Percutaneous renal artery intervention versus medical therapy in patients with renal artery stenosis: a meta-analysis

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Abstract

Aims: Patients with renal artery stenosis are treated with percutaneous intervention, but randomised studies are inconclusive. We aimed to compare renal percutaneous revascularisation versus medical therapy.

Methods and results: A systematic search for randomised controlled studies yielded three studies comparing renal angioplasty and two studies comparing renal angioplasty with stenting versus medical therapy, respectively. Six sets of data were extracted focusing on systolic and diastolic blood pressure as well as serum creatinine at follow-up. The five trials included 1,030 patients with renal artery stenosis. There was a trend toward, but no significant improvement in, systolic blood pressure (weighted mean difference [WMD] –2.76 mmHg, 95% confidence interval (CI) –5.71 to 0.18; p=0.07), diastolic blood pressure (WMD –1.18 mmHg, 95% CI –2.69 to 0.32; p=0.12), or serum creatinine (WMD –7.26 mmol/L, 95% CI –14.99 to 0.47; p=0.07) in the patients who underwent percutaneous intervention compared to the medical therapy group. All but one trial showed at least a moderate overall bias risk.

Conclusions: We did not find a significant improvement in blood pressure or renal function in patients with renal artery stenosis treated with renal artery revascularisation compared to medical therapy alone. However, trial quality was a limitation.

Keywords

• renal artery stenosis
• angioplasty
• percutaneous intervention
• stent
• meta-analysis

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Renal artery stenosis (RAS) is the most common secondary cause of hypertension and affects 1-5% of hypertensive patients, but the true prevalence of RAS is not known. In autopsy studies, the prevalence of RAS ranges from 26 to 62% 2-3. The prevalence of RAS among patients older than 65 years of age has been shown to be 6.8% 4. It has been estimated that there are 2-4 million people with RAS in the United States alone 5.

Clinically, patients with RAS typically present with hypertension, renal insufficiency, or both. Renovascular hypertension results from hypoperfusion of one or both kidneys, which stimulates the renin-angiotensin system resulting in vasoconstriction, and salt and water retention. Intravascular fluid shifts can have significant clinical consequences for patients with congestive heart failure and/or coronary artery disease. RAS can be associated with episodic decompensations of heart failure, “flash” or sudden onset of pulmonary oedema, or unstable or refractory angina 6. Hypoperfusion from RAS can also result in ischaemic injury to the renal parenchyma. It has been estimated that at least 10-15% of patients entering dialysis programs have RAS as a primary cause of renal failure although it is unclear based on current data what percentage of these patients have bilateral RAS, unilateral RAS, or RAS of a solitary functioning kidney 7.

Over 40,000 percutaneous renal artery interventions are performed in the United States on a yearly basis 8. The most common indications for these procedures include refractory hypertension, preservation of renal function and cardiac destabilisation syndromes, including congestive heart failure and unstable angina. Several randomised control trials have looked at the benefits of percutaneous renal artery interventions and medical therapy versus medical therapy alone, and have provided conflicting results. We conducted a systematic review and meta-analysis of randomised trials comparing percutaneous renal artery intervention (PTRI) (renal artery angioplasty or without stenting) versus medical therapy.

Methods
A systematic search for randomised trials of revascularisation in ath erosclerotic renal artery stenosis (ARAS) was undertaken searching PubMed, CENTRAL, mRCT, BioMed Central, CardioSource, ClinicalTrials.gov, and ISI Web of Science using a highly sensitive and specific strategy as previously described 9. Search keywords included “random”, “control”, “trial”, “atherosclerotic”, “renal”, “revascularisation”, “angioplasty” and “stent”. The search was extended to June 2009. No language restriction was used. In addition, major journals in the field were hand searched for relevant material. The hand search also involved a search of conference proceedings to identify presentations made at international cardiology, vascular medicine and radiology meetings. Experts in the field were contacted in an attempt to identify studies not found by the electronic and hand searches, in order to identify trials that have not been formally published. Information was also sought from reviewing reference lists of already retrieved papers, including review papers and previous meta-analyses of renal artery revascularisation.

STUDY SELECTION
Inclusion in the analysis required that the treatment group underwent PTRI with percutaneous balloon angioplasty and/or endovascular stenting in addition to medical treatment, that the control group received medical therapy alone, and that the group assignments were randomly allocated.

OUTCOME MEASURES AND STATISTICS
The main outcome measures were systolic blood pressure (SBP), diastolic blood pressure (DBP) and serum creatinine (SCr) at follow-up. The mean and standard deviations for each outcome measure were extracted from published papers 10. Standard methods for meta-analyses of study level data were employed 11. Specifically, we tested the hypothesis of statistical homogeneity by means of the Q-statistic and χ² test, and measured the extent of statistical consistency by computing the I-square index. Small study effects (e.g., publication bias) was assessed for the main endpoints by visual examination for funnel plots and the Egger method 12.

RESULTS
Five randomised controlled trials comparing PTRI plus medical therapy and medical therapy alone in patients with ARAS were identified. In the study by Plouin et al, 49 patients with hypertension and unilateral ARAS were randomised with 26 allocated to the medical therapy group and 23 allocated to the PTRI group 13. Of the 23 patients in the PTRI group, 21 underwent renal artery angioplasty and two underwent renal artery angioplasty and stent placement. With regard to renal artery lesion severity, 65% of the patients in the PTRI group had renal artery lesions between 60 and 74%. The study by Webster et al enrolled patients with hypertension and was stratified according to whether the patient had unilateral or bilateral ARAS. These patients were analysed sepa-
rately, resulting in two sets of data (28 patients with bilateral ARAS and 27 patients with unilateral ARAS). Of the 28 patients with bilateral ARAS, 12 were randomised to the PTRI group with 10 undergoing percutaneous renal artery angioplasty. Of the 27 patients with unilateral ARAS, 13 were randomised to the PTRI group with 10 undergoing renal artery angioplasty. The only assessment of severity of the renal artery lesions of the patients enrolled in this study was that the lesions were >50%. In the study by van Jaarsveld et al, 106 patients with hypertension and unilateral or bilateral ARAS were randomised; 56 patients (23% with bilateral ARAS) in the renal artery angioplasty group and 50 patients (30% with bilateral ARAS) in the medical therapy group. Of the 56 patients randomised to the PTRI group, 54 underwent renal artery angioplasty and two underwent renal artery stenting. Of those 18 patients, 12 patients were found to have ARAS <50%. In the study from the ASTRAL investigators, 806 patients were randomised and 403 (50%) were allocated to the PTRI group. Eighty-six patients (21%) were not percutaneously revascularised after randomisation. Thirty-three patients (8%) were reported to have minimal stenoses.

Table 1. Published randomised trials comparing intervention to medical therapy for renal artery stenosis.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients (n)</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Main endpoint(s)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plouin et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>49</td>
<td>Balloon angioplasty (with or without stent placement)</td>
<td>6 months</td>
<td>Primary: BP at termination and change from baseline Secondary: treatment score and incidence of complications</td>
<td>No significant change in SBP or DBP No significant change in SCr</td>
</tr>
<tr>
<td>Webster et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>55</td>
<td>Balloon angioplasty</td>
<td>1, 3, 6 months, then at 6-monthly intervals</td>
<td>Primary: BP and SCr at 6 months and the change in these from baseline Secondary: major events</td>
<td>Bilateral RAS: Significant improvement in SBP after angioplasty. No significant change in DBP. No significant change in SCr</td>
</tr>
<tr>
<td>Van Jaarsveld et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>106</td>
<td>Balloon angioplasty</td>
<td>3 months and 12 months</td>
<td>Primary: BP at 3 and 12 months Secondary: treatment score, SCr, SCr clearance</td>
<td>No significant change in SBP or DBP No significant change in SCr</td>
</tr>
<tr>
<td>Bax et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>140</td>
<td>Renal artery stenting</td>
<td>3 to 24 months</td>
<td>Primary: 20% or greater reduction in creatinine clearance Secondary: BP, cardiovascular morbidity and mortality</td>
<td>No significant effect on progression of renal dysfunction No significant effect on BP</td>
</tr>
<tr>
<td>ASTRAL investigators&lt;sup&gt;15&lt;/sup&gt;</td>
<td>806</td>
<td>Renal artery stenting</td>
<td>3 months to 5 years</td>
<td>Primary: change in renal function Secondary: BP, time to first renal event, time to first cardiovascular event, and mortality</td>
<td>No significant effect on renal function No significant effect on BP No significant effect on mortality</td>
</tr>
</tbody>
</table>

BP: blood pressure; DBP: diastolic blood pressure; RAS: renal artery stenosis; SBP: systolic blood pressure; SCr: serum creatinine

Table 2. Evaluation of internal validity and quality of included studies.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Plouin et al (1998)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
<tr>
<td>Webster et al (1998)</td>
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<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
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<tr>
<td>Van Jaarsveld et al (2000)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Low (3 month results) High (12 month results)</td>
<td></td>
</tr>
<tr>
<td>Bax et al (2009)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>ASTRAL (2009)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Six sets of results from five trials were included in this meta-analysis. The six sets of data included 1,030 patients with ARAS with the smallest data set including 27 patients (Webster - unilateral ARAS) and the largest data set including 680 patients (ASTRAL investigators). Although 806 patients were randomised in the ASTRAL trial, only data from 680 were available at 12 months and used for analysis. In total, the final analysis had 500 (48.4%) randomised to receive PTRI (angioplasty with or without stent placement) and 533 patients (51.6%) randomised to receive medical therapy alone. Follow-up data for the studies by Plouin et al and Webster et al were taken at six months. The study by van Jaarsveld et al had follow-up data from three and 12 months, but this trial was criticised because nearly half of the patients randomised to medical management underwent angioplasty between three and 12 months post-randomisation.

Consequently, in our analysis, the results for this trial are presented at three months, when there had been no crossovers from medical management to angioplasty. In the study by Bax et al, results at 24 months follow-up were used. In the study by the ASTRAL investigators, results were available up to five years after initial randomisation. In this case, our study used the results from 12 months because it provided the largest number of patients for analysis.

Comparisons between patients with ARAS who underwent PTRI versus those who received medical therapy alone were made for SBP, DBP, and SCr at follow-up intervals from three to 24 months, as noted above. SBP was decreased, but not significantly so in the group undergoing PTRI (WMD -2.76 mmHg [-5.71 to 0.18], p for effect=0.07, p for heterogeneity=0.84, I-square=0) (Figure 1), and DBP was also not significantly decreased (WMD -1.18 mmHg [-2.69 to 0.32], p for effect=0.12, p for heterogeneity=0.17, I-square=36%) (Figure 2). In addition, the SCr was lower, but not significantly so in patients who underwent PTRI compared to the medical therapy group (WMD -7.26 mmol/L [-14.99 to 0.47], p for effect=0.07, p for heterogeneity=0.38, I-square=6%) (Figure 3). The corresponding funnel plots for SBP, DBP, and SCr did not suggest that there was significant publication bias associated with these results (Figure 4). Accordingly, Egger regression tests showed non-significant results in all cases (all p>0.05), although the small number of studies makes it difficult to draw firm conclusions.

**Figure 1.** Systolic blood pressure at follow-up (Mean[SD]) with corresponding forest plot. B/L: bilateral; CI: confidence interval; Rx: treatment; SD: standard deviation; U: unilateral; WMD: weighted mean difference

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>WMD (fixed)</th>
<th>Weight</th>
<th>WMD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plouin 1998</td>
<td>23</td>
<td>25</td>
<td>12.03</td>
<td>1.00</td>
<td>-1.00</td>
</tr>
<tr>
<td>Webster 1998 (B/L)</td>
<td>12</td>
<td>15</td>
<td>1.04</td>
<td>1.00</td>
<td>-6.11</td>
</tr>
<tr>
<td>Webster 1998 (U)</td>
<td>11</td>
<td>11</td>
<td>1.97</td>
<td>1.97</td>
<td>0.06</td>
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<tr>
<td>van Jaarsveld 2000</td>
<td>55</td>
<td>50</td>
<td>6.76</td>
<td>6.76</td>
<td>-7.00</td>
</tr>
<tr>
<td>ASTRAL 2009</td>
<td>321</td>
<td>336</td>
<td>11.76</td>
<td>11.76</td>
<td>-4.00</td>
</tr>
<tr>
<td>Bax 2009</td>
<td>57</td>
<td>68</td>
<td>100.00</td>
<td>100.00</td>
<td>-2.76</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>479</strong></td>
<td><strong>504</strong></td>
<td><strong>-1.18</strong></td>
<td><strong>1.18</strong></td>
<td><strong>[-2.69, 0.32]</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Ch²=2.06, df=5 (p=0.84), F=0%
Test for overall effect: Z=1.84 (p=0.07)

**Figure 2.** Diastolic blood pressure at follow-up (Mean[SD]) with corresponding forest plot. B/L: bilateral; CI: confidence interval; Rx: treatment; SD: standard deviation; U: unilateral; WMD: weighted mean difference

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment</th>
<th>Control</th>
<th>WMD (fixed)</th>
<th>Weight</th>
<th>WMD (fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plouin 1998</td>
<td>23</td>
<td>25</td>
<td>7.05</td>
<td>1.00</td>
<td>-3.00</td>
</tr>
<tr>
<td>Webster 1998 (B/L)</td>
<td>12</td>
<td>15</td>
<td>1.54</td>
<td>1.54</td>
<td>-1.00</td>
</tr>
<tr>
<td>Webster 1998 (U)</td>
<td>11</td>
<td>11</td>
<td>3.35</td>
<td>3.35</td>
<td>10.00</td>
</tr>
<tr>
<td>van Jaarsveld 2000</td>
<td>55</td>
<td>50</td>
<td>65.33</td>
<td>65.33</td>
<td>-1.28</td>
</tr>
<tr>
<td>ASTRAL 2009</td>
<td>320</td>
<td>335</td>
<td>13.71</td>
<td>13.71</td>
<td>-2.00</td>
</tr>
<tr>
<td>Bax 2009</td>
<td>57</td>
<td>68</td>
<td>100.00</td>
<td>100.00</td>
<td>-1.18</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>478</strong></td>
<td><strong>504</strong></td>
<td><strong>-1.18</strong></td>
<td><strong>1.18</strong></td>
<td><strong>[-2.69, 0.32]</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Ch²=2.06, df=5 (p=0.84), F=0%
Test for overall effect: Z=1.84 (p=0.07)
A subgroup meta-analysis of the two trials comparing renal artery stenting versus medical therapy (Figure 5) comprised fewer patients and did not materially change the results of our analysis at this time. Specifically, no significant differences were found in SBP (WMD -2.76 mmHg [-6.10 to 0.58], p for effect=0.11, p for heterogeneity=0.76, I-square=0), DBP (WMD -1.40 mmHg [-3.10 to 0.29], p for effect=0.10, p for heterogeneity=0.75, I-square=0), and SCr (WMD -0.94 mmol/L [-15.55 to 13.67], p for effect=0.90, p for heterogeneity=0.30, I-square=8%).

Discussion

This meta-analysis of 1,030 patients who received renal artery intervention and medical therapy for ARAS or medical therapy alone showed a trend toward, but no statistically significant benefit of, PTRI in combination with medical therapy on SBP, DBP, or SCr. Based on this data, the effect of renal revascularisation intervention in the populations studied is likely small and inconsistent.

Intuitively, these results do not make physiologic sense. Alleviation of significant renal artery lesions should decrease the substrate for renovascular hypertension and improve renal blood flow resulting in improved renal function or at least prevent deterioration of renal function.

Several considerations need to be taken into account before definitive conclusions are drawn from these results. All the trials included in this meta-analysis were subject to potential bias. The risk of bias, defined by the Cochrane Collaboration Handbook, was at least moderate for four out of the five studies included. The three-month results from the trial by van Jaarsveld et al were considered to have a low risk of bias whereas the 12-month results of this study were considered to have a high risk of bias due to the significant crossover of patients from the medical treatment group to the angioplasty group. One of the most important contributors to bias in these studies was the varying definitions of ARAS with some authors admitting that certain patients who were randomised did not have “significant” ARAS at the time of angiography. The majority of patients in these trials were screened with Doppler ultrasound, CT, and/or MRI to determine ARAS severity prior to

Figure 3. Serum creatinine at follow-up (Mean[SD]) with corresponding forest plot. B/L: bilateral; CI: confidence interval; Rx: treatment; SD: standard deviation; U: unilateral; WMD: weighted mean difference

Figure 4. Begg funnel plots for: A) systolic blood pressure; B) diastolic blood pressure; C) serum creatinine. SE: standard error; WMD: weighted mean difference
The size of the studies is also an important consideration and the fact that only one trial had more than 100 patients in each arm is a serious limitation of the available data. This is further compounded by the fact that the total number of patients is about 1,000, which limits the power of detecting smaller effects. Moreover, 95 (19%) patients who underwent PTRI in our analysis had angioplasty alone. It is generally accepted that for ARAS, renal artery stenting is the standard of care for PTRI with higher procedural success rates and lower restenosis rates. As a result, having a significant percentage of patients who underwent only renal angioplasty may have altered the results of the analysis.

More recent studies have supported the idea that identifying patients who have clearly documented haemodynamically significant ARAS or high risk clinical features such as renal dysfunction...
and/or myocardial dysfunction may be more likely to benefit from PTRI. Leesar et al showed that a hyperaemic systolic gradient, as measured by a pressure guidewire after a 30 mg bolus dose of papaverine of >21 mmHg, identified haemodynamically significant ARAS and predicted sustained improvement in blood pressure at 12 months\(^1\). Also of note, the majority of patients in the study by Bax et al and ASTRAL had normal or near-normal renal function as measured by Scr, which likely makes it difficult to show any benefit from revascularisation on renal function. Kalra et al looked at patients with ARAS with stage four and stage five chronic kidney disease and found that PTRI improved renal function and was associated with increased survival\(^2\).

These more recent studies lend support to the argument that patient selection has been the major shortcoming of the randomised control trials so far\(^3,9,22\), and that broad conclusions regarding PTRI cannot be made at this time. The next challenge is to design studies to examine PTRI in patients with haemodynamically significant ARAS looking at clinical endpoints. Upcoming prospective studies such as CORAL\(^2\), NITER\(^2\), RAVE\(^2\) and RADAR\(^2\) will hopefully help us refine our approach and identify those patients who benefit most from PTRI and provide a larger data set that would allow a meta-analysis of renal artery stenting versus medical therapy in patients with renal artery stenosis.

**Conclusion**

The patient diagnosed with ARAS should first undergo aggressive medical therapy for hypertension. The question whether to also treat with PTRI remains. Based on the data so far available, it appears that patients who have bilateral ARAS or ARAS of a solitary functioning kidney benefit most from PTRI. In unselected patients with unilateral ARAS, the effects of revascularisation in addition to optimal medical therapy are probably small and have not been proven by our meta-analysis. However, because of the limitations of the studies published up to this point, the data needs to be interpreted with caution.

**Conflict of interest statement**

The authors have no conflict of interest to declare.

**References**


