

## Evidence-based Practice Center Systematic Review Protocol

### Project Title: Renal Artery Stenosis Update

Initial publication date if applicable: 2006, with a 2007 update

#### I. Background and Objectives for the Systematic Review

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 improving or preventing symptoms, including those related to congestive heart failure, 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 antihypertensive agents, lipid-lowering drugs, and antiplatelet agents are all FDA approved for hypertension and/or reduction of cardiovascular risk, for which they are being used. The risks and adverse events of the drugs are well-understood and include symptomatic hypotension, myalgia, liver dysfunction, peptic ulcer, and bleeding, among others.

The current standard for revascularization in most patients is percutaneous transluminal angioplasty with stent placement across the stenosis. Angioplasty without stent placement is currently infrequently 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.

Only recently has the FDA approved stents for RAS.<sup>1,2</sup> Thus, almost all stents used in studies and extant in patients were not approved for RAS. Frequently, the stents used were approved for biliary ducts, which are not indicated for use in any part of the vasculature,<sup>3</sup> and there is concern that these unapproved stents may have resulted in significant harms (e.g., renal artery dissection).

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 also resolve dissections, minimize stenosis recoil and restenosis, and correct translesional pressure gradients.

The 2006 Comparative Effectiveness Review and its 2007 update found a paucity of comparative studies, particularly randomized controlled trials (RCTs), to adequately compare the various interventions. The large majority of the evaluated studies were single-group studies (without a comparison intervention). Only two relatively small RCTs truly compared angioplasty with medical therapy alone;<sup>4,5</sup> a third trial allowed subsequent angioplasty in people randomized to medical therapy.<sup>6</sup> Furthermore, none of the comparative studies cleanly evaluated angioplasty with stent placement (as opposed to without stent). Because of the limitations in the evidence, the review was unable to come to firm conclusions about the relative value of the various interventions on clinically important, long-term benefits and harms. It did, however, find a large heterogeneity of treatment effect within single-group studies where some patients had rapid, marked improvement in blood pressure and/or kidney function, but others had worsening function. The evidence, though, was inadequate to fully evaluate this phenomenon.

In part due to the state of the evidence reviewed to date, it remains the case that vascular surgeons promote open surgery,<sup>7,8</sup> interventional radiologists promote angioplasty with stenting,<sup>9</sup> and nephrologists advocate aggressive medical therapy with stenting in selected cases.<sup>10</sup> Especially given the inconclusive evidence to date, it is important to best understand which patient characteristics and other factors may best predict which patients are likely to do best with which intervention.

Given the limitations of the evidence in the original reports, an update is critical to allow a re-evaluation of the evidence in patients with atherosclerotic RAS, particularly for applicability to contemporary interventions and to patients diagnosed with atherosclerotic RAS by contemporary standards. Since the original review and its first update, several new RCTs have been published, which focus on angioplasty and stent and contemporary aggressive medical therapy.

## II. The Key Questions

Listed here are the original Key Questions (from 2006 and 2007), which remain unchanged.

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?

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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.

### **III. Analytic Framework**

We applied the analytic framework depicted in the Figure to answer the Key Questions in the evaluation of the treatment modalities for atherosclerotic RAS. This framework addressed relevant clinical outcomes. It also examined clinical predictors that affected treatment outcomes.

## Figure

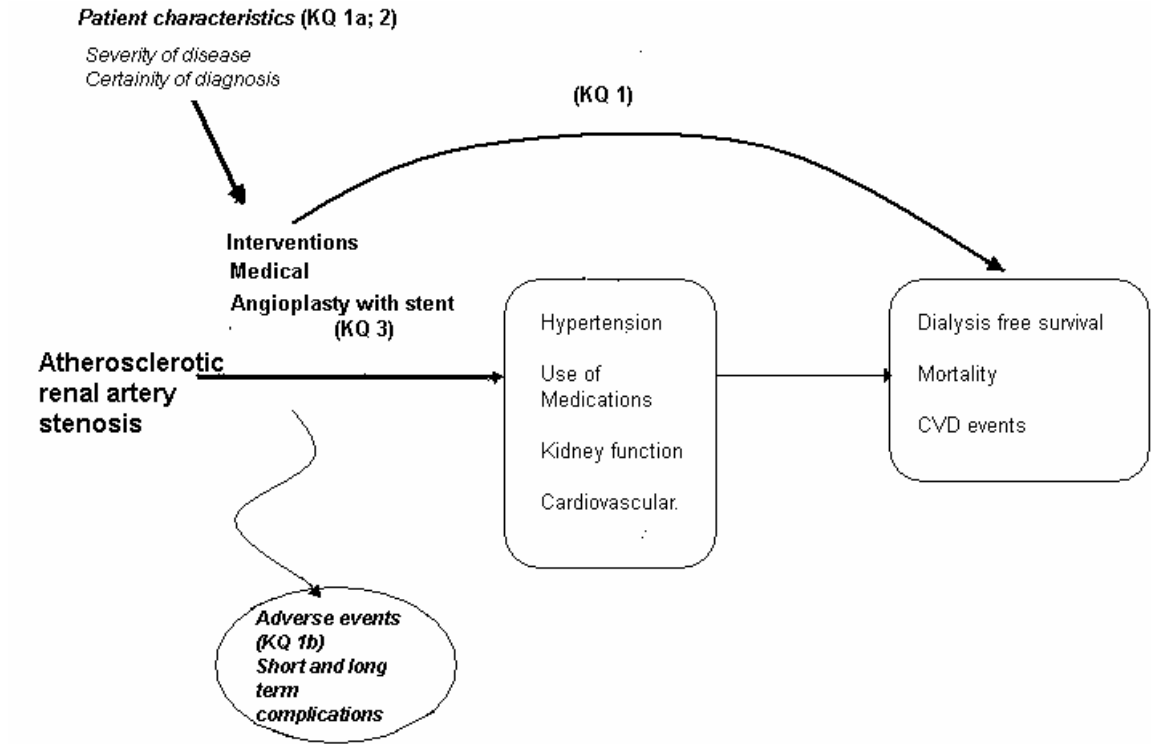


Figure. Analytic framework for evaluating the effectiveness and safety of treatments for renal artery stenosis.

Arrows depict studies sought to address key questions formulated in this report

Abbreviation: CVD, cardiovascular; KQ, key question.

## IV. Methods

The present Comparative Effectiveness Review (CER) update evaluates the effects of alternative interventions for people with atherosclerotic RAS. The Evidence-based Practice Center (EPC) will review the existing body of evidence on the relative effects and harms of medications, angioplasty with stenting, and surgery on intermediate and clinical outcomes in people with atherosclerotic RAS. The CER will be based on a systematic review of the published scientific literature using established methodologies as outlined in the Agency for Healthcare Research and Quality's (AHRQ) Methods Guide for Comparative Effectiveness Reviews.<sup>11</sup>

### A. Eligibility Criteria

The currently proposed eligibility criteria are mostly similar to the criteria used in the original 2006 CER and its 2007 update. Some narrowing of scope has been applied for the current CER to focus the review more closely on the original key questions and the current standards of practice. The main modifications that narrow the scope are the removal of "natural history" studies and angioplasty without stents as interventions of interest. Because of a concern that current studies underrepresent patients with acute decompensation due to atherosclerotic RAS, such as acute renal failure, flash pulmonary

edema, or malignant hypertension, study eligibility have been expanded to include case reports and series of patients with acute decompensation. In addition, to better capture real-world scenarios for when open surgical options are chosen for patients, we will now allow studies in which patients receive renal artery and aortic surgery, as long as the primary indication for the surgery is to repair the renal artery. For example, surgical studies that included patients whose small aortic aneurysms were repaired at the time of their renal artery surgery will not be excluded. All modifications to the eligibility criteria have been made in conjunction with a Technical Expert Panel.

For all Key Questions, the Eligibility Criteria used will be:

#### Population

- Adults ( $\geq 18$  yo) with atherosclerotic RAS
- Exclude previous surgical or angioplasty interventions for RAS
- Exclude kidney transplant patients
- Exclude renal artery aneurysms or dissections requiring repair
- Exclude renal artery interventions conducted as an “add on” to aortic, coronary, or other vascular surgery (e.g., “drive-by” angioplasty during coronary artery angiography, RAS angioplasty done as a secondary indication at the time of aortic or other vascular repair)

#### Interventions/Comparators

- Angioplasty with stenting
- Any medical therapy, including “aggressive medical therapy” (antihypertensive, antiplatelet, *and* lipid-lowering drugs)
- Surgical repair

#### Outcomes

- Mortality, all cause
- Kidney function
  - Event (eg, need for renal replacement therapy)
  - Categorical (eg, better/worse)
  - Continuous (ie, GFR, CrCl, SCr)
- Blood pressure
  - Event (eg, hypertensive crisis)
  - Categorical (eg, better/worse)
  - Continuous BP
  - Medication need (eg, number of antihypertensive drugs used)
  - ACE inhibitor tolerance
- Restenosis (after angioplasty or surgery), as defined by authors
- CHF events, including flash pulmonary edema (including hospitalization)
- Other cardiovascular events (cardiac, cerebrovascular, peripheral vascular)
- Adverse events (eg, post-procedure in-hospital or 30-day deaths, peri- and post-procedure events, drug reactions)

#### Timing

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- $\geq 6$  months (except adverse events) ( $\geq 12$  months of primary interest)

#### Setting

- Any
- Any language, as feasible

#### Study Design

- RCTs
  - All interventions/comparators
- Non-randomized comparative studies, prospective or retrospective
  - All interventions/comparators
- Single group studies
  - Angioplasty with stenting: prospective only,  $N \geq 30$
  - Medication: prospective only,  $N \geq 10$
  - Surgery: prospective or retrospective:  $N \geq 10$
- Case reports/series
  - Vascular interventions for acute decompensation

For single group studies of angioplasty or medications, only prospective design studies are included to minimize the biases common to retrospective studies related to incomplete availability of data and retrospective selection of eligible participants. This decision will be re-evaluated if studies based on registry datasets are available. Retrospective surgical studies are included because of the expected sparseness of prospective surgical studies.

#### B. Literature Search

We will conduct literature searches of studies in MEDLINE®, the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, and EMBASE from the time of the 2007 updated search to current, with overlap. We will also include all studies from the original and updated reviews that continue to meet eligibility criteria. Titles and abstracts will be screened to identify articles relevant to each Key Questions. For the primary search, we will use the same search strategy used in the original CER. We will also search for eligible case reports in a separate search restricted to terms related to acute decompensation. We will also review reference lists of related systematic reviews and selected narrative reviews and primary articles. In electronic searches, we will combine terms for renal artery stenosis, renal hypertension, and renal vascular disease, limited to adult humans, and relevant research designs. We will invite TEP members to provide additional citations. The search will be updated upon submission of the draft report for peer and public review. The **Appendix** displays the current complete search strategy.

We will also be conducting a focused grey literature search to find unpublished or nonpeer-reviewed data, in particular the Food and Drug Administration 510(k) database and abstracts from recent relevant scientific meetings of professional societies. With the assistance of the TEP, we will also be compiling a list of professional organization meetings that were most likely to have published oral presentations and poster abstracts on RAS management. Based on this list we will retrieve and screen abstracts from

conferences. In addition, we will search for ongoing research on routine preoperative tests in the ClinicalTrials.gov registry to identify relevant studies. In addition, Scientific Information Packets will be solicited from manufacturers of angioplasty devices and stents.

All citations found by literature searches will be independently screened by two researchers. Upon the start of citation screening, we will implement a training session where all researchers screen the same articles and conflicts will be discussed. We will iteratively continue training until we have reached agreement regarding the nuances of the eligibility criteria for screening. During double-screening, we will resolve conflicts as a group. All screening will be done in the open-source, online software Abstrackr (<http://abstrackr.cebm.brown.edu/>).

### C. Data Extraction and Management

Each study will be extracted by one experienced methodologist. The extraction will be reviewed and confirmed by at least one other methodologist. Any disagreements will be resolved by discussion amongst the team. Data will be extracted into customized forms in Systematic Review Data Repository (SRDR) online system (<http://srdr.ahrq.gov>) designed to capture all elements relevant to the Key Questions. The basic elements and design of these forms will be the similar to those we have used for other comparative effectiveness reviews, and will include elements that address population characteristics including description of their RAS; descriptions of the interventions (and comparators) analyzed;; outcome definitions; enrolled and analyzed sample sizes; study design features; results; and risk of bias assessment. The form will be developed off the forms used for the original CER. We will test the forms on several studies and revise as necessary before full data extraction. All eligible studies from the original CER (and update) will also be entered into SRDR.

### D. Assessment of Methodological Risk of Bias of Individual Studies

We will assess the methodological quality of each study based on predefined criteria. We will use the Cochrane risk of bias tool,<sup>12</sup> which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For RCTs, we will primarily consider 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. For all studies, we will use (as applicable): the report of eligibility criteria, the similarity of the comparative groups in terms of baseline characteristics and prognostic factors, the report of intention-to-treat analysis, crossovers between interventions, important differential loss to follow-up between the comparative groups or overall high loss to follow-up, and the validity and adequacy of the description of outcomes and results. Any quality issues pertinent to specific outcomes within a study will be noted and applied to those outcomes.

### E. Data Synthesis

All included studies will be summarized in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, and results. We plan to build off of and improve on the tables used in the original review. These included descriptions of the study design, intervention(s), mean baseline blood pressure and kidney function, description of the degree and location of

renal artery stenosis, calendar years enrolled, follow-up duration, hypertension and blood pressure outcomes, kidney outcomes, cardiovascular outcomes, and study quality. We evaluated mortality separately in figures and tables.

We expect to organize the report using the same basic structure as the original CER. Namely, by study design first (medical treatment vs. angioplasty; medical treatment single group studies; and angioplasty single group studies), then by Key Question and outcome, within each study design section.

We expect to conduct random effects model meta-analyses of comparative studies, if they are sufficiently similar in population, interventions, and outcomes. If appropriate data are available, we may also conduct meta-regression analyses to evaluate study features to explain any heterogeneity. If appropriate data are available, we may also estimate summary incidence rates of outcomes across single group (and comparative studies). We do not expect there to be sufficient or adequate data to allow network meta-analyses to explore indirect comparisons of interventions across studies. However, we will qualitatively compare results across single group studies of different interventions. We will explore subgroup differences within (and possibly across) studies based on the list of comparisons described in Key Questions 1a, 2 and 3.

#### F. Grading the Strength of Evidence

We will grade the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence. We plan to assess the strength of evidence for each outcome. Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we will assess the number of studies, their study designs, the study limitations (i.e., risk of bias), the directness of the evidence to the Key Questions, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Based on these, we will, in group discussion among the whole research team, determine the strength of evidence as being either high, moderate, or low, or there being insufficient evidence to estimate an effect.

We plan to incorporate the concept of minimally importance differences (MIDs) into the determination of the summary effect (benefit or harm) within the strength of evidence. The MID is the threshold difference in effect to distinguish superiority or equivalence of interventions (e.g., the upper bound of the 95 percent confidence interval of the relative risk for death would need to be <0.90 for a test and treat strategy to be considered clinically superior). However, the specific MIDs for each outcome will need to be determined with the TEP. To the degree possible, we plan to guide the discussion of MIDs for each outcome with the TEP by (nonsystematically) searching for any guidelines or comparable CERs that may inform the choice of MIDs.



## V. References

1. FDA. FDA-Approved Medical Devices for Cardiology and Vascular Diseases. 2012; <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/CardiovascularInfo/ucm294411.htm>. Accessed 06/24/2014.
2. FDA. RX Herculink Elite Renal Stent System – P110001. Last updated 09/06/2013. <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm266191.htm>. Accessed 06/24/2014.
3. Cavanaugh K. Evaluation of renal artery stenting. Clinical study design, nonclinical testing, and regulatory considerations for appropriate use of this technology. *Endovascular Today*. 2006;5(9):105-107.
4. Plouin PF, Chatellier G, Darne B, Raynaud A. Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group. *Hypertension*. Mar 1998;31(3):823-829.
5. Webster J, Marshall F, Abdalla M, et al. Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. *Journal of Human Hypertension*. May 1998;12(5):329-335.
6. Krijnen P, van Jaarsveld BC, Deinum J, Steyerberg EW, Habbema JD. Which patients with hypertension and atherosclerotic renal artery stenosis benefit from immediate intervention? *Journal of Human Hypertension*. Feb 2004;18(2):91-96.
7. Abela R, Ivanova S, Lidder S, Morris R, Hamilton G. An analysis comparing open surgical and endovascular treatment of atherosclerotic renal artery stenosis. *European Journal of Vascular and Endovascular Surgery: The Official Journal of the European Society for Vascular Surgery*. Dec 2009;38(6):666-675.
8. Edwards MS, Corriere MA. Contemporary management of atherosclerotic renovascular disease. *Journal of Vascular Surgery*. Nov 2009;50(5):1197-1210.
9. Carr TM, 3rd, Sabri SS, Turba UC, et al. Stenting for atherosclerotic renal artery stenosis. *Techniques in Vascular and Interventional Radiology*. Jun 2010;13(2):134-145.
10. Dworkin LD, Murphy T. Is there any reason to stent atherosclerotic renal artery stenosis? *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation*. Aug 2010;56(2):259-263.

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11. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012. Chapters available at: [www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov).
12. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. In: Higgins JPT, Green S, eds. The Cochrane Collaboration; 2011.

## **VI. Definition of Terms**

Not applicable. All terms are defined above, as needed.

## **VII. Summary of Protocol Amendments**

No protocol amendments to date.

## **VIII. Review of Key Questions**

The key questions will be reviewed and refined as needed by the EPC with input from the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the key questions will be posted for public comment and finalized by the EPC after review of the comments.

## **IX. Key Informants**

Key Informants will not be employed for this update to an existing CER.

## **X. Technical Experts**

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

**XI. Peer Reviewers**

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

**XII. EPC Team Disclosures**

EPC core team members must disclose any financial conflicts of interest greater than \$1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators. The EPC core team members have not financial or other conflicts to report.

**XIII. Role of the Funder**

This project was funded under Contract No. HHSA-290-2012-0012-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

## Appendix

### Primary literature search

Medline, Cochrane databases (Equivalent search conducted in Embase)

1. exp Hypertension, Renal/
2. exp Renal Artery Obstruction/
3. renal arter\$ stenosis.tw.
4. renal arter\$ dis\$.tw.
5. renovascular dis\$.tw.
6. reno vascular dis\$.tw.
7. renal vascular dis\$.tw.
8. (arvd or "atherosclerotic renovascular dis\$").tw.
9. renal steno\$.tw.
10. steno\$ kidney.tw.
11. renovascular steno\$.tw.
12. or/1-11
13. limit 12 to humans
14. limit 13 to english language
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")
16. 14 not 15
17. limit 16 to "all adult (19 plus years)"
18. 16 not 17
19. limit 18 to "all child (0 to 18 years)"
20. 16 not 19
21. limit 20 to (guideline or practice guideline or "review" or review, academic or "review literature" or review, multicase or review, tutorial)
22. limit 20 to meta analysis
23. 20 not (21 or 22)
24. follow-up studies/
25. (follow-up or followup).tw.
26. exp Case-Control Studies/
27. (case adj20 control).tw.
28. exp Longitudinal Studies/
29. longitudinal.tw.
30. exp Cohort Studies/
31. cohort.tw.
32. (random\$ or rct).tw.
33. exp Randomized Controlled Trials/
34. exp random allocation/
35. exp Double-Blind Method/
36. exp Single-Blind Method/

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[Type text]

[Type text]

37. randomized controlled trial.pt.
38. clinical trial.pt.
39. controlled clinical trial.pt.
40. (clin\$ adj trial\$.tw.
41. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw.
42. exp PLACEBOS/
43. placebo\$.tw.
44. exp Research Design/
45. exp Evaluation Studies/
46. exp Prospective Studies/
47. exp Comparative Study/
48. or/24-47
49. 23 and 48
50. (2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$ or 2014\$).ed.
51. 49 and 50

### **Case report/series literature search**

1. exp Hypertension, Renal/
2. exp Renal Artery Obstruction/
3. renal arter\$ stenosis.af.
4. renal arter\$ dis\$.af.
5. renovascular dis\$.af.
6. reno vascular dis\$.af.
7. renal vascular dis\$.af.
8. (arvd or "atherosclerotic renovascular dis\$").af.
9. renal steno\$.af.
10. steno\$ kidney.af.
11. renovascular steno\$.af.
12. or/1-11
13. High risk.af.
14. Critical stenosis.af.
15. Critical lesion.af.
16. exp Acute Kidney Injury/
17. (Subacute and (renal failure or renal insufficiency or kidney failure)).af.
18. (Renovascular and crisis).af.
19. exp Kidney Failure, Chronic/
20. (Acute and ischemic nephropathy).af.
21. (Acute and (renal failure or renal insufficiency or kidney failure)).af.
22. ((chronic kidney disease or CKD) and (stage IV or stage V)).af.
23. Rescue.af. and (RRT.af. or exp renal replacement therapy/ or renal replacement therapy.af. or dialysis.af.)
24. Flash pulmonary edema.af.
25. (Acute adj diastolic dysfunction).af.
26. exp Heart Failure/
27. Acute heart failure.af.
28. Hypertensive crisis.af.

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[Type text]

[Type text]

29. exp Hypertension, Malignant/
30. exp Hypertensive encephalopathy/
31. (Hospitalization adj10 hypertension).af.
32. (Bilateral and severe).af.
33. (Single and functioning and kidney).af.
34. hypertensive emergency.af.
35. or/13-34
36. 12 and 35
37. limit 36 to english language
38. limit 37 to humans
39. case.af.
40. 38 and 39