

Comparative Effectiveness Review

Number 5 Update

Comparative Effectiveness of Management Strategies for Renal Artery Stenosis: 2007 Update



Agency for Healthcare Research and Quality
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Comparative Effectiveness Review (Update)

Number 5 Update

Comparative Effectiveness of Management Strategies for Renal Artery Stenosis: 2007 Update

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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 (CERs) 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 strength 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 CERs 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

This report is an update to a Comparative Effectiveness Review on management strategies for renal artery stenosis (RAS) from October 2006. The systematic review included all studies of patients with atherosclerotic RAS (ARAS) that compared two or more interventions. It also reviewed recent prospective cohort (single arm) studies of angioplasty with stent placement, prospective cohort studies of medical interventions, cohort studies of RAS natural history, and prospective or large retrospective studies of surgical bypass. This update evaluated the same questions and used the same eligibility criteria, updating the literature search through April 23, 2007. This report does not address the management of fibromuscular dysplasia, renal transplant recipients, or patients who have a previous failed revascularization.

The Key Questions addressed by the original report and this update are:

1. For patients with atherosclerotic renal artery stenosis in the modern management era (i.e., since JNC-5 in 1993ⁱ), 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?

The original report evaluated 60 unique studies. The updated search found an additional nine articles, representing eight new studies. One article provided new data on quality of life (QoL) from a previously published trial; a second article reported on a nonrandomized comparative study; and the remaining articles were on cohort studies of angioplasty with stent. Notably, only two trials have compared angioplasty (without stent placement) with medical therapy and followed patients for at least 6 months. The other comparative studies were of shorter duration, were nonrandomized, or had other limitations. The remaining studies were cohort studies of different interventions.

An analysis of a previously reported randomized trial that compared immediate angioplasty and either medical therapy alone or medical therapy followed by angioplasty at 3

ⁱ 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.

months found either no significant differences or inconsistent differences in QoL at 3 and 12 months. The other recently published studies had results generally similar to those from the previously published articles included in the original report.

None of the studies evaluated the principal question of interest—namely, the relative effects of intensive medical therapy and angioplasty with stent for patients with ARAS. The quality of the evaluated studies was limited because of inadequate reporting and/or collection of data, incomplete analyses, and often inconsistent use of interventions (e.g., combining angioplasty with and without stent); limited applicability due to restrictive patient eligibility or inadequate reporting; and limited power of studies due to small sample size.

The evidence does not support one treatment approach over the other for the general population of people with ARAS.

- Weak evidence suggests no difference in mortality rates.
- There is acceptable evidence that, overall, there is no difference in kidney outcomes between patients treated medically only and those receiving angioplasty without stent, although the relevance of this finding to current practice is questionable due to changes in treatment options. However, improvements in kidney function were reported only among patients receiving angioplasty.
- There is acceptable evidence that combination antihypertensive treatment results in large decreases in blood pressure, but there is inconsistent evidence regarding the relative effect of angioplasty and medication on blood pressure control.
- 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.
- Weak evidence suggests no difference in QoL with medical treatment alone or with angioplasty.
- The evidence does not adequately assess comparisons of adverse events between medical treatment alone and angioplasty.
- There is weak evidence that patients with bilateral RAS may have more favorable outcomes with angioplasty than medical therapy.
- Weak or inconsistent evidence does not support statements on whether other clinical features (such as demographics or indicators of RAS severity) or diagnostic tests predict whether patients would have better clinical outcomes with angioplasty or with medical therapy alone.
- There is no evidence regarding the value of periprocedural interventions with angioplasty.

Chapter 1. Introduction

The Tufts-New England Medical Center Evidence-based Practice Center (EPC) completed the report on Comparative Effectiveness of Management Strategies for Renal Artery Stenosis¹ with a simultaneous publication, Comparative Effectiveness of Management Strategies for Renal Artery Stenosis: A Systematic Review,² in December 2006. Those documents evaluated the evidence on various interventions for, and the natural history of, atherosclerotic renal artery stenosis (RAS) in adults. The literature searches were performed through September 2005. The systematic review included all studies of patients with atherosclerotic RAS (ARAS) that compared two or more interventions, recent prospective cohort studies (single arm, non-comparative) of angioplasty with stent placement, prospective cohort studies of medical interventions, recent cohort studies of ARAS natural history, and prospective or large retrospective, recent studies of surgical bypass interventions. The Centers for Medicare and Medicaid Services (CMS) requested an update to the original report for the purpose of a Medicare Evidence Development & Coverage Advisory Committee (MedCAC) meeting on renal artery stenosis in July 2007. The original review and this update were conducted to clarify the current state of the literature and science and to better understand the state of evidence.

As described in greater detail in the Methods section, this update used the same eligibility criteria for studies. As with the original report, it is important to note that 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. In addition, this report does not address the management of fibromuscular dysplasia, renal transplant recipients, or patients who have a previous, failed revascularization.

This report represents an update and summary of the original report. Sections of the original report and the Annals of Internal Medicine article are copied here, but many of the specifics of that report are not repeated. This document focuses more on the conclusions reached from the (updated) systematic review than the details of the reviewed articles or the findings. This document is not meant to supplant or replicate the original report. Reference to the full report may be necessary for details. This document does not repeat information about the ongoing Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial.³ Updated versions of the summary tables are provided as an appendix to this document.

Background

This section is largely reproduced from Balk et al. in the Annals of Internal Medicine.²

RAS is defined as the narrowing of the lumen of the renal artery. Atherosclerosis accounts for 90 percent of cases of RAS.⁴ ARAS is a progressive disease that may occur alone or in combination with hypertension and ischemic kidney disease.⁴ The prevalence of ARAS ranges from 30 percent among patients with coronary artery disease to 50 percent among elderly or those with diffuse atherosclerotic vascular diseases.^{5,6} In the United States 12 to 14 percent of new patients entering dialysis programs have been found to have ARAS, although the contribution of ARAS to end stage renal disease is unclear.⁷

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.^{8,9} 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, 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 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 (ACC/AHA) recently published guidelines for the management of patients with peripheral arterial disease, including renal artery stenosis.^{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 mortality or substantial morbidity in a small percentage of patients.

Placement of renal artery stents can resolve dissections, minimize stenosis recoil and restenosis, and correct translesional pressure gradients. The evidence for durability of clinical benefit is unclear; the majority of 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.⁴

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. There is uncertainty as to whether patients with anatomically amenable lesions truly benefit from invasive interventions when compared with medical treatment. 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 interventions increasing from 7,660 to 18,520.¹⁰ Data provided to the Tufts-New England Medical Center EPC by the Cordis Corporation of Medicare Provider Analysis and Review (MEDPAR) File for 2003 to 2005 may indicate a leveling off of the number of RAS lesions being treated with angioplasty and stent (summary data available from the Tufts-New England Medical Center EPC). According to their data, there were 15,339 stents placed in renal arteries in 2003, 17,544 in 2004, and 17,643 in 2005.[†]

[†] These data are graphically represented by Cordis at <http://www.cms.hhs.gov/determinationprocess/downloads/id202.pdf> (accessed September 4, 2007) in their letter of March 27, 2007 to the Medicare Evidence Development & Coverage Advisory Committee.

Scope and Key Questions

This section is reproduced verbatim from the original RAS Comparative Effectiveness Review.¹

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 updated 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?

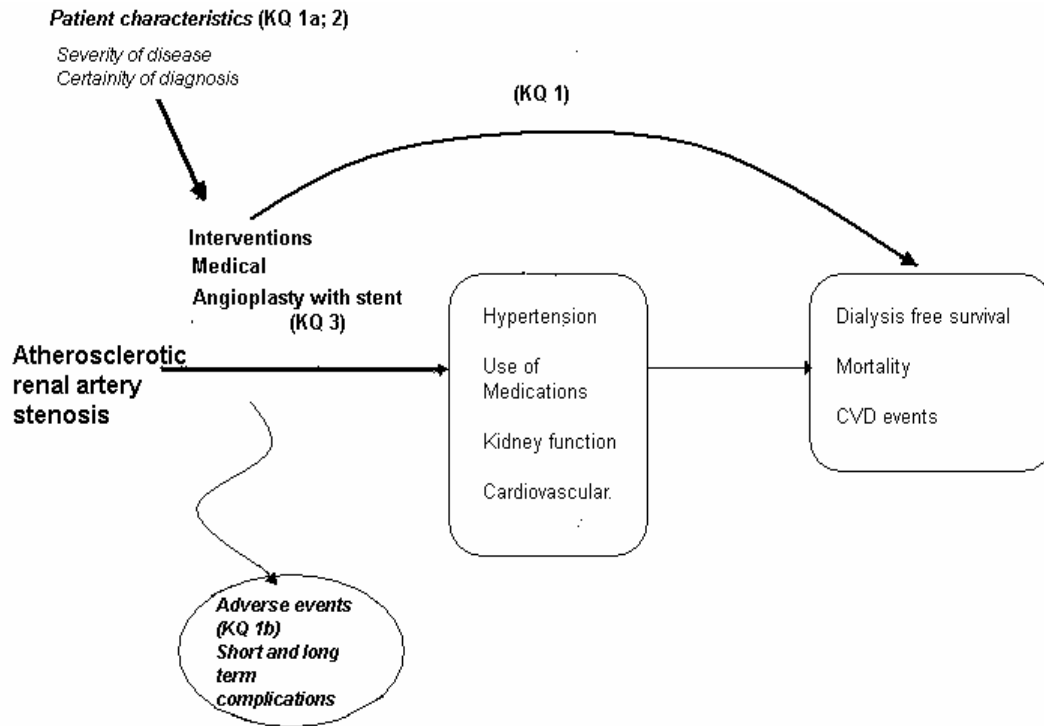
Analytic Framework

This section is reproduced verbatim from the original RAS Comparative Effectiveness Review.¹

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 (RCTs) was preferred, these data were rare, so nonrandomized and uncontrolled studies were used to augment the evidence.

^{††} 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.

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: CVD, cardiovascular disease; KQ, key question.

Chapter 2. Methods

Data Sources and Selection

This chapter was largely reproduced from both Balk et al. in the *Annals of Internal Medicine*² and the original RAS Comparative Effectiveness Review.¹

For the original report we searched the MEDLINE database from inception to 6 September 2005 for studies involving adults with atherosclerotic renal artery stenosis. This update includes articles in the MEDLINE database as of April 23, 2007.

We combined search terms for renal artery stenosis, renal hypertension, and renal vascular disease, and we limited the search to English-language articles of studies in adult humans that had relevant research designs. We included peer reviewed primary studies of adult patients treated for ARAS and excluded studies that evaluated patients with RAS in the setting of a transplanted kidney, renal artery aneurysm requiring repair, aortic disease requiring invasive intervention, or concurrent cancer or patients who had had previous surgical or angioplasty interventions for RAS. We included only studies that reported outcomes of interest (mortality rate, kidney function, blood pressure, cardiovascular events, and quality of life) at 6 months or more after the initial intervention. We excluded studies in which more than 20 percent of patients had RAS due to other causes.

We used different eligibility criteria for studies of different interventions, based on the varying number of studies available for each intervention and the relevance of the intervention to current practice. The criteria were made in conjunction with a Technical Expert Panel (TEP) convened for the original report. We included all direct comparisons of medical treatment with angioplasty and all uncontrolled (cohort) studies of medical treatment that had at least 10 patients in each group, regardless of study design. For angioplasty, surgical, or natural history studies, we included only those in which at least some patients were recruited in 1993 or later, after the publication of the Fifth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-5). These guidelines marked a substantial change from previous guidelines in treatment recommendations for hypertension, including more aggressive blood pressure targets.¹¹ In addition, at this time point, angiotensin-converting enzyme inhibitors began to be used more routinely in the treatment of patients with severe hypertension.

We included angioplasty studies only if they used stent placement in at least some patients, were prospective, and had at least 30 patients; and retrospective surgery studies that included at least 100 patients. Any prospective surgery study (with at least 10 subjects) that otherwise met criteria was eligible.

Assessing the Quality, Applicability, and Relevance of the Evidence

The system used for grading the quality and applicability used here is well-established, though not universally used, by EPCs. The Tufts-New England Medical Center EPC has been using a similar system for almost all its systematic reviews for almost a decade. The system used for grading the body of evidence is based on a system being used for all the CERs; however, this system is still evolving. The system for assessing the relevance of the individual studies (tiers of evidence) was designed *de novo* specifically for this report. It was designed to clarify the

relevance of a body of evidence that fails to directly address the main questions of interest. It should be noted that none of the systems used directly correspond to the “Levels of Evidence” used by the ACC/AHA guidelines for the management of patients with peripheral arterial disease, which simply denote the study designs of the evaluated literature.^{8,9}

Data Extraction

Data from each study were extracted by one of the authors and confirmed by another. The extracted data included information about patient samples, interventions, outcomes, adverse events, study design, quality, and applicability. 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.

Quality Assessment

We used predefined criteria to grade study quality as good, fair, or poor. 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)

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.

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 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.

The original Comparative Effectiveness Review used the terminology Robust, Acceptable, and Weak to describe the levels of evidence. To improve clarity the levels of

evidence, for the purposes of this update, the category Inconsistent was added, as described below:

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.

Inconsistent

There is disagreement across or within studies, preventing a conclusion about the actual effect.

Tiers of Evidence

For the purposes of this systematic review, where there is no evidence directly addressing the primary Key Questions and few comparative studies of any kind, we developed tiers of evidence to highlight the relevance of particular groups of studies to the Key Questions. These are:

Tier I

RCTs that compared angioplasty with stent placement to aggressive medical therapy. These studies would directly address Key Question 1. No published studies qualify for Tier I.

Tier II

RCTs that compared angioplasty with or without stent to medical therapy with at least 6 months of followup. These were the best available studies that studied interventions similar to those of interest.

Tier III

Other comparative studies that compared angioplasty or vascular surgery to medical therapy (regardless of followup time). These are less relevant comparative studies or comparative studies with poorer study designs than Tier II studies.

Tier IV

Noncomparative cohort (pre-post) studies of interventions of interest. These studies do not directly provide information about the relative value of different interventions.

Chapter 3. Results

The original 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. Many articles represented multiple publications arising from the same studies. Thus the original report evaluated 60 unique studies, 5 of which met criteria only to provide data on adverse events.

The updated search yielded 185 new citations. An additional 9 articles met eligibility criteria. These represented 8 new studies and 1 article with newly reported data from a previously reported trial. **Figure 2** summarizes the search and selection of articles. **Table 1** summarizes the evaluated studies.

Key Question 1: Clinical Effects of Interventions

Direct Comparisons of Angioplasty (or Surgery) With Medical Treatment of Atherosclerotic Renal Artery Stenosis (Appendix Tables 2-3, Figures 3-5)

The original CER included three RCTs published in five articles involving a total of 208 patients with ARAS (analyzed, in their randomized arms) that compared angioplasty to medical treatments.¹²⁻¹⁶ Six additional studies,¹⁷⁻²² and a nonrandomized third arm from one of the RCTs,¹² 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.

In the update, two additional articles met criteria. One²³ is a further analysis of a previously included RCT.¹⁴⁻¹⁶ The other is a newly published nonrandomized study comparing two cohorts of patients treated either medically or with angioplasty.²⁴

Description of randomized controlled trials of angioplasty vs. medical treatment

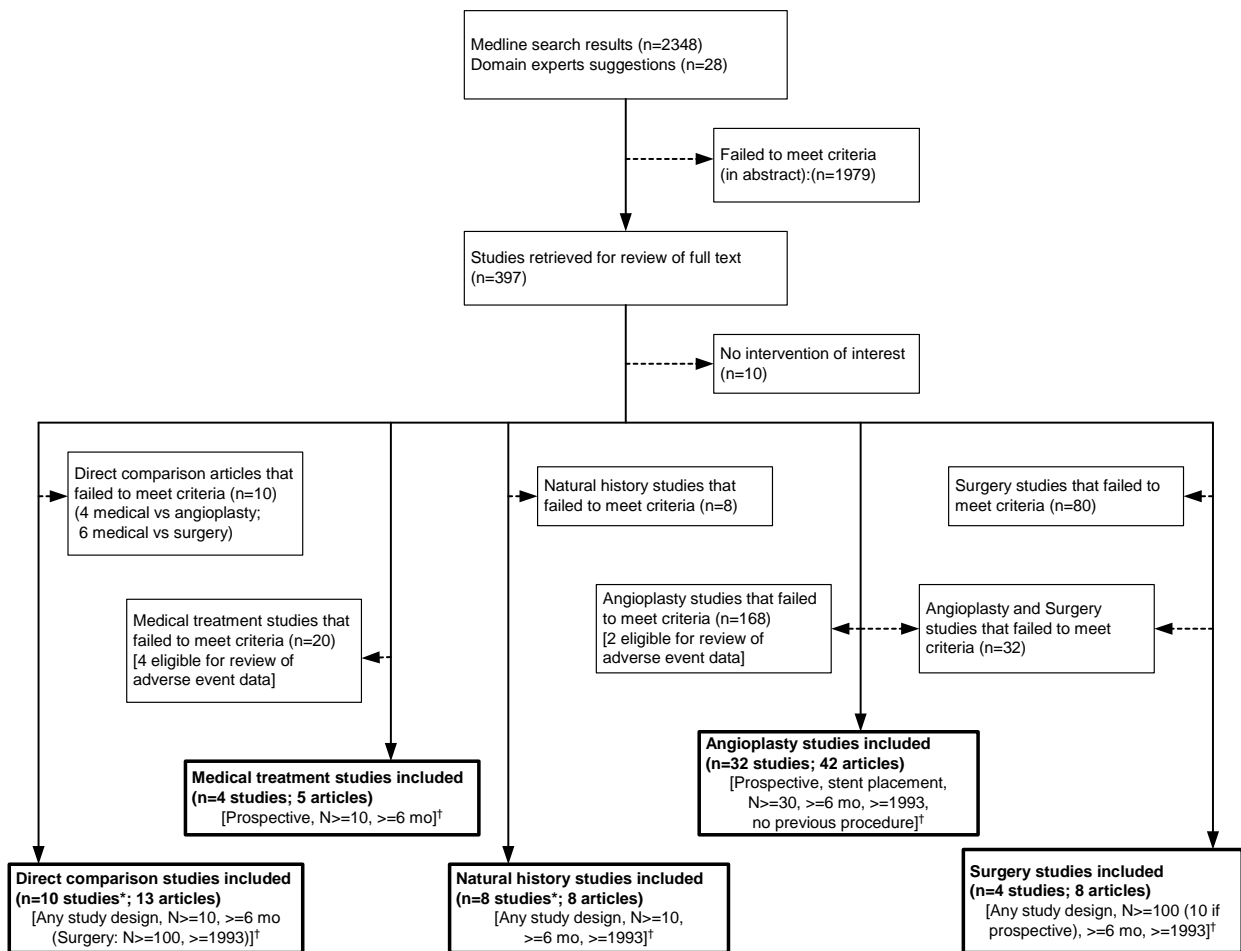
No studies were of Tier I evidence (RCTs of angioplasty with stent vs. aggressive medical therapy).

Two RCTs met eligibility criteria for Tier II evidence, comparing angioplasty without stent to medical treatment, with at least 6 months of followup. Notably, the trials were small and clearly too small to be adequately powered for clinical outcomes including mortality, cardiovascular and kidney events. Stents were used only rarely and medical therapies varied both between and within studies. One study did not use ACE inhibitors¹² and the other used enalapril in only some patients.¹³ Thus neither trial compared patients being treated with interventions currently being used. The trials were of fair quality and either moderate or low applicability to the general population with ARAS. Because these trials are the most pertinent studies that address the key questions, they are summarized in some detail. This information is largely reproduced from the original RAS Comparative Effectiveness Review.¹

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.¹² In a multicenter study, 55 patients with resistant hypertension with at least 50 percent stenosis were randomized to either angioplasty without stent placement (n=25) or treatment with, preferentially, atenolol, bendrofluzide and/or a

calcium antagonist (n=30). Other eligibility criteria applied. Their protocol resulted in two randomized groups (bilateral and unilateral disease) and a nonrandomized group of patients with unilateral disease. 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, and 6 months after the end of a run-in period or after angioplasty, and then at 6 month intervals thereafter; the primary endpoint was at 6 months. 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. The nonrandomized comparisons are included with the other comparative studies below.

Figure 2. Search and selection of studies for review



* One study had data for both direct comparison of medical treatment to angioplasty and of natural history.
† Intervention-specific study-eligibility criteria.

Information in square brackets is eligibility criteria for studies based on intervention. N, minimum sample size; >=6 mo, minimum duration 6 months; >=1993, patients included had interventions in 1993 or later.

This figure is an updated version of a draft figure published in Balk et al. in the Annals of Internal Medicine.²

The EMMA study (Plouin 1998) compared angioplasty (mostly without stent placement) to drug treatment, primarily for blood pressure outcomes.¹³ 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. The principal results were recorded at 6 months.

Table 1. Summary of reviewed studies*

Study Type	Evidence Tier †	Intervention	Studies, n	Quality †, n			Applicability †, n			Participants, n	Years of Intervention
				Good	Fair	Poor	High	Moderate	Low		
Randomized trials	I	Angioplasty + stent placement vs medical therapy	0								
Randomized trials	II	Angioplasty ± stent placement vs medical therapy	2‡	2			1	1	103	1992–1995§	
Randomized trials	III	Angioplasty ± stent placement vs medical therapy ± subsequent angioplasty	1	1			1		106	1993–1998	
Comparison studies#	III	Revascularization vs medical therapy	8‡	2	6		1	7	681	1981–2003§	
Cohort studies	IV	Medical treatment	4	1	3		1	3	83	Not reported	
Cohort studies	IV	Natural history	8	3	5		3	5	721	1970–1998§	
Cohort studies	IV	Angioplasty + stent placement	27	14	13	6	16	5	3750	1989–2004§	
Cohort studies	IV	Surgical revascularization	4		4			4	921	1980–2004	
Any	II-IV	Studies that reported adverse events	37						5503	1989-2004	

* This table is updated from Table 1 in Balk et al. Effectiveness of management strategies for renal artery stenosis: a systematic review. *Ann Intern Med.* 145(12):901-12, 2006 Dec 19.²

† See Methods, *Assessing the Quality, Applicability, and Relevance of the Evidence*, pages 7-10..

‡ One study had both a randomized and nonrandomized component.

§ Some studies did not report the intervention years.

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

Description of the comparative studies

Nine other studies compared various interventions in randomized and nonrandomized studies (Tier III evidence). The DRATIC trial (van Jaarsveld 2000), which has had multiple articles published with results,^{14-16,23} including a new article found for the update²³ randomized patients 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). 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), we categorized this trial as Tier III. 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). 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. The goal of the study was to evaluate

changes in blood pressure and kidney function after 1 year of treatment. 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 digital subtraction angiography. Other eligibility criteria applied. Results 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.

The other comparative studies include 3 prospective^{12,22,24} and 2 retrospective^{17,21} nonrandomized comparisons of angioplasty (mostly without stent use) and medical therapy, 2 prospective nonrandomized comparisons of angioplasty or surgery on one hand and medical therapy on the other,^{18,20} and 1 randomized trial of surgery versus medical therapy.¹⁹

The recently published study, Losito 2005²⁴ compared patients who were referred either from a renal unit where they were treated medically or from units that routinely performed angioplasty, mostly without stents. Patients were followed for an average of 4.5 years.

Outcomes

Mortality (study duration 6 months or greater)

Figure 3 graphically presents mortality rates over time in studies of the different interventions, including 4 of the comparative studies. 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. Among the RCTs of angioplasty versus medical therapy, only the SNRASC random trial (Webster 1998) reported mortality data.¹² The survival curves were nearly identical for the two groups over 42 months. Five of the other comparative studies, including Losito 2005, reported mortality analyses.^{17-20,24} Most found no difference in mortality rates. Only the retrospective study found that patients treated with angioplasty (with or without stent) had a lower mortality rate than those treated medically;¹⁷ however, the medically treated patients were older and probably had more severe cardiovascular disease and worse cardiovascular risk factors.

Overall, the comparative studies do not indicate a survival difference between the two modes of intervention.

Kidney function

The two RCTs (Webster 1998 and Plouin 1998) found no significant, clinically meaningful or consistent differences in change in kidney function between those who received angioplasty and those who were treated medically. Figure 4 presents forest plots of changes in kidney function after different interventions, including the net differences between angioplasty and medical therapy from the two RCTs. The remaining comparative studies had inconsistent findings. Four studies (including the recently added study) found that kidney function after angioplasty (or surgery) was better than with continuing medical therapy,^{15,17,22,24} though not all studies performed statistical analyses; one study found significantly worse change in serum creatinine after angioplasty or surgery;¹⁸ and three studies found no difference.^{12,19,21} Notably, only one study (Taylor 1989²²) found that kidney function, on average, improved after angioplasty or surgery, though this was a poor quality study that was extremely small (5 with angioplasty, 15 without).

Overall, the comparative studies provide evidence that the different modes of intervention do not result in different changes in kidney function.

Blood pressure control

The two RCTs (Webster 1998 and Plouin 1998) had heterogeneous (inconsistent) findings in regard to the comparative effect on blood pressure control of angioplasty or medical treatment. In the SNRASCG study (Webster 1998),¹² among those with unilateral ARAS at 6 months (the primary endpoint) no difference in blood pressure was found. However, an analysis of the final blood pressure readings recorded, adjusted for time (but over a period in which some patients assigned to medical treatment had angioplasty), found 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 statistically significant. In contrast, among patients with bilateral disease, there was a large decrease in blood pressure (−24/−9 mm Hg at 6 months and −34/−11 mm Hg at final visit) in those who had angioplasty compared to a more modest reduction among patients treated medically (−13/−10 mm Hg at 6 months and −8/−1 mm Hg at final visit). However, only the differences at the final visit, adjusted for time, were statistically significant. Similarly, although to a lesser extent, EMMA (Plouin 1998) found a greater reduction in blood pressure after angioplasty (−14/−8 mm Hg) than with medical treatment (−7/−1 mm Hg, nonsignificant for systolic blood pressure, P=0.04 for diastolic blood pressure).¹³ Figure 5 presents forest plots of changes in blood pressure after different interventions, including the net differences at 6 months between angioplasty and medical therapy from the two RCTs.

Of note, a 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.^{25,26}

The other comparative studies mostly found no difference in effect on blood pressure. Six of eight studies found no significant difference in blood pressure, with a mix of whether blood pressures were lower after angioplasty/surgery, or with continued medical therapy. The recent study, Losito 2005,²⁴ and a similar retrospective comparison¹⁷ found significantly greater improvement in blood pressure after angioplasty or surgery.

Overall, the evidence found that both invasive and medical therapy result in decreases in blood pressure, but the evidence only weakly supports a conclusion that angioplasty may result in better blood pressure control, particularly in people with bilateral disease.

Cardiovascular outcomes

Only Webster 1998 (SNRASCG) reported on cardiovascular outcomes.¹² The study combined data from the randomized unilateral and bilateral ARAS arms. Event rates for heart failure, stroke, and myocardial infarction were similar regardless of intervention. Uzzo 2002 in the RCT of surgical versus medical treatment found no difference in a combined stop point of resistant hypertension, kidney function worsening, atherosclerotic cardiovascular event, or death.¹⁹

Quality of life

Quality of life was not explicitly included in the original CER; however, this decision was made in part due to a lack of data. A recently published article regarding the DRASTIC study (that compared immediate angioplasty versus medical therapy or delayed angioplasty) reported on several measures of quality of life.²³ These included a validated questionnaire on physical symptoms associated with hypertension and treatment; SF-36, which measures physical functioning, role functioning, social functioning, psychological well-being, health perceptions, and pain; and EuroQol, which measures ability to walk, to perform activities of daily living,

depression, anxiety and pain. Overall, for all three measures no significant differences were found at 3 months comparing all patients who received angioplasty or were treated medically, and at 12 months comparing those immediately treated with angioplasty and those who remained on medical treatment. SF-36 social functioning was better at 3 months among patients after angioplasty, but at 12 months was better among those who never received angioplasty.

Adverse events (including 30 day mortality)

No new data on adverse event rates among comparative studies has been reported. The following summary is from the original CER.

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.²¹ Similar 30-day mortality rates, given the small number of patients, were found in both the angioplasty (3 percent) and medical treatment (5 percent) arms.

Cohort Studies of Medical Therapy or Natural History (Appendix Tables 4-6, Figures 3-5)

No new cohort studies of medical therapy or natural history of RAS have been published since the original CER (Tier IV evidence). To briefly summarize the CER findings, four prospective studies, including 83 participants, evaluated different medical therapy regimens for patients with ARAS.²⁷⁻³¹ Three additional studies provided only adverse event data.³²⁻³⁵ These included multidrug regimens (aspirin, statins, and antihypertensive agents) and/or specific angiotensin converting enzyme (ACE) inhibitors. One study was of fair quality and moderate applicability; the other studies were of poor quality and low applicability, largely due to incomplete reporting. An additional eight studies, six of which were prospective, followed the natural history of 721 patients who mostly received various medical therapies.^{18,36-42} Three were of fair quality and five of poor quality; three were of moderate applicability and five of low applicability.

Among the drug studies, all four 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.^{27,31} One study reported an overall mortality rate of 5 percent after 8 to 32 months of followup.³¹ In one study of 40 ARAS patients on aggressive medical treatment including blood lipid control, one patient (2.5 percent) experienced stroke and one patient (2.5 percent) experienced myocardial infarction during the follow-up period.²⁷ A wide variety of adverse effects were reported for each antihypertensive agent.

Among the natural history studies, kidney function outcomes were reported in six studies; in general patients' kidney function deteriorated over time, although to different degrees in the different studies. Two studies reported blood pressure outcomes. In one study of 35 people with unilateral ARAS, median diastolic blood pressure did not change significantly over time.¹⁸ In a second study of 20 ARAS patients, two-thirds of whom had bilateral stenosis, mean blood pressures decreased substantially (39/17 mm Hg) after medical treatment.³⁸ One study reported eight fatal cardiovascular events in 20 patients with severe stenosis (≥ 75 percent) during 3 to 36

months followup.⁴⁰ Mortality outcomes were reported in four studies.^{37,40-42} Six-month, 2-, 4-, and 5-year survival rates were 77 percent, 60 to 68 percent, 64 percent, and 38 percent, respectively.

The studies found that antihypertensive therapy is effective at reducing blood pressure in patients with RAS. However, data on clinical outcome event rates were sparse or inconsistent across studies.

Cohort Studies of Angioplasty With Stent (Appendix Tables 7-8, Figures 3-5)

Summary of cohort studies

The original CER evaluated 21 studies (with a total of 3,368 patients) in 28 publications that placed stents in all patients (Tier IV evidence).⁴³⁻⁷³ Two additional studies^{74,75} that reported only adverse events were also included. The studies followed patients from 6 months to 48 months. The original CER included a separate section on four studies that evaluated patients who received angioplasty with or without stent. One of these was an RCT of stent versus no stent.⁷⁶ For the purposes of this update, we have added the stent arm of this study to the collection of cohort studies of angioplasty with stent.

In the update, six additional articles⁷⁷⁻⁸² met eligibility criteria, one of which reported only adverse event data.⁸² These studies included a total of 431 patients and followed patients from 6 months to 84 months. One additional recent cohort study evaluated patients who received angioplasty either with or without stent placement. This study is not included here, but is discussed below under Key Question 2.

Outcomes

Mortality (study duration 6 months or greater)

In the original CER, data on mortality 30 days after angioplasty with stent placement was reported in 18 studies. Only one of the new studies reported mortality data.⁷⁹ Overall, the mortality rates ranged from 0.5 to 53 percent up to about 5 years; eight studies reported 10 percent or greater mortality at follow up. 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. However, no obvious factors were reported to explain the different mortality rates.

Overall no unifying pattern was found regarding mortality rates after angioplasty with stent.

Kidney function

Overall, 22 studies reported kidney outcomes as either changes in estimated glomerular filtration rate (or creatinine clearance) or changes in serum creatinine during followup; five of these were published recently.⁷⁷⁻⁸¹ A quarter of the studies reported statistically significant improvements in kidney function during followup, on average across all patients. Kidney outcomes were quantified using different definitions and categorized as improved, unchanged, and worsened in 16 studies. Patients with improved kidney function ranged from 8 to 51 percent.

Patients with worse kidney function ranged from 0 to 31 percent. Studies also noted that some patients were able to stop dialysis.

The cohort studies found a range of effects on kidney function of angioplasty with stent; however, consistent with the comparative studies and in contrast to patients treated medically, some patients were found to have improved kidney function.

Blood pressure control

Twenty-seven studies, five of which were published recently⁷⁷⁻⁸¹ reported blood pressure outcomes. All studies reported blood pressure outcomes as change from baseline and/or categories of cured, improved, unchanged, and worsened hypertension. Cure generally was defined as maintaining normal blood pressure without medication. Hypertension cure ranged from 4 to 18 percent; hypertension improvement ranged from 35 to 79 percent; and worsening in hypertension ranged from 0 to 13 percent. The majority of the patients had cured or improved blood pressure rates at followup compared to baseline.

The majority of studies observed consistent systolic or diastolic blood pressure reduction at followup after stent placement.

Cardiovascular outcomes

Only three studies reported cardiovascular event rates, including one of the recently published studies.^{45,60,77} They found that patients remain at increased risk of cardiovascular disease after angioplasty with stent placement. A fourth study reported a statistically significant reduction in the New York Heart Association Functional Class after stent placement.⁵⁴

Restenosis rate

Restenosis was evaluated between 3 to 40 months after percutaneous interventions and the rates of restenosis ranged from 6 to 21 percent. A total of 22 studies evaluated restenosis rates during follow-up, including four new studies.⁷⁸⁻⁸¹ Of these only three studies evaluated the whole cohort of patients who underwent stent placement for restenosis at follow-up.^{43,44,54} A proportion of the original cohort who presented with clinical symptoms was evaluated in the remainder of the studies. 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 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.⁶³

The cohort studies found that restenosis after stent placement occurs in up to a fifth of renal arteries.

Adverse events (including 30 day mortality)

A total of 22 studies reported adverse events immediately following angioplasty with stent intervention. The 30-day mortality was reported in 12 studies and ranged from <1 to 3 percent. A transient deterioration in kidney function following procedure was reported in nine studies, which ranged from 1 to 13 percent, including five studies that reported contrast-induced nephropathy. A severe decline in kidney function was reported in four studies (“severe deterioration of kidney function” in 1.5 percent of patients in one study; kidney failure in 6 to 12 percent of patients in three studies).^{45,67,69,76} Renal artery or parenchymal injury during procedures ranged from <1 to 10 percent in eight studies. Other complications included: major hemorrhage 1 percent (two studies); renal artery occlusion or spasm 0.5 to 4 percent (six

studies); false aneurysms 0.7 to 9 percent (eight studies); severe bleeding 1 to 16 percent (six studies); and localized hematoma 0.4 to 10 percent (seven studies).

Cohort Studies of Surgical Interventions (Appendix Tables 11-12)

In the original CER, four studies of surgical interventions met eligibility criteria (Tier IV evidence).⁸³⁻⁹⁰ No recent studies were found. All four studies were retrospective; they included 921 patients. The mean follow up times in these studies ranged from 4 months to 56 months. All four studies were of methodologically poor quality. The results from these studies are generally applicable to patients with hypertension, chronic kidney disease, and hemodynamically significant ARAS.

All four studies reported similar long-term mortality (about 30-40 percent at 5 years). In one study, three-quarters of the late deaths were due to cardiovascular disease.⁸⁵ Three studies reported kidney function data. One study found that 74 percent of patients were free of kidney disease at 5 years.⁸⁴ One study found that glomerular filtration rate (GFR) rose by a small but statistically significant amount (from 41 to 48 mL/min P <0.0001);⁸⁵ 17 percent of patients eventually became dialysis dependent over 1 to 159 months. The third study found that 72 percent of patients had improved or unchanged kidney function up to 46 months after surgery;⁹⁰ 17 percent of patients developed end stage renal disease up to 17 months after surgery. One study reported cured or improved hypertension in 68 percent of the patients at 3 years and 59 percent of the patients had improvement at 5 years.⁸⁴ Another study reported that 12 percent were cured of hypertension and 73 percent had improved blood pressure 8 weeks or more after surgery.⁸⁵

These four studies described the following adverse events. Thirty-day mortality rates in the four studies were 3.7 percent,⁸⁴ 4.6 percent,⁸⁵ 6.0 percent,⁹⁰ and 9.4 percent.⁸³ One study reported that perioperative morbidity occurred in 16 percent of patients, including myocardial infarction, stroke, significant arrhythmia, and pneumonia.⁸⁵ Another study reported a procedural complication rate of 22 percent, including bleeding / hematoma, occlusion / thrombosis, infection, and distal embolism.⁸³

Mortality Findings Across Study Designs

We compiled mortality data from all studies. We updated **Figure 3** (and the Appendix figure, which includes study details) with the three recently published studies that provided mortality data. Our findings remain the same, that regardless of intervention mortality rates rise over a period of 5 to 10 years. The range of mortality rates is wide for each type of intervention and we found no consistent factor to explain differences across studies. The current data are inadequate to determine whether mortality rates differ based on intervention, though there are no clear differences based on intervention.

Key Question 2: Predictors of Outcomes

In the original CER, 37 studies provided some data relevant to whether any pre-intervention factors may predict clinical outcomes. The synthesis from the Executive Summary of the original CER is provided below, followed by a description of the findings of two relevant recently published studies.

Among the studies reviewed, the value of diagnostic tests either for predicting long-term outcomes or to help 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.

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

The Tier III RCT (DRASTIC), 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.

Among angioplasty studies with (or without) stent, 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.^{15-17,20} 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.

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 were found to have significant progression in kidney impairment, while those with spiral flow did not.⁷⁸

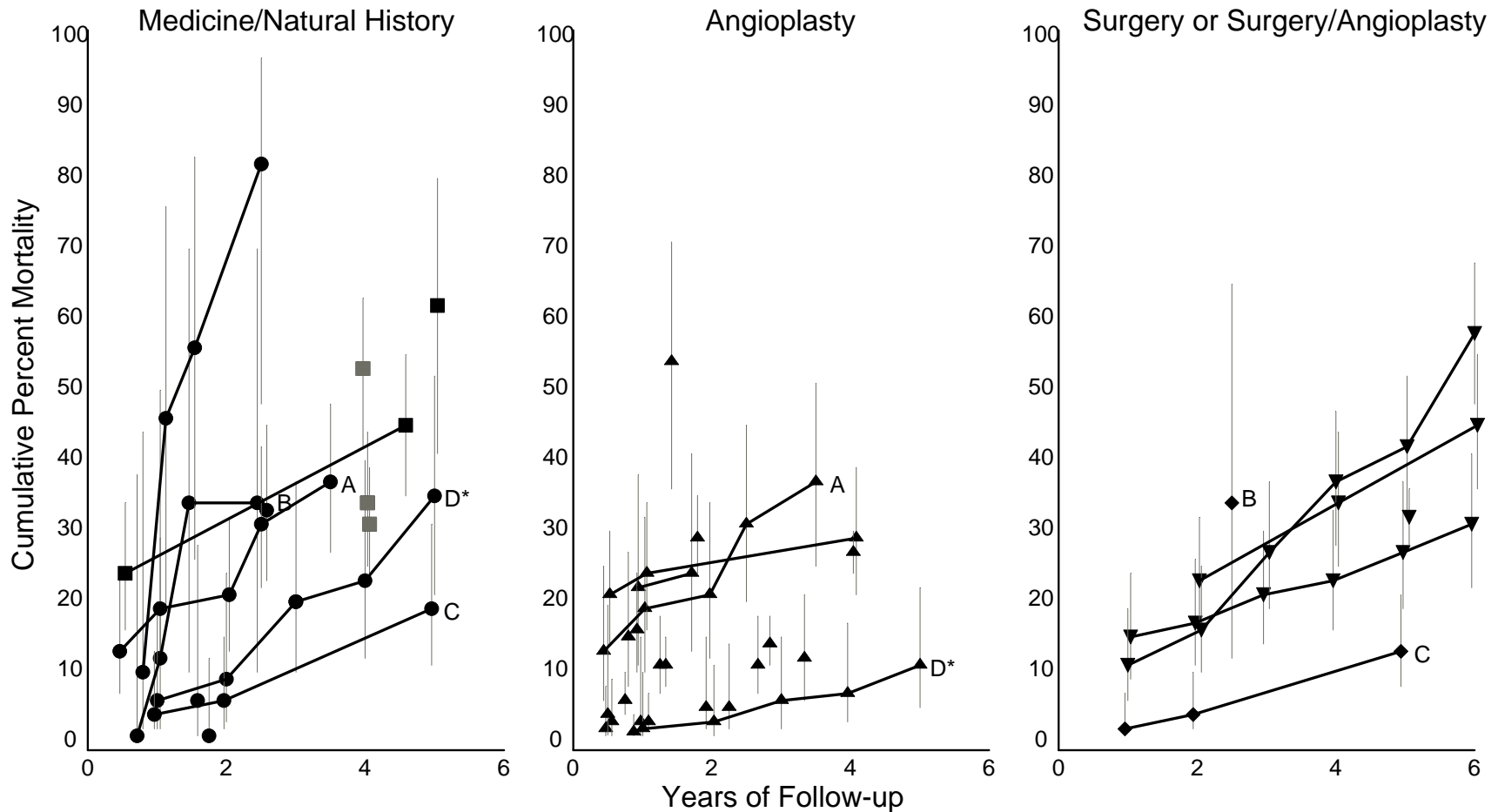
Holden 2006⁷⁸ categorized patients prior to angioplasty with stent according to modified KDOQI (Kidney Disease Outcomes Quality Initiative⁹¹) criteria of chronic kidney disease (CKD) stage, namely: CKD 3A, GFR 41-59 mL/min; CKD 3B, GFR 30-40 mL/min; and CKD 4, GFR 15-29 mL/min. The effect of angioplasty with stent in the three categories was analyzed separately. At 6 months, they found no difference in percent of patients with improved, stable, or worse kidney function across the three CKD stages.

Garcia-Criado 2005⁹² evaluated preangioplasty renal artery blood flow by Doppler examination (resistive index [RI] and acceleration). After angioplasty (with or without stent), blood pressure improved in 85 percent of patients with RI<0.8 and improved in 50 percent of patients with an RI>0.80 (P < 0.05). Acceleration was not predictive of the effect of angioplasty on blood pressure.

Key Question 3: Treatment Variables as Predictors of Outcomes After Angioplasty

No recent studies addressed this question. 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.

Figure 3. Cumulative mortality after intervention (or start of study period) from 6 months to 6 years, with estimated confidence intervals



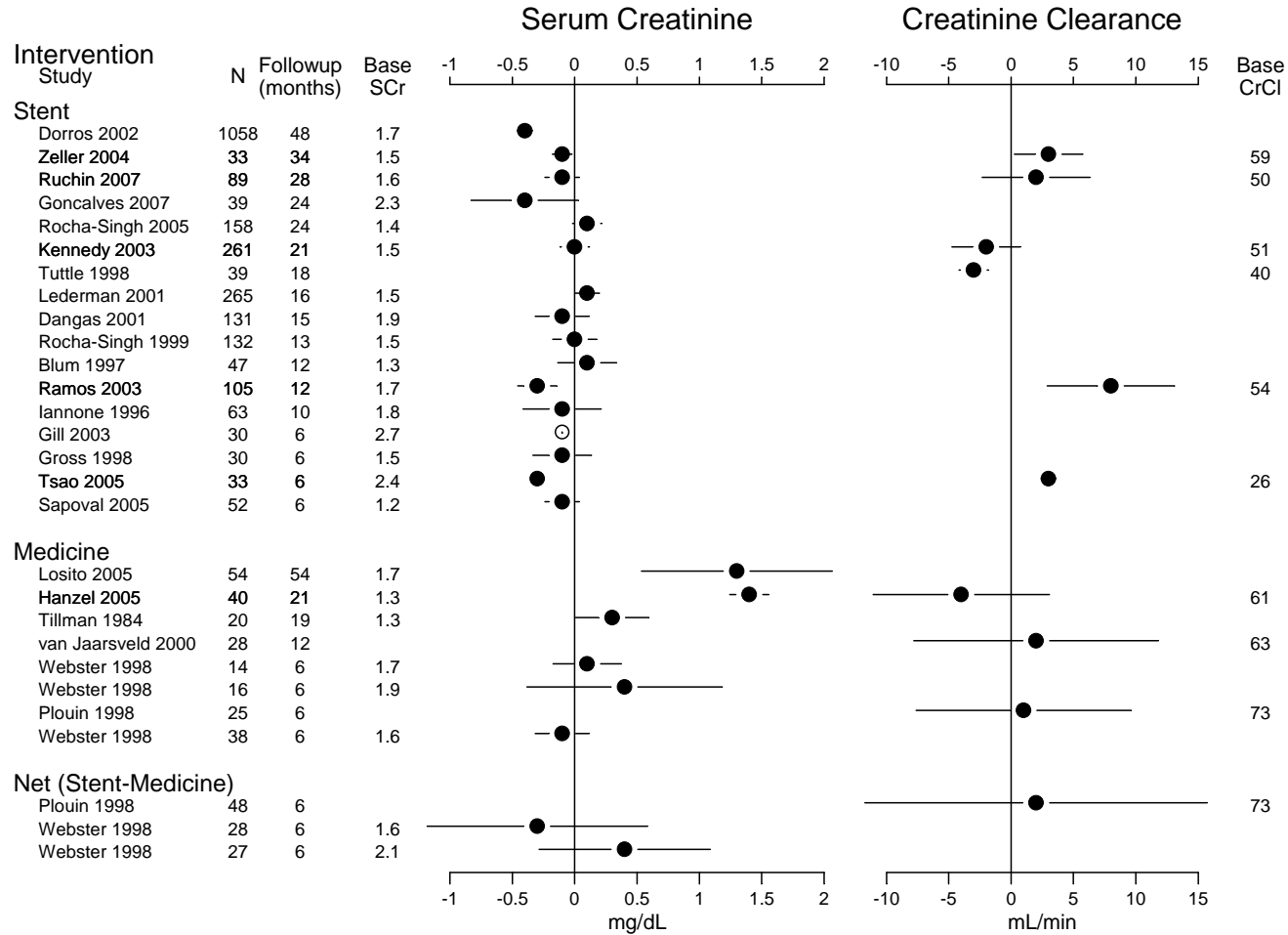
* Markedly different eligibility criteria for angioplasty and medicine treatment cohorts. See summary table.

● = medicine; ■ = natural history; ▲ = angioplasty; ▼ = surgery; ◆ = angioplasty or surgery. Vertical lines represent 95 percent confidence intervals calculated with equation of GA Diamond.⁹³ 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,¹² B,¹⁸ C,²⁰ and D¹⁷ indicate that these studies reported mortality rates for both medical treatment and an invasive intervention. Conlon 2001³⁷ 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 Figure for study specific mortality data.

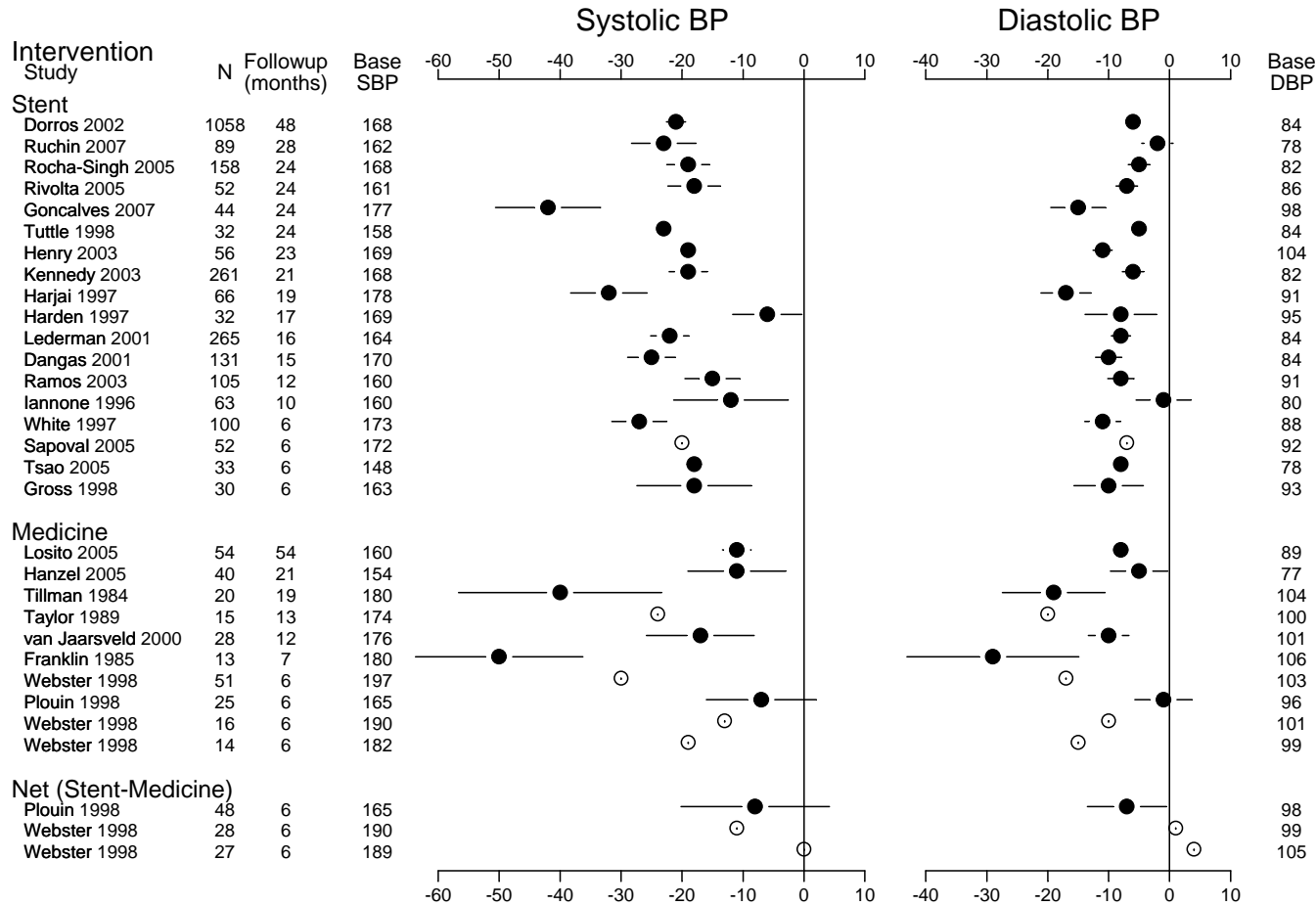
Figure 4. Forest plot of change in kidney function after interventions



Change in Kidney Function

Studies categorized by intervention (angioplasty with stent studies, medicine alone studies, and comparative studies that report net difference between angioplasty (without stent) and medicine. SCr, serum creatinine; CrCl, creatinine clearance (or glomerular filtration rate). 95% confidence intervals were estimated based on reported data (generally the baseline and final standard deviations). Open circles represent studies for which 95% confidence intervals could not be calculated. Studies ordered from longest to shortest duration of followup, then sample size.

Figure 5. Forest plot of change in blood pressure (BP) after interventions



Change in Blood Pressure (mm Hg)

Studies categorized by intervention (angioplasty with stent studies, medicine alone studies, and comparative studies that report net difference between angioplasty (without stent) and medicine. DBP/SBP, diastolic/systolic blood pressure. 95% confidence intervals were estimated based on reported data (generally the baseline and final standard deviations). Open circles represent studies for which 95% confidence intervals could not be calculated. Studies ordered from longest to shortest duration of followup, then sample size.

Discussion

Nine recently published articles met eligibility criteria for inclusion in this systematic review of interventions for RAS. In general, these new studies had the same limitations as the other 72 studies included in the original CER. Namely, none of the studies evaluated the principal question of interest, the relative effects of intensive medical therapy and angioplasty with stent for patients with ARAS; the quality of the studies was limited due to inadequate reporting and/or collection of data, incomplete analyses, and often inconsistent use of interventions (e.g., combining angioplasty with and without stent); limited or difficult to assess applicability due to restrictive patient eligibility or inadequate reporting; inconsistent outcome metrics; and limited power of studies due to small sample size. Importantly, only two small RCTs (about 50 patients randomized in each) compared angioplasty and medical therapy with at least 6 month outcomes. Including a third RCT with a substantial treatment crossover (medical therapy to angioplasty) at 3 months, only 4 patients had stents placed and only some patients were treated with ACE inhibitors; statins and antiplatelet agents were not included in drug protocols. Therefore these trials may be of limited relevance to current practice.

It is important to note that this review focuses on comparative studies and larger, more recent single-arm studies. Many hundreds of other studies have been published that did not meet eligibility criteria, particularly single-arm studies of angioplasty without stent. Thus, there may be evidence for specific issues that are not addressed by this report. These may include some diagnostic tests and special high risk populations such as people with rapid declines in kidney function, recurrent flash pulmonary edema, or unstable angina in the setting of RAS. This report also does not address the management of fibromuscular dysplasia, renal transplant recipients, or patients who have a previous, failed revascularization. The reviewed studies did not explicitly address the population of patients who may need acute intervention because of rapid clinical deterioration, so the conclusions of this review do not apply to these patients. The approach of this systematic review, and of most of the primary studies, was to evaluate the average outcome of treated patients. In many studies a group of individuals had rapid, marked improvement in blood pressure and/or kidney function, but others had worsening function. Additional research is needed to determine which patients would be most likely to benefit (or be harmed) by the various interventions. Furthermore, none of the studies explicitly evaluated patients being aggressively treated with ACE inhibitors or angiotensin reuptake blockers, statins, and antiplatelet agents, regardless of other interventions being used. This further complicates any direct or indirect comparisons of invasive interventions to available medical treatment. In addition, another important consideration when evaluating the current literature to answer the comparative value of the intervention alternatives is that our limited ability to make comparisons across types of studies. It is highly likely that the types of patients included in cohort studies of angioplasty – based on disease severity, comorbidities, general health, socioeconomic factors, etc. – were very different than those who remained on medical treatment. Thus expected rates of outcomes including death, cardiovascular disease, and kidney failure, may be very different across studies based more on the patients' underlying disease than on the intervention.

Overall, the findings of the new studies were consistent with the previously summarized studies. The only newly reported result was in a new article about the previously described DRASTIC study that compared immediate angioplasty with either medical therapy or delayed angioplasty. This study evaluated quality of life and found no consistent difference between patients who had immediate angioplasty and those who remained on medical therapy. Otherwise, our findings remain generally the same:

- Almost two-thirds of the studies were of poor methodological quality and more than half were of limited applicability to the population of interest.
- No RCTs compare angioplasty with stent and aggressive medical treatment with ACE inhibitors, statins, and anti-platelet drugs (Tier I studies).
- The two most relevant RCTs (Tier II studies) do not compare interventions that are currently used for patients with RAS; only 2 patients received stents and ACE inhibitors were rarely employed.
- Other comparative studies (Tier III) are methodologically flawed or did not compare angioplasty and medical treatment.
- There are a substantial number of cohort studies (Tier IV) that prospectively evaluated angioplasty with stent, but very few cohort studies of medications, none of which explicitly evaluated aggressive medical treatment with ACE inhibitors, statins, and anti-platelet drugs. Thus indirect comparisons across the cohort studies are limited.
- Among the comparative studies there was some evidence of a relative benefit in blood pressure after angioplasty, particularly in patients with bilateral disease; however, this conclusion is based largely on the end-of-study (not primary endpoint, after which some treatment cross-over occurred) of one RCT (Webster 1998) and either clinically though not statistically significant differences, partially statistically significant differences, or nonrandomized trial data.
- Among the comparative studies there was no difference in kidney function outcomes, and possibly no differences in mortality, cardiovascular event rates, and quality of life, 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.
- 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.
- Direct and indirect comparisons of interventions mostly found no clinical or statistically significant differences in kidney outcomes. However, only in some of the angioplasty with stent placement studies did patients have improved kidney function. This implies that, at least in a (poorly described)

subset of patients with ARAS, kidney function is more likely to improve after angioplasty with stent placement than with continued medical treatment.

- 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. In contrast, cohort studies of angioplasty generally found somewhat lower reductions in blood pressure (6-32/0-17 mm Hg) than cohorts of medical interventions (20-50/8-42 mm Hg), though it is not possible to draw conclusions about the relative effect on blood pressure measurements of the different interventions.
- Comparative studies found similar rates of cardiovascular disease regardless of intervention, though these studies were not designed to find significant differences in cardiovascular events. The data from cohort studies on cardiovascular events were too sparse to draw conclusions.
- A single trial found no consistent difference in quality of life between angioplasty and medical therapy.
- Adverse events, variably defined, occurred in up to 13 percent of patients receiving angioplasty, though serious long-term adverse events were rare. Reported adverse events from antihypertensives were relatively minor and transient.
- A variety of indicators of the severity of ARAS and of health problems, such as poorer kidney function, severity of stenosis, and coexisting cardiovascular disease predict poorer outcomes in patients with ARAS. The reviewed studies did not report any indicators that may predict improved outcomes. Two trials found that patients with bilateral RAS had better outcomes after angioplasty than medical therapy, compared to patients with unilateral disease.
- In comparative studies, 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. Among patients receiving angioplasty, there was little consistent evidence about which diagnostic tests would predict more favorable outcomes. Two studies found that Doppler ultrasonography findings were predictive of outcomes after angioplasty, but they disagreed as to whether resistive index predicted worse or better outcomes.
- No study that met eligibility criteria reported analyses of whether periprocedural interventions, such as different drugs or different approaches, affected either complications or long-term outcomes.

Our conclusions about the evidence are:

- Overall, the evidence does not currently support one treatment approach over the other for the general population of people with ARAS.
- The evidence on this topic is generally inconclusive due to small numbers of RCTs with few patients comparing angioplasty to medical therapy, questions of relevance of trials to current practice due to lack of stent placement and relative lack of ACE inhibitor use, and poor quality and limited applicability of many of

the remaining, primarily cohort, studies. No trials comparing interventions commonly in use (Tier I) have been published.

- Weak evidence suggests no difference in mortality rates with medical treatment alone or with angioplasty.
- There is acceptable evidence that overall there is no difference in kidney outcomes between patients treated medically only or those receiving angioplasty without stent; though the relevance of this finding to current practice is questionable due to changes in treatment options. However, improvements in kidney function were only reported among patients receiving angioplasty.
- There is acceptable evidence that combination antihypertensive treatment results in large decreases in blood pressure. The evidence regarding the relative effect of angioplasty and medication on blood pressure control is inconsistent. The RCTs did not find a consistent effect; other comparative studies mostly found no difference; cohorts of medical treatment generally found larger decreases in blood pressure than cohorts of angioplasty with stent. However, cohort studies of angioplasty with stent did report that up to 18 percent of patients had cure of hypertension.
- 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.
- Weak evidence suggests no difference in quality of life with medical treatment alone or with angioplasty.
- The evidence does not adequately assess the relative harms due to adverse events and complications of medical treatment and angioplasty.
- There is weak evidence that patients with bilateral RAS may have more favorable outcomes with angioplasty than with medical therapy compared to patients with unilateral disease.
- Weak or inconsistent evidence does not support whether any other clinical features or diagnostic tests predict outcomes after angioplasty or with medical therapy.
- There is no evidence regarding the value of interventions done at the time of angioplasty (Key Question 3).

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The recently published articles added in this update are in bold text.

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Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ARAS	Atherosclerotic renal artery stenosis
ARB	Angiotensin-receptor blocker
BP	Blood pressure
CER	Comparative Effectiveness Review
CKD	Chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions trial
CrCl	Creatinine clearance
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DRASTIC	Dutch Renal Artery Stenosis Intervention Cooperative trial
EMMA	Essai Multicentrique Medicaments vs. Angioplastie trial
EPC	Evidence-based Practice Center
GFR	Glomerular filtration rate
JNC-5	5 th Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (1993)
KDOQI	Kidney Disease Outcomes Quality Initiative
KQ	Key Question
LDL	Low density lipoprotein
MedCAC	Medicare Evidence Development & Coverage Advisory Committee
MEDPAR	Medicare Provider Analysis and Review
mo	Month
QoL	Quality of life
RAS	Renal artery stenosis
RCT	Randomized controlled trial
RI	Resistive index
SBP	Systolic blood pressure
SCr	Serum creatinine
SNRASCg	Scottish and Newcastle Renal Artery. Stenosis Collaborative Group trial
TEP	Technical expert panel