

## **Renal Artery Stenosis**

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**Author:** Merlin Thomas

### **GUIDELINES**

- a. Correction of renal artery stenosis (RAS), either by re-vascularisation surgery or percutaneous methods, has been shown to be effective in treating hypertension associated with renal artery stenosis. (Level II evidence)**
- b. Balloon angioplasty has not been shown to be superior to medical management for preserving renal function in patients with RAS. (Level I evidence)**
- c. Balloon angioplasty has not been shown to be superior to angioplasty with stenting for preserving renal function in patients with renal artery stenosis. (Level II evidence - multiple studies)**
- d. Balloon angioplasty has not been shown to be superior to surgical management in experienced centres for preserving renal function in patients with renal artery stenosis. (Level II evidence - one RCT)**

### **SUGGESTIONS FOR CLINICAL CARE**

**(Suggestions are based on Level III and IV evidence)**

- In the absence of trials showing benefit from revascularisation over conventional therapy and the significant risk of complications it seems reasonable to restrict procedures to patients who fail medical therapy with resistant or poorly-controlled hypertension; recurrent flash pulmonary oedema; dialysis-dependent kidney failure resulting from renal artery stenosis; chronic renal insufficiency and bilateral renal artery stenosis; or renal artery stenosis to a solitary functioning kidney.
- In the absence of significant differences in long-term outcome measures, given the rates of restenosis following simple balloon angioplasty and the complications and costs of surgical intervention, it would seem reasonable to consider angioplasty with stenting as the revascularisation procedure of choice for medically recalcitrant renal artery stenosis. (Level IV evidence)
- The above clinical guidelines refer to patients with significant de novo renal artery stenosis (generally more than 50%–80% reduction in luminal diameter). There have been no studies in patients identified with lesser degrees of stenosis. It seems reasonable to offer medical therapy in these individuals, given the natural history of progressive stenosis in atherosclerotic renal disease.

## **Background**

RAS is an important cause of renal insufficiency, having an estimated prevalence of 10% to 15% among patients approaching end-stage kidney disease (ESKD) (Rimmer et al 1993). Stenosis of the extra-parenchymal renal arteries caused by atherosclerotic lesions may lead to progressive renal ischaemia and the development of an 'ischaemic atrophic nephropathy', chronic renal insufficiency and loss of renal mass. Fifty per cent of patients with RAS have some degree of renal excretory function impairment, and nearly one third have only a single functioning kidney (Mailloux et al 1994). The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of interventions on renal functional decline in patients with RAS. This guideline does not address the potential utility of these interventions in reducing cardiovascular risk.

## **Search strategy**

**Databases searched:** MeSH terms and text words for renal artery stenosis were searched for in Medline (1966 to September Week 2 2004). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of searches:** 17 September 2004.

## **What is the evidence?**

Correction of RAS, either by re-vascularisation surgery or percutaneous methods, has been shown to be effective in treating hypertension. Some uncontrolled studies report either a cure or improvement of hypertension of between 59% to 78% of patients (Scoble et al 1989), although blood pressure improvements may have been overestimated in some of these studies due to optimization of drug treatment in interventional arms (Ritz et al 2000). While improvements may be achieved with re-vascularisation, it is sometimes at the expense of serious complications, including mortality. The extent to which any intervention delays the progression to ESKD independent of BP control has not been clearly established. Moreover, accurate interpretation of renal function outcomes in many of these studies is difficult, given the short duration of many of these trials.

### *A. Balloon angioplasty*

There have been three randomised controlled trials (RCTs) comparing balloon angioplasty with medical therapy in hypertensive patients with significant RAS (greater than 50% reduction in luminal diameter) involving 210 patients.

- In the DRASTIC study (Mann 2000), 106 patients with hypertension, significant atherosclerotic RAS and a serum creatinine concentration less than 200 µmol/L were randomly assigned to undergo percutaneous transluminal renal angioplasty or to receive antihypertensive drug therapy, followed by balloon angioplasty (if needed) at 3 months. Overall BP and renal function were similar in the two groups at 3 and 12 months, although angioplasty reduced the need for 1 additional daily antihypertensive agent. However, after

subgroup analysis, it was found that in patients with bilateral stenoses, the creatinine clearance (Ccr) improved in the angioplasty group, but fell in patients assigned to the delayed intervention group.

- A Scottish group reported a prospective randomised trial of percutaneous angioplasty vs. medical therapy in patients with bilateral or unilateral atherosclerotic RAS and sustained hypertension (van Jaarsveld et al 2000). In the bilateral group (n = 28), the drop in systolic pressure was significantly larger following angioplasty than following medical therapy, but diastolic pressure and creatinine after 24 months was not different with either intervention. In the unilateral group (n = 27), there was no difference in serum creatinine or BP control between angioplasty or medical therapy.
- In the EMMA study (Webster et al 1998), hypertensive patients were randomly assigned antihypertensive drug treatment (n = 26) or angioplasty (n = 23). They also found that BP at 6-months did not differ between control ( $141 \pm 15/84 \pm 11$  mm Hg) and angioplasty ( $140 \pm 15/81 \pm 9$  mmHg) groups. Angioplasty reduced the requirement for antihypertensive therapy at the cost of some procedural morbidity.
- A meta-analysis of these studies determined that there was a consistent but statistically non-significant trend towards lower blood pressure in the balloon angioplasty group. In addition, there were no differences in renal function. However, patients treated with balloon angioplasty required fewer antihypertensive drugs in 2 of 3 trials. In addition, there were significantly fewer cardiovascular and renovascular complications in patients treated with angioplasty (OR 0.32, 95%CI: 0.15 to 0.70, test for heterogeneity  $p > 0.1$ ).

Despite achieving changes in arterial patency, none of these studies has shown significant advantage in slowing of renal progression through renal angioplasty over and above conventional medical therapy. Interpretation is limited by the fact that each of these studies has focused on patients with hypertension rather than those with documented progressive renal impairment.

### *B. Renal artery stenting*

Some studies have suggested that angioplasty followed by intravascular stenting is a better technique than angioplasty alone to achieve vessel patency, particularly in ostial atherosclerotic renal-artery stenosis (Plouin et al 1998). It has also been suggested that hypertension is better controlled, re-stenosis is minimized and athero-embolic injury limited with stenting compared with conventional balloon angioplasty (Mark et al 2000). There have been 5 uncontrolled prospective studies on the effect of renal stenting on progression of kidney disease.

- Watson et al (2000) prospectively studied the effect of renal artery stenting on renal function and size in 33 patients with chronic renal insufficiency and bilateral renal artery stenosis or unilateral stenosis in the presence of a solitary or single functional kidney. Before stent deployment, all patients had evidence of progressive renal insufficiency. After stent deployment, renal function improved in 18 and slowed in 7 patients. Ultrasonography revealed preservation of kidney size.

- Harden et al (1997) studied 33 patients with atherosclerotic RAS undergoing renal stenting. Renal function improved or stabilized in 69% of patients.
- Rundback et al (1998) evaluated the effect of renal artery stenting in 45 patients with renal impairment (creatinine  $\geq$  1.5 mg/dL) and atheromatous renal artery stenosis untreatable by, or recurrent after, balloon angioplasty. Stent implantation was unilateral in 32 cases and bilateral in 11 cases. With use of life-table analysis, clinical benefit was seen in 78% of patients at 6 months ( $n = 36$ ) and 72% at 1 year ( $n = 24$ ). In patients with clinical benefit, average creatinine concentration was reduced from 2.21 mg/dL  $\pm$  0.91 before treatment to 2.05 mg/dL  $\pm$  1.05 after treatment. Lower initial serum creatinine concentration was associated with a better chance of clinical benefit.
- Shannon et al (1998) described the use of renal artery stents in the solitary functioning kidney of 21 patients with impaired renal function as a result of atherosclerotic RAS. At follow-up (range, 6–25 months), renal function had returned to normal in five patients (24%), improved in four patients (19%), stabilized in six patients (29%), and deteriorated in six patients (29%). Dialysis was discontinued in all four dialysis patients.
- Bucek et al (2003) prospectively followed 40 patients who had undergone successful stenting of a main renal artery. All patients still suffered from arterial hypertension but compared with the preinterventional situation, arterial hypertension was improved in 37.5%. Serum creatinine was increased in 25% of patients, mean creatinine level was 1.3  $\pm$  0.4 mg/dL.
- Dorros et al (2004) followed 544 patients who underwent 714 successful RAS stent revascularizations. The mean serum creatinine was unchanged at 4 years (1.6  $\pm$  1.0 mg/dl versus 1.6  $\pm$  0.9 mg/dl) when compared with baseline values.

At this time, there are no controlled studies comparing renal arterial stenting with medical therapy alone.

Leertouwer et al (2000) performed a meta-analysis of renal arterial stent placement in comparison with renal angioplasty in patients with renal arterial stenosis, including studies published up to August 1998. The cure rate for hypertension was higher after stent placement than after renal angioplasty but probability of improvement in renal function following intervention was lower after stenting compared to conventional angioplasty (20% vs. 10% and 30% vs. 38%, respectively;  $P < .001$ ). This may be because the stent studies included more patients with impaired renal function instead of hypertension, which may affect the clinical outcome in terms of renal function. In addition, many of these studies used an isolated serum creatinine concentration as a measure of renal impairment, which is an imprecise measure of renal progression.

Since this meta-analysis, there have been two additional studies (Leertouwer et al, 2000).

- Van der Ven et al (1999) undertook a randomised prospective study to compare angioplasty ( $n = 43$ ) to angioplasty with stenting ( $n = 42$ ) in patients with ostial atherosclerotic renal-artery stenosis. At 6 months, the primary patency rate was 29% (12 patients) for angioplasty alone, and 75% (30

patients) for angioplasty with stenting. However, the proportion of patients with cured or improved hypertension was not different between the two groups.

Current large clinical trials including ASTRAL and CORAL will also specifically address the issue of whether renal arterial revascularisation with balloon angioplasty and/or endovascular stenting can safely prevent progressive renal failure among a wide range of patients with RAS.

### *C. Surgical intervention for RAS*

Some researchers have suggested that surgical interventions may produce better outcomes than angioplasty or stenting. Certainly, some patients have improved renal function following surgery in centres of expertise. However, results of surgery may be highly variable between centres. Moreover, significant comorbid vascular disease with atherosclerotic RAS means that major surgery can only be considered in selected individuals.

In one study, arterial reconstruction was shown to be superior to surgical nephrectomy in preserving renal function in patients with unilateral RAS and severe hypertension (Mackay et al 1980).

There are no randomised studies comparing the renal outcomes of surgical revascularisation to conservative (medical) therapy.

There is one randomised study comparing surgical correction of RAS to angioplasty.

- In this study, Weibull et al (1993) compared surgery and percutaneous angioplasty in 58 patients with unilateral atherosclerotic RAS with severe hypertension, who did not have diabetes. Hypertension was said to be cured or improved after additional treatment in 90% of the patients after angioplasty and 86% after operation. Renal function improved or unchanged in 83% of the patients after angioplasty and 72% after surgery. Although 17% of the patients initially treated with angioplasty required subsequent surgery, BP, renal function and renal artery patency rate did not differ between angioplasty and surgery arms 24 months after treatment. Critics of this study have argued that surgical patency may produce better outcomes in the long term (5–10 years) although this remains to be reproduced in other studies and probably depends on surgical expertise.

### *D. Type of medical therapy*

Medical therapies in the above mentioned trials have focused on the use of agents to control BP without specifying agents of a particular class. The drugs that are most effective in medical management of renovascular hypertension-angiotensin-converting enzyme inhibitors and angiotensin receptor-1 blockers- have tended to be avoided because of potential risk of acute renal failure in patients with bilateral renal artery stenosis or unilateral stenosis in a single functioning kidney.

Only one trial exists of angiotensin converting enzyme inhibition versus alternative medical therapy (Spence 2002).

## **Summary of the evidence**

Correction of RAS, either by re-vascularisation surgery or percutaneous methods, including stenting, has been shown to be effective in treating hypertension associated with RAS. While hypertension is a key component of progressive nephropathy in these patients, none of these interventions appear to be significantly superior to medical management of hypertension and other risk factors, for preserving renal function in patients with RAS. Consequently, it seems reasonable to consider procedures to correct RAS in patients who fail medical therapy with resistant or poorly-controlled hypertension; recurrent flash pulmonary oedema; dialysis-dependent renal failure resulting from RAS; chronic renal insufficiency and bilateral RAS; or RAS to a solitary functioning kidney.

## **What do the other guidelines say?**

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**UK Renal Association:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** No recommendation.

**International Guidelines:** No recommendation.

## **Implementation and audit**

No recommendation.

## **Suggestions for future research**

No recommendation.

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Apendicies

**Table 1** Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Jaarsveld et al. 2000	106	Randomised controlled clinical trial	Multicentre, US	106 patients with hypertension who had atherosclerotic renal-artery stenosis	Percutaneous transluminal renal angioplasty	Anti-hypertensive drug therapy	12 mo	
van de Ven et al. 1999	85	Randomised controlled clinical trial	Utrecht University hospital, Netherlands	85 patients with ostial atherosclerotic renal artery stenosis	Percutaneous transluminal angioplasty (PTA)	Angioplasty with stent placement (PTAS)	6 mo	
Weibull et al. 1993	58	Randomised controlled clinical trial	Hospital, Sweden	58 patients without diabetes with severe hypertension and significant stenosis	Percutaneous transluminal renal angioplasty (PTRA)	Operation	24 mo	

**Table 2** Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Jaarsveld et al, 2000	Central	No	Yes	Not specified	Yes	1.9 %
van de Ven et al, 1999	Independent nurse	no	no	yes	Yes	4.7%
Weibull et al. 1993	Sealed envelopes	No	No	No	Yes	6.9%

**Table 3** Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Jaarsveld et al, 2000	Mean SBP at 12 mo (mmHg)	160 (26)	163 (25)	-3.00 (95%CI: -12.72, 6.72)
	Mean DBP at 12 mo (mmHg)	93 (13)	96 (10)	-3.00 (95%CI:-7.39, 1.39)

**Table 4** Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Jaarsveld et al. 2000	Improved BP control at 12 mo	38/56	<b>18/48</b>	1.81 (95%CI: 1.20, 2.72)	0.30 (95%CI: 0.12, 0.49)
	Worsened BP control at 12 mo	5/56	16/48	0.27 (95%CI:0.11, 0.68)	-0.24 (95%CI: -0.40, -0.09)
	Cured hypertension	4/56	0/48	7.74 (95%CI: 0.43, 140.15)	0.07 (95%CI:0.00, 0.15)
	Occlusion of affected artery	0/56	8/48	0.05 (95%CI:0.00, 0.85)	-0.17 (95%CI:-0.28, -0.06)
	Increase of $\geq$ 50% serum Cr	2/56	6/48	0.29 (95%CI:0.06, 1.35)	-0.09 (95%CI:-0.19, 0.02)
van de Van et al. 1999	Success rate (<50% residual stenosis)	24/42	37/43	0.66 (95%CI:0.50, 0.89)	-0.29 (95%CI:-0.47, -0.11)

Table 4 Continued

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
	Patency at 6 mo	12/42	30/43	0.41 (95%CI:0.24, 0.69)	-0.41 (95%CI: -0.61, -0.22)
	Death	1/42	0/43	3.07 (95%CI:0.13, 73.30)	0.02 (95%CI:-0.04, 0.09)
	Technical failure	3/42	3/42	1.00 (95%CI:0.21, 4.67)	0.00 (95%CI: -0.11, 0.11)
	Acute restenosis	15/42	2/42	7.50 (95%CI:1.83, 30.78)	0.31 (95%CI: 0.15, 0.47)
	Bleeding	8/42	8/42	1.00 (95%CI:0.41, 2.42)	0.00 (95%CI:-0.17, 0.17)
	Femoral artery aneurysm	2/42	3/42	0.67 (95%CI:0.12, 3.79)	-0.02 (95%CI:-0.12, 0.08)
	Renal artery injury	2/42	3/42	0.67 (95%CI:0.12, 3.79)	-0.02 (95%CI:-0.12, 0.08)
	Cholesterol embolism	4/42	4/42	1.00 (95%CI: 0.27, 3.74)	0.00 (95%CI:-0.13, 0.13)
	Improved renal function	4/41	5/40	0.78 (95%CI:0.23, 2.70)	-0.03 (95%CI:-0.16, 0.11)
	Deteriorated renal function	8/41	9/40	0.87 (95%CI:0.37, 2.02)	-0.03 (95%CI:-0.21, 0.15)
	Cured hypertension	2/41	6/40	0.33 (95%CI: 0.07, 1.52)	-0.10 (95%CI:-0.23, 0.03)

Table 4 Continued

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
	Improved hypertension	18/41	17/40	1.03 (95%CI:0.63, 1.70)	0.01 (95%CI:-0.20, 0.23)
	Failing hypertension	21/41	17/40	1.21 (95%CI:0.75, 1.92)	-0.01 (95%CI:-0.23, 0.20)
Weibull et al. 1993	Technical success	24/29	28/29	0.86 (95%CI: 0.72, 1.03)	-0.14 (95%CI: -0.29, 0.01)
	Technical failure	5/29	1/29	5.00 (95%CI: 0.62, 40.20)	0.14 (95%CI:-0.01, 0.29)
	Patency rate at 24 mo	21/29	27/29	0.78 (95%CI:0.61, 0.99)	-0.21 (95%CI:-0.39, -0.02)
	Hypertension cured or improved	26/29	25/29	1.04 (95%CI:0.86, 1.26)	0.03 (95%CI:-0.13, 0.20)
	Renal function improved or unchanged	24/29	21/29	1.14 (95%CI:0.86, 1.51)	0.10 (95%CI:-0.11, 0.32)
	Death	1/29	0/29	3.00 (95%CI:0.13, 70.74)	0.03 (95%CI:-0.06, 0.12)
	Major complications	5/29	9/29	0.56 (95%CI: 0.21, 1.46)	-0.14 (95%CI: -0.36, 0.08)