

Atherosclerotic renal artery stenosis: Current therapy and future developments

Ranjith Shetty, MD,^a Mitesh S. Amin, MD,^a and Ion S. Jovin, MD, ScD^{a,b} *Richmond, VA*

Atherosclerotic renal artery stenosis affects between 2 and 4 million people in the United States alone and likely has a higher prevalence than previously thought. Renal artery stenosis has been increasingly recognized in recent years, especially in patients with cardiovascular disease. It has been associated with hypertension, renal dysfunction, and sudden onset of pulmonary edema. Patients with symptomatic and hemodynamically significant renal artery stenosis are candidates for revascularization. Revascularization is most often accomplished by renal artery stenting, which has high success rates in terms of patency and low complication rates. An important element in managing patients with renal artery stenosis is selecting those patients who are most likely going to benefit from revascularization. This review article focuses on the clinical diagnosis, current treatment options, and future directions regarding treatment of patients with renal artery stenosis. (*Am Heart J* 2009;158:154-62.)

Renal artery stenosis (RAS) is the most common secondary cause of hypertension and affects 1% to 5% of hypertensive patients, but the true prevalence of RAS is not known.¹ In autopsy studies, the prevalence of RAS has ranged from 26% to 62%.^{2,3} Renal artery stenosis can be unilateral, bilateral, or associated with a solitary functioning kidney. In an ultrasound screening study of 834 Medicare patients, RAS (>60%) was present in 57 patients (6.8%); and of these 57 patients, 12% had bilateral RAS.⁴ The prevalence of RAS is thought to be higher in patients with systemic cardiovascular disease. In 1,235 patients undergoing diagnostic cardiac catheterization, RAS ($\geq 50\%$) was demonstrated in 15% (11% unilateral and 4% bilateral).⁵ Prevalence of RAS in patients with a solitary functioning kidney was not clearly defined in either of these studies. Lastly, in 218 patients undergoing peripheral angiography for investigation of peripheral vascular disease, RAS was present in 36.2%.⁶ This article reviews the etiology, clinical implications, diagnosis, functional assessment, clinical indications, and treatment strategies for RAS.

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The most common etiology of RAS is atherosclerosis, which accounts for approximately 90% of cases. The next most common cause is fibromuscular dysplasia (FMD),

most commonly in younger females. Atherosclerotic RAS (ARAS) typically involves the ostium and proximal third of the renal artery, whereas FMD typically involves the middle third of the vessel. In a study of 14,152 patients undergoing abdominal aortography during cardiac catheterization, independent predictors of ARAS included coronary artery disease (CAD), elevated creatinine, peripheral arterial disease, cerebrovascular disease, hypertension, ejection fraction of <30%, diabetes mellitus, female gender, and a family history of CAD.⁷

Clinical implications

Independent of comorbid conditions, the presence of ARAS has important clinical consequences. Guo et al⁸ studied 146,973 patients and showed that 9.2% had been diagnosed with atherosclerotic renovascular disease in the 2-year period before initiation of dialysis. Conlon et al⁹ studied 3,987 patients who underwent abdominal aortography immediately after coronary angiography to investigate the effect of the severity of RAS on all-cause mortality. The 4-year unadjusted survival rates for patients with and without significant RAS were 57% and 89%, respectively ($P < .001$); and the presence of RAS was independently associated with decreased survival.⁹ In addition, there was an incremental increase in mortality according to the severity of RAS at baseline.⁹

Clinically, patients with RAS typically present with hypertension, renal insufficiency, or both. Renovascular hypertension results from hypoperfusion of one or both kidneys, which stimulates the renin-angiotensin system resulting in vasoconstriction and salt and water retention. With unilateral RAS, a volume overloaded state is avoided when the contralateral kidney responds to the rise in blood pressure (BP) with a natriuresis. If both kidneys or a solitary functioning kidney is involved, there is no compensatory diuresis. These intravascular fluid shifts

From the ^aCardiovascular Division, Department of Internal Medicine, Virginia Commonwealth University Health System/Medical College of Virginia, Richmond, VA, and ^bCardiovascular Division, Department of Internal Medicine, McGuire Veterans Administration Medical Center, Richmond, VA.

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Reprint requests: Ion S. Jovin, MD, ScD, 1201 Broad Rock Blvd 111J1, Richmond VA, 23249.

E-mail: isjovin@yahoo.com

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can have significant clinical consequences for patients with congestive heart failure (CHF) and/or CAD. Renal artery stenosis can be associated with episodic decompensations of heart failure, “flash” or sudden onset of pulmonary edema, or unstable or refractory angina.¹⁰

In addition to affecting BP and volume status, significant RAS can lead to hypoperfusion resulting in ischemic injury to the renal parenchyma. It has been estimated that at least 10% to 15% of patients entering dialysis programs have ARAS as a primary cause of renal failure, although it is unclear based on current data what percentage of these patients have bilateral RAS, unilateral RAS, or RAS of a solitary functioning kidney.¹¹ It is also well accepted that ARAS is a progressive disease. Over a 7-year period, 1,189 patients underwent 1 or more abdominal aortograms at >6-month intervals to assess the incidence of RAS progression; and 6% of subjects with 1 year between examination demonstrated disease progression in 1 or more renal arteries compared with 28% of subjects who demonstrated disease progression with 6 years between examinations.⁷ In addition, progression of RAS was shown to be associated with loss of renal function: serum creatinine level at follow-up was significantly higher in the group that demonstrated progression to ≥75% stenosis compared with patients with no disease at follow-up ($P = .01$).⁷

Diagnosis

Table I shows the class I American College of Cardiology and American Heart Association (ACC/AHA) guidelines for identifying patients who should be screened for RAS (class I is generally a recommendation for and class III is a recommendation against a certain action, whereas level of evidence [LOE] A is very robust [several large randomized trials] and LOE C is weak [case reports and expert opinion]).¹² Screening can be accomplished by noninvasive methods such as duplex ultrasound, computed tomography angiography (CTA), and magnetic resonance angiography (MRA), or by invasive angiography if noninvasive modalities are inconclusive.

Diagnosis of RAS by duplex ultrasound is a class I recommendation with an LOE B according to the ACC/AHA guidelines.¹² Both the sensitivity and specificity of duplex ultrasound have been shown to be as high as 98% when compared with angiography.¹³ This sensitivity and specificity can be variable, however, based on operator skill, patients' body habitus, intervening bowel gas patterns, and diminished ability to visualize accessory renal arteries.¹⁴ In addition to diagnosis, duplex ultrasound is also useful to monitor renal artery patency after endovascular revascularization because ultrasound transmission through a stent is not distorted like with other imaging modalities such as MRA.¹⁴

With current multidetector-row scanners, CTA can provide high-resolution, noninvasive detection of RAS in addition to 3-dimensional angiographic images of the

Table I. The ACC/AHA guidelines for class I recommendations for screening for RAS

Clinical characteristics	Level of evidence
Onset of hypertension <30 y	B
Onset of severe hypertension >55 y	B
Accelerated hypertension*	C
Resistant hypertension [†]	C
Malignant hypertension [‡]	C
New azotemia or worsening renal function after ACEI or ARB	B
Unexplained atrophic kidney or discrepancy in size between 2 kidneys of >1.5 cm	B
Suddenly unexpected pulmonary edema (especially in azotemic patients)	B

* Sudden and persistent worsening.

[†] Full doses of a 3-drug regimen that includes a diuretic.

[‡] Hypertension with coexistent evidence of acute end-organ damage, that is, acute renal failure, acute decompensated heart failure, new visual or neurologic disturbance, and/or (grade III to IV) retinopathy.

aorta, renal arteries, and visceral arteries; it is a class I, LOE B recommendation based on ACC/AHA guidelines to establish the diagnosis of RAS in patients with normal renal function.¹² When compared with digital subtraction angiography, Willmann et al¹⁵ studied the diagnosis of RAS with CTA and found a sensitivity of 91% and 92% and specificity of 99% and 99% for 2 separate readers, respectively. Computed tomography angiography, however, remains limited by the need for iodinated contrast that is problematic in this population of patients with a high prevalence of renal insufficiency.

Contrast-enhanced MRA with gadolinium is also a class I recommendation with an LOE B by the ACC/AHA guidelines for the diagnosis of RAS.¹² Willmann et al¹⁵ also showed that contrast-enhanced MRA had a sensitivity of 92% and 93% and specificity of 100% and 99% among the 2 readers, respectively, for the diagnosis of RAS when again compared with digital subtraction angiography. Use of contrast-enhanced MRA is limited by the cost and the inability to image within a previously placed metallic stent. Lately, concern over the use of contrast-enhanced MRA to diagnose RAS has been increased because of the possibility of systemic nephrogenic fibrosis that is seen more frequently in patients with abnormal renal function.¹⁶

Catheter-based angiography is not a first-line screening tool but remains the criterion standard for anatomical assessment of renal artery lesions. Catheter-based angiography has a class I, LOE B recommendation based on the ACC/AHA guidelines for the diagnosis of RAS when noninvasive tests are inconclusive but clinical suspicion is high.¹² If angiographic access has been obtained for another indication (peripheral or coronary angiography), renal angiography should only be performed if the patient meets one of the class I recommendations for screening noted in Table I. So-called drive-by angiography of the renal arteries is not recommended.

Functional assessment of renal artery lesions

There is little doubt that some patients benefit from renal artery revascularization with stenting, but the treatment effect is not universal for patients with RAS. Most of the studies performed thus far have used anatomical assessment of renal artery lesions without functional assessment as the main entry criterion. Anatomical assessment of RAS does not always correlate with a hemodynamically significant lesion. Regardless of the imaging modality, ideally, diagnosis of RAS requires not only an anatomical assessment of RAS but also identification of a flow-limiting renal artery lesion to help determine which patients will most likely benefit from renal artery intervention.

Several modalities to assess the hemodynamic significance of renal artery lesions exist, but their clinical usefulness still remains in question. A traditional method has been to measure translesional pressure gradients. No systematic evidence exists regarding the significance of translesional pressure gradients, but an expert consensus panel has recommended that a renal translesional mean pressure of at least 10 mm Hg or a systolic pressure gradient of at least 20 mm Hg be adopted as indicating a "functionally significant" lesion.¹⁷

Renal fractional flow reserve (FFR) can also be used to assess severity of RAS using maximal vasodilation with papaverine, an endothelial-independent vasodilator. Mitchell et al¹⁸ prospectively studied 17 patients with RAS and uncontrolled hypertension, and patients with an abnormal baseline FFR (<0.8) had a significantly higher rate of BP improvement after renal artery stenting. The same study showed that the sensitivity of an abnormal renal FFR in predicting improvement in BP control after renal stenting was 88%.¹⁸ De Bruyne et al¹⁹ studied 15 patients using a model of controlled, graded stenosis by progressive inflation of a compliant angioplasty balloon after renal stenting and found that a ratio of the distal renal artery pressure to aortic pressure (Pd/Pa) of <0.90 corresponds to an approximate systolic gradient of 25 mm Hg and is associated with a significant increase in renin production that was directly measured from the renal vein.

A recent study by Mahmud et al²⁰ attempted to look at other angiographic parameters such as renal frame count (RFC) (using digital cineangiography at 30 frames per second) to predict success of renal stenting to improve hypertension. *Clinical responders*, defined as systolic BP (SBP) decrease of 15 mm Hg, had a decrease in RFC of 7.7 ± 4.6 frames per second as compared with nonresponders who had a decrease in RFC of 1.7 ± 5.1 frames per second ($P = .009$). Although this is a small case series, digital angiography is universally available and may provide a readily available quantitative measure for predicting those patients who may benefit from renal artery stenting if validated in larger studies.

Renal scintigraphy is no longer recommended for diagnosis of RAS because of poor sensitivity and specificity compared with catheter-based angiography as shown by Huot et al²¹ (74% and 59%, respectively). Safian and Madder²², however, have advocated its use to identify patients with RAS and renal ischemia. With the use of technetium-labeled pentetic acid (^{99m}Tc-DTPA), fractional renal blood flow can be measured; and when combined with ¹²⁵Iothalamate, both total and single kidney glomerular filtration rate (GFR) can be measured. They argue that evidence of hypoperfusion through this modality provides reasonable evidence of renal ischemia and possibly identifies patients who may benefit from renal artery revascularization.²²

Duplex ultrasound-derived parameters have also been proposed for the hemodynamic assessment of RAS. Olin et al¹³ showed that Doppler ultrasound-derived peak systolic velocity (PSV) of >200 cm/s, end-diastolic velocity of >150 cm/s, and aortic to renal artery ratio of >3.5 predict RAS of $\geq 60\%$. A recent study performed by Drieghe et al²³ compared these duplex ultrasound-derived parameters and anatomical assessment of RAS by catheter-based angiography using catheter-derived Pd/Pa ratio of <0.9 as the criterion standard for a hemodynamically significant lesion. The study looked at 56 patients with RAS and found that, using a cutoff of 50% for significant RAS, catheter-based angiography falsely identified significant RAS in 38% of cases. A PSV of >180 cm/s falsely identified significant RAS in 55%.²³ Finally, aortic to renal artery ratio was falsely positive in 15% of the cases.²³ These results suggest that catheter-based angiography and duplex ultrasound-derived parameters of PSV and aortic to renal artery ratio overestimate the significance of RAS.²³

Another duplex ultrasound method that can be used to predict responsiveness to revascularization is measuring a renal resistive index (RRI). The RRI is calculated using the following equation: $1 - (\text{end-diastolic velocity} \div \text{maximal systolic velocity})$. An elevated RRI (≥ 0.8) suggests damage to small blood vessels of the kidney. Rademacher et al²⁴ looked at 5,950 patients with hypertension with Doppler ultrasound; and 138 patients had RAS of $\geq 50\%$ and underwent revascularization by angioplasty, stenting, or surgery. They found that an elevated RRI of ≥ 0.8 was associated with a lack of treatment response.²⁴ Although this appeared promising, Zeller et al²⁵ showed in a subsequent prospective study of 241 patients with RAS of $\geq 70\%$ who were treated with stent placement that an elevated RRI did not predict nonresponders for hypertensive or renal functional improvement.

Thus, conclusive data do not yet exist to support the use of nuclear scintigraphy or duplex ultrasound for determining the hemodynamic significance of renal artery lesion. Angiographic parameters for prediction of clinical responders to renal artery stenting such as measurement of translesional gradients, renal FFR, and reduction in RFC, on the other hand, appear promising; but further

prospective, randomized studies still need to be performed to prove their clinical utility.

Treatment

After diagnosis and functional assessment of RAS, treatment involves medical therapy, revascularization, or both. Medical therapy thus far has focused on BP control. Angiotensin-converting enzyme inhibitors (ACEIs) (class I, LOE A), angiotensin receptor blockers (ARBs) (class I, LOE B), and calcium-channel blockers (class I, LOE A) are recommended for the treatment of hypertension in unilateral RAS; and β blockers (class I, LOE A) are recommended for the treatment of hypertension in patients with RAS in general.¹² The use of ACEIs and ARBs is sometimes limited in patients with RAS over concerns of precipitating acute renal failure. Hackam et al²⁶ suggest that these concerns may be overstated and may be applicable only to a specific subset of patients with RAS. van de Ven et al²⁷ looked at the initiation of enalapril in 93 patients with ARAS and used an increase in serum creatinine of $\geq 20\%$ from baseline as the threshold for discontinuation of the medication. The study showed that all patients with severe bilateral RAS ($\geq 50\%$) could not tolerate ACEIs because of increases of serum creatinine beyond the established threshold.²⁷ On the other hand, most (63%) patients with unilateral RAS or lesser degrees of bilateral RAS ($< 50\%$) showed no significant increase in serum creatinine.²⁷ All elevations in serum creatinine induced by initiation of ACEIs in this study were reversible with discontinuation of the medication, and no cases of renal failure were seen.²⁷ These results suggest that treatment with ACEIs can be safely initiated in patients with RAS as long as it is performed with careful supervision. If elevations in serum creatinine of $\geq 20\%$ from baseline do occur, the medication should be promptly discontinued; and further investigation to the severity of their RAS may be warranted. The same rationale has been used for the use of ARBs in patients with RAS, although no prospective studies currently exist.

In addition to BP control, aspirin use, lipid lowering, and smoking cessation have been proposed for slowing the progression of RAS and preserving renal function. Even with medical therapy, however, progression of RAS can result in adverse cardiovascular and renal events. Chabova et al²⁸ looked at 69 patients with RAS $> 70\%$ who were treated medically and followed for 36 months. Mean serum creatinine increased from 1.4 to 2.0 mg/dL ($P < .05$), 10% progressed to end-stage renal disease, and there was a 29% mortality.²⁸ These data suggest that medical therapy alone may not be sufficient to prevent progression of and adverse outcomes associated with RAS.

Further treatment options beyond medical therapy involve renal artery revascularization that can be accomplished surgically or percutaneously by balloon angioplasty or balloon angioplasty and stent placement. Before the advancements in medical management and percutaneous techniques, open surgical revascularization was the

main treatment option for significant RAS. Vascular surgical reconstruction is indicated by ACC/AHA guidelines for FMD, especially when it extends into segmental arteries (class I, LOE B); for ARAS when it involves multiple small renal arteries or early branching primary renal artery (class I, LOE B); and for patients with RAS undergoing pararenal aortic reconstruction for aortic aneurysms or aortoiliac occlusive disease (class I, LOE C).¹² Weibull et al²⁹ compared surgical revascularization with percutaneous transluminal renal angioplasty (PTRA) and showed no difference in secondary patency rates. The clinical end points of hypertension control and preservation of renal function were no different, but major complications were seen in twice as many surgical patients compared with balloon angioplasty patients (34% vs 17%, respectively).²⁹ As a result, the authors concluded that, in patients with RAS who were candidates for either surgery or balloon angioplasty, balloon angioplasty should be the treatment of choice.²⁹

Renal artery stent placement has since replaced PTRA as the treatment of choice for RAS. van de Ven et al³⁰ conducted a prospective trial that randomized 51 renal arteries in 42 hypertensive patients to angioplasty (with bailout stenting) or primary stent placement. Procedural success was significantly greater in the primary stenting group (90%) versus the balloon angioplasty group (63%), and restenosis rates were significantly lower in the primary stenting group (14%) versus the balloon angioplasty group (48%).³⁰ The superiority of primary renal artery stenting over PTRA was further confirmed in a meta-analysis that compared 14 studies in which patients underwent primary renal artery stenting for RAS with 10 studies in which patients underwent PTRA.³¹ Procedural success rates were higher for stents than PTRA (98% vs 77%, $P < .001$), and restenosis rates were lower for stents than PTRA (17% vs 26%, $P < .0001$).³¹

Most of the studies looking at renal artery stenting so far have been performed with bare metal stents (BMS). As a result, the question arises of whether drug-eluting stents (DES) would reduce restenosis rates further. Zahringer et al³² looked at 105 patients with RAS; 52 patients underwent renal artery stenting with BMS, and 53 underwent renal artery stenting with sirolimus-eluting stents. The binary restenosis rate was 6.7% for sirolimus-eluting stents versus 14.6% for BMS, showing a 50% relative risk reduction in restenosis with DES; but the difference did not reach statistical significance.³² At this point, reference vessel diameter (RVD) of the renal arteries appears to be a major limiting factor for the use of DES in renal artery interventions, as DES expandable to > 5 mm are not commercially available.³³ Lederman et al³⁴ looked at follow-up angiography in 102 patients who underwent renal artery stenting and found that the restenosis rate for vessels with an RVD < 4.5 mm was 36% compared with 6.5% in patients with an RVD > 6.0 mm ($P < .01$). The patients with restenosis also had significantly smaller postprocedure minimal lumen diameter (5.27 vs 6.06 mm, $P < .01$).³⁴

Predictors of in-stent restenosis include smoking, vessel diameter, and time to follow-up.³⁵ To this point, no specific guidelines exist for routine follow-up of patients who have undergone renal artery interventions. Of the noninvasive modalities, duplex ultrasound seems to be useful for follow-up because of the ability to image within a previously placed stent; and duplex ultrasound does not require potentially nephrotoxic agents unlike CTA and MRA. Blum et al³⁶ followed 68 patients for 24 months using serial ultrasound studies at 3, 6, 12, and 24 months. They found significant restenosis in 8 patients using the ultrasound parameter of a change in RRI of >0.05 , and restenosis was confirmed by angiography.³⁶ Seven of the 8 (88%) restenoses found in this study occurred within the first year, supporting a protocol of more frequent ultrasound examinations in the first year after intervention.³⁶ Safian and Madder²² have proposed the use of nuclear scintigraphy to measure GFR and split renal blood flow. They propose obtaining a baseline study after intervention and repeated nuclear blood flow studies at 3 months and annually thereafter.

With regard to follow-up and preventing restenosis, an issue that arises in patients after renal artery interventions is the need for long-term antiplatelet therapy with aspirin and clopidogrel. Specific recommendations do not yet exist for renal artery interventions, so it appears prudent to adapt the recommendations for the treatment of coronary stents with antiplatelet agents at this point. Given, however, that renal arteries are larger than coronary arteries, there may be differences in the duration of antiplatelet therapy required after intervention; but additional studies are required to provide further insights.

Treatment of in-stent renal artery stenosis (IRAS) is also a major consideration when following patients who have undergone renal artery stenting. Zeller et al³⁷ looked at 65 renal artery lesions with their first IRAS; and 19 were treated with balloon angioplasty, 42 with BMS, and 4 with DES. Reoccurrence of IRAS occurred in 37% (7/19) of those treated with angioplasty, 33% (14/42) of those treated with BMS, and none (0/4) of those treated with DES.³⁷ There was a trend toward lower restenosis rates with stent-in-stent placement versus angioplasty, but the results were not significant. The best result with the stent-in-stent strategy was seen with DES, but no conclusions can be drawn from this result because only 4 patients were in this group. Larger studies will be needed to identify the most appropriate treatment of IRAS.

Another important consideration is complications that may arise as a result of a renal artery intervention. Despite high procedural success rates, renal function can deteriorate in up to 32% of patients who undergo renal artery stenting.³¹ Many factors can account for renal dysfunction after renal artery intervention such as contrast-induced nephropathy or worsening of underlying nephropathy. Atheroembolism as a potential etiology for postprocedure renal dysfunction has been increasingly recognized, but

the true prevalence of atheroemboli is not known. Henry et al³⁸ examined the use of embolic protection devices in a prospective, observational study during stenting of 65 renal arteries in which no patients showed a deterioration of renal function at 6 months. Cooper et al,³⁹ however, performed a prospective study of an embolic protection device (Angioguard, Cordis, Miami, FL) in which patients were randomized to undergo renal artery stenting alone, stenting with embolic protection, stenting with abciximab, or stenting with embolic protection and abciximab. Stenting alone, stenting with embolic protection, and stenting with abciximab alone were all associated with a decline in GFR.³⁹ Unexpectedly, the combination of embolic protection and abciximab showed a significant increase in GFR.³⁹ When filter debris was examined in the groups that used embolic protection, there was a significant reduction in platelet-rich thrombi in the group that used embolic protection and abciximab compared with embolic protection alone (42% vs 7%, $P < .01$), which raised the concern of intravascular thrombi formation associated with this device.³⁹

Overall, treatment of ARAS begins with aggressive risk factor management through medical therapy. If revascularization is needed for ARAS, primary renal stenting is the treatment of choice. Because larger vessel diameter and larger poststent lumen diameter are associated with decreased incidence of restenosis, BMS currently play a larger role than DES. Follow-up can be performed with duplex ultrasound or nuclear scintigraphy. Regardless of the modality, examinations should be performed more frequently in the first year because restenosis is more common in this time frame. Antiplatelet therapy is also important in preventing restenosis. However, specific guidelines do not exist for antiplatelet therapy after renal artery stenting; so recommendations for the coronary circulation should be followed. Restenosis is not the only postprocedural concern. Renal function often declines postprocedure, and atheroemboli may play an important role. Embolic protection devices may be useful, but more studies are necessary to assess their safety and efficacy.

Clinical indications for percutaneous renal artery intervention

Three clinical indications for renal artery revascularization in the presence of significant stenosis have been identified by the ACC/AHA guidelines. The first indication is accelerated (sudden or persistent worsening), resistant (to full doses of a 3-drug regimen that includes a diuretic), or malignant (associated with end-organ damage) hypertension; hypertension with unilateral small kidney; or hypertension with intolerance to medication (class IIa, LOE B).¹² Three randomized control trial have investigated the efficacy of medical therapy in addition to percutaneous renal angioplasty (PTRA) versus medical therapy alone in the treatment of hypertension. Plouin et al⁴⁰ randomized 49

Table II. Published randomized trials looking at interventions for RAS

Trial	Patients (n)	Intervention	Follow-up	Main end points	Outcome
Plouin et al ⁴⁰	49	Balloon angioplasty (with or without stent placement)	6 m	Primary: BP at termination and change from baseline Secondary: treatment score and incidence of complications	No significant change in SBP or DBP No significant change in SCr
Webster et al ⁴¹	55	Balloon angioplasty	1, 3, and 6 m, then at 6-m intervals	Primary: BP and SCr at 6 m and the change in these from baseline Secondary: major events	Bilateral RAS: significant improvement in mean change in SBP after angioplasty No change in DBP No significant change in SCr Unilateral RAS: Significant improvement in mean SBP with medical therapy No change in DBP. No change in SCr
van Jaarsveld et al ⁴²	106	Balloon angioplasty	3 and 12 m	Primary: BP at 3 and 12 m Secondary: treatment score, SCr, SCr clearance	No significant change in SBP or DBP No significant change in SCr

SCr, Serum creatinine.

patients with uncontrolled hypertension and RAS to medical therapy versus PTRAs and showed no significant difference in the primary outcome measure that was 24-hour ambulatory BP measurement at 6-month follow-up. Another study randomized 55 patients with hypertension and RAS (28 had bilateral RAS) to medical therapy versus PTRAs.⁴¹ Only the group with bilateral RAS had a statistically significant BP improvement with PTRAs (152/83 versus 171/91 mm Hg, $P < .05$).⁴¹ The DRASTIC trial is the third randomized controlled trial, which involved 106 patients with hypertension and RAS undergoing medical therapy or PTRAs.⁴² At 3 months, mean SBP and diastolic BP (DBP) did not differ.⁴² After 3 months, 22 medically treated patients crossed over into the angioplasty group; but the cohort was analyzed on an intention-to-treat basis. Patients were followed for an additional 9 months; and again, there were no significant differences in mean BPs between the medical therapy group and the PTRAs group. However, the high rate of crossover may have confounded the results.⁴² (Table II). A meta-analysis of these 3 randomized trials showed that PTRAs were more effective than drug therapy in reducing BP at 3 months.⁴³ However, if the pooled analysis of 12-month follow-up from the DRASTIC trial is used in the meta-analysis, the BP difference is no longer significant, which, again, may be due to the high rate of crossover at 3 months to the PTRAs group in this trial.⁴³

Preservation or improvement of renal function is the second indication for renal artery stenting. Two trials have suggested that renal artery stent placement improves or stabilizes renal function in patients with hemodynamically significant RAS.^{44,45} Both series together had a total of 65 patients; and of these patients, 58 had bilateral RAS or

unilateral RAS in a solitary functioning kidney. Three prospective studies have looked at renal function after renal artery stenting and showed that the GFR for the treated kidney improves. However, GFR of the contralateral kidney, previously in a state of hyperfiltration, decreases toward normal; and as a result, there probably is no change in overall GFR with unilateral RAS.⁴⁶⁻⁴⁸ The ACC/AHA guidelines suggest renal artery stenting for progressive chronic kidney disease with bilateral RAS or RAS associated with a solitary functioning kidney as a class IIa, LOE B recommendation, whereas renal artery stenting for RAS and chronic renal insufficiency with unilateral RAS is a class IIb, LOE C recommendation.¹²

The third indication for renal artery stenting is the treatment of cardiac destabilization syndromes such as unexplained heart failure exacerbations, episodes of flash pulmonary edema, and refractory or unstable angina. Khosla et al¹⁰ looked at 20 patients with unstable angina and RAS; and 13 underwent PTCA and renal stenting, whereas 7 underwent renal stenting alone. At 8 months, both groups showed sustained improvement based on the Canadian Cardiovascular Society angina classification, with no statistical difference between groups.¹⁰ In the same study, there were 28 patients with CHF and RAS; 6 underwent PTCA and renal artery stenting, whereas 22 underwent renal artery stenting alone.¹⁰ Again, at 8 months, there was sustained improvement in New York Heart Association class in both groups, with no significant difference between groups.¹⁰ The ACC/AHA guidelines suggest percutaneous revascularization for hemodynamically significant RAS and recurrent, unexplained CHF, or sudden unexplained pulmonary edema as a class I, LOE B indication, whereas unexplained

Table III. Ongoing randomized trials looking at interventions for RAS

Trial	Patients (n)	Intervention	Follow-up	Main end points
ASTRAL ⁴⁹	1000	PTRS	1-3 m, 6-8 m, 1 y, then annually	Primary: rate of progression of renal dysfunction Secondary: BP control, renal events (ARF, dialysis, transplant, or nephrectomy), serious vascular events (MI, angina, stroke), mortality
CORAL ⁵⁰	1080	PTRS	Driven by primary end point	Primary: composite of CV or renal death, stroke, MI, hospitalization for CHF, progressive renal insufficiency, or the need for permanent renal replacement therapy Secondary: all-cause mortality, subgroup interactions (gender, African Americans, diabetic persons, global vs partial renal ischemia), longitudinal kidney function, SBP, patency, RRI, correlation between stenosis severity and kidney function, QOL, cost effectiveness
NITER ⁵¹	100	PTRS	7 d; 1, 3, and 6 m; then every 6 m with extended follow-up to 4th y	Primary: combined end point of death or dialysis initiation or reduction by >20% in estimated GFR Secondary: SBP and DBP at 6 m, 1 y, and 2 y with extended follow-up after 2 y; number of hypotensive drugs; results of renal scintigraphy; incidence of complications due to interventions; changes in the incidence of extrarenal vascular complications
RAVE ⁵²	240	PTRS	Monthly for 6 m, then every 3 m	Primary: composite end point of death, dialysis, or doubling of Cr Secondary: compare BP and medications used, determine sensitivity and specificity of RRI, determine baseline factors associated with indication for revascularization
STAR ⁵³	140	PTRS	2 y and extended 5-y follow-up	Reduction of Cr clearance by >20% from baseline

PTRS, Percutaneous transluminal renal artery stenting; ARF, acute renal failure; MI, myocardial infarction; CV, cardiovascular; QOL, quality of life.

unstable angina is a class IIa, LOE B indication for revascularization of RAS.¹²

The evidence presented thus far would suggest that there is not a consistent effect on BP and renal function in patients who undergo renal artery revascularization. The only individuals shown to benefit thus far are those with bilateral RAS or RAS in a solitary functioning kidney. Intuitively, this does not make sense. Alleviation of significant renal artery lesions should decrease the substrate for renovascular hypertension and improve renal blood flow resulting in improved renal function or at least prevent deterioration of renal function. Why then has this not been shown in the randomized studies thus far? Safian and Madder²² suggest that the reason that BP does not consistently improve is that true renovascular hypertension is much more rare than we think and that most patients with RAS and hypertension have essential hypertension that would not be expected to respond to renal artery revascularization. Safian and Madder also suggest that the lack of improvement in renal function after renal artery revascularization is, in part, a result of patient selection. Serum creatinine does not give you a true measure of renal dysfunction because serum creatinine is not affected until >50% of the renal mass is lost. Therefore, patients who have an elevated serum creatinine may have already had significant damage to their renal parenchyma and may not recover from increased blood flow provided by renal artery revascularization.²²

Safian and Madder²² have further proposed a new classification system to identify candidates for renal artery revascularization with and without nephropathy and with and without renal ischemia: type I, normal kidneys (no nephropathy); type 2, nephropathy (parenchymal disease); type A, no renal ischemia (hemodynamically insignificant RAS); and type b, renal ischemia (hemodynamically significant RAS). By this classification, type IB patients would be the most likely candidates to benefit from renal artery intervention; and type 2A would be the least likely to benefit.²² This classification system has not been validated by prospective studies but provides an interesting framework for future investigation.

In all, the lack of definitive results from these randomized studies underscores the need for more comprehensive long-term randomized controlled trials. To this end, there are several prospective studies underway including ASTRAL (Angioplasty and Stent for Renal Artery Lesions),⁴⁹ CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions),⁵⁰ NITER (Nephropathy Ischemic Therapy),⁵¹ RAVE (Rubeosis Anti-VEGF),⁵² and STAR (Study of Tamoxifen and Raloxifene)⁵³ to further examine the role of renal artery stenting. The largest of these trials is ASTRAL, which has been criticized by some for the inclusion criteria that favored the enrollment of patients without clinically significant RAS but with other comorbidities.⁵⁴ Preliminary reports from ASTRAL show no significant benefits for the patients treated

with renal artery stenting as compared with the patients treated with medical therapy, but the results have not been published yet (Table III).⁵⁵

Conclusions

Renal artery stenosis is prevalent, and screening for RAS appears to be warranted because it provides objective evidence of atherosclerotic renal vascular disease. The diagnosis of RAS should precipitate aggressive medical management for secondary prevention. However, the question regarding which patients to treat with percutaneous renal revascularization remains.

At this point, the randomized clinical trials on this topic do not provide much guidance because they all failed individually to show any significant improvement in BP or renal function. No randomized studies have shown a reduction in heart failure exacerbations, flash pulmonary edema, or refractory angina as a result of renal artery intervention. In meta-analyses of the published trials, there seems to be a favorable effect of renal angioplasty on hypertension; however, the recently presented (unpublished) results of the large ASTRAL trial did not seem to confirm this. The group of patients for which there is solid evidence in favor of renal artery revascularization is the group of individuals with bilateral RAS or solitary functioning kidney who were shown to benefit with improved BP control and renal function postintervention.

In conclusion, the additional value of renal artery stenting needs to be established in patients who are aggressively medically managed; and a functional test to help us discern patients who would benefit from renal revascularization from patients who would not is needed. Because the issue of benefit from renal artery revascularization is still undecided, patients should be encouraged to enroll in randomized clinical trials. Only when we have solid evidence that patients will benefit significantly from renal artery revascularization in addition to optimal medical therapy should we incorporate RAS revascularization into routine medical practice.

Addendum

While this paper was in production another report of a randomized trial of renal artery stenting versus medical therapy was published (Bax L, Woittiez AJ, Kouwenberg HJ, et al. Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function: A Randomized Trial. *Ann Intern Med* 2009;150:840-8.). The trial, which enrolled 140 patients with impaired renal function and renal artery stenosis of 50% or greater, found no significant difference in the primary endpoint of increase in serum creatinine or in all cause mortality, but, as pointed out by the journals' Editors' Notes, the study was underpowered to provide a definitive estimate of efficacy.

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