concealment, and blinding as well as the use of intention-to-treat analysis, the report of dropout rate and the extent to which valid primary outcomes were described, as well as clearly reported. Only RCTs could receive an A grade. For nonrandomized trials and prospective and retrospective cohort studies, we used (as applicable) the report of eligibility criteria, and the similarity of the comparative groups in terms of baseline characteristics and prognostic factors, the report of intention-to-treat analysis, and the crossovers, important differential loss to followup between the comparative groups or overall high loss to followup, the validity, and the adequacy of the description of outcomes and results.

A (good)

Category A studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality including the following: a formal randomized controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; clear reporting of dropouts; and no obvious bias.

B (fair/moderate)

Category B studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category A because they have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C (poor)

Category C studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information, or discrepancies in reporting.

Applicability Assessment

Applicability addresses the relevance of a given study to a population of interest. Every study applies certain eligibility criteria when selecting study subjects. Most of these criteria are explicitly stated (e.g., disease status, age, comorbidities). Some may be implicit or due to unintentional biases, such as those related to location (e.g., multicenter vs. single center, hypertension clinic vs. surgical practice), intervention (e.g., stent or no stent placement, which antihypertensive agents were used, angioplasty vs. surgery), factors resulting in study withdrawals or issues related to compliance with stated criteria, and other issues. The applicability of a study is dictated by the key questions, the populations, and the interventions that are of interest to this review, as opposed to those of interest to the original investigators.

To address this issue, we categorized studies within a target population into 1 of 3 levels of applicability that are defined as follows:

High	Sample is representative of the target population. It should be sufficiently large to cover a range of ARAS severity, including percent stenosis, percent with bilateral stenosis, blood pressure, and kidney function. The mean values of these parameters should be at least broadly similar to the mean for the typical patient receiving treatment for ARAS. In addition, the intervention should be applicable to currently used interventions, including angioplasty with stent placement and/or those antihypertensive drugs currently used commonly. At least 30 subjects analyzed.
Moderate	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 ARAS, atypically high blood pressure, or serum creatinine.
Low	Sample is representative of a narrow subgroup of subjects only, and is of limited applicability to other subgroups. For example, a study of a surgical

intervention or mostly from the early 1980s when ACE inhibitors, calcium antagonists, and beta-blockers were either not or rarely used.

Data Synthesis

As described in the Results section, the reviewed studies were highly heterogeneous in terms of interventions, study designs, and outcomes. In addition, only two randomized controlled trials fully met eligibility criteria. Given these limitations, and the relatively limited value of the cohort studies to fully answer the key questions, it was agreed with the TEP that all analyses would be descriptive and metaanalytic techniques would not be applied.

Summary Tables

Summary tables succinctly report summary measures of the main outcomes evaluated. They include information regarding study design, interventions, mean blood pressure, kidney function, percent renal artery stenosis, bilateral RAS and ostial lesions, number of subjects analyzed, including the number with ARAS, mean study duration and range, years of intervention, quality and applicability, and principal blood pressure, kidney function, and cardiovascular disease outcomes of interest.

Data on mortality were compiled across studies into a separate table and graphs. Data on adverse events were also compiled into a separate set of tables.

Overall Comparative Synthesis Table

To aid discussion, we summarized the comparative data (both direct and indirect comparisons) in one table in Chapter 4. Separate cells were constructed for each key question. Important comparative findings for each key question were summarized whenever the data were available.

Grading a Body of Evidence for Each Key Question

We assigned an overall grade describing the body of evidence for each key question that was based on the number and quality of individual studies, duration of followup and the consistency across studies. The grades corresponded to the following definitions:

Robust – There is a high level of assurance with validity of the results for the key question based on at least two high quality studies with long-term followup of a relevant population. There is no important scientific disagreement across studies in the results for the key question.

Acceptable – There is a good to moderate level of assurance with validity of the results for the key 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 key question.

Weak – There is a low level of assurance with validity of results for the key question based on either moderate to poor quality studies or on studies of a population that may have little direct relevance to the key question. There could be disagreement across studies in the results for the key question.

The grades provide a shorthand description of the strength of evidence supporting the major questions we addressed. However, they may oversimplify the many complex issues involved in appraising a body of evidence. The individual studies involved in formulating the composite grade differed in their design, reporting, and quality. As a result, the strengths and weaknesses of the individual reports addressing each key question should also be considered, as described in detail in the text and tables.

Peer Review

A draft version of this report was reviewed by a panel of expert reviewers (see Appendix D), including representatives from the American College of Cardiology, the Society for Cardiovascular Angiography and Intervention, the pharmaceutical industry, and the Food and Drug Administration. The reviewers included experts in cardiology, interventional radiology, vascular surgery, nephrology, and vascular disease. These experts were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft were made, where appropriate, based on their comments. The draft and final reports were also reviewed by staff from the Scientific Resource Center at Oregon Health and Science University. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Chapter 3. Results

The MEDLINE® search yielded 2,163 citations. Members of the Technical Expert Panel and other domain experts added an additional 28 articles for consideration. We identified 375 of these as potentially relevant and retrieved them for further evaluation. Of these 303 did not meet eligibility criteria (see Appendix C for a list of rejected articles along with reasons for rejection); thus 72 articles were included in this report. Due to multiple publications arising from the same studies these 72 articles represent 55 unique studies as per Table 1. An additional five studies met criteria only to provide data on adverse events.

Table 1. Summary of reviewed studies

Intervention	No. Studies	No. Subjects	Intervention Years	Quality			Applicability		
				A	B	C	III	II	I
Angioplasty+Stent vs Medical RCT	0								
Angioplasty±Stent[A] vs Medical RCT	2[B]	103	1992-5 & nd		2			1	1
Revascularization vs Medical Comparison[C]	8[D]	597	1981-2003 & nd		2	6	1		7
Medical treatment cohorts	4	83	nd		1	3		1	3
Natural History cohorts	8	721	1970-98 & nd		2	5		3	4
Angioplasty+Stent cohorts	21	3368	1989-2002 & nd		10	11	2	5	14
Angioplasty±Stent[E] cohorts	4	427	1993-1999		3	1	1	2	1
Surgical cohorts	4	921	1980-2004			4			4
Adverse events	37[F]	5378							

nd, no data; RCT, randomized controlled trials.

[A] Angioplasty without stent or combination of angioplasty with stent and angioplasty without stent.
[B] DRASTIC study[15-17] is included under revascularization vs medical since the randomized phase of the trial lasted only 3 months, too short a duration to meet eligibility criteria. Later followup included comparison between combinations of interventions.
[C] Combination angioplasty and surgery or surgery vs. medical therapy, either randomized or nonrandomized, or angioplasty vs. medical therapy in a nonrandomized study.
[D] Includes one the nonrandomized arms of one RCT.
[E] Combination of angioplasty with stent and angioplasty without stent.
[F] Including 5 studies that did not qualify for other key questions.

Direct Comparisons of Angioplasty (or Surgery) With Medical Treatment of Atherosclerotic Renal Artery Stenosis
(Tables 2-3, Figures 2-3)

Key Points for Direct Comparison of Angioplasty (or Surgery) With Medical Treatment of Atherosclerotic Renal Artery Stenosis

- Two randomized controlled trials directly compared angioplasty (mostly without stent placement) to medical treatment only. A third randomized trial compared angioplasty (without stent placement) at the start of the trial (immediate) to a combination of medical

treatment alone (56 percent of subjects) and 3 months of medical treatment alone for 3 months followed by angioplasty (delayed, 44 percent of subjects). All trials used a variety of antihypertensive agents. These trials reported outcomes principally at 6 or 12 months; though one followed patients for up to 4.5 years. The studies had methodological flaws making them susceptible to some bias, but not sufficient to invalidate the results (Grade B).

- The randomized trials ranged in applicability to the general population with atherosclerotic RAS (ARAS) from low to high. Two of the studies were conducted in the mid-1990s; the third did not report when enrollment occurred, but it was probably about the same time. Two trials included subjects with at least 50 percent stenosis, one set a minimum of 60 percent stenosis. One trial restricted eligibility to those with unilateral disease, one ran parallel trials of patients with unilateral or bilateral disease, and the third included approximately one-quarter patients with bilateral disease. In the two trials that reported location of stenosis, approximately 40 to 50 percent had ostial disease, as defined by the study authors. On average, all trials included patients with stage 2 chronic kidney disease (glomerular filtration rate 60-89 mL/min). Mean blood pressure in two trials was approximately 180-190/100 mm Hg; the trial restricted to patients with unilateral disease had a lower mean blood pressure of approximately 165/97 mm Hg.

- All trials found clinically small, statistically nonsignificant differences in kidney function; although the trial comparing immediate to delayed angioplasty or medical treatment alone found that substantially fewer patients with immediate angioplasty had worsened kidney function at 1 year (4 vs. 12 percent, statistical significance not reported).

- Differences in blood pressure outcomes varied across the randomized trials. One found substantially greater blood pressure reduction 1 year after angioplasty than with medical treatment among patients with bilateral stenosis (–34/–11 vs. –8/–1 mm Hg), but no difference among patients with unilateral disease. In both groups, the total number of antihypertensive drugs required was similar regardless of intervention. The trial that was restricted to patients with unilateral disease found a net 7 mm Hg greater fall in both systolic and diastolic blood pressure 6 months after angioplasty, but only the change in diastolic blood pressure was statistically significant. In addition, 6 months after angioplasty patients required approximately half as many antihypertensive drugs as those with medical treatment alone (1.0 vs. 1.8). The trial of immediate versus delayed or no angioplasty found no difference in either blood pressure or number of drugs at 12 months.

- Only one trial reported cardiovascular outcomes and found no difference at 12 months in the rate of congestive heart failure, stroke, or myocardial infarction in patients who had either angioplasty or medical treatment only.

- Seven additional studies (including a separate nonrandomized analysis of patients from one of the randomized trials) provided other, either prospective or retrospective, analyses of either angioplasty (mostly without stent placement) or surgery to a wide range of

medical regimens. One trial of surgery versus medical treatment was randomized; the remaining studies were not randomized. Of the nonrandomized studies, four evaluated angioplasty, one of which placed stents in approximately two-thirds of patients, and two combined patients who received either angioplasty or surgery. The medical treatments used were generally poorly or not described. Mean study durations ranged from approximately 6 months to 7 years. All but one of these studies were found to be likely to have significant bias that may invalidate the results (Grade C).

- All additional studies were deemed to be of low applicability due to combinations of difficulties assessing study populations due to incomplete reporting, small sample size, high rates of bilateral disease, time period of investigation, inclusion of some patients with fibromuscular displasia, and inclusion of surgical interventions. Four studies included patients first evaluated or treated primarily in the 1980s or earlier; the remaining three included patients from the 1990s or later. Most studies included patients with at least 50 percent stenosis, though the surgical trial included only patients with at least 75 percent stenosis. One study restricted evaluation to those patients with bilateral disease; most of the rest did not report how many patients had bilateral disease. Location of stenosis (ostial versus nonostial) was generally not reported. Of those studies that reported average kidney function, most appeared to include patients with stage 2 chronic kidney disease; an older retrospective study had a population with substantially more severe kidney disease (mean serum creatinine almost 4 mg/dL). Mean blood pressure across studies ranged from approximately 160/95 to 195/110 mm Hg.

- Four of six studies that reported kidney function outcomes found no differences at various time points regardless of intervention. One early prospective study found a significant difference in change in serum creatinine in followup between 1 and 21 months among patients who had either angioplasty or surgery, or had no revascularization (–0.5 vs. +1.0 mg/ dL). Another study reported that a substantially greater percentage of patients who had angioplasty (two-thirds of whom had stent placement) had improved or stable kidney function compared to those who were treated medically (82 vs. 52 percent); although they did not report statistical significance.

- Four of six studies that reported blood pressure outcomes found no significant differences in blood pressure control; although two found substantially greater reduction in blood pressure among those who did not have angioplasty, but were treated medically only (–24/–20 vs. –23/–6 mm Hg and –24/–12 vs. –9/–5 mm Hg). One study found no difference in blood pressure change, but a significant difference in the number of antihypertensive drugs required (angioplasty –0.5 vs. medical +0.3). Another found that significantly more patients had improved blood pressure control after angioplasty (two-thirds with stent placement) than medical treatment (57 vs. 29 percent).

- Only the randomized trial of surgical revascularization versus medical treatment of patients with higher grade stenosis reported any outcomes related to cardiovascular disease. They found no difference up to 7 years in the rate of atherosclerotic events, death, worsening kidney function, or resistant diastolic hypertension.

- Three of four studies that reported mortality outcomes found no difference in mortality with either revascularization or medical treatment at a range of time points up to 10 years. However, these studies were not powered to detect differences in mortality. One retrospective study, which used different eligibility criteria for those who had received angioplasty and those treated medically alone found a large and statistically significant higher death rate among patients who did not receive angioplasty.

- No study evaluated quality of life.

- No study reported adverse events due to medical treatment, thus no meaningful comparisons between interventions were made.

- Only two studies evaluated whether baseline variables could predict differential outcomes by intervention. The study comparing immediate to delayed or no angioplasty found that of two diagnostic tests, recent hypertension, bilateral stenosis, and severe stenosis (>70 percent), only bilateral disease was found to be associated with better creatinine clearance at 12 months in those patients who had immediate angioplasty, in contrast to those with unilateral disease, where creatinine clearance was statistically similar in the two groups. No variable predicted relative effectiveness of intervention strategy when diastolic blood pressure was the outcome. The randomized trial of surgical versus medical treatment, found that demographic factors did not help to predict which patients would fare better with either intervention.

- A variety of baseline variables were found to be statistically significantly associated with outcomes (regardless of intervention) across studies. These included higher serum creatinine, percent stenosis, presence of bilateral stenosis, history of cardiovascular disease, and age. However, most of these variables were found not to be associated with outcomes in other studies. Baseline captopril test, renogram, blood pressure, arterial norepinephrine, and angiotensin converting enzyme (ACE) genotype were not associated with outcomes in studies that performed these analyses.

- No study reported data related to any coprocedures or differences in procedures being associated with differential outcomes.

Because of the sparseness of data regarding direct comparisons of revascularization to medical therapy alone, all comparative studies with at least 10 patients, whether prospective or retrospective, were included. For studies that compared medical treatment to angioplasty, we included studies regardless of enrollment date. For studies of either natural history or surgery, that were of lessened applicability due to the interventions used, only studies that included patients whose interventions occurred in 1993 or later were eligible. Comparisons between different revascularization methods or different medical treatments were not included in this section.

Three randomized controlled trials (RCTs, published in five articles) involving a total of 208 patients with ARAS (analyzed, in their randomized arms) compared angioplasty to medical treatments.[15-19] Notably, the small sample sizes of the trials suggest that they are likely to be underpowered for the clinical outcomes including mortality, cardiovascular and kidney events.

All patients had ARAS. Almost all patients receiving angioplasty did not have stent placement. Medical therapies varied both between and within studies. One study reported results at 6 months, one at 1 year, and one at a variety of time points including 1 year and "most recent" up to 54 months. All three studies had some methodological flaws resulting in a B quality rating. One study each was rated to be of high, moderate, and low applicability.

Six additional studies,[20-25] and a nonrandomized third arm from one of the RCTs,[18] reported comparisons of either angioplasty or surgery and various medical treatments in a total of 491 patients with RAS; it is unclear how many of these patients had ARAS. One study (Uzzo 2002) was a randomized trial comparing surgery to medical treatment;[22] the remaining were nonrandomized comparisons of angioplasty or either angioplasty or surgery to medical treatment. Three studies evaluated angioplasty without stent placement, one evaluated angioplasty with (67 percent) or without (33 percent) stent placement, two evaluated a combined cohort of patients who received either angioplasty (approximately 80 percent) or surgery (approximately 20 percent). The final study evaluated surgical treatment. All compared the invasive intervention with conservative treatment either with or without antihypertensive drugs. Five studies were run prospectively, two retrospectively. Only the nonrandomized arm of the RCT was deemed to be of moderate methodological quality and moderate applicability. The rest were found to have sufficient flaws and of sufficiently limited applicability to be of poor quality and low applicability.

With only two RCTs that directly addressed the comparison of angioplasty with medical treatment for long-term outcomes (≥6 months), and the remainder of the comparative studies being both clinically heterogeneous and mostly nonrandomized, metaanalyses were not performed as these would have added little additional information.

Methodology Details of Randomized Controlled Trials of Angioplasty Versus Medical Treatment

The three RCTs have previously been reviewed by a Cochrane systematic review.[26,27]

The SNRASCG study (Webster 1998) was designed to determine if invasive intervention or continued medical therapy resulted in improved blood pressure and preservation of kidney function in hypertensive patients with ARAS.[18] In a multicenter study, 55 patients with resistant hypertension with at least 50 percent stenosis were randomized to either angiography without stent placement (n=25) or treatment with, preferentially, atenolol, bendrofluazide and/or a calcium antagonist (n=30). Other eligibility criteria applied. The original intent was to restrict the study to patients with bilateral disease, but those with unilateral disease were subsequently added, but analyzed separately. Their protocol resulted in two randomized groups (bilateral and unilateral disease) and a nonrandomized group of patients with unilateral disease (this latter cohort is reviewed here as a separate, nonrandomized trial). Five of the 25 patients randomized to angioplasty had either a nephrectomy or a surgical bypass at the discretion of the local investigators. Patients were followed at 1 month, 3 months, 6 months after the end of a run-in period or after angioplasty, and then at 6 month intervals thereafter. During the followup period (3 to 54 months) five patients (6 percent) who had been randomly or nonrandomly assigned to medical treatment had an angioplasty. Results are discussed below.

The EMMA study (Plouin 1998) compared angioplasty (mostly without stent placement) to drug treatment, primarily for blood pressure outcomes.[19] The multicenter trial randomized 49 patients referred for hypertension and unilateral ARAS of at least 60 percent with a positive

lateralization test or stenosis of at least 75 percent without thrombosis, from 1992 to 1995. Patients had resistant hypertension, but a creatinine clearance of at least 50 mL/min. Other eligibility criteria applied. Patients were randomized either to angioplasty alone (n=21) or with stent placement (n=2) or to drug treatment (n=26) by a predefined protocol based on diastolic blood pressure. Seven patients randomized to medical treatment were subsequently excluded from analysis due to a major hypotensive event in one patient and to refractory hypertension for which angioplasty was performed prior to 6 months in six patients. Results, discussed below, were recorded at 6 months.

The largest of the three trials was the DRASTIC trial (van Jaarsveld 2000), which has had three articles published with results.[15-17] The goal of the study was to evaluate changes in blood pressure and kidney function after 1 year of treatment in patients who were randomized between immediate angioplasty without stent placement (angioplasty was performed at the start of the trial) and drug therapy (followed by angioplasty if hypertension persisted or kidney function deteriorated). The multicenter study included 106 patients between 1993 and 1998 who had difficult to treat hypertension associated with normal kidney function or a serum creatinine up to 2.26 mg/dL and were found to have ARAS of 50 percent or more by arterial digital subtraction angiography. Other eligibility criteria applied. Patients were randomized to receive either immediate angioplasty (n=56) or to drug therapy (n=50, either amlodipine with atenolol, enalapril with hydrochlorothiazide, or other drug regimens if patients could not tolerate the drugs). Importantly, the primary question addressed involved immediate versus delayed angioplasty, since if after 3 months of medical treatment patients were offered angioplasty if resistant hypertension or kidney deterioration continued. Likewise, a second treatment, including surgical revascularization, was considered after 3 months in patients who received immediate angioplasty. Results data were reported at both 3 and 12 months by intention to treat analysis. By 12 months, 22 of the 50 patients randomized to drug treatment had received angioplasty; 28 remained on antihypertensive treatment alone. Because the randomized portion of the study ended after 3 months, prior to the agreed upon minimum duration of interest for this review (6 months), this trial is categorized with the "other comparative studies."

Key Question 1:

Mortality (Study Duration 6 Months or Greater)

Although mortality was commonly stated to be a primary outcome of the comparative studies, no study was reported to be adequately powered to detect a difference between interventions for this outcome.

RCTs of Angioplasty vs. Medical Treatment

Only the SNRASCG randomized trial (Webster 1998) reported mortality data.[18] Over 0 to 42 months, the survival curves were nearly identical for those randomized to medical therapy or angioplasty.

Other Comparative Studies (Angioplasty or Surgery vs. Medical Treatment)

Mortality data were reported by Pizzolo 2004 in a retrospective analysis of angioplasty with or without stent placement vs. medical treatment,[20] two prospective studies of either angioplasty or surgery (Pillay 2002 and Johansson 1999), and the RCT of surgery versus medical treatment (Uzzo 2002).[21-23] Pillay 2002 found no difference in all-cause death rates after 2 years between 12 patients who received an invasive intervention and 73 who were treated medically. Johansson 1999 also found no difference in mortality by Kaplan-Meier curve analysis up to 14 years after either angioplasty or surgery (n=105) or of medical treatment (n=64). Only Pizzolo 2004 reported a statistically significant difference in mortality by Cox regression analysis, such that after 5 years of followup, 10 percent of those who had received angioplasty (n=63) had died compared to 34 percent of those who were treated conservatively (n=37). However, eligibility criteria were markedly different for the two retrospective cohorts. Patients who were treated conservatively were diagnosed with RAS based on an angiographic evaluation performed for another cause, primarily peripheral vascular disease. Some of these patients were not treated with angioplasty because of cardiac conditions such as symptomatic coronary artery disease. In contrast, patients who received angioplasty had resistant hypertension or unexplained azotemia. Those treated with angioplasty were significantly younger, by 5 years, had significantly higher high density lipoprotein (HDL) cholesterol, by 5 mg/dL, but had higher baseline diastolic blood pressure, by 5 mm Hg. In the RCT of surgery versus medical treatment, Uzzo 2002 reported only that there were no statistically significant differences in survival in the two groups.[22]

Kidney Function

RCTs of Angioplasty vs. Medical Treatment

The two RCTs either estimated creatinine clearance either at 6 months or serum creatinine at multiple time points. Both found nonsignificant, clinically small differences in change in kidney function between those who received angioplasty and those who were treated medically.

The SNRASCG study (Webster 1998) reported that among patients who received angioplasty 8 percent had “renal failure” and 8 percent had “death or dialysis” and among those who were treated medically 7 percent had kidney failure and 13 percent had death or dialysis.[18]

Other Comparative Studies (Angioplasty or Surgery vs. Medical Treatment)

The DRASTIC study reported that 4 percent of patients receiving immediate angioplasty and 12 percent of patients receiving either medical treatment or delayed angioplasty experienced a 50 percent or more increase in serum creatinine level;[15-17] however, this was reported as a complication only, no statistical analysis was reported, and it is not reported when or in which patients (those with treatment only or those with delayed angioplasty) this occurred.

Among the three nonrandomized studies comparing angioplasty to medical treatment, two found clinically small, statistically nonsignificant differences in effect on serum creatinine (+0.1 and +0.4 mg/dL). (Taylor 1989 included subjects who had surgical interventions and is discussed below.[25]) In contrast, Pizzolo 2004 in a retrospective analysis of patients who either received angioplasty with or without stent placement, or (currently used) medical therapy, about 2.5 times more patients on medical therapy (48 percent) had kidney function deterioration at a median of

28 months than those who had had angioplasty (18 percent).[20] In a logistic regression model, this outcome was predicted by only intervention type (odds ratio [OR] 3.65, 95 percent confidence interval [CI] 1.28-10.5) and age.

Three studies evaluated kidney outcomes comparing patients who had received either angioplasty or surgery to medical treatment. Taylor 1989 was the only study to find an improvement in kidney function, as measured by serum creatinine, in 12 patients who had an invasive intervention, as compared to an increase among 12 patients who were treated medically.[25] The net difference (–1.5 mg/dL) was arguably clinically important and was statistically significant. In contrast, Pillay 2002 found a small, though statistically significant increase in serum creatinine from baseline in 12 patients who had angioplasty or surgery for bilateral stenosis compared to no change from baseline in 21 patients treated medically.[21] Only one patient with bilateral stenosis, who had an invasive intervention, required dialysis after over 2 years of followup. Uzzo 2002 in the RCT of surgery versus medical treatment reported no difference in either dialysis-free survival or change in glomerular filtration rate.[22]

Blood Pressure Control

RCTs of Angioplasty vs. Medical Treatment

The two RCTs had heterogeneous findings in regard to the comparative effect on blood pressure control of angioplasty or medical treatment. In the SNRASCG study,[18] among those with unilateral ARAS a larger reduction in blood pressure occurred among patients treated medically (–10/–2 mm Hg) than those treated with angioplasty (–2/–2 mm Hg); although this difference was not significant. Likewise the total number of drugs used did not significantly differ in the two study arms. In contrast, among patients with bilateral disease, there was a large decrease in blood pressure (–34/–11 mm Hg) in those who had angioplasty, which was highly significantly different than the more modest reduction among patients treated medically (–8/–1 mm Hg, P<0.005). Similarly, although to a lesser extent, EMMA found a greater reduction in blood pressure after angioplasty (–14/–8 mm Hg) than with medical treatment (–7/–1 mm Hg, nonsignificant [NS] for systolic blood pressure, P=0.04 for diastolic blood pressure).[19] EMMA also found that those treated with angioplasty were on significantly fewer antihypertensive drugs to control their blood pressure (1.0) than those treated only medically (1.8, P=0.009).

Of note, the Cochrane review performed metaanalysis on different blood pressure results than reviewed here because it used the 3 month data for the DRASTIC study, prior to any crossover of patients from medical treatment to angioplasty.[26,27]

Other Comparative Studies (Angioplasty or Surgery vs. Medical Treatment)

The DRASTIC study, comparing early angioplasty versus either medical treatment or later angioplasty found a clinically large decrease in both systolic and diastolic blood pressures in both study arms (–19/–11 and –17/–7 mm Hg), but no statistically significant difference between the study arms.[15-17] Although a greater mean reduction in the number of antihypertensive drugs was found among patients who had early angioplasty, this difference was not statistically significant.Six other comparative studies reported on blood pressure effects. The four that reported changes in blood pressure all found no significant difference between types of intervention. Englund 1991 actually found a larger fall in blood pressure among patients treated

medically, though these patients had a substantially higher baseline mean blood pressure.[24] The three studies that reported on mean number of antihypertensive drugs all found a larger decrease among patients treated with an invasive intervention than medicine alone, but only Webster 1998 (SNRASCG)[18] reported a statistically significant difference (in contrast with the randomized comparisons in the same trial). In addition, one study reported only no difference in blood pressure control.[22] However, Pizzolo 2004 in a retrospective analysis of patients who had received angioplasty with or without stent placement or (currently used) medical therapy found that almost twice as many patients treated with angioplasty (57 percent) had improvement in their blood pressure control by standardized criteria than those treated medically alone (29 percent, $P<0.05$).[20]

Cardiovascular Outcomes

RCTs of Angioplasty vs. Medical Treatment

Only Webster 1998 (SNRASCG) reported any cardiovascular outcomes.[18] The study combined data from the randomized unilateral and bilateral ARAS arms. Event rates for heart failure, stroke, and myocardial infarction were similar in the two groups. Cox regression that included kidney failure and death or dialysis found no difference after adjustment.

Other Comparative Studies (Angioplasty or Surgery vs. Medical Treatment)

The only outcome that was mostly cardiovascular that was reported was a combined stop point of resistant hypertension (diastolic blood pressure > 100 mm Hg on treatment), kidney function worsening, atherosclerotic cardiovascular event, or death. Uzzo 2002 in the RCT of surgical versus medical treatment found no difference.[22] This combined outcome was reached in two-thirds of patients at a mean of 6.2 years, regardless of intervention.

Adverse Events (Including 30-Day Mortality)

None of the studies reported data to allow a comparison of adverse event or other complication rates between patients receiving angioplasty and those receiving only medical treatment. In general, complication rates related to angioplasty (or angiography) alone were reported. Therefore, these data have been added to the adverse event section below on angioplasty cohort studies.

Only Englund 1991, in a retrospective study of 38 patients from the 1980s, clearly reported 30-day mortality.[24] Similar 30-day mortality rates were found in both the angioplasty (3 percent) and medical treatment (5 percent).

Key Question 2:

Predictors of Outcomes

Six of the nine studies comparing interventions reported analyses of baseline variables as predictors of outcomes or related subgroup analyses.

Baseline Variables as Predictors of Outcomes

Baseline kidney function

One retrospective comparison of angioplasty to medical therapy (Pizzolo 2004), one prospective comparison of either angioplasty or surgery to medical therapy (Johansson 1999), and the RCT of surgery to medical treatment (Uzzo 2002) evaluated the association between baseline serum creatinine and outcomes or subgroup analyses.[20,22,23]

Pizzolo 2004 reported that a baseline serum creatinine greater than 1.5 mg/dL was a borderline predictor of mortality (hazard ratio [HR] = 2.9, 95 percent CI 1-8.3, P=0.05), independent of intervention; however serum creatinine was not a predictor of either blood pressure improvement or of stable or improved kidney function.[20] Similarly, Johansson 1999 found that below study median baseline serum creatinine (1.2 mg/dL) was significantly associated with better overall survival through 14 years (P<0.01); however, this univariate analysis did not consider which intervention the patients received.[23] In the surgical RCT, in contrast with the finding that intervention type did not predict survival, Uzzo 2002 found that among an unreported number of subjects with azotemia (defined as serum creatinine between 2 and 4 mg/dL), those who had surgical procedures were less likely to die than those treated medically (P=0.01).[22]

Baseline severity of renal artery stenosis

Five studies (in seven articles) evaluated the association between either baseline percent stenosis and outcomes or the comparison between those with unilateral and bilateral ARAS.[15-18,20,21,23]

The association between percent stenosis and outcomes was reported in two angioplasty RCTs and a prospective study of angioplasty or surgery compared to medical treatment. The DRASTIC study (van Jaarsveld 2000) analyzed the effect of baseline percent stenosis in several ways.[15,16] Among the patients randomized to receive immediate angioplasty, baseline stenosis of greater than 70 percent was not associated with blood pressure or dose of antihypertensive drugs compared to lower percent stenosis. However, this analysis was not performed for those who received either delayed angioplasty or medical treatment alone. In analysis of all patients, though, when dichotomized at 80 percent stenosis, there was no significant difference in either creatinine clearance or diastolic blood pressure at 12 months, regardless of intervention. Webster 1998 (SNRASCG), in an analysis of only those patients randomized in the bilateral stenosis part of the trial found that those with an undefined designation of "more severe index of stenosis" ..."tended to have higher blood pressure during followup."[18] In a prospective study of either angioplasty or surgery and medical treatment, Johansson 1999 found that stenosis of at

least 70 percent was of borderline significance in predicting death, though not accounting for intervention type (relative risk [RR] 1.7, 95 percent CI 1.0-2.9).[23]

The DRASTIC study also found that presence of bilateral stenosis was not associated with differences in change in diastolic blood pressure between those with either immediate angioplasty or medical therapy with possible delayed angioplasty.[15,16] However, among patients with bilateral stenosis those who received immediate angioplasty had significantly better changes in creatinine clearance (+10 mL/min) than those with medicine alone or delayed angioplasty (–4 mL/min). In contrast, there was no difference among patients with unilateral stenosis. Pizzolo 2004 in a retrospective study comparing angioplasty to medical treatment found a borderline association between presence of bilateral disease and the odds of improving blood pressure, independent of intervention.[20] Those with bilateral disease were more likely to have blood pressure improvement (OR 3.2, 95 percent CI 0.97-11). Johansson 1999 also found a significant difference in survival among those with either unilateral or bilateral disease such that those with bilateral disease had a 60 percent mortality at 10 years and had all died by 13 years, while those with unilateral disease had approximately 35 percent mortality at 10 and 13 years ($P<0.01$).[23] The RR of death with bilateral stenosis was 2.8 (95 percent CI 1.8-4.6). Visual inspection of the survival graph shows a marked separation of survival by 3 years. In contrast, in another prospective comparison of angioplasty or surgery to medical treatment, Pillay 2002 found no difference in overall survival up to 3 years between those with unilateral or bilateral disease.[21]

Clinical test predictors

Two studies evaluated the predictive value of clinical tests prior to intervention.[15,17,23] In the DRASTIC study, neither a positive captopril test nor an abnormal renogram (scintigram) predicted either followup diastolic blood pressure or creatinine clearance in patients receiving immediate angioplasty or medical treatment or delayed angioplasty.[15,17] Likewise, in those patients receiving immediate angioplasty abnormal renogram did not predict systolic blood pressure or antihypertensive drug dose at followup. In the Johansson 1999 study, neither arterial norepinephrine level nor unilateral renin secretion was associated with survival.[23]

Two other studies evaluated baseline ambulatory blood pressure as a predictor of outcomes.[17,20] Neither the DRASTIC study nor the Pizzolo 2004 study found an association between either "recent hypertension," diastolic blood pressure, or baseline number of antihypertensive drugs and either death, followup diastolic blood pressure or creatinine clearance.

Other predictors

Pizzolo 2004 found a borderline association between a history of coronary artery disease and death due to a cardiovascular cause (HR 4.3, 95 percent CI 0.9-20, $P=0.07$).[20] Johansson 1999 also found significant RRs for death with histories of diabetes (RR 2.4, 95 percent CI 1.3-4.4), congestive heart failure (RR 2.6, 95 percent CI 1.2-5.7), and coronary heart disease (RR 2.3, 95 percent CI 1.3-3.8); borderline significant RR for death with a history of a cerebrovascular lesion (RR 1.9, 95 percent CI 0.99-3.7), but no association with a history of claudication (RR 1.9, 95 percent CI 0.9-4.0).[23]

Various demographic variables were also analyzed. Webster 1998, in the randomized bilateral disease group, found that older patients tended to have higher blood pressure at

followup. Pizzolo 2004 found that age was not associated with death due to cardiovascular disease, when adjusted for intervention, history of coronary artery disease, and elevated baseline serum creatinine.[20] But younger age was independently associated with stable or improved kidney function at followup. Johansson 1999 found that women were less likely to die than men after intervention (RR 0.41, 95 percent CI 0.23-0.72), but that smoking did not predict mortality.[23] Uzzo 2002 reported that "interacting baseline demographic factors" did not identify significant differences in reaching a severe end point between the medical or surgical groups.[22]

Pizzolo 2004 also examined ACE I/D polymorphisms and found that the distribution of genes was not associated with mortality.[20]

Baseline Variables as Predictors of Differential Outcomes by Intervention

Only two studies clearly reported on whether any baseline variables might predict whether patients would fare better with either angioplasty (or surgery) or continued medical treatment. The DRASTIC study, though, actually compared immediate versus delayed angioplasty or continued medical treatment. As described above, among five predictors (captopril test, renogram, recent hypertension, bilateral stenosis, and severe stenosis [>70 percent]) most failed to predict differences in intervention on either diastolic blood pressure or creatinine clearance. Only the presence of bilateral stenosis was found to be associated with better creatinine clearance at 12 months in those patients who had immediate angioplasty, in contrast to those with unilateral disease, where creatinine clearance was statistically similar in the two groups. However, no analysis was performed comparing those who received angioplasty to those who remained on medical treatment only.

Uzzo 2002, in the RCT of surgical versus medical treatment, found that demographic factors did not help to predict which patients would fare better with either intervention.[22]

Key Question 3:

Coprocedure Interventions as Predictors of Outcomes

No study reported data related to any coprocedures or differences in procedures being associated with differential outcomes.

Table 2. Direct comparisons of angioplasty or surgery and medical treatment for renal artery stenosis
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data, and Table 3 for 30-day mortality data.

Author, Year Study Design	Intervention	Mean BP Mean GFR [SCr]	Mean % Stenosis % Bilateral Stenosis	No. Evaluated RAS (ARAS)	RAS Location Years Enrolled	Mean Duration Range	Results HTN (%) and BP Δ Cured	Imp	UnΔ	Worse	CKD (%) and GFR / SCr Δ Imp	UnΔ	Worse	CVD (%)	Qual Appl
Angioplasty vs Medical Treatment, RCT															
Webster, 1998[18] SNRASCG	Angioplasty	190/99	>50%	12	Ostial 46%	(3-54 mo)	BP Δ = -34/-11				SCr Δ = +0.11 "Renal failure":[A] 8%			Angio-plasty:[A] CHF 9% CVA 4% MI 4%	B
	No stent	[2.1]		(12)											
RCT (bilateral disease, see other entries)	Medicine 2-3 of atenolol, bedrofluazide, CCB[B]	190/101 [1.7]	100%	16 (16)	nd		BP Δ = -8/-1 P<0.005 (net) Total Rx Δ: NS (net)				SCr Δ = +0.05 NS (net) "Renal failure":[A] 7%				
RCT (unilateral disease, see other entries)	Angioplasty No stent	189/105 [1.6]	>50%	13 (13)	Ostial 52%	(3-54 mo)	BP Δ = -2/-2				SCr Δ = +0.09			Medical:[A] CHF 13% CVA 13% MI (unclear)	Mod
	Medicine 2-3 of atenolol, bedrofluazide, CCB[B]	182/99 [1.9]	0%	14 (14)	nd		BP Δ = -10/-2 NS (net) Total Rx Δ: NS (net)				SCr Δ = 0 NS (net)				
Plouin, 1998[19] EMMA	Angioplasty +/-stent[C]	165/98 73	>60%	23 (23)	Ostial 39%	6 mo	BP Δ = -14/-8 Total Rx Final = 1.0				CrCl Δ = +4		0/23		B
RCT	Medicine[D] Multiple regimens[F]	165/96 73	0%	25 (25)	1992-1995		BP Δ = -7/-1 p=NS/0.04 (net) Total Rx Final = 1.8 P=0.009 (net)				CrCl Δ = 0 NS (net)		1/19[E]		Low
Angioplasty vs Medical Treatment or Delayed Angioplasty, RCT															
van Jaarsveld, 2000[15-17] DRASTIC	Angioplasty No stent[G]	179/104 67	76% 23%	56 (56)	nd	1 yr	BP Δ = -19/-12 Total Rx Δ = -0.8				CrCl Δ = +3		4%		B
RCT	Medicine[H] (n=28) Multiple regimens[I] Delayed angioplasty (n=22)	180/103 60	72% 22%	50 (50)	1993-1998		BP Δ = -17/-7 NS (net) Total Rx Δ = -0.1 P=0.10 (net)				CrCl Δ = +2 NS (net)		12%		High
Angioplasty vs Medical Treatment, Nonrandomized, Controlled Trial															
Webster, 1998[18]	Angioplasty No stent	196/109 [1.9]	>50%	28 (28)	Ostial 63%		BP Δ = -13/-11 Total Rx Δ= -0.5 NS (base)				SCr Δ = +0.15				B
NRCT (see other entries)	Medicine 2-3 of atenolol, bedrofluazide, CCB[B]	197/103 [1.6]	nd	51 (51)	nd	(3-54 mo)	BP Δ = -12/-6 NS (net) Total Rx Δ= +0.3 P=0.01 (base)				SCr Δ = 0.05 NS (net)				Low

Table 2. Direct comparisons of angioplasty or surgery and medical treatment for renal artery stenosis. Continued

Author, Year / Study Design	Intervention	Mean BP / Mean GFR [SCr]	Mean % Stenosis / % Bilateral Stenosis	No. Evaluated RAS (ARAS)	RAS Location / Years Enrolled	Mean Duration / Range	Results: HTN (%) and BP Δ				Results: CKD (%) and GFR / SCr Δ			Results: CVD (%)	Qual / Appl
							Cured	Imp	UnΔ	Worse	Imp	UnΔ	Worse		
Angioplasty vs Medical Treatment, Nonrandomized, Controlled Trial, continued															
Taylor, 1989[25]	Angioplasty	160/96	>60%	5	nd	6.5 mo			nd						
	No stent	nd		(nd)		1-21 mo		BP Δ = -23/-6 Total Rx Δ= -1			SCr Δ = -0.5 (including 7 receiving surgery)				C
Prosp	No revascularization	174/100	nd	15	nd	13 mo			20%						
	nd (0-3 drugs)	nd		(nd)		7-20 mo		BP Δ = -24/-20 Total Rx Δ= 0			SCr Δ = +1.0 P=0.08 (base); P<0.01 (net)				Low
Englund, 1991[24]	Angioplasty	165/96	nd	21	nd	17 mo	0								
	No stent	[3.9]		(?19-21)				BP Δ = -9/-5 Total Rx Δ= -1			SCr Δ = +1.05				C
Retro	Medicine	185/101	nd	17	1981-1988	16 mo	0								
	nd	[3.8]		(17)				BP Δ = -24/-12 NS (net) Total Rx Δ= 0 NS (net)			SCr Δ = 0.+69 NS (net)				Low
Pizzolo, 2004[20 J]	Angioplasty +/-stent[K]	168/95 [1.5]	~88% 30%	63 (63)	nd	28 mo	0	57%		43%	82%		18%		C
Retro	Medicine Multiple regimens[L]	159/91 [1.4]	~79% 27%	37 (37)	1996-2002	1-60 mo	0	29% P<0.05		71%	52%		48%		Low
Angioplasty or Surgery vs Medical Treatment, Nonrandomized,Controlled Trial															
Pillay, 2002[21]	Procedure Various[M]	nd	>50%	12 (nd)	nd	2.5 yr		DBP Δ = -15 Total Rx Δ= +0.03			SCr Δ = +0.6 P=0.01 (base) Dialysis: 1/12				C
Prosp	Medicine nd		100%	21 (nd)	1994-1998	>2 yr		DBP Δ = -6 NS (net) Total Rx Δ= +0.13 NS (net)			SCr Δ = 0 NS (base) Dialysis 0/12				Low
Johansson, 1999[23]	Procedure Various[N]	179/91	≥ 50%	105 (~91)	nd	7.1 yr	53% (1 yr)								C
Prosp	Medicine nd	61	nd	64 (~56)	1983-1984 & 1988-1994		nd								Low
Surgery vs Medical Treatment, RCT															
Uzzo, 2002[22]	Surgery Multiple	nd	≥ 75%	25 (25)	nd	6.2 yr	No difference in "blood pressure control" (NS)				No difference in dialysis-free survival or change in GFR (NS)			Stop point:[O] 68%	C
RCT	Medicine nd	nd	nd	27 (27)	nd	up to 7 yr								67% NS[P]	Low

Δ, change; Appl, applicability rating; ARAS , atherosclerotic renal artery stenosis; BP, blood pressure; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular event (stroke); CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate (or creatinine clearance, mL/min or mL/min/1.73 m^2);

HTN, hypertension; Imp, improved; MI, myocardial infarction; mo, months; nd, no data; NS, nonsignificant; Qual, quality rating; RAS, renal artery stenosis; Rx, prescriptions; SCr, serum creatinine (mg/dL); UnΔ, unchanged (or stable); yr, years.

[A] Combined unilateral and bilateral RAS.
[B] Or, frusemide, methyldopa, or prazosin. Angiotensin converting enzyme inhibitors were not allowed.
[C] 21 angioplasty alone, 2 angioplasty with stent.
[D] Intention to treat. 7 of 26 patients randomized to medical therapy received angioplasty within 6 months.
[E] ≥ 50% increase in plasma creatinine.
[F] Goal diastolic blood pressure (DBP)<95 mm Hg, using, if necessary, atenolol 50 mg, furosemide 40 mg, and/or enalapril 10 mg.
[G] Protocol called for no stent, but stents were placed in 2 patients.
[H] Intention to treat. 22 of 50 patients randomized to medical therapy at 3 months received angioplasty because of persistent hypertension or deterioration of kidney function.
[I] Randomized to amlodipine 10 mg (+ atenolol 50 mg if age >40 yr) or enalapril 20 mg (+ hydrochlorothiazide 25 mg if age >40 yr), or if could not tolerate either regimen, atenolol 100 mg (+ hydrochlorothiazide 25 mg if age >40 yr).
[J] Entry criteria for those receiving angioplasty and those receiving medical therapy were markedly different. Those receiving angioplasty had primary evaluation for resistant hypertension or unexplained azotemia. Those receiving conservative therapy had angiographic evaluation for other causes, primarily lower extremity arteriopathy. Endovascular therapy not considered for this latter group.
[K] 21 angioplasty alone; 42 angioplasty with stent.
[L] Goal BP≤140/90. Most frequent used classes of drugs were ACE inhibitors (62%), diuretics (62%), calcium antagonists (49%), and beta-blockers (30%).
[M] Among 12 patients, "9 angioplasties (1 failure) and 1 bilateral stent. 4 kidneys had... surgery."
[N] 88 angioplasty, 17 reconstructive surgery or nephrectomy.
[O] DBP>100 on treatment, or kidney function worsening (by GFR, SCr, or dialysis), or atherosclerotic cardiovascular event, or death.
[P] By Cox proportional hazard survival analysis.

Table 3. Adverse events associated with medical and angioplasty treatments of renal artery stenosis in direct comparison studies
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data.

Author Year	N RAS (ARAS)	Intervention	Kidney-related	CVD-related	Thrombosis/ occlusion	Bleeding	30 d mortality	Other
Pizzolo 2004[20]	122 (122)	Angioplasty (+/- stent) vs Medical (multiple regimens)	Partial kidney infarction 3% (Angioplasty) Periprocedure acute worsening kidney insufficiency 3% (Angioplasty)	Periprocedure MI 1.6% (Angioplasty)	Cholesterol embolism 1.6% (Angioplasty)			3 of the 4 adverse events occurred in the same person. No data on adverse events in medicine arm
Webster 1998[18]	55 (55)	Angioplasty (no stent) vs. Medical (atenolol, bedrofluazide, and/or calcium antagonist, or others)		In hospital stroke 5% (Angioplasty) Symptomatic hypotension 2% (Angioplasty)	No dissections, perforation, or renal artery thrombosis	Bleeding at arterial site 20% (Angioplasty)	No deaths	Pain requiring narcotic analgesic 10% (Angioplasty) No data on adverse events in medicine arm
Plouin 1998[19]	49 (49)	Angioplasty (+/- stent) vs. Medical (multiple regimens)	Renal artery dissection 4% (Angioplasty) 0% (Medical)		No occlusions	Hematoma at puncture site 22% (Angioplasty) 4% (Medical)		
Englund 1991[24]	38 (36)	Angioplasty (no stent) vs. Medical (nd)	Rupture of dilated renal artery & nephrectomy 3% (Angioplasty)				3% (Angioplasty) 5% (Medical)	
Van Jaarsveld 2000[15-17]	106 (106)	Angioplasty (no stent) vs. Medical (multiple regimens) or delayed angioplasty		Periprocedural angina 0% (Angioplasty) 2% (Medical / Delayed angioplasty) Periprocedural MI 0% (Angioplasty) 2% (Medical / Delayed angioplasty)	Occlusion of affected artery 0% (Angioplasty) 16% (Medical / Delayed angioplasty) Rupture of affected artery 0% (All)	Groin hematoma necessitating transfusion or intervention 4% (Angioplasty) 8% (Medical / Delayed angioplasty)		Embolization of cholesterol crystals 0% (Angioplasty) 14% (Medical / Delayed angioplasty) Symptomatic hypotension at angioplasty 1.8% (Angioplasty) 0% (Medical / Delayed angioplasty)

ARAS, atherosclerotic renal artery stenosis; CVD, cardiovascular disease; d, day; MI, myocardial infarction; N, number evaluated; nd, no data; RAS, renal artery stenosis.

Medical Treatments for Blood Pressure or Lipid Control of Atherosclerotic Renal Artery Stenosis
(Tables 4-5, Figures 2-3)

Key Points for Medical Treatments for Blood Pressure Maintenance of Atherosclerotic Renal Artery Stenosis

- One cohort study evaluated a combination of aggressive medical treatments, including antihypertensives, aspirin and a statin; this study had some methodological flaws (Grade B). An additional three studies evaluated an ACE inhibitor, in addition to timolol and hydralazine. All three studies had methodological flaws making them susceptible to bias (Grade C).

- Patients' blood pressures significantly decreased; their kidney function worsened over time. All four studies showed that, on average, the various treatment regimens examined were effective for lowering blood pressures in ARAS patients to or near the normal range. Two studies reported that kidney function worsened over time.

- A wide variety of adverse effects were reported for each antihypertensive agent.

- No study analyzed potential predictors of outcomes.

For the evaluation of medical therapies (not directly compared to revascularization) only prospective trials with at least 10 patients were included, regardless of publication date. Retrospective studies and nonspecified medical treatments were considered in the Natural History section, below.

One prospective trial (Hanzel 2005) involving a total of 40 ARAS (with ≥70% stenosis) patients with hypertension and hyperlipidemia (88%) at baseline used an aggressive medical treatment regimen to achieve a low density lipoprotein (LDL) cholesterol level less than 100 mg/dL in combination with antihypertensive therapy.[28] All patients received aspirin 325 mg/day and a statin to achieve the blood lipid control. Antihypertensive therapy was initiated with an ACE inhibitor or angiotensin-receptor blocker (ARB), and other agents were added as necessary. Seven (18%) patients had bilateral stenosis and one (2.5%) patient had stenosis of a solitary kidney. Six patients (15%) who developed progressive decreases in glomerular filtration rate (GFR) subsequently underwent angioplasty with stenting. After stent placement, patients received ticlopidine 250 mg twice daily or clopidogrel 75 mg/day for more than 30 days. Patients were followed up for their clinical outcomes every 3 to 6 months for a median of 21 months. This study also included a cohort of 26 patients who, based on their advanced clinical disease were treated with angioplasty with stent. Because the samples of patients receiving medical treatment alone or angioplasty had substantially different severity of ARAS disease, this study was not included as a study directly comparing the interventions. Because of the small number of patients receiving angioplasty with stent, this study also did not qualify for review as an angioplasty cohort study.

Three prospective studies (published in four articles) involving a total of 43 ARAS patients with stage II hypertension at baseline used different medical treatment regimens for lowering patients' blood pressures.[29-32] Franklin 1985 used a triple-drug regimen, which consisted of initial dosages of timolol 10 mg twice daily, hydralazine 50 mg twice daily, and hydrochlorothiazide, 50 mg (or 100 mg if GFR less than 60 mL/min) daily, with increases in doses as necessary.[29,30] After treatment at the maximal dosage for 6 weeks, patients crossed-over to enalapril at an initial dosage of 5 mg twice daily, which could be increased to 10 to 20 mg twice daily, along with hydrochlorothiazide. Ogihara 1991 used delapril with an initial dose of 7.5 mg twice daily.[31] The dosage was increased to 30, 60, or 120 mg daily if needed. Tillman 1984 employed enalapril 10 to 40 mg, titrated to blood pressure less than 140/90 four hours after dose.[32] The number of patients with ARAS were not described in two studies, and was less than the number of evaluated patients in one study. It is difficult to determine the patients' kidney functions at baseline based on the limited data reported. The duration of followup ranged from 12 weeks (in some and 12 months in others) to 32 months.

Key Question 1:

Mortality (Study Duration 6 Months or Greater), Kidney Function, and Blood Pressure Control

The study of aggressive medical treatment for blood lipid control (targeting LDL cholesterol <100 mg/dL) in combination with antihypertensive therapy showed that, on average, patients' blood pressures significantly decreased from 154/77 to 143/72 mm Hg at follow-up. However, there was a 7% increase in serum creatinine concentration (from mean 1.3 to 1.4 mg/dL), and 6% and 8% decreased in the total kidney and stenotic kidney GFR respectively. Six patients (15%) developed progressive decreases in single-kidney GFR and underwent late renal artery stenting.

All four studies of medical treatments for blood pressure control showed that, on average, various treatment regimens were effective for lowering blood pressures to the normal ranges (or the prespecified blood pressure goals). The three studies that analyzed statistical significance found that the blood pressure reduction was statistically significant compared to baseline. Two studies examined the changes in patients' kidney function and found similar small, but statistically significant worsening in kidney function over approximately 2 years.[28,32] Tillman 1984 also reported an overall mortality rate of 5 percent after 8 to 32 months of followup.[32]

Cardiovascular Outcomes

Among the 40 ARAS patients in the study of aggressive medical treatment including blood lipid control, one patient (2.5%) experienced stroke and one patient (2.5%) experienced myocardial infarction during the follow-up period.

The studies of antihypertensive drugs alone did not report any cardiovascular outcomes.

Adverse Events (Including 30-Day Mortality)

Adverse events associated with the use of enalapril included orthostatic hypotension symptoms, muscle cramps, headaches, increased serum creatinine levels, developing or worsening Raynaud's phenomenon, angina, and symptomatic tachycardia. No rash, taste disturbance, leucopenia, dysgeusia, neutropenia, or proteinuria was reported.

Adverse events associated with the use of timolol and hydralazine included central nervous system symptoms, digestive symptoms, headaches and nausea.

Adverse events associated with the use of captopril included hypotension and transient kidney insufficiency.

Key Questions 2 & 3:

Predictors of Outcomes

No analyses were reported that evaluated baseline variables as predictors of outcomes.

Table 4. Medical treatments for blood pressure maintenance of atherosclerotic renal artery stenosis
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data, and Table 5 for 30-day mortality data.

Author, Year Study Design	Mean BP Mean GFR [SCr]	Mean % Stenosis % Bilateral Stenosis	No. Evaluated RAS (ARAS)	Intervention Study Years	Mean Followup Duration (Range)	Results BP Control	Results Kidney Function	Results Cardio-vascular Disease	Qual Appl
Hanzel, 2005[28]	154/77	≥70%	40	Aspirin, statin, and antihypertensive therapy[A]	21 mo		SCr Δ +0.1 (+7%) *P=0.02*		B
Prosp	[≤2.0]	18%	(40)	nd	(nd)	BP Δ –11/-5 *P=0.03/0.01*	GFR Δ –4 (–6%) *P=0.03*	Stroke 1/40 MI 1/40	Mod
Franklin, 1985[29,30]	180/106	>50%	13	Triple-drug regimen cross to enalapril 5-20 mg	7.5[D] mo	BP Δ –50/-29			C
RCT & Prosp[B]	[1.3][C]	49%[C]	(nd)	nd	(nd)	*P≤0.01*			Low
Ogihara, 1991[31]	172/103	nd	10	Delapril 7.5-120 mg	Mostly 12 wk >1 yr in some	8/10 BP Δ ≥ -20/-10			C
Prosp	nd	nd	(nd)	nd		5/10 BP Δ ≥ -30/-15			Low
Tillman, 1984[32]	180/104[E]	nd	20	Enalapril 10-40 mg	19 mo	BP Δ -40/-19[D]	SCr Δ +0.3		C
Prosp	[1.3]	25%	(≤19)	nd	(8-32 mo)	*P<0.05*	*P<0.05*		Low

Δ, change; Appl, applicability rating; ARAS , atherosclerotic renal artery stenosis; BP, blood pressure; GFR, glomerular filtration rate (mL/min or mL/min/1.73 m^2); HTN, hypertension; mo, months; nd, no data; Mod, moderate; Prosp, prospective nonrandomized study; Qual, quality rating; RAS, renal artery stenosis; RCT, randomized controlled trial; SCr, serum creatinine (mg/dL); wk, weeks; yr, year.

[A] All patients received aspirin 325 mg/day and a statin to achieve LDL cholesterol <100 mg/dl. Antihypertensive therapy was initiated with an ACE inhibitor or ARB, and other agents were added as necessary. Six patients (15%) developed progressive decreases in single-kidney GFR underwent late renal artery stenting. After stenting, patients received ticlopidine 250 mg twice daily or clopidogrel 75 mg/day for more than 30 days.
[B] Initially an RCT, then an open-label trial during a "maintenance period."
[C] Data was based on the total of 39 patients who were randomized to standard triple therapy group. Of these, in 13 patients therapy was switched from the triple-drug regimen to enalapril during the extension period, and the outcomes were based on these 13 patients.
[D] Median
[E] Value was estimated from graph.

Table 5. Adverse events associated with the medical treatment of renal artery stenosis
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data.

Author Year	N RAS (ARAS)	Intervention	Kidney-related	CVD-related	Thrombosis/ occlusion	Bleeding	30 d mortality	Other
Franklin 1985[29,30]	75 (57)	Medical (Enalapril vs STT)		Orthostatic hypotension 11% (enalapril) CNS symptoms 18% (STT)				No leucopenia, dysgeusia, rash, or proteinuria
Takabatake 1987[33]	21	Medical (Captopril)		Hypotension comparable in bilateral and unilateral stenosis (nd on %)				
Tillman 1984[32]	20 (≤19)	Medical (Enalapril)		Symptomatic tachycardia 20% Angina 5%				
Jackson 1986[34,35]	16 (16)	Medical (Enalapril)	Increased SCr 25%					No rash, taste disturbance, or neutropenia
Hricik 1983[36]	11 (nd)	Medical (Captopril)	Transient kidney insufficiency 100%					

ARAS, atherosclerotic renal artery stenosis; CNS, central nervous system; CVD, cardiovascular disease; d, day; GFR, glomerular filtration rate; MI, myocardial infarction; N, number evaluated; nd, no data; RAS, renal artery stenosis; STT, "standard triple therapy"; SCr, serum creatinine.

[A] All patients received aspirin 325 mg/day and a statin to achieve LDL cholesterol <100 mg/dl. Antihypertensive therapy was initiated with an ACE inhibitor or ARB, and other agents were added as necessary. Six patients (15%) developed progressive decreases in single-kidney GFR underwent late renal artery stenting. After stenting, patients received ticlopidine 250 mg twice daily or clopidogrel 75 mg/day for more than 30 days.

Natural History or Nonspecified Medical Treatments for Atherosclerotic Renal Artery Stenosis
(Table 6, Figures 2-3)

Key Points for Natural History or Nonspecified Medical Treatments for Atherosclerotic Renal Artery Stenosis

- Eight studies reported outcomes of natural history or nonspecified medical treatments for ARAS. Of these, the four that reported intervention dates, ranged from 1970 to 1998. Almost all patients in these studies received no revascularization interventions and presumably all patients were under standard care by their physician. Populations were heterogeneous across studies. The majority of studies had methodological flaws making them susceptible to bias (Grade C), while three studies were of moderate quality (Grade B).

- Mortality outcomes were reported in five studies. Six-month, 2-, 4-, and 5-year survival rates were 77 percent, 60 to 68 percent, 64 percent, and 38 percent, respectively.

- Kidney function outcomes were reported in six studies. In general patients' kidney function deteriorated over time, although to different degrees in the different studies.

- Outcomes of blood pressure control were reported in two studies. The results were not comparable due to substantial differences in the ARAS populations examined.

- One study reported eight fatal cardiovascular events in 20 patients with severe stenosis (≥ 75 percent) during 3 to 36 months followup.

- Four studies analyzed various predictors of mortality and/or outcomes of kidney function. Percent stenosis and baseline kidney function were found to be strong predictors of death (or dialysis) in separate studies. Another study found that nonspiral blood flow in the renal arteries predicted kidney function deterioration. Other variables related to cardiovascular disease were also found to predict death. One study found that bilateral versus unilateral disease did not predict progressive kidney disease.

- One study found that patients with bilateral disease had higher cardiovascular mortality rate than with unilateral disease.

For observational studies of natural history or nonspecified medical treatments of ARAS, we included both prospective and retrospective studies with at least 10 patients. At least some of patients in the included studies had to be followed in or after 1993.

Six prospective studies,[21,37-41] one retrospective study,[42] and one mixed prospective and retrospective study[43] involving a total of 721 patients reported outcomes of natural history or nonspecified medical treatments for ARAS. Of these, four studies reported the intervention dates, ranging from 1970 to 1998. Almost all patients in these studies received no

revascularization interventions (among five studies reporting on this) and presumably all patients were under standard care by their physician. Populations were heterogeneous across studies. Only one study described the number of patients with ARAS.[37] The mean serum creatinine levels ranged from 1.2 to 3.2 mg/dL at baseline, implying at least stage 2 chronic kidney disease (GFR 60-89 mL/min). The percent stenosis ranged from greater than 20 percent to greater than 75 percent; the percentage of bilateral stenosis ranged from 17 to 100 percent. The duration of followup for individual patients ranged from 1 to 120 months. The majority of patients had hypertension although the severity varied.

Key Question 1:

Mortality (Study Duration 6 Months or Greater)

Mortality outcomes were reported in five studies. Six-month, 2-, 4-, and 5-year survival rates were 77 percent, 60 to 68 percent, 64 percent, and 38 percent, respectively. Conlon 2001 also analyzed the survival rate by severity of ARAS.[38] All 362 patients had coronary artery diseases at enrollment. The 4-year survival in patients with 50 to 75 percent, 75 to 95 percent, and >95 percent ARAS was 70 percent, 68 percent, and 48 percent respectively ($P<0.001$ for trend).

Kidney Function

Kidney function outcomes were reported in seven studies. A variety of outcomes for kidney function were examined. Although different measures of kidney function were measured, data from all studies showed that in general patients' kidney function deteriorated over time, although to different degrees. Caps 1998 showed that the cumulative incidence of kidney atrophy (defined as a reduction in kidney length greater than 1 cm from baseline) was 21 percent over a 2-year period in 100 patients with ARAS.[37] Cheung 2002 showed that the mean annual change in GFR was –4.9 mL/min/year in 11 patients with bilateral stenosis.[43] Of these patients, six had GFR fall by more than 20 percent during the followup period. Four studies examined the changes in serum creatinine; all showed that, on average, serum creatinine levels increased over time in a total of 178 ARAS patients. Two studies reported the rate of dialysis in a total of 72 ARAS patients. One study found that two (4 percent) of the 52 patients with significant unilateral stenosis (>50 percent) required dialysis in the 2-year followup, while the other study reported that eight (40 percent) of the 20 patients with severe stenosis (≥ 75 percent) required dialysis during 3 to 36 months followup.

Blood Pressure Control

Blood pressure control was reported in two studies. Pillay 2002 showed that median diastolic blood pressure did not change significantly in 35 unilateral ARAS survivors.[21] Fergany 1994 showed that the mean blood pressures decreased 39/17 mm Hg after medical treatment in 20 ARAS patients (65 percent with bilateral stenosis).[39]

Cardiovascular Outcomes

Uzu 2002 reported eight fatal cardiovascular events in 20 patients with severe stenosis (≥ 75 percent) during 3 to 36 months of followup.[41] These fatal cardiovascular events included cerebral hemorrhage (n=2), myocardial infarction (n=4), and cerebral infarction (n=2).

Adverse Events (Including 30-Day Mortality)

These studies of natural history did not report adverse events.

Key Questions 2 & 3:

Predictors of Outcomes

Two studies examined various predictors (e.g. baseline clinical, laboratory and anatomic characteristics) of mortality using multivariable Cox proportional hazard models.[38,43] Conlon 2001 found that the presence of significant ARAS (≥ 75 percent stenosis), increased age, the severity of coronary artery disease (CAD), the presence of comorbid disease, reduced ejection fraction, symptoms of congestive cardiac failure, and the mode of treatment of CAD were all independently associated with reduced survival in ARAS patients with CAD. Also, as noted above, in univariate analysis, patients with greater percentage stenosis had progressively higher mortality rates. Cheung 2002 reported that the baseline kidney function was the most important prognostic variable, with renal vascular anatomy having no additional, or independent, prognostic impact on combined death and dialysis-need end point. Compared to patients with baseline GFR more than 50 mL/min, the hazard ratio of death or dialysis was 1.4, 4.4, and 29 in patients with baseline GFR 25 to 50 mL/min, 10 to 25 mL/min, and less than 10 mL/min, respectively.

Three other studies evaluated the predictors of outcomes of kidney function by univariate analyses.[40-42] Houston 2004 found that patients with nonspiral blood flow (an evaluation of the direction of flow on magnetic resonance angiography) of the kidneys had significant progression in kidney impairment (P=0.007), while patients with spiral blood flow of kidneys did not. Iglesias 2000 reported that bilateral stenoses did not worsen kidney disease prognosis. Uzu 2002 found that the cardiovascular mortality rates were 13 and 18 per 100 patient-years in patients with unilateral ARAS and bilateral ARAS respectively.[41] The difference was statistically significant (P=0.01).

Table 6. Natural history or nonspecified medical treatments of atherosclerotic renal artery stenosis
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data.

Author, Year	Mean BP	Mean % Stenosis	No. Evaluated RAS	Intervention	Mean Followup Duration	Results			Qual
Study Design	Mean GFR [SCr]	% Bilateral Stenosis	(ARAS)	Study Years	(Range)	BP Control	Kidney Function	Cardiovascular Disease	Appl
Caps, 1998[37]	163/84[A]	≥60%	100[B]	Medical Rx	nd		Kidney atrophy: 21% [C]		B
Prosp	[1.6] [A]	nd	(100)	1990-1993	(2-24 mo)				Mod
Cheung, 2002[43]	167/87	≥50%	26 or 11[D]	Mostly medical Rx[E]	35 mo		ΔGFR: -4.9/yr (n=11)		C
Prosp & Retro	35.5	100%	(nd)	nd	(1-82 mo)		GFR Δ >20%: 6/11		Low
Conlon 2001[38]	nd	≥50%	362	Various	3.2 y		Only mortality data reported		B
Prosp	[1.2]	17%	(nd)	nd	(6-90 mo)				Low
Fergany, 1994[39]	179/102	nd	20	Medical Rx	43 mo	BP Δ -39/-17 *P=0.03*	SCr Δ +0.2 *NS*		C
Prosp	[1.2]	65%	(nd)	1970-1990	(4-120 mo)				Low
Houston, 2004[40]	nd	>60%	45	nd	9 yr		SCr Δ +0.3[F] *P=0.004*		C
Prosp	[~1.8][F]	nd	(nd)	nd					Mod
Iglesias, 2000[42]	143/84	>20%	96 or 78[G]	nd	55 mo		ΔSCr: +0.06 / yr (n=78)		C
Retro	[1.2]	20%	(nd)	nd	(nd)				Mod
Pillay, 2002[21]	nd/88[F]	>50%	52 or 35[H]	Medical Rx	2 yr	DBP Δ -8[F] *P=NS*	SCr Δ +0.2[F] (n=35) *P=0.002* Dialysis: 2/52		C
Prosp	[1.2][F]	0%	(nd)	1994-1998	(2 yr)				Low
Uzu, 2002[41]	170/77	≥ 75%	20	Medical Rx	nd		Dialysis: 8/20	CVD deaths: 8/20	B
Prosp	[3.2]	59%	(nd)	1996-1998	(3-36 mo)				Low

Δ, change; Appl, applicability rating; ARAS , atherosclerotic renal artery stenosis; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate (or creatinine clearance, mL/min or mL/min/1.73 m^2); mo, months; Mod, moderate; nd, no data; NS, nonsignificant; Qual, quality rating; RAS, renal artery stenosis; Rx, prescription; SCr, serum creatinine (mg/dL); yr, years.

[A] Data were based on all 204 kidneys, including 43 (21 percent) kidneys with normal baseline arteries at baseline.
[B] Number of kidneys
[C] Cumulative incidence of kidney atrophy (a reduction in kidney length >1 cm during followup compared to the length at baseline examination) over a period of 2 year
[D] Only nondialysis and survived patients with baseline renal functional data were analyzed for followup renal function analyses.
[E] Very few patients received angioplasty; of which only one received stent.
[F] Value was estimated from graph.
[G] Patients who died within 180 days excluded from analyses of annual changes SCr. These patients had better survival rate than the whole cohort.
[H] Survivors only.

Angioplasty With Stent Placement of Atherosclerotic Renal Artery Stenosis
(Tables 7-8, Figures 2-3)

Key Points for Angioplasty With Stent Placement for Atherosclerotic Renal Artery Stenosis

- This review evaluated 21 studies that placed stents in all patients that included a total of 3368 patients for clinical outcomes. Only prospective studies that evaluated at least 30 patients, at least some of whom were treated since 1993, were included. Almost all studies evaluated outcomes using before and after designs of interventions without controls (cohort study designs), and thus have important sources of biases. Approximately half the studies were rated to be moderate quality (Grade B), half poor quality (Grade C).

- Overall, uncontrolled hypertension was the most common indication for a percutaneous intervention. At baseline, patients frequently had diffuse atherosclerotic vascular diseases. The studies followed patients for 1 to 2 years after intervention. Almost two-thirds of the studies were of moderate applicability to the populations of interest; only two studies were of high applicability.

- The majority of the patients had cured or improved blood pressure rates at followup compared to baseline. However the improved kidney outcomes and mortality rates varied across the studies and handful of studies reported cardiovascular disease outcomes. The most frequent cause of mortality was related to cardiovascular disease.

- Restenosis was evaluated between 3 to 40 months after percutaneous interventions and the rates of restenosis ranged from 10 to 21 percent. One study noted a statistically significant higher rate of restenosis among those who had undergone stent placement for ostial lesions compared to those with nonostial lesions

- Adverse events following angioplasty included 30-day mortality that ranged from <1 to 3 percent and transient decline in kidney function that ranged from 1 to 13 percent.

- A decreased baseline kidney function predicted mortality outcome. However, the studies differed in their description of decreased baseline kidney function. Of note, the studies also varied if decreased kidney function at baseline predicted deterioration or improvement in kidney function following intervention. Improved kidney function was also observed with baseline resistance index of more than 80 percent.

- Baseline congestive heart failure (CHF) and the extent of CAD predicted an increased risk of cardiovascular- and kidney-related mortality. Survival after stent placement was adversely influenced by the presence of baseline bilateral ARAS with and without baseline chronic kidney disease.

- Only one study analyzed the effect of periprocedural interventions – simultaneous bilateral stent placement on outcomes.

Because of the relatively large number of studies on angioplasty, it was agreed to restrict the review to the most applicable studies that are less likely to have substantial bias. Thus only prospective studies of angioplasty with stent placement, with at least 30 patients who were treated and analyzed after 1993 are included. Studies in which more than 20 percent of the subjects had a previous revascularization procedure were excluded. Studies that evaluated both angioplasty with stent placement and angioplasty are reviewed separately, below. Importantly, the agreed-upon eligibility criteria excluded very-long-term studies that spanned the 1980s and 1990s, and large retrospective studies, limiting our reviews of questions related to long-term (≥6 months) clinical outcomes and patient-level predictors of outcomes.

We identified 21 studies (with a total of 3368 patients) in 28 publications that assessed the effectiveness of percutaneous renal angioplasty with stent placement for the treatment of ARAS and reported data on clinical outcomes. Two additional studies[44,45] that reported adverse events, but not long-term outcomes were also included. The studies followed patients from 6 months to 48 months; 17 studies followed their cohorts prospectively and four studies used both prospective and retrospective study designs.

Three studies were multicenter.[46-48] Eight explicitly reported consecutive patient enrollment.[49-56] In seven studies patients with ARAS underwent primary stent placement;[49-51,57-60] in five studies some patients with prior failed angioplasty were included (fewer than 20 percent of patients);[54,56,61-63] and eight studies had no such data available. The studies mostly included patients with a mean age of 65 years and above, and those who had one or more additional atherosclerotic vascular diseases. The most common indication for angioplasty was uncontrolled hypertension while on two or more medications. Two studies included all patients with cardiovascular disease or flash pulmonary edema.[58,60]

The definitions of RAS varied across studies. Three included patients with over 80 percent stenosis,[47,50,51] 13 with over 60 percent or 70 percent stenosis,[48,49,53-55,57-62,64,65] and four studies included patients with over 50 percent.[52,56,63,66] The percent stenosis was not stated in one study.[46]

In 20 studies ARAS was diagnosed in the preoperative period by renal angiography;[47-66] and in four studies digital subtraction was utilized in addition to renal angiography.[47,50,60,66] One study did not report the method of preoperative diagnoses of ARAS.[46] Sixteen studies reported that ostial lesions ranged from 32 to 100 percent of the involved arteries. However, the studies differed in their description of ostial stenosis, which were defined as stenosis of the renal artery within 3 mm[51,53] or 4 mm[66] or 5 mm[49,60,63] or 10 mm[48,56,61] of the aortic lumen. Patients with bilateral ARAS ranged from 9 to 50 percent.

Data on femoral or brachial approaches to access was available in 11 studies,[46-48,51,54,56-58,60,63,65,66] which reported femoral as the most common access approach. The Palmaz stents were used in 14 studies;[46,48,52-59,61-63,66] multiple stents including the Palmaz stents were used in six studies, [47,49,51,60,64,65] and one study did not report data on the type of stent used.[50] Only one study reported utilizing a distal protection device.[47] Preprocedural and procedural prophylaxis against thrombosis was reported in 16 studies with varying regimes: nine studies reported heparin only regimens,[51-54,58,60,61,63,65] four studies reported combination regimens of heparin with ticlopidine,

clopidogrel, or aspirin,[47,48,56,64] and three other studies reported combination regimens of aspirin with dipyramidamole, clopidogrel, or warfarin.[46,49,55]

Key Question 1:

Mortality (Study Duration 6 Months or Greater)

Data on mortality 30 days after angioplasty with stent placement was reported in 18 studies. The mortality rates ranged from 0.5 to 53 percent; seven studies reported over 10 percent mortality at follow up.[46,49,51,59,61,64,66] The most common cause of mortality reported was due to cardiovascular-related deaths. Across studies, there was an expected rise in mortality with increasing duration of followup. However, by visual inspection, there appear to be two groups of studies, those with mortality rates rising from approximately 12 to 30 percent over 4 years, and those with lower mortality rates rising from 0 percent to under 10 percent over 5 years. We were unable to identify any clear factor that explained the differences in mortality rates across studies.

Kidney Function

Four studies reported kidney outcomes as changes in estimated glomerular filtration rate (or creatinine clearance).[49,57,61,64,67] Thirteen other studies reported changes in followup serum creatinine Of these, statistically significant improvements in kidney function were observed from 12 to 24 months in three studies, statistically significant deterioration was reported in two studies, and the remaining 12 studies found no significant changes. Kidney outcomes were quantified using different definitions and categorized as improved, unchanged, and worsened in 12 studies. Improved kidney function ranged from 8 to 51 percent. Several studies noted that some patients were able to stop dialysis.

Blood Pressure Control

All 21 studies reported blood pressure outcomes as change from baseline and/or categories of cured, improved, unchanged, and worsened. The categories were quantified using a variety of cut-off levels of both systolic and diastolic blood pressure. The cure rates ranged from 4 to 18 percent, and the improved rates ranged from 35 to 79 percent. The studies also noted decreased use of antihypertensive medications compared to baseline.

Cardiovascular Outcomes

Two studies reported cardiovascular event rates, indicating that patients remain at increased risk of cardiovascular disease after angioplasty with stent placement.[53,64] Gray 2002, however, reported a statistically significant reduction in the New York Heart Association of Functional Class after stent placement.[58]

Restenosis Rate

A total of 17 studies evaluated restenosis rates during follow-up.[48,50-52,54-66] Of these only three studies evaluated the whole cohort of patients who underwent stent placement for restenosis at follow-up.[50,58,63] A proportion of the original cohort who presented with clinical symptoms was evaluated in the remainder of the studies. Five studies reported restenosis rates per artery evaluated.[48,55,56,59,61] The restenosis were diagnosed between 3 to 40 months after percutaneous interventions and the rates ranged from 10 to 21 percent. The majority of the studies used stenosis greater than 50 percent as their definition and utilized angiography to evaluate or confirm restenosis. Only one study utilized duplex ultrasound.[59] The interobserver variability in diagnosing restenosis rates was examined in Bucek 2003 that noted disagreement in one patient.[50] Ramos 2003 found a statistically significant higher rate of restenosis among those who had undergone stent placement for ostial lesions compared to those with nonostial lesions (27 versus 8 percent).[57]

Adverse Events (Including 30-Day Mortality)

A total of 16 studies reported adverse events immediately following angioplasty with stent intervention. The 30-day mortality was reported in 11 studies and ranged from <1 to 3 percent. A transient deterioration in kidney function following procedure was reported in 8 studies, which ranged from 1 to 13 percent, including four studies that reported contrast-induced nephropathy. A severe decline in kidney function was reported in three studies. Renal artery or parenchymal injury during procedures ranged from <1 to 10 percent in seven studies. Other complications included: major hemorrhage 1 percent (one study); renal artery occlusion or spasm 0.5 to 4 percent (five studies); false aneurysms 0.7 to 9 percent (six studies); severe bleeding 1 to 16 percent (six studies); and localized hematoma 0.4 to 10 percent (five studies).

Key Question 2:

Predictors of Outcomes

Fourteen of the total 21 studies evaluating treatment of angioplasty with stent placement also analyzed baseline variables and coprocedure interventions as predictors of outcomes.

Baseline Variables as a Predictor of Outcomes

Baseline kidney function

Eight studies evaluated levels of baseline kidney function as predictors of outcomes.[49,52,54,57,61,64-67]

Two studies (Kennedy 2003 and Lederman 2001), in multivariable analyses, found that lower baseline kidney function – defined by creatinine clearance under 40 mL/min or on a continuous

scale of serum creatinine – predicted cardiovascular- and kidney-related mortality (RR = 1.9, P = 0.01) and overall mortality (OR 1.7, 95 percent CI 1.1-2.5).[54,64]

Gill-Leertouwer 2002 and Harden 1997 both reported that better kidney function at baseline – as indicated by serum creatinine less than 2.5 mg/dL or 4.5 mg/dL – predicted favorable clinical outcomes after stent placement.[52,66]

Kennedy 2003 also found that decreased baseline creatinine clearance was associated with at least one poor outcome during followup including myocardial infarction, CHF, stroke, uncontrolled hypertension, and kidney events.[64]

Five studies evaluated kidney function as a predictor of poor kidney outcomes with heterogeneous findings. Lederman 2001 noted that two-thirds of the patients with decreased baseline kidney function had late deterioration in kidney function after angioplasty with stent placement.[54] However Tuttle 1998 found no difference in kidney outcomes between the groups stratified by baseline serum creatinine levels at 2 mg/dL.[61] In contrast, Zeller 2004, in adjusted analyses, found that kidney outcomes improved statistically significant after intervention among those with more severe baseline kidney function.[49] Ramos 2003 found a mixed effect, such that patients with baseline creatinine clearance below 50 mL/min had worse blood pressure control, but better kidney function improvement after angioplasty with stent placement than patients with better baseline kidney function.[57] The prestenting serum creatinine level did not predict the primary outcome, changes in kidney function after stenting, in Rivolta 2005.[65]

Baseline severity of ARAS

Seven studies evaluated whether the presence of bilateral versus unilateral stenosis, or percent stenosis, affected the rate of poor outcomes.[46,48,49,51,55,57,64,68]

Two studies came to opposite conclusions regarding whether bilateral disease was a predictor of increased mortality. Dorros 2002 found that survival rates were lower with bilateral than unilateral ARAS (36 vs. 55 percent, P<0.05).[46] Similarly, the survival rates were significantly lower among patients with mild to moderate chronic kidney disease and bilateral ARAS (serum creatine >1.4 vs. <2.0 mg/dL) compared to those with mild to moderate chronic kidney disease and unilateral ARAS (78 versus 68 percent, P<0.05). Kennedy 2003, however, found that bilateral stenosis at baseline was not an independent predictor of cardiovascular- and kidney-related mortality, although it was associated with at least one poor clinical outcome.[64]

Three of four studies reported no statistically significant differences in kidney and blood pressure outcomes between those patients with bilateral or unilateral disease after interventions;[48,51,57,68] only one study[55] reported baseline bilateral lesions independently predicted statistically significant benefit for blood pressure control at followup.

Zeller 2004 found that each increase in percent diameter stenosis at baseline independently predicted a decrease in serum creatinine at followup (OR 1.05 per each 1 percent increase stenosis, 95 percent CI 1.01-1.02, P=0.02).[49] Thus patients with higher grade stenosis had greater improvements in kidney function after angioplasty with stent placement.

Baseline cardiovascular disease as a predictor

Four studies evaluated the association between various measures of baseline cardiovascular disease and either mortality, other poor outcomes, or kidney function.[49,54,58,64]

Three studies (Kennedy 2003, Lederman 2001, Gray 2002) reported that either baseline CHF, number of diseased epicardial coronary arteries, and moderate to severe left ventricular dysfunction were associated with either cardiovascular- and kidney-related mortality or all-cause mortality.[54,58,64] However, Kennedy 2003 and Lederman 2001 also found that either baseline myocardial infarction or ejection fraction, CHF, hyperlipidemia, and global ARAS did not predict increased mortality.

Kennedy 2003 also found that baseline CHF, either CHF or chronic kidney disease as indications for an angiographic evaluation, and increased number of vessels treated by revascularization were associated with at least one poor outcome including myocardial infarction, CHF, stroke, uncontrolled hypertension, and kidney events.[64]

Zeller 2004 found that three-vessel CAD independently predicted a 61 percent lower probability of improved kidney function at followup after successful angioplasty with stent placement compared to those without relevant CAD.[49]

Diagnostic tests and other predictors

One study evaluated baseline resistance index as a predictor of kidney function and blood pressure after angioplasty with stent placement. Consistent with their other findings, Zeller 2004 found that patients with more severe kidney dysfunction at baseline, including resistance index over 80 percent benefited most from angioplasty with stent placement in terms of change in kidney function and blood pressure control.[49]

Again, consistent with their other findings, Zeller 2004 found that patients with higher baseline mean arterial pressure or higher number of antihypertensive medications had relatively improved blood pressure after angioplasty with stent placement.

In contrast, Kennedy 2003 found that beta-blocker or diuretic use at baseline were not independent predictors of cardiovascular- and kidney-related mortality. This study also found that patients with diabetes had a less favorable clinical outcome after angioplasty with stent placement.[64]

Two studies (Lederman 2001 and Kennedy 2003) found that age was not associated with mortality rates.[54,64] Lederman 2001 also found that sex was not associated with mortality.

Key Question 3:

Coprocedure Interventions as Predictors of Outcomes

One study, Zeller 2004, in a multivariable analysis, simultaneous bilateral stenosis predicted improved kidney function (decreased serum creatinine) with OR = 2.57 (95% CI 1.55, 4.25).[49] No other prospective study reported analyses of whether other peri-procedural interventions, such as different drugs or different approaches, affected either complications or long-term outcomes.

Table 7. Angioplasty with stent placement for treatment of renal artery stenosis
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data, and Table 8 for 30-day mortality data.

Author, Year / Study Design	Mean BP / Mean GFR [SCr]	Mean % Stenosis / % Bilateral Stenosis	No. Evaluated RAS (ARAS)	RAS Location / Years Enrolled	Mean Duration / Range	Results: HTN (%) and BP Δ				Results: CKD (%) and GFR / SCr Δ			% Restenosis	Qual / Appl
						Cured	Imp	UnΔ	Worse	Imp	UnΔ	Worse		
Kennedy, 2003[64,69 A]	168/82	>60[B]	261	nd	21 mo								48	B
Prosp	51	38	(253)	1993-2001	1-85		BP Δ = -19/-6 P=0.0001				CrCl Δ = -2 P <0.05		17 mo	High
Rocha-Singh, 2005[48]	168/82	>70	208	Ostial 100%	nd								17[C]	B
Prosp	[1.4]	21	(208)	1997-1999	9-24 mo		BP Δ = -19/-5 P=0.001				SCr Δ = +0.10 P<0.04		9 mo	Mod
Dangas, 2001[53 D]	170/84	74	131	Ostial 75%	15 mo		47	40	13	18	61	21	nd	B
Prosp	[1.9]	17	(nd)	nd	nd		BP Δ = -15/-10 P<0.001							Mod
White, 1997[56]	173/88	>50	100	Ostial 81%	6 mo								19[C]	B
Prosp	[2.4]	33	(100)	1992-1994	nd		BP Δ = -27/-11 P<0.01						6 mo	Mod
Gill, 2003[51]	191/98[E]	>50[F]	100[G]	Ostial 78%	25 mo	4	79	17		31	42	31	66[H]	B
Prosp	[2.7][I]	26	(100)	1993-1999	1-66		BP Δ = -27/-12 P<0.01				SCr Δ = -0.6 mg/dL[J] NS		11 mo	Mod
Blum, 1997[63]	MAP 133	>50	68	Ostial 100%	27 mo	11	42	15					12	B
Prosp	[1.2]	9	(68)	1989-1996	3-84		MAP Δ = -20 P<0.0001				SCr Δ= 0 NS		3-24 mo	Low
Iannone, 1996[59]	160/80	67	63	Ostial 78%	10 mo	4	35	54	7	36	46	18	14[c]	B
Prosp	[1.8]	22	(63)	1992-1993	1-22		BP Δ = -15 / 0 P=0.004/NS				SCr Δ = 0.2 NS		11 mo	Mod
Harden, 1997[66]	169/95	>50	32	Ostial 75%	17 mo					34	34	28	12.5	B
Prosp	nd	34	(32)	1992-1995	nd		BP Δ = -6 / -8 NS/ <0.01						6 mo	Mod
Zeller, 2004[49,70-73]	102	>70	354[K]	Ostial 95%	34 mo		46	43	11	10	39	27	nd	B
Prosp	[1.5]	nd	(340)	1996-2002	2-79		MAP Δ = -8 P<0.0001				GFR Δ = +3.0 NS			Mod
Gross, 1998[60]	163/93	75	30	Ostial 100%	6 mo		69	31					12.5	B
Prosp	[1.4]	23	(30)	nd	nd		BP Δ =-18/-10 P=0.004/0.007						6 mo	Low

Table 7. Angioplasty with stent placement for treatment of renal artery stenosis. Continued.

Author, Year Study Design	Mean BP Mean GFR [SCr]	Mean % Stenosis % Bilateral Stenosis	No. Evaluated RAS (ARAS)	RAS Location Years Enrolled	Mean Duration Range	Results HTN (%) and BP Δ Cured	Imp	UnΔ	Worse	CKD (%) and GFR / SCr Δ Imp	UnΔ	Worse	% Restenosis	Qual Appl
Dorros, 2002[46,74-77]	168/84	nd	1058	nd	nd								nd	C
Prosp	[1.7]	36	(1058)	1990-1997	1-4 yr	BP Δ = -21/-6 P<0.05				SCr Δ = -0.4 P<0.05				Mod
Ledermen, 2001[54]	164/84	62	300	Ostial: 95%	16 mo		70			8	78	14	21	C
Prosp and Retro	[1.5]	41	(293)	1993-1998	6-24	BP Δ = -22/ -8				SCr Δ = +0.11 P=0.05			17 mo	Mod
Rocha-Singh, 1999[55]	110 MAP[L]	>75	150	Ostial 43%	13 mo	6	50	44		23	69	8	12[C]	C
Prosp	[1.5][M]	20[N]	(150)	1993-1995	nd					SCr Δ = +0.04 NS			13 mo	Mod
Tuttle, 1998[61]	160/84	>70	129	Ostial 100%	nd	55				15	81		14[C]	C
Prosp & Retro	40	15	(129)	1991-1996	6-24	BP Δ = -8/-4[O] P<0.05				CrCl Δ= 0 NS			8 mo	Mod
Ramos, 2003[57]	160/91	>70	105	Ostial 32%	12.2 mo	18	47						14	C
Prosp	54	43	(105)	nd	3.3-23	BP Δ = -15/-8 P<0.0001				GFR Δ = +8 P=0.007			12 mo	Mod
Harjai, 1997[62]	178/91	>70	66	Ostial 73%	19 mo	66							25	C
Prosp	[1.6]	27	(66)	1992-1995	nd	BP Δ = -32/-17 nd							9 mo	High
Henry, 2003[47]	169/104	85	56	Ostial 100%	23 mo	18	59	23		18	82	0		C
Prosp [P]	[1.3]	14	(56)	1999-2002	2-47	BP Δ = -19/-11 P<0.01				SCr Δ = -0.1 mg/dL NS			nd	Low
Rivolta, 2005[65]	161/86	>70	52	nd	24					15	60	25	10	C
Prosp	[2.9]	37	(52)		9-54	BP Δ = -18/-7 P<0.01[Q]							6 mo	Mod
Gill-Leertouwer, 2002[52,78]	177/96[R]	>50	40	nd	1 yr								14	C
Prosp	[1.3][S] [2.4][T]	nd	(40)	1996-1998	nd	Clinical success 85%				Clinical success 25%			12 mo	Low
Bucek, 2003[50]	nd	>80	40	Ostial 100%	3.3 yr[U]		38	43				25	13-15	C
Prosp & Retro	nd	nd	(40)	1997-2002	0.8-6.3								40 mo	Low
Gray, 2002[58 V]	174/85	>70	39	nd	21 mo		72	15		51	26	23	10	C
Prosp	[3.2]	46	(39)	1991-1997	1-61								21 mo	Mod

Δ, change; Appl, applicability rating; ARAS, atherosclerotic renal artery stenosis; BP, blood pressure; ,CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate (or creatinine clearance, mL/min or mL/min/1.73 m^2)); HTN, hypertension; Imp, improved;, mo, months; MAP, mean arterial pressure; Mod, moderate; nd, no data; NS, nonsignificant; ,Prosp, prospective nonrandomized study; Qual, quality rating; RAS, renal artery stenosis; Retro, retrospective study; SCr, serum creatinine (mg/dL); UnΔ, unchanged (or stable); yr, years.

[A] CVD outcomes: myocardial infarction 11%; CHF 20%; stroke 7%.
[B] Diagnosed by digital caliper technique.
[C] % restenosis reported according to the arteries evaluated.
[D] Myocardial infarction 5%.
[E] Among 48/50 with resistant HTN.
[F] N=102/126 > 85% stenosis.
[G] N analyzed at baseline for BP=48 and CKD=65.
[H] Of the arteries evaluated: Neointimal hyperplasia 61%; stent migration 22%, and true stent restenosis 17%.
[I] Among 65/75 with CKD at baseline.
[J] N analyzed = 18.
[K] Evaluated at follow-up n=113.
[L] Outcomes evaluated n=127.
[M] Outcomes evaluated n=132.
[N] Among those with follow-up (n=127).
[O] Analyzed at 12 mo (n=41).
[P] Utilized distal protection device and follow-up data available for maximum numbers at 6 month.
[Q] Significant only for systolic blood pressure.
[R] 60% less than 2 yr duration of HTN.
[S] Baseline value among those with clinical success (n=27).
[T] Baseline value among those with clinical failure (n=13).
[U] Median.
[V] New York Heart Association class Δ=-1.4 P<0.001.

Table 8. Adverse events associated with angioplasty with stent placement treatment of renal artery stenosis
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data.

Author Year	N RAS (ARAS)	Intervention	Kidney-related	CVD-related	Thrombosis/ occlusion	Bleeding	30 d mortality	Other
Dorros 2002[46,74-77]	1058	Angioplasty stent placement	Contrast induced acute kidney failure 13%			Retroperitoneal hemorrhage 1 %	Deaths 0.3%	
Zeller 2004[49,70-73]	340 268 (268)	Angioplasty stent placement	Severe deterioration of kidney function 1.5% Local dissection or perforation 4%		False aneurysm 1% Access site occlusion 0.3%	Severe access site bleeding 2%	30 d mortality 0.6% Death after 3 d due to embolic stroke 0.3%	Stent displacement 1%
Lederman 2001[54]	300 (293)	Angioplasty stent placement	Guidewire induced dissection of renal artery branch 0.3%		Intraprocedural thrombosis of the target renal artery 0.3%		Death from MI 0.3%	Acute/flash pulmonary edema 0.3% Stent migration into aorta 0.3% Aspirin hypersensitivity 0.3%
Kennedy 2003[64,69]	261 (253) 127 (127)	Angioplasty stent placement			Total occlusion of stented artery 0.8%	Hematuria due to vessel perforation 0.8%		Access site complications with brachial approach 3% Access site complications with femoral approach 3% Dislodged stent 1.0% Dislodged unexpanded stent 0.8%
Rocha-Singh 2005[48]	208 (208)	Angioplasty stent placement		In-hospital Major hemorrhage 1% Major vascular event 2% Out of hospital up to 2 yr Major hemorrhage 0.5%	In-hospital Major embolic event 1.4% Stent thrombosis 0.5%			Access site complications 5%
Rocha-Singh 1999[55]	150 (150)	Angioplasty stent placement	Contrast induced nephropathy 5% Kidney parenchymal guidewire perforations 1.3%				Death from tubular necrosis and multiorgan failure 0.7% Death from GI hemorrhage after stent implant while on warfarin 0.7%	Overall major complication rate 3%

Table 8. Adverse events associated with angioplasty with stent placement treatment of renal artery stenosis. Continued.

Author Year	N RAS (ARAS)	Intervention	Kidney-related	CVD-related	Thrombosis/ occlusion	Bleeding	30 d mortality	Other
Dangas 2001[53]	131 (nd)	Angioplasty stent placement	Kidney failure 6%		Femoral artery pseudoaneurysms 1.5%		Death 0.8%	
Tuttle 1998[61]	129 (129)	Angioplasty stent placement	Contrast induced acute kidney failure 12%		Atheroembolic disease 0.7% Arterial thrombosis 0.4%	Groin hematoma 7% Perirenal hematoma 0.4%	Death 3%	Stent migration 0.7%
Gill 2003[51]	100 (100)	Angioplasty stent placement	Transient SCr rise 1%		Transient lobar branch renal artery occlusion 2% Femoral artery false aneurysm 2% Femoral artery trauma 2% Non flow limiting intimal dissection 1%	Groin hematoma 6%	Death after lower limb cholesterol embolization 1% Death after thrombosis of aortofemoral prosthetic graft 1%	Migrating stent 1%
White 1997[56]	100 (100)	Angioplasty stent placement	Transient contrast nephropathy 2% No perforations		Femoral artery pseudoaneurysm 1% Brachial artery occlusion 1% Subacute stent thrombosis after 3 d 1%	Groin hematoma 5%	Ischemic cardiac death after 2 d 1%	
Blum 1997[63]	68 (68)	Angioplasty stent placement				Local hematomas at puncture site 4%		No major complications
Harjai 1997[62]	66 (nd)	Angioplasty stent placement	Temporary rise in SCr 5%			Minor bleeding from vascular access site 5%		
Iannone 1996[59]	63 (61)	Angioplasty stent placement	Acute kidney failure 13% Renal artery perforation 5%		Psuedoaneurysm at insertion site 1.6%	Minor groin hematoma 10% Bleeding requiring transfusion including peripheral embolus requiring thrombolysis 16%	Death after perirenal bleeding 1.6%	
Henry 2003[47]	56 (56)	Angioplasty stent placement			Arterial spasm at site of protection device 4%		Death on d 3 from MI 1.8%	No device related complications
Harden 1997[66]	32 (32)	Angioplasty stent placement			Femoral artery pseudoaneurysm 9%	Hemorrhage 9%	Death from circulatory collapse after stent placement 3%	
Gross 1998[60]	30 (30)	Angioplasty stent placement	Dissection after predilatation 10%		No vessel had early or subacute thrombotic occlusion			No guidewire perforation detected.

ARAS, atherosclerotic renal artery stenosis; CKD, chronic kidney disease; CVD, cardiovascular disease; d, days; GI, gastrointestinal; MI, myocardial infarction; N, number of subjects; nd, no data; PTRA, percutaneous renal angioplasty; RAS, renal artery stenosis; SCr, serum creatinine.

Angioplasty of Atherosclerotic Renal Artery Stenosis
(Tables 9-10, Figures 2-3)

Key Points for Angioplasty for Atherosclerotic Renal Artery Stenosis

- This review evaluated four studies of angioplasty that placed stents in some patients and included a total of 427 patients for clinical outcomes. Three studies were rated to be moderate quality (Grade B), one poor quality (Grade C).

- Overall, at baseline, patients frequently had diffuse atherosclerotic vascular diseases. The studies followed patients for 1 to 2 years after intervention. Almost one half of the studies were of moderate applicability to the populations of interest; only one study was of high applicability.

- The majority of the patients had cured or improved blood pressure rates at followup compared to baseline. However the improved kidney outcomes and mortality rates varied across the studies. No studies reported cardiovascular disease outcomes.

- Adverse events following angioplasty included 30-day mortality that ranged from 1 to 2 percent and transient decline in kidney function that ranged from 3 to 24 percent.

- A decreased baseline kidney function predicted deterioration in kidney function following intervention. A decline in kidney function was also observed with baseline resistance index of at least 80 percent or more.

- The angioplasty intervention in the presence of bilateral versus unilateral stenosis, or percent stenosis did not predict outcomes.

- No differences in outcomes were seen in studies that placed stents or no stents during angioplasty.

We identified one RCT[79] and three cohort studies[67,68,80] that treated ARAS with various approaches: angioplasty, angioplasty with stent placement, or surgical revascularization. Followup ranged from 6 to 32 months and included a total of 427 patients. Three studies included patients with over 60 percent stenosis.[67,79,80] Fewer than 30 percent of the included patients had ostial stenosis in two studies;[68,80] and the RCT included only patients with ostial stenosis.[79] About 40 percent or less of the included patients had bilateral stenosis. The RCT and one nonrandomized study compared outcomes in patients who had angioplasty and angioplasty with stent placement.[67,80] One study evaluated baseline resistance index as a predictor of outcomes. [67] In this study patients were categorized based on the baseline resistance index values of 80 or more and those with values of less than 80.

Key Question 1:

Mortality (Study Duration 6 Months or Greater)

Data on mortality 30 days after angioplasty was reported in all four studies that ranged from 1 to 10 percent. Studies did not clearly document the most common cause of mortality.

Kidney Function

Only one study reported kidney outcomes as changes in creatinine clearance.[67] Kidney outcomes were quantified using different definitions and categorized as improved, unchanged, and worsened in three other studies.[68,79,80] Improved kidney function ranged from 10 to 33 percent. In two studies, there was no difference in kidney outcomes observed between the procedures.[79,80]

Blood Pressure Control

One study reported blood pressure outcomes as mean arterial pressure (MAP) change from baseline.[67] The other three studies reported blood pressure as categories of cured, improved, unchanged, and worsened.[68,79,80] The categories were quantified using a variety of cut-off levels of both systolic and diastolic blood pressure. The cure rates ranged from 4 to 15 percent, and the improved rates ranged from 43 to 68 percent. The studies also noted decreased use of antihypertensive medications compared to baseline.

Cardiovascular Outcomes

No study reported data on cardiovascular outcomes.

Adverse Events (Including 30-Day Mortality)

Six studies reported adverse events immediately following angioplasty intervention, including two studies that did not qualify for evaluation of other clinical outcomes.[44,45,67,68,79,80] The 30-day mortality was reported in three studies and ranged from 1 to 2 percent. A transient deterioration in kidney function following procedure was reported in two studies (3 and 24 percent), including one study that reported contrast-induced nephropathy. Renal artery or parenchymal injury during procedures were 5 and 21 percent in two studies. Other complications included: renal artery occlusion or spasm 0.5 to 4 percent (four studies); false aneurysms 0.7 to 2 percent (four studies); severe bleeding 2 and 19 percent (two studies); and localized hematoma 5 percent (one study).

Key Question 2:

Predictors of Outcomes

Two studies evaluating treatment of angioplasty also analyzed baseline variables as predictors of outcomes.

Baseline Variables as a Predictor of Outcomes

Baseline kidney function

Radermacher 2001 evaluated levels of baseline kidney function as predictors of outcomes.[67] This study reported that a baseline creatinine clearance of less than 40 mL/min predicted a 13-fold increased risk for a decline in kidney function at follow-up in both univariate and multivariable analyses. In addition, various factors before revascularization including proteinuria and small size of the kidneys (<9 cm) predicted worse kidney function at follow-up in univariate analyses only.

Baseline severity of ARAS

Ziakka 2002 evaluated whether the presence of bilateral versus unilateral stenosis, or percent stenosis, affected the rate of poor outcomes.[68] This study reported no statistically significant differences in kidney and blood pressure outcomes between those patients with bilateral or unilateral disease after interventions.

Diagnostic tests and other predictors

Radermacher 2001 evaluated baseline resistance index as a predictor of kidney function and blood pressure after angioplasty, angioplasty with stent placement or surgical revascularization. They found that patients with resistance index above 80 percent were more likely to have worsening kidney function and less likely to have either improved blood pressure or reduced use of antihypertensive medication after revascularization, both by univariate and adjusted multivariable analyses.

The same study also found that men had less favorable clinical outcomes following revascularization.

Key Question 3:

Coprocedure Interventions as Predictors of Outcomes

Among the studies that used angioplasty or angioplasty with stent placement for the treatment of ARAS, there were no differences in blood pressure and kidney outcomes between the procedures.[79,80] No other study reported analyses of whether other periprocedural interventions, such as different drugs or different approaches, affected either complications or long-term outcomes.

Table 9. Angioplasty for treatment of renal artery stenosis
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data, and Table 10 for 30-day mortality data.

Author, Year Study Design	Mean BP Mean GFR [SCr]	Mean % Stenosis % Bilateral Stenosis	No. Evaluated RAS (ARAS)	RAS Location Years Enrolled	Mean Duration Range	Results: HTN (%) and BP Δ				Results: CKD (%) and GFR / SCr Δ			Qual Appl
						Cured	Imp	UnΔ	Worse	Imp	UnΔ	Worse	
Angioplasty with or without stent in patients with severe ARAS													
Stent placed in some													
Baumgartner, 2000[80]	179/95[A]	>60	188	Ostial 29%	9 mo		43		12	33	42	25	B
Prosp	[2.0] [2.9][B]	37	(188)	1994-1998	nd								Low
van de Ven, 1999[79]	186/103	>50	81	Ostial 100%	6 mo	15	43	43		13	65	20	B
						Stent group NS							
RCT	[1.8]	18	(81)	1993-1997	nd	4	44	51		10	29	20	High
						No stent group							
Ziakka, 2002[68]	177/94	nd	117	Ostial 30%	1 yr	6	68	26		18	55	27	C
Prosp	[2.3]	30	(107)	1993-1998	nd								Mod
Angioplasty with or without stent or surgery in patients with severe ARAS													
Stent placed in some													
Radermacher, 2001[67]	MAP 109	70	138	nd	32 mo								B
Prosp	59	nd	(nd)	1994-1999	up to 60 mo	MAP Δ =-7 (P nd)				GFR Δ =+15 (P nd)			Mod

Δ, change; Appl, applicability rating; ARAS, atherosclerotic renal artery stenosis; BP, blood pressure; CKD, chronic kidney disease; Imp, improved; GFR, glomerular filtration rate (or creatinine clearance, mL/min or mL/min/1.73 m^2); HTN, hypertension; MAP, mean arterial pressure; mo, months; Mod, moderate; nd, no data; Prosp, prospective nonrandomized study; Qual, quality rating; RAS, renal artery stenosis; RCT, randomized controlled trial; SCr, serum creatinine (mg/dL); UnΔ, unchanged (or stable); yr, years.

[A] Evaluated n=163 at follow-up.
[B] CKD outcomes evaluated among those with CKD at baseline (n=107).

Table 10. Adverse events associated with angioplasty treatment of renal artery stenosis
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data.

Author Year	N RAS (ARAS)	Intervention	Kidney-related	CVD-related	Thrombosis/ occlusion	Bleeding	30 d mortality	Other
Baumgartner 2000[80]	163 (163)	Angioplasty or stent placement		Peripheral atheroembolization 1.1% (overall)	Acute renal artery occlusion 0.5% (overall) Femoral pseudoaneurysm 1.6% (overall)	Bleeding requiring transfusion 1.6% (overall)	Death 1.6% (unrelated to procedure) (overall)	PTRA complications 3% Stent placement complications 9%
Radermacher 2001[67]	138 (nd)	Angioplasty or stent placement or surgical revascularization	Intimal dissections corrected with stent placement 21%	Aortic dissection 0.7%	Renal artery occlusion 2% False aneurysm requiring surgery 0.7%			Dislocated stent into or beyond aorta 1.4%
Ziakka 2002[68]	117 (107)	Angioplasty or stent placement	Transient ARF due to probable cholesterol embolism and contrast nephrotoxicity 1.7%			Femoral artery hematoma 5%	Patient with atheromatous disease died within 24 hours 0.9%	
van de Ven 1999[79]	85 (85)	Angioplasty v stent placement	Transient decrease in kidney function due to radiography contrast agent 24% (Angioplasty) 21% (Stent) Kidney failure induced by cholesterol embolism 10% (Angioplasty) 10% (Stent) Renal artery injury 5% (Angioplasty) 7% (Stent)		Renal artery occlusion: 2% (Angioplasty) 2% (Stent) Acute thrombosis 2% (Stent) Femoral artery aneurysm 5% (Angioplasty) 5% 7% (Stent) (including 1 arteriovenous fistula)	Bleeding 19% (Angioplasty) 19(%(Stent)		Technical failure 7% (Angioplasty) 7% (Stent)

Table 10. Adverse events associated with angioplasty treatment of renal artery stenosis. Continued.

Author Year	N RAS (ARAS)	Intervention	Kidney-related	CVD-related	Thrombosis/ occlusion	Bleeding	30 d mortality	Other
Gross 2001[44]	38 (nd)	Angioplasty						No complications were observed
Spinosa 2001[45]	14 (nd)	Angioplasty	Contrast induced nephropathy 3% Injury to renal artery branch 0.6%	Transient mesenteric ischemia 1.3% Cerebral vascular accident 0.6% MI 0.6%	Pseudoaneurysm at puncture site 0.6%		2 deaths within 30 d 1.3% (1 due to cholesterol embolization, 1 unrelated to procedure)	

ARAS, atherosclerotic renal artery stenosis; CKD, chronic kidney disease; CVD, cardiovascular disease; d, day; GI, gastrointestinal; MI, myocardial infarction;; N, number evaluated; nd, no data; PTRA, percutaneous renal angioplasty; RAS, renal artery stenosis; SCr, serum creatinine.

Surgical Treatments of Atherosclerotic Renal Artery Stenosis
(Tables 11-12, Figures 2-3)

Key Points for Open Revascularizations for Atherosclerotic Renal Artery Stenosis

- Four studies that reported outcomes of surgical treatments for ARAS met eligibility criteria. All four studies had methodological flaws making them susceptible to bias.
- All four studies reported similar long-term mortality (about 30-40 percent at 5 years).
- Two studies reported that 60-70 percent of patients had improvements in hypertension.
- One study reported 17 percent of the patients became dialysis-dependent during a mean follow up period of 56 months.
- Thirty-day mortality rate ranged from 3.7 to 9.4 percent.

Given the limited applicability of studies of surgical interventions to angioplasty with stent placement, the eligibility criteria for these studies were restricted to include only those most likely to have greater applicability. Thus, only studies that included at least some patients who had surgery after the publication of JNC-5 (1993) were included. Prospective studies with at least 10 subjects and retrospective studies with least 100 subjects were eligible. As with the limitations to the eligibility criteria for angioplasty studies, these criteria limited our review of long-term clinical outcomes (≥6 months) and patient-level predictors of outcomes.

Four studies met criteria. Two retrospective comparative studies,[81,82] and two retrospective cohort studies,[83,84] provided surgical outcomes in 921 patients. The comparative studies compared surgical to percutaneous interventions, but only the surgical cohorts were included here since the key questions did not relate to this comparison and the data from the angioplasty cohorts were retrospective. The mean follow up times in these studies ranged from 4 months to 56 months. All four studies were of methodological quality C (poor). The results from these studies are generally applicable to patients with hypertension, chronic kidney disease, and hemodynamically significant ARAS.

The four studies had similar inclusion criteria and reviewed similar populations of patients with ARAS with hypertension, chronic kidney disease, or both hypertension and chronic kidney disease. Galaria 2005 included only patients with at least 60 percent stenosis.[82] All the patients in the study by Marone 2004 had at least 75 percent stenosis.[84] Cherr 2002 reported that 41 percent of the patients had at least 80 percent ostial stenosis or occlusion.[83] Alhadad 2004. did not provide explicit information regarding the stenosis. The mean age of the subjects in all studies was in the mid-60s.[81]

Key Question 1:

Mortality (Study Duration 6 Months or Greater)

Galaria 2005 reported 5-year mortality of 27 percent.[82] Marone 2004 reported a 5-year mortality of about 41 percent.[84] Cherr 2002 estimated 5-year and 10-year mortality for all patients at 31 and 66 percent, respectively.[83] Cardiovascular events accounted for most of the late deaths (74 percent). Six-year mortality in Alhadad 2004 was 42 percent and 10-year was 62 percent.[81]

Kidney Function

Galaria 2005 reported cumulative freedom from dialysis, kidney disease-related mortality, or serum creatinine > 1.5 mg/dL was 74 percent at 5 years.[82] Cherr 2002 reported that in all the patients who survived surgery, there was a significant increase in postoperative estimated GFR as compared with preoperative GFR (41 vs. 48 mL/min, P <0.0001) .[83] Eighty-four patients (17 percent) eventually became dialysis-dependent during the follow up period of 1 to 159 months. The median survival rate after dialysis-dependence was 18.6 months, with 27 percent of the patients alive at 5 years.

Marone 2004 reported that 72 percent of the patients in the 1990-2001 cohort, with a mean follow up of 46 months, had improved or unchanged excretory function after surgery.[84] Dialysis was instituted in 16 patients from this cohort during a mean follow up of 17 months, resulting in a crude rate of progression to end-stage renal disease of 17 percent. Dialysis-free survival at 5 years was 55 percent.

Blood Pressure Control

Galaria 2005 reported either cured or improved hypertension in 68 percent of the patients at 3 years.[82] At 5 years, 59 percent of the patients showed improvement. Cherr 2002 reported that, of the 477 patients who survived surgical repair, 12 percent were considered to have cured hypertension, 73 percent were improved, and 15 percent had failed blood pressure response.[83] Blood pressure measurements were taken at 8 weeks or more after surgery.

Cardiovascular Outcomes

Alhadad 2004, Galaria 2005, and Marone 2004 did not report long-term cardiovascular outcomes.

Cherr 2002 reported that cardiovascular events accounted for most of the late deaths (74 percent), including coronary artery disease (41 percent), and stroke (9 percent) .[83] Of the late deaths, 24 percent occurred from the treatment of or complications from aneurysmal disease or noncoronary atherosclerosis. There were 218 nonfatal cardiovascular events that occurred in 139 patients (28 percent). They included angina (49 patients), myocardial infarction (29 patients), percutaneous transluminal coronary angioplasty (19 patients), and coronary artery bypass grafting (22 patients). Cerebrovascular events included transient ischemic attacks (18 patients), stroke (22 patients), and carotid endarterectomy (27 patients). Lower extremity revascularization

was necessary in 11 patients. Twenty-four patients had other types of vascular reconstructions. Multivariable analysis showed that preoperative angina showed a significant and independent association with late cardiovascular morbidity rate. Neither blood pressure nor kidney function response showed an association with followup cardiovascular morbidity rate.

Adverse Events (Including 30-Day Mortality)

Thirty-day mortality in the four studies was 4/109 (3.7 percent),[82] 23/500 (4.6 percent),[83] 15/235 (6 percent),[84] and 10/106 (9.4 percent).[81]

Out of the 4 deaths reported by Galaria 2005, two died from cardiac events, one from systemic infection, and one from pulmonary complications. Major morbidity from procedural complications was 4 percent. Twenty percent of the patients developed one of more of the following complications: cardiac (14 percent), respiratory (9 percent), kidney (6 percent), systemic infection (8 percent), and/or other wound-related events (6 percent).

Cherr 2002 reported that perioperative morbidity occurred in 81 patients (16 percent). These events included myocardial infarction (15 patients), stroke (5 patients), significant arrhythmia (22 patients), and pneumonia (36 patients). Five patients had worsening kidney function after operation that resulted in permanent dialysis-dependence within 1 month of surgery.

Alhadad 2004 reported that the early adverse events (deterioration or death within a month) occurred in 14 patients (19 percent) treated with open renal artery surgery. The overall procedural complication rate was 22 percent. Following 30-day complications were reported: bleeding/hematoma 7/92 (8 percent); occlusion/thrombosis 6/92 (7 percent); infection 3/92 (3 percent); distal embolization 2/92 (2 percent).

Key Question 2:

Predictors of Outcomes

Galaria 2005 reported that a patent vessel predicted improvement in kidney function and freedom from dialysis.[82] And in all patients, preprocedure hemodialysis led to poorer functional kidney function recovery.

Cherr 2002 reported that preoperative chronic kidney disease (HR = 2.4, 95 percent CI 1.9-3.0, P <0.001), diabetes mellitus (HR = 2.1, 95 percent CI 1.2-4.0, P = 0.007), prior stroke (HR = 1.5, 95 percent CI 1.0-2.2, P = 0.04), and severe aortic occlusive disease (HR = 1.7, 95 percent CI 1.2-2.3, P = 0.003) showed significant and independent associations with death or dialysis during the followup examination period.[83] After surgery, in comparison with blood pressure improved or failed, blood pressure cured was significantly and independently associated with improved dialysis-free survival rate (OR = 0.5, 95 percent CI 0.3-0.9, P = 0.01). Improved postoperative kidney function showed significant and independent associations with increased dialysis-free survival rate as compared with kidney function unchanged.

Marone 2004 reported that in logistic regression analysis, an early favorable response to surgery (OR = 16, 95 percent CI 1.6-308, P <0.0001) and the initiation of dialysis prior to surgery (OR = 22, 95 percent CI 1.6-308, P = 0.02) were positive predictors of long-term improvement in kidney function.[84] Also, the probability of continued deterioration in kidney

function was increased for those patients who exhibited a baseline serum creatinine of 3 mg/dL or greater.

Key Question 3:

Coprocedure Interventions as Predictors of Outcomes

No reviewed study reported data related to any coprocedures or differences in procedures being associated with differential outcomes.

Table 11. Surgical renal artery revascularization for the treatment of renal artery stenosis
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data, and Table 12 for 30-day mortality data.

Author, Year / Study Design	Mean BP / Mean GFR [SCr]	Mean % Stenosis / % Bilateral Stenosis	No. Evaluated RAS (ARAS)	RAS Location / Years Enrolled	Mean Duration / Range	Results: HTN (%) and BP Δ — Cured	Imp	UnΔ	Worse	CKD (%) and GFR / SCr Δ — Imp	UnΔ	Worse	CVD (%)	Qual / Appl
Cherr, 2002[83,85-88]	200/104	≥ 80%	500	Ostial: nd	4.7 yr	12%	73%		15%	43%	47%	10%	74% of late deaths 2°to CVD; nonfatal events 28% (angina, MI, PTCA, CABG)	C
Retro	41	59%	(500)	1987-1999	1-159 mo	BP Δ = -53/-23 P<0.0001 (base)				GFR Δ = 7.1 P<0.0001 (base) 17% became dialysis dependent				Low
Galaria, 2005[82]	171/82	≥ 50%	100	Ostial: nd	3.5 yr	68% (3 yr) 59% (5 yr)								C
Retro	51	44%	(100)	1984-2004	0-17 yr					CKD event[A] = 20% (3 yr), 26% (5 yr)				Low
Alhadad, 2004[81]	180/100	nd	106	Ostial: nd%	nd									C
Retro	nd	nd	(86)	1987-1996	0-12 yr	Only mortality data reported (after 6 mo). See mortality figure								Low
Marone, 2004[84]	nd	Both cohorts ≥ 75%	Cohort 1: 139 (139)	Ostial: nd	48 mo	Cohort 1: kidney function improved or unchanged in 76% Cohort 2: kidney function improved or unchanged in 72% Dialysis free survival at 5 years was 55% (both cohorts?)								C
Retro	Cohort 1: [>2]Cohort 2: [≥1.5]	nd	Cohort 2: 96 (96)	Cohort 1: 1980-1990 Cohort 2: 1990-2001	6 wk to 12.6 yr									Low

Δ, change; Appl, applicability rating; ARAS , atherosclerotic renal artery stenosis; BP, blood pressure; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate (or creatinine clearance, mL/min or mL/min/1.73 m^2); HTN, hypertension; Imp, improved; MI, myocardial infarction; mo, months; nd, no data; PTCA, percutaneous transluminal coronary angioplasty; Qual, quality rating; RAS, renal artery stenosis; SCr, serum creatinine (mg/dL); UnΔ, unchanged (or stable); wk, weeks; yr, years.

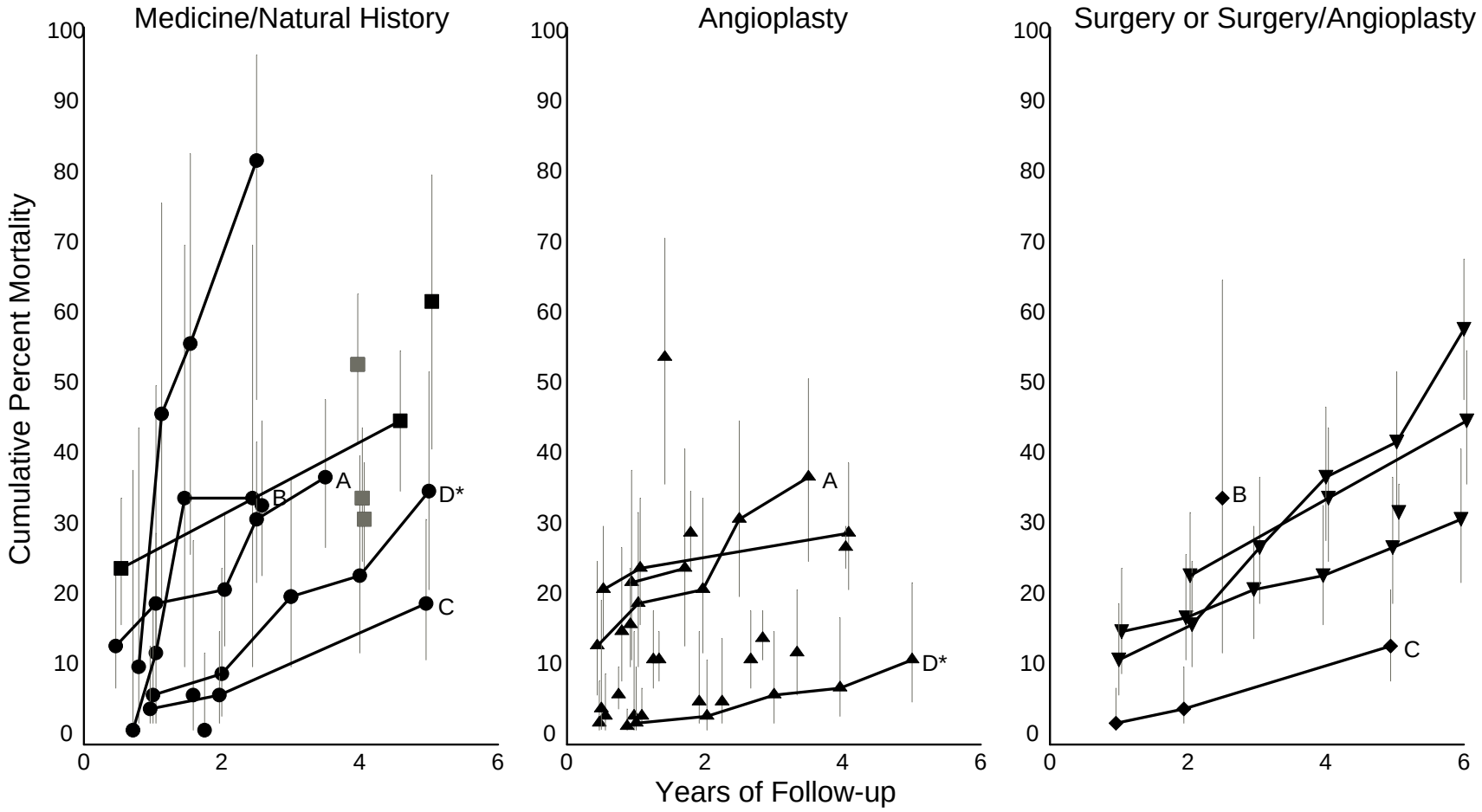
[A] Dialysis, CKD-related mortality, or SCr>1.5 mg/dL.

Table 12. Adverse events associated with the surgical treatment of renal artery stenosis
See Figure 2 (page 72) and Appendix E Figure for long-term mortality data.

Author Year	N RAS (ARAS)	Intervention	Kidney-related	CVD-related	Thrombosis/ occlusion	Bleeding	30 d mortality	Other
Cherr 2002[83,85-88]	500 (500)	Surgery		Perioperative: MI 3% Stroke 1% Significant arrhythmia 5% Nonfatal CVD 28%			Death: 5%	Perioperative morbidity 17% Including pneumonia 8%
Marone 2004[84]	325 (325)	Surgery					Perioperative mortality 6%, mostly secondary to coronary and cerebrovascular events	
Galaria 2005[82]	247 (247)	Angioplasty-Surgery	Perioperative kidney morbidity: 0% (Angioplasty) 6% (Surgery)	Perioperative minor cardiac morbidity <1% (Angioplasty) 14% (Surgery)			Deaths <0.1% (Angioplasty) (all due to cardiac events) Deaths 0.1% (Surgery) 6/10 due to cardiac complications, 3/10 pulmonary, 1/10 sepsis Major morbidity: 4% (Angioplasty) 4% (Surgery)	Technical complication rate: 18% (Angioplasty) 0% (Surgery) Pulmonary adverse events: 0% (Angioplasty) 9% (Surgery) Systemic infection: 0% (Angioplasty) 8% (Surgery) Other wound related events: 0% (Angioplasty) 6%(Surgery)
Alhadad 2004[81]	106 (86)	Angioplasty-Surgery					2% (Angioplasty) 9% (Surgical)	Multiorgan failure 0% (Angioplasty) 2% (Surgery) Sepsis 0% (Angioplasty) 1% (Surgery)

ARAS, atherosclerotic renal artery stenosis; CVD, cardiovascular disease; d, day; MI, myocardial infarction; mo, months; N, number evaluated; RAS, renal artery stenosis; SCr, serum creatinine.

Figure 2. Cumulative mortality after intervention (or start of study period) from 6 months to 6 years, with estimated confidence intervals. See Adverse Events Tables for 30-day mortality data.



* Markedly different eligibility criteria for angioplasty and medicine treatment cohorts. See summary table.

● = medicine; ■ = natural history; ▲ = angioplasty; ▼ = surgery; ♦ = angioplasty or surgery. Vertical lines represent 95 percent confidence intervals calculated with equation of GA Diamond.[89] Points have been jittered along the x-axis to allow for visualization of overlapping data points.

Studies reporting mortality rates at multiple time points within the time period of interest have been connected with solid lines. Letters A,[18] B,[21] C,[23] and D[20] indicate that these studies reported mortality rates for both medical treatment and an invasive intervention. Conlon 2001[38] reports different mortality rates for 3 subsets of patients with different degrees of stenosis (see Appendix E Figure for details) so is represented by grey boxes.
See Appendix E Figure for study specific mortality data.

Summary of Direct and Indirect Comparisons of Angioplasty to Medical Therapy for Treatment of Atherosclerotic Renal Artery Stenosis

No study has directly compared angioplasty with stent placement (the most common invasive intervention for ARAS) with medical treatment. Two RCTs directly compared angioplasty without stent placement to medical treatment, with outcomes primarily reported at 6 and 12 months.[18,19] A third RCT compared immediate angioplasty without stent placement to angioplasty delayed by 3 months in half the remaining patients and medical treatment alone in the other patients.[15-17] The comparison between angioplasty and medical treatment alone is possible only at 3 months (shorter than the long-term duration outcomes of interest); the final comparison was reported at 12 months. The remaining seven comparative studies (one of which was a nonrandomized subgroup of one of the RCTs) compared multiple types of revascularization with a variety of medical treatments for a wide range of durations – from about 6 months to 7 years – in both prospective and retrospective studies.

Hundreds of studies of cohorts of patients receiving angioplasty, both prospective and retrospective, have been published since 1980. Of these, 21 were prospective studies that analyzed at least 30 patients who received angioplasty with stent placement mostly after 1993 and reported long-term (≥6 months) outcomes of interest; an addition four studies followed at least 30 patients who had angioplasty either with or without stent placement. Few studies specifically evaluated the effect of medical treatments that are currently commonly in patients with ARAS. Only four cohort studies evaluated ACE inhibitors or "triple therapy," treatment with three classes of antihypertensive agents. An additional eight natural history studies evaluated cohorts of patients who mostly received medical treatment (although for the most part this is not clear).

All the studies reviewed either implicitly or explicitly included only patients with generally stable blood pressure, kidney function, and cardiovascular status. Patients with acutely decompensation due to progressive ARAS were not included.

Mortality (Study Duration 6 Months or Greater)

RCTs of Angioplasty vs. Medical Treatment

Only the SNRASCG randomized trial (Webster 1998) reported mortality data.[18] Over 0 to 42 months, the survival curves were nearly identical for those randomized to medical therapy (30 patients) or angioplasty (25 patients).

Other Direct Comparisons

In two other studies that directly compared similar patients who received either renal artery revascularization or medical treatment alone, no difference was found in mortality up to about 5 years.

Cross-Study (Indirect) Comparisons

Mortality rates (Figures 1-2) were grossly similar across angioplasty studies, medical treatment studies, and natural history studies. There were four studies, particularly among the natural history studies, that reported mortality rates within 6 years over 40 percent,[38,41-43] however, three of these studies had such high mortality rates only among those with either high-grade stenosis (>75 percent) or bilateral disease.

Kidney Function

RCTs of Angioplasty vs. Medical Treatment

Both RCTs found no clinical or statistically significant differences in kidney outcomes.

Other Direct Comparisons

Seven other studies with direct comparisons between revascularization and medical treatment mostly agreed in their findings of no clinical or statistically significant differences in kidney outcomes. Exceptions included the DRASTIC study (van Jaarsveld 2000)which found a modestly higher rate of worsened kidney function among those with delayed or no angioplasty, but no difference in mean creatinine clearance, and a prospective study that found a modest, but significant relative improvement in serum creatinine after revascularization compared to medical treatment.

Cross-Study (Indirect) Comparisons

Among 17 angioplasty with stent placement cohort studies, improved kidney function ranged from 8 to 51 percent, there were small to modest changes in creatinine clearance (–2 to +8 mL/min) or serum creatinine (–0.1 to +0.2 mg/dL). Only a single cohort study of medical treatment reported change in serum creatinine over an average of 1.5 years, which rose by 0.3 mg/dL. Seven natural history studies also found similar increases in serum creatinine or progressive decreases in kidney function.

Among the 17 angioplasty with stent placement cohort studies many found similar changes in kidney function as the medical and natural history studies, however, only in some of the angioplasty with stent placement studies were patients found to have improved kidney function. This implies that, at least in a subset of patients with ARAS, kidney function is more likely to improve after angioplasty than with continued medical treatment.

Blood Pressure Control

RCTs of Angioplasty vs. Medical Treatment

Of the two RCTs, one found a clinically and significantly larger decrease in blood pressure after angioplasty than medical treatment in patients with bilateral disease, but a nonsignificantly larger decrease in systolic blood pressure in those patients with unilateral disease who were treated medically, rather than with angioplasty. This study also found no difference in the number of antihypertensive drugs required at followup in both sets of patients, regardless of intervention. The other RCT found a modestly greater decrease in both systolic and diastolic blood pressure after angioplasty, but only the change in diastolic pressure was statistically significant compared to medical treatment. In addition, after angioplasty patients required about half as many antihypertensive drugs.

Other Direct Comparisons

Six of the seven other comparative studies that reported blood pressure outcomes found no significant difference in blood pressure control, regardless of intervention. Although one of these found a nonsignificant decrease in blood pressure medication use after angioplasty, in contrast to a significant small increase in medication use in those patients treated only medically. In addition, two of these studies found larger, though nonsignificant, decreases in blood pressure among those patients who did not receive revascularization. Only one problematic, retrospective study reported a significant difference in blood pressure control, such that twice as many patients had improved blood pressure control after angioplasty, with or without stent placement, than with medical treatment alone.

Cross-Study (Indirect) Comparisons

The 21 angioplasty with stent placement cohort studies found that between 4 and 18 percent of patients were cured of hypertension (generally defined as maintaining blood pressure control without medication); although two comparative studies of angioplasty that placed stents in some patients found that no patients were cured after revascularization. Neither medical nor natural history studies reported cure, improvement, or worsening blood pressure rates, possibly implying very small or no "cures."

Across all angioplasty studies, after revascularization with stent placement, blood pressure fell between 6-32/0-17 mm Hg. Blood pressure changes were actually larger among the one medical and seven natural history studies, where blood pressure generally decreased by 20-50/8-42 mm Hg. However, because of differences in antihypertensive treatments both within and between studies, it is impossible to draw conclusions about the relative effect on blood pressure measurements of the different interventions.

Cardiovascular Outcomes

RCTs of Angioplasty vs. Medical Treatment

Only the SNRASCG study(Webster 1998) reported cardiovascular outcomes. No difference was found in event rates for CHF, stroke, or myocardial infarction, regardless of intervention, up to 54 months of followup.

Other Direct Comparisons

Only one other comparative study reported an outcome that included cardiovascular events. In an RCT of revascularization surgery to medical treatment in patients with high-grade stenosis, almost identical rates were found of a combined outcome of atherosclerotic cardiovascular event, death, diastolic hypertension, or worsening kidney function.

Cross-Study (Indirect) Comparisons

The reporting of cardiovascular outcomes in cohort studies was inadequate to allow cross-study comparisons. No study of medical interventions reported cardiovascular outcomes.

Restenosis Rate

A total of 17 studies of angioplasty with stent placement evaluated restenosis rates during follow-up between 3 to 40 months. Of these only three studies evaluated the whole cohort of patients who underwent stent placement for restenosis at follow-up. A proportion of the original cohort who presented with clinical symptoms was evaluated in the remainder of the studies. The restenosis rates ranged from 10 to 21 percent. Only one study noted a statistically significant higher rate of restenosis among those who had undergone stent placement for ostial lesions compared to those with nonostial lesions (27 versus 8 percent).

Adverse Events (Including 30-Day Mortality)

RCTs of Angioplasty vs. Medical Treatment

Neither RCT compared adverse event rates between interventions.

Other Direct Comparisons

No study reported adverse events related to medical treatment, precluding comparisons. One early retrospective study reported that 30-day mortality was similar in both groups of patients.

Cross-Study (Indirect) Comparisons

Adverse events reported in angioplasty studies included 30-day mortality of <1 to 3 percent, transient deterioration of kidney function, renal artery or parenchymal injury, periprocedural cardiovascular events, hemorrhage and hematomas, and renal artery occlusion. Medical studies

did not report 30-day mortality. Adverse events related to blood pressure medications (ACE inhibitors, beta blockers, and hydralazine) included orthostatic hypotension, central nervous system symptoms, digestive symptoms, Raynaud's phenomenon, and others.

Predictors of Outcomes

RCTs of Angioplasty vs. Medical Treatment

Neither RCT directly analyzed whether any baseline predictors, including diagnostic tests, would predict relative outcomes between interventions. Although, in the SNRASCG study (Webster 1998), patients with bilateral stenosis had larger decreases in blood pressure after angioplasty than with medical treatment, in contrast to patients with unilateral disease.

Other Direct Comparisons

The DRASTIC study (van Jaarsveld 2000), comparing early versus either delayed or no revascularization, found that in contrast to patients with unilateral disease, patients with bilateral disease had better improvement in diastolic blood pressure, but not in creatinine clearance. Captopril test, renogram, recent hypertension, and stenosis greater than 80 percent were not predictors of either worse outcome overall or of which intervention would result in better outcomes.

Cross-Study (Indirect) Comparisons

Cohort studies of angioplasty with stent placement found that various baseline variables related to degree of ARAS, coexisting cardiovascular disease, kidney function, and demographics were (or sometimes were not) associated with likelihood of outcomes after the start of an intervention. However, these analyses cannot determine which predictors would be useful to differentiate those patients who might have better outcomes with or without revascularization.

Chapter 4. Summary and Discussion

The following table summarizes the main findings that address the three Key Questions. Discussion regarding the report follows.

Table 13. Summary of Comparative Data in Treatments of Renal Artery Stenosis

Key Questions	Strength of evidence	Summary/conclusion/comments
Key Question 1: Comparisons		
Angioplasty with or without stent vs. medical treatment	N/A	• 2 RCTs evaluated long-term outcomes comparing angioplasty without stent placement to various medical treatments; 6 nonrandomized prospective or retrospective studies compared angioplasty (with or without stent) or surgical revascularization to various medical treatments. • 20 prospective cohorts that met criteria evaluated angioplasty with stent placement; 4 cohort studies evaluated angioplasty with or without stents. • Studies that compared stent placement to no stent placement found no difference in outcomes. • 3 cohort studies evaluated different antihypertensive medical treatments; no studies evaluated anti-hyperlipidemia or lipid-lowering drugs; 8 cohort studies evaluated the natural history of patients with RAS, on various management regimens.
Mortality	Weak	• 1 RCT, 3 nonrandomized comparative studies, and 31 cohort studies of various interventions suggest no difference in mortality up to about 5 years between revascularization and medical treatment.
Kidney function	Acceptable	• 2 RCTs found no difference in kidney outcomes, mostly at 6 and 12 months. • Among 7 other comparative studies, most found no difference in kidney outcomes, although 2 found some supporting evidence for better kidney function after angioplasty (with or without stent). • The cohort studies mostly support the conclusion that kidney outcomes are similar with either angioplasty or medical treatment, although improvements in kidney function were reported only among the angioplasty cohort studies.
Blood pressure	Acceptable	• The 2 RCTs both found some evidence of greater blood pressure improvement after angioplasty than with medical treatment, although this relative effect may be limited to patients with bilateral disease. • Most other comparative studies found larger blood pressure reductions among patients having revascularization than medical treatment alone, although the difference was often clinically small and statistically nonsignificant. However, 2 studies found larger reductions in blood pressure among patients treated without revascularization, although the differences were not statistically significant. • Among cohort studies, larger reductions in blood pressure were found among medical treatment or natural history studies than in angioplasty studies, although the effect of pre-angioplasty antihypertensive medication use cannot be corrected for. Only in cohort studies of angioplasty were patients cured of hypertension, no longer requiring medication to maintain normal blood pressure.
Cardiovascular	Weak	• 1 RCT found similar rates of cardiovascular events at 3 to 54 months of followup after angioplasty or with continued medical treatment. • Reporting of cardiovascular outcomes was too sparse among studies to make meaningful indirect comparisons.
Adverse events	N/A	• The evidence does not support meaningful conclusions about relative adverse events or complications from angioplasty compared to medical treatment.
Key Question 2: Baseline predictors of outcomes		
Angioplasty with or without stent vs. medical treatment	Weak	• In one RCT, patients with bilateral disease had larger decreases in blood pressure after angioplasty compared with medical treatment, in contrast to patients with unilateral disease.
Angioplasty	N/A	• 5 comparative studies and 15 cohort studies analyzed baseline variables as possible predictors of outcomes. Most of the comparative studies, however, did not distinguish between interventions in these analyses.

Key Questions	Strength of evidence	Summary/conclusion/comments
Baseline kidney function	Acceptable	• The 10 studies that evaluated baseline kidney function generally found that poorer kidney function (with a wide range of definitions) predicted higher mortality, poorer clinical outcomes including cardiovascular events, and/or poorer blood pressure control. However, among 4 studies, 2 found that kidney function after angioplasty improved more among patients with worse baseline kidney function, 1 found no difference in effect among patients with different baseline kidney function, and 1 found less improvement in kidney function among patients with worse baseline kidney function.
Baseline RAS severity	Weak	• 4 studies evaluated baseline percent stenosis. The studies were heterogeneous in their analyses and their conclusions. 1 found a borderline increase in mortality among patients with >70% stenosis. 1 found that higher percent stenosis was associated with higher blood pressure after revascularization. 1 found no association with either kidney function or diastolic blood pressure. 1 found that patients with higher grade stenosis had greater benefits in their kidney function than patients with lower grade stenosis. • 11 studies evaluated whether bilateral vs. unilateral RAS was a predictor of outcomes. The studies were heterogeneous in their analyses and their conclusions. 2 found bilateral disease was associated with increased mortality, but 2 found no association (although 1 of these did find an association with a combined poor clinical outcome). Among 7 studies, most found no association with either change in kidney function or blood pressure, but 2 found that patients with bilateral disease had better improvement in blood pressure, and 1 found better improvement in kidney function than patients with unilateral disease.
Baseline cardiovascular disease	Acceptable	• Among 6 studies, a range of cardiovascular measures, including history of disease, were found to be associated with increased risk of death, new cardiovascular events, or decreased likelihood of improvement in kidney function after revascularization. 2 studies, though, found that some baseline cardiovascular factors, including history of myocardial infarction, CHF, or hyperlipidemia, or reduced ejection fraction, did not predict increased mortality.
Diagnostic tests	Weak	• 3 diagnostic tests were evaluated by 4 studies. The captopril test, renogram, and unilateral renin secretion were not associated with differential outcomes in blood pressure, kidney function, or mortality. 2 studies evaluated a resistance index of over 80%; 1 found that these patients had worse kidney and blood pressure outcomes and 1 found that they had better changes in both kidney function and blood pressure levels.
Demographics	Weak	• Among 5 studies evaluating age, 1 found that older patients had higher followup blood pressure, 1 that they had lower followup blood pressure, and 3 found that after adjustment for other predictors, age was not associated with poor clinical outcomes. • Among 3 studies evaluating sex, 2 found that men had worse outcomes than women, but 1 found no difference after adjustment for other predictors.
Medical treatment	N/A	• No study evaluated potential predictors of outcomes.
Natural history	N/A	• 4 natural history studies examined various predictors, 2 of which performed multivariate analyses.
Baseline kidney function	Weak	• 1 study found that lower baseline GFR was independently associated with higher mortality or dialysis.
Baseline RAS severity	Weak	• 2 studies found that higher grade stenosis was independently associated with higher mortality (1 by multivariate, 1 univariate analysis); 1 study found that bilateral disease was not associated with kidney disease prognosis.
Baseline cardiovascular	Weak	• 1 study found that various markers of cardiac disease predicted mortality in patients with coronary artery disease and RAS.

Key Questions	Strength of evidence	Summary/conclusion/comments
disease		
Diagnostic tests	Weak	• 1 study found that patients with nonspiral blood flow in the renal arteries had significant progression in kidney impairment, while those with spiral flow did not.
Demographics	Weak	• 1 study found that older age predicted mortality in patients with coronary artery disease and RAS.
Key Question 3: Effect of periprocedural interventions on outcomes		
Angioplasty with or without stent	Weak	• 2 studies found no difference in blood pressure and kidney outcomes between patients who had stents placed and those who did not.
Other interventions	N/A	• No study that met eligibility criteria reported analyses of whether other periprocedural interventions, such as different drugs or different approaches, affected either complications or long-term outcomes.

Abbreviations: CHF = congestive heart failure; GFR = glomerular filtration rate (or creatinine clearance); N/A = not applicable; RAS = renal artery stenosis; RCT = randomized controlled trial.

As evidenced from discussion among nephrologists, surgeons, interventional cardiologists and radiologists, and other experts, in addition to perusal of both review articles and primary studies on management of atherosclerotic renal artery stenosis (ARAS), there remains uncertainty about the best specific interventions for patients; although the American College of Cardiology and the American Heart Association have issued clinical guidelines on management of renal artery stenosis (RAS). These guidelines are based in part on evidence also included in this review, in addition to retrospective and small studies that did not meet this review's eligibility criteria, and expert opinion.

A number of issues complicate the process of making decisions both for individual patients and for populations of patients. For one, the exact definition of ARAS varies depending on which diagnostic test is used, what threshold for stenosis is preferred, what degree of either resistant hypertension or of kidney damage is required, and whether other evidence of atherosclerotic disease is present. Furthermore, the definition and relative importance of these items have been and continue to change as new diagnostic tests are used or existing tests are refined, as definitions of chronic kidney disease change, as treatments for hypertension improve, and also as techniques and modalities of surgical and percutaneous interventions change and, presumably, improve. In addition, for individual patients, the evaluation of RAS may be complicated by the risks, difficulties, and expense of the diagnostic tests. Each diagnostic test has potential limitations related to operator skill, their invasive nature, risks due to contrast dye, or lack of availability, in addition to the use of various thresholds for and definitions of RAS.

The challenge of treating ARAS to achieve the targeted outcomes of improved blood pressure control and preservation of kidney function lies in the significant overlap between etiologic factors of aortorenal vascular disease and parenchymal kidney disease. While diabetes mellitus, dyslipidemia, and elevated blood pressure are associated with atherosclerotic narrowing of the renal arteries and consequent worsening of blood pressure and kidney function, they are independently associated with direct kidney injury. In a great many cases, overcoming the renal artery lesion fails to improve hypertension or kidney function, which may be mediated not only by ARAS but also by underlying kidney disease. Systematically evaluating the role of ARAS in hypertension and kidney dysfunction will assist in determining whether intervention should be directed towards improving kidney perfusion through angioplasty with stent placement or more aggressively targeting the underlying factors of parenchymal kidney disease with combination medical therapy.

For individual patients and their clinicians the question of what the preferred treatment for ARAS may be is fraught with difficulties largely related to the frequent frailty of these patients and the known complications from any of the interventions. These patients are generally elderly, often with severe cardiovascular disease including atherosclerosis and diastolic left ventricular dysfunction, often with moderate or severe chronic kidney disease, and with diabetes. Each of the antihypertensive agents carries substantial risks of bothersome and dangerous adverse events, which may be more likely or serious when multiple drugs are used. These drugs in general need to be taken lifelong and may only prevent further worsening of cardiovascular or kidney disease, as opposed to lessening the severity of disease. Invasive interventions, whether open or percutaneous, however, also carries risks of immediate death, cardiovascular events, kidney damage, and pain, or other effects on quality of life. Also, the procedure may not carry any noticeable benefit to patients, in that they are likely to continue to require antihypertensive medications and may have no survival, cardiovascular, or kidney benefit. Thus the relative overall effectiveness of angioplasty and continued aggressive medical treatment for most patients with ARAS remains unclear. For some patients with acutely worsening kidney or cardiovascular function, anecdotal evidence strongly suggests a benefit to revascularization; however, very few studies explicitly include such patients. Thus this review is not applicable to patients with clinical conditions necessitating acute intervention.

In 1993, the 5th Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-5) came out with recommendations that placed greater emphasis on attempting to achieve lower blood pressure levels than earlier sets of recommendations had made. This coincided with the increased use of angiotensin converting enzyme (ACE) inhibitors, and subsequently angiotensin receptor blockers (ARBs), which for many patients were both more effective and better tolerated than other drugs for reducing blood pressure, particularly when used in combination with some of the other drugs. Thus, in the early to mid-1990s many patients with previously "resistant" hypertension could now be better controlled, whether they had RAS or another cause of hypertension.

At about the same time, percutaneous angioplasty began to be more commonly used to revascularize patients' stenotic renal arteries instead of major open surgical techniques. Also as stent placement has become more common for atherosclerotic coronary and other arteries, stents also have been more commonly placed during renal artery angioplasty. This shift can be seen in the literature, where the majority of cohort studies on angioplasty did not use stents (or at least did not report using stents), while 80 percent of the cohort studies that included patients treated since 1993 did employ stents.

These changes, however, have been occurring in an era when there has been little high quality evidence (prospective comparative trials) to support the relative benefit of angioplasty, with or without stents, compared to aggressive medical treatment. While the theoretical benefits of revascularization are appealing, there is no robust evidence to allow individual patients and clinicians to decide which treatment option is best.

For this reason, the CORAL trial has been designed to address both whether clinical benefits are greater with angioplasty with stent placement or aggressive medical treatment, and to determine which patients may benefit most from one intervention or the other. However, currently the evidence base includes two relatively short duration randomized trials of moderate methodological quality that compared angioplasty, mostly without stent placement, to a wide variety of antihypertensive treatment.

The two trials evaluated only 103 patients, who at baseline had ARAS of greater than 50 or 60 percent, only 16 of whom had bilateral disease, and about half of whom had ostial disease. Their blood pressure prior to the studies was generally poorly controlled with mean blood pressures ranging from 165-190/96-105 mm Hg. Even after treatment, on average their blood pressures remained elevated at approximately 151-187/88-103 mm Hg. It is difficult to assess from the reports, but it appears that only a small minority of patients were treated with ACE inhibitors or ARBs. In one study, the mean serum creatinine was under 2.0 mg/dL, probably implying stage 2 or 3 chronic kidney disease. In the study restricted to patients with unilateral disease, patients may have had better kidney function, with a mean creatinine clearance of 73 mL/min (stage 2 chronic kidney disease).

The two trials found no difference in kidney function or progression to end stage renal disease, or (in one study) cardiovascular event rates. The effects on blood pressure are mixed. One study found a substantially greater benefit on blood pressure in those patients with bilateral disease who had angioplasty compared to those who did not (–34/–11 vs. –8/–1 mm Hg), but no difference among patients with unilateral disease. In the other trial of only patients with unilateral disease, both diastolic and systolic blood pressure decreased by 7 mm Hg more after angioplasty than with medical treatment, but only the change in diastolic pressure was statistically significant. However, after angioplasty, patients took only half as many antihypertensive drugs as those who continued on medical treatment. Though, on average, patients in both arms remained hypertensive (151/90 and 158/95 mm Hg).

The CORAL study in contrast is enrolling patients with over 60 percent stenosis, poorly controlled hypertension on two or more drugs, but not chronic kidney disease. It will also be comparing interventions that are more current than the two trials published in 1998, including angioplasty with stent placement, the antiplatelet agent clopidogrel, and the ARB candesartan. The two published randomized controlled trials (RCTs) that compare angioplasty to medical treatment alone used somewhat different eligibility criteria that imply inclusion of patients with different severity of ARAS compared with patients being enrolled in CORAL. One RCT used similar criteria for percent stenosis, but only in patients with unilateral disease; blood pressure and kidney function criteria were narrower, suggesting that on average hypertension and kidney disease were less severe. The other RCT included patients with lower grade stenosis (>50 percent), but did not exclude patients with more severe hypertension and included patients with more severe kidney disease. Among the remaining studies that compared revascularization to medical treatment and the noncomparative cohort studies, there were a wide range of eligibility criteria, commonly including patients with stenosis as low as 50 percent, or with either more or less severe blood pressure and kidney function. Across studies there was no clear evidence that differences in eligibility criteria were predictive of outcomes – except possibly that patients with bilateral disease had greater improvement after angioplasty, compared to those with unilateral disease. However, it was evident, by comparing mortality rates or change in kidney function across studies, that studies did differ in the severity of disease among their enrolled patients; although, eligibility criteria such as percent stenosis, blood pressure, kidney function, and others were not clearly associated with overall outcomes. Furthermore, the evidence does not adequately address how differences in eligibility criteria may affect the comparison between angioplasty and medical treatment.

The remainder of the current literature consists of randomized trials comparing immediate to delayed or no revascularization, or comparing surgical revascularization to medical treatment, prospective and retrospective nonrandomized comparative studies, and prospective and

retrospective uncontrolled cohort studies. Gleaning comparative effectiveness from these studies is fraught with numerous biases due to lack of randomization (among the large majority of these studies) and poor applicability. It is highly likely in many of these studies that patients were chosen either for revascularization or for medical treatment based on many factors separate from their ARAS alone including age, comorbidities, severity of symptoms or of associated conditions, clinician preferences, and others.

Assessing the applicability of these studies to the population being enrolled for the CORAL study is also problematic, both because of the same biases discussed and because, as discussed above, the definition of ARAS, the diagnostic tools used, and the interventions employed have changed both subtly and greatly over the past 15 years that make up the bulk of this review. One place where the literature review theoretically can be helpful to the current stage of the CORAL study is in estimating the power needed to address the primary and secondary outcomes and planned analyses. However, this review has found great heterogeneity in all outcomes assessed across studies, with little or no indication what the specific causes of the heterogeneity are. As an example the mortality rates across studies vary from nil to 80 percent at various time points over the first 5 years of followup. It is probably a truism that those studies with higher mortality rates included sicker patients (or possibly more poorly treated patients), reviewing the available data it is unclear which factors at baseline would have predicted mortality rates in any given study.

Another limiting issue was that adverse event reporting was generally sparse and not reported in a consistent manner. Revascularization studies tended to focus exclusively on periprocedure complications, without considering any RAS-related drug adverse events. Natural history studies did not report any adverse events. Even the adverse events reported by drug studies were incompletely reported. In particular, none of the studies addressed complications or adverse events in a manner that could allow comparison of risks between the two interventions, except one study that reported 30-day mortality.

Regarding Key Question 2, on the value of baseline factors for predicting clinical outcomes after either revascularization or continued medical treatment, few studies performed adequate multivariable analyses, controlling for the many confounding factors. In addition only one comparative study attempted to determine which baseline variables might predict a better outcome with one intervention or the other. This study concluded that the benefit of angioplasty over medical treatment in reducing blood pressure was confined to those patients with bilateral disease. Also, very few studies evaluated the value of diagnostic tests to predict outcomes. None analyzed whether any diagnostic tests would predict a better outcome with alternate treatments, except for the RCT comparing immediate versus delayed or no revascularization, where the captopril test and renogram did not predict outcomes.

The question of whether any procedure-related variables might affect complication rates or long-term outcomes was addressed by only a few studies that compared stent placement to no stent placement, where no difference was found. Among the studies that met eligibility criteria, no study evaluated any procedure-related drug or technique. In addition, no study evaluated any drugs other than antihypertensive agents, such as antilipid or antiplatelet drugs.

In conclusion, there is no published evidence directly comparing angioplasty with stent placement and “aggressive” medical treatment with currently available drugs for ARAS. Overall, the evidence does not currently support one treatment approach over the other for the general population of people with ARAS. Notably, almost two-thirds of the studies were of poor methodological quality and more than half were of limited applicability to the population of interest. A very limited evidence base directly compares angioplasty without stent placement and

medical treatment. While there was a benefit in blood pressure measurements after angioplasty, particularly in patients with bilateral disease, there was no difference in kidney function outcomes, and possibly no differences in mortality and cardiovascular event rates, although studies generally were included too few patients and were of too short a duration to make definitive assessments regarding these clinical event outcomes. Comparison of adverse events and complications across the various interventions is difficult. However, it is clear that various complications after revascularization do occur in a small percentage of patients, and each of the antihypertensive drugs has associated adverse events. Among the studies reviewed, the predictive value of diagnostic tests either for long-term outcomes or to help determine the best treatment is unclear. A variety of indicators of the severity of ARAS or of health problems, such as poorer kidney function, worse blood pressure, and coexisting cardiovascular disease predict poorer outcomes in patients with ARAS. The reviewed studies did not report any indicators that may predict improved outcomes. Very limited evidence from direct comparisons suggests there is no difference in outcomes based on whether patients had stents placed or not. The studies that met eligibility criteria (generally larger and/or prospective studies, excluding case reports and series) did not address the effect of any other procedure-related intervention. As the reviewed studies did not explicitly address the population of patients who may need acute intervention because of rapid clinical deterioration, the conclusions of this review do not apply to these patients.

Chapter 5. Future Research

- The CORAL trial is currently enrolling patients to compare aggressive medical treatment of hypertension with an angiotensin receptor blocker (ARB), along with a statin and aspirin, to angioplasty with stent placement followed by aggressive medical treatment along with the antiplatelet agent clopidogrel. Results are expected, after up to 5.5 years followup, in 2010. The trial is powered and designed to address the bulk of the Key Questions posed by this report, including effects on clinical outcomes, adverse events, and possibly through secondary analyses the interaction of baseline features such as diagnostic test results, patient characteristics, or cointerventions with outcomes.

- The CORAL trial will not address the following issues

    a. The relative value of angioplasty with stent placement in patients with lower grade atherosclerotic renal artery stenosis (ARAS), including those with less than 60 percent stenosis.

    b. The relative value of angioplasty with stent placement in patients with high stage kidney disease (serum creatinine ≥ 3.0 mg/dL) as well as in certain patients cardiovascular disease.

    c. The use of antilipid medications (except possibly in post hoc analyses).

- Additional randomized controlled trials would be required to address the issues that will not be covered by the CORAL trial. A potential risk without such trials will be that the findings of the CORAL trial will be broadened to be considered applicable to patients with less or more severe ARAS than those patients included in the CORAL trial. Without confirmatory evidence, it will be unclear whether this will be appropriate. For example, if angioplasty with stent is found to be of benefit in the CORAL trial, it is likely that the procedure will become more common also in patients with mild disease, even though there will not be evidence to support this.

- There are additional topics of interest that the CORAL trial may be able to evaluate, primarily through post hoc analyses, but may require additional studies to adequately address. These include

    a. The value of different diagnostic tests to determine which intervention would be best for individual patients.

    b. Other baseline characteristics as predictors of relative outcomes.

    c. The value of cointerventions at the time of angioplasty, or alternative methods of performing angioplasty with stent placement, or alternative types of stents.

d. The effect of different combinations of antihypertensive medications with other interventions such as antilipid and antiplatelet drugs.

- The ARAS research community should consider how to improve and/or standardize definitions of ARAS and severity of disease. These considerations should be based on how these definitions and disease severity scale would correlate with clinical outcomes.

- The CORAL trial and other studies of ARAS should use the current suggested methods for estimating kidney function, including preferential use of estimated glomerular filtration rate over serum creatinine, and stage of chronic kidney disease.

- The community of clinicians and professional organizations involved in performing renal artery angioplasty should consider how to improve procedural techniques and minimize variations in techniques and clinical outcomes across interventionalists, as clinically warranted. This may require quality improvement and other types of studies.

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List of Abbreviations/Acronyms

Δ	change
ACE	angiotensin converting enzyme
AHRQ	Agency for Healthcare Research and Quality
Appl	applicability rating
ARAS	atherosclerotic renal artery stenosis
ARB	angiotensin-receptor blocker
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHF	congestive heart failure
CI	(95 percent) confidence interval
CKD	chronic kidney disease
CNS	central nervous system
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions trial
CTA	computed tomographic angiography
CVA	cerebrovascular accident (stroke)
CVD	cardiovascular disease
d	days
DBP	diastolic blood pressure
EPC	Evidence-based Practice Center
GFR	glomerular filtration rate (or creatinine clearance, mL/min or mL/min/1.73 m^2)
GI	gastrointestinal
HDL	high density lipoprotein
HR	hazard ratio
HTN	hypertension
JNC-5	5th Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure
Imp	improved
KQ	key question
LDL	low density lipoprotein
MAP	mean arterial pressure
MI	myocardial infarction
mo	month(s)
Mod	moderate
MRA	magnetic resonance angiography
N	number evaluated
N/A	not applicable
nd	no data
NIH	National Institutes of Health
NS	nonsignificant
OR	odds ratio
Prosp	prospective nonrandomized study
PTCA	percutaneous transluminal coronary angioplasty
PTRA	percutaneous renal angioplasty
Qual	quality rating
RAS	renal artery stenosis
RCT	randomized controlled trial
Retro	retrospective study
RR	relative risk (risk ratio)
Rx	prescription(s)
SCr	serum creatinine (mg/dL)
STT	"standard triple therapy" of antihypertensive drugs
TEP	Technical Expert Panel
Tufts-NEMC	Tufts-New England Medical Center
UnΔ	unchanged (or stable)
wk	weeks
yr	year(s

Appendix A. Search Strategy

MEDLINE 1966-August Week 4 2005

#	Search History	Results
1	exp Hypertension, Renal/	15140
2	exp Renal Artery Obstruction/	7388
3	renal arter$ stenosis.tw.	3264
4	renal arter$ dis$.tw.	390
5	renovascular dis$.tw.	613
6	reno vascular dis$.tw.	6
7	renal vascular dis$.tw.	156
8	(arvd or "atherosclerotic renovascular dis$").tw.	302
9	renal steno$.tw.	49
10	steno$ kidney.tw.	137
11	renovascular steno$.tw.	27
12	or/1-11	20249
13	limit 12 to humans	15628
14	limit 13 to english language	10148
15	limit 14 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or "review of reported cases")	2736
16	14 not 15	7412
17	limit 16 to "all adult (19 plus years)"	4222
18	16 not 17	3190
19	limit 18 to "all child (0 to 18 years)"	488
20	16 not 19	6924
21	limit 20 to (guideline or practice guideline or "review" or review, academic or "review literature" or review, multicase or review, tutorial)	1316
22	limit 20 to meta analysis	8
23	20 not (21 or 22)	5601
24	follow-up studies/	303611
25	(follow-up or followup).tw.	332435
26	exp Case-Control Studies/	288665
27	(case adj20 control).tw.	43581
28	exp Longitudinal Studies/	498762
29	longitudinal.tw.	61304
30	exp Cohort Studies/	536922
31	cohort.tw.	70605
32	(random$ or rct).tw.	315873
33	exp Randomized Controlled Trials/	38577

Appendix A. Search Strategy (continued)

#	Search History	Results
34	exp random allocation/	53586
35	exp Double-Blind Method/	82631
36	exp Single-Blind Method/	9171
37	randomized controlled trial.pt.	204593
38	clinical trial.pt.	412355
39	controlled clinical trials/	2929
40	(clin$ adj trial$).tw.	88180
41	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.	79196
42	exp PLACEBOS/	23902
43	placebo$.tw.	90025
44	exp Research Design/	194218
45	exp Evaluation Studies/	529271
46	exp Prospective Studies/	190597
47	exp Comparative Study/	1211784
48	or/24-47	2748065
49	23 and 48	2167

Sample Data Extraction Form

Author (first)	Year	Identifier	Interventions	Modifier topics
		Medline UI: **Ref ID:**	Angioplasty vs Medical Angioplasty only Medical treatment only Natural history only	Pre-intervention predictors of outcome (Q2) Treatment variable predictors of outcome (Q3)

Study Design		**Intervention Dates:**	**Follow-up dates**
Randomized controlled trial Non-randomized comparative trial Prospective cohort (pre-post, single arm) Retrospective cohort			**Follow-up times**
Per patient analysis?	**Both ?**	**Setting / Country:**	**Mean Follow-up**
Per Kidney analysis?			**Funding:**

Inclusion criteria	**Exclusion criteria**
Definition of RAS:	
Other:	
Comments:	

Were eligibility criteria the same for all arms? (Describe differences)
Comments:

Description of ANGIOPLASTY Intervention	**Description of MEDICAL Intervention**		
Stent type:	**BP Goal:**		
Distal protection device:	**Drug**	**Dose**	**Frequency**
Other adjunct technique:			
Peri-procedural Rx:			
Other information:			
Comments:			

Outcomes	**Incl?**	**Definitions**
Survival / Mortality		
Acute / Flash pulmonary edema		
Diastolic dysfunction		
Other CVD outcomes:		
Kidney function/structure:		

Appendix B. Sample Data Extraction Form (continued)

Blood pressure control:			
Adverse events			
Comments:			

Cofactors / Predictors	**Incl?**	**Definitions**	**Threshold**
Imaging test:			
Laboratory test:			
Clinical exam test:			
Demographics:			
Concurrent diseases:			
Anatomic characteristic:			
% Stenosis:			
Bilateral stenoses / solitary kidney stenosis			
Peri-procedural Rx:			
Type of stent:			
Distal protection device:			
ARAS etiology:			
Predominant clinical presentation:			
Blood pressure:			
Other:			
Comments:			

Quality Assessment for RCTs	
Blinding:	**Allocation concealment?**
Intention-to-treat?	**Other:**
Comments:	

Quality Assessment for non-randomized and cohort studies:
Limitations:
Comments:

Characteristics of Enrolled Patients at Baseline			
Mean Age:	**Age range:**		**Race:**
% Male:			
Mean BP	**BP range:**		**Duration of HTN:**
% Stenosis:	**Location of stenoses:**		**Test used to measure stenosis:**
% Bilateral stenosis:			
Mean GFR/CrCl/SCr:	**units:**	**Range:**	**Other kidney:**
CVD:			

Medical management at baseline:
Other:
Comments:

Sub-Groups Enrolled & Analyzed		
N enrolled with RAS (total):	**with ARAS:**	**ARAS analyzed separately (if mixed population)?**
N analyzed with RAS (total):	**with ARAS:**	
N analyzed who had angioplasty (total):	**plasty+stent:**	**Stent analyzed separately (if mixed interventions)?**
Other mixtures of populations:		
Comments:		

Disposition of Patients (Arteries if nd on patients)			
ANGIOPLASTY			
N enrolled:	**N had Plasty:**		**N successful Plasty**
Other details re: patients:			
N complete follow-up:	**Dropout %:**	**Dropout reasons:**	
Mean duration follow-up:			**Duration range:**
MEDICAL TREATMENT			
N enrolled:	**N received Rx:**		
Other details re: patients:			
N complete follow-up:	**Dropout %:**	**Dropout reasons:**	
Mean duration follow-up:			**Duration range:**
Comments:			

(Copy a Separate table for each outcome-duration combination)

Outcome:				**Time of follow-up:**		
	ANGIOPLASTY			**MEDICAL TREATMENT**		
	N	**Value (or n)**	**SE/SD**	**N**	**Value (or n)**	**SE/SD**
Baseline value						
Final value						
Difference						
***P* Difference**						

Net Difference							
***P* Net difference**							
(RR/OR/HR)							
***P* (RR/OR/HR)**							
Comments:							

FOR ANALYSES OF PREDICTORS OF OUTCOMES:

IF GROUPS DIVIDED BY PREDICTORS (eg, Low GFR v High GFR) INCLUDE *DETAILED* RESULTS BELOW:	
Univariate:	
Multivariate:	

IF GROUPS DIVIDED BY OUTCOMES (eg, Dead v Alive) INCLUDE *LIST OF SIGNIFICANT* ASSOCIATIONS ONLY BELOW:	
Univariate:	
Multivariate:	

Adverse Events
Comments:

Quality: (A/B/C)	**Comments:**
Applicability: (Low/Medium/High)	**Comments:**

Other comments:

Excluded Studies

Acher CW, Belzer FO, Grist TM, Turnipseed WD, Hoch JR, Archibald JE. Late renal function in patients undergoing renal revascularization for control of hypertension and/or renal preservation. Cardiovasc Surg 4(5):602-6. 1996
Pre-1993 (Surgery study)

Adams MB, Harris SS, Kauffman HM, Towne JB. Effect of primary renal disease in patients with renovascular insufficiency. J Vasc Surg 1(3):482-6. 1984
N<100 (Surgery study)

Ahmadi R, Schillinger M, Sabeti S, et al. Renal artery PTA and stent implantation: immediate and late clinical and morphological outcome. Wien Klin Wochenschr 114(1-2):21-7. 2002
Retrospective (PTRA study)

Alhadad A, Mattiasson I, Ivancev K, Gottsater A, Lindblad B. Sustained beneficial effects on blood pressure during long time retrospective follow-up after endovascular treatment of renal artery occlusion. J Human Hypertens 18(10):739-44. 2004
Retrospective (PTRA study)

Allie DE, Lirtzman MD, Wyatt CH, et al. Bivalirudin as a foundation anticoagulant in peripheral vascular disease: a safe and feasible alternative for renal and iliac interventions. J Invasive Cardiol 15(6): 334- 42. 2003.
Prospective treatment vs retrospective control (Question 3)

Arlart IP, von Dewitz H, Bargon G. Transvenous digital subtraction angiography (DSA) for diagnostic control following percutaneous transluminal angioplasty (PTA) in patients with renovascular hypertension. Eur J Radiol 5(2):115-9. 1985
N<30 (PTRA study)

Arlart IP. Digital subtraction angiography (DSA) in renal and renovascular hypertension: diagnostic value and application in follow-up studies after PTA. Uremia Invest 9(2):217-29. 1985
Pre-1993 (Surgery study)

Askari A, Novick AC, Stewart BH, Straffon RA. Surgical treatment of renovascular disease in the solitary kidney: results in 43 cases. J Urol 127(1):20-2. 1982
N<100 (Surgery study)

Baert AL, Wilms G, Amery A, Vermylen J, Suy R. Percutaneous transluminal renal angioplasty: initial results and long-term follow-up in 202 patients. Cardiovasc Intervent Radiol 13(1):22-8. 1990
Pre-1993 (Surgery study)

Bakker J, Goffette PP, Henry M, et al. The Erasme study: a multicenter study on the safety and technical results of the Palmaz stent used for the treatment of atherosclerotic ostial renal artery stenosis. Cardiovasc Intervent Radiol 22(6):468-74. 1999
Post-failed PTRA

Barbalias GA, Liatsikos EN, Siablis D, et al. Virtual endoscopy in renal artery stenosis: an innovative approach for diagnosis and follow-up. J Endourol 18(6):540-3. 2004
N<30 (PTRA study)

Bardram L, Helgstrand U, Bentzen MH, Buchardt Hansen HJ, Engell HC. Late results after surgical treatment of renovascular hypertension. A follow-up study of 122 patients 2-18 years after surgery. Ann Surg 201(2):219-2. 1985
N<100 (Surgery study)

Baumgartner I, Triller J, Mahler F. Patency of percutaneous transluminal renal angioplasty: a prospective sonographic study. Kidney Int 51(3):798-803. 1997
Prior publication of accepted study

Baus S, Radermacher J, Galanski M, Chavan A. Kissing balloon technique for angioplasty of renal artery bifurcation stenoses. J Vasc Interv Radiol 14(11):1455-9. 2003
Retrospective (PTRA study)

Bax L, Mali WP, van de Ven PJ, Beek FJ, Vos JA, Beutler JJ. Repeated intervention for in-stent restenosis of the renal arteries. J Vasc Interv Radiol 13(12):1219-24. 2002
Retrospective (PTRA study)

Bedoya L, Ziegelbaum M, Vidt DG, Badhwar K, Novick AC, Gifford RW. Baseline renal function and surgical revascularization in atherosclerotic renal arterial disease in the elderly. Cleve Clin J Med 56(4):415-21. 1989
Pre-1993 (Surgery study)

Beebe HG, MacFarlane SD. Antegrade aortorenal bypass graft: a new alternative. Am J Surg 155(5):647-50. 1988
N<100 (Surgery study)

Bell GM, Reid J, Buist TA. Percutaneous transluminal angioplasty improves blood pressure and renal function in renovascular hypertension. Qjm 63(241):393-403. 1987
Retrospective (PTRA study)

Bergrem H, Jervell J, Solheim DM, Flatmark A. Prognostic value of renal vein renin determination in suspected renovascular hypertension. Acta Med Scand Suppl 211(5):387-91. 1982
N<100 (Surgery study)

Beutler JJ, Van Ampting JM, van de Ven PJ, et al. Long-term effects of arterial stenting on kidney function for patients with ostial atherosclerotic renal artery stenosis and renal insufficiency. J Am Soc Nephrol 12(7):1475-81. 2001
>20% had previous plasty

Bhandari S, Wilkinson A, Nicholson A, Farr MJ, Sellars L. Atherosclerotic renovascular disease in the elderly: angioplasty with stenting versus reconstructive surgery. Geriatr Nephrol Urol 7(2):87-94. 1997
Retrospective (PTRA) / N<100 (Surgery)

Binkert CA, Debatin JF, Schneider E, et al. Can MR measurement of renal artery flow and renal volume predict the outcome of percutaneous transluminal renal angioplasty?. Cardiovasc Intervent Radiol 24(4):233-9. 2001
N<30 (PTRA study)

Blaufox MD, Fine EJ, Heller S, et al. Prospective study of simultaneous orthoiodohippurate and diethylenetriaminepentaacetic acid captopril renography. The Einstein/Cornell Collaborative Hypertension Group. J Nucl Medicine 39(3):522-8. 1998
No intervention

Blaufox MD. Cost-effectiveness of nuclear medicine procedures in renovascular hypertension. Semin Nucl Med 19(2):116-21. 1989
Review

Bloch MJ, Trost DA, Whitmer J, Pickering TG, Sos TA, August P. Ostial renal artery stent placement in patients 75 years of age or older. Am J Hypertens 14(10):983-8. 2001
N<30 (PTRA study)

Bloch MJ, Trost DW, Pickering TG, Sos TA, August P. Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. Am J Hypertens 12(1 Pt 1):1-7. 1999
Retrospective (PTRA study)

Boisclair C, Therasse E, Oliva VL, et al. Treatment of renal angioplasty failure by percutaneous renal artery stenting with Palmaz stents: midterm technical and clinical results. AJR Am J Roentgenol 168(1):245-51. 1997
Post-failed PTRA

Bonelli FS, McKusick MA, Textor SC, et al. Renal artery angioplasty: technical results and clinical outcome in 320 patients. Mayo Clin Proc 70(11):1041-52. 1995
Retrospective (PTRA study)

Bonner G, Lederle RM, Scholze J, Stumpe KO. Therapeutic safety of perindopril in the treatment of mild hypertension with concomitant nephropathy. Arzneimittel-Forschung 43(8):852-5. 1993
Exclusion population

Bush RL, Martin LG, Lin PH, et al. Endovascular revascularization of renal artery stenosis in the solitary functioning kidney. Ann Vasc Surg 15(1):60-6. 2001
N<30 (PTRA study)

Bush RL, Najibi S, MacDonald MJ, et al. Endovascular revascularization of renal artery stenosis: technical and clinical results. J Vasc Surg 33(5):1041-9. 2001
Retrospective (PTRA study)

Cambria RP, Brewster DC, L'Italien GJ, et al. The durability of different reconstructive techniques for atherosclerotic renal artery disease. J Vasc Surg 20(1):76-85. 1994
Pre-1993 (Surgery study)

Cambria RP, Brewster DC, L'Italien GJ, et al. Renal artery reconstruction for the preservation of renal function. J Vasc Surg 24(3):371-80. 1996
Pre-1993 (Surgery study)

Cambria RP, Kaufman JL, Brewster DC, et al. Surgical renal artery reconstruction without contrast arteriography: the role of clinical profiling and magnetic resonance angiography. J Vasc Surg 29(6):1012-21. 1999
N<100 (Surgery study)

Campo A, Boero R, Stratta P, Quarello F. Selective stenting and the course of atherosclerotic renovascular nephropathy. J Nephrol 15(5):525-9. 2002
Retrospective (PTRA study)

Canzanello VJ, Millan VG, Spiegel JE, Ponce PS, Kopelman RI, Madias NE. Percutaneous transluminal renal angioplasty in management of atherosclerotic renovascular hypertension: results in 100 patients. Hypertension 13(2):163-72. 1989
Pre-1993 (Surgery study)

Caps MT, Perissinotto C, Zierler RE, et al. Prospective study of atherosclerotic disease progression in the renal artery. Circulation 98(25):2866-72. 1998
No outcome of interest

Carmichael DJ, Mathias CJ, Snell ME, Peart S. Detection and investigation of renal artery stenosis. Lancet 1(8482):667-70. 1986
Retrospective (PTRA) / N<100 (Surgery)

Chabova V, Schirger A, Stanson AW, McKusick MA, Textor SC. Outcomes of atherosclerotic renal artery stenosis managed without revascularization. Mayo Clin Proc 75(5):437-44. 2000
Pre-1993 (Surgery study)

Chaikof EL, Smith RB, Salam AA, et al. Empirical reconstruction of the renal artery: long-term outcome. J Vasc Surg 24(3):406-14. 1996
N<100 (Surgery study)

Chatterjee SS, Pahari DK, Sharma RK, et al. Long term follow-up of percutaneous transluminal renal angioplasty with special reference to aorto-arteritis. Indian Heart J 47(2):120-4. 1995
Retrospective (PTRA study)

Chatziioannou A, Mourikis D, Agroyannis B, et al. Renal artery stenting for renal insufficiency in solitary kidney in 26 patients. Eur J Vasc Endovascular Surg 23(1):49-54. 2002
Retrospective (PTRA study)

Cianci R, Lavini R, Letizia C, et al. Low-contrast medium doses for ultrasound imaging during renal revascularization by PTA-stenting. J Nephrol 17(4):520-4. 2004
Retrospective (PTRA study)

Cicuto KP, McLean GK, Oleaga JA, Freiman DB, Grossman RA, Ring EJ. Renal artery stenosis: anatomic classification for percutaneous transluminal angioplasty. AJR Am J Roentgenol 137(3):599-601. 1981
Retrospective (PTRA study)

Cioni R, Vignali C, Petruzzi P, et al. Renal artery stenting in patients with a solitary functioning kidney. Cardiovasc Intervent Radiol 24(6):372-7. 2001
Retrospective (PTRA study)

Cognet F, Garcier JM, Dranssart M, et al. Percutaneous transluminal renal angioplasty in atheroma with renal failure: long-term outcomes in 99 patients. Eur Radiol 11(12):2524-30. 2001
Retrospective (PTRA study)

Colapinto RF, Stronell RD, Harries-Jones EP, et al. Percutaneous transluminal dilatation of the renal artery: follow-up studies on renovascular hypertension. AJR Am J Roentgenol 139(4):727-32. 1982
Pre-1993 (Surgery study)

Conlon PJ, Athirakul K, Kovalik E, et al. Survival in renal vascular disease. J Am Soc Nephrol 9(2):252-6. 1998
Pre-1993 (Surgery study)

Connolly JO, Higgins RM, Walters HL, et al. Presentation, clinical features and outcome in different patterns of atherosclerotic renovascular disease. Qjm 87(7):413-21. 1994
Retrospective (PTRA study)

Cormier JM, Fichelle JM, Laurian C, Gigou F, Artru B, Ricco JB. Renal artery revascularization with polytetrafluoroethylene bypass graft. Ann Vasc Surg 4(5):471-8. 1990
N<100 (Surgery study)

Crinnion JN, Gough MJ. Bilaterial renal artery atherosclerosis--the results of surgical treatment. Eur J Vasc Endovascular Surg 11(3):353-8. 1996
>50% had aortic reconstruction

Crowley JJ, Santos RM, Peter RH, et al. Progression of renal artery stenosis in patients undergoing cardiac catheterization. Am Heart J 136(5):913-8. 1998
No outcome of interest

Dal Canton A, Russo D, Iaccarino V, Caputo A, D'Anna F, Andreucci VE. Percutaneous angioplasty for treatment of renovascular hypertension. Proc Eur Dial Transplant Assoc 20:582-6. 1983
N<30 (PTRA study)

de Fraissinette B, Garcier JM, Dieu V, et al. Percutaneous transluminal angioplasty of dysplastic stenoses of the renal artery: results on 70 adults. Cardiovasc Intervent Radiol 26(1):46-51. 2003
Retrospective (PTRA study)

Dean RH, Kieffer RW, Smith BM, et al. Renovascular hypertension: anatomic and renal function changes during drug therapy. Archives Surg 116(11):1408-15. 1981
Pre-1993 (Surgery study)

Dean RH, Krueger TC, Whiteneck JM, et al. Operative management of renovascular hypertension. Results after a follow-up of fifteen to twenty-three years. J Vasc Surg 1(1):234-42. 1984
N<100 (Surgery study)

Dean RH, Tribble RW, Hansen KJ, O'Neil E, Craven TE, Redding JF. Evolution of renal insufficiency in ischemic nephropathy. Ann Surg 213(5):446-55. 1991
N<100 (Surgery study)

Dean RH. Late results of aortorenal bypass. Urol Clin North Am 11(3):425-34. 1984
Pre-1993 (Surgery study)

Denolle T, Chatellier G, Julien J, Battaglia C, Luo P, Plouin PF. Left ventricular mass and geometry before and after etiologic treatment in renovascular hypertension, aldosterone-producing adenoma, and pheochromocytoma. Am J Hypertens 6(11 Pt 1):907-13. 1993
Retrospective (PTRA) / N<100 (Surgery)

Desai TR, Meyerson SL, McKinsey JF, Schwartz LB, Bassiouny HS, Gewertz BL. Angioplasty does not affect subsequent operative renal artery revascularization. Surgery 128(4):717-25. 2000
N<100 (Surgery study)

Dondi M, Fanti S, De Fabritiis A, et al. Prognostic value of captopril renal scintigraphy in renovascular hypertension. J Nucl Medicine 33(11):2040-4. 1992
Pre-1993 (Surgery study)

Donohoe P, de Takats D, Bishop N, et al. A four-year audit of interventional treatment for atheromatous renal artery stenosis. Contrib Nephrol 119:78-82. 1996
Retrospective (PTRA) / N<100 (Surgery)

Dorros G, Prince C, Mathiak L. Stenting of a renal artery stenosis achieves better relief of the obstructive lesion than balloon angioplasty. Catheter Cardiovasc Diagn 29(3):191-8. 1993
N<30 (PTRA study)

Eldrup-Jorgensen J, Harvey HR, Sampson LN, Amberson SM, Bredenberg CE. Should percutaneous transluminal renal artery angioplasty be applied to ostial renal artery atherosclerosis?. J Vasc Surg 21(6):909-14. 1995
Retrospective (PTRA study)

England WL, Roberts SD, Grim CE. Surgery or angioplasty for cost-effective renal revascularization?. Med Dec Making 7(2):84-91. 1987
Retrospective (PTRA) / N<100 (Surgery)

Erbsloh-Moller B, Dumas A, Roth D, Sfakianakis GN, Bourgoignie JJ. Furosemide-131I-hippuran renography after angiotensin-converting enzyme inhibition for the diagnosis of renovascular hypertension. Am J Med 90(1):23-9. 1991
N<30 (PTRA study)

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Retrospective (PTRA) / N<100 (Surgery)

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Retrospective (PTRA study)

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Pre-1993 (Surgery study)

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Pre-1993 (Surgery study)

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N<30 (PTRA study)

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N<100 (Surgery study)

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Retrospective (PTRA study)

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<50% with ARAS

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Retrospective (PTRA) / N<100 (Surgery)

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Retrospective (PTRA study)

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Retrospective (PTRA study)

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N<30 (PTRA study)

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N<100 (Surgery study)

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Pre-1993 (Surgery study)

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Post-failed PTRA

Hansen KJ, Ditesheim JA, Metropol SH, et al. Management of renovascular hypertension in the elderly population. J Vasc Surg 10(3):266-73. 1989
N<100 (Surgery study)

Hansen KJ, Lundberg AH, Benjamin ME, et al. Is renal revascularization in diabetic patients worthwhile?. J Vasc Surg 24(3):383-92. 1996
N<100 (Surgery study)

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N<100 (Surgery study)

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Pre-1993 (Surgery study)

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N<30 (PTRA study)

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N<30 (PTRA study)

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N<30 (PTRA study)

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N<30 (PTRA study)

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Retrospective (PTRA study)

Henry M, Amor M, Henry I, et al. Stents in the treatment of renal artery stenosis: long-term follow-up. J Endovascular Surg 6(1):42-51. 1999
Post-failed PTRA

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N<30 (PTRA study)

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<6 mo (nd AE)

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Retrospective (PTRA study)

Holden A, Hill A. Renal angioplasty and stenting with distal protection of the main renal artery in ischemic nephropathy: early experience. J Vasc Surg 38(5):962-8. 2003
Retrospective (PTRA study)

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Pre-1993 (Surgery study)

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Pre-1993 (Surgery study)

Ilkay E, Gunal IA, Yavuzkir M, et al. Effect of renal artery stenting on renal function in patients with ischemic nephropathy. Jpn Heart J 45(4):637-45. 2004
N<30 (PTRA study)

Isles C, Main J, O'Connell J, et al. Survival associated with renovascular disease in Glasgow and Newcastle: a collaborative study. Scott Med J 35(3):70-3. 1990
Pre-1993 (Surgery study)

Ivanovic V, McKusick MA, Johnson CM, et al. Renal artery stent placement: complications at a single tertiary care center. J Vasc Interv Radiol 14(2 Pt 1):217-25. 2003
Retrospective (PTRA study)

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Retrospective (PTRA study)

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Retrospective (PTRA study)

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N<30 (PTRA study)

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Retrospective (PTRA study)

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N<30 (PTRA study)

Karagiannis A, Douma S, Voyiatzis K, et al. Percutaneous transluminal renal angioplasty in patients with renovascular hypertension: long-term results. Hypertens Res 18(1):27-31. 1995
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Kaylor WM, Novick AC, Ziegelbaum M, Vidt DG. Reversal of end stage renal failure with surgical revascularization in patients with atherosclerotic renal artery occlusion. J Urol 141(3):486-8. 1989
N<100 (Surgery study)

Keith TA. Renovascular hypertension in black patients. Hypertension 4(3):438-43. 1982
Pre-1993 (Surgery study)

Kent KC, Salvatierra O, Reilly LM, Ehrenfeld WK, Goldstone J, Stoney RJ. Evolving strategies for the repair of complex renovascular lesions. Ann Surg 206(3):272-8. 1987
N<100 (Surgery study)

Khilnani NM, Trost D, Jagust MB, Sos TA. Multiple-side-hole catheter technique for selective over-the-wire completion angiography following renal angioplasty. J Vasc Interv Radiol 5(2):387-9. 1994
Retrospective (PTRA study)

Khosla S, White CJ, Collins TJ, Jenkins JS, Shaw D, Ramee SR. Effects of renal artery stent implantation in patients with renovascular hypertension presenting with unstable angina or congestive heart failure. Am J Cardiol 80(3):363-6. 1997
N<30 (PTRA study)

Kim PK, Spriggs DW, Rutecki GW, Reaven RE, Blend D, Whittier FC. Transluminal angioplasty in patients with bilateral renal artery stenosis or renal artery stenosis in a solitary functioning kidney. AJR Am J Roentgenol 153(6):1305-8. 1989
Retrospective (PTRA study)

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Pre-1993 (Surgery study)

Klinge J, Mali WP, Puijlaert CB, Geyskes GG, Becking WB, Feldberg MA. Percutaneous transluminal renal angioplasty: initial and long-term results. Radiology 171(2):501-6. 1989
Retrospective (PTRA study)

Klow NE, Paulsen D, Vatne K, Rokstad B, Lien B, Fauchald P. Percutaneous transluminal renal artery angioplasty using the coaxial technique. Ten years of experience from 591 procedures in 419 patients. Acta Radiol 39(6):594-603. 1998
Retrospective (PTRA study)

Korsakas S, Mohaupt MG, Dinkel HP, et al. Delay of dialysis in end-stage renal failure: prospective study on percutaneous renal artery interventions. Kidney Int 65(1):251-8. 2004
N<30 (PTRA study)

Koyanagi T, Nonomura K, Takeuchi I, Watarai Y, Seki T, Kakizaki H. Surgery for renovascular diseases: a single-center experience in revascularizing renal artery stenosis and aneurysm. Urol Int 68(1):24-31. 2002
N<100 (Surgery study)

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Retrospective (PTRA study)

Krishnamurthi V, Novick AC, Myles JL. Atheroembolic renal disease: effect on morbidity and survival after revascularization for atherosclerotic renal artery stenosis. J Urol 161(4):1093-6. 1999
N<100 (Surgery study)

Kuhlmann U, Greminger P, Gruntzig A, et al. Long-term experience in percutaneous transluminal dilatation of renal artery stenosis. Am J Med 79(6):692-8. 1985
Pre-1993 (Surgery study)

Kuhlmann U, Vetter W, Furrer J, Lutolf U, Siegenthaler W, Gruntzig A. Renovascular hypertension: treatment by percutaneous transluminal dilatation. Ann Intern Med 92(1):1-6. 1980
Retrospective (PTRA study)

Kuhn FP, Kutkuhn B, Torsello G, Modder U. Renal artery stenosis: preliminary results of treatment with the Strecker stent. Radiology 180(2):367-72. 1991
Retrospective (PTRA study)

Kumagai H, Suzuki H, Matsukawa S, Ryuzaki M, Saruta T. Captopril therapy following percutaneous transluminal angioplasty for bilateral renal artery stenosis. Arch Intern Med 149(9):1973-6. 1989
N<30 (PTRA study)

Kvist S, Mulvany MJ. Reduced medication and normalization of vascular structure, but continued hypertension in renovascular patients after revascularization. Cardiovas Res 52(1):136-42. 2001
Retrospective (PTRA) / N<100 (Surgery)

La Batide-Alanore A, Azizi M, Froissart M, Raynaud A, Plouin PF. Split renal function outcome after renal angioplasty in patients with unilateral renal artery stenosis. J Am Soc Nephrol 12(6):1235-41. 2001
N<30 (PTRA study)

Laasonen L, Edgren J, Forslund T, Eklund B. Renal transplant artery stenosis and percutaneous transluminal angioplasty. Acta Radiol 26(5):609-13. 1985
Exclusion population

Lagneau P, Michel JB. Surgical management and results of renal artery revascularization. Int Angiol 4(3):329-33. 1985
Pre-1993 (Surgery study)

Lamawansa MD, Bell R, House AK. Short-term and long-term outcome following renovascular reconstruction. Cardiovasc Surg 3(1):50-5. 1995
N<100 (Surgery study)

Lawrie GM, Morris GC, DeBakey ME. Long-term results of treatment of the totally occluded renal artery in forty patients with renovascular hypertension. Surgery 88(6):753-9. 1980
Pre-1993 (Surgery study)

Lawrie GM, Morris GC, Glaeser DH, DeBakey ME. Renovascular reconstruction: factors affecting long-term prognosis in 919 patients followed up to 31 years. Am J Cardiol 63(15):1085-92. 1989
Pre-1993 (Surgery study)

Lawrie GM, Morris GC, Soussou ID, et al. Late results of reconstructive surgery for renovascular disease. Ann Surg 191(5):528-33. 1980
Pre-1993 (Surgery study)

Leertouwer TC, Derkx FH, Pattynama PM, Deinum J, van Dijk LC, Schalekamp MA. Functional effects of renal artery stent placement on treated and contralateral kidneys. Kidney Int 62(2):574-9. 2002
Retrospective (PTRA study)

Lewis BE, Leya FS, Johnson SA, et al. Improved hemodynamic, angiographic and functional results after renal artery stenting. J Invasive Cardiol 6(4):136-40. 1994
N<30 (PTRA study)

Li JJ, Fang CH, Jiang H, et al. Increased C-reactive protein level after renal stent implantation in patients with atherosclerotic renal stenosis. Angiology 55(5):479-84. 2004
No outcome of interest

Losinno F, Zuccala A, Busato F, Zucchelli P. Renal artery angioplasty for renovascular hypertension and preservation of renal function: long-term angiographic and clinical follow-up. AJR Am J Roentgenol 162(4):853-7. 1994
Retrospective (PTRA study)

Lovaria A, Nicolini A, Meregaglia D, et al. Interventional radiology in the treatment of renal artery stenosis. Ann Urol (Paris) 33(3):146-55. 1999
Retrospective (PTRA study)

Lyons D, Fowler G, Petrie JC, Webster J. The haemodynamic effects of GR 32191, a thromboxane A2 receptor antagonist, in patients with renal artery stenosis and hypertension. Br J Clin Pharmacol 36(3):271-3. 1993
Single dose

Mackrell PJ, Langan EM, Sullivan TM, et al. Management of renal artery stenosis: effects of a shift from surgical to percutaneous therapy on indications and outcomes. Ann Vasc Surg 17(1):54-9. 2003
Retrospective (PTRA) / N<100 (Surgery)

MacLeod M, Taylor AD, Baxter G, et al. Renal artery stenosis managed by Palmaz stent insertion: technical and clinical outcome. J Hypertens 13(12 Pt 2):1791-5. 1995
N<30 (PTRA study)

Madias NE, Kwon OJ, Millan VG. Percutaneous transluminal renal angioplasty. A potentially effective treatment for preservation of renal function. Arch Intern Med 142(4):693-7. 1982
N<30 (PTRA study)

Mahler F, Probst P, Weidmann P, Krneta A. Transluminal dilatation of renal artery stenoses due to atherosclerosis and fibromuscular dysplasia : early results and follow-up of twelve consecutive cases. Ann Radiol (Paris) 24(5):355-6. 1981
Retrospective (PTRA study)

Marekovic Z, Mokos I, Krhen I, Goreta NR, Roncevic T. Long-term outcome after surgical kidney revascularization for fibromuscular dysplasia and atherosclerotic renal artery stenosis. J Urol 171(3):1043-5. 2004
N<100 (Surgery study)

Marshall FI, Hagen S, Mahaffy RG, et al. Percutaneous transluminal angioplasty for atheromatous renal artery stenosis--blood pressure response and discriminant analysis of outcome predictors. Qjm 75(277):483-9. 1990
Retrospective (PTRA study)

Martin LG, Casarella WJ, Alspaugh JP, Chuang VP. Renal artery angioplasty: increased technical success and decreased complications in the second 100 patients. Radiology 159(3):631-4. 1986
Retrospective (PTRA study)

Martin LG, Casarella WJ, Gaylord GM. Azotemia caused by renal artery stenosis: treatment by percutaneous angioplasty. AJR Am J Roentgenol 150(4):839-44. 1988
Retrospective (PTRA study)

Martin LG, Cork RD, Kaufman SL. Long-term results of angioplasty in 110 patients with renal artery stenosis. J Vasc Interv Radiol 3(4):619-26. 1992
Pre-1993 (Surgery study)

Martinez-Amenos A, Rama H, Sarrias X, Galceran J, Alsina J, Montanya X. Percutaneous transluminal angioplasty in the treatment of renovascular hypertension. J Human Hypertens 5(2):97-100. 1991
Retrospective (PTRA study)

Matalon TA, Thompson MJ, Patel SK, Brunner MC, Merkel FK, Jensik SC. Percutaneous transluminal angioplasty for transplant renal artery stenosis. J Vasc Interv Radiol 3(1):55-8. 1992
Exclusion population

Mathias CJ, Wilkinson AH, Pike FA, Sever PS, Peart WS. Clonidine in unilateral renal artery stenosis and unilateral renal parenchymal disease--similar antihypertensive but different renin suppressive effects. J Hypertens Suppl 1(2):123-5. 1983
Single dose

May J, Sheil R, Harris J, Horvath J. Failure of patent aorto-renal grafts to cure hypertension in renin positive patients. J Cardiovasc Surg 28(5):535-7. 1987
N<100 (Surgery study)

McCready RA, Daugherty ME, Nighbert EJ, Hyde GL, Freedman AM, Ernst CB. Renal revascularization in patients with a single functioning ischemic kidney. J Vasc Surg 6(2):185-90. 1987
N<100 (Surgery study)

McDonald DN, Smith DC, Maloney MD. Percutaneous transluminal renal angioplasty in the patient with a solitary functioning kidney. AJR Am J Roentgenol 151(5):1041-3. 1988
Retrospective (PTRA study)

Mestres CA, Campistol JM, Ninot S, et al. Improvement of renal function in azotaemic hypertensive patients after surgical revascularization. Br J Surg 75(6):578-80. 1988
N<100 (Surgery study)

Milot A, Lambert R, Lebel M, Cusson JR, Larochelle P. Prostaglandins and renal function in hypertensive patients with unilateral renal artery stenosis and patients with essential hypertension. J Hypertens 14(6):765-71. 1996
No intervention

Miranda JF, Perez MC, Plavnik F, Francisco JJ, Burihan E. Percutaneous transluminal angioplasty in the treatment of renovascular hypertension: sequential prospective study. Sao Paulo Med J 116(1):1613-7. 1998
Retrospective (PTRA study)

Miyamori I, Yasuhara S, Matsubara T, Takasaki H, Takeda R. Comparative effects of captopril and nifedipine on split renal function in renovascular hypertension. Am J Hypertens 1(4 Pt 1):359-63. 1988
Case Report

Moncure AC, Brewster DC, Darling RC, Atnip RG, Newton WD, Abbott WM. Use of the splenic and hepatic arteries for renal revascularization. J Vasc Surg 3(2):196-203. 1986
N<100 (Surgery study)

Morellato C, Bergelin RO, Cantwell-Gab K, et al. Clinical and duplex ultrasound follow-up after balloon angioplasty for atherosclerotic renal artery stenosis. Vasc Surg 35(2):85-93. 2001
Retrospective (PTRA study)

Morganti A, Quorso P, Ferraris P, et al. Time-course of the changes in blood pressure and in plasma renin activity during the first week after dilation of renal artery stenosis. J Hypertens Suppl 7(6):S186-7. 1989
N<30 (PTRA study)

Morganti A, Quorso P, Ferraris P, et al. Initial versus long-term results of percutaneous transluminal renal angioplasty in patients with renovascular hypertension. J Hypertens Suppl 9(6):S238-9. 1991
N<30 (PTRA study)

Morin JE, Hutchinson TA, Lisbona R. Long-term prognosis of surgical treatment of renovascular hypertension: a fifteen-year experience. J Vasc Surg 3(3):545-9. 1986
N<100 (Surgery study)

Mounier-Vehier C, Haulon S, Lions C, et al. Renal atrophy in atherosclerotic renovascular disease: gradual changes 6 months after successful angioplasty. J Endovascular Ther 9(6):863-72. 2002
N<30 (PTRA study)

Muray S, Martin M, Amoedo ML, et al. Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. Am J Kidney Dis 39(1):60-6. 2002
Retrospective (PTRA study)

Nahman NS, Maniam P, Hernandez RA, et al. Renal artery pressure gradients in patients with angiographic evidence of atherosclerotic renal artery stenosis. Am J Kidney Dis 24(4):695-9. 1994
No outcome of interest

Neymark E, LaBerge JM, Hirose R, et al. Arteriographic detection of renovascular disease in potential renal donors: incidence and effect on donor surgery. Radiology 214(3):755-60. 2000
No intervention

Nolan BW, Schermerhorn ML, Powell RJ, et al. Restenosis in gold-coated renal artery stents. J Vasc Surg 42(1):40-6. 2005
Retrospective (PTRA study)

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Retrospective (PTRA study)

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RCT of PTRA v surgery, not v medical.
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Pre-1993 (Surgery study)

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N<30 (PTRA study)

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Retrospective (Medical) / N<100 (Surgery)

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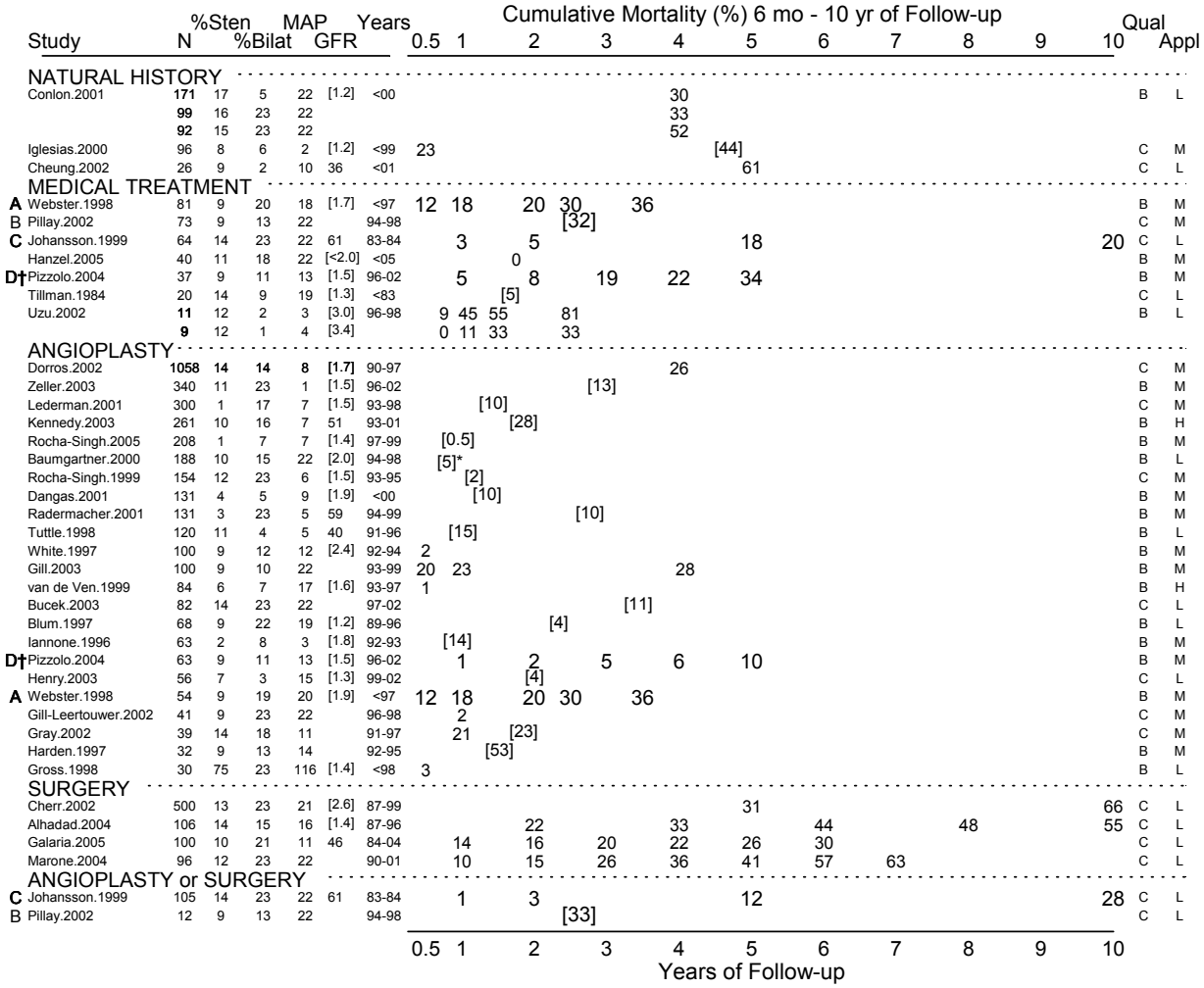
Drs. Cambria, Gilbert, Rundback, Textor and Tuttle were also members of the EPC's Technical Expert Panel
Dr. Cambria served as the EPC technical expert consultant. As such his comments were provided on an ongoing basis.

Appendix E. Detailed Mortality Figure

Detailed Mortality Figure

Figure. Cumulative percent mortality from 6 months to 10 years of followup.



	Study	N	%Sten	%Bilat	MAP	GFR	Years	Qual	Appl
	NATURAL HISTORY								
	Conlon.2001	171	17	5	22	[1.2]	<00	B	L
		99	16	23	22				
		92	15	23	22				
	Iglesias.2000	96	8	6	2	[1.2]	<99	C	M
	Cheung.2002	26	9	2	10	36	<01	C	L
	MEDICAL TREATMENT								
A	Webster.1998	81	9	20	18	[1.7]	<97	B	M
B	Pillay.2002	73	9	13	22		94-98	C	M
C	Johansson.1999	64	14	23	22	61	83-84	C	L
	Hanzel.2005	40	11	18	22	[<2.0]	<05	B	M
D†	Pizzolo.2004	37	9	11	13	[1.5]	96-02	B	M
	Tillman.1984	20	14	9	19	[1.3]	<83	C	L
	Uzu.2002	11	12	2	3	[3.0]	96-98	B	L
		9	12	1	4	[3.4]			
	ANGIOPLASTY								
	Dorros.2002	1058	14	14	8	[1.7]	90-97	C	M
	Zeller.2003	340	11	23	1	[1.5]	96-02	B	M
	Lederman.2001	300	1	17	7	[1.5]	93-98	C	M
	Kennedy.2003	261	10	16	7	51	93-01	B	H
	Rocha-Singh.2005	208	1	7	7	[1.4]	97-99	B	M
	Baumgartner.2000	188	10	15	22	[2.0]	94-98	B	L
	Rocha-Singh.1999	154	12	23	6	[1.5]	93-95	C	M
	Dangas.2001	131	4	5	9	[1.9]	<00	B	M
	Radermacher.2001	131	3	23	5	59	94-99	B	M
	Tuttle.1998	120	11	4	5	40	91-96	B	L
	White.1997	100	9	12	12	[2.4]	92-94	B	M
	Gill.2003	100	9	10	22		93-99	B	M
	van de Ven.1999	84	6	7	17	[1.6]	93-97	B	H
	Bucek.2003	82	14	23	22		97-02	C	L
	Blum.1997	68	9	22	19	[1.2]	89-96	B	L
	Iannone.1996	63	2	8	3	[1.8]	92-93	B	M
D†	Pizzolo.2004	63	9	11	13	[1.5]	96-02	B	M
	Henry.2003	56	7	3	15	[1.3]	99-02	C	L
A	Webster.1998	54	9	19	20	[1.9]	<97	B	M
	Gill-Leertouwer.2002	41	9	23	22		96-98	C	M
	Gray.2002	39	14	18	11		91-97	C	M
	Harden.1997	32	9	13	14		92-95	B	M
	Gross.1998	30	75	23	116	[1.4]	<98	B	L
	SURGERY								
	Cherr.2002	500	13	23	21	[2.6]	87-99	C	L
	Alhadad.2004	106	14	15	16	[1.4]	87-96	C	L
	Galaria.2005	100	10	21	11	46	84-04	C	L
	Marone.2004	96	12	23	22		90-01	C	L
	ANGIOPLASTY or SURGERY								
C	Johansson.1999	105	14	23	22	61	83-84	C	L
B	Pillay.2002	12	9	13	22		94-98	C	L

* Excluded patients who died within first 6 months

† Markedly different eligibility criteria for angioplasty and medicine treatment cohorts. See summary table.

N, number of subjects; %Sten, mean percent renal artery stenosis or minimum threshold (indicated by ">"); %Bilat, percent subjects with bilateral renal artery stenosis; MAP, mean arterial pressure; GFR, mean glomerular filtration rate or creatinine clearance in mL/min (or serum creatinine in mg/dL if in brackets); Years, years of intervention (years indicated by "<" mean indicate that year not reported; intervention assumed to have occurred at some time at least one year prior to publication date); Qual, study quality (A, good; B, fair; C, poor); Appl, study applicability (L, low; M, moderate; H, high).

Percentages in brackets indicate that exact time of followup not reported; mean or median time of followup used.

Letters A-D indicate that these studies reported mortality rates for both medical treatment and an invasive intervention. The values of these studies are in larger type to increase ease of comparison.

Detailed Summary Table

Table. Summary of medical, angioplasty and surgical treatments

	Angioplasty (or Surgery) vs. Medical Treatment	Medical / Natural history	Angioplasty	Surgical
Data Source	• 4 RCTs (1 a mix of medical treatment and delayed angioplasty)	• 4 RCTs (1 a mix of medical treatment and delayed angioplasty) • 6 nonrandomized comparative studies of medical treatment, 4 prospective, 2 retrospective • 3 prospective cohort studies with medical treatments for blood pressure control • 8 cohort studies (6 prospective, 1 retrospective, and 1 mixed) of natural history or nonspecified medical treatments	• 3 RCTs • 6 nonrandomized comparative studies, 4 prospective, 2 retrospective; 2 included surgical revascularization • 20 prospective cohort studies with stent placement • 4 prospective cohort studies that used various approaches	• 1 RCT (versus medical treatment) • 2 retrospective comparisons with percutaneous angioplasty • 2 retrospective cohorts
Population studied	• See other columns	• Medical treatment studies included patients with hypertension, mean blood pressure 172-180/103-106. • One study included patients with >50% stenosis, half of whom had bilateral disease. One included a population where 25% had bilateral disease, though the definition of RAS was unclear. The third study did not describe degree of stenosis or bilateral disease. • In two studies the mean serum creatinine was 1.3 mg/dL. • Patients had mean ages approximately in the mid-50s; however, all studies included patients in their 20s or younger. • In all three studies either some patients did not have ARAS or this was not reported. • All 3 studies were from the 1980s or earlier.	• Patients with ARAS with HTN as the most frequent indication. Also included patients with CKD, CHF • About 1/3 of studies included patients populations with >50% stenosis, about 1/4 included only >70% stenosis. Other thresholds were also used. • Mostly populations with both uni- and bilateral disease, range of bilateral disease generally 25-50% of patients; some populations of unilateral or bilateral disease only. • Comparative studies mostly had about 50% with ostial disease, when reported; cohort studies mostly with about 75% or more with ostial disease. • Mean age generally about 65. • Mean blood pressure generally in the range of 160-180/90-100. • Mean serum creatinine generally in the range of 1.5-2.4 mg/dL, or mean GFR about 55 mL/min.	• Patients with ARAS with HTN, CKD, or both HTN and CKD • Populations had ≥60% to ≥80% stenosis • Populations had unilateral and bilateral diseases; the range of bilateral disease was 40-60% • Mean age was in the 60s • Mean blood pressure was in the approximate range of 175-200/85-105 • Mean serum creatinine was in the approximate range of 1.5-2.5 mg/dL • The interventions occurred from 1980-1999

Appendix F. Detailed Summary Table (continued)

Table. Summary of medical, angioplasty and surgical treatments

	Angioplasty (or Surgery) vs. Medical Treatment	Medical / Natural history	Angioplasty	Surgical
Population studied, continued		• In the 8 natural history studies, populations studied were patients with RAS who received no revascularization interventions and presumably were under standard care by their physician. • The mean serum creatinine levels ranged from 1.2 to 3.2 mg/dL at baseline, implying at least stage 2 chronic kidney disease. • The mean stenosis ranged from greater than 20% to greater than 75%. • The percentage of bilateral stenosis ranged from 17% to 100%. • Mean blood pressure ranged from 143-179/77-102, although several studies did not report blood pressure. • The mean age was around 70 years in most studies, though 1 study followed younger patients, between 34-55 years. • Patients were followed from the 1970s through the late 1990s; although several studies did not report time periods.	• Comparative studies almost all did not use stents and included populations from the 1980s and 1990s. 80% of cohort studies used stents and all included populations from the mid 1990s and later.	
Limitations	• Only 2 RCTs compared angioplasty to medical treatment. Neither used stents. Both were of short duration (1 6-month, 1 with main analyses at 12 months, but patients followed from 3-54 months). • Other comparative studies were nonrandomized, retrospective, and/or evaluated interventions of secondary interest	• Data on medical treatments or natural history were from cohort studies without controls. • Populations studied were highly heterogeneous, limiting comparability across studies. • 3 studies on medical treatments reported only outcomes of blood pressure control and limited data on mortality and kidney function. • Treatments were not specified in 8 natural history studies. • Limited data on cardiovascular outcomes.	• Majority of data on angioplasty from before-after intervention studies (cohorts) without controls • Generally short duration of followup, often only single average time estimates of outcomes, despite range of followup time within studies. • Very limited data on cardiovascular outcomes. • Analyses of baseline variables as predictors of outcomes frequently inadequate.	• Retrospective cohort studies

Appendix F. Detailed Summary Table (continued)

Table. Summary of medical, angioplasty and surgical treatments

	Angioplasty (or Surgery) vs. Medical Treatment	Medical / Natural history	Angioplasty	Surgical
Mortality	• In the 3 comparative studies with similar patients receiving each intervention, mortality was similar with angioplasty or angioplasty / surgery and with medical treatment.	• 3 natural history studies found that between 1/3 and 2/3 of patients died within 4-5 years. • Among 6 studies with medical treatment (4 comparative), wide range of mortality estimates across studies, from 0-12% at 6-9 months, and 3-38% at 1 year, and 19-69% at 2-3 years.	• Wide range of mortality estimates across studies, from 1-20% at 6 months, and 0.5-23% at 1 year, and 2-53% at about 2 years. Most studies, though reported only a single mortality rate at an unspecified time point. • Cardiovascular related death was the most frequent reported cause	• 5 -year mortality ranged from 12-41% in studies that used surgical revascularization or both surgery and angioplasty.
Kidney outcomes	• No difference in kidney function (change in serum creatinine or GFR, worsening kidney function, need for dialysis) after revascularization compared to medical treatment in all but one study. One prospective nonrandomized study found a significant difference between a small decrease in serum creatinine (-0.5 mg/dL) after revascularization and a modest increase (+1.0) on medical treatment.	• Kidney function outcomes were reported in seven studies (1 medical treatment and 6 natural history studies). In general patients' kidney function deteriorated over time, although to different degrees in the different studies.	• Among cohort studies the improved kidney function ranged from 8-51% with the majority of studies reporting statistically non significant improvements in serum creatinine • Kidney function improvement varied among those with lower baseline kidney function	• 17 % of patients became dialysis-dependent during the follow up (2 studies)

Appendix F. Detailed Summary Table (continued)

Table. Summary of medical, angioplasty and surgical treatments

	Angioplasty (or Surgery) vs. Medical Treatment	Medical / Natural history	Angioplasty	Surgical
Blood pressure outcomes	• Comparative studies heterogeneous regarding relative effect of interventions on blood pressure. • One RCT of angioplasty vs. medicine found a significant net improvement with angioplasty among patients with bilateral, but not unilateral, disease. The second RCT found a net decrease in both systolic and diastolic blood pressure with angioplasty, but only the change in diastolic pressure was statistically significant. This study also found that after angioplasty, patients required fewer anti-HTN drugs; which was not found in the first RCT. • Most other comparative studies found no difference in blood pressure outcomes, regardless of intervention; however 2 found that blood pressure decreased more in patients on medical treatment than after angioplasty, although this effect was not significant.	• All three studies of medical treatments for blood pressure control showed that, on average, the various treatment regimens examined were effective for lowering blood pressures in RAS patients to normal ranges. • Outcomes of blood pressure control were reported in two natural history studies. The results were not comparable due to substantial differences in the RAS populations examined.	• The cure rates for BP outcome ranged from 4-18%, and the improved rates ranged from 35-79%. The studies also noted decreased use of anti-HTN medications compared to baseline.	• 60 - 70% of patients reported improvements in HTN (2 studies)
CVD outcomes	• 1 RCT of angioplasty vs. medical treatment and 1 RCT of surgery vs. medical treatment both found no differences in CVD outcomes, regardless of treatment.	• CHF events 13% and strokes 13% over 3-54 months (1 study) • CVD stop point (including hypertension, death, and also dialysis) 67% at about 6 years (1 study) • One natural history study reported eight fatal cardiovascular events in 20 patients with severe stenosis (≥ 75%) during 3 to 36 months followup.	• CHF events 9%, strokes 4%, and MI 4% over 3-54 months (1 study) • CVD stop point (including hypertension, death, and also dialysis) 68% at about 6 years (1 study) • CHF 20%, MI 11%, and stroke 7% at a mean of 21 months (1 study) • MI 5% at 15 months (1 study) NYHA class changed by –1.4 at 21 months, which was a significant improvement from baseline (1 study)	• Cardiovascular events accounted for most of the late deaths (1 study) • Nonfatal cardiovascular events occurred in 28% of patients at an average of almost 5 years (1 study)

Appendix F. Detailed Summary Table (continued)

	Angioplasty (or Surgery) vs. Medical Treatment	Medical / Natural history	Angioplasty	Surgical
Adverse Events	• Comparative studies did not address the relative adverse events or complications between interventions (except that 30-day mortality was similar in one study, 3% vs. 5%).	• No study reported the 30-day mortality. • A wide variety of adverse effects were reported for the use of enalapril, timolol, hydralazine, and captopril • None of the 8 natural history studies reported adverse events	• The 30-day mortality ranged from 0-3%. • A transient deterioration in kidney function following procedure was reported ranged from 1-24% that included contrast-induced nephropathy. Severe decline in kidney function was also noted. • Renal artery or parenchymal injury during procedure ranged from 1-10%. • Periprocedural acute myocardial infarction ranged from 1-7%. • Other complications included: major hemorrhage; renal artery occlusion or spasm; false aneurysms; severe bleeding; and localized hematoma	• 30 -day mortality ranged from 4-9% • Procedural complication rate was significantly higher in combined renal artery and aortic reconstruction compared with renal artery reconstruction alone (2 studies)
Factors that influence outcomes	• The study comparing immediate to delayed or no angioplasty found that of two diagnostic tests, recent hypertension, bilateral stenosis, and severe stenosis (>70%), only bilateral disease was found to be associated with better creatinine clearance at 12 months in those patients who had immediate angioplasty, in contrast to those with unilateral disease, where creatinine clearance was statistically similar in the two groups.	• Among cohort studies of medical treatment, no analyses evaluated baseline variables as predictors. • 4 natural history studies analyzed various predictors of mortality and/or outcomes of kidney function. Percent stenosis and baseline kidney function were f predictors of death (or dialysis) in separate studies. Another study found that nonspiral blood flow in the renal arteries predicted kidney function deterioration. Other variables related to cardiovascular disease were also found to predict death. 1 study found that bilateral versus unilateral disease did not predict progressive kidney disease. • 1 natural history study found that patients with bilateral disease had higher CVD mortality.	• Worse baseline kidney function was associated with increased mortality, poor clinical outcomes, and relatively worse blood pressure after revascularization. • History of, or markers of, cardiovascular disease was associated with increased mortality, poor clinical outcomes, and relatively worse kidney function after revascularization.	• Preprocedure hemodialysis led to poorer functional kidney recovery but initiation of dialysis prior to surgery was predictive of long-term kidney function improvement in another (2 studies) • Preoperative CKD, DM, prior stroke, and severe aortic occlusive disease showed significant and independent associations with death or dialysis during the follow up (1 study)

Appendix F. Detailed Summary Table (continued)

	Angioplasty (or Surgery) vs. Medical Treatment	Medical / Natural history	Angioplasty	Surgical
Factors with no effect	• The study comparing immediate to delayed or no angioplasty found that no variable predicted relative effectiveness of intervention strategy when diastolic blood pressure was the outcome. • The randomized trial of surgical versus medical treatment, found that demographic factors did not help to predict which patients would fare better with either intervention.		• Age and beta blocker or diuretic use at baseline were not significant predictors of mortality or other clinical outcomes. • Baseline captopril test, renogram, arterial norepinephrine, and ACE genotype were generally not associated with outcomes. • The association between baseline predictors and outcomes was uncertain for several factors including baseline kidney function as a predictor of followup kidney function, baseline cardiovascular disease as a predictor or blood pressure effect, percent stenosis before angioplasty, bilateral vs. unilateral RAS, and sex.	
Periprocedural factors	• N/A	• N/A	• Among the studies that used angioplasty with and without stent, there were no differences in blood pressure and kidney outcomes between the procedures. • No study reported analyses of whether other periprocedural interventions, such as different drugs or different approaches, affected either complications or long-term outcomes.	• N/A
Overall Summary	• The 2 applicable RCTs found no difference in kidney cardiovascular, or mortality outcomes between angioplasty without stent placement and medical treatment. The studies suggest a better reduction in blood pressure control after angioplasty, particularly in patients with bilateral disease.	• Data on medical treatments or natural history were from cohort studies without controls. • Populations studied were highly heterogeneous • 3 natural history studies found that between 1/3 and 2/3 of patients died within 4-5 years. • Among 6 studies with medical treatments, wide range of mortality estimates across studies.	• Data mostly from prospective cohorts without a control group that indicate BP outcomes as the significantly improved outcome especially among those with higher baseline kidney function • Mortality was mostly CVD-related; was predicted by lower baseline kidney function, CHF, and influenced by bilateral disease with or without baseline CKD	• Data from retrospective cohort analyses. Some data were poorly reported. • Major outcomes like long-term mortality, improvements in HTN, and proportion of patients who became dialysis-dependent were similar across studies.

Appendix F. Detailed Summary Table (continued)

	Angioplasty (or Surgery) vs. Medical Treatment	Medical / Natural history	Angioplasty	Surgical
Overall Summary, continued	• The other comparative studies mostly agree with these conclusions, although the studies are heterogeneous in regards to blood pressure outcomes. • The comparative studies do not adequately address comparative adverse events or the predictive value of baseline variables to determine whether any of these factors would favor one intervention over the other. • Indirect comparisons between cohort studies of revascularization and of medical treatment confirm the lack of difference in mortality rates between treatments, in resultant kidney function, with the caveat that improvement was reported only in cohort studies of revascularization, • Across cohort studies, the difference in blood pressure outcomes with either revascularization or medical treatment was uncertain, except that improvement was reported only in cohort studies of revascularization. • No conclusions could be reached about differences in cardiovascular outcomes or adverse events based on the cohort studies.	• In general patients' kidney function deteriorated over time, although to different degrees in the different studies. • All 3 studies of medical treatments for blood pressure control showed that, on average, the various treatment regimens examined were effective for lowering blood pressures in RAS patients to normal ranges.	• There was no difference in blood pressure and kidney outcomes between procedures with and without stent. Studies did not analyze the predictive value of periprocedural interventions	

ARAS, atherosclerotic renal artery stenosis; CHF, congestive heart failure; CKD, chronic kidney disease (renal insufficiency); CVD, cardiovascular disease; DM, diabetes mellitus; GFR, glomerular filtration rate; HTN, hypertension; MI, myocardial infarction; N/A, not applicable; NYHA class, New York Heart Association functional class.