

Natural history and progression of atherosclerotic renal vascular stenosis

Date written: December 2008

Final submission: October 2009

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

GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- Atherosclerotic renovascular stenosis is a potentially progressive disease.
- Risk factors for progressive stenosis and renal artery occlusion include:
 - uncontrolled systolic hypertension (>160 mmHg)
 - diabetes mellitus
 - high grade (>70%) ipsilateral and contralateral atherosclerotic renal vascular disease (ARVD), and
 - significant baseline proteinuria.
- Risk factors for atrophy include:
 - systolic hypertension (>160 mmHg)
 - stenosis of more than 60%, and
 - decreased renal cortical blood flow.
- Risk factors for decline in glomerular filtration rate (GFR) include:
 - abnormal baseline creatinine (>128 $\mu\text{mol/L}$)
 - bilateral ARVD or ARVD in solitary kidney.
- Atherosclerotic renovascular stenosis is associated with high mortality and morbidity due to atherosclerosis elsewhere, particularly coronary artery disease.

IMPLEMENTATION AND AUDIT

Not relevant to this subtopic.

BACKGROUND

This guideline covers the following areas:

- ARVD
- renal artery stenosis (RAS) without surgical and endovascular intervention
- RAS with or without medical management.

For the purposes of this guideline and after accommodating for variability between studies (reviewed below), ARVD has been classified into the following grades based on the degree of stenosis:

- high (>70%)
- intermediate (50–70%), and
- low grade (<50%).

The following endpoints have been addressed when considering the natural history of ARVD:

- Clinical: requirement of hypertensive medications
- Laboratory: change in GFR
- Ultrasound: change in kidney sizes
- Angiographic/duplex sonography: progression of stenosis, and
- Other vascular comorbid events: stroke, coronary events.

Approximately 1–6% of hypertensive patients have renovascular lesions on arteriography.^{1–4} Unselected autopsy data suggest that 27% of patients over 50 years have more than 50% stenosis of at least one renal artery.⁵ It is the primary cause of renal failure in 5–22% of patients over 50 years who begin dialysis. Various risk factors have been identified in relation to the occurrence and progression of ARVD.

Management of ARVD is made controversial by the lack of randomized controlled trials. Available studies differ widely in the variables that may influence renal survival such as hypertension control, interventions for revascularization (surgery, angioplasty alone, and angioplasty with stenting with and without distal protection devices) and medical therapy. Furthermore, the potential risks of the intervention such as contrast nephropathy and cholesterol embolism may cause significant morbidity. Knowledge of the natural history and risk factors for progression of RAS can thus be helpful in deciding whether, when and how to intervene.

A number of studies looking at the natural history of ARVD have demonstrated progression of RAS, including to renal artery occlusion. However, there is no Level I or II evidence to support any recommendations regarding the natural history. Prospective studies are scarce because of the multiple interventions that either confound the results or make such study designs impractical. Allocation of patients with very mild or very severe lesions to the conservative management arm may lead to selection bias. Knowledge of the natural progression of ARVD has been largely derived

from studies that are retrospective, have used historical controls, or case series. Moreover, imaging to determine progression has been initiated by clinical factors rather than being driven by a study protocol, and various imaging modalities have been used. Finally, many of the studies were performed before modern treatment of risk factors for atherosclerotic cardiovascular disease with drugs such as statins and renin-angiotensin system antagonists were available.

These guidelines focus on ARVD as this is the most common type of RAS and the treatment of this cohort is most contentious. Fibromuscular dysplasia (FMD) is not specifically addressed by this guideline. FMD has at least five different types with varied rates of progression and it is not currently possible on the basis of angiography to classify lesions to a particular FMD subtype. Furthermore, FMD is usually associated with hypertension and interventional therapy is unequivocally favoured irrespective of the subtype.

SEARCH STRATEGY

Databases searched: The terms used to define atherosclerotic renovascular disease 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 were searched. MeSH terms and text words for natural history and progression were combined with MeSH terms and text words for atherosclerotic renovascular disease. The search was performed in Medline (1950–April 2009). In addition, the reference lists of manuscripts retrieved by the above method were manually reviewed for additional studies. The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 2 April 2009.

WHAT IS THE EVIDENCE?

The following text summarizes the studies identified by the literature search. Table 1 in the Appendix presents a brief description of the studies.

Progression of stenosis

Qualitative data have been reviewed from prospective studies that recruited patients with varying degrees of stenoses to assess the variation in the rates of disease progression in patients with different grades of stenoses.

Arteriographic studies

A number of studies have performed follow-up renal angiograms in patients to examine the progression of lesions. These are predominantly older studies with small sample sizes. The first observational evidence for the progressive nature of ARVD came in 1966 from Dustan and co-workers.

Using urographic and angiographic studies, they demonstrated that 61% of 18 patients progressed over a 6-year period.⁶

In 1968, Meaney *et al.* reported angiographic follow-up results for 39 patients with ARVD (36 with ARVD and 3 with both ARVD and FMD). Of these patients, 14 were noted to have progressive disease over the period of follow up of 7 years with 7 patients showing progression within 2 years and 3 patients within 1 year.⁷

Wollenweber *et al.* in 1968 reported a study involving 30 patients with a mean age of 52.7 years for females and 54.5 years for males. Patients with hypertension and/or azotemia were selected for the study. After an initial aorto-renal arteriogram they were followed up with a second study after a mean interval of 28.1 months. A worsening of stenosis was reported in the renal artery to one kidney in 13 patients and in arteries to both kidneys in 6 patients.⁸

In a study by Schreiber *et al.* 44% of 85 patients had progression of ARVD on mean follow up of 52 months. A total of 16% progressed to total occlusion. Half the patients with less than 50% stenosis demonstrated no change in the sequential angiogram. The rate of progression to complete occlusion was 39% in the '75–99% stenosis' group compared with 5% in the '<50%' group. The average monthly rate of progression in the three patient groups (<50%, 50–75%, 75–99%) were 1.59, 1.37 and 2.01, respectively.⁹

Dean *et al.* performed a subset analysis of a prospective randomized study and reported progression in patients designated to the medical management arm. The method of randomization was not specified. Over a mean follow-up period of 28 months, progression to total occlusion occurred in four patients (12%). No data were provided regarding the baseline degree of stenosis in these arteries.¹⁰

Renal duplex sonography studies

Renal duplex sonography (RDS), although fraught with drawbacks of reproducibility and availability of technical expertise, is currently considered a useful tool for monitoring ARVD when optimal sonographic conditions can be ensured. A number of studies have looked at the stenosis progression with RDS.

A large prospective observational study by Caps *et al.* looked at 295 renal arteries in 170 patients over a 5-year period using RDS. They used the principle that blood flow velocity across the stenosis was proportional to the degree of vessel diameter reduction. An increase in peak systolic velocity (PSV) of ≥ 100 cm/s was derived as being significant based on the between-observer variability for renal artery PSV measurements. Disease progression was defined as any detectable increase in the degree diameter reduction in the renal artery, including renal artery occlusion. The 3-year cumulative incidence of renal artery disease progression was 18%, 28% and 49% for renal arteries initially classified as normal, <60% stenosis and $\geq 60%$ stenosis, respectively. Systolic blood pressure (BP) ≥ 160 mmHg, diabetes mellitus, ipsilateral or contralateral stenosis $\geq 60%$, and occlusion of contralateral renal artery were identified as independent risk

factors for stenosis progression in a stepwise Cox proportional hazard analysis.¹¹ Study limitations, apart from being observational included:

- selected patients had hypertension or reduced kidney function. Patients with ARVD and normal BP and renal function were not included.
- use of ultrasound as a tool to follow up has its limitations. These include the potential for variability introduced by inter-observer variability when multiple sites and technicians are involved, and test–retest reproducibility.
- inadequate power to detect the influence of other well-known risk factors for atherosclerosis disease progression such as lipid profiles, race and renal function, and
- no data on the use of important medical therapies such as inhibitors of the renin-angiotensin system or statins.

Despite these limitations, this study provides insight into the risk factors associated with the progression of stenosis.

The first population-based prospective study looking at incident RAS and its progression was reported by Pearce *et al.* in 2006.¹² RDS was applied to a selected geographic cohort of elderly patients (mean age 82 ± 4 years) participating in the Cardiovascular Health Study, an observational population-based study for cardiovascular disease and stroke risk factors. The study included all free-living persons in each sampled household aged ≥ 65 years. Among the 834 participants, a RAS of $\geq 60\%$ was identified in 6.8% (57/834) of participants. There was a significant association with increasing participant age, decreased HDL and increased systolic BP. After an 8-year period, 119 participants had a second RDS, which was technically satisfactory in 235 kidneys. At first examination, ARVD was present in 13 kidneys (5.5%). None of the subjects who had $> 60\%$ stenosis at baseline progressed to occlusion at the second study. New stenoses of $\geq 60\%$ ('incident' stenoses) were identified in 9 kidneys (2.9%). By univariate analysis, the increase in diastolic BP ($P = 0.01$) and decrease in renal size ($P < 0.001$) were significantly associated with incident stenoses.

A healthy cohort effect from healthy participants and significantly less participant re-recruitment at follow up was collectively considered to have led to an underestimation of RAS progression. The criteria for progression was change in PSV of greater than twice the standard deviation of the predicted change in an age-matched cohort over a median follow-up period of 2 years. In the control group, 95% had some of the recognized risk factors for atherosclerosis. This could have resulted in a control cohort with a higher than expected rate of progression resulting in an underestimation of the progression in the study cohort.

Other notable sources of bias were technological improvements in RDS using colour flow Doppler technology at the second follow up, inter-observer differences in reporting and a loss to follow up, with only a small number of patients who participated in the second study. Of the participants, 224 died after the initial study. There were little data on the cause of death, which was presumed by the authors to be mostly from cardiovascular causes. This could have selected participants with less severe vascular disease to complete the follow-up duplex, thus underestimating the progression rate.

Renal atrophy

A number of studies suggest that ARVD can cause renal atrophy, and some risk factors for this have been identified.

Renal duplex sonography studies

Caps *et al.* in their stenosis progression study discussed above examined the risk factors and rate of atrophy of kidneys with a $\geq 60\%$ stenosis on RDS.¹³ A total of 204 kidneys with such stenoses in 122 participants were followed for a mean of 33 months (range 5–72 months). They excluded kidneys with renal artery occlusion and prior intervention to their arteries as well as those with renal sizes < 8.5 cm.

The baseline lengths were close to those expected in an age- and sex-matched population. A reduction of renal length greater than 1 cm occurred in 16.2% of the kidneys. The cumulative incidence of atrophy at 2 years was 5.5% for kidneys with normal baseline renal arteries, 11.7% in the $\leq 60\%$ stenosis group and 20.8% in the $\geq 60\%$ group. This association was significant ($P = 0.009$). Those arteries that occluded during the study period had $\geq 60\%$ stenosis at baseline and these kidneys shrank ≥ 1 cm on follow up. The three baseline factors independently associated with renal atrophy (identified by the univariate Cox proportional analysis) were systolic hypertension, severity of RAS and diminished renal cortical blood flow velocity.

A 1.9-fold and 1.6-fold increase in the risk of renal atrophy was associated with every 20 mmHg increase in systolic BP and 10 mmHg increase in diastolic BP, respectively, at the follow-up examinations. The use of ACE inhibitors at baseline showed no significant association with renal atrophy even in kidneys with significant stenosis. There was no significant association between the presence of accessory renal arteries and a decreased risk of atrophy. Finally, the mean change in serum creatinine concentration was $+7 \mu\text{mol/L}$ per year and $+29 \mu\text{mol/L}$ per year in participants with atrophy detected in one kidney and both kidneys, respectively.

Arteriographic studies

In an observational series of patients with ARVD using intravenous pyelography, Dean *et al.* demonstrated a stability ($< 5\%$ reduction) in renal sizes in 37% of patients, mild to moderate decrease (5–9%) in 26% of patients and significant ($> 10\%$) reduction in kidney length (equated to 30% decrease in renal mass) in 37% of patients.¹⁰ This study supports the hypothesis that ARVD could be associated with progressive renal atrophy. However, there was little data relating renal atrophy to degree of baseline stenosis.

The study by Schreiber *et al.* used angiographic images for kidney sizes and reported a reduction in renal size in 70% of patients with progressive ARVD compared with 13% in those with stable stenosis ($P < 0.001$). However, there is little information about the side of the stenosis, the side of renal atrophy and correlation between them.⁹

Renal function

A number of longitudinal studies have demonstrated a decline in kidney function over time in patients with ARVD.

Schreiber *et al.* reported change in serum creatinine in different categories of baseline stenosis (<50%, 50–75%, 75–99% and 100%) over a mean follow-up period of 52 months. An increase in serum creatinine levels was seen in 54% of patients with progressive disease (defined as change from one category of stenosis to a category of higher grade stenosis), while an increase was observed in only 25% of patients without evidence of angiographic progression.⁹ However, these data are limited by the use of serum creatinine, which is a poor indicator of individual kidney function as a marker of renal function.

Chabova *et al.* in a retrospective cohort study at the Mayo Clinic, looked at 68 patients with angiographically proven high-grade stenosis (>70%) over a mean period of 38.9 months. Serum creatinine rose from 124 $\mu\text{mol/L}$ to 176 $\mu\text{mol/L}$ for the entire group. This result was skewed by 10 patients (14.7%), 6 of whom developed end-stage kidney disease. Among patients with bilateral high grade stenosis and with unilateral high grade stenosis to a solitary functioning kidney, 20% showed a rise in serum creatinine over an average follow up of 36.4 months while 12.8% of patients with unilateral high grade stenosis had a rise in serum creatinine over an average follow-up period of 40.1 months.¹⁴ Stenosis to the entire renal mass was found to be associated with higher baseline creatinine and greater likelihood of clinical deterioration.

In a cross-sectional study involving a cohort of patients from the Cardiovascular Health Study, Edwards *et al.* analysed the association between ARVD and excretory renal insufficiency.¹⁵ The presence of ARVD showed an association with renal insufficiency (odds ratio 2.21; 95% confidence interval: 1.02–4.79; $P = 0.043$) that was independent of effects of age, race, sex, body weight and diabetic status.

The prospective multicentre observational study by Pillay *et al.* in 2002 recruited patients with a >50% RAS from patients undergoing angiography for peripheral vascular disease. A total of 159 renal arteries in 85 patients with such stenoses were followed up by renal ultrasound over a mean period of 30 months. Renal length and BP were stable. A significant increase in serum creatinine was noted in the survivors of unilateral disease without intervention.¹⁶ The finding of declining renal function in patients with unilateral ARVD suggests that intrinsic parenchymal disease, rather than the disease of the large renal arteries is the major determinant of declining renal function in this population.

This hypothesis was supported by an elegant prospective study by Farmer *et al.* that looked at the relationship between presence of RAS and single kidney glomerular filtration rate (SK-GFR) using radionuclide studies in 79 patients with ARVD. The study noted a similar impairment of renal function in kidneys with and without ARVD while kidneys with occluded renal arteries were associated with significant reduction in function compared with the con-

tralateral kidney. It was concluded that unilateral ARVD could not only compromise ipsilateral SK-GFR by ischemic mechanisms but also contralateral SK-GFR by non-ischemic mechanisms.¹⁷

The study by Losito *et al.* reported on 195 patients with ARVD over an average follow up of 54 months.¹⁸ Of the total, 54 were maintained on medical management, with 38.8% on an ACE inhibitor as one of the many antihypertensives in the medical treatment arm. During the period of follow up, the mean change in creatinine in the medically treated arm was an increase of 108 $\mu\text{mol/L}$.

When worsening renal function was examined by Losito *et al.* two factors were found to be significant by multivariate analysis. The first was an abnormal baseline creatinine (>128 $\mu\text{mol/L}$) with a hazard ratio of 1.42. The second was the use of an ACE inhibitor which was associated with a reduced risk of further impairment of renal function (hazard ratio of 0.29), more pronounced in the medically treated arm. Of note, was the significant proportion of patients (17 out of 54) in the medical arm who were using statins.¹⁸

Hypertension

There are only a few studies that have looked at the changes in number and need for antihypertensive medications in patients with ARVD over time. In most of the studies, there is little information on maximizing the dose of a particular drug before resorting to a second drug.

In the Chabova *et al.* study, by design all of the patients were hypertensive and had a mean BP of 157/83 mmHg while on antihypertensive therapy.¹⁵ During the follow up, the average requirement for antihypertensive medications rose significantly from 1.6–1.9 ($P = 0.02$) per person. There was a non-significant trend towards lower systolic and diastolic BP. Only 32.4% of the patients were taking an ACE inhibitor and the proportion of patients taking each class of antihypertensive medication did not differ significantly at the end of the follow-up period.

Other vascular bed involvement and related comorbid events

Wollenweber *et al.* reported clinical evidence of associated symptomatic coronary disease or cerebrovascular disease in 31% of patients with mild to moderate RAS and 49% of patients with marked or severe RAS. New symptomatic cardiovascular disease including cardiac failure developed in 47% of patients within 5 years.⁸ This study looked at a relatively young cohort of atherosclerotic patients and the patients selected for medical treatment had a milder degree of stenosis. There were no data on the type and number of antihypertensive medications or BP control. The estimated 5-year survival rate was 66.7% in patients with ARVD compared with 91% in the comparable normal population. No significant difference in survival was noted between the medical and the surgically treated group despite the more severe atherosclerotic disease in the surgical group.

The elderly cohort of patients (mean age 71.8 years) in the study by Chabova *et al.* showed higher mortality in patients with bilateral stenosis when compared with those with unilateral disease (42% vs 21.3 %; $P = 0.07$). Disease was identified in other vascular beds in 97.1% of patients.¹⁴

SUMMARY OF THE EVIDENCE

Atherosclerotic renal vascular disease is a progressive disease, with high grade stenosis (>60%), systolic hypertension (>160 mmHg) and diabetes associated with faster progression. Abnormal baseline creatinine and bilateral stenosis are associated with greater likelihood of deterioration of renal function. Patients with ARVD have increased mortality and morbidity, particularly from cardiovascular disease.

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

1. Perform a large prospective study with ultrasound surveillance to look at risk factors for progression.
2. Investigate the variability in progression rate when different imaging modalities are used for follow up.
3. Investigate the influence of lifestyle changes, statins, renin-angiotensin system blockade alone or in combination on stenosis progression.

CONFLICT OF INTEREST

Subramanian Karthik Kumar 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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APPENDIX

Table 1 Characteristics of included studies

Study	Patients (arteries)	Age (years)	Study design	Setting	Participants	Control	Follow up	Results
Meaney <i>et al</i> (1968) ⁷	91, 39 ARVD	36–55	Observational, serial angiograms	Cleveland clinic hospital	Aortic renal arteriograms performed for hypertension +/- uremia between 1960–1963		6 months–7 years	Of the 39 patients, 14 showed progressive disease.
Wollenweber <i>et al</i> (1968) ⁸	30	52.7 (range: 40–65)	Observational, serial arteriograms	Mayo clinic	Patients with ARVD who had serial angiograms		Mean: 28.1 months	
Schreiber <i>et al</i> (1984) ⁹	85	51.3	Retrospective review	Cleveland clinic	Renovascular hypertension from ARVD randomized to medical management		52 months	44% progressed to complete occlusion (39% in the '75–99% stenosis' group and 5% in the '<50%' group).
Dean <i>et al</i> (1981) ¹⁰	35	40–65 (mean age unspecified)	Prospective randomized (method of randomization not specified)	Vanderbilt University Medical Centre	Subjects with ≥ 1 stenotic main renal artery in RDS		28 months	12% progressed to total occlusion, 17% exhibited contralateral ARVD progression.
Caps <i>et al</i> (1998) ¹¹	170 individuals, 295 renal arteries		Prospective observational	University of Washington	Selected geographic cohort of elderly patients (mean age 82 ± 4 years) participating in the Cardiovascular Health Study		33 months	The 3 years cumulative incidence of stenosis progression was 18%, 28% and 49% for renal arteries initially classified as normal, <60% stenosis, and $\geq 60\%$ stenosis, respectively.
Pearce <i>et al</i> (2006) ¹²	13 renal arteries	81.9	Population-based prospective	Wake Forest University School of Medicine	Angiographically proven high grade stenosis (>70%)		8 years	None with >60% stenosis progressed to complete occlusion. Incident ARVD occurred in 2.9% of the study population.
Chabova <i>et al</i> (2000) ¹⁴	68 patients	71.8	Retrospective cohort	Mayo clinic	Cardiovascular Health Study		38.9 months	Stenosis to the entire renal mass was associated with higher baseline creatinine and greater likelihood of clinical deterioration.
Edwards <i>et al</i> (2003) ¹⁵	834 individuals	77.2	Case control	Wake Forest University School of Medicine	Patients with peripheral arterial disease with incidentally picked up ARVD (>50% stenosis)	Subjects without ARVD		Presence of ARVD showed an association with renal insufficiency (odds ratio 2.21).
Pillay <i>et al</i> (2002) ¹⁶	159 renal arteries (in 85 patients)	71	Prospective multicentre observational	Joint vascular research group, UK	Angiographically proven ARVD		30 months	Significant increase in creatinine in patients with unilateral ARVD.
Farmer <i>et al</i> (1999) ¹⁷	79 patients	68.9	Prospective descriptive	Guy's and St Thomas renal unit	Patients in the medical treatment arm		25 months	Similar impairment of renal function in kidneys with and without ARVD. Kidneys with occluded renal arteries were associated with significant reduction in function compared with the contralateral kidney.
Losito <i>et al</i> (2005) ¹⁸	54 patients	65.6	Observational	Radiology Institute of the University of Perugia, Italy			54.4 months	Mean change in serum creatinine in the medically treated arm was +108 $\mu\text{mol/L}$.

ARVD, atherosclerotic renal vascular disease; RDS, renal duplex sonography.