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Jenks S, Yeoh SE, Conway BR

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[Intervention Review]

Balloon angioplasty, with and without stenting, versus medical therapy for hypertensive patients with renal artery stenosis

Sara Jenks¹, Su Ern Yeoh², Bryan R Conway³

¹Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK. ²College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK. ³British Heart Foundation Centre for Cardiovascular Science, Queens Medical Research Institute, University of Edinburgh, Edinburgh, UK

Contact address: Sara Jenks, Centre for Population Health Sciences, University of Edinburgh, Teviot Place, Edinburgh, EH8 9AG, UK.
sjenks@doctors.org.uk.

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ABSTRACT

Background

Atherosclerotic renal artery stenosis is the most common cause of secondary hypertension. Balloon angioplasty with stenting is widely used for the treatment of hypertensive patients with renal artery stenosis but the effectiveness of this procedure in treating hypertension, improving renal function and preventing adverse cardiovascular and renal events remains uncertain. This is an update, to include the results of recent, important large trials, of a review first published in 2003.

Objectives

To compare the effectiveness of balloon angioplasty (with and without stenting) with medical therapy for the treatment of atherosclerotic renal artery stenosis in patients with hypertension. The following outcomes were compared: blood pressure control, renal function, frequency of cardiovascular and renal adverse events, presence or absence of restenosis of the renal artery, side effects of medical therapy, numbers and defined daily doses of antihypertensive drugs.

Search methods

For this update the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched May 2014) and CENTRAL (2014, Issue 4). Bibliographies were also reviewed and trial authors were contacted for more information.

Selection criteria

Randomised controlled trials (RCTs) comparing balloon angioplasty with medical therapy in hypertensive patients with haemodynamically significant renal artery stenosis (greater than 50% reduction in luminal diameter) and with a minimum follow-up of six months.

Data collection and analysis

Data were extracted independently on trial design, participants, interventions and outcome measures. A formal meta-analysis was completed to assess the effect on blood pressure, renal function and cardiovascular and renal adverse events. Peto's odds ratios (ORs) and corresponding 95% confidence intervals (CI) for dichotomous outcomes and mean differences (MD) and corresponding 95% CIs for continuous variables were calculated.

Main results

Eight RCTs involving 2222 participants with renal artery stenosis were included in the review. The overall quality of evidence included in this review was moderate. Limited pooling of results was possible due to the variable presentation of some of the trial outcomes. Meta-analysis of the four studies reporting change in diastolic blood pressure (BP) found a small improvement in diastolic BP in the angioplasty group (MD -2.00 mmHg; 95% CI -3.72 to -0.27) whilst the meta-analysis of the five studies reporting change in systolic BP did not find any evidence of significant improvement (MD -1.07 mmHg; 95% CI -3.45 to 1.30). There was no significant effect on renal function as measured by serum creatinine (MD -7.99 μ mol/L; 95% CI -22.6 to 6.62). Meta-analysis of the three studies that reported the mean number of antihypertensive drugs found a small decrease in antihypertensive drug requirements for the angioplasty group (MD -0.18; 95% CI -0.34 to -0.03). Repeat angiography was only performed on a small number of participants in a single trial and it was therefore not possible to comment on restenosis of the renal artery following balloon angioplasty. Based on the results of the seven studies that reported cardiovascular and renal clinical outcomes there were no differences in cardiovascular (OR 0.91; 95% CI 0.75 to 1.11) or renal adverse events (OR 1.02; 95% CI 0.75 to 1.38) between the angioplasty and medical treatment groups. A small number of procedural complications of balloon angioplasty were reported (haematoma at the site of catheter insertion (6.5%), femoral artery pseudoaneurysm (0.7%), renal artery or kidney perforation or dissection (2.5%) as well as peri-procedural deaths (0.4%)). No side effects of medical therapy were reported.

Authors' conclusions

The available data are insufficient to conclude that revascularisation in the form of balloon angioplasty, with or without stenting, is superior to medical therapy for the treatment of atherosclerotic renal artery stenosis in patients with hypertension. However, balloon angioplasty results in a small improvement in diastolic blood pressure and a small reduction in antihypertensive drug requirements. Balloon angioplasty appears safe and results in similar numbers of cardiovascular and renal adverse events to medical therapy.

PLAIN LANGUAGE SUMMARY

Balloon angioplasty versus medical therapy for patients with renal artery obstruction and high blood pressure

Atherosclerosis can cause narrowing and hardening of the main blood vessel supplying the kidneys (renal artery stenosis) resulting in high blood pressure. Even using drugs that lower blood pressure (antihypertensives) atherosclerotic renal artery narrowing tends to progress. Poor blood flow results in a lack of oxygen (renal ischaemia) and loss of kidney function, causing kidney failure. Currently, possible treatments are medical treatment with blood pressure lowering drugs, balloon angioplasty with stent insertion (insertion of a balloon-like tube which is inflated to open up the artery followed by insertion of a metal tube which remains in place to try and keep the artery open), and surgery to reconstruct the artery. The review authors identified eight controlled trials in which a total of 2222 adults were randomised to have balloon angioplasty or drug treatment only. The overall quality of the evidence was considered to be moderate because the methodological quality of the studies varied substantially and two of the studies had not provided sufficient data to be able to assess their risk of bias. Overall, the data were insufficient to show that one treatment was better than the other for preventing loss of kidney function or restenosis of the renal artery. Those treated with balloon angioplasty may require fewer antihypertensive drugs or lower doses and experience a slight improvement in diastolic but not systolic blood pressure. Balloon angioplasty appears to be safe and there were similar numbers of renal and cardiovascular adverse events in participants treated with either approach. A small number of procedural complications of balloon angioplasty were reported (collection of blood outside the blood vessel at the site of catheter insertion (6.5%), dilated groin artery (0.7%), renal artery or kidney perforation or tear (2.5%) as well as deaths shortly before, during or after the procedure (0.4%)). No side effects of medical therapy were reported.

BACKGROUND

Description of the condition

Atherosclerotic renal artery stenosis (progressive narrowing and hardening of the main blood vessel supplying the kidneys) is the most common cause of secondary hypertension (high blood pressure) and accounts for 1% to 5% of all cases of hypertension (Derkx 1994). Prospective studies on renal angiography in patients starting dialysis identified atherosclerotic renal artery stenosis as the underlying cause of end stage renal failure in up to 20% of cases (Novick 1996). With increasing population age and widespread use of noninvasive screening tests, the frequency of documented renal artery stenosis will probably increase (Anderson 1994; Davidson 1992).

Despite antihypertensive drug therapy, atherosclerotic renal artery stenosis tends to progress, leading to renal ischaemia (poor blood flow resulting in a lack of oxygen) and loss of renal (kidney) function (Zierler 1997). The rate of progression has been reported to be 4% to 12% per year (Schreiber 1984; Tollefson 1991). The probability of survival in patients with renal artery stenosis depends on the severity of the impairment of renal function. In a cohort study of patients treated with stent revascularisation (insertion of a tube (stent) to keep the artery open and allow blood to flow through) three-year survival was 92% for patients with normal renal function, 74% for patients with mild renal failure and 52% for patients with more severe renal failure (Dorros 1998).

Description of the intervention

Currently, there are three possible therapeutic options for patients with atherosclerotic renal artery stenosis (ARAS). These are medical treatment with antihypertensive drugs, balloon angioplasty with or without stent insertion, and surgery to reconstruct the artery. In a trial comparing balloon angioplasty with surgical reconstruction for the treatment of renal artery stenosis, the interventions were equally effective in restoring patency of the obstructed vessel but balloon angioplasty was associated with fewer major complications (Weibull 1993). Surgical reconstruction does not therefore seem to offer any clinical benefit over balloon angioplasty in patients with ARAS. For that reason, this review focuses on the relative benefits of balloon angioplasty, with or without stenting, in comparison to medical treatment.

How the intervention might work

It is generally regarded that restoring renal artery patency may reduce blood pressure and prevent decline in renal function by improving renal blood flow. This prevents any further ischaemic damage to the renal parenchyma from subsequent progression of stenosis or catastrophic thrombosis. It also reduces stimulation of the renin-angiotensin system with a resultant reduction in vasoconstriction and a fall in salt and water retention. Blood pressure therefore falls and the renal parenchyma is protected from hypertension-induced damage.

Why it is important to do this review

Promising results from early observational studies suggested that balloon angioplasty was superior to medical therapy for the treatment of ARAS, with balloon angioplasty resulting in a cure from hypertension in 19% of patients and to improved blood pressure control (as measured by a reduction in the dosage of

antihypertensive drugs by at least half a tablet a day) in 52% of patients (Ramsay 1990). Based on these results balloon angioplasty continues to be widely used for the treatment of renal artery stenosis. However, these early findings have not been replicated in more recent randomised controlled trials and the optimal role for angioplasty is currently unclear. This systematic review of randomised controlled trials aimed to compare the effect of balloon angioplasty and medical treatment in hypertensive patients with atherosclerotic renal artery stenosis on blood pressure control, renal function and treatment complications. This is an update of a Cochrane Review last updated in 2008.

OBJECTIVES

The objective of this systematic review was to compare the effectiveness of balloon angioplasty (with and without stenting) with medical therapy for the treatment of atherosclerotic renal artery stenosis in patients with hypertension. The following outcomes were compared:

- blood pressure control;
- renal function;
- frequency of cardiovascular and renal adverse events;
- presence or absence of restenosis of the renal artery;
- side effects of medical therapy; and
- numbers and defined daily doses of antihypertensive drugs.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials comparing balloon angioplasty with medical treatment in hypertensive patients with haemodynamically significant atherosclerotic renal artery stenosis (greater than 50% reduction in luminal diameter). The trials were required to have a follow-up of at least six months.

Types of participants

Only trials including adults (older than 18 years of age) with hypertension (diastolic blood pressure higher or equal to 95 mmHg) and uni- or bilateral atherosclerotic renal artery stenosis (stenosis greater than 50%) were included. Trials analysing the effects of the two strategies in patients with fibromuscular dysplasia, total occlusion of the renal artery, an affected kidney smaller than 8 cm, malignant hypertension or a serum creatinine of greater than 500 µmol/L were excluded.

Types of interventions

All participants had to be randomised to either primary balloon angioplasty (with or without insertion of a stent) or medical therapy. Trials comparing surgical interventions with either angioplasty or medical therapy were excluded.

Types of outcome measures

All trials had to report clinically relevant outcome measures after a minimum follow-up of six months.

Primary outcomes

- Systolic and diastolic blood pressure

- Renal function as assessed by serum creatinine, creatinine clearance or estimated glomerular filtration rate

Secondary outcomes

- Numbers and defined daily doses (DDD) of antihypertensive drugs (one DDD is the average maintenance dose per day)
- Presence or absence of restenosis of the renal artery (defined as a stenosis of greater than 50%)
- Cardiovascular adverse events (myocardial infarction, angina, heart failure, stroke, non-procedure related symptomatic hypotension, or cardiovascular death), renal adverse events (defined as an increase of serum creatinine of more than 50%, cholesterol embolisation, development of renal failure, total occlusion of the stenotic artery, dissection of the renal artery, major complication during balloon angioplasty other than haematoma at the puncture site, or need for dialysis), procedural complications (bleeding at the arterial site), and side effects of medical therapy

Search methods for identification of studies

We did not apply any language restrictions on publications or any restrictions regarding publication status.

Electronic searches

For this update the Cochrane Peripheral Vascular Diseases (PVD) Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched May 2014) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 4) in *The Cochrane Library* (www.thecochranelibrary.com). See [Appendix 1](#) for details of the search strategy used to search CENTRAL. The Peripheral Vascular Diseases Group Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched as well as the search strategies used are described in the [Specialised Register](#) section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

Searching other resources

We searched the reference lists of articles retrieved by the electronic searches for additional citations. Where possible, we contacted trialists for further information in cases where there were missing data or doubts about whether to include the trials in the review.

Data collection and analysis

Selection of studies

For this update, two review authors (SJ and SEY) selected all trials which appeared to be relevant, on the basis of the title and abstract, for a full independent review. We then independently selected studies fulfilling the inclusion criteria for this review. Disagreements were resolved by consensus. The reason for each study's exclusion is presented in the [Characteristics of excluded studies](#) table.

Data extraction and management

Two review authors (SJ and SEY) extracted data independently. The following items were noted.

- Methods: allocation concealment, method of randomisation, presence or absence of run-in period, length of follow-up, dropouts and crossovers, co-interventions and other potential confounders, blinding of evaluators, methods of assessment of blood pressure and renal function.
- Participants: age, gender, mean blood pressure, duration of hypertension, number of antihypertensive agents, grade of stenosis, renal function at the beginning of the study.
- Interventions: numbers and types of additional procedures such as stenting and surgery in the balloon angioplasty group, type and number of antihypertensive drugs and additional interventions in the medical treatment group.
- Outcomes: mean systolic and diastolic blood pressure differences at end of follow-up or at two years if follow-up was longer than two years, differences in renal function at two years or the end of follow-up, angiographic assessment of vessel restenosis, cardiovascular and renal adverse events, procedural complications and drug side effects.

Disagreement on data extraction was resolved by consensus.

Authors of publications were contacted for additional details. Data were entered into Review Manager (RevMan), which is the systematic review software from The Cochrane Collaboration ([RevMan 2012](#)).

Assessment of risk of bias in included studies

Two review authors (SJ and SEY) independently assessed the methodological quality of included trials using the risk of bias criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We were not blinded to the authors or results of the trials. The risk of bias tool provides a protocol for the assessment of allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other potential sources of bias. For each of the six domains, we assessed the risk of bias as 'low', 'high' or 'unclear', with unclear indicating that there was insufficient information available to permit an assessment of either low or high risk of bias. Disagreements were resolved by consensus.

Measures of treatment effect

All analyses were conducted on an intention-to-treat basis. We set out to pool data on changes in systolic and diastolic BP, serum creatinine, and the numbers of antihypertensive drugs from each trial to arrive at an estimate of the overall effectiveness of balloon angioplasty. For continuous outcomes such as BP and creatinine we presented the statistical analysis results as mean differences (MD) with 95% confidence intervals (CI), and for dichotomous outcomes as Peto odds ratios (OR) with 95% CIs. Not all studies presented standard deviations (SD) for the change in BP or the number of antihypertensive drugs and, where necessary, these were imputed from the available data using methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

All the included studies had provided the SDs for serum creatinine measurements during follow-up and serum creatinines were therefore chosen to measure treatment effect rather than changes in serum creatinine from baseline, for which no SDs were provided. However, there are limitations in presenting serum creatinine at the

end of follow-up, the main one being that this does not take into account any differences in serum creatinine between angioplasty and medical treatment groups at baseline.

Unit of analysis issues

The unit of randomisation was the individual participant in all included studies. All of the included trials collected follow-up data at different points in time, ranging from one month to five years. In order to enable pooling of the BP and creatinine results, data from either the end of follow-up or two years into follow-up were pooled. Two years into follow-up was chosen as one study followed up participants for five years but by the end of the five-year follow-up many participants had either died or been lost to follow-up. It was therefore felt to be more appropriate to analyse the two-year follow-up data for this study.

Dealing with missing data

Where necessary, and wherever possible, we contacted the authors of included trials to clarify data and obtain missing data. Not all studies presented the SDs for change in BP or the number of antihypertensive drugs and, where necessary, these were imputed from the available data using methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We assessed heterogeneity of trials with the I^2 statistic, using the analysis programme within RevMan, with heterogeneity being identified by $I^2 > 50\%$. No evidence of heterogeneity was found and therefore a fixed-effect model was applied for each meta-analysis.

Assessment of reporting biases

Since only eight trials were included in this systematic review, no funnel plots to evaluate potential publication bias were prepared.

Data synthesis

We performed a meta-analysis where two or more studies were available. Results for serum creatinine were stated in $\mu\text{mol/L}$. Changes in BP were stated in mmHg. Continuous variables were reported as MDs with 95% CIs and dichotomous outcomes were reported as ORs with 95% CIs; a P value less than 0.05 was considered as evidence of a statistically significant difference between the balloon angioplasty and medical treatment groups. All meta-analyses were based on a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

The available data did not permit the pre-planned subgroup analyses for patients with ostial versus non-ostial stenosis, uni-versus bilateral stenosis, or trials of high and low risk of bias. We performed a subgroup analysis restricting all the meta-analyses to the five studies that carried out angioplasty with stenting rather than angioplasty alone. There was no evidence of heterogeneity (defined as $I^2 > 50\%$).

Sensitivity analysis

The [ASTRAL](#) and [CORAL](#) trials were much larger than any of the other included studies and a sensitivity analysis was carried out to establish whether either of these trials heavily influenced any results.

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Results of the search

See [Figure 1](#).

Figure 1. Study flow diagram.

Five additional studies ([ASTRAL](#); [CORAL](#); [NITER](#); [RADAR](#); [STAR](#)) were included in the update, making a total of eight included studies ([ASTRAL](#); [CORAL](#); [DRASTIC](#); [EMMA](#); [NITER](#); [RADAR](#); [SNRASC](#); [STAR](#)). Three of these studies had been ongoing studies in the previous version of the review ([CORAL](#); [NITER](#); [STAR](#)).

Two additional ongoing studies were identified, [METRAS](#) ([Rossi 2012](#)) and [RAVE](#) ([Tobe 2007](#)).

Included studies

This review includes eight eligible trials: three from the original review ([DRASTIC](#); [EMMA](#); [SNRASC](#)) and five from the update ([ASTRAL](#); [CORAL](#); [NITER](#); [RADAR](#); [STAR](#)). Seven trials were fully randomised ([ASTRAL](#); [CORAL](#); [DRASTIC](#); [EMMA](#); [NITER](#); [RADAR](#); [STAR](#)) whilst one trial ([SNRASC](#)) reported results of randomised and non-randomised participants separately. We only considered the results of the randomised participants for this review.

No randomised controlled trial with a shorter follow-up than six months was found.

Since only eight trials were identified, no kappa test to assess inter-rater agreement was performed.

In all eight included trials hypertensive men and women with renal artery stenosis were randomly allocated to balloon angioplasty or medical therapy with antihypertensive drugs. The number of included participants in the studies ranged from 49 to 947. Follow-up was six months in the [EMMA](#) and [SNRASC](#) trials, 12 months in the [DRASTIC](#) trial, 24 months in the [STAR](#) trial, 32 months in the [RADAR](#) trial, 43 months in the [NITER](#) and [CORAL](#) trials and five years in the [ASTRAL](#) trial. The [EMMA](#) and [SNRASC](#) trials had two to six-week run-in periods on standardised antihypertensive treatment. In the [EMMA](#) and [DRASTIC](#) trials antihypertensive drug therapy was stopped at the time of the intervention in participants assigned to balloon angioplasty, and subsequently reinstated if necessary. In the [ASTRAL](#), [CORAL](#), [SNRASC](#) and [STAR](#) trials antihypertensive drug therapy was continued after balloon angioplasty. Information on the presence or absence of any run-in period or the discontinuation of antihypertensive drug therapy was not available for the [NITER](#) and [RADAR](#) trials.

Not all participants allocated to balloon angioplasty underwent the procedure, predominantly due to minimal stenosis being present at the time of angiography. In the [ASTRAL](#) trial 335 of the 403 (83%) participants allocated to balloon angioplasty underwent attempted revascularisation compared with 46 out of 64 (72%) in the [STAR](#) trial and 442 out of 467 (95%) in the [CORAL](#) trial. All of these three trials ([ASTRAL](#); [CORAL](#); [STAR](#)) analysed their data on an intention-to-treat basis. All participants allocated to balloon angioplasty in the [EMMA](#), [DRASTIC](#), [SNRASC](#) and [NITER](#) trials underwent attempted revascularisation, although in five participants in the intervention group in the [SNRASC](#) trial this was in the form of either a vein bypass or a nephrectomy. Data for the [RADAR](#) trial were not available.

In the [SNRASC](#) trial no patient in the balloon angioplasty group underwent stent insertion. In the [DRASTIC](#) trial 2 of 56 (4%) participants assigned to balloon angioplasty received a stent compared with 2 of 23 (9%) participants in the [EMMA](#) trial; 46 of 64 (72%) in the [STAR](#) trial; 317 of 403 (79%) in the [ASTRAL](#) trial and 442 out of 467 (95%) in the [CORAL](#) trial. All of the participants assigned

to angioplasty underwent stent insertion in the [NITER](#) trial. Data for the [RADAR](#) trial were not available.

There was a large variation between trials in the proportion of participants crossing over from medical treatment to balloon angioplasty. In the [EMMA](#) trial seven of 26 (27%) participants assigned to medical therapy stopped drug treatment early due to refractory hypertension (defined as diastolic BP greater than 104 mmHg despite a maximal tolerated antihypertensive regimen) and subsequently underwent angioplasty. The clinical characteristics of these seven participants immediately before angioplasty were used for data analysis. In the [DRASTIC](#) trial 22 of 50 (44%) participants underwent angioplasty due to diastolic BP measures greater than 95 mmHg despite treatment with three or more antihypertensive drugs; or progressive renovascular occlusive disease, defined as an increase of at least 18 µmol/L in serum creatinine or worsening of the time-activity renogram on scintigraphy, after three months of medical therapy. The data from these participants were analysed in the medical therapy group at 12 months follow-up although they had undergone balloon angioplasty after three months follow-up. In the [STAR](#) trial one out of 76 participants (1%) underwent angioplasty with stenting due to refractory hypertension (defined as BP greater than > 180/100 mmHg despite a maximal tolerated antihypertensive regime). The data for this one participant were included in the medical therapy group follow-up data. In the [ASTRAL](#) trial 24 out of 403 (6%) underwent balloon angioplasty. The specific reasons for participants crossing over were not given and these participants were included in the medical treatment group follow-up data. In the [CORAL](#) trial 19 out of 480 (4%) crossed over. They were included in the intention-to-treat analysis in the medical treatment group. No participants in the [SNRASC](#) trial that were assigned to medical treatment subsequently underwent balloon angioplasty. Data for the [RADAR](#) and [NITER](#) trials were not available.

In the [EMMA](#) trial ambulatory BP was the primary outcome of the study, whereas the [SNRASC](#) and [DRASTIC](#) trials used office BP as the primary outcome measure (office BP is the average of three sitting BP measurements taken in the presence of a physician after five minutes rest). The more recent [ASTRAL](#) and [STAR](#) trials both defined renal endpoints as their primary outcomes with the [ASTRAL](#) trial assessing the change in renal function (measured by the mean slope of the reciprocal of the serum creatinine level over time) and the [STAR](#) trial assessing worsening renal function (defined as a 20% or greater decrease in estimated creatinine clearance compared with baseline). Changes in BP were measured in both studies as a secondary outcome. The primary outcome of the [NITER](#) trial was unclear as full details of this study have not yet been published. The [CORAL](#) trial had a primary outcome that was a composite of adverse cardiovascular and renal events. The [RADAR](#) trial primary endpoint was the change in estimated glomerular filtration (eGFR) rate over 12 months.

The [SNRASC](#) trial presented the results for participants with bilateral renal artery stenosis separately from those with unilateral stenosis. These results were pooled to enable comparison with the five other studies which did not present separate analyses for participants with uni- and bilateral stenoses.

For further details see [Characteristics of included studies](#).

Excluded studies

Two studies were excluded in this update because they did not meet the inclusion criteria. One was excluded as it was not a randomised controlled trial ([Ziakka 2008](#)) and the other as it compared surgery to balloon angioplasty without a medical treatment control group ([Balzer 2009](#)). See [Characteristics of excluded studies](#) for further details.

Risk of bias in included studies

The methodologic quality of the included trials varied substantially. See [Figure 2](#) and [Figure 3](#) for a graphical presentation of the risk of bias. Insufficient information was the main reason for an 'unclear' rating being given. The methods used for two of the trials ([NITER](#); [RADAR](#)) have not yet been fully published and there was therefore insufficient information to assess the risk of bias of these studies. The description of bias given below therefore relates to the six studies for which methodological information was available.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ASTRAL	+	+	-	?	+	+	-
CORAL	+	+	-	+	+	+	?
DRASTIC	+	+	-	?	+	+	-
EMMA	?	+	-	+	+	+	+
NITER	?	?	-	?	?	?	?
RADAR	?	?	-	?	?	?	?
SNRASCG	?	?	-	+	+	+	-
STAR	+	+	-	?	+	+	-

Allocation

Four of the studies adequately described the random sequence generation used (ASTRAL; CORAL; DRASTIC; STAR) with all three using computer generated randomisation. The remaining studies

(EMMA; SNRASCG) did not state the method used to generate the allocation sequence and therefore the risk of selection bias was unclear for these studies.

Blinding

Participants could not be blinded due to the nature of the trials. In one trial ([SNRASC](#)) the evaluators performing BP measurement were blinded to the participants' allocation. In another trial ([EMMA](#)) the evaluators were not blinded but an objective outcome measurement (ambulatory BP monitoring) was used. In other trials ([ASTRAL](#); [CORAL](#); [DRASTIC](#); [STAR](#)) the exact method of BP measurement and whether evaluators were blinded to participants' allocation was unclear.

Incomplete outcome data

All six studies with available methodological information ([ASTRAL](#); [CORAL](#); [DRASTIC](#); [EMMA](#); [SNRASC](#); [STAR](#)) had only small numbers of participants lost to follow-up and were deemed to be at low risk of attrition bias.

Selective reporting

All six studies with available methodological information ([ASTRAL](#); [CORAL](#); [DRASTIC](#); [EMMA](#); [SNRASC](#); [STAR](#)) reported on all the pre-specified outcomes and were therefore judged to be at low risk of reporting bias.

Other potential sources of bias

Four studies were felt to be at high risk of other sources of bias. This was due to large numbers of participants crossing over from medical treatment to balloon angioplasty ([DRASTIC](#)), significant numbers of participants allocated to angioplasty not undergoing revascularisation ([ASTRAL](#); [STAR](#)), or participants undergoing surgical interventions in place of angioplasty ([SNRASC](#)). One trial ([ASTRAL](#)) introduced a source of heterogeneity and bias as it enrolled participants into the trial only if their clinician was uncertain as to whether revascularisation would be of clinical benefit. Therefore, patients who otherwise met the study criteria but were felt to be likely to benefit from angioplasty were excluded from the study.

Effects of interventions

Systolic and diastolic blood pressure

Five of the eight trials reported systolic BP as an outcome and data were pooled from the 1743 participants in these five trials ([ASTRAL](#); [CORAL](#); [DRASTIC](#); [EMMA](#); [STAR](#)). Only four of the seven trials reported diastolic BP and data were pooled from the 809 participants in these four trials ([ASTRAL](#); [DRASTIC](#); [EMMA](#); [STAR](#)). One of these trials ([STAR](#)) reported BP at either the end of two-year follow-up or when participants reached the primary endpoint (defined as a greater than 20% decline in creatinine clearance). Another trial ([ASTRAL](#)) reported BP results for each year during the five-year follow-up period and the BP results from the end of the second year of follow-up were selected for inclusion in the meta-analysis. The [EMMA](#) and [DRASTIC](#) trials reported BP results at the end of the six-month and 12-month follow-up periods, respectively. The [CORAL](#) trial only reported changes in systolic BP results at the end of follow-up, where the median follow-up was 43 months.

Only the [EMMA](#) and [CORAL](#) trials reported SDs for change in BP during follow-up. SDs were therefore imputed for the [ASTRAL](#), [DRASTIC](#) and [STAR](#) trials using the data available from the [EMMA](#) trial to calculate a correlation coefficient, as per the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Data from the [SNRASC](#) trial were not pooled as the results were reported separately for participants with unilateral ($n = 27$) and bilateral renal artery stenosis ($n = 28$); the authors did not report any significant differences in BP after six months. In the bilateral group, BP decreased by 19/4 (systolic/diastolic) mmHg in the balloon angioplasty group and by 2/2 mmHg in the medical therapy group. In the unilateral group, BP decreased by 9/5 mmHg in the angioplasty group and by 8/6 mmHg in the medical therapy group. No P values or SDs were indicated. Data from the [NITER](#) and [RADAR](#) trials were not available.

The pooled change in BP in the balloon angioplasty group in comparison to the medical treatment group, from the trials included in the meta-analysis, showed a non-significant MD of -1.07 mmHg for systolic BP and a significant MD of -2.00 mmHg for diastolic BP (95% CI -3.45 to 1.30; $P = 0.38$, $I^2 = 0\%$ ([Analysis 1.1](#)); 95% CI -3.72 to -0.27; $P = 0.02$, $I^2 = 4\%$ ([Analysis 1.2](#)), respectively).

Renal function as assessed by serum creatinine, creatinine clearance or estimated glomerular filtration rate (eGFR)

The [ASTRAL](#), [STAR](#) and [SNRASC](#) trials all reported serum creatinine as an outcome and the data were pooled from the 725 participants in these three trials. The [STAR](#) trial reported serum creatinine at either the end of two-year follow-up or when participants reached the primary endpoint (defined as a greater than 20% decline in creatinine clearance). The [ASTRAL](#) trial reported creatinine results for each year during the five-year follow-up period; the creatinine results from the end of the second year of follow-up were selected for inclusion in the meta-analysis. The [SNRASC](#) trial reported creatinine results at the end of the six-month follow-up period.

The other five trials could not be included in the meta-analysis as they all reported on different renal outcomes ([CORAL](#); [DRASTIC](#); [EMMA](#); [NITER](#); [RADAR](#)). The [EMMA](#) trial reported creatinine clearance, the [DRASTIC](#) trial reported median serum creatinine and creatinine clearance, the [NITER](#) trial reported worsening renal failure, the [RADAR](#) trial reported change in eGFR after 12 months, and the [CORAL](#) trial reported progressive renal insufficiency.

There was no significant difference in serum creatinine, creatinine clearance, worsening renal failure or progressive renal insufficiency between the angioplasty and medical treatment groups in any of the eight individual trials.

The pooled serum creatinine results from the three trials included in the meta-analysis identified a non-statistically significant MD of -7.99 $\mu\text{mol/L}$ (95% CI -22.6 to 6.62; $P = 0.28$, $I^2 = 12\%$) in the balloon angioplasty group compared to the medical treatment group ([Analysis 1.3](#)).

Numbers and defined daily doses of antihypertensive drugs

The [CORAL](#), [DRASTIC](#) and [ASTRAL](#) trials all reported the mean number of antihypertensive drugs as an outcome and data were pooled from the 1717 participants. The [DRASTIC](#) trial reported the mean number of antihypertensive drugs after one year and the [CORAL](#) trial at the end of follow-up. SDs were available for both the [CORAL](#) and [DRASTIC](#) trials. The [ASTRAL](#) trial reported the mean number of antihypertensive drugs after one year of follow-up. SDs were not reported and these were imputed by calculating the mean of the SDs from the [CORAL](#) and [DRASTIC](#) trials. The pooled results from the three trials included in the meta-analysis found that there was a statistically significant MD of -0.18 (95% CI -0.34 to -0.03;

$P = 0.02$, $I^2 = 0\%$) for the number of antihypertensive drugs in the angioplasty group compared to the medical treatment group (Analysis 1.4).

The EMMA trial reported the median defined daily doses (DDD) only, with a significant decrease in median DDD in the balloon angioplasty group. The median DDD at baseline was 1.33 in both groups and decreased to 1.0 (range 0 to 6) in the balloon angioplasty group. In the medical therapy group the median DDD increased to 1.78 (range 0 to 4.3; $P = 0.009$) for the difference between the two groups. The SNRASCG and STAR trials only indicated that there were no statistically significant differences in the number of antihypertensive drugs used at the end of follow-up without providing more specific information. Data from the NITER and RADAR trials were not available for this outcome.

Presence or absence of restenosis of the renal artery

Restenosis rates could not be assessed in the SNRASCG trial because they did not indicate separate restenosis rates for randomised and non-randomised participants. In the EMMA trial none of the stenotic arteries in either of the two groups were totally occluded on the termination angiogram, but no data on restenosis rates were indicated. In the DRASTIC trial angiography was performed in 48 of 56 participants in the angioplasty group, and in 43 of 50 participants in the medical therapy group. Significantly more participants (52%) assigned to balloon angioplasty compared to medical therapy (19%) had a stenosis of less than 50% after 12 months (OR 4.2; 95% CI 1.8 to 9.8). In the STAR trial angiography was repeated in five participants in the intervention group only. This was due to a decline in renal function, and two of the five were found to have restenosis and this was revascularised. Neither of the CORAL or ASTRAL trials performed repeat imaging studies on participants to assess restenosis rates during follow-up. Data for the NITER and RADAR trials were not available.

Cardiovascular and renal adverse events, procedural complications and side effects of medical therapy

The DRASTIC trial reported adverse events during a follow-up of 12 months. The complication rate in the DRASTIC trial (table 2 of their paper) was erroneously reported as number rather than percentage of participants according to the principal author. The EMMA and SNRASCG trials reported adverse events during a follow-up of six months, the STAR trial during a follow-up of 24 months, the NITER and CORAL trials during a follow-up of 43 months and the ASTRAL trial during a follow-up of five years (Table 1; Table 2). Data for the RADAR trial were not available.

There were similar numbers of cardiovascular and renal adverse events in participants treated with balloon angioplasty relative to medical therapy. Using the correct values for the DRASTIC trial, overall there were 366 out of 1039 (32%) major cardiovascular adverse events and 99 out of 1036 (10%) renal adverse events in participants undergoing balloon angioplasty compared with 395 out of 1071 (37%) and 100 out of 1068 (9%), respectively, in participants treated with medical therapy (OR 0.91; 95% CI 0.75 to 1.11; $I^2 = 0\%$ for cardiovascular adverse events (Analysis 1.5) and OR 1.02; 95% CI 0.75 to 1.38; $I^2 = 42\%$ (Analysis 1.6) for renal adverse events).

Of the participants who underwent balloon angioplasty, 64 out of 987 (6.5%) developed a significant haematoma at the site of catheter insertion, using individual trial definitions for

this complication, seven out of 987 (0.7%) femoral artery pseudoaneurysm, 25 out of 987 (2.5%) renal artery or kidney perforation or dissection. There were four (0.4%) peri-procedural deaths (defined as death from procedure-related causes within 30 days of the procedure): two from the STAR trial following a perforated renal artery, and two from the ASTRAL trial due to cardiac causes.

No trial reported side effects of medical therapy.

Subgroup analysis

A subgroup analysis restricting all the meta-analyses to the five studies that carried out angioplasty with stenting (ASTRAL; CORAL; NITER; RADAR; STAR) did not significantly alter any of the results apart from the change in diastolic BP, where the MD between the angioplasty and the medical treatment group reduced and became non-significant (MD -1.24 mmHg, 95% CI -3.23 to 0.75; $P = 0.22$, $I^2 = 0\%$).

The available data did not permit the pre-planned subgroup analyses for patients with ostial versus non-ostial stenosis, uni-versus bilateral stenosis, or trials of high and low risk of bias.

Sensitivity analysis

The ASTRAL trial had 806 participants and the CORAL trial had 947 participants; these trials therefore accounted for the majority of the participants included in the meta-analysis. A sensitivity analysis was carried out and this showed that these studies did not heavily influence any of the meta-analysis results with the exception of the meta-analysis of the number of antihypertensive drugs. If either the CORAL or ASTRAL trial was excluded from this meta-analysis then the MD between antihypertensive drug requirements in the angioplasty group relative to the medical treatment group reduced and became non-significant (MD -0.15; 95% CI -0.43 to 0.12; $P = 0.27$, $I^2 = 10\%$ and MD -0.18; 95% CI -0.36 to 0.00; $P = 0.05$, $I^2 = 14\%$, respectively).

DISCUSSION

We reviewed eight randomised controlled trials comparing medical treatment to balloon angioplasty, with or without stenting, in hypertensive patients with atherosclerotic renal artery stenosis.

Summary of main results

Our meta-analysis did not identify any statistically significant difference in serum creatinine or in cardiovascular or renal adverse events between the balloon angioplasty and medical treatment arms. There was a small improvement in diastolic BP and a small reduction in the number of antihypertensive drugs required in the angioplasty group relative to the medical treatment group. However, the quality and methodology of the studies is variable and not all the available data from all eight studies could be combined as part of a pooled analysis.

There is a non-significant trend towards a reduction in cardiovascular and renal adverse events in the angioplasty group relative to the medical treatment group. A type beta error with false acceptance of the null hypothesis is therefore a possibility and larger trials with increased power are required to address this issue.

A small number of procedural complications of balloon angioplasty were reported (haematoma at the site of catheter insertion (6.5%),

femoral artery pseudoaneurysm (0.7%), renal artery or kidney perforation or dissection (2.5%) as well as peri-procedural deaths (0.4%). No side effects of medical therapy were reported.

Overall, the available evidence suggests that the benefits of balloon angioplasty for patients with renal artery stenosis are at best limited to a small improvement in diastolic blood pressure (BP) and a small reduction in antihypertensive medication.

Overall completeness and applicability of evidence

The quality of the included studies is variable and overall there is insufficient evidence to determine whether or not patients with renal artery stenosis benefit clinically from balloon angioplasty. None of the studies presented data separately according to the severity of the renal artery stenosis, and only one trial ([SNRASCG](#)) analysed results separately for participants with unilateral and bilateral stenosis. We were therefore unable to carry out any subgroup analyses to try and identify groups of patients who may potentially have a greater clinical benefit from angioplasty.

An additional limitation to the analysis was the fact that only two studies ([CORAL](#); [EMMA](#)) reported SDs for changes in systolic BP and only one study ([EMMA](#)) for the change in diastolic BP during follow-up. SDs were therefore imputed for the five other studies included in the meta-analysis ([ASTRAL](#); [DRASTIC](#); [NITER](#); [SNRASCG](#); [STAR](#)) using the available data from the [EMMA](#) trial. Additionally, one study ([ASTRAL](#)) did not report SDs for the mean number of antihypertensive drugs and these were imputed using the SD data available for the other two included studies ([CORAL](#); [DRASTIC](#)). The imputation of SDs, particularly in the changes in systolic and diastolic BP meta-analyses where three out of five and four out of five studies, respectively, were missing SDs, may reduce the validity of the meta-analysis results.

It should also be noted that angiographic techniques are constantly improving, with the five more recent trials ([ASTRAL](#); [CORAL](#); [NITER](#); [RADAR](#); [STAR](#)) all comparing angioplasty with stent insertion to medical treatment rather than angioplasty alone. The most recently published trial ([CORAL](#)) also included the use of distal protection devices. As yet, these technological advances do not appear to have translated into improved patient outcomes. A subgroup analysis restricting all the meta-analyses to the five studies that carried out angioplasty with stenting ([ASTRAL](#); [CORAL](#); [NITER](#); [RADAR](#); [STAR](#)) did not significantly alter any of the results apart from the change in diastolic BP, where the mean difference (MD) between the angioplasty and the medical treatment group reduced and became non-significant (MD -1.24 mmHg; 95% CI -3.23 to 0.75; $P = 0.22$, $I^2 = 0\%$).

Quality of the evidence

A significant limitation of this review is that several of the studies did not provide enough information to accurately judge the risk of bias, and the majority of studies were considered to be at high risk of bias in at least two areas. Selection bias could not be determined in half of studies as authors failed to report the methods used for random number generation and concealing allocation. Due to the nature of the trials, allocation concealment was not possible. Detection bias could not be assessed for the majority of the trials as insufficient information was provided with regards to the blinding of personnel. The majority of studies were low risk for attrition

and reporting bias as they had reported on all pre-specified study outcomes and accounted for all participants.

Four of the studies were considered to be high risk for other sources of bias, which was largely due to either significant numbers of participants crossing over from medical treatment to balloon angioplasty or not all participants allocated to angioplasty undergoing revascularisation. This may have reduced any benefits of angioplasty relative to medical treatment. One trial enrolled participants only if their clinician was uncertain as to whether revascularisation would be of clinical benefit ([ASTRAL](#)). Therefore, patients who otherwise met the study inclusion criteria but were felt to be likely to benefit from angioplasty were excluded from the study, and this may have resulted in the potential benefits of angioplasty being underestimated.

A further source of heterogeneity is the different BP regimes employed in the different studies. In some of the studies specific antihypertensive treatment protocols were provided ([CORAL](#); [EMMA](#); [STAR](#)) whilst in other studies ([ASTRAL](#)) local centres used their own treatment protocols.

The [ASTRAL](#) trial had 806 participants and the [CORAL](#) trial had 947 participants, and these trials therefore accounted for the majority of the participants included in the meta-analysis. A sensitivity analysis was carried out and this showed that these studies did not heavily influence any of the meta-analysis results, with the exception of the meta-analysis of the number of antihypertensive drugs. If either the [CORAL](#) or [ASTRAL](#) trial was excluded from this meta-analysis then the MD between antihypertensive drug requirements in the angioplasty group relative to the medical treatment group reduced and became non-significant (MD -0.15; 95% CI -0.43 to 0.12; $P = 0.27$, $I^2 = 10\%$ and MD -0.18; 95% CI -0.36 to 0.00; $P = 0.05$, $I^2 = 14\%$, respectively).

The overall quality of the evidence was considered to be moderate because the methodological quality of the studies varied substantially and two of the studies had not provided sufficient data to be able to assess their risk of bias.

Potential biases in the review process

In this systematic review we identified all the randomised controlled trials that compared angioplasty to medical therapy in hypertensive patients with haemodynamically significant renal artery stenosis. We believe our search for randomised controlled trials has been inclusive and that our standardised methods of study selection and data extraction should not have introduced bias. We were not always able to pool the available data due to the variable presentation of some of the trial outcomes.

Serum creatinine at two years or end of follow-up was selected as an outcome as SD data were not available for change in creatinine during follow-up. The main limitation of presenting final serum creatinine levels as an outcome is that the final value does not take into account the change from baseline.

Only the [EMMA](#) and [CORAL](#) trials reported SDs for change in BP during follow-up. SDs were therefore imputed for the [ASTRAL](#), [DRASTIC](#) and [STAR](#) trials from the available data using methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Similarly, only the [DRASTIC](#) and [CORAL](#) trials reported SDs for the mean number of antihypertensive drugs and SDs were therefore imputed for the [ASTRAL](#) trial.

Agreements and disagreements with other studies or reviews

To date, one other meta-analysis has examined the effect of angioplasty on atherosclerotic renal artery stenosis (Kumbhani 2011). The findings of this meta-analysis were similar, with the authors concluding that although there may be a small reduction in the use of antihypertensive medications there was no evidence that angioplasty improved serum creatinine or clinical outcomes when compared to optimal medical treatment.

AUTHORS' CONCLUSIONS

Implications for practice

The available data does not allow us to conclude that balloon angioplasty is superior to medical therapy in lowering the blood pressure of patients with renal artery stenosis in whom blood pressure can be controlled with medical therapy. However, angioplasty does appear to be safe and there is no evidence of increased complications relative to medical therapy.

Overall, the data does not provide any evidence that angioplasty reduces the incidence of cardiovascular or renal adverse events when compared to the best available medical therapy. Angioplasty does seem to have a small drug-saving effect and may result in a small improvement in diastolic blood pressure, but the clinical importance of these benefits is unclear as there is no evidence that these improvements translate into improved cardiovascular and renal outcomes.

Implications for research

Further well-conducted randomised controlled trials comparing the effect of medical therapy and balloon angioplasty in

patients with atherosclerotic renal artery stenosis should be performed to overcome methodological errors evident in the published literature. These trials should ensure a sufficient number of participants are included to provide statistical power, unambiguous participant selection criteria, blinded outcome assessment, and follow-up of three or more years in order to evaluate the long-term effect of the interventions on the preservation of renal function. Studies specifically designed to investigate whether certain patients (for example those with renal artery stenosis > 70% or severe bilateral stenosis, rapidly deteriorating renal function, or flash pulmonary oedema) may be more likely to benefit clinically from angioplasty would also be useful. Additional studies should be carried out to determine whether investigations, such as Doppler ultrasound waveform analysis, may aid in the identification of patients with true renovascular hypertension who may be more likely to benefit from revascularisation. The following outcome parameters should be considered for any future study: 1) serum creatinine, creatinine clearance or estimated glomerular filtration rate; 2) systolic and diastolic blood pressure; 3) cardiovascular and renal adverse events; 4) numbers of antihypertensive medications; and 5) peri-procedural complications. A cost-effectiveness analysis, taking into account patient preference, would also be desirable.

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Nordmann 2003

Nordmann AJ, Logan AG. Balloon angioplasty versus medical therapy for hypertensive patients with renal artery obstruction. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [DOI: [10.1002/14651858.CD002944](https://doi.org/10.1002/14651858.CD002944)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ASTRAL

Methods	Multi-centre, randomised controlled clinical trial Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no, 38 patients (5%) had withdrawn or been lost to follow-up. 20 from the BA group and 18 from the MT group. No reasons given for participants being lost to follow-up Blinding of outcome measurement: unclear (but primary outcome was serum creatinine measurement)
Participants	806 patients between 42 and 88 years (mean age 70.5 years) 403 in each group 37% women Inclusion criteria: uncontrolled or refractory hypertension OR unexplained renal dysfunction with evidence of substantial anatomical atherosclerotic stenosis in at least one renal artery that was considered potentially suitable for endovascular revascularisation. Physician uncertain as to whether revascularisation would provide a worthwhile clinical benefit Exclusion criteria: previous revascularisation, non-atheromatous cardiovascular disease, surgical intervention required, If the medical team felt it was likely that revascularisation would be required within 6 months 53 centres in the United Kingdom, 3 in Australia, 1 in New Zealand Enrolment period: between September 2000 through October 2007
Interventions	No run-in period Patients assigned to BA ± stent insertion underwent this within 4 weeks of randomisation Decision to stent was decided by local practitioners. Renal protection devices were not used Follow-up was at 1 to 3 months, 6 to 8 months, and 1 year after randomisation followed by annual follow up for 5 years. Median follow-up was 34 months

ASTRAL (Continued)

Antihypertensive regime was not fixed and BP was managed according to local hospital protocols

403 patients were assigned to revascularisation (335 underwent attempted revascularisation 18 of these were failed procedures due to a failure to cross the stenosis (13) or lesion undilatable (5); 68 were not revascularised due to minimal stenosis (33), patient not suitable for revascularisation (6), consent withdrawn (6), other or unknown (13)

403 assigned to MT, 24 (6%) crossed over to revascularisation

Outcomes	Renal function (measured by the reciprocal of serum Cr) BP Time to renal and major cardiovascular events and mortality Complications
Notes	Revascularisation was attempted in 335 out of 403 patients and was deemed to be technically successful in 317 95% undergoing revascularisation received a stent 103 participants had bilateral disease Complications: see Table 1 and Table 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computerized minimized-randomisation procedure"
Allocation concealment (selection bias)	Low risk	"Randomization was determined by means of a telephone call to the central trial office or through an online randomizations system"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind for this type of intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Primary outcome based on serum creatinine measurements. No details provided with regard to the measurement of BP
Incomplete outcome data (attrition bias) All outcomes	Low risk	38 patients (5%) had withdrawn or been lost to follow-up. 20 from the BA group and 18 from the MT group
Selective reporting (reporting bias)	Low risk	Reported on all appropriate outcomes
Other bias	High risk	Only 335 of the 403 (83.1%) participants allocated to balloon angioplasty underwent attempted revascularisation Patients were enrolled in the trial only if their clinician was uncertain as to whether revascularisation would be of clinical benefit. Therefore patients who otherwise met the study criteria but were felt to be likely to benefit from angioplasty were excluded from the study

CORAL

Methods	<p>Multi-centre randomised controlled trial</p> <p>Blinding of randomisation: yes</p> <p>Blinding of intervention: no</p> <p>Complete follow-up: no, 143 patients (15%) either withdrew or were lost to follow-up, 62 from the stent group and 81 from the MT group. 16 participants enrolled at a single site were also excluded due to concerns regarding the informed consent and eligibility of participants enrolled at that site</p> <p>Blinding of outcome measurement: Yes (a single endpoint committee whose members were unaware of the group assignments adjudicated all endpoints)</p>
Participants	<p>947 participants (mean age 69 ± 9 years)</p> <p>467 assigned to stent + MT, 480 to MT alone</p> <p>49% women in stent group, 51% women in MT group</p> <p>Inclusion criteria: atherosclerotic renal artery stenosis (defined as stenosis of 80% to 99% or 60% to 79% with a systolic pressure gradient of > 20 mmHg) and elevated blood pressure (defined as SBP > 155 mmHg) or chronic kidney disease (defined as an MDRD eGFR < 60 mL/min/1.73m²), or both</p> <p>Exclusion criteria: renal artery stenosis due to fibromuscular dysplasia, chronic kidney disease from a cause other than ischaemic nephropathy or associated with a serum creatinine of > 354 μmol/L (4 mg/dL), kidney length of < 7 cm and a lesion that could not be treated with the use of a single stent</p> <p>112 centres</p> <p>Enrolment period: between May 2005 through January 2010</p>
Interventions	<p>No run-in period</p> <p>Patients assigned to revascularisation underwent stent insertion. Embolic protection devices were used</p> <p>Median follow-up was 43 months (interquartile range 31 to 55)</p> <p>Antihypertensive regime was fixed (candesartan $\pm$ hydrochlorothiazide and combination amlodipine-atorvastatin) and BP treatment was managed according to study protocol (target BP $< 140/90$ if no co-existing conditions or $< 130/80$ if diabetes or CKD)</p> <p>467 patients were assigned to revascularisation (442 underwent revascularisation and 25 did not. Of the 25 who did not undergo stenting, 13 did not meet the lesion criteria, 3 could not have the stent delivered and 9 did not have the stent procedure attempted)</p> <p>480 assigned to MT. 19 (4%) crossed over to revascularisation. These were included in the intention-to-treat analysis in the MT alone group</p>
Outcomes	<p>Adverse cardiovascular and renal events (composite endpoint of death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalisation for congestive heart failure, progressive renal insufficiency or the need for renal replacement therapy)</p> <p>Secondary outcomes included the individual components of the primary endpoint as well as all-cause mortality and blood pressure</p>
Notes	<p>The original trial enrolment criteria were modified during the trial. Initially all participants were required to have a systolic BP > 155 mmHg and be on at least 2 antihypertensive medications but later on this requirement was relaxed and participants without hypertension with CKD were also recruited</p>

CORAL (Continued)

Crossovers from MT to stenting were only approved if acute anuric renal failure, complete occlusion of all renal arteries and at least one kidney > 8 cm in length

All participants who underwent randomisation were included in an intention-to-treat analysis with the exception of the 16 participants (9 in each group) who were enrolled at a single site at which scientific integrity issues were identified

Emboolic protection devices were used during all stent procedures

Complications: see [Table 1](#) and [Table 2](#)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was performed by means of an interactive voice randomisation system with the use of a permuted block design."
Allocation concealment (selection bias)	Low risk	"Randomisation was performed by means of an interactive voice randomisation system with the use of a permuted block design."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind for this type of intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A single end point committee whose members were unaware of the group assignments adjudicated all end points"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear reporting of participant dropouts and reasons; performed analyses by intention-to-treat with all randomised participants
Selective reporting (reporting bias)	Low risk	Reported on all appropriate outcomes
Other bias	Unclear risk	Possibly underpowered; 1080 participants would need to be enrolled, but due to slow recruitment only 947 were enrolled

DRASTIC

Methods	Multi-centre, randomised controlled clinical trial Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: yes, 2 patients in the MT group lost to follow-up, but intention-to-treat analysis performed Blinding of outcome measurement: no
Participants	106 patients between 18 and 75 years (mean age 60 years) 39% women Inclusion criteria: diastolic BP > 95 mmHg with standardised antihypertensive regimen of 2 drugs on at least 3 occasions, or increase in serum creatinine of > 20 µmol/L with ACE-inhibitor, Serum creatinine < 200 µmol/L Exclusion criteria: unstable coronary artery disease, heart failure, pregnancy, cancer, hypertension secondary to conditions other than renovascular disease 23% of patients had bilateral stenosis 26 centres in the Netherlands

DRASTIC (Continued)

Enrolment period: January 1993 to November 1998

Interventions	<p>No run-in period</p> <p>56 patients were assigned to BA (2 + stent, 3 had surgery) and antihypertensive drug therapy was discontinued on day of intervention and subsequently resumed if necessary. If diastolic BP was > 95 mmHg or serum creatinine had risen by > 20 µmol/L after 3 months, either a second BA, stent deployment, or bypass surgery was recommended</p> <p>50 patients were assigned to MT. If diastolic BP was > 95 mmHg despite treatment with 3 or more drugs, or serum creatinine increased by > 20 µmol/L or time-activity renogram on scintigraphy worsened, BA was performed</p> <p>Patients assigned to BA received oral aspirin 300 mg daily for 6 months</p> <p>Follow-up was 12 months</p>
Outcomes	<p>Mean office BP (mean of 3 office BP measurements by standard sphygmomanometry)</p> <p>Number and DDD of antihypertensive drugs</p> <p>Serum creatinine</p> <p>Restenosis of stenotic vessels</p> <p>Complications</p>
Notes	<p>The following outcomes could be ascertained from this study: mean differences in office BP, number and DDD of antihypertensive drugs given, mean difference in serum creatinine, restenosis of vessels, and complications. Results are presented after 3 months (before 44% of patients in the MT group underwent BA) and after 6 months</p> <p>Mean office BP decreased by 10/5 mmHg in the BA group, and by 4/2 mmHg in the MT group after 3 months, and by 19/11 mmHg and by 17/7 mmHg, respectively after 12 months (no SD given)</p> <p>Mean number of antihypertensive drugs decreased from 2.0 ± 0.8 to 1.9 ± 0.9 in the BA group, and increased from 2.0 ± 0.9 to 2.5 ± 1.0 in the MT group after 3 months. After 12 months the corresponding numbers were 1.9 ± 0.9 in the BA group, and 2.4 ± 0.9 in the MT group. Mean DDD after 3 months decreased from 3.3 ± 1.1 to 2.1 ± 1.3 in the BA group, and remained stable at 3.2 ± 1.5 in the MT group. After 12 months the corresponding numbers were 2.5 ± 1.7 in the BA group, and 3.1 ± 2.3 in the MT group. Median serum creatinine remained stable throughout the study at 106 µmol/L in the BA group, and stable at 115 µmol/L in the MT group after 3 months, but decreased to 106 µmol/L after 12 months in the MT group</p> <p>Mean serum creatinine clearance increased from 67 ± 23 to 70 ± 25 mL/min in the BA group after 3 and 12 months, and decreased from 60 ± 24 to 59 ± 23 mL/min after 3 months, and increased to 62 ± 27 mL/min after 12 months in the MT group</p> <p>Restenosis rate (stenosis > 50%) was 52% in the BA group, and 19% in the MT group</p> <p>Complications: see Table 1 and Table 2</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation
Allocation concealment (selection bias)	Low risk	"Randomisation was performed by computer...without investigators' knowledge of patients' groups at the time of assignment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind for this particular intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	BP measured using an automated device

DRASTIC (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	2 lost to follow-up in the MT group (1 of the 2 had crossed over to undergo BA)
Selective reporting (reporting bias)	Low risk	Reported on all relevant outcomes
Other bias	High risk	Patients assigned to MT group underwent BA at 3 months if diastolic pressure was > 95 mmHg despite treatment with 3 or more drugs – 22 out of 50 in the control group underwent BA

EMMA

Methods	Multi-centre, randomised controlled clinical trial Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no, 1 patient in the MT-group was not analysed since he was withdrawn due to the development of symptomatic hypotension Blinding of outcome measurement: no, but ambulatory blood pressure as outcome measure with limited scope for observer bias
Participants	49 patients younger than 75 years (mean age 59 years) 26% women Inclusion criteria: diastolic BP office readings > 95 mmHg on at least 3 occasions or receiving antihypertensive treatment, or both, and with a creatinine clearance > 50 mL/min Exclusion criteria: malignant hypertension, history of stroke, pulmonary oedema or myocardial infarction within the preceding 6 months 30% in BA and 46% in MT had ostial stenosis No patient had bilateral stenosis 10 centres in France and 1 in Belgium Enrolment period: January 1992 to June 1995
Interventions	2 to 6 week run-in period on standardised antihypertensive regimen (nifedipine SR 20 mg bid; if necessary idem plus clonidine 0.15 mg bid; if necessary idem plus prazosine 2.5 mg once daily) 23 patients were assigned to BA (2 of these + stent) and antihypertensive treatment was stopped 26 patients were assigned to continue pre-randomisation drug regimen If diastolic BP > 109 mmHg on first follow-up visit or > 95 mmHg on 2 successive visits atenolol 50 mg/day, furosemide 40 mg/day or enalapril 10 mg/day was added in the MT group, and drug treatment was started or resumed in BA group All patients were given oral aspirin 100 mg daily Follow-up was at 6 months
Outcomes	Mean ambulatory BP Number of antihypertensive agents and DDD administered at 6-month follow-up Creatinine clearance Rates of occluded arteries Complications
Notes	The following outcomes could be ascertained from this study: mean differences in ambulatory BP, number and DDD of antihypertensive drugs given, mean difference in creatinine clearance, restenosis (defined as totally occluded vessels), and complications Mean ambulatory BP decreased by $12 \pm 20/10 \pm 11$ mmHg in the BA group, and by $8 \pm 16/5 \pm 10$ mmHg in the MT group. The rate of patients taking more or the equal of 2 antihypertensive drugs rose from 54 to 88% in the MT group, and declined from 65 to 35% in the BA group. Median number of DDD rose from 1.33 to 1.78 in the MT group, and decreased from 1.33 to 1.0 in the BA group. There was no significant difference in creatinine clearance between the two groups (73.2 ± 25 at baseline and 76.8 ± 27 mL/min)

EMMA (Continued)

after 6 months, and 73.2 ± 24 at baseline and 73.8 ± 9.8 mL/min after 6 months in the MT group. In neither of the groups was the stenotic renal artery totally occluded. Although the primary outcome of the study was ambulatory blood pressure at termination, office BP values were used for analysis in order to compare results with other studies. 7/26 (27%) in the MT group received BA after termination due to refractory hypertension (diastolic BP > 104 mmHg despite maximal tolerated antihypertensive drug regimen). Results for these 7 participants prior to them undergoing BA was included in the final analysis.

Complications: See [Table 1](#) and [Table 2](#)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided about how the random sequence was generated
Allocation concealment (selection bias)	Low risk	Randomisation was stratified by centre and sealed, numbered envelopes opened in sequential order were used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind for this particular intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary endpoint was ambulatory blood pressure at termination
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient in the MT group was withdrawn due to the development of symptomatic hypotension
Selective reporting (reporting bias)	Low risk	Reported all appropriate outcomes
Other bias	Low risk	No apparent other sources of bias

NITER

Methods	Randomised controlled trial Blinding of randomisation: unknown Blinding of intervention: unknown Complete follow-up: unknown Blinding of outcome measurement: unknown
Participants	52 patients with mean age of 72 years 40.4% women Inclusion criteria: patients with stable renal failure (creatinine clearance > 30 mL/min), hypertension and haemodynamically significant atherosclerotic ostial renal artery stenosis Exclusion criteria: unknown Number of centres: unknown

NITER (Continued)

Enrollment period: unknown

51.5% had bilateral stenosis

Mean stenosis was 80%

Interventions	Medical therapy versus medical therapy plus renal artery stenting 28 participants were assigned to BA + stent insertion 24 participants were assigned to MT 100% participants in the intervention arm underwent stenting 1.9% crossed over from control to the intervention arm Follow-up duration was 43 months
Outcomes	Reduction by 20% in estimated GFR Need for renal replacement therapy Death
Notes	The results of this trial have not yet been fully published (NITER)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind for this particular intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	Information not available
Other bias	Unclear risk	Information not available

RADAR

Methods	Randomised controlled trial Blinding of randomisation: unknown
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RADAR (Continued)

	Blinding of intervention: unknown Complete follow-up: unknown Blinding of outcome measurement: unknown
Participants	67 participants with a mean age of 67 years 33% women Inclusion criteria: patients with renal artery stenosis and an indication for revascularisation. Detailed inclusion criteria: unknown Exclusion criteria: unknown Number of centres: 13 sites in 4 countries Enrollment period: unknown
Interventions	Medical therapy versus medical therapy plus renal artery stenting 34 participants were assigned to BA + stent insertion 33 participants were assigned to MT Follow-up duration was 32 months
Outcomes	Change in eGFR between baseline and 12 months
Notes	The results of this trial have not yet been fully published (RADAR). The published abstract states that this study was terminated prematurely but does not give any reasons for this. It also states that 89 patients were enrolled but data is presented for only 67. The reason for this is again not given No information regarding cardiovascular or renal complications were provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind for this particular type of intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	Information not available
Other bias	Unclear risk	Information not available

SNRASCG

Methods	Multi-centre, randomised controlled clinical trial Blinding of randomisation: unclear Blinding of intervention: no Complete follow-up: no, 2 patients in the BA group and 4 in the MT group lost to follow-up, no reasons for lost to follow-up given Blinding of outcome measurement: yes (for blood pressure assessment)
Participants	55 patients between 40 and 75 years (mean age 61 years) 42% women Inclusion criteria: diastolic BP $\geq$ 95 mmHg on at least 2 antihypertensive drugs, serum creatinine $\geq$ 500 μ mol/L Exclusion criteria: age $<$ 40 or $>$ 75 years, serum creatinine $<$ 500 μ mol/L, stroke or myocardial infarction within the previous 3 months 28/55 stenoses (51%) were bilateral, 27/55 stenoses (49%) were ostial 7 centres in the United Kingdom Enrolment period: No enrolment period indicated
Interventions	4-week run-in period on fixed antihypertensive regimen (recommended regimen was atenolol, bendrofluzide, and calcium antagonist in any combination of at least two of these) 25 patients were assigned to BA (3 of these had nephrectomy, and 2 had a vein bypass) 30 patients continued MT. After 1, 3 and 6 months clinicians were encouraged to "step down" treatment if BP levels permitted All patients were given oral aspirin daily Follow-up was at 6 months
Outcomes	Office BP (measurement with either a standard or a Hawksley random zero sphygmomanometer in the sitting position, no indication if mean of multiple or single BP-measurement) Serum creatinine Complications
Notes	The following outcomes could be ascertained from this study: Mean differences in office BP and differences in serum creatinine Mean BP decreased by 14/5 mm Hg in the BA group, and by 4/3 mm Hg in the MT group, when results of patients with uni- and bilateral stenoses were combined (19/4 in BA group, and 2/2 mm Hg in the MT group with bilateral, and 9/5 in the BA group, and 8/6 mm Hg in the MT group with unilateral stenosis) Mean serum creatinine increased by 5 μ mol/L in the BA group, and by 22 μ mol/L in the MT group (combined for uni- and bilateral stenosis) No statistically significant difference in number of antihypertensive drugs (exact number of antihypertensive drugs not indicated) No significant difference in DDD between groups (no exact numbers given) Restenosis and complication rates could not be used for analysis since they were not reported separately for randomised and non-randomised patients (complications of BA occurred in 25 randomised and in 15 non-randomised patients: significant bleeding at the arterial site in 20%, and pain requiring administration of narcotic analgesics in 10%). Study was originally restricted to patients with bilateral stenosis, but subsequently extended to patients with unilateral disease. For analysis results from patients with bi- and unilateral renal artery stenoses were pooled together Complications: See Table 1 and Table 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation not provided

SNRASC (Continued)

Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible to blind for this particular intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	BP was measured by an "observer unaware of the allocation to intervention or medical therapy"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients in the BA group and 4 in the MT group lost to follow-up, no reasons given
Selective reporting (reporting bias)	Low risk	Reported on relevant outcomes
Other bias	High risk	Of the 25 participants assigned to BA 5 (20%) had a surgical intervention (3 nephrectomies, 2 vein bypasses)

STAR

Methods	Multi-centre randomised controlled trial Blinding of randomisation: yes Blinding of intervention: no Complete follow-up: no, 2 participants from the stent group and 2 from the MT group were lost to follow-up. No reasons given for participants being lost to follow-up Blinding of outcome measurement: unclear (but primary outcome was serum creatinine measurement)
Participants	140 patients (mean age 66.5 yrs) 55% women Inclusion criteria: patients with impaired renal function ($\text{CrCl} < 80 \text{ mL/min per } 1.73 \text{ m}^2 \text{ CG formula}$) with ostial stenosis of $> 50\%$ Exclusion criteria: $\text{CrCl} < 15 \text{ mL/min}$, renal artery diameter $< 4 \text{ mm}$, renal size $< 8 \text{ cm}$, diabetes mellitus with proteinuria or malignant hypertension 48% had bilateral stenosis 10 centres – 9 in Netherlands, 1 in France Enrolment period: June 2000 and December 2005
Interventions	No run-in period 74 were assigned to MT 64 were assigned to BA with stent insertion – 46 of these underwent the allocated treatment. 18 did not (1 BA only, 2 declined stent insertion, 1 died prior to stent insertion, 12 had stenosis $< 50\%$ at angiography, 2 technical failure to place stent). All 46 had successful stent insertion with a residual stenosis of $<$

STAR (Continued)

20%. An intention-to-treat analysis was carried out with follow-up data available for 62 of the intervention group and 74 of the MT group

1 patient from MT group crossed over due to refractory HTN

Participants were followed up until they reached the primary end point or for 2 years with follow up visits at 1 month, then 3 months and then 3 monthly for 2 years. Fasting serum Cr and 3 x sitting BP measured at each visit

Outcomes	<p>Worsening of renal function (defined as a > 20% decline in Cockcroft-Galt estimated Cr clearance)</p> <p>BP</p> <p>Incidence of refractory or malignant HTN</p> <p>Pulmonary oedema,</p> <p>CV morbidity, CV mortality, total mortality</p> <p>Complications</p>
Notes	<p>16 patients in the MT group and 10 in the stent group reached the primary endpoint. Event free survival did not differ significantly between groups. A by protocol analysis comparing the 90 patients who received MT to the 50 who received an intervention revealed similar results</p> <p>Complications: see Table 1 and Table 2</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated permuted block randomisation"
Allocation concealment (selection bias)	Low risk	"Study personnel were unaware of the permuted block size"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind for this type of intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Primary outcome based on serum creatinine measurements. No details provided with regards to the measurement of BP
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients lost to follow-up and 6 deaths in the MT group; 2 patients lost to follow-up and 5 deaths in the BA group
Selective reporting (reporting bias)	Low risk	Reported all appropriate outcomes
Other bias	High risk	Only 46 out of the 64 participants allocated to balloon angioplasty underwent revascularisation

BA: balloon angioplasty
bid: twice daily
BP: blood pressure
CrCl: creatinine clearance

CV: cardiovascular

DDD: defined daily doses (defined as average maintenance dose per day for adults)

HTN: hypertension

MT: medical therapy

ns: non-significant

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Balzer 2009	This study consisted of a comparison between angioplasty and surgical intervention. There was no medical treatment group
Ziakka 2008	This study was not randomised

Characteristics of ongoing studies *[ordered by study ID]*

Rossi 2012

Trial name or title	NCT01208714 Medical and Endovascular Treatment of Atherosclerotic Renal Artery Stenosis (METRAS) study
Methods	Multicentre randomised controlled trial
Participants	120 participants with renal artery stenosis and hypertension
Interventions	Optimum medical therapy alone compared to stenting with optimum medical treatment
Outcomes	Primary outcomes include change in eGFR Secondary outcomes include blood pressure, need for renal replacement therapy, cardiovascular events and quality of life
Starting date	2012
Contact information	GP Rossi - gianpaolo.rossi@unipd.it
Notes	5-year follow-up planned

Tobe 2007

Trial name or title	NCT00127738 Renal Atherosclerotic revascularization Evaluation (RAVE Study)
Methods	Single centre randomised pilot study
Participants	20 participants with renal artery stenosis and an indication for revascularisation
Interventions	Optimum medical therapy alone compared to angioplasty ± stenting with optimum medical therapy
Outcomes	Primary outcomes include doubling of serum creatinine, need for renal replacement therapy, death

Tobe 2007 (Continued)

	Secondary outcomes include cardiovascular disease, blood pressure, antihypertensive medications
Starting date	2007
Contact information	Sheldon W Tobe - sheldon.tobe@sunnybrook.ca
Notes	This study will also aim to assess the renal resistance index to see if this is a useful tool for identifying patients with particularly severe renal artery stenosis who may be most likely to benefit from angioplasty

eGFR: estimated glomerular filtration rate

DATA AND ANALYSES

Comparison 1. Balloon angioplasty versus medical therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in systolic BP at 2 years or end of follow-up	5	1743	Mean Difference (IV, Fixed, 95% CI)	-1.07 [-3.45, 1.30]
2 Change in diastolic BP at 2 years or end of follow-up	4	809	Mean Difference (IV, Fixed, 95% CI)	0.00 [-3.72, -0.27]
3 Serum creatinine at 2 years or end of follow up	3	725	Mean Difference (IV, Fixed, 95% CI)	-7.99 [-22.60, 6.62]
4 Number of antihypertensive drugs	3	1717	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.34, -0.03]
5 Cardiovascular adverse events	7	2110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.75, 1.11]
6 Renal adverse events	7	2104	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.75, 1.38]

Analysis 1.1. Comparison 1 Balloon angioplasty versus medical therapy, Outcome 1 Change in systolic BP at 2 years or end of follow-up.

Study or subgroup	Balloon angioplasty		Medical therapy		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			

Test for overall effect: $Z=0.88(P=0.38)$

Favours Balloon angioplasty Favours Medical therapy

Analysis 1.2. Comparison 1 Balloon angioplasty versus medical therapy, Outcome 2 Change in diastolic BP at 2 years or end of follow-up.

Study or subgroup	Balloon angioplasty		Medical therapy		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			

ASTRAL	256	-4.1 (14.8)	262	-3.3 (10.6)		60.53%	-0.8[-3.02,1.42]
DRASTIC	56	-11 (14.3)	50	-7 (8)		15.77%	-4[-8.35,0.35]
EMMA	23	-10 (11)	26	-5 (10)		8.54%	-5[-10.91,0.91]
STAR	62	-6 (15.3)	74	-3 (10)		15.17%	-3[-7.44,1.44]
Total ***	397		412			100%	-2[-3.72,-0.27]

Heterogeneity: $\tau^2=0$; $\chi^2=3.12$, $df=3(P=0.37)$; $I^2=3.71\%$
Test for overall effect: $Z=2.26(P=0.02)$

Favours Balloon angioplasty Favours Medical therapy

Analysis 1.3. Comparison 1 Balloon angioplasty versus medical therapy, Outcome 3 Serum creatinine at 2 years or end of follow up.

Study or subgroup	Balloon angioplasty		Medical therapy		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			

ASTRAL	263	188 (115)	272	199 (116)		55.7%	-11[-30.58,8.58]
SNRASCG	24	188 (106)	30	159 (76)		8.41%	29[-21.38,79.38]
STAR	62	156 (69)	74	168 (76)		35.89%	-12[-36.39,12.39]
Total ***	349		376			100%	-7.99[-22.6,6.62]

Heterogeneity: $\tau^2=0$; $\chi^2=2.27$, $df=2(P=0.32)$; $I^2=11.72\%$
Test for overall effect: $Z=1.07(P=0.28)$

Favours Balloon angioplasty Favours Medical therapy

Analysis 1.4. Comparison 1 Balloon angioplasty versus medical therapy, Outcome 4 Number of antihypertensive drugs.

Study or subgroup	Balloon angioplasty		Medical therapy		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			

ASTRAL	332	2.8 (2.2)	348	3 (1.6)		28.95%	-0.2[-0.49,0.09]
CORAL	459	3.3 (1.5)	472	3.5 (1.4)		68.04%	-0.2[-0.39,-0.01]
DRASTIC	56	3.3 (2.8)	50	3 (1.8)		3.01%	0.3[-0.59,1.19]
Total ***	847		870			100%	-0.18[-0.34,-0.03]

Heterogeneity: $\tau^2=0$; $\chi^2=1.18$, $df=2(P=0.55)$; $I^2=0\%$
Test for overall effect: $Z=2.36(P=0.02)$

Favours Balloon angioplasty Favours Medical therapy

Analysis 1.5. Comparison 1 Balloon angioplasty versus medical therapy, Outcome 5 Cardiovascular adverse events.

Analysis 1.6. Comparison 1 Balloon angioplasty versus medical therapy, Outcome 6 Renal adverse events.

ADDITIONAL TABLES

Table 1. Cardiovascular complications

Complications	ASTRAL	CORAL	DRASTIC	EMMA	NITER	SNRASCG	STAR
Angina/myocardial infarction/heart failure	112 in BA, 131 in MT	40 in BA, 37 in MT	0 in BA, 2 in MT	0 in any group	Data not available	4 in each group	4 in BA, 6 in MT (defined as CAD + HF)
Cholesterol embolisation	3 in BA, 0 in MT	6 in BA, 0 in MT	0 in BA, 1 in MT	0 in any group	Data not available	0 in any group	1 in BA, 0 in MT
Non-procedure-related symptomatic hypotension	Data not available	Data not available	0 in any group	0 in BA, 1 in MT	Data not available	0 in any group	Data not available
Stroke	24 in BA, 23 in MT	16 in BA, 23 in MT	0 in any group	0 in any group	3 in BA, 4 in MT	1 in BA, 4 in MT	0 in BA, 1 in MT (defined as cerebrovascular disease)
Death	103 in BA, 106 in MT	63 in BA, 76 in MT	0 in any group	0 in any group	3 in BA, 3 in MT	2 in BA, 4 in MT	6 in MT, 5 in BA

BA: balloon angioplasty group
CAD: coronary artery disease
HF: heart failure
MT: medical therapy group

Table 2. Renovascular complications

Complications	ASTRAL	CORAL	DRASTIC	EMMA	NITER	SNRASCG	STAR
> 50% increase in serum creatinine or > 20% decrease in estimated creatinine clearance	Data not available	Data not available	1 in BA, 3 in MT	0 in BA, 1 in MT	Data not available	0 in any group	10 in BA, 16 in MT (data provided for 20% fall in CrCl only)
Renal failure	55 in BA, 54 in MT (defined as AKI + dialysis for	16 in BA, 8 in MT (defined as permanent RRT)	0 in any group	0 in any group	10 in BA, 8 in MT (but unclear how worsening	2 in each group	Data not available

Table 2. Renovascular complications (Continued)
end stage renal disease)

					renal failure was de- fined)		
Total occlusion of stenotic artery	5 in BA, 4 in MT	Data not avail- able	0 in BA, 4 in MT	0 in any group	Data not available	0 in any group	Data not available

AKI: acute kidney injury

BA: balloon angioplasty group

CrCl: creatinine clearance

MT: medical therapy group

RRT: renal replacement therapy

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MESH DESCRIPTOR Angioplasty EXPLODE ALL TREES	3965
#2	(angioplas* or percutan* or PTA):TI,AB,KY	9496
#3	(recanali* or revascular*):TI,AB,KY	5021
#4	dilat*:TI,AB,KY	5684
#5	(balloon or baloon):TI,AB,KY	5600
#6	MESH DESCRIPTOR Endovascular Procedures EXPLODE ALL TREES	5436
#7	endovascular:TI,AB,KY	772
#8	MESH DESCRIPTOR Blood Vessel Prosthesis EXPLODE ALL TREES	380
#9	MESH DESCRIPTOR Blood Vessel Prosthesis Implantation EXPLODE ALL TREES	362
#10	MESH DESCRIPTOR Stents EXPLODE ALL TREES	2649
#11	(stent* or graft* or endograft* or endoprosthe*):TI,AB,KY	17228
#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	32959
#13	MESH DESCRIPTOR Renal Artery Obstruction EXPLODE ALL TREES	97
#14	MESH DESCRIPTOR Hypertension, Renal EXPLODE ALL TREES	241
#15	(renal or reno* or kidney):TI,AB,KY	29792
#16	#13 OR #14 OR #15	29792
#17	#12 AND #16	4327

WHAT'S NEW

Date	Event	Description
7 May 2014	New search has been performed	Searches rerun, five new studies included, two excluded and one ongoing study identified.
7 May 2014	New citation required but conclusions have not changed	New authors have taken over this review. Searches rerun, five new studies included, two excluded and one ongoing study identified. Risk of bias tables completed. Conclusions not changed.

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 3, 2003

Date	Event	Description
9 July 2008	New search has been performed	Secondary references added to included studies. NITER and CORAL trials added to ongoing studies.
30 May 2008	Amended	Converted to new review format.
8 November 2006	Amended	Search dates changed. Plain language summary added.
24 June 2005	Amended	Search dates changed. STAR study added to ongoing studies.

CONTRIBUTIONS OF AUTHORS

Dr Sara Jenks selected trials for inclusion in the review, assessed trial quality, extracted data and updated the review.

Su Ern Yeoh selected trials for inclusion in the review, assessed trial quality and extracted data.

Dr Bryan Conway assisted in writing the review.

DECLARATIONS OF INTEREST

SJ: none known

SEY: none known

BRC: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- The Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

The PVD Group editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review title was amended from 'Balloon angioplasty versus medical therapy for hypertensive patients with renal artery obstruction' to 'Balloon angioplasty, with and without stenting, versus medical therapy for hypertensive patients with renal artery stenosis' to reflect the content of the review more accurately.

The secondary outcome 'presence or absence of patency of the renal artery' has been revised to 'presence or absence of restenosis of the renal artery' to reflect more accurately the intended outcome.

We performed an additional subgroup analysis restricting all the meta-analyses to the five studies that carried out angioplasty with stenting rather than angioplasty alone to assess the effect of improving angiographic techniques.

INDEX TERMS

Medical Subject Headings (MeSH)

*Angioplasty, Balloon; *Stents; Antihypertensive Agents [*therapeutic use]; Combined Modality Therapy [methods]; Hypertension [*therapy]; Randomized Controlled Trials as Topic; Renal Artery Obstruction [*therapy]

MeSH check words

Humans