AHRQ Comparative Effectiveness Review Surveillance Program

CER-Update # 5:

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

Original release date:

2007

Surveillance Report:

August, 2012

Key Findings:

- KQ1: 8 of 15 conclusions are probably out of date
- KQ2: 1 of 3 conclusions is possibly out of date
- KQ3: is up-to-date
- Expert opinion: One of the 4 experts stated that the majority of conclusions for KQ1-KQ2 were not still valid
- No FDA, Health Canada, and MHRA safety alerts

Summary Decision:

This CER's priority for updating is **Medium**

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None of the investigators has any affiliation or financial involvement that conflicts with material presented in this report.

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1. Introduction

The purpose of this mini-report is to apply the methodologies developed by the Ottawa and RAND EPCs to assess whether the CER-update No. 5 (Comparative Effectiveness of Management Strategies for Renal Artery Stenosis: 2007 Update) [1]is in need of updating. This CER- update was originally released in November, 2007, and was added to the list of CERs for assessment post-hoc in June 2012. It was due for a surveillance assessment immediately.
This CER- update included 8 publications identified by using searches through April 23, 2007 and addressed three key questions to evaluate studies of patients with atherosclerotic RAS (ARAS) that compared two or more interventions. The single arm prospective studies of angioplasty with stent placement, and prospective cohort studies of medical interventions, cohort studies of RAS natural history, and prospective or large retrospective surgical bypass were included.
The key questions of the original CER-update were as the following:

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

    a. What are the patient characteristics, including etiology, predominant clinical presentation, and severity of stenosis, in the studies?
    b. 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 conclusion(s) for each key question are found in the executive summary of the CER report.[1]

2. Methods

We followed *a priori* formulated protocol to search and screen literature, extract relevant data, and assess signals for updating. The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might need to be updated. The Food and Drug Administration (FDA), Health Canada and MHRO surveillance alerts received from the Emergency Care Research Institute (ECRI) were examined for any relevant material for the present CER. The clinical expert opinion was also sought. All of this evidence was taken into consideration leading to a consensus-based conclusion decision on whether any given conclusion warrants updating (up to date, possibly out of date, or out of date). Based on this assessment, the CER was categorized into one of the three updating priority groups: high priority, medium priority, or low priority. Further details on the Ottawa EPC and RAND methods used for this project are found elsewhere.[2-4]

2.1 Literature Searches

The CER search strategies were reconstructed in Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R). The search was limited to 2006 to present (June 22nd, 2012). The syntax and vocabulary included both controlled MeSH subject headings and keywords. The search was limited to five general medical journals (Annals of Internal Medicine; BMJ; JAMA; Lancet; and New England Journal of Medicine) and five specialty journals (Journal of Endovasc Therapy, Journal of Vascular Surgery, American Journal of Medicine, Kidney International, and American Journal of Kidney Diseases). Further details on the search strategies are provided in the Appendix A of this mini-report.

2.2 Study Selection

All identified bibliographic records were screened using the same inclusion/exclusion criteria as described in the original CER-update. [1]

2.3 Expert Opinion

In total, 15 experts (13 experts who had either served as part of the technical expert panel for and/or peer reviewed the original report and 2 local experts) were requested to provide their feedback in a provided their opinion/feedback in a pre-specified matrix table on whether or not the conclusions as outlined in the Executive Summary of the original CER were still valid.

2.4 Check for Qualitative and Quantitative Signals

All relevant reports eligible for inclusion in the CER were examined for the presence of qualitative and quantitative signals using the Ottawa EPC method (see more details in Appendix B). CERs with no meta-analysis were examined for qualitative signals only. For any CER that contains meta-analysis(es), we first assess for the qualitative signal(s), and if no qualitative signal(s) are found,we then assess for quantitative signal(s). The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might need updating. The definition and categories of updating signals are presented in Appendix B and publications. [2-4]

2.5 Compilation of Findings and Conclusions

All of the information obtained during the updating process (i.e., data on qualitative/quantitative signals, the expert opinions, and FDA surveillance alerts) was collated, summarized, and presented in a table. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, and FDA surveillance alerts) presented in a tabular form, a conclusion was drawn whether or any conclusion(s) of the CER warrant(s) updating.

Conclusions were drawn based on four category scheme:

- Original conclusion is still **up to date** and this portion of CER does not need updating
- Original conclusion is **possibly out of date** and this portion of CER may need updating
- Original conclusion is **probably out of date** and this portion of CER may need updating
- Original conclusion is **out of date** and this portion of CER is in need of updating

We used the following factors when making our assessments to categorize the CER conclusions:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still up to date.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.

- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.

- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

Determining the priority groups (i.e., Low, Medium, and High) for updating any given CER is based on the following two criteria:

- How many conclusions of the CER are up to date, possibly out of date, or certainly out of date?

- How out of date are the conclusions (e.g., consideration of magnitude/direction of changes in estimates, potential changes in practice or therapy preference, safety issue including withdrawn from the market drugs/black box warning, availability of a new treatment)

3. Results

3.1 Update Literature Searches and Study Selection

A total of 89 bibliographic records were identified from MEDLINE, of which 14 records were deemed potentially eligible for full text screening. Of the 14 full text records, 7 were included in this update.[5-10] We also included one additional study [11] identified from the bibliography of one of the systematic reviews (SR)[12] that was excluded from this report because all of the included studies in that SR were either included in this report or in the original review. Thus, a total of 8 publications are included in this report. [5-11]

3.2 Signals for Updating in Newly Identified Studies

3.2.1 Study overview

The study population demographics, treatment characteristics, and results for the 8 included publications are presented in Appendix C (Evidence Table).

Three of the 8 included publications were randomized controlled trials (RCTs) [7,8,11], and 5 were observational (1 was a prospective study [6] , and 4 were retrospective [5,9,10,13]) studies. The length of the follow-up across the RCTs ranged from 2 years [8] to 5 years [7], and across observational studies from 1 year [6] to 5.5 years [10]. The sample size of the randomized trials ranged from 82 [11] to 806 [7]. The sample size of the observational studies ranged from 40 [13] to 149 [5] participants.

Of the 8 included studies, 5 [7-9,11,13] were comparative and 3 non-comparative [5,6,10]. Two [7,8] of the 5 comparative reports compared patients undergoing revascularization with stenting plus medical therapy versus patients with receiving therapy alone, 1 study compared patients undergoing angioplasty with stenting versus patients taking medical therapy [11], 1 study compared patients undergoing renal artery stenting versus patients in medical therapy [13], and 1 study compared patients undergoing angioplasty with stenting versus contemporaneous patients [9].

The mean age of patients in these publications ranged from 63.7 [6] – 68 [5] years old. The majority of the participants in these reports were male ranging from 23% [5] to 76% [11].

3.2.2 Qualitative signals

See also Table 1 (Summary Table), Appendix B, and Evidence Table (Appendix C)

Key question #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?

Survival/mortality:
The findings from two pivotal trials confirmed the weak evidence in the original CER suggesting no significant difference in mortality between the groups.[7,8] Consistent finding was observed in a retrospective study. [13]

1. In Revascularization + medical therapy versus medical therapy, the HR for death was 0.90 with 95% CI= 0.69, 1.18, and p = 0.46.[7] **1 Signal**
2. In Medical versus PTA+ stenting:
   a. The HR for overall death was 0.99 with 95% CI= 0.30, 3.24
   b. The HR for Cardiovascular mortality was 0.59 with 95% CI= 0.11, 3.25
   c. The HR for Primary end point or death was 0.81 with 95% CI= 0.42, 1.56
   [8] **1 Signal**
3. In renal artery stenting compared to medical treatment the HR for mortality was 0.016 with 95% CI= 0, 15.16, and p= 0.616. [13] **1 Signal**

Blood pressure control:

1. The inconsistent results in the original CER-update was supplemented by a pivotal trial showing no significant between-group differences in systolic blood pressure; however, a smaller decrease in diastolic blood pressure in the revascularization group was observed when compared to the medical-therapy group:
   Diastolic BP Mean Difference; 95% CI; p-value at 4 years were: 3.48; 0.51, 6.45; 0.02
   Systolic BP Mean Difference; 95% CI; p-value at 4 years were: 0.61; -5.83, 7.05; 0.85
   [7] **1 Signal**

2. The findings from a retrospective study were not informative. [13] **No Signal**

3. The findings from an RCT with smaller sample size (n=82) favored the revascularization group:
   Medical versus PTA+ stenting: N (%) cured = 0 vs. 4 (11.1%); p<0.001. [11] **1 Signal**

Kidney Function:
Consistent to the original CER-update, the findings from one RCT [11] and one retrospective study [13] favored those receiving angioplasty. However, no significant between- group difference were observed in two pivotal trials. [7,8]

1. In revascularization+medical therapy versus medical therapy the mean serum creatinine difference was 0.02 mg per deciliter with 95% CI= −0.10, 0.06. [7] **No Signal**
2. In medical versus PTA+ stenting, the HR for ≥ 20% decrease in creatinine clearance was 0.73; with 95% CI= 0.33, 1.61. [8] **No Signal**

3. In medical versus PTA+ stenting, the number (%) of patients improved were 0 vs. 11 (30.5%); p<0.001. [11] **No Signal**

Cardiovascular events including flash pulmonary edema:

1. The weak evidence in the original CER showing similar between-group rates was confirmed by two pivotal trials [7,8] and one retrospective study [13]demonstrationg no significant difference among the groups:
    a. In revascularization + medical therapy versus medical therapy the HR was 0.94 with 95% CI= 0.75, 1.19, and p = 0.61. [7] **1 Signal**
    b. In medical versus PTA+ stenting:
    Heart failure: HR= 0.39; 95% CI= 0.04, 3.71
    Coronary artery disease: HR= 1.16; 95% CI= 0.23, 5.73
    Cardiovascular mortality: HR= 0.59; 95% CI= 0.11, 3.25
    Pulmonary edema, n (%): 1(1) vs. 0
    [8] **1 Signal**
    c. In medical treatment versus renal artery stenting, the HR for myocardial events was 0.338 with 95% CI= 0.069, 1.668, and p=0.183. [13] **1 Signal**

Quality of life:
No new evidence was found on this outcome. **No Signal**

Adverse events:
Consistent to the original CER, the adverse events were not adequately assessed in comparison to the medical versus angioplasty. [7,8] **No Signals**

Key Question # 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?

Opposite to the original CER findings, a pivotal trial did not find any significant difference in improved or worse outcomes in patients with or without bilateral RAS (p=0.23). [7] **1 Signal**

Two observational studies suggested some predictors such as:
In renal artery stenting patient's three independent predictors of BP response were found:

1) Requirement for ≥4 hypterntion medications: OR= 29.9; 95% CI= 5.6, 159.4; p=0.0001
2) Diastolic BP of >90 mmHG: OR= 31.4; 95% CI= 4.1, 241.6; P=0.0001
3) Clonidine use: OR= 7.3; 95% CI= 1.2, 43.5; p=0.029
    [5]**No Signal**

In patients with percutaneous revascularization of RAS the following independent factors were found:

Independent CV event risk factors:
Coronary artery disease severity: RR= 1.27; *p*= .023
Smoking: RR =1.29; *p*=0 .016

Baseline LVM: RR= 1.21; p= 0.07
Independent factors associated with SBP and DBP improvement:
Grade of renal stenosis: RR, 1.28; p=. 0.006
Bilateral RAS procedure: RR= 1.17; p= 0.07
Baseline DBP value: RR= 1.74; p < 0.001
[6]**No Signal**

Key Question # 3b

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

No new evidence was identified for this question. **No Signal**

3.2.3 Quantitative signals

See also Table 1 (Summary Table), Appendix B, and Evidence Table (Appendix C)

The presence of quantitative signals (B1 and B2) was checked only if none of the studies identified through the update search indicated a qualitative signal.

3.3 FDA surveillance alerts

No FDA alerts was identified.

3.4 Expert opinion

Four of the 15 contacted clinical experts (three CER-specifics and one local expert) provided their responses/feedback in the matrix table (Appendix D). The responses from these experts varied: For key question 1, one of them said the majority of concusions were not still valid, and he referenced the ASTRAL trial that is already included in this study. However, 3 experts said the conclusions were still valid and one of them suggested awaiting the CORAL trials results that is going to be published in fall 2012.

For key question 2, one expert said the conclusion was not still valid and he referenced ASTRAL trial that is already included in this report. The two experts did not know and suggested to await the CORAL trial results. The one another expert said the conclusions were not still valid.

For key question3, two experts did not know and one of them suggested awaiting the CORAL trial results. Two experts said the conclusions were still valid.

4. Conclusion

Summary results and conclusions according to the information collated from different sources (updating signals from studies identified through the update search, FDA surveillance alerts, and expert opinion) are provided in Table 1 (Summary Table). Based on the assessments, this CER is categorized in **Medium** priority group for updating.

Key Question # 1

Signals from studies identified through update search: 8 of 15 qualitative signals were identified. **1 Signal**
Experts: One of the four experts stated that majority of the conclusions in the key question # 1 were not still valid.
FDA surveillance alerts: No alert was identified.
Conclusion: **8 of 15 conclusions are probably out of date**

Key Question # 2

Signals from studies identified through update search: Only 1 of 3 qualitative signals was identified. **1 Signal**
Experts: One of the four experts stated that the conclusions in the key question # 2 were not still valid.
FDA surveillance alerts: No alert was identified.
Conclusion: **1 of 3 conclusions is possibly out of date**

Key Question # 3

Signals from studies identified through update search: No new evidence was identified for this question. **No Signal**
Experts: Two experts stated that conclusions in the key question # 3 were still valid, and two experts did not know if it was valid or not.
FDA surveillance alerts: No alert was identified.
Conclusion: **The conclusions are up-to-date**

Summary Table (Renal Artery Stenosis)

Conclusions from CER's Executive Summary	Update literature search results	Signals for updating		FDA, Health Canada, and MHRA surveillance alerts	Expert opinion (CER + local)	Conclusion on validity of CER conclusion(s)
		Qualitative	**Quantitative**			
Key question 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?						
Survival/mortality Weak evidence suggests no difference in mortality rates. The following text is taken from the body of CER: "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 SNRASCG randomized trial (Webster 1998) reported mortality data. [sample size =55] 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-	**1 RCT** [7] **1 RCT** [8]	**1 Signal** **Revascularization (95% pts with stent) + medical therapy vs. medical therapy** Death: HR= 0.90; 95% CI= 0.69, 1.18; p = 0.46 **1 Signal** **Medical vs. PTA+ stenting** Overall deaths, n (%): 6 (8) vs. 5 (8); HR= 0.99; 95% CI= 0.30, 3.24 Cardiovascular mortality, n (%):	**Not assessed**	**None**	3 experts stated that the result for this outcome is valid and they were not aware of any evidence to invalidate the finding. One expert said he does not know and suggested to await the CORAL trial results that will be released in Fall 2012 and will have a major impact on this question.	**Probably out of date**

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."	**1 Retrospective** [13]	(5) vs. 2 (3); HR= 0.59; 95% CI= 0.11, 3.25 Primary end point or death, n (%): 22 (30) vs. 15 (24); HR= 0.81; 95% CI= 0.42, 1.56 **1 Signal** **Renal artery stenting vs. Medical treatment** Mortality: HR= 0.016; CI= 0, 15.16; p= 0.616 Event Free Survival **Patient with sent:** 78 months, 95% CI= 55, 100 **Patients without stent:** 79 months, 95% CI= 68, 90 **Mean survival for stented patients:** 104 months; 95% CI= 84, 124months				
Blood pressure control 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	**1 RCT** [7]	**1 Signal** **Revascularization (95% pts with stent) +medical therapy vs. medical therapy** "There was no significant between-group difference in systolic blood pressure; the decrease in diastolic blood pressure was smaller in the revascularization group than in the medical-therapy group." Rate of Systolic BP slope divergence:	**Not assessed**	**None**	One expert said the conclusion was not valid and he referenced the ASTRAL trial that is already included in this report. 3 experts stated that the result for this outcome is valid (2 of them were not aware of any evidence to invalidate the finding and one was not sure.	

		0.27 mm Hg per year; 95% CI= −0.83, 1.38; p = 0.63 <u>Rate of Diastolic BP slope divergence:</u> "The slopes for diastolic blood pressure diverged at a rate of 0.61 mm Hg per year (95% CI, 0.07 to 1.16; P = 0.03)" <u>Diastolic BP Mean Difference; 95% CI; p-value</u> <u>Baseline:</u> 0.43; -1.33, 2.18; 0.63 <u>1-3 month:</u> -0.37; -2.21, 1.48; 0.70 <u>6-8 month:</u> 0.20; -1.62, 2.02; 0.83 <u>1 year:</u> -1.28; -3.15, 0.59; 0.18 <u>2 year:</u> -1.28; -3.15, 0.59; 0.18 <u>3 year:</u> 0.53; -1.79, 2.85; 0.65 <u>4 year:</u> 3.48; 0.51, 6.45; 0.02 <u>5 year:</u> 2.59; -1.75, 6.93; 0.24 <u>Systolic BP Mean Difference; 95% CI; p-value</u> <u>Baseline:</u> -3.27; -6.76, 0.23; 0.07 <u>1-3 month:</u> -3.83; -7.63, -0.03; 0.05 <u>6-8 month:</u> -2.52; -6.30, 1.27; 0.19 <u>1 year:</u> -2.54; -6.18, 1.10; 0.17 <u>2 year:</u> -3.75; -7.93, 0.44; 0.08 <u>3 year</u>: -0.99; -5.68, 3.70; 0.68 <u>4 year:</u> 0.61; -5.83, 7.05; 0.85 <u>5 year</u>: -0.11; -8.90, 8.69; 0.98				
	1 Retrospective [13]	**No Signal** **Medical treatment vs. Renal artery stenting**				

	1 RCT [11]	BP mmHg: **Time 0** SBP: 142 ± 21 vs. 162 ± 17; p:NR DBP: 73 ± 13 vs. 75 ± 13; p:NR Medication (n): 4 vs. 3.5; p:NR **Month 3:** SBP: 152 ± 12 vs. 148 ± 21; p:NR DBP: 73 ± 8 vs. 80 ± 15; p:NR Medication (n): 4 vs. 3; p<0.05 **Month 48** SBP: 137 ± 37 vs. 166 ± 30; p:NR DBP: 78 ± 28 vs. 80 ± 20; p:NR Medication (n): 4 vs. 4; p:NR **1 Signal** **Medical vs. PTA+ stenting** Blood Pressure Control: Cured, n (%): 0 vs. 4 (11.1%); p<0.001 Improved, n (%): 33 (71.4%) vs. 24 (66.6%); p=NS Fail to improve, n (%):13 (28.6%) vs. 8 (22.3%); p=NS				
Kidney function 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	**1 RCT** [7]	**No Signal** **Revascularization (95% pts with stent) +medical therapy vs. medical therapy** Mean Serum Creatinine difference: 0.02 mg per deciliter; 95% CI= −0.10, 0.06 "In a per-protocol analysis, there	**Not assessed**	**None**	3 experts stated that the result for this outcome is valid and they were not aware of any evidence to invalidate the finding. One expert said he does not know.	

function were reported only among patients receiving angioplasty.		was no significant difference in the primary outcome between the 317 patients who underwent successful revascularization and the 379 patients who received medical therapy only."				
	1 RCT [8]	**No Signal** **Medical vs. PTA+ stenting** <u>≥ 20% decrease in creatinine clearance or death, n (%):</u> 22 (30) vs. 15 (24); HR= 0.81; 95% CI= 0.42, 1.56 <u>≥ 20% decrease in creatinine clearance, n (%):</u> 16 (22) vs.10(16); HR= 0.73; 95% CI= 0.33, 1.61				
	1 RCT [11]	**No Signal** **Medical vs. PTA+ stenting** <u>Serum creatinine/ Renal function</u> <u>Improved, n (%):</u> 0 vs. 11 (30.5%); p<0.001 <u>Unchanged, n (%):</u>30 (69.8%) vs. 12 (33.3%); p<0.001 <u>Worsened, n (%):</u>16 (30.26%) 13 (36.2%); p= NS				

	1 Retrospective [13]	**No Signal** "- Compared with a cohort that was followed up with medical management, the rate of renal function decline improved from _0.08 mg/dL per month to 0.00 mg/dL per month ($P < .05$) after intervention."				
Cardiovascular events (including flash pulmonary edema) 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	**1 RCT [7]** **1 RCT [8]** **1**	**1 Signal** **Revascularization (95% pts with stent) + medical therapy vs. medical therapy** Cardiovascular event: HR= 0.94; 95% CI= 0.75, 1.19; p = 0.61 **1 Signal** **Medical vs. PTA+ stenting** Heart failure, n (%): 3 (4) vs. 1 (2) ; HR= 0.39; 95% CI= 0.04, 3.71 Coronary artery disease, n (%): 3 (4) vs. 3 (5); HR= 1.16; 95% CI= 0.23, 5.73 Cardiovascular mortality, n (%): (5) vs. 2 (3); HR= 0.59; 95% CI= 0.11, 3.25 Pulmonary edema, n (%):	**Not assessed**	**None**	One expert said the conclusion is not valid and he referenced the ASTRAL trial that is included in this report. [7] 3 experts stated that the result for this outcome is valid. 2 of them suggested that the CORAL and RADAR trials will report on this	

	Retrospective [13]	1(1) vs. 0 **1 Signal** **Medical treatment vs. Renal artery stenting** <u>Myocardial events:</u> HR= 0.338, 95% CI= 0.069, 1.668; p=0.183				
<u>Quality of life</u> Weak evidence suggests no difference in QoL with medical treatment alone or with angioplasty	**No evidence**	**No Signal**	**Not assessed**	**None**	All 4 experts said the result is valid, one of them said to await the results from CORAL trial.	
<u>Adverse events</u> The evidence does not adequately assess comparisons of adverse events between medical treatment alone and angioplasty	**1 RCT** [7]	**No Signal** **Revascularization (95% pts with stent) + medical therapy vs. medical therapy** *(N=335) vs. (N=24)* *<u>Within 24 hours; n (%)</u>* <u>Renal or stent embolization:</u> 5 (1.5%) vs. 0 (-) <u>Renal arterial thrombosis or occlusion</u>: 4 (1%) vs. 0 (-) <u>Renal arterial perforation or dissection:</u> 3 (1%) vs. 1 (4%) <u>Non-renal embolization</u>: 3 (1%) vs. 0 (-) <u>Stent misplacement requiring additional stent</u>: 10 (3%) vs. 0 (-) <u>Distal stent retrieval or deployment</u>: 1 (0.3%) vs. 0 (-) <u>Balloon rupture</u>: 1 (0.3%) vs. 0 (-) <u>Need for surgical rescue</u> 0 (-) vs. 0 (-)	**Not assessed**	**None**	2 of the experts said the conclusion was not valid and they referenced the ASTRAL trial that is already included in this report. Of the 2 other experts, one did not know and the other said the conclusion was valid but was not aware of any evidence to invalidate the conclusion.	

	1 RCT [8]	Access vessel damage 7 (2%) vs. 0 (-) Pulmonary edema 1 (0.3%) vs. 0 (-) Femoral artery aneurysm at puncture site: 1 (0.3%) vs. 0 (-) Myocardial infarction 1 (0.3%) vs. 0 (-) Number of events / Number of patients 37 / 30 vs. 1 / 1 *Post-operative (between 24 hours and 1 month post procedure) (N=280)* Groin hemorrhage/hematoma: 32 (11%) vs. - Deterioration in renal function :30 (11%) vs. - Pseudoaneurysm: 3 (1%) vs. - Renal artery occlusion: 1 (0.4%) vs.- Local infection at puncture site: 1 (0.4%) vs. - Death within 30 days: 2 (0.7%) vs. Number of events / Number patients: 69 / 55 vs. – **No Signal** "Two patients in the stent group died of procedure related causes within 30 days after stent placement. These adverse events occurred at different centers and with Different providers. The most				

		common complications after stent placement were minor and mainly consisted of hematoma at the puncture site (11 patients [17%]). Minor side effects of medication were reported in 15 patients in the medication group and 4 in the stent group."				
Key question # 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?						
There is weak evidence that <u>patients with bilateral RAS may have more favorable outcomes with angioplasty than medical therapy</u> 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	**1 RCT** [7] **1 Retrospective** [5]	**1 Signal** **Revascularization (95% pts with stent) + medical therapy vs. medical therapy** "We also found no significant difference in the primary outcome between the 163 patients with severe anatomical disease (103 patients with bilateral renal-artery stenosis of more than 70% and 60 patients with renal-artery stenosis of more than 70% in a single functioning kidney) and patients without such severe anatomical disease (P = 0.23)" **No Signals** <u>Renal Artery Stenting</u> **Three independent predictors of BP response:** 4) Requirement for ≥4 hypertension medications:	**Not assessed**	**None**	One of the experts said the conclusion was not valid and he referenced ASTRAL trial that is already included in this report. The other 2 experts did not know and suggested to await the CORAL trial. One expert said the conclusion was still valid and he did not know any evidence to invalidate the results.	**Possibly out of date**

	1 Prospective cohort [6]	OR= 29.9; 95% CI= 5.6, 159.4; p=0.0001 5) Diastolic BP of >90 mmHG: OR= 31.4; 95% CI= 4.1, 241.6; P=0.0001 6) Clonidine use: OR= 7.3; 95% CI= 1.2, 43.5; p=0.029 **BP response rate among patients with 3- hypertensions drug:** Larger ipsilater kidney (volume ≥ 150 cm^3) vs. patients with smaller kidneys 63% vs. 18%; p=0.018 **No Signals** Percutanous revascularization of RAS **Independent CV event risk factors:** Coronary artery disease severity: RR= 1.27; *p*= .023 Smoking: RR,=1.29; *p*=0 .016 Baseline LVM: RR= 1.21; p= 0.07 **Independent factors associated with SBP and DBP improvement** Grade of renal stenosis: RR, 1.28; p=. 0.006 Bilateral RAS procedure: RR= 1.17; p= 0.07 Baseline DBP value: RR= 1.74; p < 0.001				
Key question # 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?						

There is no evidence regarding the value of periprocedural interventions with angioplasty	**No evidence**		**Not assessed**	**None**	Two experts said they don't know, one of them suggested awaiting CORAL trial. The other 2 experts said the conclusion was valid and they were not aware of any evidence to invalidate the findings.	**Up-to-date**
Abbreviations: CER=comparative effectiveness review; FDA=food and drug administration; vs.: versus; MD: mean difference; yrs: years old; NR: Not reported; RCT: Randomized Clinical Trial; vs.: versus; no: number; %: percent; pts: patients; NS: Not significant; SD: Standard Deviation ;N: total number; LVM: left ventricle mass; HR: Hazard ratio; OR: Odd ratio; MHRA: Medicines and Healthcare products Regulatory Agency						

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Appendix A: Search Methodology

All MEDLINE searches were limited to the following journals:

General biomedical – Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine

Specialty journals – Journal of Endovasc Therapy, Journal of Vascular Surgery, American Journal of Medicine, Kidney International, and American Journal of Kidney Diseases

Database: Ovid MEDLINE(R)

Time period covered: 2008 to June 22nd, 2012

Main Search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:
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1 exp Hypertension, Renal/ (17920)
2 exp Renal Artery Obstruction/ (9214)
3 renal arter$ stenosis.tw. (4394)
4 renal arter$ dis$.tw. (480)
5 renovascular dis$.tw. (863)
6 reno vascular dis$.tw. (11)
7 renal vascular dis$.tw. (194)
8 (arvd or "atherosclerotic renovascular dis$").tw. (543)
9 renal steno$.tw. (72)
10 steno$ kidney.tw. (127)
11 renovascular steno$.tw. (34)
12 or/1-11 (24806)
13 limit 12 to humans (18036)
14 limit 13 to english language (12212)
15 14 (12212)
16 limit 15 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) (3399)
17 15 not 16 (8813)
18 jama.jn. (62388)
19 "annals of internal medicine".jn. (27403)
20 bmj.jn. (73496)
21 "new england journal of medicine".jn. (65451)
22 (lancet or lancet oncology).jn. (125331)

23 "journal of endovascular therapy".jn. (1576)
24 "journal of vascular surgery".jn. (10331)
25 "american journal of medicine".jn. (20664)
26 (kidney international or kidney international supplement).jn. (16851)
27 "american journal of kidney diseases".jn. (9130)
28 or/18-27 (412621)
29 17 and 28 (1032)
30 ("20061024" or "20061025" or "20061026" or "20061027" or "20061028" or "20061029" or "20061030" or "20061031" or 200611* or 200612* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012*).ed. (4924944)
31 29 and 30 (89)
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Appendix B: Updating Signals

Qualitative signals*

Potentially invalidating change in evidence

This category of signals (A1-A3) specifies findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of "opposing findings" – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007 for further definitions and details

**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix B: Updating Signals (Continued)

Quantitative signals (B1-B2)*

Change in statistical significance (B1)

Refers to a situation in which a statistically significant result in the original CER is now NOT statistically significant or vice versa- that is a previously non-significant result become statistically significant. For the 'borderline' changes in statistical significance, at least one of the reports (the original CER or new updated meta-analysis) must have a p-value outside the range of border line (0.04 to 0.06) to be considered as a quantitative signal for updating.

Change in effect size of at least 50% (B2)

Refers to a situation in which the new result indicates a relative change in effect size of at least 50%. For example, if relative risk reduction (RRR) new / RRR old <=0.5 or RRR new / RRR old >=1.5. Thus, if the original review has found RR=0.70 for mortality, this implies RRR of 0.3. If the updated meta-analytic result for mortality were 0.90, then the updated RRR would be 0.10, which is less than 50% of the previous RRR. In other words the reduction in the risk of death has moved from 30% to 10%. The same criterion applied for odds ratios (e.g., if previous OR=0.70 and updated result were OR=0.90, then the new reduction in odds of death (0.10) would be less 50% of the magnitude of the previous reduction in odds (0.30). For risk differences and weighted mean differences, we applied the criterion directly to the previous and updated results (e.g., RD new / RD old <=0.5 or RD new / RD old >=1.5).

* Please, see Shojania et al. 2007 for further definitions and details

Appendix C: Evidence Table (Renal Artery Stenosis)

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration/ Study period	Primary outcome	Findings
Key Question 1. 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?						
ASTRAL Investigators, 2009 [7]	RCT	806 pts with atherosclerotic renovascular disease; Mean age: 70.5 yrs; Male: 63%	Revascularization (95% pts with stent) + medical therapy (statins, antiplatelet agents, and optimal blood-pressure control), (dose= NR ; n=403) vs. medical therapy (statins, antiplatelet agents, and optimal blood-pressure control), (dose= NR ; n=403)	5 years Median (34 months)	Primary: renal function, Secondary: BP, the time to renal and major cardiovascular events, and mortality.	**Revascularization (95% pts with stent) + medical therapy vs. medical therapy** <u>Cardiovascular event:</u> HR= 0.94; 95% CI= 0.75, 1.19; p = 0.61 <u>Death:</u> HR= 0.90; 95% CI= 0.69, 1.18; p = 0.46 <u>Mean Serum Creatinine difference:</u> 0.02 mg per deciliter; 95% CI= −0.10 to 0.06 <u>Rate of Systolic BP slope divergence:</u> 0.27 mm Hg per year; 95% CI= −0.83, 1.38; p = 0.63 “The mean serum creatinine level was 1.6 μmol per liter (95% CI, −8.4 to 5.2 [0.02 mg per deciliter; 95% CI, −0.10 to 0.06]) lower in the revascularization group than in the medical-therapy group.” <u>Rate of Systolic BP slope divergence:</u> 0.27 mm Hg per year; 95%

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration/ Study period	Primary outcome	Findings
						CI= −0.83, 1.38; p = 0.63 <u>Rate of Diastolic BP slope divergence:</u> "The slopes for diastolic blood pressure diverged at a rate of 0.61 mm Hg per year (95% CI, 0.07 to 1.16; P = 0.03)" <u>Diastolic BP Mean Difference; 95% CI; p-value</u> <u>Baseline:</u> 0.43; -1.33, 2.18; 0.63 <u>1-3 month:</u> -0.37; -2.21, 1.48; 0.70 <u>6-8 month:</u> 0.20; -1.62, 2.02; 0.83 <u>1 year:</u> -1.28; -3.15, 0.59; 0.18 <u>2 year:</u> -1.28; -3.15, 0.59; 0.18 <u>3 year:</u> 0.53; -1.79, 2.85; 0.65 <u>4 year:</u> 3.48; 0.51, 6.45; 0.02 <u>5 year:</u> 2.59; -1.75, 6.93; 0.24 <u>Systolic BP Mean Difference; 95% CI; p-value</u> <u>Baseline:</u> -3.27; -6.76, 0.23; 0.07 <u>1-3 month:</u> -3.83; -7.63, -0.03; 0.05 <u>6-8 month:</u> -2.52; -6.30, 1.27; 0.19 <u>1 year:</u> -2.54; -6.18, 1.10; 0.17 <u>2 year:</u> -3.75; -7.93, 0.44; 0.08 <u>3 year</u>: -0.99; -5.68, 3.70; 0.68 <u>4 year:</u> 0.61; -5.83, 7.05; 0.85 <u>5 year</u>: -0.11; -8.90, 8.69; 0.98
Bax L, 2009 [8]	RCT	140 patients with creatinine clearance and ARAS of 50% or greater; Mean Age:66.5 yrs; Male:	Stent placement and medical treatment; dose: NR (n=64 patients) vs. medical treatment (antihypertensive	Two years	Primary: 20% or greater decrease in creatinine	**Medical vs. PTA+ stenting** <u>Heart failure, n (%):</u> 3 (4) vs. 1 (2) ; HR= 0.39; 95% CI= 0.04, 3.71

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration/ Study period	Primary outcome	Findings
		63%	treatment, a statin, and aspirin only); dose:NR; (n=76)		clearance; Secondary: safety and cardiovascular morbidity and mortality.	<u>Coronary artery disease, n (%):</u> 3 (4) vs. 3 (5); HR= 1.16; 95% CI= 0.23, 5.73 <u>Overall deaths, n (%):</u> 6 (8) vs. 5 (8); HR= 0.99; 95% CI= 0.30, 3.24 <u>Cardiovascular mortality, n (%):</u> (5) vs. 2 (3); HR= 0.59; 95% CI= 0.11, 3.25 <u>Primary end point or death, n (%):</u> 22 (30) vs. 15 (24); HR= 0.81; 95% CI= 0.42, 1.56 <u>Primary end point, n (%):</u> 16 (22) vs.10(16); HR= 0.73; 95% CI= 0.33, 1.61 <u>Pulmonary edema, n (%):</u> 1(1) vs. 0
Arthurs Z, 2007 [13]	Retrospective	40 Patients with atherosclerotic renal artery disease; Mean age: 69.5 yrs; Male: NR	Renal artery stenting (dose: NA; n= 18) vs. Medical Treatment (dose:NR ; n= 22)	Mean follow up 15 months	improvements in hypertension and renal excretory function	<u>Medical treatment vs. Renal artery stenting</u> <u>BP mmHg:</u> **Time 0** SBP: 142 ± 21 vs. 162 ± 17; p:NR DBP: 73 ± 13 vs. 75 ± 13; p:NR Medication (n): 4 vs. 3.5; p:NR **Month 3:** SBP: 152 ± 12 vs. 148 ± 21; p:NR DBP: 73 ± 8 vs. 80 ± 15; p:NR Medication (n): 4 vs. 3; p<0.05

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration/ Study period	Primary outcome	Findings
						Month 48 SBP: 137 ± 37 vs. 166 ± 30; p:NR DBP: 78 ± 28 vs. 80 ± 20; p:NR Medication (n): 4 vs. 4; p:NR Cox regression showed that renal artery stenting did not significantly impact **mortality:** HR= 0.016; CI= 0, 15.16; p= 0.616 Event Free Survival **Patient with sent:** 78, 95% CI= 55, 100 **Patients without stent:** 79, 95% CI= 68, 90 **Mean survival for stented patients:** 104 months; 95% CI= 84, 124months Myocardial events: HR= 0.338, 95% CI= 0.069, 1.668; p=0.183 "- Compared with a cohort that was followed up with medical management, the rate of renal function decline improved from _0.08 mg/dL per month to 0.00 mg/dL per month ($P < .05$) after intervention. -Patients with baseline chronic renal insufficiency experienced the greatest benefit from renal artery stenting. - Conclusions: Renal artery stenting initially improves hypertension control, but the durability is lost after 6 months. Renal artery

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration/ Study period	Primary outcome	Findings
						stenting dramatically slows the rate of renal function decline and could potentially delay a patient's requirement for haemodialysis."
Kashyap S.V, 2007 [10]	Retrospective	125 pts with renal artery stenosis; Mean age: 71 yrs; Male: 59%	percutaneous transluminal angioplasty and stenting (PTA/S)(Dose:NR; n= 125)	1999 and 2004	Renal function (GFR)	Renal Artery Stenting Mortality, n (%): 2 (1.6) in the 30-day postoperative period BP decrease (before vs. 1 month after surgery): 151/79 mm Hg vs. 139/72 mm Hg; P < .03 GFR change: 33±12 mL · min-1 · 1.73 m-2 (mean ± SD) to 37 ±19 mL · min-1 · 1.73m-2 at 6 months ;P= .10 Improvement in GFR ((>10% increase) or stabilization of renal function: 67% of treated patients Not improvement in GFR after PTA/S : Association with eventual dialysis need (P = .01; mean follow-up, 19 months) Survival at 3 years: 76% Dialysis-free survival 63%
Zeller T, 2007 [9]	Retrospective	102 pts with atherosclerotic renal artery stenosis and	stent-supported percutaneous transluminal renal angioplasty (PTRA)	Mean 24614 months, range 6–60).	change in left ventricular	**PTRA vs. control** Mean BP reduction:

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration/ Study period	Primary outcome	Findings
		101 pts with essential hypertensions; Mean age: 67.5 yrs; Male: 62%	(Dose:NA; n= 102) vs. contemporaneous patients (Dose:NR; n=101)		mass index	99±11 mmHg to 90±11 mmHg (p<0.0001) vs. 102±11 mmHg to 105± mmHg (p=0.008)
Ziakka S, 2008 [11]	RCT	82 pts with atherosclerotic renal artery stenosis; Mean age: 64.5 yrs; Male: 76 %	Percutaneous transluminal angioplasty (PTA) with stenting (Dose: NA; N=36) vs. medical treatment (Dose:NR; n=46)	47.5 ± 35.4 months (range 35–89 months)	BP Control, Renal function	**Medical vs. PTA+ stenting** Serum creatinine/ Renal function Improved, n (%): 0 vs. 11 (30.5%); p<0.001 Unchanged, n (%):30 (69.8%) vs. 12 (33.3%); p<0.001 Worsened, n (%):16 (30.26%) 13 (36.2%); p= NS Blood Pressure Cured, n (%): 0 vs. 4 (11.1%); p<0.001 Improved, n (%): 33 (71.4%) vs. 24 (66.6%); p=NS Fail to improve, n (%):13 (28.6%) vs. 8 (22.3%); p=NS Cox regression for increase of serum creatinine 20% above baseline value: Eosinophils: HR= 1.002; 95% CI= 1.0003, 1.0028; p= 0.01 ROS: HR= 1.005; 95% CI= 1.00077, 1.0099; p= 0.02 - Cox regression analysis showed that higher levels of eosinophil count and higher levels of ROS, irrespectively of mode of treatment, were associated with renal function deterioration (i.e., serum creatinine increases more than 20% during follow- up).
Key question # 1a: What are the patient characteristics, including etiology, predominant clinical presentation, and severity of stenosis, in the studies?						

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration/ Study period	Primary outcome	Findings
Bax L, 2009 [8]	RCT	140 patients with creatinine clearance and ARAS of 50% or greater; Mean Age:66.5 yrs; Male: 63%	Stent placement and medical treatment; dose: NR (n=64 patients) vs. medical treatment (antihypertensive treatment, a statin, and aspirin only); dose:NR; (n=76)	Two years	Primary: 20% or greater decrease in creatinine clearance; Secondary: safety and cardiovascular morbidity and mortality.	**Medical vs. PTA+ stenting** Degree of stenosis of the most affected kidney, n (%) 50%–70%: 24 (32) vs. 22 (34) 70%–90%: 35 (46) vs. 20 (31) >90%: 17 (22) vs. 22 (34) Type of ostial stenosis, n (%) Unilateral: 41 (54) vs. 32 (50) Bilateral: 35 (46) vs. 32 (50) Occlusion or shrunken kidney: 11 (31) vs. 14 (44) Single kidney: 3 (8) vs. 1 (3)
ASTRAL Investigators, 2009 [7]	RCT	806 pts with atherosclerotic renovascular disease; Mean age: 70.5 yrs; Male: 63%	revascularization + medical therapy (statins, antiplatelet agents, and optimal blood-pressure control), (dose= NR ; n=403) vs. medical therapy (statins, antiplatelet agents, and optimal blood-pressure control), (dose= NR ; n=403)	5 years Median (34 months)	Primary: renal function, Secondary: BP, the time to renal and major cardiovascular events, and mortality.	**Revascularization vs. Medical therapy** Stenosis, Mean (range) − % 76 (40‑100) vs. 75 (20‑99) 0.29 Severity − no. (%) <50% : 2 (<1) vs. 4 (1);p= 0.68 50‑70%: 159 (39)vs. 164 (41);p=NR >70%: 242 (60)vs. 235 (58); p=NR
Key question # 1b: What adverse events and complications have been associated with aggressive medical therapy or renal artery angioplasty with stent placement?						
Bax L, 2009 [8]	RCT	140 patients with creatinine clearance and ARAS of 50% or greater; Mean	Stent placement and medical treatment; dose: NR (n=64 patients) vs. medical treatment	Two years	Primary: 20% or greater decrease in	**Medical vs. PTA+ stenting** Complications:

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration/ Study period	Primary outcome	Findings
		Age:66.5 yrs; Male: 63%	(antihypertensive treatment, a statin, and aspirin only); dose:NR; (n=76)		creatinine clearance; Secondary: safety and cardiovascular morbidity and mortality.	1- Two patients in the stent group died of procedure related causes within 30 days after stent placement 2- The most common complications after stent placement were minor and mainly consisted of hematoma at the puncture site (11 patients [17%]).
ASTRAL Investigators, 2009 [7]	RCT	806 pts with atherosclerotic renovascular disease; Mean age: 70.5 yrs; Male: 63%	revascularization + medical therapy (statins, antiplatelet agents, and optimal blood-pressure control), (dose= NR ; n=403) vs. medical therapy (statins, antiplatelet agents, and optimal blood-pressure control), (dose= NR ; n=403)	5 years Median (34 months)	Primary: renal function, Secondary: BP, the time to renal and major cardiovascular events, and mortality.	"1- A total of 31 serious complications of revascularization occurred in 23 patients. Of these 12 (in 11 patients) were considered to be serious: 2 deaths (both from cardiac causes), 4 cases of groin hematoma or hemorrhage requiring hospitalization, 5 cases of clinically significant acute kidney injury, and 1 renal-artery occlusion. 2- A total of 38 periprocedural complications were reported in 31 of the 359 patients (9%) who underwent revascularization (including 1 of the 24 patients in the medical-therapy group who crossed over to revascularization) 19 of these events (in 17 patients) were considered to be serious complications, including: pulmonary edema in one patient and myocardial infarction in another. In addition, there were five renal embolizations, four renal arterial occlusions, four renal-artery perforations, one femoral-artery aneurysm, and three cases of cholesterol embolism leading to peripheral gangrene and amputation of toes or limbs."
Key question # 2: What clinical, imaging, laboratory, and anatomic characteristics are associated with improved or worse outcomes when treating with either						

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration/ Study period	Primary outcome	Findings
aggressive medical therapy alone or renal artery angioplasty with stent placement?						
Modrall JG, 2011 [5]	Retrospective	149 pts primary ARAS; Median age: 68 yrs; Male: 23%	Renal Artery Stenting, (n=149; dose: NA)	Median follow-up was 19 months (interquartile range [IQR] 10.0-29.5 months)	BP	Renal Artery Stenting **Three independent predictors of BP response:** 7) Requirement for ≥4 hypotension medications: OR= 29.9; 95% CI= 5.6, 159.4; p=0.0001 8) Diastolic BP of >90 mmHG: OR= 31.4; 95% CI= 4.1, 241.6; P=0.0001 9) Clonidine use: OR= 7.3; 95% CI= 1.2, 43.5; p=0.029 **BP response rate among patients with 3-hypertensions drug:** Larger ipsilater kidney (valume ≥ 150 cm^3) vs. patients with smaller kidneys 63% vs. 18%; p=0.018
Rzeznik D, 2011 [6]	Prospective	84 pts with RAS; Mean age:63.7 yrs; Male: 50%	Percutaneous revascularization of RAS, (n= 84; dose:NA)	12 months	BP Cardiovascular events	Percutaneous revascularization of RAS **CV Deaths n (%):** 12 (14.3) **BP (Baseline vs. 12 month):** **Mean SBP:** 133.5 ± 16.9 mm Hg vs. 127.9 ± 13.2 mmHg ; p = .007 **Mean DBP:** 75.4 ± 10.2mmHg vs. 73.1 ± 8.8mmHg ; p= .035 **Multivariate logistic regression analysis** **Independent CV event risk factors:** Coronary artery disease severity: RR= 1.27; *p*= .023 Smoking: RR,=1.29; *p*= .016

Author year Study name (if applicable)	Study design	participants	Intervention groups (n; dose)	Treatment duration/ Study period	Primary outcome	Findings
						Baseline LVM: RR= 1.21; p= .07 **Independent factors associated with SBP and DBP improvement** Grade of renal stenosis: RR, 1.28; p= .006 Bilateral RAS procedure: RR= 1.17; p= .07 Baseline DBP value: RR= 1.74; p < .001
Key question # 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?						
No relevant study identified.						
Abbreviations: yrs: years old; NR: Not reported; RCT: Randomized Clinical Trial; vs.: versus; no: number; %: percent; pts: patients; NS: Not significant; SD: Standard Deviation ;N: total number; HR: Hazard ratio; OR: Odd ratio						

Appendix D: Questionnaire Matrix

Comparative Effectiveness of Management Strategies for Renal Artery Stenosis Update

AHRQ Publication No. 07(08)-EHC004-U-EF, November 2007

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Clinical expert name:

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question 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:			
Survival/mortality Weak evidence suggests no difference in mortality rates			
Blood pressure control 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			
Kidney function 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.			
Cardiovascular events (including flash pulmonary edema) 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			
Quality of life Weak evidence suggests no difference in QoL with medical treatment alone or with angioplasty			
Adverse events The evidence does not adequately assess comparisons of adverse events between medical treatment alone and angioplasty			
Key Question 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?			
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			
Key Question 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?			
There is no evidence regarding the value of periprocedural interventions with angioplasty			
CER=comparative effectiveness review;			