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Endovascular treatment

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[Correction added after online publication on 1 April 2010: Authors' names added.]

GUIDELINES

a. At 5 years (median 34 months), correction of renal artery stenosis (RAS), by balloon angioplasty with or without stenting (no distal protection) has no beneficial effect on blood pressure (BP) compared with medical therapy and is associated with an adverse event rate of 10–25%. (Level I Evidence)

b. At 5 years (median 34 months), correction of RAS, by balloon angioplasty with or without stenting (no distal protection) does not improve kidney function (glomerular filtration rate) more than medical therapy. (Level I Evidence)

c. Stenting of the artery (particularly ostial lesions) is technically better than angioplasty alone. (Level II Evidence)

d. Surgical management of atherosclerotic renal vascular disease (ARVD) has not been shown to be better than either angioplasty or medical therapy in patients with atherosclerotic RAS. (Level II Evidence)

SUGGESTIONS FOR CLINICAL CARE

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

- **In the absence of any substantial benefit from revascularization over conventional therapy in five randomized controlled trials (RCTs) of patient populations with controlled BP and very little renal decline and significant risk of procedural complications, it seems reasonable to restrict revascularization only to patients with high-grade lesions associated with specific clinical problems (see Table 1) performed in specialized centres with low complication rates.**
- **In making a decision re endovascular intervention in renovascular disease the age of the patient and relative prognosis in regard to other comorbidities must be taken into consideration (i.e. older patients should generally have a conservative approach).**
- **When the clinical decision to revascularize has been reached, the procedure of choice should be renal artery stenting with or without distal protection device. This is because angioplasty alone has been associated with significant rates of restenosis, surgical revascularization is very expensive and there are no differences in long-term outcome measures.**
- **The above clinical guidelines refer to patients with moderate or high-grade RAS. There have been no studies in patients identified with lesser degrees of stenosis. It seems prudent to offer medical therapy early to these individuals, given the natural history of progressive stenosis in atherosclerotic renal disease.**
- **Fibromuscular dysplasia (FMD) should be treated by balloon angioplasty, based on currently available uncontrolled data.**

IMPLEMENTATION AND AUDIT

Consider an Australian registry of renovascular intervention *versus* medical therapy.

BACKGROUND

Renal artery vascular disease is increasing in prevalence with the increase in atherosclerosis risk factors such as advancing age, hypertension, diabetes and renal disease[1] in the general population. Although this is both large vessel RAS and ischemic small vessel disease, only the former is amenable to interventional angioplasty. Most authorities consider BP control, preservation or salvage of kidney function and prevention of flash pulmonary oedema to be the goals of treatment of RAS. Optimal medical therapy is considered to be BP-lowering agents, particularly angiotensin converting enzyme inhibitors, antiplatelet agents and lipid-lowering agents. However, angioplasty with stent placement is often now done. The use of distal protection agents are also now more commonly used. Surgical intervention is rarely used, and only in specialized centres. There is no information on the risk of athero-embolic disease after endovascular intervention. This includes peripheral athero-emboli in the feet as well as renal athero-emboli and is not considered in this document but is referred to in the distal protection subtopic in this series.

This document presents a summary of the evidence to date for endovascular treatment and the populations that may benefit, to help guide patient selection for a procedure that has significant peri-procedural morbidity.

SEARCH STRATEGY

Databases searched: The terms used to define artherosclerotic renal artery stenosis were 'renal artery obstruction' (as a MeSH term and text word) and 'renal artery stenosis', 'renovascular disease$' and 'renal artery occlusion$' as text words. To define this further, the terms 'atherosclerosis' and 'arteriosclerosis', as both MeSH terms and text words along with text words 'angioplasty$' and 'stent$' were searched along with MeSH terms and text words for antihypertensives, flash pulmonary oedema and FMD. MeSH terms and text

words for renal artery stenosis were searched for in Medline (1950 to May 2009). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline. **Date of searches:** 10 October 2008, 14 May 2009.

WHAT IS THE EVIDENCE?

There is one systematic review with grading of the evidence up until September 2005 by Balk *et al.*[2] Since this review, one large trial of 806 patients was completed in 2008 (ASTRAL) reported in November 2009 with a median follow up of 34 months making this the largest and longest RCT in the area to date.[3]

Further large RCTs (>1000 patients) that are due to be published in the next few years include the CORAL study, RAVE study and NITER study. These controlled studies will examine improvements in BP and kidney function, and also clinical outcomes such as all-cause mortality, in patients treated by revascularization with angioplasty compared with medical therapy.

ASTRAL enrolled 806 patients from 56 centres with a mean follow up of 34 months (total follow up was 5 years reported for a small number of patients).[3] The average degree of RAS was 76% and the 5-year mortality in the whole group was 51%. Methodological issues that have been raised include:

(1) ASTRAL recruited patients in whom there was 'uncertainty about the value of revascularization . . .'. This was considered a strength by the authors, because it represented the 'real world' situation. However, it may lead to an ascertainment bias in favour of medical therapy because patients with the highest grade of stenosis may not have been entered into the study but treated with revascularization.

(2) The study did not look at stenting in addition to maximal medical therapy. At the 1 year follow-up assessment only half of the ASTRAL patients were on a renin–angiotensin system blocker with more occurring in the intervention group than in the medical group (50% *vs* 43%, $P = 0.05$).[4]

(3) The cross over rate from the medical group crossed to the intervention group was 6% and 17% from the intervention group to the medical group.

(4) The primary end-point of ASTRAL was decline in function, which is a very slow process (refer to Natural History guidelines) with cardiovascular end-points as secondary outcomes. Arguably, the trial follow up is too short in duration and has too few end-points.

(5) The trial included a large group who were unlikely to benefit from intervention since only 59% had >70% stenosis and only 60% had a creatinine >150 µmol/L.

(6) The progression of the rate of increase in serum creatinine was slower than expected in both the intervention and the medical group which weakened the power of the study. Finally, the lack of robust evidence for or against angioplasty use is further negated by the 9% perioperative complication rate and the 20% 1 month complication rate in the intervention arm in ASTRAL.

The DRASTIC study,[5] the largest published RCT, enrolled 106 patients with hypertension, high-grade atherosclerotic RAS and a serum creatinine concentration <200 µmol/L. Patients were randomly assigned to undergo percutaneous transluminal renal angioplasty (PTRA) 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 one additional daily antihypertensive agent. However, after subgroup analysis, it was found that in patients with bilateral stenoses the creatinine clearance improved in the angioplasty group, but fell in patients assigned to the delayed intervention group. This was at a cost of 11% peri-procedural morbidity.

A Scottish group reported a prospective randomized trial of percutaneous angioplasty *versus* medical therapy in patients with bilateral or unilateral atherosclerotic RAS and sustained hypertension.[6] 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 were not different with either intervention. In the unilateral group ($n = 27$), there was no difference in serum creatinine or BP control between angioplasty and medical therapy. This was at a cost of 25% peri-procedural morbidity.

In the EMMA study reported by Plouin *et al.*,[7] 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 ± 15/84 ± 11 mmHg) and angioplasty (140 ± 15/81 ± 9 mmHg) groups. Angioplasty reduced the requirement for antihypertensive therapy at the cost of some procedural morbidity of 25%.

van der Ven *et al.*[8] undertook a randomized prospective study to compare angioplasty ($n = 43$) to angioplasty with stenting ($n = 42$) in patients with ostial atherosclerotic RAS. 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.

Leertouwer *et al.*[9] 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 (60–70%) but the probability of improvement in renal function following intervention was lower after stenting compared with conventional angioplasty (20% *vs* 10% and 30% *vs* 38%, respectively; $P < 0.001$). 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 disease progression. The complication rate of the stent procedure was 8–25%.

Rocha-Singh *et al.*[10] looked at stenting after failed PTRA in the ASPIRE-2 study. This population with uncontrolled hypertension and multiple comorbidities had an

80% procedural success, a 9-month restenosis rate of 17.4% and a 19 mmHg reduction in systolic BP at 24 months. Serum creatinine was unchanged and the complication rate was 19.7% at 2 years.

Zahringer *et al.*[11] in the 'Great Trial' compared a sirolimus-eluting stent with a bare metal stent and demonstrated a 20/10 mmHg BP reduction, a small trend to improved creatinine, and a 26% complication rate.

Balloon angioplasty with/without stenting for blood pressure control

There have been five RCTs comparing balloon angioplasty with medical therapy in hypertensive patients with high-grade RAS (greater than 50% reduction in luminal diameter) now totalling >1000 patients.

Three meta-analyses have been undertaken that look at the first three trials before the ASTRAL study and one systematic review which graded the quality of uncontrolled studies. The few additional uncontrolled studies since are mainly using distal protection.

Two of the meta-analyses demonstrate no clear difference in BP, and the third demonstrates a weighted mean difference of a 7 mmHg reduction in systolic BP, and a 3 mmHg reduction in diastolic BP, with no difference in renal function. However, the likelihood of a patent artery from angioplasty at 12 months was 52% compared with 19% with medical therapy. This difference is considered significant in the literature but the small trial that this difference is based on has both a marked occlusive rate and only a 50% patency rate in both populations, making it difficult to conclude robustly that this is a real phenomenon.

The ASTRAL trial showed no difference in BP at 5 years, however, only 72 intervention patients and 61 medical therapy patients were reported on at that time point which weakens the strength of the long-term data.[3]

In the systematic review by Balk *et al.*,[2] published after the three meta-analyses, the authors reviewed all uncontrolled and controlled data in total. The authors identified 2 RCTs, 8 comparative studies and 25 cohort studies and found that when considering all evidence there was a better BP reduction (8 mmHg) in the angioplasty *versus* medical treatment arm. However, the studies were uncontrolled and non-randomized so many methodological issues existed in the majority and in particular, there was the suggestion that the 'intensive medical therapy' was not equal between the groups. In addition, the combined adverse event rates included death by 30 days which was 3% with the other complications of transient deterioration in kidney function of up to 13%, renal artery injury of 5% and peri-procedural cardiovascular system (CVS) events of 3%. Thus, one can conclude that the review does not favour one treatment modality, that there is weak evidence for similar CVS outcomes and the small improvement in BP (mainly in bilateral renal disease) is likely outweighed by the morbidity.

Leertouwer *et al.*[9] performed a meta-analysis of renal arterial stent placement in comparison with renal angioplasty in patients with RAS, including studies published up to August 1998. This systematic review did not report on the quality of the studies as did Balk *et al.*[2] and included uncontrolled studies. It suggested that stents are better but is very weak in the quality of its conclusions because of the uncontrolled nature of the data it surveyed.

Balloon angioplasty with/without stenting for slowing the progression of renal decline, renal and cardiovascular system outcomes

Despite achieving changes in arterial patency, none of the four studies mentioned above has shown significant advantage in slowing 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. In the ASTRAL study the rate of progression of renal impairment (as shown by the slope of the reciprocal of the serum creatinine level) was -0.67×10^{-3} L/μmol per year in the revascularization group, compared with -0.13×10^{-3} L/μmol per year in the medical therapy group, a nonsignificant difference favouring revascularization of 0.06×10^{-3} L/μmol per year (95% confidence interval, –0.002–0.13; $P = 0.06$).[3]

This nonsignificant trend is weakened by the fact that the number of patients able to be reported on at 5 years was 72 (revascularization) *versus* 61 (medical). Further to this, the pre determined subgroup analysis, which should have favoured a positive result failed to find that persons with reduced baseline serum creatinine, reduced estimated glomerular filtration rate, severe stenosis, reduced kidney length at start of trial, previous rate of deterioration in creatinine, bilateral renovascular disease or single kidneys showed any benefit between intervention verus medical therapy.[3] Thus until further studies are completed, the available evidence shows that there is no benefit in any subgroup or the population as a whole, to the progression of kidney disease following revascularization when compared with medical therapy.

Recently, Bax *et al.*[12] studied 122 patients with the inclusion criteria including well-controlled BP of less than 140/90 mmHg who were followed for 2 years. They concluded that stent therapy had no clear benefit on progression of impaired renal function but led to a significant complication rate. The study was powered to detect an outcome in 140 original patients but many methodological issues weakened this power. For example, 18 patients in the stent group failed to get a stent due to the fact that the degree of stenosis was <50% at the time of procedure and the operator did not do the intervention. Other problems included an imbalance in the randomization due to stratification errors, inadequate medical therapy with angiotensin blockade being limited and definitely not first line, imbalance in other cardiovascular risk factors including diabetes, and inadequate medical therapy with differences in cholesterol levels reached. Overall, it is hard to reach a conclusion from this paper because of its underpowered nature and multiple confounded outcomes.

Surgical intervention for renal artery stenosis

All surgical comparative studies have been done by specialized centres and in very small cohorts. The numerous uncontrolled surgical audits suggesting better outcomes are weakened by the methodological problems of only looking at selected patients and all studies are prior to 2000 and recent angioplasty with distal protection.

There is one randomized study comparing the renal outcomes of surgical revascularization with conservative (medical) therapy.[13] Both groups had the same 67% event-free survival with no statistically significant differences between the groups regarding outcomes of BP and renal function. The power was limited by the small sample size ($n = 52$).

There are two studies that randomized patients to either surgery or angioplasty:

Balzer *et al.*,[14] compared surgery in 27 patients with angioplasty in 23 patients in a randomized trial where selection from a large cohort of 330 patients to participate in the trial was decided by a committee of clinicians. Both groups showed significant improvement of hypertension (20 mmHg reduction) as well as improvement or stabilization in patients with insufficient renal function. Freedom from restenosis (>70%) was achieved in 90.1% of the surgical group and 79.9% of the interventional group. There were significant complications however, with periprocedural morbidity of 13% in the interventional group and 4% in the surgical group. In addition, 4-year follow-up mortality was 18% in the interventional group and 25% in the surgical group, suggesting a very cardiovascular-prone population.

Weibull *et al.*,[15] compared surgery with percutaneous angioplasty in 58 patients with unilateral atherosclerotic RAS and 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 remained 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 the renal artery patency rate did not differ between the 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.

Flash pulmonary oedema studies

Since the first description of a patient with RAS responding to revascularization by Pickering *et al.*,[16] many studies have confirmed 'flash pulmonary oedema' as a clinical entity. All of these studies are case reports or case series that show a reduction of the 'flash pulmonary oedema' (recurrent pulmonary oedema with normal left ventricular function associated with renovascular disease) by the use of angioplasty with/without stenting of the renal artery. No prospective data exist, the data are descriptive, and there are no long-term follow-up data.

Treatment of those with end-stage kidney disease on dialysis by renal angioplasty

Prior to any studies in angioplasty in this area, a few case reports have suggested surgical revascularization of the renal artery may lead to people coming off dialysis. Dwyer *et al.*[17] demonstrated in a case series that there was improvement in renal function in dialysis-dependent patients submitted to percutaneous transluminal coronary angioplasty (PTCA). In these and the surgical patients, urine output was established immediately without the need for further dialysis. The authors recommended urgent investigation with Doppler ultrasound and Technetium MAG3 before angiography to determine which kidney is to be targeted based on viability of renal tissue. Since that case series, a few additional case reports have been published but no prospective series with long-term follow up.

Treatment of fibromuscular dysplasia

Fibromuscular dysplasia is a non-atherosclerotic, non-inflammatory vascular disease of largely unknown pathogenesis that primarily affects the renal and cerebral arteries. Because FMD is not common, no large controlled studies exist to help guide therapy. The disease can present in a number of ways, ranging from asymptomatic to a multisystem disorder with a clinical picture that mimics necrotizing vasculitis, involving mesenteric ischemia, renal vascular hypertension, renal failure, claudication, transient ischemic attack or stroke. Commonly, for FMD of the kidneys, the presentation is that of a young woman with sudden onset of hypertension.

Currently, the mainstay of intervention is PTCA for patients with difficult to control hypertension, renal insufficiency or arterial dissection. Percutaneous transluminal angioplasty is less costly than surgical revascularization, less invasive, can be performed on an outpatient basis, and is associated with lower morbidity. However, if it is unsuccessful, surgical therapy may still be used. Technical success of PTCA is now approaching 100% with hypertension cure in 14–59% and improvement in 21–74%.[18] Recurrence rates are 28% at 5 years in the largest retrospective data review by Davies *et al.*[19] A longer duration of hypertension, concomitant atherosclerotic disease and complex branch-vessel repair all adversely affect the results of revascularization. Successful angioplasty often results in a substantial and rapid reduction of both the systolic and diastolic BP. Correlates of successful outcome include an age of less than 50 years, the absence of associated coronary or carotid stenoses, and duration of hypertension of less than 8 years. All reviews in this area suggest the need for regular follow up but the timing of this is yet to be determined prospectively.

SUMMARY OF THE EVIDENCE

Overall, the current evidence suggests that patients with ARVD should not be subjected to PTCA because there is no clear equal benefit of PTCA over medical therapy for control of BP or preservation of kidney function in patient groups that include stable or slowly declining renal function or relatively stable BP. There is a significant complication rate of 10–25% from PTCA. There may be selected patients (see Table 1) who are likely to benefit based on case series, although such subgroups have not been defined from prospective controlled studies. Ideally, the procedure should be performed in specialized centres with low complication rates. Further large studies are underway that may clarify the populations that are most likely to benefit.

Surgery at specialized centres is likely to produce similar results as PTCA in selected individuals.

FMD is unlikely to be studied in prospective controlled trials, however, it is appropriate to treat FMD with angioplasty in specialized centres based on the uncontrolled data that currently exists.

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.

SUGGESTIONS FOR FUTURE RESEARCH

Existing data suggest that there are subgroups that may benefit from revascularization, especially patients with mild to moderate chronic renal insufficiency, critical RAS (>80% diameter loss) and a recent decline (past 6 months) in renal function. These patients should be revascularized with the optimum technique, possibly including embolic protection. It is hoped that subgroup analysis from the CORAL study may provide an answer for these patients (ASTRAL showed a positive trend). Alternatively, a dedicated trial could be performed.

CONFLICT OF INTEREST

Rob MacGinley has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1 Situations where revascularization of high-grade renal artery stenoses might be considered

(a) To improve severe hypertension (>160/100 mmHg or resistant to >4 drugs)
(b) Patients with a strong indication for blockade of the renin-angiotensin system who experience a >30% rise in serum creatinine after therapy is commenced
(c) Progressive and rapid decline in kidney function with other causes excluded
(d) Episodes of proven flash pulmonary oedema, in a patient with normal baseline left ventricular function
(e) To attempt to recover dialysis-independent kidney function in a patient recently commenced on dialysis who has viable kidney tissue by nuclear scanning and a high-grade stenosis

Table 2 Randomized controlled trials – methods

Study	*N*	Participants	Experiment	Follow up (months)	Allocation concealment	Blinding	Intention to treat	Loss (%)	Cross over
Bax *et al.* (2009)[12]	122	Selected by clinicians with stable blood pressure <140/90 mmHg but impaired renal function	PTRA (stented) *vs* medical therapy (not including ACE initially)	24	Central	Outcomes	Y	10%	18 did not get a stent (13%)
The ASTRAL Investigators, (2009)[3]	806	Selected by clinicians with RAS and uncertainty if they should have PTRA	PTRA (95% stents – no distal protection) *vs* medical therapy alone	5 years	Central	Outcomes	Y	80% (5 years)	6% medical were revascularized, 17% intervention were not revascularized
van Jaarsveld *et al.* (2000)[5]	106	106 patients with hypertension who had atherosclerotic renal artery stenosis	PTRA *vs* antihypertensive drug therapy	12	Central	Researchers	Y	1.9%	27% PTRA and 45% medical
van de Ven *et al.* (1999)[8]	85	85 patients with ostial RAS	PTA *vs* stent	6	Independent nurse	Outcome	Y	4.7%	8% PTRA
Webster *et al.* (1998)[6]	55	Population of 135 (highly selected group were randomized)	PTA *vs* medical therapy	6	Central	Outcome	Y	3%	0%
Plouin *et al.* (1998)[7]	49	Unilateral >75% stenosis on angiogram	PTA (±stent)	6	Central	BP only	Y	0.5%	27%

ACE, angiotensin converting enzyme; PTRA, percutaneous transluminal renal angioplasty; RAS, renal artery stenosis.

Table 3 Randomized controlled trials – results

Study	Outcomes	Intervention mean (standard deviation)	Control	Difference/relative risk
Bax *et al.* (2009)[12]	RF	Increased to 168 µmol/L	Increased to 156 µmol/L	0.37
The ASTRAL Investigators, (2009)[3]	RF – rate of change of the reciprocal of serum creatinine (L/µmol per year)	Decreased -0.07×10^{-3} L/µmol per year	Decreased -0.13×10^{-3} L/µmol per year	0.06×10^{-3} (95% CI: –0.002 to 0.13)
	SBP	10 mmHg decrease	8 mmHg decrease	–0.11 (95% CI: –8.90 to 8.69)
van Jaarsveld *et al.* (2000)[5]	Mean SBP	160 (26)	163 (25)	–3.00 (95% CI: 12, 6.72)
	Mean DBP	93 (13)	96 (10)	–3.00 (95% CI:7.39, 1.39)
van de Ven *et al.* (1999)[8]	RF improved	4/41	5/40	0.78 (95% CI: 0.23, 2.70)
	RF worse	8/42	9/40	0.87 (95% CI: 0.37, 2.02)
	Htn better	20/41	23/40	0.33 (95% CI: 0.07, 1.52)
	Htn worse or as bad	21/41	17/40	
Webster *et al.* (1998)[6]	Bilateral RAS SBP better	152 mmHg (12)	171 mmHg (16)	34 mmHg (Mean change from run in) <0.05
	Bilateral RAS DBP better	3 mmHg (12)	91 mmHg (16)	11 mmHg (mean change from run in)
	Unilateral RAS SBP better	173 mmHg (13)	161 mmHg (14)	2 mmHg (mean change from run in)
	Unilateral RAS DBP better	83 mmHg (13)	91 mmHg (14)	10 mmHg (mean change from run in)
Plouin *et al.* (1998)[7]	24 h BP systolic	12 ± 20 mmHg	8 ± 16 mmHg	Diff 0.46
	24 h BP diastolic	10 ± 11 mmHg	5 ± 10 mmHg	

CI, confidence interval; DBP, diastolic blood pressure; Htn, hypertension; RAS, renal artery stenosis; RF, renal failure; SBP, systolic blood pressure.